PHENOTYPIC DISSECTION OF MOOD DISORDER

by

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Summary

The pathogenesis of affective disorders is not clearly understood and the diagnostic validity of psychiatric disorders remains unclear. The aim of this thesis was to identify sub-phenotypes in affective disorders that may be biologically validated by future molecular genetic studies.

The dataset comprised over 1000 subjects meeting diagnostic criteria (DSM-IV) for bipolar I disorder (BPI) or major recurrent depression (MDDR) who were previously recruited as part of ongoing molecular genetic studies. Subjects had been assessed in detail using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and case-note reviews. I undertook hypotheses testing and exploratory analyses in this dataset using a range of univariate and multivariate statistical tests.

I found that a depressive episode at illness onset in BPI subjects was associated with a more depressive course of illness. I also found clinical characteristics of depression that were associated with a bipolar, rather than unipolar, course of illness. Using the HCL-32, I identified a substantial number of MDDR subjects (17%) who reported bipolar symptoms at a level similar to that reported by BPI subjects.

I found significant differences in the clinical course of illness of MDDR and BPI subjects according to the lifetime presence of recurrent panic attacks, as well as clinical characteristics that appeared to be associated with the presence of panic attacks only in BPI subjects.

In the unipolar sample, I found that within subjects psychotic episodes tended to be more severe than non-psychotic episodes. However, between subjects there was wide variation in severity in both those that did, and did not, experience psychotic episodes.

In MDDR subjects, I found that episodes of postpartum depression clustered in families ($p=0.015$). I found no significant evidence for the familiality of reporting of life events in the MDDR sample.

These studies identify sub-phenotypes that may be of use in future genetic studies.

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1 Introduction

1.1 Summary

In this introductory chapter I will begin by briefly describing the history of the concept and classification of affective disorders, with reference to the descriptions, definitions and later diagnostic systems that were developed for both clinical and research purposes. I will then briefly discuss what is known about the aetiology and pathogenesis of affective disorder before describing some of the ways in which these disorders may be treated. The main focus of this chapter will be a consideration of the family and genetic studies that have been conducted to date that have examined whether there are familial or genetic risk factors associated with susceptibility for affective disorders. The final section of this chapter will describe the aims and layout of this thesis.

1.2 Background

The term "affective (mood) disorder" includes a wide range of conditions, ranging from common, mild episodes of mood variation, to more severe psychotic affective episodes, which represent some of the most severe forms of illness seen in psychiatric practice. The core features of affective disorder include a pathological disturbance in mood (ranging from severe elation to severe depression) and disturbances in thinking and behaviour, which may include psychotic features, such as delusions or hallucinations.

Historically the concept of affective disorders is very old, although by the late nineteenth century the writings of Falret and Baillarger began to describe a disorder ('folie a double forme' and 'folie circulaire') resembling affective disorders as they are known today. The disorder they described had an acute onset, was bipolar in character, and alternated between periods of normality and episodic exacerbations (Jelliffe, 1931, Lewis, 1934). In the early twentieth century, Emil Kraepelin (1921) distinguished manic depressive illness from the other psychotic disorders (dementia praecox). Manic depressive illness tended to be relatively severe, episodic, and recurrent, with a good prognosis and periods of normality between illness episodes. Kraepelin's description of manic depressive illness included syndromes featuring both mania and depression, as well as recurrent depression alone.

Modern diagnostic systems classify affective disorders as either unipolar or bipolar in nature, a distinction first described by Leonhard (1959). The unipolar/ bipolar distinction has received some support through the work of

investigators who published family studies during the 1960s. These studies suggested that predisposition to the two forms of affective disorders was specific for each disorder, and that the hereditary loading was more pronounced in bipolar than in unipolar probands (Angst, 1966, Perris, 1966, Winokur et al., 1969).

By the 1970s, classification of psychiatric disorders began to rely on a descriptive approach and the use of operational criteria, for example, the Feighner criteria (Feighner et al., 1972) and the Research Diagnostic Criteria (Spitzer et al., 1978). In modern classification systems, such as DSM-IV (APA, 2000), a diagnosis of bipolar disorder requires the presence of at least one episode of mania during the course of the illness, which may also be accompanied by one or more episodes of major depression. The main clinical distinction between bipolar and unipolar disorders is the requirement of an episode of mania for a bipolar diagnosis. Bipolar disorder can also be classified as either bipolar I disorder (BPI) or bipolar II disorder (BPII) according to DSM-IV. A diagnosis of BPI requires that the patient has experienced a period of mania that has lasted for at least a week and that has caused the patient significant impairment in work, social or personal functioning. BPII requires that a patient has experienced a period of hypomania (a milder form of mania) for at least four days. These episodes may also cause impairment in functioning but to a lesser degree than episodes of mania. A diagnosis of BPII also requires the presence of a major depressive episode(s), which may or may not be present for a diagnosis of BPI.

Patients with major depression (unipolar depression/ disorder) may be diagnosed according to DSM-IV as either major depressive disorder single episode (MDDS) or major depressive disorder recurrent episodes (MDDR) depending on whether the patient has experienced a depressive episode previously.

Prevalence estimates for affective disorders vary according to the diagnostic criteria, methodology and sample employed. However, the US National Comorbidity Survey estimated lifetime prevalence of DSMIII-R major depression to be 17.1%. (Kessler et al., 1994). The rate for women was almost twice that of men, being 21.3% and 12.7% respectively (Kessler et al., 1994), demonstrating the consistent gender differences that have been found for unipolar depression.

The prevalence rate for narrowly defined bipolar disorder is substantially less than for unipolar disorder and has been estimated to be between 0.5% and 1.5%, with no consistent evidence for any gender distinction (Smith and Weissman, 1992).

The pathogenesis of affective disorders is not clearly understood. Studies have suggested that imbalances in certain neurotransmitters or malfunctioning of neurotransmitter receptors may be implicated in mood disorders (Gelder et al., 2006). The monoamines, norepinephrine, serotonin and dopamine are the neurotransmitters traditionally associated with affective

disorders, however, more recently other neurotransmitters, such as glutamate and GABA, have also been implicated (Leonard, 2007). Neurophysiological abnormalities have been found in patients with affective disorders (Gelder et al., 2006), although it is difficult to establish whether abnormalities in brain structure and function in individuals with affective disorders are causes or correlates of the illness. Considerable experimental and clinical evidence has suggested that neuroendocrine abnormalities may play a role in the pathogenesis of mood disorders (Gelder et al., 2006). A well replicated example of this is the dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis seen in patients with major depression (Young and Korszun, 1998).

Treatments for affective disorders range from biological treatments, such as medication or electro-convulsive therapy (ECT), to psychological treatments, such as cognitive-behavioural therapy (CBT) or psychodynamic therapy, to socio cultural based treatments, such as interpersonal therapy (Gelder et al., 2006).

Antidepressant and mood stabilising medications that are used to treat affective disorders exert their effects by altering levels of neurotransmitters or sensitivity of receptors to neurotransmitters (these findings contributed to the monoamine hypothesis of mood disorders). Antidepressant medications are generally classified into tricyclic antidepressants, monoamine oxidase inhibitors, or selective serotonin reuptake inhibitors (and other second generation antidepressants). These drug classes vary in their effectiveness across individuals and in their potential to produce side effects (Healy, 2002).

Psychological treatments, such as CBT, blend cognitive and behavioural theories of depression (Beck et al., 1974). They aim to change negative patterns of thinking and enable individuals to solve concrete problems in their lives though the development of new life skills.

Socio-cultural approaches to the treatment of depression focus on an individual's roles and relationships in society. Interpersonal therapy is a socio-cultural approach to treating depression because it views the individual's symptoms in the context of their relationships and interpersonal roles (Nolen-Hoeksema, 2001).

Currently, the diagnostic validity of psychiatric disorders remains unclear. Due to a limited understanding of the biological systems involved in affective disorders, current classification systems aim to identify patients that display signs and symptoms that appear to consistently co-occur and are therefore thought to best represent an affective disorder. Such descriptive, syndromal approaches are based on the best available evidence (Kendell, 1987, Farmer and McGuffin, 1989), but their usefulness is limited by unknown biological validity. At present, many patients fail to respond adequately to mood stabilising or antidepressant medication, and many experience undesirable side effects from medication. There are important management differences between bipolar and unipolar depression. For example, in bipolar depression antidepressants have to be used more cautiously and with closer ongoing

monitoring of mental state after the initial improvement because of the substantial risk of mood switch or mood cycling (NICE, 2006b).

The identification of genes that may make an individual susceptible to developing a mood disorder will lead to an increased understanding of the biological and neuro-chemical pathways involved in affective illness. Such findings will introduce new possibilities into classification and diagnosis. It is hoped that this will result in a classification of disorders that is biologically validated, enabling the development and use of more targeted, and therefore more efficient, treatments both pharmacological and non-pharmacological.

1.3 Measuring Genetic and Environmental Risk Factors

1.3.1 Family, Adoption and Twin Studies

Family studies compare the prevalence of mood disorders in biological relatives (usually first-degree relatives) of probands with mood disorders to the prevalence of mood disorders in relatives of suitably matched individuals with no history of mood disorder. Family studies provide an estimate of familiality (how much a disorder aggregates in families). Family studies cannot, however, establish whether a disorder aggregates in families as a result of genetic factors, or as a result of environmental risk factors that are also familial (or as a result of both).

Adoption and twin studies are the two main approaches used to disentangle genetic and environmental effects. In both adoption studies and twin studies,

it is possible to separate the variance in liability to affective disorder into three components: genetic influences, shared environmental influences, and unique environmental influences (see Figure 1-1).

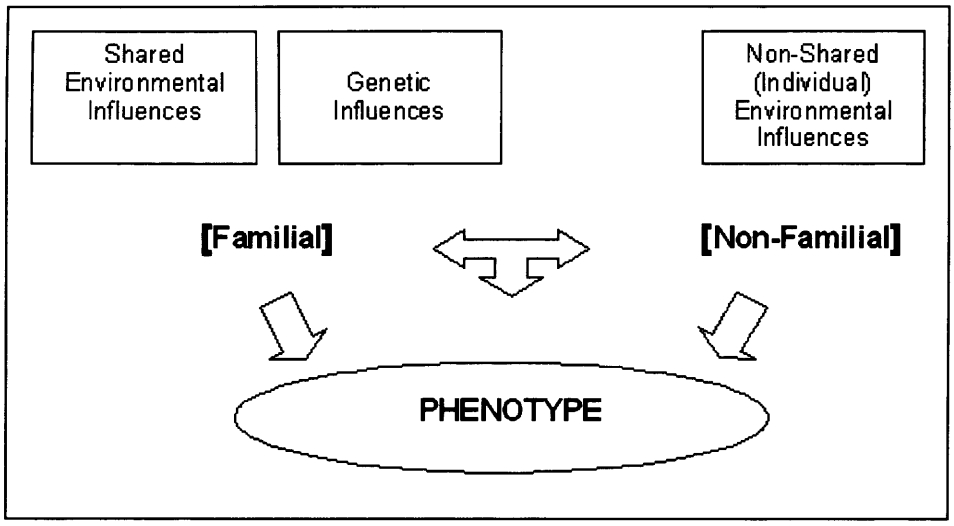


Figure 1-1: Genetic and Environmental Influences on the Phenotype

Shared environmental influences and genetic influences (which are familial) and non- shared environmental influences (which are non-familial) interact and impact on the phenotype.

Adoption studies are based on the offspring of one set of parents being reared from early in life by unrelated strangers. Aggregation of disease in biological parents of an affected individual suggests that a genetic component may influence liability. Aggregation of disease in unrelated parents of an adopted affected individual suggests that environmental factors may play an important role in contributing to disease susceptibility. This study design has become more difficult to conduct as a result of declining adoption rates.

Twin studies compare genetically identical (monozygotic) twins with fraternal twins who share half their genes on average (dizygotic). Higher concordance rates for disease in monozygotic twin pairs compared with dizygotic twin pairs

suggests the involvement of a genetic component in disease susceptibility. Twin studies rely on the equal environment assumption, that monozygotic and dizygotic twins are equally correlated in their exposure to environmental risk factors for affective disorders. If this assumption is incorrect, a greater similarity between monozygotic than dizygotic twin pairs, could result from environmental and not genetic factors. However, the equal-environment assumption has been examined repeatedly, and there is considerable evidence supporting its validity for major depression (Kendler et al., 1994, Kendler and Gardner, 1998).

1.3.2 Molecular Genetic Studies

Molecular genetic studies can be divided into the positional and candidate gene approaches. The positional approach determines the chromosomal locations of susceptibility genes, usually by linkage studies.

Linkage Studies

Linkage studies aim to find regions within the genome that are likely to harbour susceptibility genes by examining genetic marker allele sharing in members of families with more than one affected member (most commonly using an affected sibling-pair design). Linkage studies require no knowledge of disease pathophysiology and are therefore useful for the study of psychiatric illnesses where pathogenesis is poorly understood. However, the use of linkage analysis in studies of affective disorder is complicated by an unknown model of inheritance, genetic heterogeneity and the likely importance of non-genetic factors. It is now recognised that due to the

expected small or modest genetic effect sizes, large samples (hundreds to thousands) are required to provide adequate power to detect linkage.

Association Studies

Association studies compare allele frequencies at a marker locus for unrelated affected individuals (cases) and appropriate comparison individuals (controls). Differences indicate either that the variant itself is directly involved in influencing disease susceptibility or that it is very close to a DNA variant that influences susceptibility (called "linkage disequilibrium"). The great advantage of association is that it can detect genes of very small effect that will be overlooked by linkage studies. Association approaches usually focus on variants in a specific gene or genes thought to be candidates for involvement in illness ("candidate gene studies").

Since the completion of the Human Genome Project in 2003 and the International Hapmap Project in 2005 it is now possible to conduct whole genome association studies, where whole genome samples can be quickly and accurately analysed for genetic variations that may contribute to disease susceptibility.

1.4 Family, Adoption and Twin Studies and Affective Disorders

1.4.1 Family, Adoption and Twin Studies and Bipolar Disorder

There is consistent evidence for the increased risk of bipolar disorder in the relatives of bipolar probands. A meta-analysis of eight studies (Jones et al., 2002) provided an estimate of risk (as measured by odds ratios, OR, and 95% confidence intervals, CI) in first degree relatives of probands diagnosed with bipolar I disorder of 7% (CI 5-10%). There is also evidence for increased rates of other affective disorders in the relatives of bipolar probands, compared to the risk for the general population. The studies used in the meta-analysis mentioned above also found high rates of unipolar illness in the relatives of bipolar probands. These rates of unipolar disorder were higher in the relatives of bipolar probands than the rates of bipolar disorder, although when taking into account the larger population prevalence for unipolar disorder, the relative risk is much lower, at approximately double the risk (McGuffin and Katz, 1989). Interestingly, Blacker & Tsuang (1993) estimated that two-thirds to three-quarters of cases of unipolar disorder in the relatives of individuals with bipolar disorder, can be considered to be "genetically bipolar", meaning that they share a common genetic susceptibility with the bipolar form of affective illness.

There is also strong evidence for the increase in rates of bipolar II disorder in the relatives of bipolar I probands, (Gershon et al., 1982, Rice et al., 1987). There has been no consistent evidence for an increased risk of schizophrenia

in bipolar relatives although schizoaffective disorder, in which manic features occur, has shown consistent familial aggregation with bipolar disorder (Rice et al., 1987, Gershon et al., 1982, Kendler et al., 1998).

Several adoption studies have considered the genetic and environmental factors associated with mood disorders, although only two of these have been based on a modern definition of bipolar disorder (Mendlewicz and Rainer, 1977, Wender et al., 1986). The results of both of these studies are consistent with a role for genetic factors influencing susceptibility for affective disorders, including bipolar disorder.

Studies have consistently shown an increased probandwise concordance rate in monozygotic (MZ) twins when compared with dizygotic (DZ) twins (Kringlen, 1967, Allen et al., 1974, Bertelsen et al., 1977, Torgersen, 1986, Kendler et al., 1993d, Cardno et al., 1999). Pooling the data from these studies provides an estimate of MZ concordance for narrowly defined bipolar disorder of 50%. More recently, a Finnish twin study (Kieseppa et al., 2004) of bipolar I disorder reported a probandwise concordance rate of 43% in MZ twins compared to 6% in DZ twins. They found that genetic and specific environmental factors contributed to the best fitting model, with a heritability estimate of 0.93.

Twin studies have also suggested that familial factors may be shared across the functional psychoses. McGuffin et al (2003) concluded from their twin study that there are substantial genetic and non-shared environmental factors

conferring susceptibility to mania and depression, but that most of the genetic variance in liability to mania is specific to the manic syndrome. Similarly, Cardo et al (2002) found that there appeared to be an overlap in genetic susceptibility between schizophrenia, bipolar disorder and schizoaffective disorder, but that there are also separate components to schizophrenia and bipolar disorder (but not schizoaffective disorder).

Certain proband and illness characteristics have been identified as important in the prediction of morbidity rates in relatives. Life time risk of affective disorders in family members is increased with earlier age at onset (Strober, 1992), as well as with the number of affected relatives (Gershon et al., 1982).

Potash et al (2003) found that a history of psychotic bipolar disorder in probands increased the risk of bipolar disorder in relatives. They also found that psychotic bipolar disorder itself clustered in families of probands with psychotic bipolar disorder. O' Mahony et al (2002) also found that the degree of psychosis appeared to be familial in bipolar families.

Risk for panic disorder in families segregating bipolar disorder appears to be a familial trait (MacKinnon et al., 1997, MacKinnon et al., 2002) and there is evidence to suggest that vulnerability to the puerperal triggering of episodes may be a marker for a more familial form of bipolar illness (Jones and Craddock, 2002).

Another aspect of the phenotype that has been shown to cluster in the families of patients with bipolar disorder is response to lithium prophylaxis (Grof et al., 2002). The authors found a higher frequency of bipolar disorder in the relatives of lithium responders, and a higher frequency of schizophrenia in families of non-responders.

1.4.2 Family, Adoption and Twin Studies and Major Depressive Disorder

Family studies have provided strong evidence for the familial aggregation of major depression. A meta-analysis by Sullivan et al (2000) found that all five of the studies that met the inclusion criteria for the meta-analysis supported the familial aggregation of major depressive disorder. Studies have consistently shown increased rates of unipolar illness in the relatives of unipolar probands. However, there is no evidence to suggest that rates of bipolar disorder are increased in the relatives of unipolar probands (McGuffin and Katz, 1989).

Although adoption studies have been inconsistent in supporting the role of genetic influences on liability to major depression, Sullivan et al (2000) found that two of three studies included in their meta-analysis were consistent with genetic influences on liability to major depression.

Twin studies have consistently shown higher concordance rates for monozygotic twins that for dizygotic twins, consistent with a genetic contribution to the development of major depression. Sullivan et al (2000)

concluded from their meta-analysis of five twin studies that familial aggregation was due to additive genetic effects (37%), and individual-specific environmental effects (63%), with a minimal contribution of shared environmental effects.

Some studies have shown major depression with an earlier age at illness onset to be more familial than later onset depression, although this was not supported by a meta-analysis (Sullivan et al., 2000). Recurrence of depressive episodes appears to be the characteristic most strongly and consistently associated with increased familiality and heritability (Sullivan et al., 2000).

Other clinical features, such as impairment during depression (Kendler et al., 1994, Kendler et al., 1999) and duration of the longest depressive episode (McGuffin et al., 1996, Kendler et al., 1999) have also been found to be associated with increased familiality of major depression.

Major depressive disorder is often divided into reactive (triggered by an event) and endogenous (coming from within) depression. Family studies provide little support for this distinction (Rush and Weissenburger, 1994) with no difference in family history being found for the two types of depression. However, it has been suggested that reactive (neurotic) depression may be less familial than endogenous depression, but only when severe depression in relatives is taken as the relevant phenotype (McGuffin et al., 1987). Twin studies suggest that the genetic contribution to neurotic depression is probably small,

compared to endogenous depression, at most accounting for about 20% of the variance in liability (McGuffin et al., 1994).

Atypical subtypes of major depression have been shown to be at least partially distinct from typical subtypes from a clinical, longitudinal and familial genetic perspective (Kendler et al., 1996). Melancholic depression has been found to identify a subset of individuals with distinct clinical features and a particularly high familial liability to depressive illness (Kendler, 1997). However, from a familial perspective, the differences between melancholic and non-melancholic major depression are quantitative, not qualitative (i.e. melancholic major depression is more severe than, but not aetiologically distinct from, non-melancholic major depression).

Evidence for the familiality of psychotic features in bipolar patients has been demonstrated (Potash et al., 2001, O'Mahony et al., 2002, Potash et al., 2003), however, findings in unipolar disorder have not been so consistent.

Winokur et al (1985) found no evidence that psychotic probands were more likely than the non-psychotic to have psychotic relatives. This was supported by the findings of Coryell et al (1985) who found that patterns of familial psychopathology were similar for psychotically depressed inpatients and non-psychotic depressed inpatients. However, Coryell et al (1985) also found increased rates of schizophrenia and decreased rates of depression in the families of depressed patients with mood-incongruent psychosis compared to those with mood-congruent psychotic features. Recently, interesting findings

have emerged in relation to phenotypic overlap between bipolar disorder and schizophrenia and have pointed to the possibility of common psychosis susceptibility genes (Craddock et al., 2005). Further investigation of the relationship between major depression and psychosis is needed.

Research has consistently found that influences on anxiety and depression, both as symptoms and disorders, are almost entirely shared (Jardine et al., 1984, Kendler et al., 1992, Roy et al., 1995). Familial factors may explain a limited proportion of cases where unipolar depression is comorbid with panic disorder, however, Maier et al (1995a) concluded from their study that the majority of comorbidity between unipolar depression and panic disorder may still be due to non-familial factors. Interestingly, a more recent study found that the temporal relationship between comorbid panic and depression may play an important role in determining the familial risk for depression in family members (Dindo and Coryell, 2004).

The literature supporting the familiality of antidepressant response is sparse, however, studies to date have been consistent in finding that positive response to antidepressant medication clusters in families in both patients with unipolar depression (O'Reilly et al., 1994) and also in patients with bipolar disorder (Franchini et al., 1998).

There has been no evidence supporting an influence of the sex of the proband on rates of illness among relatives, although the risk of unipolar illness in female relatives of unipolar probands is greater than the risk to male

relatives (Weissman et al., 1984a, Winokur et al., 1982). Whether this increased risk is due to biological or social factors is an issue of much debate.

Although women are twice as likely to experience major depression compared with men, heritability estimates using a clinical twin sample have been reported to be the same for men and women (McGuffin et al., 1996). However, a recent population-based twin study by Kendler et al (2006) suggests that the heritability of major depression is higher in women than in men and that some genetic risk factors for major depression may be sex specific in their effect. Some twin studies have suggested that there may be sex differences in the genes conferring liability to depression (Bierut et al., 1999), though other studies show no such difference (Agrawal et al., 2004). A possible explanation for these findings is that males and females share most but not all genetic influences for major depression.

It has been suggested that when focusing on clinical samples or more severe or clear-cut cases in the community, the heritability of major depression increases and is only slightly less than the 80% figure usually quoted for schizophrenia or bipolar disorder (McGuffin et al., 2007). However, contrasting with this suggestion, Sullivan et al (2000) found that estimates of heritability were similar in subjects ascertained from community and clinical sources.

These studies have also demonstrated a graduation in risk of major depression between various classes of relatives, with monozygotic co-twin

showing the highest risk, through first degree relative to unrelated member of the general population showing the lowest risk. The majority of studies suggest a relative risk to siblings (λs) of affective disorder in the region of three (Jones et al., 2002). However, one study comparing the siblings of unipolar depressives with the siblings of healthy controls found a substantially higher λs of over nine (Farmer et al., 2000).

Heritability estimates (the proportion of variance explained by additive genetic factors) for major depression range from 40% to 70%, depending on the methodology and diagnostic criteria employed (Kendler et al., 1993b, McGuffin et al., 1996). All studies to date are consistent with models of inheritance that include multiple genes that interact with each other and environmental factors to confer susceptibility to illness [for example, Craddock et al (1995)].

1.4.3 Gene-Environment Interactions

In considering gene-environment interactions, Kendler et al (1998c) considered two potential processes by which genetic and environmental factors impact on liability to depression. Firstly, the genetic control of sensitivity to the environment theory, suggests that genetic factors alter an individual's sensitivity to the depressogenic effects of stressful life events, and therefore impact on liability to depression. Although few studies have examined this, Kendler et al (1995a) found supportive evidence in their study of female twin pairs from the Virginia Twin Registry. They found that an

increased risk for major depression given a severe life event was about twice as high in those at high genetic risk, as in those at low genetic risk.

The second model proposed by Kendler et al (1998c) involved genetic control of exposure to the environment. According to this model, genes influence the probability that an individual will be exposed to a depressogenic environment. There have been more studies of this theory, and McGuffin et al (1988) found not only increased rates of depression among relatives of depressed probands, but also an increased reporting of life events. Other studies suggest that familial or genetic factors influence risk of exposure to severe life events (Kendler et al., 1993a, Breslau et al., 1991, Plomin et al., 1990, Lyons et al., 1993). A sibling pair study conducted by Farmer et al (2000) found significant correlations for sibling pairs only for life events that were shared by both members of the pair, for example, the death of a parent.

It is clear that for a complete understanding of the aetiology of affective disorders it will be necessary to understand the complex interplay between genetic and environmental factors. Table 1-1 provides a summary of family, twin and adoption studies with reference to findings in unipolar and bipolar disorder.

Table 1-1: Key Features of Family, Adoption and Twin Studies with Reference to Findings in Affective Disorders

	Family Studies	Adoption Studies	Twin Studies
What does this study design aim to assess?	The degree of familial clustering of a disorder (in families or sibling pairs).	Resemblance in a) genetically related individuals who do not share a common family environment (biological parents and adopted-away offspring) and/ or b) individuals who are not genetically related but share the family environment (adoptive parents and adopted offspring)	The similarity of Monozygotic (MZ) twin pairs (who are genetically identical) compared to Dizygotic (DZ) twin pairs. (who share approximately 50% of their genes).
How is a familial or genetic effect shown?	Familial aggregation is indicated by a significantly higher morbid risk (lifetime expectation) for the disorder in relatives of probands (index cases) than controls.	a) Increased similarity between biological parents and adopted-away offspring suggests a genetic effect. b) Increased similarity between adoptive parents and adopted offspring implicates the contribution of family (shared) environment.	If genetic factors are important, MZ twins will be more similar pheno-typically than DZ twins. Although it is usually easy to tell if twins pairs are MZ or DZ based on their physical similarities, DNA markers may be used to test the zygosity of twin pairs.
Can this study design distinguish between genetic and shared environmental effects?	No	Yes	Yes
To date, do these studies provide evidence for the influence of familial and/or genetic factors in contributing to susceptibility for affective disorders?	A large number of family studies have demonstrated the familial aggregation of bipolar disorder and of unipolar disorder.	The few studies of unipolar depression that have been conducted have provided inconsistent support for the influence of familial or genetic factors. The two studies that have used current definitions of bipolar disorder are consistent with a role for genetic factors in susceptibility to bipolar disorder.	Several large scale studies have provided robust evidence for the involvement of genetic and shared environmental factors in influencing susceptibility to unipolar and to bipolar disorder.

1.5 Molecular Genetic Studies and Affective Disorders

1.5.1 Molecular Genetic Studies and Bipolar Disorder

Linkage Studies and Bipolar Disorder

Badner and Gershon (2002) examined seven published genome scans for bipolar disorder and concluded from their meta-analysis that the strongest evidence for susceptibility loci was on 13q and 22q. A more recent meta-analysis by Segurado et al (2003) did not find genome-wide significant evidence for linkage but provided a more modest level of support for regions on chromosomes 9p, 10q, 14q, and 18. Several further genome-wide scans have since been published providing genome-wide significant or suggestive evidence for linkage. One of the best supported regions for bipolar disorder is the 6p21-q25 region which demonstrated genome wide significance in one study, (Middleton et al., 2004) and genome-wide suggestive signals in three further studies (Dick et al., 2003, Ewald et al., 2002, Lambert et al., 2005). This region achieved genome-wide significance in a recent combined analysis of eleven bipolar linkage scans (McQueen et al., 2005).

Two genome scans have reported genome-wide significance for the 12q23-24 region (Ewald et al., 2002, Shink et al., 2005), which is also supported by linkage analysis in unipolar depression (McGuffin et al., 2005).

Candidate Gene Studies and Bipolar Disorder

Most candidate gene studies have focussed on neurotransmitter systems influenced by the medications that are used to treat mood disorders, particularly the dopamine, serotonin, and noradrenaline systems (reviewed by

Craddock and Jones (2001)). For most genes studied there are one or few positive studies, but also a number of negative replications. However, meta-analyses of polymorphisms of known functional relevance in three genes have shown significance at the $p<0.05$ level. These are monoamine oxidase A (MAOA), (Preisig et al., 2000), catechol-o-methyltransferase (COMT), (Jones and Craddock, 2001a) and the serotonin transporter (5HTT), (Anguelova et al., 2003, Lasky-Su et al., 2005).

Most of the reports in the literature are from modestly sized samples, which are likely to be underpowered for plausible effect sizes. Independent, large samples are required to determine whether these genes contribute to susceptibility to bipolar disorder.

Examination of candidate genes should be predicated on more sophisticated models of pathogenesis or directed by positional information from linkage studies. Recently, replicable positive findings have begun to emerge from such approaches.

For example, at least five independent datasets have contributed evidence that variation at the D-amino acid oxidase activator (DAOA) G30 locus on chromosome 13q influences susceptibility to bipolar disorder. (Hattori et al., 2003, Chen et al., 2004, Schumacher et al., 2004, Williams et al., 2006). No pathologically relevant variant has yet been identified and the biological mechanism remains to be found.

A gene on chromosome 11, brain derived neurotrophic factor (BDNF), has been associated with bipolar disorder in some reports (Sklar et al., 2002, Neves-Pereira et al., 2002, Geller et al., 2004), but not in others (Oswald et al., 2004, Skibinska et al., 2004, Hong et al., 2003, Nakata et al., 2003). However, Green et al (2006) found a significant association with bipolar disorder in a subset of cases that had experienced rapid cycling, (four or more episodes per year) at some time, and a similar association on reanalysis of a previously reported family based association sample. This suggests that the BDNF gene may not play a major role in influencing susceptibility to bipolar disorder as a whole but, in fact, may be associated with susceptibility to a specific aspect of the clinical bipolar phenotype. Again, further systematic study of variation across the whole gene is required in further independent samples.

Genome-wide association studies and Bipolar Disorder

The first genome-wide association study of bipolar disorder (WTCCC, 2007) has confirmed that there are many genes that influence susceptibility to the illness and that each gene makes a relatively small contribution to risk. The strongest signal for bipolar disorder was on chromosome 16 and there are several genes at the particular locus that could have pathological relevance. Other higher ranked signals in this study provide support for the previously suggested importance of GABA and glutamate neurotransmission, and synaptic function.

1.5.2 Molecular Genetic Studies and Major Depressive Disorder

Linkage Studies and Major Depressive Disorder

Compared with other major psychiatric illnesses, (for example schizophrenia and bipolar disorder) there have been relatively few genome scans of major depressive disorder as the main phenotype although, more recently, several large affected sibling-pair and case-control collections of DNA for recurrent major depression have become available for analysis and results of genome scans have recently been reported.

McGuffin et al (2005) conducted a whole genome linkage scan of recurrent depressive disorder with two regions showing genome-wide significant evidence for linkage; 12q23.3-24.11 and 13q31.1-q31.3. Chromosome 12q22-23 overlaps with a region previously implicated by linkage studies of unipolar and bipolar disorders (Abkevich et al., 2003) and contains a gene, D-amino acid oxidase (DAO) that has been associated with both bipolar disorder and schizophrenia. The 13q peak lies within a region previously linked strongly to panic disorder (Hamilton et al., 2003). A more modest peak was also found at 15q within a region that showed genome wide significant evidence of a locus for recurrent depression in a previous sibling-pair study of depression (Holmans et al., 2004). More recently, in the second wave of the study by Holmans et al (2007), evidence for linkage was again observed on chromosome 15q, and also on 17p and 8p when sex was included as a covariate. These results suggest that multiple loci contribute to risk for major depression.

A study by Zubenko and colleagues of recurrent early onset depression identified a surprisingly large number of linkage signals; the strongest signal was at 2q close to the gene encoding CREB1 (Zubenko et al., 2003). A theme that seems to be emerging from this and other linkage studies of unipolar disorder is a gender-specificity in linkage signals. For example, the 12q signal in the study of Abkevich and colleagues (2003) was present only in males; the 2q signal of Zubenko and colleagues (2003) was present only in females. These findings await replication.

Linkage Studies, Major Depressive Disorder and Comorbidity

Linkage studies have also been undertaken in which the clinical phenotype has included unipolar depression as a major component, together with other comorbid (and putatively pathogenetically related) psychiatric phenotypes. Nurnberger et al (2001) observed a higher prevalence of depression in alcoholic than non alcoholic subjects in families multiply affected with alcoholism. Genome-wide sibling-pair linkage analysis suggested that a gene or genes on chromosome 1 may predispose some individuals to alcoholism and others to depression.

The co-occurrence of anxiety and depression is extremely common in clinical practice. Twin studies have suggested that pure anxiety may be genetically distinct from both major depression and major depression with anxiety (Torgersen, 1990).

High premorbid neuroticism scores are a robust predictor of future onset of major depression (Kendler et al., 1993c, Kendler et al., 2004). Kendler estimated that 55% of the genetic risk of major depressive disorder was shared with neuroticism. There may be common genetic factors that can predispose to major depressive disorder, neuroticism and anxiety disorders. Camp et al (2005) studied recurrent, early onset major depressive disorders and anxiety disorders and found linkage evidence for a novel locus at 3p12.3-q12.3, and at 18q21.33-q22.2, a susceptibility locus previously reported for bipolar disorder.

Although there is some evidence for convergence of linkage findings across studies, substantially more data are needed to permit meta-analysis, which will be needed to give appropriate power.

Candidate Gene Studies and Major Depressive Disorder

To date, as with linkage studies, less attention has been given to genetic association studies of unipolar disorder than has been the case for bipolar disorder or schizophrenia. There are no unambiguous positive findings but the literature is developing rapidly. Given the expected smaller effect sizes and the possibility of greater clinical heterogeneity in unipolar disorder compared with bipolar disorder and schizophrenia, it can be expected that larger samples are likely to be required both for detection and replication of susceptibility loci.

Perhaps the most interesting finding to emerge to date is the report of interaction between a functional variant at the serotonin transporter gene (5-HTTLPR) and the occurrence of stressful life events. Caspi et al (2003) found that individuals with one or more short alleles who were exposed to adult stressful life events were more likely to develop depression than those homozygous for the long allele.

They also found that childhood maltreatment predicted adult diagnosed depression among individuals carrying at least one copy of the short allele. There have been both positive (Kaufman et al., 2004, Kendler et al., 2005) and negative (Surtees et al., 2005, Gillespie et al., 2005) attempts at replication. It is widely assumed that gene-environment interactions and co-action will occur in mood disorder and this finding may prove to be the first such example. However, the evidence that effect of stressful life events on depression is moderated by 5-HTTLPR genotype is far from robust.

Genome-wide association studies and Major Depressive Disorder

To date, there are no published genome-wide association studies of major depressive disorder, although such studies are under way.

1.6 Refining the Phenotype

1.6.1 General Aims and Outline of Thesis

Some of the difficulties in identifying susceptibility genes for affective disorders are likely to be related to the phenotypic properties of the illness. An

interesting example can be seen in the literature on type 2 diabetes. FTO is a gene which has been shown to influence susceptibility for obesity and type 2 diabetes. The gene was originally identified in genome-wide association studies of type 2 diabetes (for example, (WTCCC, 2007)) but did not show a signal in other genome-wide studies of type 2 diabetes which had controlled for body weight (i.e. individuals who were obese were excluded) (Zeggini, 2007). This example illustrates how selection on phenotypic variables can greatly alter the findings of genetic studies.

In psychiatry, high rates of comorbidity and instability of diagnoses throughout the lifespan make for heterogeneous disorders. It is likely that, rather than reflecting homogeneous groups, diagnostic categories represent common final pathways of different pathophysiological processes (Charney et al., 2002).

Recently, researchers have begun to focus on improving phenotype definition in studies investigating the aetiology of affective disorder with the aim of identifying more homogeneous disorders that may be more likely to share some common aetiological basis.

For many of the "sub-phenotypes" that showed evidence for familiality in affective disorders (mentioned previously in section 1.4), molecular genetic studies have been conducted which have provided support for the existence of genetic factors influencing susceptibility to the particular "sub-phenotype". For example, early age at onset (Faraone et al., 2004), lithium

responsiveness (Turecki et al., 2001), bipolar affective puerperal psychosis (Jones et al., 2007, Jones and Craddock, 2001b, Coyle et al., 2000), and occurrence of psychotic features (O'Mahony et al., 2002, Craddock et al., 2004, Potash et al., 2003).

A number of "sub-phenotypes", such as rapid cycling in bipolar disorder, have been found to be influenced by genetic factors (Kirov et al., 1998), despite previous studies failing to find any evidence of familial aggregation (Nurnberger et al., 1988, Lish et al., 1993).

Table 1-2: Summary of Chapter 1

1.	The usefulness of current diagnostic classification systems is limited by unknown biological validity.
2.	The influence of genetic and environmental risk factors on illness susceptibility can be assessed using family, twin and adoption studies.
3.	Family, adoption and twin studies have provided robust evidence for the familiality and heritability of affective disorder.
4.	Certain patient and illness characteristics may influence the familiality and heritability of affective disorders.
5.	Men and women likely share most, but not all, genetic influences for affective disorder.
6.	Molecular genetic studies, using linkage and association techniques, may identify specific genes and genetic regions that may influence susceptibility to affective disorders.
7.	The literature on genetic studies and affective disorder is developing rapidly.
8.	Studies to date are consistent with models of inheritance that include multiple genes that interact with each other and environmental factors to confer susceptibility to illness.
9.	Both the improvement of phenotype definition and increased focus on sub-phenotypes may facilitate the identification of susceptibility genes.
10.	A complete understanding of the aetiology of affective disorders will require an understanding of the complex interplay between genetic and environmental factors.

Table 1-2 provides a summary of the main points and findings from research into affective disorders that have been described in chapter 1.

The overall aim of this thesis is to refine phenotype definition in affective disorders through the identification of novel sub-phenotypes that may be biologically validated by future molecular genetic studies. This will involve the

examination of various aspects of the phenotype in well defined and characterised samples of subjects with affective disorder diagnoses. The samples will be described in chapter 2.

Studies have suggested that episode polarity at illness onset in bipolar disorder is familial and may predict some aspects of illness course (Kassem et al., 2006). Chapter 3 will investigate whether episode polarity at illness onset in bipolar disorder may be a characteristic of the phenotype that may identify sub-groups of subjects who are distinct in terms of some aspects of lifetime clinical characteristics.

It is generally held that there are no clear differences in the clinical presentation of unipolar and bipolar depression. In chapter 4, I will compare clinical course variables and depressive symptom profiles in samples of unipolar and bipolar subjects.

The Hypomania Check List (HCL-32) self-report questionnaire is a tool designed to screen for hypomanic components in patients with major depressive disorder. The main aim of chapter 5 is to assess the presence of hypomanic symptoms in a highly selected "unipolar" sample using the HCL-32.

Previous studies have illustrated the frequent co-morbidity of panic disorder and mood disorder. In chapter 6, I will examine lifetime clinical characteristics

of illness and the lifetime presence of recurrent panic attacks in both the unipolar and bipolar samples.

The presence of psychotic features may identify a sub-phenotype within unipolar disorder. In chapter 7 I will examine the relationship between the presence of psychotic features and the severity of depression, using both lifetime and episode severity measures, in the unipolar sample.

Strong evidence for the familial aggregation of episodes of postpartum (puerperal) psychosis in women with bipolar disorder has previously been reported (Jones and Craddock, 2001b). In chapter 8, I will examine whether vulnerability to the postpartum triggering of depressive episodes in unipolar depression aggregates in families and will assess how this aggregation varies with the definition of postpartum depression.

Occurrence of stressful life events is associated with the onset of major depressive episodes. In chapter 9 I will assess whether there may be a familial contribution to individual variation in susceptibility to precipitation of depression by life events.

The in depth phenotypic analyses involved in these studies of unipolar and bipolar disorders should enable the identification of distinct and shared features of the phenotype that may help to identify underlying disease processes that may be specific to the particular phenotypic sub-group, as well as disease processes that may be shared across the disorders. In chapter 10,

I will provide a general summary and discuss the implications of these studies, as well as presenting recommendations for future work.

2 Methodology

2.1 Summary

This chapter describes the recruitment and assessment procedures used to ascertain the samples studied throughout this thesis. The samples were recruited by the Mood Disorders Research Team at Cardiff University and The University of Birmingham. I was a member of the team in Birmingham prior to starting my postgraduate studies and a substantial proportion of the subjects that were recruited to the Depression Network (DeNT) sibling-pair study (described below) were recruited and interviewed by myself. I was also involved in diagnostic and clinical rating assessments of subjects (with a range of mood disorders).

Methodology and sample characteristics specific to individual analyses will be described at the relevant points in the appropriate chapters.

2.2 Sample Recruitment

Subjects were recruited as part of ongoing molecular genetic and clinical studies of affective disorders using both systematic and non-systematic recruitment methods. Systematic recruitment involved the screening of Community Mental Health Teams and Lithium Clinics for patients with affective disorders. With the permission of the Responsible Medical Officer, all potentially suitable patients were invited to participate in the study. Non-systematic recruitment involved advertisements in local family practitioner offices, local media, and via patient support organisations (for example, the Manic Depressive Fellowship and Depression Alliance).

The study received all necessary Multi-Region and Local Ethical Approval (MREC and LREC).

2.2.1 Unipolar Samples

The multi-centre Depression Case Control Study (DeCC) recruited subjects with recurrent major depressive disorder from three sites (Birmingham, Cardiff and London, UK). This study was funded by the Medical Research Council (MRC). The principle investigators for the study were Professors Peter McGuffin, Anne Farmer, Michael Owen and Nick Craddock.

The international multi-centre Depression Network (DeNT) sibling-pair study recruited families multiply affected with recurrent major depression for a linkage genome screen (Farmer et al., 2004, McGuffin et al., 2005). The eight sites involved in the recruitment of these families were Aarhus, Denmark;

Bonn, Germany; Dublin, Ireland; Lausanne, Switzerland; St Louis, USA; and Birmingham, Cardiff and London, UK. This study was funded by GlaxoSmithKline (GSK) research and development. The overall principle investigators for the study were Professors Peter McGuffin and Anne Farmer. The individual site principle investigators were Ole Mors (Aarhus), Marcella Rietschel and Wolfgang Maier (Bonn), Mike Gill (Dublin), Martin Preisig (Lausanne), Theodore Reich (St Louis), Nick Craddock, Lisa Jones and Ian Jones (Birmingham), Ania Korszun and Michael Owen (Cardiff), and Anne Farmer and Peter McGuffin (London).

Subjects recruited to the Depression Case Control (DeCC) Study and the Depression Network (DeNT) sibling-pair study at the Birmingham site form the unipolar sample described in this thesis. For studies where the analysis is not focused on sibling pairs, an algorithm was used to randomly select one member of each sibling pair recruited to the DeNT study, so that all individuals within the sample were unrelated.

Inclusion/ Exclusion Criteria

Subjects were included in the Depression Case Control Study (DeCC) study if they met the following criteria: i) met Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition) (DSM-IV) (APA, 2000) or the International Classification of Diseases, (10^{th} edition) (IDC-10) (WHO, 1993) criteria for major recurrent depressive disorder (MDDR) of at least moderate severity; ii) were above 18 years of age; and iii) were of UK/ Eire white ethnicity (due to the fact that they were recruited for molecular genetic studies).

Subjects were excluded if they: i) had ever had psychotic symptoms that were mood incongruent or were prominent at a time when there was no evidence of mood disturbance; ii) had a lifetime diagnosis of intravenous drug dependency; iii) had depression only as a result of alcohol or substance dependence, or secondary to medical illness or medication; or iv) had a first or second degree relative with a clear diagnosis of bipolar affective disorder or schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders or schizoaffective disorder.

Subjects in the Depression Network (DeNT) sibling-pair study were required to meet the above inclusion and exclusion criteria. In addition, probands were required to have at least one full biological sibling also meeting all of the above inclusion criteria, who was not a monozygotic twin of the proband.

Assessment Procedure

After complete description of the study to the subjects, written informed consent was obtained. Subjects were interviewed using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). SCAN is a set of instruments aimed at assessing, measuring and classifying the psychopathology and behaviour associated with the major psychiatric disorders of adult life. It consists of a structured clinical interview schedule, glossary of differential definitions, Item Group Checklist (IGC) (not used in this study), and Clinical History Schedule (CHS) (also not used in this study).

The SCAN has two main parts. Part 1 consists of the following non-psychotic sections: relating to physical health, worrying, tension, panic, anxiety and phobias, obsessional symptoms, depressed mood and ideation, impaired thinking, concentration, energy, interests, bodily functions, weight, sleep, eating disorders, alcohol and drug abuse, and a screen for psychotic symptoms. Part 2 consists of sections used to assess psychotic symptoms and cognitive disorders and part 3 allows the interviewer to record observations of any abnormalities in the respondent's behaviour, speech, cognition or affect. Individual SCAN items can be rated for any two time frames.

Subjects were asked to identify their two worst ever episodes of depression and SCAN items were rated for the worst and second worst episodes of depression. Psychiatric and family practice case-notes were also reviewed. These data were combined to form a written case vignette. Based on this vignette, best-estimate lifetime diagnoses were made according to DSM-IV (APA, 2000) and ICD-10 (WHO, 1993). The vignettes were also used to rate the Global Assessment Scale (GAS) (Endicott et al., 1976) for the worst ever episode of depression; the Bipolar Affective Disorder Dimension Scale (BADDS) (Craddock et al., 2004) and other key clinical variables (such as age at onset and number of episodes of illness).

The GAS (see appendix A) is a rating scale for measuring the overall functioning of an individual during a specified time frame on a continuum from psychological or psychiatric illness to health. The scale values range from 1,

which represents the hypothetically most unwell individual, to 100, the hypothetically healthiest.

The BADDS (see appendix B) comprises four dimensions that provide a quantitative measure (on a 0-100 scale) of lifetime experience of psychopathology in each of four domains (Mania, Depression, Psychosis, and Congruence of Psychosis). The Mania dimension is a measure of the frequency and severity of manic-like episodes, and the Depression dimension a measure of the severity and frequency of depressive-like episodes. Higher ratings on the scale indicate higher frequency and severity. The Psychosis dimension is a measure of the prominence of lifetime psychotic features. The scale takes into account both the number and duration of episodes with and without psychotic features. Higher ratings indicate an increased prominence of psychosis as a lifetime feature of the illness. The fourth dimension is an estimate as to how congruent psychotic features have been with mood state during episodes, with 0 representing complete congruence (i.e., psychotic symptoms are completely congruent with affective state and only occur during affective episodes) and 100 representing complete incongruence (i.e., psychotic symptoms predominate the illness and occur chronically outside, or in absence of, affective episodes).

The OPCRIT (OPerational CRITeria) symptom checklist (McGuffin et al., 1991, Craddock et al., 1996) (see appendix C) was used to rate the presence or absence of items of depressive, manic and psychotic symptomatology on a lifetime ever basis as well as for the worst episode of depression.

Each subject was diagnosed, and had key clinical variables (see appendix D), GAS, BADDS and OPCRIT rated independently by at least two members of the research team and consensus was reached. Team members involved in the interview, rating and diagnostic procedures were either a fully trained research psychologist or psychiatrist. The research teams were supervised by Professor Nick Craddock, Dr Lisa Jones and Dr Ian Jones. Every two months all members of the research team (including myself) and supervisors (NC, LJ and IJ) would participate in a joint consensus reliability exercise where we would all diagnose and rate two cases and, as a group, come to a consensus for each case.

Inter-rater reliability was formally assessed using joint ratings of 20 cases with a range of mood disorder diagnoses. Mean overall kappa statistics of 0.85 and 0.83 were obtained for DSM-IV and ICD10 diagnoses respectively. Mean kappa statistics and intraclass correlation coefficients (ICCs) for other key clinical variables ranged from 0.81-0.99, and 0.85-0.97 respectively (Jones et al., 2005).

The subjects completed a pack of self-rating questionnaires which, after the semi-structured interview, were left with them to complete. They were given written instructions to complete all of the questionnaires at the same time, within one week of receiving them, and to then return them in the stamped, addressed envelope provided. If the questionnaires were not returned after one month, a reminder letter was sent with another copy of the questionnaires

and a return envelope. If the questionnaires were still not returned after a further two weeks, a reminder telephone call was made.

In order to obtain a measure of the subject's current mood state, two of the questionnaires included in the pack were the Beck Depression Inventory (BDI) (Beck and Steer, 1987) (see appendix E) and Altman Self- Rating Mania Scale (ASRM) (Altman et al., 1997) (see appendix F). The BDI assesses the presence and severity of current depressive symptoms. It comprises 21 items scored from 0 (absent) to 3 (present to a severe degree). Total scores range from 0-63. The ASRM assesses the presence or absence and severity of current manic symptoms. It comprises five items scored from 0 (absent) to 4 (present to a severe degree). Total scores range from 0 to 20.

All clinical and demographic data collected was manually entered by members of the research team (including myself) into an access database (The Molecular Psychiatry Database MPDB).

2.2.2 Bipolar Samples

Subjects in the bipolar sample described in this thesis were recruited for molecular genetic association studies of bipolar disorder at The University of Birmingham and Cardiff University (although predominantly at the Birmingham site). This study was funded by the Wellcome Trust and the principle investigators were Professor Nick Craddock, Dr Lisa Jones and Dr Ian Jones.

Subjects in the bipolar sample met Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) (APA, 2000) and International Classification of Diseases (ICD-10) (WHO, 1993) criteria for bipolar I disorder (BPI)/ bipolar disorder (with mania). Participants were above 18 years of age and were of UK/ Eire white ethnicity.

Subjects who had a lifetime diagnosis of intravenous drug dependency or had mood episodes only as a result of alcohol or substance dependence, or secondary to medical illness or medication were not included in the sample.

The assessment procedure for the subjects in the bipolar sample was the same as for the unipolar sample, with the following exceptions: subjects with bipolar disorder were asked to identify their worst ever episode of mania instead of their second worst ever episode of depression; the OPCRIT was rated for the worst episode of mania (as well as the worst episode of depression and on a lifetime ever basis); the GAS was rated for the worst ever episode of mania (as well as the worst episode of depression).

Both the unipolar and bipolar samples were recruited and assessed using consistent methodology. The samples were well defined and comprehensively characterised.

The numbers of bipolar and unipolar subjects (sample sizes) may vary between individual studies. This is because the mood disorders research team are continuously recruiting subjects to participate in the studies and at

the time a particular piece of research was conducted, the greatest number of suitable subjects was selected to form the sample for that study.

2.3 Questionnaire Follow-up Assessment

Samples

All subjects recruited to our study sites at Cardiff University and the University of Birmingham were sent a postal questionnaire pack in the summer of 2007. The median number of months between the initial research interview and the completion of the follow-up questionnaire pack was 49.

Measures

The questionnaire pack included, amongst other self-report questionnaires, the Hypomania Checklist (HCL-32) (Angst et al., 2005a) (see appendix G) and a questionnaire asking about panic attacks (see appendix H). The panic questionnaire included six questions relating to panic attacks and panic disorder, taken from the Patient Health Questionnaire (PHQ) (questions 2a to 2e and question 3 of the PHQ) (Spitzer et al., 1999). The questionnaire pack also included the Beck Depression Inventory (BDI) (Beck and Steer, 1987) (appendix E) and the Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997) (appendix F). The BDI and ASRM referred to in chapters 5 and 6 are the versions described here which were completed with the 2007 questionnaire pack.

Procedure

The Mood Disorders Research Team keeps in regular contact with study subjects through annual newsletters. The questionnaire pack was sent to all of the subjects in the unipolar and bipolar samples who were on the newsletter mailing list.

Instructions were sent along with the questionnaire to the subjects stating that they should i) complete the questionnaires as soon as possible, preferably within one week; ii) write the date of completion in the space provided at the front of the pack; iii) complete all the questionnaires at the same time and iv) return the questionnaires in the freepost envelope provided.

Subjects were also informed that they did not have to complete the questionnaires and that they could choose not to complete them without giving a reason. If subjects did not want to complete the questionnaires, they were asked to return the blank copies to the team so that records could be kept up to date.

The subjects who did not return the questionnaires were sent a reminder letter two weeks after the initial questionnaire pack was sent, and then again after a further two weeks.

The total numbers of bipolar (BPI) and unipolar (MDDR) subjects who were sent questionnaire packs, along with the response rates, are shown in Table 2-1. The response rates for the bipolar (BPI) and unipolar (MDDR) samples were 57% and 48% respectively.

Table 2-1: Questionnaire Response Rates in the Unipolar and Bipolar Samples

TOTAL NUMBER OF SUBJECTS WHO...	Unipolar (MDDR) Sample	Bipolar (BPI) Sample	Total Sample (MDDR & BPI)
...were sent a questionnaire pack	774	513	1287
...returned a completed questionnaire pack	373 (48%)	291 (57%)	664 (52%)
...did not return a completed questionnaire pack	401 (52%)	222 (43%)	623 (48%

The rate at which the questionnaires were returned can be seen in Figure 2-1. Twenty-two percent of the questionnaires were returned within the first week following the questionnaire mail-out and forty-two percent were returned during the second week. Thirty-five percent were returned between weeks three and ten following the mail-out. So, of the total number of completed questionnaires that were returned, ninety-nine percent were returned within ten weeks following the mail-out.

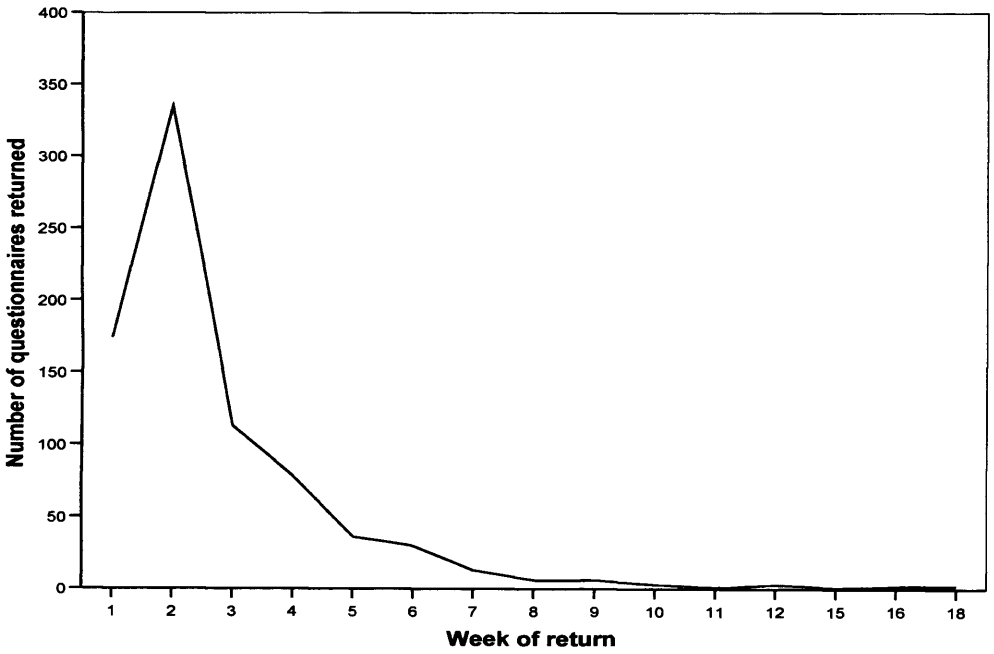


Figure 2-1 : Number of Questionnaires Returned in Each Week Following the Mail-Out

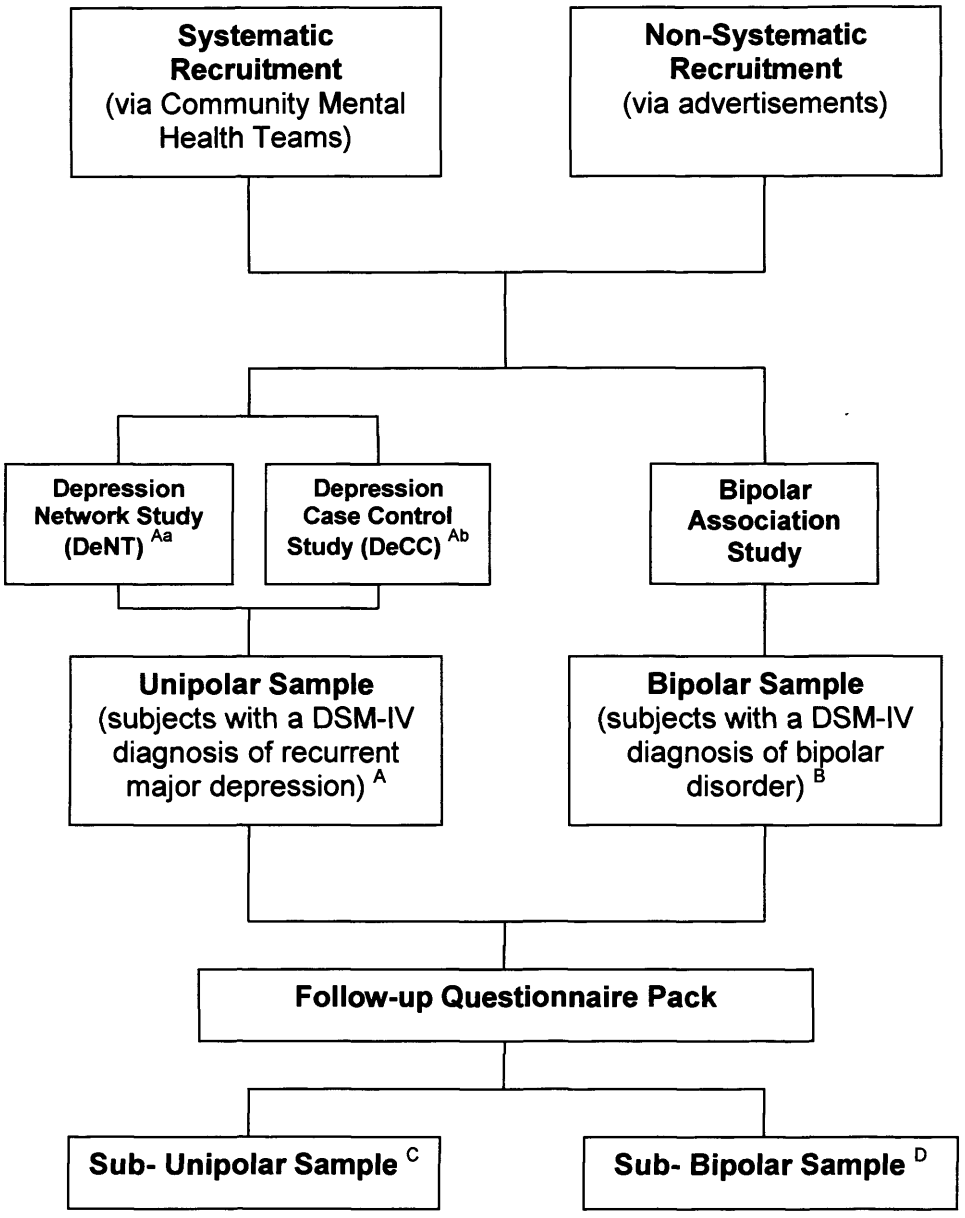
Nearly two-thirds of the completed questionnaires were returned within the first two weeks following the mail-out. By week ten, ninety-nine percent of the completed questionnaires had been returned.

Data Capture

Formic fusion (Formic Ltd: Middlesex, UK) is a data capture system that includes four modules. The first module allows the user to design a questionnaire in a specific format suitable for scanning. Completed forms can then be scanned using the second module, where verification checks can also be made. The verification checks are based on the settings that were specified in the design module. The third module enables the user to view and export the data. The fourth module is for managing the system (i.e. deleting files, specifying users).

The questionnaires were designed, scanned and validated by myself using the formic system. The data were then exported into SPSS for statistical analyses. Data integrity was assessed by checking that the data in the SPSS file matched the hard copy of the questionnaire for a sub-sample of participants. From a file sorted in order of the date that the questionnaires were returned, every twentieth participant was selected (for example, the twentieth, fortieth, sixtieth, and so on) until there were thirty participants included in the sub-sample. For these thirty participants, there were no discrepancies in the data.

The studies described in chapters 5 and 6 include analyses based on the data collected from the follow-up questionnaire assessment. Figure 2-2 illustrates the derivation of the samples that are used for each chapter in this thesis.



A Chapter 7; Aa Chapters 8 & 9; B Chapter 3; A + B Chapter 4; C + D Chapters 5 & 6

Figure 2-2: Recruitment diagram to illustrate the derivation of the samples used for each chapter of the thesis.

The main samples A + B were collected and assessed as part of ongoing molecular genetic studies of affective disorders. All of the subjects in these samples were sent a follow-up questionnaire pack in the summer of 2007 which was completed and returned to the research team by just over half of the subjects. These subjects formed the second set of samples C + D.

Statistical Analysis

Methods of statistical analysis are described in individual chapters. All analyses were performed using SPSS version 12 unless stated otherwise. As the continuous data were not normally distributed, medians, interquartile ranges, and ranges are reported and non-parametric tests are used throughout the thesis. Histograms showing the distributions of scores in the unipolar and bipolar samples for the scales and questionnaires used throughout the thesis can be found in appendix J.

3 Polarity at Illness Onset in Bipolar I Disorder and Clinical Course of Illness

Reported by Forty et al (2009b)

3.1 Summary

Studies have suggested that episode polarity at illness onset in bipolar disorder may be predictive of some aspects of lifetime clinical characteristics. Here I examine this possibility in a large, well characterized, sample of subjects with bipolar I disorder.

I assessed polarity at onset in subjects with bipolar I disorder (N=553) recruited as part of ongoing studies of affective disorders. Lifetime clinical characteristics of illness were compared in subjects who had a depressive episode at first illness onset (N=343) and subjects who had a manic episode at first illness onset (N=210).

Several lifetime clinical features differed between subjects according to the polarity of their onset episode of illness. A logistic regression analysis showed that the lifetime clinical features significantly associated with a depressive episode at illness onset in this sample were: an earlier age at illness onset; a predominantly depressive polarity during the lifetime; more frequent and more severe depressive episodes; and less prominent lifetime psychotic features.

Knowledge of pole of onset may help the clinician in providing prognostic information and management advice to an individual with bipolar disorder and may also be useful in genetic studies of phenotypically refined sub-groups.

3.2 Introduction

Bipolar disorders are heterogeneous and the identification of more homogeneous sub-groups of patients/ subjects has the potential to facilitate more targeted clinical advice and interventions, as well as being useful in studies investigating the aetiology of affective disorders. One clinical feature that may identify such sub-groups is the type of episode, depressive or manic, that occurs first in the bipolar illness. This "polarity at onset" has been shown to be familial (Kassem et al., 2006) and to distinguish groups of bipolar individuals who differ in lifetime clinical features of illness (Kassem et al., 2006, Perlis et al., 2005, Perugi et al., 2000, Daban et al., 2006).

The aim of the present study was to examine lifetime clinical course characteristics in a large sample of subjects with bipolar I disorder according to the episode polarity at illness onset. I have examined a large, well characterized sample of unrelated subjects with narrowly defined bipolar I disorder recruited within the UK. Unlike previous studies I have also examined measures of episode severity and frequency using the Bipolar Affective Disorders Dimension Scales (BADDS) (Craddock et al., 2004). These scales were developed by our group as an adjunct to conventional categorical diagnosis in order to provide a richer characterization of the individual's lifetime experience of illness (Craddock and Owen, 2007, Peralta and Cuesta, 2007) and we have found them useful in our research (Macgregor et al., 2006, Green et al., 2005, O'Mahony et al., 2002, Raybould et al., 2005).

Based on the findings of previous studies (Daban et al., 2006, Kassem et al., 2006, Perlis et al., 2005, Perugi et al., 2000), I hypothesised that patients whose onset episode of illness was depression would have a predominantly depressive course of illness and that there may be differences between manic-onset and depressive-onset patients in clinical characteristics such as age at onset, predominant pole of illness, rapid cycling and lifetime experience of psychosis.

3.3 Method

3.3.1 Subjects

For further methodological details, see chapter 2. Of 553 suitable subjects with bipolar I disorder, 210 (38%) were included in the manic onset group (predominant polarity coded as "1") and 343 (62%) were included in the depressive onset group (predominant polarity coded as "0"). There were 173 subjects for whom I could not clearly establish the polarity of the onset episode of illness. These individuals were not included in this study.

3.3.2 Assessment

Polarity of the onset episode (first ever episode of mood illness) was determined by comparing the reported age at onset for the first ever major depressive episode and the first ever manic episode (episodes displaying predominantly manic features, including mixed episodes and hypomanic episodes). Where subjects reported the same age at onset for both episode poles, vignettes were examined to establish which pole occurred first. Only

subjects for whom the polarity of the onset episode could clearly be established were included in the analyses (N=553).

3.3.3 Statistical Analysis

As the continuous data were not normally distributed, medians, interquartile ranges, and ranges are reported. The demographic and lifetime clinical characteristics of the two groups were compared using chi-square tests for categorical data and the Mann-Whitney test for continuous data.

Binary logistic regression using forward stepwise likelihood ratio for variable selection was performed to assess which variables were most associated with the polarity of the onset episode of illness. Odds ratios of greater than 1 indicate that a higher score is associated with greater likelihood of a manic episode at illness onset; whereas odds ratios of less than 1 indicate that a higher score is associated with a greater likelihood of a depressive episode at illness onset.

3.4 Results

There was no statistically significant difference between the two groups for age at interview or method of recruitment. There were significantly less males (28.3%) in the depression onset group compared to the mania onset group (37.6%) (p=0.022). The mean illness duration for the depressive onset group (22 years) was significantly longer than for the mania onset group (15 years)

(p<0.001). Family history of affective disorder was not significantly different between the two groups.

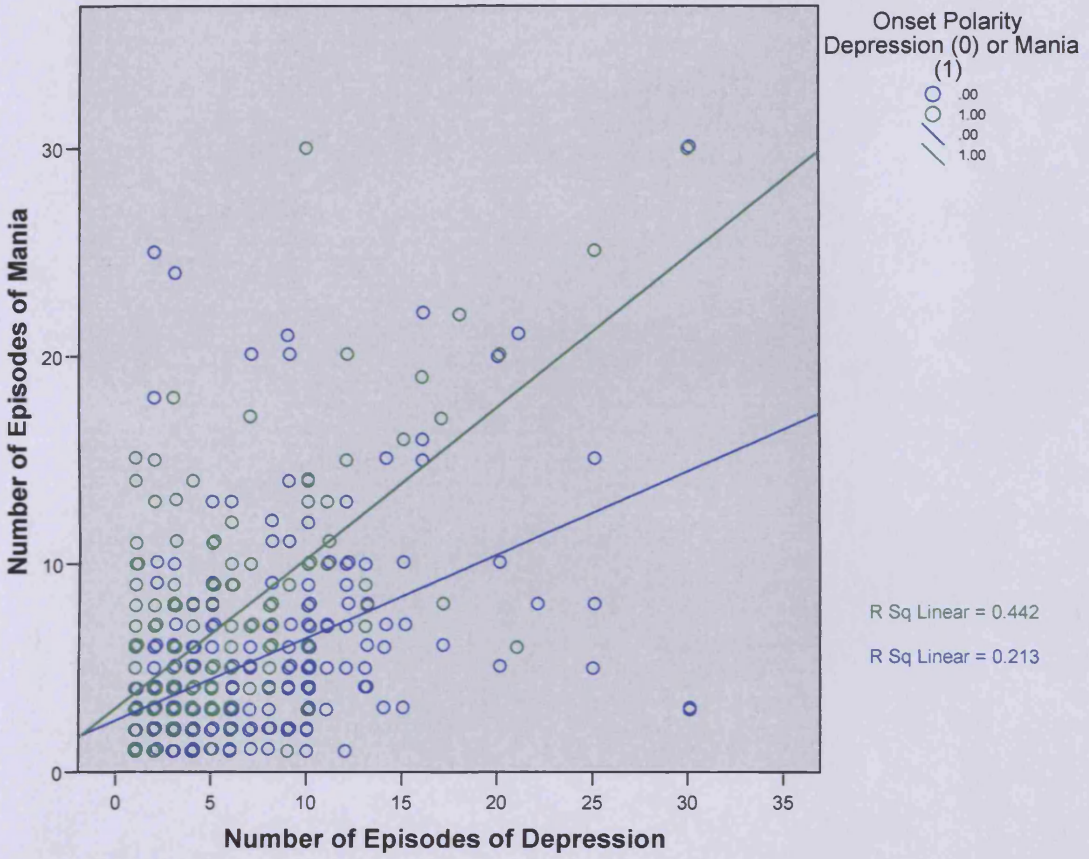


Figure 3-1: Number of Episodes of Depression and Number of Episodes of Mania According to the Polarity of the Onset Episode of Illness in Subjects with a Diagnosis of Bipolar I Disorder

This figure illustrates how subjects whose onset episode was depression reported more depressive episodes during their lifetime, and less manic episodes (blue regression line), when compared to subjects whose onset episode was mania (green regression line).

Table 3-1 shows the clinical characteristics that differed significantly between the two groups. Subjects in the depression onset group experienced significantly more illness episodes (p= 0.031), more depressive episodes (p<0.001), and less manic episodes (p=0.004) when compared to the mania onset group (see Figure 3-1). The lifetime predominant polarity of episodes of

illness experienced by the depressive onset group was depression (57.7% of episodes), whereas for the mania onset group the lifetime predominant polarity was mania (57.1% of episodes). Subjects in the depressive onset group had a significantly longer duration of the longest ever depressive episode ($p<0.001$) compared to subjects in the mania onset group, whereas there was no significant difference in the mean duration of the longest ever manic episode between the two groups.

Table 3-1: Lifetime Clinical Characteristics (N=553) that Differed Significantly Between Subjects According to the Polarity of the Onset (First Ever) Episode of Illness in Subjects with a Diagnosis of Bipolar I Disorder

Clinical Characteristic		Onset Episode Mania 210 (38%)	Onset Episode Depression 343 (62%)	p-value
Gender	Male Female	79 (37.6%) 131 (62.4%)	97 (28.3%) 246 (71.7%)	0.022
Illness Duration (years)	Median Interquartile Range Range	15 16 1-57	22 18 1-54	<0.001
Number of Episodes of Depression	Median Interquartile Range Range	3 5 1-50	5 6 1-70	<0.001
Number of Episodes of Mania	Median Interquartile Range Range	5 5 1-75	4 4 1-100	0.004
Total Number of Episodes	Median Interquartile Range Range	9 9.15 2-125	9.2 8.9 2-110.2	0.031
Predominant Polarity of Episodes	Mania Depression Equal	120 (57.1%) 42 (20%) 48 (22.9%)	95 (27.9%) 196 (57.7%) 49 (14.4%)	<0.001
Longest Episode of Depression (weeks)	Median Interquartile Range Range	14 19 1-156	26 40 2-416	<0.001
Age at First Episode of Mood Illness (mania or depression) (years)	Median Interquartile Range Range	25 12 7-64	21 11 10-59	<0.001
Age at First Episode of Depression (years)	Median Interquartile Range Range	29 13 16-65	21 11 10-59	<0.001
Age at First Episode of Mania (years)	Median Interquartile Range Range	25 12 7-64	30 16 13-64	<0.001

Table 3-1 Continued

Clinical Characteristic		Onset Episode Mania 210 (38%)	Onset Episode Depression 343 (62%)	p-value
Suicide Attempt	Absent Present	141 (73.1%) 52 (26.9%)	170 (53.5%) 148 (46.5%)	<0.001
Rapid Cycling (4 or more episodes in a year)	Present Absent	26 (17.7%) 121 (82.3%)	65 (28.5%) 163 (71.5%)	0.017
GAS **Worst Depression**	Median Interquartile Range Range	39 18 12-71	35 10 10-59	<0.001
Worst Mania	Median Interquartile Range Range	25 10 8-51	28 15 9-68	<0.001
BADDS **Depression**	Median Interquartile Range Range	61 16 40-95	66 20 40-97	<0.001
Mania	Median Interquartile Range Range	82 7 60-100	81 19 60-100	<0.001
Psychosis	Median Interquartile Range Range	27 32 0-100	22 32 0-100	<0.001

GAS: Global Assessment Scale
BADDS: Bipolar Affective Disorder Dimension Rating Scale

Comparisons of dichotomous items were analysed using chi-square tests and the Mann-Whitney test was applied to continuous data. N values may vary due to missing data.

As can be seen in Table 3-1, the mean age at illness onset (age at first mood episode) and age at onset of depression for subjects in the depression onset group was significantly lower (both $p<0.001$), and the age at onset of mania higher ($p<0.001$), compared to the mania onset group. There were no significant differences between the two groups in the age at first contact with psychiatric services or in the number of psychiatric admissions. There was significantly more suicidal behaviour in the depressive onset group ($p<0.001$) and more rapid cycling (4 or more episodes in a year) ($p=0.017$) when compared to the mania onset group.

Subjects in the depressive onset group were significantly less functionally impaired according to the GAS during their worst ever manic episode ($p<0.001$), but more impaired during their worst ever depressive episode ($p<0.001$), than subjects in the mania onset group. Similarly, subjects in the depressive onset group scored significantly higher on the BADDS Depression dimension ($p<0.001$), but lower on the BADDS Mania dimension ($p<0.001$), reflecting the increased occurrence and severity of depressive episodes, and the decreased occurrence and severity of manic episodes in the depressive onset group, when compared to the mania onset group (see Table 3-1).

When comparing the presence of psychotic features in the two groups as a categorical variable (present or absent on a lifetime ever basis) there was no statistically significant difference. However, significantly lower scores on the BADDS Psychosis dimension for the depression onset group ($p<0.001$) reflect a lower prominence of psychotic features in episodes of illness during the lifetime of subjects in the depression onset group compared to subjects in the mania onset group.

Logistic regression was carried out to determine which combination of lifetime clinical features was best associated with the polarity of the onset episode of illness. Variables that were significant at the $p<0.05$ level in the univariate comparisons were entered into the regression, including gender and illness duration. The significant variables in the best fitting model were: predominant polarity (OR=4.4, 95% CI 2.3-8.4), age at onset of illness (OR=1.06, 95% CI

1.03-1.09), BADDS Depression (OR=0.96, 95% CI 0.94-0.98) and BADDS Psychosis (OR=1.026, 95% CI 1.01-1.04).

3.5 Discussion

This study provides supporting evidence for significant differences in the clinical features of subjects with bipolar I disorder according to the polarity of their onset episode of illness. Consistent with the hypothesis, several measures indicating a more "depressive" lifetime course were significantly more common in those whose illness started with a depressive episode. Thus, in agreement with previous studies I found that a depressive onset was associated with a greater number of depressive episodes (Daban et al., 2006, Perlis et al., 2005, Perugi et al., 2000), an increased risk of suicide attempt during the lifetime (Perugi et al., 2000, Daban et al., 2006, Perlis et al., 2005) and more rapid cycling (four or more episodes in a year) (Perugi et al., 2000) compared to subjects with an onset episode of mania.

Previous studies examining clinical characteristics in relation to polarity at onset have not included measures of functional impairment in episodes of depression or mania. In addition to assessing the frequency of depressive episodes, as has been done in previous studies, the use of the Bipolar Affective Disorder Dimension Scale (BADDS) (Craddock et al., 2004) and the Global Assessment Scale (GAS) (Endicott et al., 1976) also enabled me to take into account the severity of episodes. I found more severe impairment in functioning during the worst ever episode of depression in subjects whose onset episode was depression, compared to those whose onset episode was

mania. Similarly, I found that subjects whose onset episode was mania experienced more severe impairment in functioning during their worst ever manic episode compared to subjects with an onset episode of depression.

Some previous studies have suggested that there is no difference in the presence of psychotic features according to the polarity of the onset episode of illness (Perlis et al., 2005, Kassem et al., 2006), although others have found that subjects with a depressive episode at illness onset are less likely to experience psychosis during their life course (Daban et al., 2006, Perugi et al., 2000). When I compared the definite presence or absence of lifetime psychotic features as a binary variable in this sample I found no difference between those with depressive and those with manic poles of onset. This lack of difference is consistent with two of four previous studies (Kassem et al., 2006, Perlis et al., 2005). However, using the BADDS Psychosis scale I found that the lifetime prominence of psychotic features during mood episodes is significantly greater in subjects who experienced a manic episode at illness onset compared to those who experienced a depressive episode at onset. This is consistent with the other two of four previous studies (Daban et al., 2006, Perugi et al., 2000). So, although there is no difference between the mania onset and depression onset groups in terms of presence or absence of lifetime psychotic features, there is a difference in the predominance of lifetime psychotic features between the two groups. This illustrates the importance of a more detailed consideration of clinical features beyond a simple "presence/ absence" dichotomy.

The finding of the current study that a depressive onset is more common in females contrasts with Kassem et al (2006) but is in agreement with Perlis et al (2005). The finding of depressive onset being associated with an earlier age at onset is consistent with two previous studies (Kassem et al., 2006, Perlis et al., 2005).

These findings are of potential clinical importance. Once a patient has experienced his/ her first manic episode, the clinician can use knowledge of polarity of the illness onset as an indicator of the likely predominant pole of illness. This may be helpful in providing information and advice to the patient. This applies to the situation where a patient has experienced their first manic episode and, hence, a diagnosis of bipolar disorder can be made. It is of note that studies have suggested that there are differences in the clinical characteristics of depressive episodes in subjects with unipolar and bipolar disorder (Forty et al., 2008, Bowden, 2005, Mitchell et al., 1992) and this will be investigated further in chapter 4. Such differences could potentially be of use in predicting the risk of bipolar disorder in patients who experience a depressive episode without having experienced a prior manic episode.

Strengths of this study include a large, well characterized sample and the use of measures of episode frequency, severity and impairment. None-the-less, a number of limitations should be considered when interpreting these findings. First, retrospective assessment measures were used to obtain clinical course information and to establish the polarity of the onset episode of illness. However, I found good agreement between the information obtained from

subjects during the in depth semi-structured interviews and the information obtained from the case note reviews. Another limitation relating to the retrospective nature of this study was that I was unable to assess the effects of medication on illness course. It is possible that there may have been differences in treatment regimes between the two groups that could potentially impact on illness course/ severity.

I focused my analyses on a narrowly defined sample of subjects with bipolar I disorder and, hence, these findings relate to this group of bipolar subjects. It will be important for future studies to also examine polarity at onset in subjects with bipolar II disorder in order to establish the generalizability of these findings across the bipolar spectrum.

This study focused on the first clinically significant mood episodes. Some individuals in the mania onset group may have experienced sub-clinical depressive symptoms prior to the first clinically significant episode. It is possible that these subjects may represent a clinically significant subgroup, however assessing this was beyond the scope of this study.

In summary, I found, in agreement with previous studies, that the polarity of the first episode of illness in bipolar disorder is depressive for at least two thirds of individuals (Judd et al., 2003, Perugi et al., 2000, Daban et al., 2006). This study also found that subjects with a depressive pole of onset tend to have a course of illness characterised by more frequent depressive episodes and more lifetime depressive morbidity. The increase in severity of depressive

episodes and the associated impairment in functioning in subjects with an onset episode of depression illustrate a need for treatment regimes more targeted at preventing and reducing the burden associated with depressive episodes in individuals for whom depressive episodes are associated with greater morbidity. Similarly, the findings regarding increased severity and associated impairment during manic episodes in subjects with a manic episode at onset, point to the need for improved prevention and treatment regimes in order to reduce the burden of manic episodes in individuals for whom these episodes result in the greatest impairment. The division of patients/ subjects with bipolar I disorder according to polarity at onset and predominant polarity during illness course (i.e., "depression prone" and "manic prone" sub types) may not only have implications in clinical practice, but may also provide more homogenous sub groups of subjects for the purpose of research.

4 Clinical Differences Between Bipolar and Unipolar Depression

Reported by Forty et al (2008)

4.1 Summary

It is commonly, but wrongly, assumed that there are no important differences in the clinical presentation of unipolar and bipolar depression.

Here I compare clinical course variables and depressive symptom profiles in a large sample of subjects with a diagnosis of recurrent major depressive disorder (MDDR) (N=593) or bipolar I disorder (BPI) (N=443).

Clinical characteristics associated with a bipolar course included the presence of psychosis; diurnal mood variation and hypersomnia during depressive episodes; and a greater number of shorter depressive episodes.

Such features should alert a clinician to a possible bipolar course. This is important because optimal management varies between bipolar and unipolar depression. These features may identify useful sub-groups of subjects for the purposes of molecular genetic studies focusing on more refined phenotypes.

4.2 Introduction

Distinguishing between unipolar and bipolar depression is an important issue because there are differences in optimal management. Antidepressant treatment of bipolar depression can adversely affect long-term prognosis by causing destabilisation of mood, more frequent depressive episodes and can lead to the development of treatment resistance (Sharma et al., 2005). Most bipolar patients experience depression rather than mania as their first episode of illness. It is clinically desirable to recognise, or at least have a high degree of suspicion of, bipolar depression at an early stage of a bipolar illness.

If depressive episodes occurring in unipolar and bipolar disorders do have distinctive clinical characteristics it is possible that these reflect at least partially distinct, underlying, biological processes. The identification of factors that distinguish bipolar and unipolar depression, as well as factors that appear to be common to both forms of illness, is therefore of both clinical and theoretical importance.

Here, I compare clinical course and depressive symptomatology in unipolar and bipolar depression by analysing phenotypic data in the unipolar and bipolar samples.

4.3 Method

4.3.1 Subjects

For further methodological details, see chapter 2. The sample comprised 443 subjects with a diagnosis of bipolar I disorder (BPI) and 593 subjects with a diagnosis of recurrent major depressive disorder (MDDR).

4.3.2 Assessment

Assessment procedures are described in chapter 2.

4.3.3 Statistical Analysis

The demographic and lifetime clinical characteristics of the two groups were compared using chi-square tests for categorical data and the Mann-Whitney test for non-parametric continuous data.

Binary logistic regression using forward stepwise likelihood ratio for variable selection was performed to examine which variables relating to depression significantly predicted BPI versus MDDR classification.

4.4 Results

The proportions of females in the MDDR group and the BPI group were 70.2% and 71.3% respectively (p=0.68). The median age at interview was 49 for the MDDR group, and 46.5 for the BPI group (p=0.31). Forty-six percent of the MDDR group were recruited systematically, compared to 37% of the BPI

group (p=0.004). The median illness duration was 19 years for the MDDR group and 20 years for the BPI group (p=0.48). The MDDR group had a median BDI score at interview of 16, compared to a median BDI score of 8 in the BPI group (p<0.001).

Forward step-wise logistic regression was used to establish the best depression-related predictors of bipolar versus unipolar group membership. All lifetime variables relating to depressive episodes that were significant at the p<0.1 significance level in univariate analyses comparing bipolar and unipolar groups were entered into the regression. To control for sample differences in recruitment and current mental state, BDI score at interview and method of recruitment were included in the regression. Gender was also included in the logistic regression analysis.

Significant predictors of diagnosis in the logistic regression model are shown in Table 4-1.

Table 4-1: Lifetime Clinical Characteristics Predicting Bipolar (BPI) Versus Unipolar (MDDR) Group Membership (N=1036)

Clinical Characteristic		Unipolar Group 593 (57%)	Bipolar Group 443 (43%)	Odds Ratio	95% Confidence Interval	p-value
Psychotic Features During Depression	Present Absent	61 (10.5%) 522 (89.5%)	134 (30.2%) 309 (69.8%)	0.160	0.080-0.318	< 0.001
No. of Episodes of Depression	Median Interquartile Range Range	4 2 2-40	5 6 1-70	0.932	0.886-0.980	0.006
Longest Episode of Depression (weeks)	Median Interquartile Range Range	69 60 8-624	26 29 2-416	1.011	1.006-1.016	< 0.001
Diurnal Mood Variation	Present Absent	285 (50.4%) 281 (49.6%)	219 (59%) 152 (41%)	0.536	0.305-0.942	0.030

Table 4-1 Continued

Clinical Characteristic		Unipolar Group 593 (57%)	Bipolar Group 443 (43%)	Odds Ratio	95% Confidence Interval	p-value
Excessive Self-Reproach	Present Absent	550 (96.2%) 22 (3.8%)	342 (87.7%) 48 (12.3%)	6.272	2.335-16.847	< 0.001
Loss of Energy	Present Absent	584 (99.2%) 5 (0.8%)	386 (95.5%) 18 (4.5%)	6.031	1.003-36.266	0.050
Hypersomnia	Present Absent	120 (21.5%) 437 (78.5%)	148 (42.8%) 198 (57.2%)	0.371	0.205-0.671	< 0.001
Diminished Libido	Present Absent	231 (63.5%) 133 (36.5%)	123 (34.8%) 230 (65.2%)	7.537	4.135-13.738	< 0.001

The odds ratios shown are from a logistic regression analysis predicting bipolar or unipolar group membership according to lifetime clinical characteristics.

With the coding used, odds ratios of greater than 1 indicate that a higher score is associated with greater likelihood of unipolar group membership whereas odds ratios of less than 1 indicate that a higher score is associated with a greater likelihood of bipolar group membership.

N values may vary due to missing/ unclear data.

4.5 Discussion

Although there were, of course, similarities between unipolar and bipolar depression, I also found important clinical differences: characteristics that best predicted bipolar over unipolar depression were the presence of psychosis, diurnal mood variation and hypersomnia during depressive episodes, a greater number of depressive episodes and a shorter duration of the longest depressive episode. Unipolar subjects were characterised by the presence of excessive self-reproach, loss of energy and diminished libido during depressive episodes.

These results are consistent with, and extend the findings of, previous studies that have shown "atypical" depressive features (such as hypersomnia and weight gain) may be more common in bipolar than in unipolar depression (Bowden, 2005, Swann et al., 2005, Mitchell et al., 2001). Compared to previous studies, this study has several advantages, including the very large number of subjects involved and the high degree of consistent and comprehensive clinical data collected.

Distinguishing between bipolar and unipolar depression is of great clinical importance as optimal management is very different. For example, antidepressants should be used with caution in bipolar depression because of the risk of precipitating mood switches, cycling or mixed or agitated states (NICE, 2006a). It is desirable that clinicians use all available information to guide management (including choice of treatment, advice to patient and intensity of monitoring). The clinical features of depression are not, of course, a definitive guide to diagnosis but can help alert the clinician to a possible bipolar course.

The finding of differences, as well as similarities, in clinical features of depression between groups of bipolar and unipolar subjects suggests the presence of both distinct (at least partially) as well as shared underlying disease processes. This is in keeping with a recent twin study analysis using bivariate structural equation modelling suggesting both genetic overlap and qualitative distinctions between the two syndromes (McGuffin et al., 2003).

These findings also have important implications for future research on bipolar II disorder and sub-threshold bipolar disorders. Current evidence suggests that between 25% and 50% of all patients with recurrent unipolar depression (and particularly those within atypical, early-onset or treatment-refractory sub-groups) may in fact suffer from a broadly-defined bipolar disorder (Angst, 2007). Currently, very little is known about how best to treat these broadly-defined bipolar patients. Future studies in this field will need to move beyond strict diagnostic categories and examine sub-groups of subjects defined by extended phenotypic measures such as dimensional assessments of bipolar features, bipolar symptom clusters and longitudinal illness course variables (Smith et al., 2008).

An important limitation of the current study is that there may be differences between the unipolar and bipolar samples that I have not been able to examine, for example, subtle differences in treatment regimes or patterns of comorbid illness. It is of note that although the proportion of females in the unipolar sample is typical of studies of this nature, the proportion of females in the bipolar sample is higher than is typically reported (nearly three quarters compared to 50%) and this may limit the generalisability of the findings. A further limitation was the use of retrospective rather than prospective assessments, even though in-depth semi-structured clinical interviews were used, supplemented by a case note review. Prospective ratings of symptoms are obviously preferable but can be prohibitively expensive.

The key message from this study is that it is not appropriate or sensible to assume that membership of an operational diagnostic category adequately defines homogenous sets of individuals for the purposes of aetiological research or clinical management. It is essential to take account of both the overlapping elements as well as the distinct elements of illness seen in diagnostically defined groups.

In summary, these findings support and add substantially to evidence that there are differences between the depressive symptomatology and illness course of bipolar and unipolar mood disorders. Clinical factors such as the occurrence of psychosis, hypersomnia, diurnal mood variation and frequent episodes should lead clinicians to a high index of suspicion for a bipolar, rather than unipolar, depressive illness.

The implication for research aimed at studying the biology and psychology of depression is that more attention should be paid to describing the clinical characteristics of research samples and undertaking analyses that take account of clinical characteristics.

5 Identifying Hypomanic Features in Major Depressive Disorder using the Hypomania Checklist (HCL-32)

Reported by Forty et al (2009c)

5.1 Summary

Recent studies have challenged the traditional unipolar/ bipolar divide with increasing support for a more dimensional view of affective disorders.
Here I examine the occurrence of hypomanic symptoms in subjects with a history of major depression selected to exclude indicators of underlying bipolarity.

The presence of hypomanic symptoms was assessed by the Hypomania Checklist (HCL-32) self-report questionnaire in a sample of almost 600 subjects meeting DSM-IV criteria for bipolar I disorder (BPI N=260) or recurrent major depressive disorder (MDDR N=322). Subjects were recruited and assessed using consistent, robust methodology.

I found that a score of 20 or more on the HCL-32 yielded the best combination of sensitivity (65%) and specificity (83%) to distinguish between BPI and MDDR. Within this highly selected and well defined MDDR sample (for which exclusion criteria included personal or family histories of bipolar or psychotic illness), 17% of MDDR subjects scored over the threshold of 20 on the HCL-32.

The HCL-32 identified a substantial number of subjects meeting DSMIV criteria for recurrent major depression (even when selected to exclude personal and family histories of bipolar illness) who reported bipolar symptoms at a level similar to that reported by subjects meeting diagnostic

criteria for bipolar disorder. This demonstrates the limitations of using DSM-IV criteria to distinguish those with and without bipolar features of illness.

5.2 *Introduction*

Kraepelin's description of manic depressive illness included syndromes featuring both mania and depression, as well as recurrent depression alone (Kraepelin, 1921). Modern diagnostic systems take into account the chronicity of the disorder and classify affective disorders as either unipolar or bipolar in nature, a distinction introduced into modern psychiatry by Leonhard (1959). Recent thinking has begun to question the categorical splitting of mood disorders into bipolar and unipolar disorders and there is increasing support for a more dimensional view of affective disorders (Akiskal, 2003, Angst et al., 2003, Cassano et al., 2004, Ghaemi et al., 2002, Angst, 2007).

The Hypomania Check List (HCL-32) self-report questionnaire is a tool designed to screen for hypomanic components in patients with Major Depressive Disorder (MDD) (Angst et al., 2005a). It has been used in different countries and languages (Meyer et al., 2007, Wu et al., 2008, Vieta et al., 2007). In a study of Italian and Swedish subjects with bipolar I (BPI, N=102) or bipolar II disorder (BPII, N=164) or MDD (N=160), Angst et al (2005a) found that a cut off score of 14 or more on the HCL-32 yielded the best combination of sensitivity (true bipolars) (80%) and specificity (true non-bipolars) (51%) to distinguish between bipolar disorder (BP) and MDD. They concluded that the HCL-32 is a sensitive instrument for distinguishing between BP and MDD, although it does not distinguish between BPI and BPII disorders.

The primary aim of this study was to assess the presence of hypomanic symptoms in a highly selected "unipolar" sample. In order to do this I first established the cut-off score on the HCL-32 that best distinguished between recurrent major depressive disorder (MDDR) and bipolar I disorder (BPI), in this large, well characterised UK sample.

5.3 Method

5.3.1 Subjects

For further methodological details, see chapter 2. The sample comprised 260 subjects with a diagnosis of bipolar I disorder (BPI) and 322 subjects with a diagnosis of recurrent major depressive disorder (MDDR) who correctly completed the Hypomania Checklist (HCL-32) in the 2007 questionnaire pack.

5.3.2 Assessment

Subjects completed the HCL-32 (appendix G), the Beck Depression Inventory (BDI) (Beck and Steer, 1987) (appendix E) and the Altman Self Rating Mania Scale (ASRM) (Altman et al., 1997) (appendix F) as part of the questionnaire pack that was sent out in 2007.

The HCL-32 is a self-report measure that comprises a checklist of 32 possible symptoms of hypomania that are rated yes (present or typical of me) or no (not present or not typical). The questionnaire also includes a question about current mood state (relative to usual mood state) where subjects rate

themselves on a seven point scale (worse than usual - neither worse no better than usual - better than usual). The total score on the HCL-32 was obtained by summing all items rated "Yes" on the 32 item checklist (so each item rated "Yes" scored 1 to give a total out of 32).

5.3.3 Statistical Analysis

Comparisons of dichotomous items were analysed using chi-square tests and the Mann-Whitney test was applied to continuous data. Spearman correlations were used to assess the relationship between HCL-32 score and current mood state, as assessed by the HCL-32 current mood state item, the BDI and the ASRM.

Logistic regression analysis yielded the sensitivity and specificity of the HCL-32 to discriminate between MDDR and BPI. The area under the ROC curve (AUC) was also computed as a measure of the overall predictive validity of the HCL-32, where AUC=0.50 signals random prediction, $0.60<AUC\leq0.70$ poor, $0.70<AUC\leq0.80$ fair, $0.80<AUC\leq0.90$ good and $AUC>0.90$ excellent predictive validity (Tape, 2004).

5.4 Results

Clinical characteristics of the sample are described in Table 5-1. Although the BPI group had a significantly younger age at interview (p=0.019) when compared to the MDDR group, there was no significant difference in illness duration (p=0.80) between the two groups. The total BDI score was

significantly higher for the MDDR group compared to the BPI group ($p<0.001$), and the total ASRM score was significantly higher for the BPI group compared to the MDDR group ($p=0.03$).

Table 5-1: Clinical Characteristics of the Bipolar (BPI) and Unipolar (MDDR) Samples and the Unipolar (MDDR) with HCL-32 Score >19 Sub-Sample

Clinical Characteristic		BPI N=260	MDDR N=322	MDDR HCL-32 >19 N=47
Total HCL 32 Score (out of 32)	Median Interquartile Range Range	24 7.25 4-31	17 7 0-29	23 3 20-29
Beck Depression Inventory Total score	Median Interquartile Range Range	10 12 0-52	14 15 0-46	14 12 1-35
Altman Mania Scale Total score	Median Interquartile Range Range	3 4 0-15	2 3 0-13	3 3 0-12
Age at Interview (years)	Median Interquartile Range Range	47 17 21-73	51 16 18-85	46 15 26-69
Gender	Male Female	76 (29.2%) 184 (70.8%)	105 (32.6%) 217 (67.4%)	20 (42.6%) 27 (57.4%)
Illness Duration (years)	Median Interquartile Range Range	22 19 1-54	21 18.75 1-71	19 17.25 4-49
Age at 1st Impairment	Median Interquartile Range Range	24 59 7-66	27 54 9-63	22.5 13 12-46
Age at 1st Contact	Median Interquartile range Range	28 15 11-66	34 20 10-63	27 12 12-49
Age at 1st Admission	Median Interquartile Range Range	29 15 16-66	34 18 17-68	31 11 17-47
Number of Admissions	None One or more	26 (10%) 233 (90%)	156 (48.4%) 166 (51.6%)	18 (38.3%) 29 (61.7%)

Comparisons of dichotomous items were analysed using chi-square tests and the Mann-Whitney test was applied to continuous data [to compare BPI (N=260) versus MDDR (N=322)].

There was no significant difference in gender between the BPI and MDDR samples ($p=0.38$). As expected, total HCL-32 scores were significantly lower in the MDDR sample, compared to the BPI sample ($p<0.001$). Of the subjects in the MDDR sample, 156 (48.4%) rated feeling "neither better nor worse than usual" when asked how they were feeling today compared to their usual state (the first question on the HCL-32). Of the subjects in the BPI sample, 94 (36.2%) reported feeling "neither better nor worse than usual" on the HCL-32 (see Table 5-2). There was no significant correlation between the HCL-32 total score and the subject's rating on the HCL-32 of current mental state or between the HCL-32 total score and the BDI total score (Spearman's correlations, $p > 0.5$). There was a significant correlation between the HCL-32 total score and the ASRM total score ($p=0.002$). Table 5-2 also shows that BPI subjects were more likely to complete the questionnaire pack when they were feeling "a little better", "better" or "much better than usual", a finding not seen in the MDDR sample.

Table 5-2: Current Mental state of the Bipolar (BPI) and Unipolar (MDDR) Samples as Assessed by the HCL-32

How are you feeling today compared to your usual state?	BPI N=260	MDDR N=322
Much worse than usual	11 (4.2%)	11 (3.4%)
Worse than usual	20 (7.7%)	26 (8.1%)
A little worse than usual	35 (13.5%)	45 (14%)
Neither better nor worse than usual	94 (36.2%)	156 (48.4%)
A little better than usual	47 (18.1%)	36 (11.2%)
Better than usual	39 (15%)	33 (10.2%)
Much better than usual	14 (5.4%)	15 (4.7%)

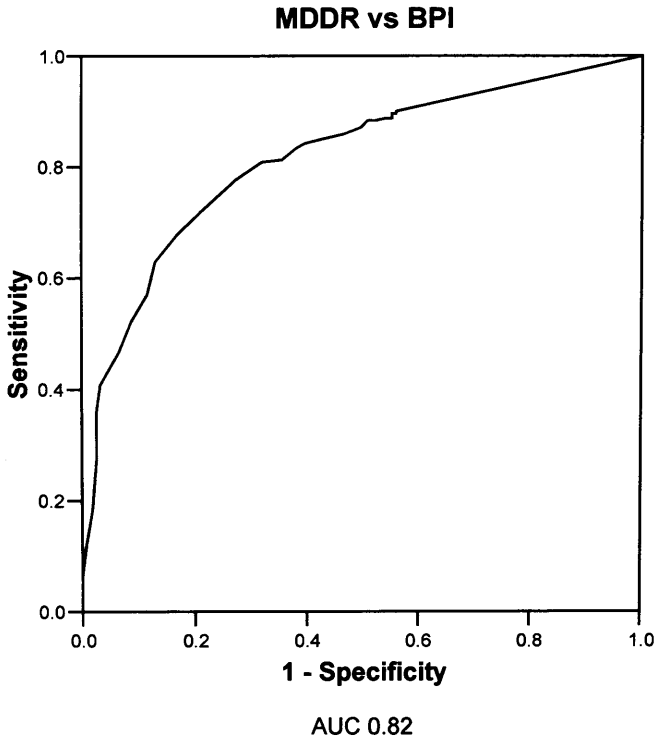


Figure 5-1: ROC Curve Showing the Power of the HCL-32 to Discriminate Between Bipolar (BPI) and Unipolar (MDDR) Subjects (AUC= Area Under Curve)

The ROC curve (Figure 5-1) shows the ability of the HCL-32 to discriminate between MDDR and BPI cases. The AUC of 0.82 reflects the "good" overall predictive validity of the HCL-32 (Tape, 2004). Data on sensitivity and specificity of the checklist suggest that a score of 20 or more yields the best combination of sensitivity (65%) and specificity (83%) to distinguish between BPI and MDDR cases when accounting for current mental state (BDI total score and AMS total score). This cut-off was selected as optimal as it correctly classified the largest number of subjects (75%). The positive and negative predictive values for this cut-off were 76% and 75% respectively.

Including gender as a covariate did not alter the optimal cut-off score on the HCL-32.

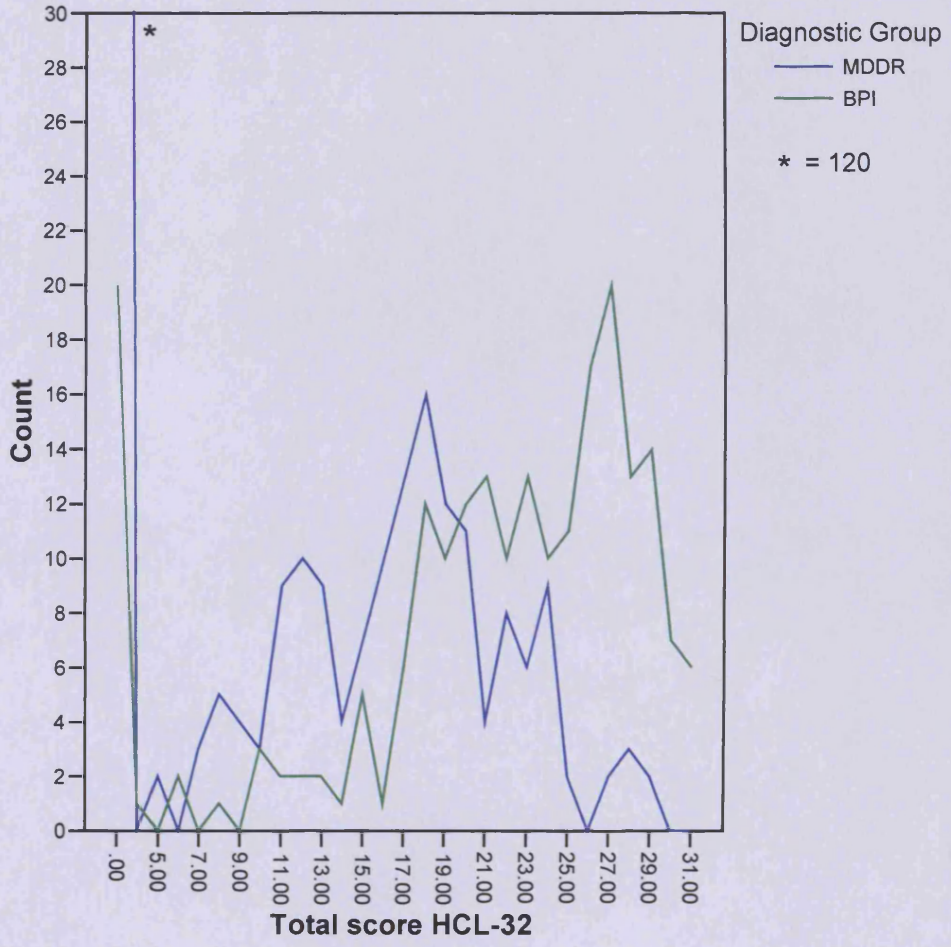


Figure 5-2: Total Scores on the Hypomania Checklist (HCL-32) According to Diagnostic Group: Bipolar Disorder (BPI) Versus Unipolar Disorder (MDDR)

Of the MDDR subjects, 47 (17.2%) rated 20 or more symptoms on the HCL-32 and 105 (32.6%) subjects rated 14 or more symptoms on the HCL-32. Figure 5-2 shows the total HCL-32 scores for the MDDR subjects and the BPI subjects. Table 5-1 also shows the clinical characteristics of the 47 MDDR subjects who rated 20 or more on the HCL-32.

5.5 Discussion

This study focussed on subjects with MDDR and BPI and did not include subjects in the "middle ground" – those with BPII and those MDDR individuals with a family history of bipolar disorder or who have shown mood incongruent psychotic symptoms. Unsurprisingly given these inclusion criteria and in agreement with previous studies (Angst et al., 2005a), the HCL-32 showed good discrimination between BPI and MDDR subjects. In this sample I found that a cut-off score of above 20 offered the best combination of sensitivity (true bipolars) (65%) and specificity (true non-bipolars) (83%). The cut-off score found in this study is higher than the cut-off score of 14 found by Angst et al (2005a). This is consistent with my focus on subjects with BPI disorder, contrasting to Angst et al's focus on BPI (38%) and BPII (62%) disorder. As might be expected, the higher cut-off score used in this study resulted in a reduced sensitivity and higher specificity when compared to the study of Angst et al (2005a).

Given the exclusion of bipolar and unipolar subjects in the middle ground of the spectrum I do not suggest that the cut off is of use in other contexts, rather I have used it to examine the proportion of selected unipolar subjects who score higher than this more conservative level. Even in this highly selected sample, 47 (17.2%) unipolar subjects rated 20 or more hypomanic symptoms on the HCL-32 and 105 (32.6%) rated 14 or more symptoms on the HCL-32. These findings are consistent with previous reports suggesting that individuals with recurrent unipolar depression experience a substantial number of manic/

hypomanic symptoms over their lifetimes (Cassano et al., 2004, Angst et al., 2005b). It is of interest that these 47 "unipolar" subjects resembled the bipolar subjects in that they had a younger age at onset, younger age at first contact with psychiatric services, younger age at first admission, and more hospital admissions. Thus, it is possible that they represent a form of mood disorder which, although meeting DSM-IV criteria for unipolar recurrent depression, share features of pathogenesis with bipolar disorder. This has implications for understanding of nosology and classification and may also have implications for treatment.

BPI subjects were younger at interview when compared to MDDR subjects, although as they also had an earlier age at illness onset (as would be expected when comparing bipolar and unipolar subjects), there was no significant difference between the two samples in terms of illness duration.

Angst et al (2005a) found that current mental state had no impact on the self-assessment of hypo-manic symptoms using the HCL-32 and in agreement with this, I found no correlation between total HCL-32 scores and current mental state as assessed by the HCL-32 or by the Beck Depression Inventory. As would be expected there was a significant correlation between total HCL-32 score and current mental state as assessed by the Altman Self-Rating Mania Scale. Interestingly, subjects in the bipolar sample were more likely to complete the questionnaire pack when they were feeling "a little better", "better" or "much better than usual". However, this finding does not affect the conclusions of this study focusing on the unipolar sample.

A major strength of this study, along with the large sample size of nearly 600 subjects, is that all subjects in the unipolar and bipolar samples were recruited from within the same geographical regions within the UK and were assessed using the same standardised procedures. To the best of my knowledge, this is the first report from the UK using the HCL-32.

The time duration between the initial research interview and the completion of the questionnaire pack, of 3.8 years, can be seen as the main limitation of this study. It is possible that at least some of the MDDR subjects who scored highly on the HCL-32 may have experienced a hypomanic or manic episode since the time of the research interview and may therefore have switched from a unipolar to a bipolar categorical diagnosis. Angst el al (2005b) found that a diagnostic change from depression to bipolar I disorder occurred in about 1% of patients per year and to bipolar II disorder in about 0.5% of patients per year. However, studies have suggested that younger subjects, with a personal history of psychotic features or a family history of bipolar disorder, are more likely to switch to a bipolar diagnosis than unipolar subjects without such characteristics (Coryell et al., 1995).

The focus on subjects with BPI disorder (not including subjects with a diagnosis of BPII) could be seen as a limitation of this study. However, my focus was on groups of subjects who would, in theory, be at opposite ends of the bipolar diagnostic spectrum, and, in particular, on subjects with MDDR who were thought to be at low risk of experiencing hypomanic features.

Another potential limitation of this study is that I only included patients of UK/ Eire white ethnicity and so findings may therefore not be representative of all populations.

It is well known that detecting hypomanic symptoms, even via clinical interview, can be difficult as subjects/ patients may not recognise such symptoms as being significant. It is important to note, that even using the HCL-32, I may still be underestimating the presence of manic symptoms. However, I feel that this study illustrates the usefulness of the HCL-32 in detecting hypomanic symptoms, and it's potential utility in identifying individuals where there is a need for further investigations into the possibility of a bipolar II, or even bipolar I diagnosis.

In summary, these findings of an overlap in manic/ hypomanic symptoms across bipolar and unipolar diagnostic groups, challenge the traditional simple unipolar/ bipolar categorical divide and illustrate the difficulties inherent in allocating subjects to a particular diagnostic group. Dimensional measures of manic/ hypomanic symptoms across subjects with mood disorder diagnoses are likely to be useful in both clinical and etiological studies of the unipolar-bipolar interface.

6 Clinical Characteristics of Unipolar Disorder and Bipolar Disorder According to the Lifetime Presence of Recurrent Panic Attacks

Reported by Forty et al (In Press)

6.1 Summary

The frequent comorbidity of panic and affective disorders has been described in previous studies. However, it is not clear how panic disorder comorbidity in unipolar disorder and bipolar disorder is related to illness course.

I have compared lifetime clinical characteristics of illness and items of symptomatology in samples of subjects with bipolar I disorder (N=290) and unipolar disorder (MDDR) (N=335) according to the lifetime presence of recurrent panic attacks.

I found significant differences in clinical course of illness characteristics that were shared across the unipolar and bipolar samples according to the lifetime presence of panic attacks. For example, both the unipolar and bipolar samples with a history of panic attacks i) had more frequent and more severe depressive episodes (as measured by the BADDS depression dimension) and ii) were more likely to have experienced suicidal ideation and slowed activity during depressive episodes in their lifetime, compared to those with no history of panic attacks.

I also found a number of differences according to the presence of panic attacks that were specific to the diagnostic group. For example, subjects with bipolar disorder and a history of recurrent panic attacks were more likely to have i) a family history of affective disorder, ii) more severe impairment during their worst ever episode of depression, iii) attempted suicide during their

lifetime, and iv) experienced diurnal morning variation, insomnia and agitated activity during depressive episodes during their lifetime, compared to subjects in the bipolar sample with no history of panic attacks. These differences were not seen between the unipolar groups with and without a history of panic attacks.

Distinguishing patients/ subjects who have mood disorder diagnoses, especially bipolar I disorder, according to the lifetime presence of recurrent panic attacks may not only be of use in clinical practice, but may also be informative for aetiological research, such as, molecular genetic studies.

6.2 Introduction

Refining phenotypic descriptions and sub-typing in mood disorders may facilitate clinical studies that focus on improving treatment strategies for particular sub-groups of patients and may also be informative for aetiological studies of mood disorders, such as genetic studies. Studies have suggested that mood disorders may be distinguished by their relationship to specific anxiety disorders (Simon et al., 2003).

Comorbid panic disorder has been associated with a worse course of illness (Johnson and Lydiard, 1998, Fawcett et al., 1990, Brown et al., 1996) and poorer treatment outcome in major depression (Johnson and Lydiard, 1998) and in bipolar disorder (Simon et al., 2004, Frank et al., 2002, Frank et al., 2000, Feske et al., 2000, Dilsaver and Chen, 2003).

Evidence from twin studies has suggested that genes that predispose to major depression are essentially the same as those that influence generalised anxiety disorder, but are relatively distinct from those influencing panic disorder (Kendler et al., 1995b). Results from family studies (Maier et al., 1995b, Weissman et al., 1993) have indicated that although panic disorder and unipolar disorder aggregate in families, the comorbid condition does not represent a distinct subtype in terms of familial aggregation and the major proportion of comorbidity between panic disorder and unipolar disorder appears to be due to non-familial factors. Studies of bipolar disorder, however, have shown that there may be shared genetic influences in some

families for bipolar disorder and panic disorder (MacKinnon et al., 2002, Rotondo et al., 2002).

It seems that comorbid panic disorder may identify a familial subtype of bipolar disorder (MacKinnon et al., 1997), but not of unipolar disorder, suggesting that bipolar and unipolar disorders may differ in their relationship to panic disorder.

To date, no-one has examined the clinical course of illness in relation to the lifetime presence of panic attacks across unipolar and bipolar samples within the same study. The aim of the current study was to assess the lifetime clinical characteristics of illness in both subjects with bipolar disorder and subjects with unipolar disorder according to their lifetime presence of recurrent panic attacks.

6.3 Method

6.3.1 Subjects

See chapter 2 for further methodological details. The bipolar (BPI N=290) and unipolar (MDDR N=335) samples included subjects who correctly completed the panic questionnaire in the 2007 questionnaire pack.

6.3.2 Assessment

Subjects completed the panic questionnaire (appendix H), the Beck Depression Inventory (BDI) (appendix E) and the Altman Self-Rating Mania

Scale (ASRM) (appendix F) in the questionnaire pack that was sent out in 2007.

Subjects were classified as having experienced recurrent panic attacks during their lifetime according to the following criteria: The panic attacks occurred on more than one occasion (question 2) with symptoms such as shortness of breath, sweating, etc (question 5). The panic attacks caused some impairment with everyday functioning (question 6, rating of at least "somewhat difficult"). In addition, the panic attacks came suddenly out of the blue (question 3) and/ or the panic attacks bothered the subject a lot or made the subject worry about having another attack (question 4) (see appendix H).

In order to assess the reliability of the questionnaire measure of panic attacks, SCAN sections assessing anxiety and panic were completed at interview for 24 subjects. These subjects also completed the panic questionnaire. For these subjects, I was able to examine the agreement between the two methods of assessing the lifetime ever presence of recurrent panic attacks (i.e. interview versus questionnaire). A Kappa statistic (Cohen, 1960) of 0.71 was obtained, indicating good agreement (Fleiss, 1981) between the two measures for the lifetime presence of recurrent panic attacks. For twenty-one subjects the two measures were concordant, and for three subjects the measures were discordant. Using the SCAN interview as a gold standard for defining the lifetime presence of recurrent panic attacks, the panic questionnaire correctly classified 88% of subjects, with a sensitivity of 94% and a specificity of 75%.

6.3.3 Statistical Analysis

Demographic/ clinical characteristics were compared in the bipolar sample and the unipolar sample according to the lifetime presence of recurrent panic attacks. As the continuous data were not normally distributed, medians, interquartile ranges, and ranges are reported. Numbers (N) and proportions are reported for the categorical data.

In order to test for an association between a characteristic and the lifetime presence of recurrent panic attacks, a logistic regression model was constructed for each characteristic, with the presence/ absence of lifetime recurrent panic attacks as the outcome/ dependent variable. Multivariate logistic regression models were used so that the following potentially confounding variables could be included as covariates; BDI score, age at interview, and gender.

Odds ratios (OR) and 95% confidence intervals (95% CI) for the odds ratios are reported. Odds ratios of greater than 1 indicate, for the particular variable, that a higher score is associated with the lifetime presence of recurrent panic attacks; whereas odds ratios of less than 1 indicate that a higher score is associated with the lifetime absence of recurrent panic attacks.

6.4 Results

Of the 290 subjects with bipolar disorder (BPI), 136 (47%) had a lifetime history of recurrent panic attacks. Of the 335 subjects with unipolar disorder (MDDR), 194 (58%) had a lifetime history of recurrent panic attacks.

Demographic characteristics

A higher score on the BDI was significantly associated with the lifetime presence of panic attacks in the bipolar sample (OR 1.05, 95% CI 1.02-1.08, p=0.0014), as was a lower age at interview (OR 0.97, 95% CI 0.95-0.99, p=0.002). There was a trend towards a higher proportion of females in the bipolar group with a history of panic attacks, although this did not reach statistical significance. There were no significant associations between panic status and method of recruitment, illness duration or ASRM score (see Table 6-1).

A higher score on the BDI was also significantly associated with the lifetime presence of panic attacks in the unipolar sample (OR 1.05, 95% CI 1.02-1.07, p<0.001). There were no associations between panic status and age at interview, gender, method of recruitment, illness duration or ASRM score (see Table 6-1).

Table 6-1: Lifetime Clinical Characteristics of the Bipolar (BPI) and Unipolar (MDDR) Samples According to the Lifetime Presence or Absence of Panic Attacks

Clinical Characteristic		BPI -Panic N=154 (53%)	BPI +Panic N=136 (47%)	p-value	MDDR -Panic N=141 (42%)	MDDR +Panic N=194 (58%)	p-alue
Beck Depression Inventory Total score	Median Interquartile Range Range	8.5 11 0-52	12 14 0-49	**0.0014**	11.5 13 0-42	16 17 0-46	**<0.001**
Altman Mania Scale Total score	Median Interquartile Range Range	3 4 0-15	4 5 0-15	0.12	2 4 0-13	2 3 0-11	0.57
Age at Interview (years)	Median Interquartile Range Range	49 18 21-73	44.5 17 24-67	**0.023**	52 18 18-85	49 15 26-78	0.38
Method of Recruitment	Systematic Non-Systematic	66 (47%) 76 (53%)	48 (40%) 73 (60%)	0.80	54 (38%) 85 (60%)	91 (48%) 100(52%)	0.20
Gender	Male Female	54 (35%) 100(65%)	31 (23%) 105(77%)	0.057	48 (34%) 93 (66%)	58 (30%) 136(70%)	0.52
Illness Duration (years)	Median Interquartile Range Range	22 17.25 2-54	20 19.25 0-52	0.78	21 22 1-71	20 18 2-55	0.90
Age at Illness Onset (Mania or Depression)	Median Interquartile Range Range	25 15 10-66	23 13 7-49	0.80	27 18 9-61	26 14 10-63	0.90
Age at 1st Contact with psychiatric services	Median Interquartile range Range	28 17 13-66	26 15 11-51	0.89	34 22 14-63	33 53 10-63	0.88
Age at 1st Admission (if applicable)	Median Interquartile Range Range	30 14 16-66	28 15 16-53	0.76	40 16 17-68	33 17 0-61	0.25
Number of Admissions	None One or more	17 (11%) 136 (89%)	13 (10%) 123 (90%)	0.15	83 (59%) 58 (41%)	84 (43%) 110 (57%)	**0.0069**
Family History of Affective Disorder	Absent Present	40 (29%) 99 (71%)	17 (14%) 103 (86%)	**0.037**	16 (14%) 102 (86%)	18 (12%) 139 (88%)	0.68
No. of Episodes of Depression	Median Interquartile Range Range	4 7 0-70	5 7 0-40	0.58	4 3 2-70	4 3 2-30	0.51
No. of Episodes of Mania	Median Interquartile Range Range	5 5 1-50	5 5 1-100	0.97	-	-	-

Table 6-1 Continued

Clinical Characteristic		BPI -Panic N=154 (53%)	BPI +Panic N=136 (47%)	p-value	MDDR -Panic N=141 (42%)	MDDR +Panic N=194 (58%)	p-value
Predominant Polarity	Mania Depression	71 (57%) 54 (43%)	40 (40%) 60 (60%)	0.71	-	-	-
Longest Episode of Depression (weeks)	Median Interquartile Range Range	22 32 1-286	26 32 0-416	0.99	74 69 2-624	64 62 9-376	0.74
Longest Episode of Mania (weeks)	Median Interquartile Range Range	8 11 0-104	9 11 1-104	0.95	-	-	-
Suicide Attempt	Absent Present	101 (68%) 47 (32%)	68 (53%) 60 (47%)	**0. 036**	110 (79%) 30 (21%)	141 (73%) 51 (27%)	0.84
Rapid Cycling	Absent Present	78 (72%) 30 (28%)	61 (68%) 29 (32%)	0.99	-	-	-
Psychotic Features (lifetime-ever)	Absent Present	35 (25%) 103 (75%)	20 (17%) 98 (83%)	0.21	130 (93%) 10 (7%)	171 (89%) 20 (11%)	0.34
GAS Worst Depression	Median Interquartile Range Range	37 14 5-71	34 12 5-81	**0.034**	37 7 10-54	36 8 10-51	0.23
Worst Mania	Median Interquartile Range Range	28 13 10-55	28 15 9-55	0.68	-	-	-
BADDS Depression	Median Interquartile Range Range	63 21 0-99	66 22 0-93	**0.0059**	62 10 40-85	63 5 50-90	**0.028**
Mania	Median Interquartile Range Range	82 19 60-99	82 19 41-94	0.71	0 0 0-20	0 0 0-20	-
Psychosis	Median Interquartile Range Range	21.5 26 0-100	22 37 0-100	0.13	0 0 0-50	0 0 0-75	-
Incongruence	Median Interquartile Range Range	20 20 0-60	20 15 0-47	0.94	0 - -	0 0 0-20	-

P values are obtained from multivariate logistic regression models which included the demographic/ clinical characteristic (item) along with the following potentially confounding variables (BDI score, age at interview, and gender), with the outcome variable being presence/ absence of lifetime recurrent panic attacks. Significant p-values are in **bold**. N values may vary due to missing data.

Comparing clinical characteristics in unipolar and bipolar samples according to a lifetime history of recurrent panic attacks

The following characteristics were significantly associated with the lifetime presence of recurrent panic attacks in the bipolar sample: a family history of affective disorders (OR 2.09, 95% CI 1.05-4.16, p=0.037); suicide attempt (OR 1.71, 95% CI 1.04-3.01, p=0.036); more severe impairment during the worst ever depressive episode (as rated on the GAS) (OR 0.97, 95% CI 0.95-0.99, p=0.034); a higher score on the BADDS depression dimension (indicating more frequent and severe depressive episodes). There were no significant associations between panic status and any other clinical lifetime course characteristics (see Table 6-1).

The following OPCRIT rated items of depressive symptomatology were significantly associated with the lifetime presence of recurrent panic attacks in the bipolar sample: diurnal (morning) variation (OR 1.91, 95% CI 1.08-3.40, p=0.027); suicidal ideation (OR 2.07, 95% CI 1.03-4.19, p=0.042); slowed activity (OR 2.18, 95% CI 1.19-3.98, p=0.011); initial and middle insomnia (OR 2.12, 95% CI 1.15-3.92, p=0.016; OR 1.94, 95% CI 1.08-3.48, p=0.027); early morning waking (OR 3.74, 95% CI 1.99-7.06, p<0.001); agitated activity (OR 3.79, 95% CI 2.003-7.05, p<0.001). For the other OPCRIT rated items of

depressive symptomatology there were no significant associations with panic status.

I also looked for associations between panic status and items of OPCRIT rated manic symptomatology present during the lifetime and found no significant associations.

The following characteristics were significantly associated with the lifetime presence of recurrent panic attacks in the unipolar sample: inpatient treatment at least once during the lifetime (OR 1.95, 95% CI 1.20-3.15, p=0.0069); a higher score on the BADDS depression dimension (again, indicating more frequent and/ or severe depression episodes) (OR 1.033, 95% CI 1.004-1.064, p=0.028) (see Table 6-1).

The following OPCRIT rated items of depressive symptomatology were significantly associated with the lifetime presence of recurrent panic attacks in the unipolar sample: suicidal ideation (OR 2.16, 95% CI 1.079-4.34, p=0.030); slowed activity (OR 1.79, 95% CI 1.069-3.01, p=0.027). There were no other significant associations according to panic status for any other OPCRIT rated items of depressive symptomatology.

6.5 Discussion

I found that several clinical characteristics of illness, relating to the severity and frequency of depressive episodes, were significantly associated with the lifetime presence of recurrent panic attacks in both subjects with bipolar

disorder and unipolar disorder. In the bipolar sample, I found no association between the lifetime presence of panic attacks and clinical characteristics of illness relating to mania.

I believe that this study is the first to compare clinical characteristics of illness in both subjects with unipolar disorder and bipolar disorder, who were recruited using the same sampling approach and assessed using consistent methodology, according to the lifetime presence of panic attacks.

Dilsaver and Chen (2003) found that anxiety disorders appear to be related to states of depression rather than to what is regarded to be classic manic symptomatology. In agreement with this, the associations that I found in the bipolar sample with panic attacks tended to be related to the course of depression. For example, I found that subjects with bipolar I disorder and a lifetime history of recurrent panic attacks were more likely to have attempted suicide during their lifetime, to have more severe impairment during their worst depressive episode, and to have more frequent and severe depressive episodes (according to the BADDS). In terms of items of psychopathology (rated using OPCRIT), in the bipolar sample, I found a number items of depressive symptomatology that were significantly associated with the lifetime presence of recurrent panic attacks, but no associations for items of manic symptomatology. Similarly, Frank et al (2002) found that in a sample of 66 subjects with bipolar I disorder, those who rated highly on an instrument measuring the presence of lifetime panic-agoraphobic symptoms were more likely to have experienced a greater number of depressive episodes, a greater

number of depressive symptoms and more suicidal ideation than subjects with lower scores on the scale. They found no difference in the number of episodes of mania or in manic symptoms between these groups.

The measure of current mood state (BDI) indicated that at the time of the questionnaire assessment, subjects with a history of recurrent panic attacks displayed more depressive symptomatology than subjects who had never experienced panic attacks. This finding, of higher rates of current depressive symptomatology in subjects with a history of panic attacks, suggests that history of recurrent panic attacks could be a marker of a more chronic depressive course of illness. Unfortunately, my measure of panic attacks did not ask about the presence of current panic attacks. It may be that those subjects who were currently experiencing panic attacks may have been the subjects were currently experiencing higher rates of depressive symptoms.

As well as finding associations that were shared across the unipolar and bipolar samples according to the lifetime presence of panic attacks, I also found a number of associations according to the presence of panic attacks that appeared to be present only in the bipolar sample. For example, in subjects with bipolar disorder, those with a history of panic attacks were more likely to have a family history of affective disorder, to have attempted suicide and to have experienced more severe impairment during their worst episode of depression than those with no history of panic attacks. In addition, I found that subjects in the bipolar sample who had a history of panic attacks were more likely to have experienced diurnal variation, insomnia and agitated

activity than those with no history of panic attacks. These findings point to the possibility that the presence of lifetime panic attacks may differentiate between subjects with bipolar disorder to a greater degree than for unipolar subjects. If this is the case, defining the presence of panic attacks may be more useful nosologically in bipolar than in unipolar disorder. However, it is important to note that these differences may also exist in the unipolar sample, but to a smaller extent.

Previous studies have generally found significantly higher rates of comorbid panic disorder in subjects with bipolar disorder compared to subjects with unipolar disorder (Chen and Dilsaver, 1995, Simon et al., 2003), although others have not (Rihmer et al., 2001, Pini et al., 1997). In this study, I found a higher rate of recurrent panic attacks in the unipolar sample, compared to the bipolar sample. Methodological differences may explain the variation in prevalence estimates between studies. This study focused on subjects with narrowly defined bipolar I disorder or recurrent major depression. It has been argued that the inclusion of subjects with bipolar II disorder may contribute towards the higher overall prevalence of panic disorder in bipolar disorder compared to unipolar disorder seen in previous studies (Doughty et al., 2004). Some studies have shown higher rates of comorbid panic disorder in subjects with bipolar II disorder compared to subjects with bipolar I disorder (Doughty et al., 2004, MacKinnon et al., 2002, Perugi et al., 1999). Similarly, higher rates of panic disorder have been found in recurrent depressive disorder compared to single episode depressive disorder (Doughty et al., 2004, MacKinnon et al., 2002). These considerations may suggest the need for a

careful characterisation of bipolar II disorder in samples of apparently "unipolar" subjects.

My focus on recurrent panic attacks, rather than panic disorder, may also have influenced the prevalence rates in these samples. I felt that the use of a less restrictive definition of lifetime recurrent panic attacks (that caused impairment in everyday functioning), rather than a strict definition of panic disorder, would enable me to focus on the phenotype of interest whilst maximising the sample size. Mackinnon et al (2002) found that loosening the phenotype to include panic attacks not meeting criteria for panic disorder did not alter their main finding that familial bipolar disorder is associated with increased risk for panic disorder. It is important to note that some caution is indicated here. To demonstrate clinically significant differences between two groups according to the presence of a weakly defined characteristic may illustrate the robust influence of that characteristic although it is also possible that the findings may be reflecting differences in the subject's temperament or cognition, with respect to how subjects respond to questionnaires in general. In order to assess this I evaluated the main results using two more restrictive definitions of panic attacks. The first of these restrictive definitions differed from the main definition in that subjects had to answer yes to both questions 3 and 4 on the panic questionnaire (rather than 3 or 4) to be classified as having experienced recurrent panic attacks. In addition to this, for the second restrictive definition (the most restrictive definition) subjects also had to indicate that the panic attacks made it "very difficult" or "extremely difficult" to function effectively in their everyday lives.

For all of the clinical characteristics that showed statistically significant differences between groups, according to panic status using the main definition, similar effect sizes were found when using the two more restrictive definitions of panic attacks although for some of these variables the reduction in sample size resulted in the findings no longer showing statistical significance.

In agreement with previous studies (Eaton et al., 1994, MacKinnon et al., 2002) in both the unipolar and bipolar samples, I found a trend (not statistically significant) for females to have a greater prevalence of panic attacks compared to males.

I believe that this study is the first to compare unipolar and bipolar subjects with and without a history of recurrent panic attacks for clinical characteristics of illness and items of depressive psychopathology. These well characterised, relatively large unipolar and bipolar samples were recruited and assessed using consistent robust methodologies.

The use of postal questionnaires, rather than interview measures, to establish the presence or absence of panic attacks is a limitation of this study. However, when I compared the rates of lifetime recurrent panic attacks in those subjects who were assessed using the anxiety/ panic section of the SCAN interview and also completed the self-rated questionnaire measure of panic attacks I found good agreement between the two measures.

Another potential limitation of the current study is that I did not include subjects with bipolar II disorder in the study. As I was looking to see if there were differences between subjects with bipolar and unipolar disorders in terms of clinical characteristics associated with co-morbid panic attacks, I focused on well defined, homogeneous groups of subjects with either bipolar I disorder or recurrent major depression.

These results suggest that the lifetime presence of recurrent panic attacks may differentiate between sub-groups of individuals with mood disorders, especially in those with bipolar disorder. The presence of recurrent panic attacks in bipolar and unipolar disorder may be indicative of a course of illness associated with greater depressive morbidity. The clinical assessment of panic attacks may be informative in diagnostic assessment and has the potential to guide treatment decisions particularly for individuals with a diagnosis of bipolar I disorder.

Defining individuals who have a mood disorder diagnosis, especially bipolar I disorder, according to the lifetime presence of recurrent panic attacks may not only be of use in clinical practice, but may also be informative for aetiological research, such as molecular genetic studies.

7 Is Depression Severity the Sole Cause of Psychotic Symptoms During an Episode of Unipolar Major Depression? A Study Both Between and Within Subjects.

Reported by Forty et al (2009a)

7.1 Summary

Despite the common clinical assumption that psychosis is an indicator of severity in depression, it is not known what determines the presence of psychotic features in major depression. My aim was to answer the question: Is depression severity the sole cause of psychotic symptoms during an episode of unipolar major depression?

In a sample of 585 subjects with a diagnosis of major recurrent depression, I assessed measures of severity of depression and the presence of psychotic features, both within and between subjects.

Within subjects, psychotic episodes tended to be more severe than non-psychotic episodes. However, between subjects there was wide variation in severity in both those that did, and did not, experience psychotic episodes.

Subjects with a predisposition to psychotic features tend to display such features during more severe episodes of depression. However, subjects with no history of psychosis may experience non-psychotic depressive episodes of equal or greater severity, in terms of depressive symptomatology, compared to subjects with psychotic depression. Thus, there is individual variation in susceptibility to psychosis during mood episodes and severity is not the sole determinant.

and optimize the power of clinical, biological and psychological research studies. The occurrence of psychotic symptoms (delusions and/ or hallucinations) during episodes is one potentially important clinical feature tha may identify such a subgroup.

The primary aim of the current study was to examine whether the severity of depression, using both lifetime and episode severity measures, can on its owr account for the presence of psychotic features during depressive episodes. In contrast to previous studies, rather than focusing on episode diagnoses, I examined a large, well-characterized group of subjects with a lifetime diagnosis of recurrent unipolar major depressive disorder. In addition, I made comparisons between psychotic and non-psychotic episodes *within* subjects as well as *between* groups of subjects in this homogeneous sample.

7.3 Method

7.3.1 Subjects

See chapter 2 for further methodological details. Subjects recruited to the unipolar samples (DeCC and DeNT studies) were included in this study (N=585).

7.3.2 Assessment

In addition to the assessment procedure described in chapter 2, for each subject the following information was collected for the worst ever episode of depression and the second worst ever episode of depression: Psychotic features (present/ absent); age at onset of episode (years); duration of episode (weeks); psychiatric contact during episode (present/ absent); admission during episode (present/ absent); functional impairment according to the Global Assessment of Functioning Scale (GAS) (Endicott et al., 1976). As described in chapter 2, the OPCRIT symptom checklist (McGuffin et al., 1991, Craddock et al., 1996) was used to rate the presence or absence of items of depressive and psychotic symptomatology during the worst and second worst episodes of depression and also on a lifetime ever basis. As it is standard practice to define episode severity according to the number of depressive symptoms present (WHO, 1993), I have used the total number of depressive symptoms as a measure of severity that is independent of the presence of psychotic symptoms.

Of the 585 unrelated subjects with recurrent major depression (unipolar disorder), 64 (11%) had experienced one or more psychotic feature at some stage during their illness (Psychosis Group, PG) and 460 (78.6%) had never experienced a psychotic feature during their illness (No Psychosis Group, NPG). For 61 (10.4%) subjects I was unable to establish the definite presence or absence of lifetime psychotic features and so these subjects were excluded from the analysis.

7.3.3 Statistical Analysis

As the continuous data did not follow a normal distribution, non-parametric analyses were used and medians, interquartile ranges, and ranges are reported. Three sets of analyses were conducted:

i) Between Groups Analysis of Demographic and Lifetime Clinical Variables

The PG (N=64) and the NPG (N=460) were compared on lifetime demographic and clinical variables using chi-square tests for categorical variables and the Mann-Whitney test for continuous variables.

ii) Between Groups Analysis of Worst Ever Episode of Depression

Differences between the PG (N=64) and NPG (N=460) during the worst ever episode of depression were examined using chi-square tests for categorical variables and the Mann-Whitney test for continuous variables.

iii) Within Groups Analysis of Psychotic and Non-Psychotic Episodes of Depression

For the within groups analysis, subjects were selected from the PG where one of the two most severe depressive episodes featured psychotic symptoms but the other one of the two most severe episodes did not (N=37). These subjects therefore had experienced at least one psychotic depressive episode and one non-psychotic depressive episode.

Differences between the psychotic and non-psychotic episodes of the PG (N=37) were examined using McNemar tests for categorical variables and the Wilcoxon signed ranks test for continuous variables.

7.4 Results

Between Groups Analysis of Demographic and Lifetime Clinical Variables

There were no significant differences between the PG and the NPG in terms of gender, age at interview, or illness duration. Seventy percent of the PG were female compared to sixty-eight percent of the NPG (p=0.66). The median age at interview for both groups was 49 years (p=0.51), and although illness duration was less for the NPG (19 years compared to 22.5 years), the difference was not statistically significant (p=0.18). As can be seen in Table 7-1, subjects in the PG had a significantly younger age at illness onset (defined as age at first impairment) when compared to the NPG (p=0.027), were significantly more likely to have attempted suicide (p=0.042) and were more likely to have required contact with psychiatric services (p=0.0078) and received inpatient treatment (p<0.001) during their lifetime. The age at first contact with psychiatric services was significantly younger for the PG (p=0.0062).

Table 7-1: Lifetime Clinical Characteristics of the No Psychosis Group (NPG LE) and the Psychosis Group (PG LE)

Clinical Characteristic		NPG LE N= 460 (88%)	PG LE N= 64 (12%)	p-value
Age at First Illness Onset (years)	Median Interquartile Range Range	26 15 9-61	22.5 14 10-48	**0.027**
Total Number of Depressive Episodes	Median Interquartile Range Range	4 2.1 2-40	4 3 2-15	0.10
Duration of Longest Depressive Episode (weeks)	Median Interquartile Range Range	69 64 8-728	64.5 59 8-376	0.95
Suicide Attempt	Absent Present	335 (73.1%) 123 (26.9%)	39 (60.9%) 25 (39.1%)	**0.042**
Contact with Psychiatric Services	Contact No Contact	389 (84.6%) 71 (15.4%)	62 (96.9%) 2 (3.1%)	**0.0078**
Age at First Contact (years)	Median Interquartile Range Range	33 20 12-63	28 17.25 12-55	**0.0062**
Psychiatric Hospital Admission	Admission No Admission	141 (30.7%) 319 (69.3%)	39 (60.9%) 25 (39.1%)	**<0.001**
Age at First Admission (years)	Median Interquartile Range Range	35 17 13-68	31 17 19-55	0.071

Comparisons of dichotomous items were analysed using chi-square tests and the Mann-Whitney test was applied to continuous data. N values may vary due to missing/ incomplete data. Significant p-values are in **bold**.

Between Groups Analysis of Worst Ever Episode of Depression

Table 7-2: Clinical Characteristics of the Worst Ever Depressive Episode in Subjects Who Have Not (No Psychosis Group NPG) and Who Have (Psychosis Group PG) Experienced Psychotic Features During Their Lifetime

Clinical Characteristic		NPG N = 460 (88%)	PG N = 64 (12%)	p-value
Age at Onset of Episode (years)	Median Interquartile Range Range	37 19 9-73	36 19 16-57	0.41
Duration of Depressive Episode (weeks)	Median Interquartile Range Range	52 78 4-464	52 57 9-395	0.58
Total Number of Depressive Symptoms	Median Interquartile Range Range	11 2 6-17	11 3 6-16	0.42
GAS Score	Median Interquartile Range Range	37 7 10-74	31 8 10-50	**<0.001**
Psychiatric Contact During Episode	Present Absent	304 (68%) 143 (32%)	56 (88.9%) 7 (11.1%)	**<0.001**
Psychiatric Admission During Episode	Present Absent	104 (23.2%) 345 (76.8%)	36 (57.1%) 27 (42.9%)	**<0.001**

Comparisons of dichotomous items were analysed using chi-square tests and the Mann-Whitney test was applied to continuous data. N values may vary due to missing/ incomplete data. Significant p-values are in **bold**.

The PG scored significantly lower on the GAS ($p<0.001$) (indicating more severe functional impairment), and were significantly more likely to need psychiatric contact ($p<0.001$) and psychiatric admission ($p<0.001$) during their worst episode than the NPG (see Table 7-2). However, there was no difference between the two groups in terms of the amount of depressive symptomatology experienced during the worst episode of depression. Figure 7-1 illustrates this graphically.

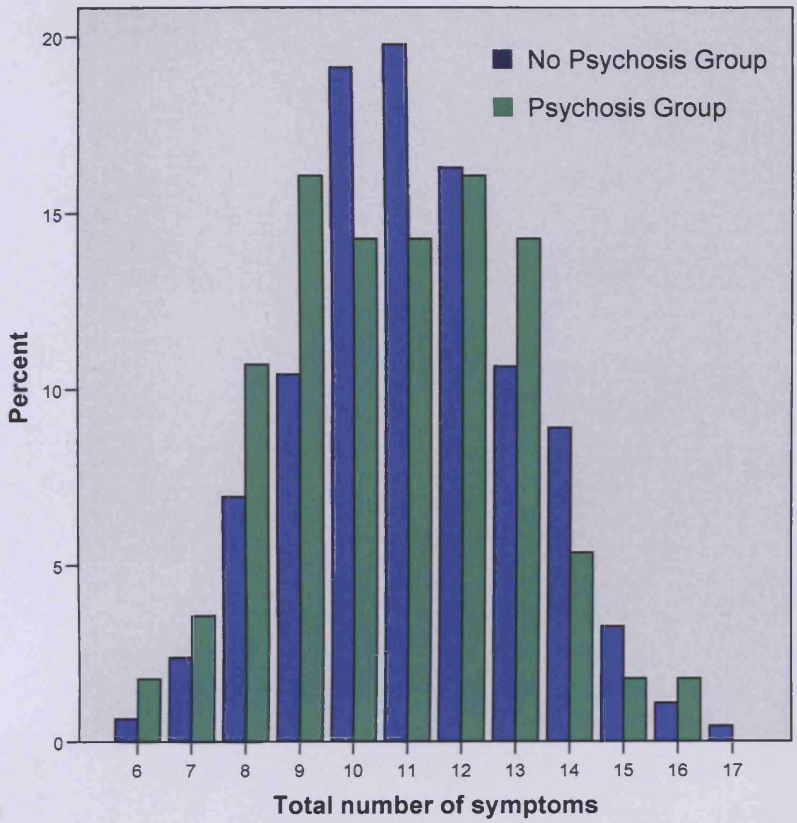


Figure 7-1: Total Number of OPCRIT Rated Depressive Symptoms in Worst Ever Depressive Episodes of Subjects With (N=64) and Without (N=460) a History of Psychotic Features

There was no statistically significant difference between the No Psychosis Group and the Psychosis Group for the total number of depressive symptoms experienced during the worst ever episode of depression (p=0.42).

There were no statistically significant differences between the PG and the NPG for the individual depressive symptoms rated as present during the worst ever episodes of depression.

Within Groups Analysis of Psychotic and Non-Psychotic Episodes of Depression

Table 7-3: Clinical Characteristics of a Non Psychotic Episode (PE) and a Psychotic Episode (NPE) Within Individuals (N=37)

Clinical Characteristic		NPE	PE	p-value
Age at Onset of Episode (years)	Median Interquartile Range Range	37 23.75 17-65	35.5 18 16-57	0.58
Duration of Depressive Episode (weeks)	Median Interquartile Range Range	34 39 2-208	38 65 9-177	0.13
Total Number of Depressive Symptoms	Median Interquartile Range Range	10 2 5-14	11 4 6-16	**<0.001**
Psychiatric Contact During Episode	Present Absent	26 (76.5%) 8 (23.5%)	32 (86.5%) 5 (13.5%)	0.34
Psychiatric Admission During Episode	Present Absent	10 (28.6%) 25 (71.4%)	20 (54.1%) 17 (45.9%)	**0.0039**

McNemar tests were used for categorical variables and the Wilcoxon signed ranks test was applied to continuous data. N values may vary due to missing/ incomplete data. Significant p-values are in **bold**.

Table 7-3 shows the significant differences in clinical characteristics for the worst psychotic and the worst non-psychotic depressive episode for the individuals in the psychosis group (N=37). Psychotic episodes were significantly more likely to require inpatient treatment ($p<0.0039$) than non psychotic episodes and involved significantly more depressive symptomatology ($p<0.001$). Figure 7-2 shows the distributions for the total number of depressive symptoms in psychotic episodes and non-psychotic episodes.

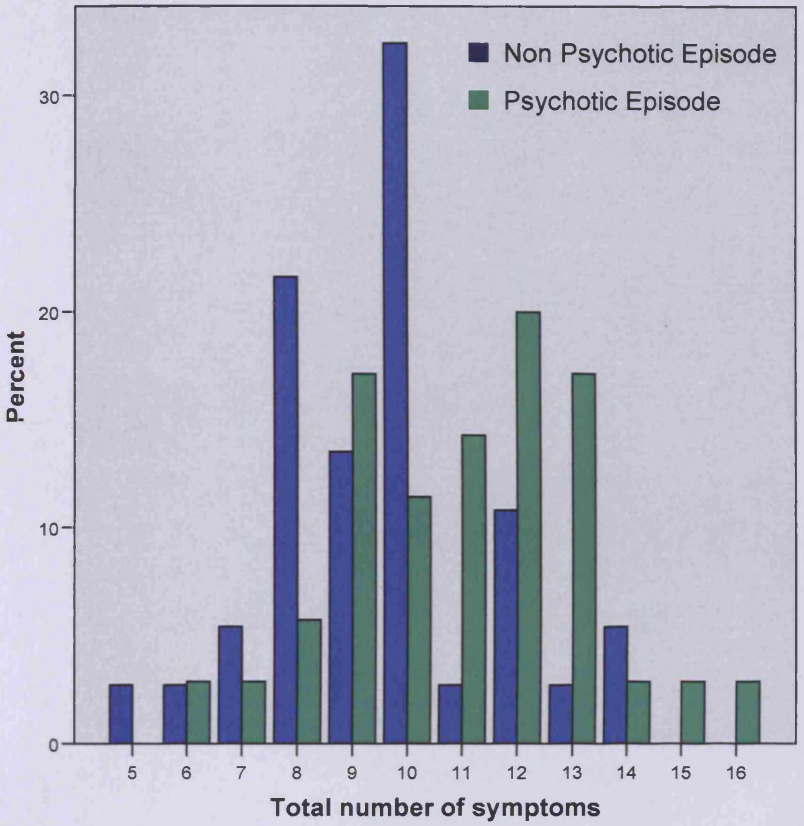


Figure 7-2: Total Number of OPCRIT Rated Depressive Symptoms in Psychotic and Non-Psychotic Depressive Episodes Within Patients With Recurrent Major Depression (N=37)

Subjects in the Psychosis Group were significantly more likely to experience a greater total number of depressive symptoms during a psychotic episode compared to a non-psychotic episode (P=0.00017).

Subjects were significantly more likely to display suicidal ideation (p=0.031) and/ or psychomotor retardation (p=0.031) during their psychotic episode compared to their non-psychotic episode. There were no other significant differences between psychotic and non-psychotic episodes in terms of the depressive symptoms experienced by the subjects.

7.5 Discussion

It is important to understand what the occurrence of psychosis indicates about the underlying depressive disease process because this has implications for treatment and research. The focus of this study is to examine the evidence in this dataset in support of the model that psychosis simply reflects severity of the depressive episode. The widespread use of this assumption by clinicians complicates attempts to study its validity. For example, the need for admission is a useful measure of episode severity but for many clinicians the presence of psychotic features may be a sufficient indication for admission. This, therefore, introduces non-independence between presence of psychosis and this measure of severity. It is important, therefore, to consider which severity measures may be directly influenced by presence of psychosis and which can be considered as an independent measure of severity.

If the severity model is correct, occurrence of psychotic features will identify individuals who tend to have more severe illness episodes but the underlying disease process will be similar to that in individuals who do not experience psychotic episodes. There are data in the prior literature for and against the model. I consider below the support in this data set for the severity model.

Within Groups Analysis of Psychotic and Non-Psychotic Episodes of Depression

The finding of the current study that a subject is likely to display psychotic features during their more severe depressive episodes (indexed by increased need for inpatient care and more depressive symptoms) is in agreement with

Coryell et al (1996). Figure 7-2 provides a graphical illustration of the increased number of depressive symptoms experienced during psychotic, as compared with non-psychotic depressive episodes. The difference in number of symptoms can be seen particularly clearly when considering whether there were more depressive symptoms described in psychotic or non-psychotic episodes within an individual (to avoid biases only non-psychotic depressive symptoms are considered). Of the 37 subjects in the within subjects analysis, 24 (65%) experienced a greater number of depressive symptoms during their psychotic episode when compared with their non-psychotic episode compared to only five subjects (14%) who experienced a greater number of depressive symptoms during their non-psychotic episode. (For the remaining subjects either there was no difference (16%) or the number of symptoms for each episode was uncertain (5%)). The preponderance of psychotic episodes having more depressive symptoms is highly statistically significant (McNemar test; $p = 0.0002$).

At the individual symptom level, psychotic episodes were significantly more associated with suicidal ideation and psychomotor retardation and all depressive symptoms were more likely to occur in psychotic than non-psychotic episodes, except for early morning waking and excessive sleep.

Thus, the within subjects analysis points clearly and consistently to severity of depressive episode having an important influence on expression of psychosis during depression.

Between Groups Analysis of Worst Ever Episode of Depression

These findings contrast with those of Serretti et al (1999) who found no differences in clinical features (for example, age at onset, number and frequency of episodes, number of admissions, suicide attempt) between subjects with delusional or non-delusional major depression.

In agreement with Johnson et al (1991), I found that the subjects in the PG tended to have a more severe lifetime course of illness than the subjects in the NPG as indexed by: a significantly younger age at first onset of depression; being significantly more likely to have attempted suicide during their lifetime; being significantly more likely to require contact with psychiatric services during their lifetime and to require inpatient treatment and experiencing such contact at a significantly younger age. Consistent with Coryell et al (1996), who found that psychosocial impairment differentiated subjects who had and had not experienced psychotic features during depression, I found that subjects who had experienced psychotic features tended to score lower on the GAS, indicating more severe impairment in functioning during their worst ever depressive episode.

Of the subjects in the PG (N=64), 53 identified a psychotic episode as their worst episode of depression. It is of note, that subjects in the psychosis group generally experienced psychotic features in only one (64%) or two (28%) of their depressive episodes, predominantly in their more severe episodes. This finding is in agreement with previous studies (Lattuada et al., 1999, Ohayon and Schatzberg, 2002) and is consistent with the argument that, in some

individuals, psychotic features are a reflection of severity. These individuals are not prone to psychosis in all depressive episodes.

However, I found no difference between subjects in terms of the total amount of depressive symptomatology experienced during the worst episode of depression. Figure 7-1 illustrates the similarity in the distributions of the two groups for the total number of depressive symptoms experienced during the worst ever episode of depression. This is in agreement with several previous findings (Johnson et al., 1991, Jeste et al., 1996, Schatzberg and Rothschild, 1992, Breslau and Meltzer, 1988) but contrasts with other studies where differences were found in the severity, type and number of depressive symptoms present in psychotic and non-psychotic depression (Thakur et al., 1999, Lattuada et al., 1999, Glassman and Roose, 1981, Parker et al., 1995).

Thus, compared to the within subjects analysis, the between subjects analysis provides less consistent support for severity being the key determinant of psychosis in depression. Two specific points are worth highlighting. First, the symptom counts can be considered independent measures of severity and show no differences between psychotic and non-psychotic groups. Second, there is huge variation in severity measures across both those with and without psychotic episodes. These observations demonstrate that factors other than severity make important contributions to influencing expression of psychosis during depressive episodes. Regardless of how severe a depressive episode may be, some individuals do not develop psychotic features. Biological and/ or psychosocial factors may influence susceptibility

to psychosis. Severity of depression does appear to be related to the expression of psychotic features in susceptible individuals.

This study has several important strengths including: i) the focus on a relatively homogeneous set of subjects with recurrent unipolar depression who were selected to have illnesses that are, as far as possible, unrelated to bipolar disorder or schizophrenia, ii) the use of standardized lifetime assessment approaches including both interview and case notes review, iii) the assessments included both psychopathology items as well as measures of lifetime illness course and functioning, and iv) the use of both within groups and between groups designs.

However, it is important to consider several limitations. First, the use of retrospective assessment of psychotic and other features is limited by the subject's ability to clearly recall, and possible reluctance to report, specific features of illness. However, subjects in the current study were asked in detail about these symptoms during a face to face interview. The researcher was able to build a rapport with the subject prior to obtaining information about more sensitive subjects such as psychotic features, which tended to be discussed towards the end of the interview. Psychiatric case notes were available for a large majority of the subjects and I found good agreement between the case note information and the subjects reports of their illness history at interview. A second limitation relates to the generalizability of the findings. Although the use of a sample, of UK/ Eire white ethnicity, selected to exclude cases likely to be related to bipolar disorder or schizophrenia has

advantages in terms of clinical homogeneity, it may limit the generalizability of findings. As with many psychiatric studies of depression, the findings may not extend to the full spectrum of recurrent depression commonly encountered in clinical practice. Although this may be a limitation, it is also important to note that for the majority of patients with unipolar depression and psychosis these findings will be relevant. A third limitation, referred to earlier, relates to the difficulty of defining measures of episode or illness severity that are independent of the presence of psychosis. For some of the differences observed between subjects with and without a history of psychosis it is not clear whether they could simply be a consequence of the presence of psychosis. For example, the presence of psychotic symptomatology directly influences scores on the GAS and could be the main factor in a decision to admit to hospital. I did, however, find significant differences that I can be confident are independent of the effects of psychosis including a significantly younger age of illness onset in the PG compared to the NPG, and a significantly increased number of depressive symptoms present in psychotic episodes compared to non-psychotic episodes in the within groups comparisons. Finally, it is of note that this analysis is limited by treating psychosis as a categorical distinction (presence or absence). Future studies may benefit from taking into account the nature, amount and the severity of the psychotic features themselves.

In summary, the results of this study suggest that in subjects who have a predisposition (biological and/ or psychosocial) to experience psychosis, psychotic features tend to emerge in their more severe depressive episodes.

However, the data also show that severity *alone* cannot account for the presence of psychotic features, as non-psychotic depressive episodes in subjects with no personal history of psychosis may be as severe as, or more severe than, those seen in subjects with psychotic depression. Thus, there is individual variation in susceptibility to psychosis during depressive episodes with psychosis being more likely to be expressed during the more severe episodes, in those subjects with increased susceptibility.

8 Familiality of Postpartum Depression in Unipolar Disorder: Results of a Family Study

Reported by Forty et al (2006)

8.1 Summary

Strong evidence for familial aggregation of episodes of postpartum (puerperal) psychosis in women with bipolar disorder has previously been reported. I here examine whether vulnerability to postpartum triggering of depressive episodes in unipolar depression aggregates in families and assess how this aggregation varies with the definition of postpartum onset.

I studied the occurrence of postpartum depression in the female members of 120 sibling pairs recruited at the Birmingham site of the DeNT study of recurrent unipolar depression. I examined the concordance for postpartum episode status in sisters, employing a range of definitions of postpartum onset.

Episodes of depression with onset within four weeks of delivery clustered in families (tetrachoric correlation coefficient = 0.55, 95% CI 0.11- 0.83, p=0.015) but there was no significant evidence of familial clustering of broadly defined postpartum depression with onset within six months. Women with recurrent major depression with a family history of narrowly defined postpartum episodes experienced postpartum depression following 42% of first deliveries compared to only 15% of first deliveries to women with no such family history. The evidence for familiaility maximised with a definition of postpartum onset of between six to eight weeks.

These results implicate familial factors in susceptibility to the triggering of narrowly defined postpartum depressive episodes in women with recurrent

major depression. They suggest that a definition of postnatal onset of within six to eight weeks of delivery may be optimal in studies of the triggering of depressive illness by childbirth.

8.2 Introduction

A spectrum of affective illness follows childbirth, from the common, mild and transient baby blues, to postpartum (puerperal) psychoses, which can be classed among the most severe episodes of illness seen in clinical practice. The postpartum period is clearly a time of increased risk for episodes of affective psychosis, particularly for bipolar women (Kendell et al., 1987, Terp and Mortensen, 1998). Compelling evidence has previously been reported for the familial clustering of postpartum episodes in women with bipolar disorder – episodes of postpartum psychosis occurred in 74% of parous bipolar women who had a family history of puerperal psychosis in a first-degree relative but in only 30% of women with bipolar disorder with no such family history (Jones and Craddock, 2001b).

Postpartum (postnatal) depression (PPD) is perhaps the most common psychiatric disorder following childbirth and is a term used to cover a wide variety of episodes of illness that occur in the months following delivery. Prevalence estimates vary widely according to the definition of postpartum onset (four weeks, six weeks, or six months for example), and the methods used to establish postpartum depression (clinical interview versus self-report). Based on the results of a large number of studies, however, a meta-analysis found the prevalence rate of non-psychotic postpartum depression to be 13% (O'Hara and Swain, 1996).

Postpartum depression is a significant mental health issue, with serious consequences for the mother, infant and family and the term has undoubtedly

been useful in the fight for clinical services for women who become ill at this time. Despite its clinical and political importance, however, there have been a number of challenges to the scientific validity of the concept of postpartum depression including the suggestion that postpartum depression is no different in nature to episodes of depression that occur at other times (Whiffen, 1991). This has led to the idea that childbirth is acting as a non-specific stressor rather than as a specific trigger for illness onset at this time.

However, while there is no evidence to support postpartum depression as a separate nosological entity, evidence that childbirth is a specific trigger of depressive illness in a proportion of women has been presented. Cooper and Murray (1995) in a study that has yet to be replicated, found that, compared to women who had postpartum depression as a recurrence of a previous non-postpartum depressive disorder, women whose postpartum depressive episode was their first experience of depressive disorder were at *greater* risk for subsequent postpartum depressive episodes, but a *lower* risk of subsequent non-postpartum depression. Second, in a paradigm that simulated the hormonal fluctuations of pregnancy and childbirth, Bloch and colleagues (2000) found that women with a history of postpartum depression display significantly greater mood sensitivity to changes in gonadal steroid levels than controls. Third, Treloar and colleagues (1999) suggested that different genetic factors may play a role in postpartum and non-postpartum depression. Although the scientific status of postpartum depression as a specific nosological category is weak, a number of lines of evidence, therefore, suggest that childbirth can act as a specific trigger of depressive

episodes in some women and that a sub group of women with major depression are vulnerable to a postpartum trigger be it biological or psychosocial in nature.

The aims of the current study were to examine further the concept of a specific childbirth related trigger, to determine whether vulnerability to the postpartum triggering of depressive episodes aggregates in families, and to assess how this aggregation varies with the definition of postpartum depression.

8.3 Method

8.3.1 Subjects

See chapter 2 for further methodological details. Of the 240 subjects from the 120 sibling pairs (one pair per family), recruited at the Birmingham site of the DeNt study, 135 were parous women. There were 60 female-female pairs, 52 male-female pairs, and 8 male-male pairs. Of the 60 female-female pairs, there were 45 where both sisters were parous, and these were the main focus of these analyses.

8.3.2 Assessment

In addition to the assessment procedure described in chapter 2, detailed information was also collected on the relationship of episodes of mood illness to childbirth. Each pregnancy was assessed according to the following criteria: i) narrowly defined postpartum depression (an onset of DSM-IV major

depression within four weeks of delivery), and ii) broadly defined postpartum depression (an onset of DSM-IV major depression within six months of delivery).

8.3.3 Statistical Analysis

The association of lifetime and first pregnancy postpartum depression status between pairs of parous sisters was assessed by the tetrachoric correlation coefficient as implemented in Mx (Neale et al., 2003).

8.4 Results

The median age at onset of depression for the 90 parous women (45 sibling pairs) was 22 years, and the median number of depressive episodes was four (see Table 8-1.). Twenty-six women (29%) had been admitted to a psychiatric unit for depression at some stage during their lives. Eight (9%) women had experienced psychotic symptoms during a depressive episode. The median number of pregnancies was 2.5, and the median number of deliveries was two.

Table 8-1: Lifetime Clinical Characteristics of 90 Parous Women Recruited Within a Study of Sibling Pairs Affected With Recurrent Major Depressive Disorder

Clinical Characteristic		Parous Women *(N=90)*
Age at Interview	Median Interquartile Range Range	47.5 11 28-72
No Episodes of Depression	Median Interquartile Range Range	4 2 2-27
Age at Onset of Depression	Median Interquartile Range Range	22 10 11-51
Number of Admissions	None One or more	64 (71.1%) 26 (28.9%)
Psychosis	Absent Present	82 (91.1%) 8 (8.9%)
Number of Pregnancies	Median Interquartile Range Range	2.5 1 1-9
Number of Deliveries	Median Interquartile Range Range	2 1 1-8
Postpartum Depression	Narrow (onset within 4 weeks) Broad (onset within 6 months)	31 (34%) 45 (50%)

Thirty-one (34%) of the women had experienced at least one postpartum depressive episode with onset within four weeks of delivery and 45 (50%) had experienced a postpartum depression with an onset within six months. Of the 210 deliveries to the 90 women, 18% were followed by postpartum depression with onset within four weeks or 26% with onset within six months of delivery.

Concordance between sibling pairs for postpartum episodes

For narrowly defined postpartum depression, 32 sibling pairs were concordant and 13 were discordant (tetrachoric correlation coefficient = 0.55, p=0.015, 95% CI 0.11-0.83) (see Table 8-2). Employing the broad definition of postpartum depression, 26 of the 45 sibling pairs were concordant and 19

were discordant (tetrachoric correlation coefficient = 0.24, p= 0.28, 95% CI 0-0.63).

Table 8-2: Concordance Within Pairs of Recurrently Depressed Parous Sisters for Narrowly Defined Postpartum Depression (PPD) and Broadly defined Postpartum Depression

	Narrow Definition of Postpartum Depression		Broad Definition of Postpartum Depression	
	Sib 2.		Sib 2.	
	No PPD	PPD	No PPD	PPD
No PPD	23	8	13	14
Sib 1.				
PPD	5	9[a]	5	13[b]

The narrow definition of postpartum depression included women with postpartum depression with onset within four weeks of delivery. The broad definition of postpartum depression included women with postpartum depression with onset within six months of delivery.

[a] Tetrachoric correlation coefficient = 0.55, p= 0.015, 95% CI 0.11-0.83

[b] Tetrachoric correlation coefficient = 0.24, p= 0.28, 95% CI 0- 0.63

Women differed in the number of children they had had, and therefore in the opportunity to experience an episode of postpartum depression. In order to take account of these differences, and to ensure that the familiality being demonstrated is not due merely to familial influences on parity, I have also analysed the concordance of postpartum episodes following the women's *first delivery* only. This analysis supports the familiality of narrowly defined postpartum depression (tetrachoric correlation coefficient = 0.62, p= 0.01, 95% CI 0.16-0.88).

Variation in the definition of postpartum onset

Given the difference in results between the narrow and broad definitions employed above I was interested to see how varying the definition of postpartum onset more widely influenced the evidence for familiality. Figure 8-1 demonstrates that in varying the definition between 1 week and 26 weeks the evidence for familiality maximised for a definition of postpartum onset in between 6 and 8 weeks.

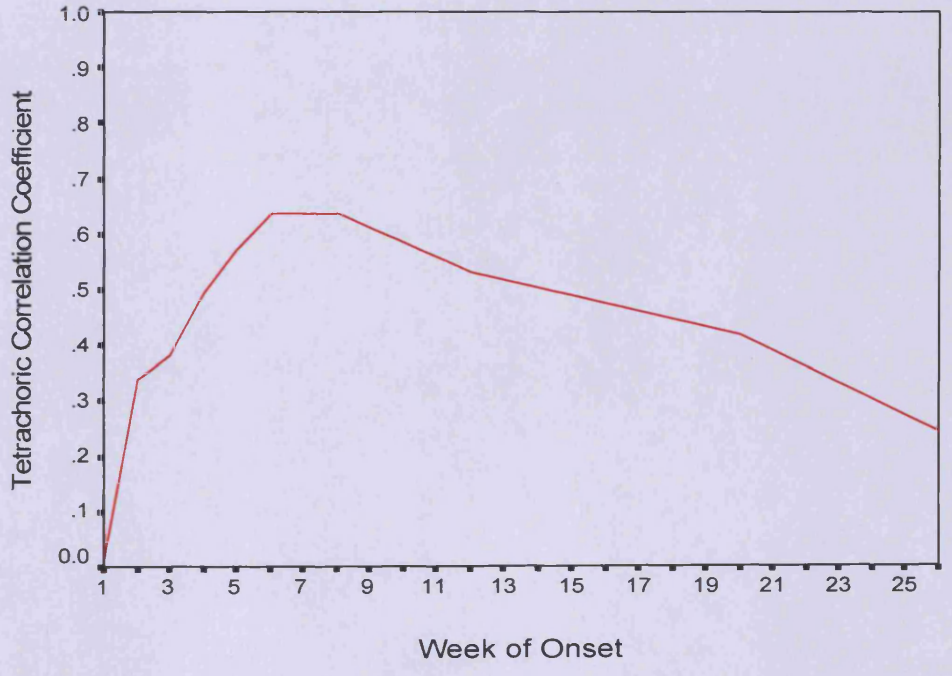


Figure 8-1: Tetrachoric Correlation Coefficient Depending on the Definition of Postpartum Onset Employed

Risk of postpartum depression per delivery

While the tetrachoric correlation coefficients reported above demonstrate the familiality of liability to narrowly defined postpartum depression, it may be of

clinical benefit to consider these results in terms of the risk of postpartum episodes per delivery.

Of the 90 parous women, 31 had a sister with a history of narrowly defined postpartum depression and 29% of all deliveries (42% of first deliveries) to these women were followed by an episode of postpartum depression. This compares to 12% of all deliveries (15% of first deliveries) to the 59 women whose sister had not suffered an episode of postpartum depression (see Figure 8-2).

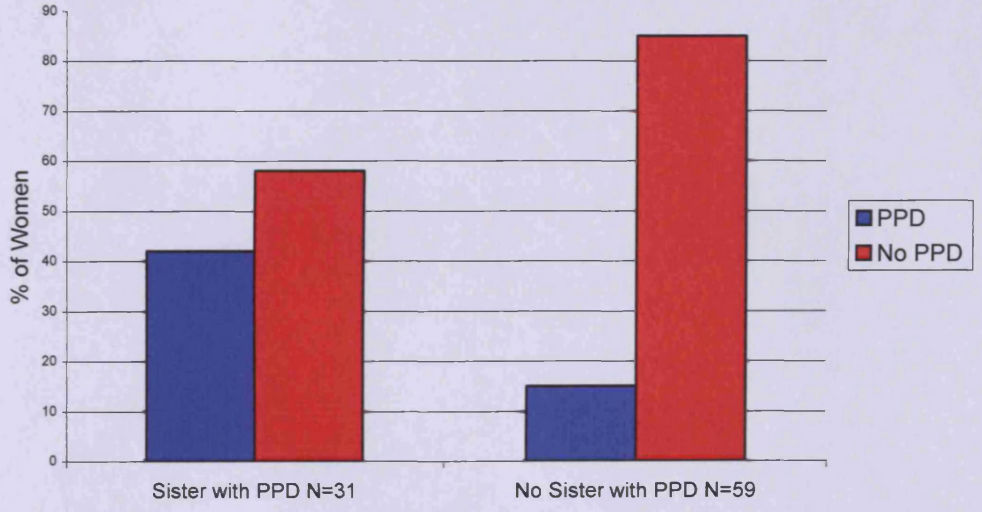


Figure 8-2: Rates of Narrowly Defined Postpartum Depression (PPD) Following First Deliveries to Women With and Without a Sister With Postpartum Depression

In those women who had a sister with a history of PPD, 42% of first deliveries were followed by an episode of PPD, compared to only 15% in women with no sister with a history of PPD.

8.5 Discussion

This study provides evidence for the familiality of postpartum depression, in a well-characterised sample of siblings with recurrent major depression. It adds to the evidence suggesting that a sub-group of women with major depression have a ***specific*** vulnerability to the triggering of episodes by childbirth. In addition, I have demonstrated that familiality is dependant on the definition of postpartum episode. The evidence for familial aggregation was significant for narrowly defined postpartum depression (onset within four weeks of delivery, corresponding to the postpartum onset specifier in DSM-IV) but not for a broader definition (onset within six months of delivery) that is perhaps more typical of the way the diagnosis is used as a lay term and applied in clinical practice. The evidence for familiality maximised with a definition of postpartum onset of six to eight weeks.

The results provide further support for the well-established finding that a history of major depression is an important risk factor for depression in the postpartum period. Of the sample of subjects diagnosed with recurrent major depression, narrowly defined postpartum depression followed 18% of deliveries and 26% of deliveries were followed by an episode of depression within 6 months. Comparisons with previous studies examining rates of postpartum depression in the general population are not straightforward due to very different methodology and definitions of episodes of illness. However, the rates reported here are higher than those described in O'Hara & Swain's (1996) meta-analysis and, furthermore, are likely to represent more severe episodes than those picked up by questionnaire measures alone.

That *family history* is an important risk factor for major depression is well established: the influence of family history on vulnerability to postpartum depression is much more controversial. Indeed, the meta-analysis of O'Hara and Swain did not support family history as a risk factor for depressive episodes at this time (O'Hara and Swain, 1996). What then, could account for the differences between this and previous studies? It is likely that there are substantial methodological differences including the definition of postpartum depression, the methods used to assess postpartum depression, and finally, the assessment of family history. In this study, episodes of depression (including postpartum depression) and family history were assessed by direct interview of subjects. Consensus diagnoses were made by at least two members of the research team and the sample consisted only of subjects who had suffered with recurrent major depression. In contrast, previous studies relying on questionnaire measures may have resulted in a more heterogeneous sample including single episode depressive disorder, minor depressive disorder and, with regard to onset, a wide definition of postpartum episode. In addition, I was asking a related, but slightly different, question to previous studies. While the question previously regarded whether a family history of depression increases risk for an episode of depression following childbirth, I have asked whether a family history of *postpartum* episodes influences vulnerability to postpartum episodes in women from families multiply affected with recurrent major depression.

The findings of this study have implications for clinical practice, nosology and research.

Clinical: Women with recurrent major depression with a family history of narrowly defined postpartum episodes are much more likely to experience a depressive episode following childbirth (42% of first deliveries), than those with no such family history (15% of first deliveries). Questions about postnatal episodes in first-degree relatives will therefore enable a more individualised risk assessment to be made for women with a history of major depression contemplating pregnancy.

Nosology: The definitions of postpartum onset in the classification systems are essentially arbitrary. Despite wide confidence intervals for the tetrachoric correlations under the various definitions of postpartum onset, this study suggests that neither a very broad nor restrictively narrow definition of postpartum onset is appropriate. These results provide some indication that the four week postpartum onset specifier in DSM-IV may be too narrow with familiality maximising for a six to eight week definition of postpartum onset.

Research: Postpartum depression remains an under-researched area, particularly with regard to studies focussing on the aetiology of episodes of depression occurring at this time. The results reported here suggest that a focus on postpartum triggering of episodes may be a productive strategy, informing us not only about postnatal episodes but having implications for the aetiology of affective disorders more generally. In addition, these results suggest that the definition of postpartum episode employed is important in

studies of the postnatal triggering of depression. Future work should concentrate on episodes with a close temporal relationship to childbirth.

The current study must be interpreted in the light of a number of limitations. First, the sample was not systematically ascertained, but rather was identified from various sources. It would be very difficult and expensive, however, to systematically recruit a similar number of parous female sibling pairs with recurrent major depression in a community sample.

Second, the sample was limited to those with a positive family history of depression and it is possible, although perhaps unlikely, that the results would not generalise to women with major depression unselected for family history. It is of note, however, that the women included here were recruited independently of their history of postpartum episodes which have not been reported to be either more or less common in women with a family history of depression. Further family studies examining postpartum episodes in women unselected for a family history of major depression would be of benefit, but would need to be considerably larger than the current study to have reasonable power to replicate the reported findings here.

Third, the assessments of postpartum depressions were made retrospectively, in some cases many years after the episode itself. Childbirth is a memorable event, however, occurring at most on only a few occasions in a woman's life. It is likely, therefore, that episodes of major depression occurring in close relationship to childbirth would be well remembered. In

addition, I was able to review contemporary case notes for one third of postpartum episodes and found excellent agreement with the woman's own account at interview. With regard to onset, for example, in only one case was there no information in the case note record enabling confirmation of the woman's account of the week of onset following delivery.

Finally, the study does not specify the cause of the apparent familiality, which may be due to either common (shared) environment, genetic factors or - perhaps most likely - a combination of both. The study of Treloar and colleagues (1999) found a moderate heritability for postpartum symptoms of depression but assessments of postpartum symptoms in this study were not ideal. Further twin studies employing more robust assessments of narrowly defined postnatal depression would be beneficial. Given the compelling evidence for the influence of genes in vulnerability to major depression (Sullivan et al., 2000), however, it is plausible that genetic factors play a role in determining an individual's susceptibility to depression in the postpartum period. Molecular genetic studies focussing on women who have experienced narrowly defined postpartum depression may therefore prove productive in identifying genetic variants that increase vulnerability to the puerperal triggering of episodes.

These results suggest that familial factors play a role in determining vulnerability to narrowly defined postpartum depression, but have either less or no effect in determining vulnerability to postpartum depressive episodes defined more widely.

If replicated, this narrowly defined subgroup provides a more homogenous sample in which to investigate the aetiological basis of postpartum depression. A greater understanding of the causes of postpartum depression will facilitate advances in the prevention and treatment of perinatal affective episodes, with obvious benefits to mother and child, and may also provide important clues into the aetiology of mood disorders in general.

9 Family Study of Life Events Preceding Depressive Episodes in Recurrent Major Depressive Disorder

9.1 Summary

Occurrence of stressful life events is associated with the onset of major depressive episodes, particularly early episodes.

In 120 sibling pairs affected by recurrent major depression I tested for a familial contribution to the reporting of life events in the six month periods prior to the first, and the worst episodes of depression.

I found no significant evidence for the familiality of reporting of life events for the two time periods studied in this sample. With a sample size of 120 sibling pairs, this study has 80% power to detect heritability of 0.5, but for lower heritabilities power is reduced.

These findings do not support a large familial (nor genetic) contribution to susceptibility to reporting life events in familial recurrent depression, however, larger studies will be needed to rule out more modest levels of familiality.

9.2 Introduction

There is a clear association between the occurrence of stressful life events and the onset of a major depressive episode, with the strength of association progressively decreasing as the number of episodes experienced by an individual increases (Paykel, 1978). The cause of individual variation in susceptibility to precipitation of depression by life events is not clear. A greater understanding of this relationship will facilitate advances in prevention and treatment. Here I have examined whether there may be a familial (perhaps genetic) contribution to this individual variation by estimating, in a sample of sibling pairs with recurrent major depression, the familiality of reporting of life events for six month periods prior to the onset (i.e. first) episode of depression and the worst ever episode of depression. I hypothesised that any evidence for familiality would be most obvious in relation to events occurring earlier rather than later in the course of illness.

9.3 Method

9.3.1 Subjects

See chapter 2 for further methodological details. Subjects (N=240) consisted of 120 sibling pairs, from 120 families, recruited at the Birmingham site of the DeNT study of unipolar depression.

9.3.2 Assessment

The Brief Life Events Questionnaire (BLEQ) (Brugha et al., 1985, Brugha and Cragg, 1990, Farmer et al., 2000) (see appendix I) was used to ask about the occurrence and impact of twelve threatening life events. The impact of the event was rated as *very distressing* (score 3), *moderately distressing* (score 2), or *not very distressing* (score 1) and a summated score produced. The time frames investigated were the six month periods prior to (a) the *first ever episode* of depression (FD) and (b) the *worst ever episode* of depression (WD).

The BLEQ for the WD time period was completed by the subject at the end of the research interview. After agreeing with the subject on the time period for the BLEQ FD, the questionnaire was then left in the questionnaire pack (described in chapter 2) for the subject to complete (due to time constraints). As previous research assessing the familiality of life events has not included childbirth as a life event, the twelfth item of the BLEQ concerning the occurrence of childbirth was excluded from the current analyses, enabling more straightforward comparison between this and previous studies. Hence, all analyses were based on the remaining 11 BLEQ items.

9.3.3 Statistical Analysis

A maximum likelihood variance components method (SOLAR) (Almasy and Blangero, 1998) was used to assess familiality in the sibling pairs for total BLEQ scores for each of the time periods. Since the data were non-normal, this familiality estimate was obtained assuming a t-distribution for the

likelihood. This estimate of familiality includes genetic and/ or shared environmental factors.

As previous findings have indicated a need to control for "shared events" (i.e. stressful life events shared by both members of a sibling pair, such as the death of a parent), (Farmer et al., 2000), the current analysis included occurrence of "shared events" for the particular time period as a covariate.

9.4 Results

Twenty-two (18.3%) probands were recruited through local Mental Health Services and the remainder through media advertisements. One hundred and seventy-one subjects (71%) were female. The number of subjects who completed each questionnaire was as follows: BLEQ FD, N= 181 (75%); BLEQ WD, N= 236 (98.3%).

Familiality estimates for logarithmically transformed BLEQ scores, including shared events as a covariate, are shown in Table 9-1. Neither of the estimates differed significantly from zero.

Table 9-1: Familiality Estimates for the Reporting of Life Events in Siblings with a Diagnosis of Recurrent Major Depression, Including Shared Events as a Covariate

Brief Life Events Questionnaire (BLEQ) for the six month period prior to the:	N	Familiality Estimate	p-value
First ever episode of depression (FD) with shared events covariate	181	0.00	0.5
Worst ever episode of depression (WD) with shared events covariate	236	0.08	0.35

"Familiality" refers to both genetic factors and environmental factors that are shared by members of a family. The estimate of familiality reflects the estimated contribution of familial factors to the variation of life events observed in this dataset. A value of 0.00 indicates no contribution of familial factors. A value of 1.00 indicates that all variation can be explained by familial factors.

There were some subjects for whom the worst ever episode of depression was also the onset (first) episode of depression. As these subjects were rating the same episode I performed the analyses on the sample removing these individuals. The results were similar to those for the entire sample, and were not significant.

9.5 Discussion

I found no significant evidence for familiality of life events for the six month periods prior to either the onset (i.e. first) episode of depression or the worst ever episode of depression. These findings suggest that neither genetic nor shared environmental factors play a major role in the susceptibility to life events directly preceding depressive episodes in individuals with familial, recurrent depression.

An important strength of this study is that I have examined the familiality of life events in relation to the onset and worst episodes of depression rather than a current episode. This is the first study to do this. Given that life events appear to have a bigger role in the earlier episodes of depression that an individual experiences, the focus on first episodes should optimize the chances of identifying pathogenetically relevant familiality. A further strength is that I have taken account of shared life events as a covariate because this has been shown to inflate estimates of familiality in studies of current depressive episodes (Farmer et al., 2000).

It is important to recognise that the findings relate to proximal life events, i.e. life events that occur in close temporal relationship to the onset of depressive episodes. I have not addressed the issue of life events occurring at other times, for example, during childhood, which may be better considered as predisposing, rather than precipitating, factors for illness.

It is also possible, that the failure of the current study to illustrate familiality for the reporting of life events occurring prior to the onset episode or worst ever episode of depression may have resulted from the use of retrospective assessment methods to establish the presence of such events. However, the questionnaire asks about *major* life events, most of which in the current study were reported to have had at least a moderate impact on the subject. Further, the List of Threatening Experiences has been shown to have high test-retest reliability and good agreement with informant information (Brugha and Cragg, 1990).

Although the current sample is of comparable size to those of previous studies that have found significant evidence for familiality of current life events, a second limitation of this study is sample size. With a sample size of 120 sibling pairs, the current study has 80% power to detect a heritability of 0.5. For lower heritabilities the power is reduced.

In conclusion, these results do not support the existence of strong familial factors (genetic or shared environmental factors) that influence susceptibility to life events in subjects with familial, recurrent major depression. I can confidently rule out large effects but larger studies will be needed to rule out more modest levels of familiality. The ideal designs would be large, prospective and include twins as well as siblings.

10 General Discussion

10.1 Summary of Main Findings

Affective disorders are both clinically highly heterogeneous and multi-factorial in their aetiology. Phenotypic definition has become more sophisticated in studies investigating the causes of affective disorders with the aim of identifying more homogeneous disorders that may be more similar in terms of aetiology.

The overall aim of this thesis was to refine phenotype definition in affective disorders through the identification of sub-phenotypes that may be biologically validated by future molecular genetic studies. This involved the examination of various aspects of the phenotype in well defined and characterised samples of subjects with affective disorders. Table 10.1 provides a summary of the main findings of my studies.

Table 10-1: Summary of Main Findings of Studies Described Within this Thesis

Chapter Number and Title	Main Findings
3. Polarity at Illness Onset in Bipolar I Disorder and Clinical Course of Illness	In subjects with a diagnosis of bipolar I disorder, a depressive episode at illness onset is associated with a more "depressive" lifetime course of illness, with more frequent and severe depressive episodes and a predominantly depressive polarity. A depressive pole at illness onset is also associated with an earlier age at illness onset and less prominent psychotic features during the lifetime.
4. Clinical Differences Between Bipolar and Unipolar Depression	Clinical characteristics associated with a bipolar course, rather than a unipolar course of illness, include the presence of psychosis; diurnal mood variation and hypersomnia during depressive episodes; and a greater number of shorter depressive episodes.
5. Identifying Hypomanic Features in Major Depressive Disorder using the Hypomania Checklist (HCL-32)	A substantial minority of subjects (17%) meeting DSMIV criteria for recurrent major depression (even when selected to exclude personal and family histories of bipolar illness) report bipolar symptoms at a level similar to that reported by subjects meeting diagnostic criteria for bipolar disorder.
6. Clinical Characteristics of Unipolar Disorder and Bipolar Disorder According to the Lifetime Presence of Recurrent Panic Attacks	Subjects, with a diagnosis of bipolar disorder or unipolar disorder, with a history of panic attacks i) have more frequent and severe depressive episodes and ii) are more likely to have experienced suicidal ideation and slowed activity during depressive episodes in their lifetime, compared to those with no history of panic attacks. Subjects with bipolar disorder and a history of recurrent panic attacks are also more likely to have i) a family history of affective disorder, ii) more severe impairment during their worst ever episode of depression, iii) attempted suicide during their lifetime, and iv) experienced diurnal morning variation, insomnia and agitated activity during depressive episodes during their lifetime, compared to subjects in the bipolar sample with no history of panic attacks. These differences were not seen between the unipolar groups with and without a history of panic attacks.
7. Is Depression Severity the Sole Cause of Psychotic Symptoms During an Episode of Unipolar Major Depression? A Study Both Between and Within Subjects	Within subjects with unipolar depression, psychotic episodes tend to be more severe than non-psychotic episodes. However, between subjects with unipolar depression there is wide variation in severity in both those that did, and did not, experience psychotic episodes.
8. Familiality of Postpartum Depression in Unipolar Disorder: Results of a Family Study	In women with recurrent major depression, episodes of post-partum depression with an onset of within four weeks following childbirth, appear to aggregate in families. The evidence for familiality is maximised with a definition of postpartum onset of between six to eight weeks.
9. Family Study of Life Events Preceding Depressive Episodes in Recurrent Unipolar Major Depression	I found no significant evidence for familiality of reporting of life events in the six month periods prior to the first, or the worst episodes of depression. These findings do not support a large familial (nor genetic) contribution to susceptibility to reporting life events in familial recurrent depression, however larger studies will be needed to rule out more modest levels of familiality.

Each chapter has included a discussion of specific issues relating to the particular study. This final discussion chapter will focus on more general issues.

10.2 Methodological Strengths and Limitations

The main strength of these studies is the use of large well characterized samples of subjects recruited from within the same geographical regions from within the UK and assessed using the same standardized, rigorous and robust clinical assessment methods.

Most of the studies within this thesis focused on samples including at least 500 subjects. With this sample size, at the $p<0.05$ significance level, these studies have 93% power to detect small effect sizes, and over 99% power to detect medium or large effect sizes when using an independent t-test (two-tailed). When using a chi-square test (2x2 table, 1 degree of freedom) these studies would have 61% power to detect small effect sizes and over 99% power to detect medium or large effect sizes (Cohen, 1988).

The clinical homogeneity of the samples employed can also be seen as a major strength of the studies included in this thesis. As samples were recruited as part of ongoing molecular genetic studies, subjects included in the unipolar and bipolar samples had to meet strict inclusion and exclusion criteria. As previously discussed, heterogeneity in mood disorders is a factor that is likely to hinder the identification of aetiological factors that contribute to susceptibility to these illnesses. By focusing on narrowly defined unipolar and

bipolar samples, this heterogeneity has been reduced. It is also important to note that this homogeneity could also be seen as a limitation in some of these studies as the samples may not be representative of all populations. When considering the generalisability of the findings of these studies it is also necessary to take into account i) the high proportion of females in the bipolar sample ii) the ethnicity of the samples (UK/ Eire White), and iii) the use of systematic and non-systematic methods of recruitment. I will now consider these points individually.

i) The proportion of females in the unipolar sample was as would be expected for studies of this nature with about two-thirds of the sample being female. This reflects firstly, the well established prevalence rates for unipolar depression indicating that women are at least twice as likely as men to experience depression during their lifetime (Kessler et al., 1994, Klerman and Weissman, 1989); and secondly, the bias often seen in studies of this nature in women being more likely than men to agree to participate. The prevalence rates for bipolar disorder have generally been shown to be similar for males and females (Mitchell et al., 2004, Goodwin and Jamison, 2007), although some studies have shown differences in the course of illness between males and females with bipolar disorder (Arnold, 2003, Kennedy et al., 2005). However, in my bipolar sample the proportion of females was greater than for males, again with around seventy percent of the sample being female. As in the unipolar sample, a bias towards women being more likely to agree to participate may partially explain the large proportion of female subjects in the sample. An additional explanation for this may be related to the research

group's focus on episodes of mood illness in relation to childbirth. This may have resulted in larger numbers of females with bipolar disorder being recruited to the studies. The greater number of females in my bipolar sample than would be expected for a study of this nature should be taken into account when considering the generalisability of the findings.

ii) As subjects were recruited as part of ongoing molecular genetic studies they were required to be of UK/ Eire white ethnicity. When studying the genetic risk factors involved in complex diseases, restricting ascertainment to a single ethnic/ racial group is important in order to reduce heterogeneity and thereby minimize the likelihood of false positives caused by differences in the genetic background of participants. However, the use of this inclusion criterion could potentially limit the generalisability of my findings.

iii) In order to obtain large sample sizes both systematic and non-systematic methods of ascertainment were used to recruit potential research subjects. It is possible that this may have introduced a recruitment bias. However, in analyses where I thought this may be a potential source of bias, I included method of recruitment as a covariate.

In chapters 5 and 6 it is possible that there may have been a response bias in terms of which subjects completed and returned the 2007 questionnaire pack. The time period between the initial research interview and the questionnaire mail-out varied between subjects and non-response, to the request to complete the questionnaires, was significantly associated with a longer

duration between the initial interview and the questionnaire mail-out. Although there were some differences in clinical characteristics between responders and non responders, for example, in age at interview, diagnosis, and BADDS scores, none of these remained statistically significant when taking into account the duration of the interval between the research interview and the questionnaire mail-out.

A limitation that has been consistently mentioned throughout this thesis relates to the retrospective assessment methods that were used. However, as I have also mentioned, I consistently found good agreement between the information obtained from subjects during the in depth semi-structured interviews and the information obtained from the case note reviews. The use of retrospective assessment methods allowed the greatest insight into the overall lifetime course of illness in these subjects with affective disorder diagnoses and was also a cost effective method of study.

Related to the use of retrospective measures, is the limitation that medication use could not be assessed effectively in these samples. It may be that some of the variables that I have considered in these chapters could have been influenced by the use of particular medication regimes, for example, the increased use of mood stabilising medication in subjects with bipolar disorder, compared to subjects with unipolar disorder.

For many of the studies included in this thesis, it would have been interesting to examine the variables of interest in samples of subjects with a diagnosis of

bipolar II disorder. However, as the molecular genetic studies have focused on subjects with a diagnosis of bipolar I disorder, the sample size of patients with bipolar II disorder (N=57) was small. Although this sample would have 99% power to detect large effects, at the $p<0.05$ significance level, power would be reduced to 73% for moderate effects and 18% for small effects when using an independent t-test (two-tailed). When using a chi-square test (2x2 table, 1 degree of freedom, $p<0.05$), this sample when compared to a sample of similar size, would have over 99% power to detect large effects, 91% for moderate effects, and only 19% for small effects (Cohen, 1988).

10.3 Future Directions

Large samples of individuals with affective disorders are continuing to be assembled. The results of the studies in this thesis highlight the importance of collecting detailed phenotypic data in such studies aimed at investigating the aetiology of these disorders. Focusing on diagnostic groups using current classification systems may not be adequate in studies aimed at identifying the multiple factors contributing to susceptibility for these illnesses.

The studies described in chapters 3, 5 and 7 also highlight the need for the use of more dimensional measures of the phenotype, rather than solely focusing on the simple categorical distinctions that are traditionally used.

As many of the studies in this thesis have been exploratory in nature (and no correction has been made for multiple testing) it will be important to replicate these findings in large independent, well characterized samples.

10.3.1 Potential sub-phenotypes for use in molecular genetic studies

The main aim of this thesis was to identify sub-phenotypes that may be biologically validated by future molecular genetic studies. Of the sub-phenotypes investigated in this thesis, there are four that I feel will be of benefit in such studies. I will now discuss these, in order, according to those that I feel most confident will be of utility in future genetic studies.

i) Familial post-partum depression in subjects with a diagnosis of major recurrent depression

In chapter 8, I found strong evidence for the familial aggregation of vulnerability to narrowly defined episodes of post-partum depression. This familial aggregation maximised with an onset of between six to eight weeks following childbirth. Familial vulnerability to postpartum episodes in women with bipolar disorder has previously been shown (Jones and Craddock, 2001b), but the study presented in chapter 8 is the first to focus on the familiality of post-partum depression in unipolar disorder. In samples of individuals with bipolar disorder, further studies have identified chromosomal regions that are likely to harbour genes that predispose individuals to affective puerperal psychosis. A genome-wide significant linkage signal was observed on chromosome 16p13, and a genome-wide suggestive linkage was observed on chromosome 8q24 (Jones et al., 2007). Additionally, candidate gene studies of women with puerperal psychosis have shown suggestive, although preliminary, evidence for an association between puerperal psychosis and a variant at the serotonin transporter gene on chromosome 17 (Coyle et al.,

2000). These previous findings illustrate the potential benefits of focusing on clinical sub-types of affective disorder in molecular genetic studies. Focusing on women with bipolar disorder who have experienced postpartum episodes has facilitated genetic studies of bipolar disorder. Future studies aimed at identifying genes and genomic regions that may be implicated in susceptibility to post-partum depression, and affective disorders more generally, could refine the phenotype by focusing on families where at least one member has experienced an episode of narrowly defined post-partum depression.

ii) Polarity at illness onset in subjects with a diagnosis of bipolar I disorder

Another clinical sub-type investigated in this thesis was defined according to the polarity of the onset episode of illness (chapter 3). Previous studies have suggested that polarity at illness onset is a familial feature of bipolar affective disorder (Kassem et al., 2006) and is associated with important clinical indicators which may help define more homogeneous subtypes of bipolar affective disorder. In support of this, I found that certain clinical characteristics were associated with a depressive pole at illness onset. In addition, I assessed the severity and impairment associated with mood episodes and found that in those subjects with a depressive pole at illness onset, the impairment associated with, and severity of, depressive episodes was increased when compared to those participants with a manic pole at onset. These sub-groups of subjects defined according to polarity at illness onset, who share clinical characteristics of illness may also share aetiological factors in common. Kassem et al (2006), as a preliminary test of genetic validity,

assessed the impact of polarity at onset on genetic linkage findings previously detected in their sample. They found that mania at onset substantially increased the genetic linkage signal on chromosome 16p but had no effect on linkage to chromosome 6q. Further large scale molecular genetic studies that take into account polarity at illness onset are required.

When considering these findings it is of interest that two sub-types of bipolar affective disorder, the first identified through a vulnerability to post-partum manic/ psychotic episodes and the second identified according to the polarity of the onset episode of illness, identified a linkage region of interest on chromosome 16p. These studies could potentially be identifying the same region and it is possible that they may be indexing the same underlying pathogenesis. It is also possible that this chromosome may harbour two or more vulnerability genes for various forms of bipolar disorder.

iii) Comorbid recurrent panic attacks in subjects with a diagnosis of bipolar I disorder or major recurrent depression

Studies have indicated that although bipolar disorder comorbid with panic disorder appears to aggregate in families (MacKinnon et al., 2002, Rotondo et al., 2002), unipolar disorder comorbid with panic disorder does not appear to represent a distinct subtype in terms of familial aggregation (Maier et al., 1995b, Weissman et al., 1993).

Although I did not assess the familial aggregation of panic disorder or recurrent panic attacks in my samples, I did find important clinical differences

between subjects with and without a lifetime history of recurrent panic attacks (chapter 6). Both unipolar and bipolar subjects with a history of recurrent panic attacks reported increased morbidity associated with depression, in that they reported more severe and more frequent depressive episodes and more suicidal ideation and slowed activity during depressive episodes. To the best of my knowledge, this is the first such study to include both subjects with unipolar disorder and bipolar disorder, where all subjects were assessed using robust, consistent methodologies.

Interestingly, in addition to the findings that were shared across the unipolar and bipolar samples, I also found additional clinical features that appeared to distinguish between subjects with and without a history of panic attacks in the bipolar sample but not in the unipolar sample. For example, subjects with a diagnosis of bipolar disorder and a history of recurrent panic attacks were more likely to have a family history of affective disorder, more severe impairment during the worst ever episode of depression, attempted suicide during their lifetime, and to have experienced diurnal morning variation, insomnia and agitated activity during depressive episodes during their lifetime.

Thus it appears that the presence of comorbid panic disorder may also identify a potentially useful sub-type for future studies investigating the aetiology of affective disorders, in particular bipolar disorder.

iv) Psychotic features in subjects with a diagnosis of major recurrent depression

The findings presented in chapter 7 suggest that in subjects who have a predisposition (biological and/ or psychosocial) to experience psychosis, psychotic features tend to emerge in their more severe depressive episodes. However, the data also illustrate how severity *alone* cannot account for the presence of psychotic features, as non-psychotic depressive episodes in subjects with no personal history of psychosis may be as severe as, or more severe than, those seen in subjects with psychotic depression.

This study found individual variation in susceptibility to psychosis during depressive episodes with psychosis being more likely to be experienced during the more severe episodes, in those individuals with increased susceptibility. However, I have not assessed the familiality of psychotic unipolar depression. The familiality of psychotic features in bipolar disorder is well established (Schulze et al., 2006, Saunders et al., 2007). Although some previous studies have found that subjects with psychotic major depression had an increased risk of family prevalence of unipolar major depression (Leckman et al., 1984, Nelson et al., 1984), and bipolar disorder, (Weissman et al., 1984b, Leckman et al., 1984), others have found that family history of unipolar depression was similar between subjects with major depression, with and without psychotic features (Coryell and Tsuang, 1982). To date, no study has examined the familiality of psychosis in siblings or families of unipolar probands. Further studies, involving systematic gathering of family data for unipolar major depression, are required in order to determine the familiality of

psychotic unipolar depression and to better understand genetic influences. The use of dimensional measures as well as binary distinctions would be beneficial.

10.3.2 Potential sub-phenotypes that may be of use in clinical terms

I will now consider three of the sub-phenotypes described in this thesis which I feel could potentially be of clinical importance. Again, I will describe the sub-phenotypes, in order, according to those that I feel would be of most use in clinical terms.

i) Polarity at illness onset in subjects with a diagnosis of bipolar I disorder

The findings in chapter 3 relating to the significance of the polarity of the onset episode of illness are of potential clinical importance. Once a patient has experienced his/ her first manic episode, the clinician can use knowledge of polarity of the illness onset as an indicator of the likely predominant pole of illness. This may be helpful in providing information and advice to the patient. This applies to the situation where a patient has experienced their first manic episode and, hence, a diagnosis of bipolar disorder can be made.

ii) Clinical characteristics of depression in subjects with a diagnosis of bipolar I disorder or major recurrent depression

Studies have suggested that there are differences in the clinical characteristics of depressive episodes in subjects with unipolar and bipolar disorder (Bowden, 2005, Mitchell et al., 1992, Mitchell et al., 2008) and my

findings in chapter 4 support previous findings in this large well characterised sample. Clinical characteristics associated with a bipolar course included the presence of psychosis; diurnal mood variation and hypersomnia during depressive episodes; and a greater number of shorter depressive episodes. Such differences could potentially be of use in increasing clinical suspicion of bipolar disorder in patients who experience a depressive episode without having experienced a prior manic episode.

iii) Hypomanic features in subjects with a diagnosis of major recurrent depression

My findings in chapter 5 highlighted an overlap in manic/ hypomanic symptoms across bipolar and unipolar diagnostic groups, challenging the traditional simple unipolar/ bipolar categorical divide. These findings illustrate the difficulties inherent in allocating subjects to a particular diagnostic group and suggest the need for dimensional measures of manic/ hypomanic symptoms across patients with mood disorder diagnoses in order to optimise treatment. For example, it may be that patients with unipolar disorder who score highly on a measure of lifetime hypomanic symptoms may respond less favourably to antidepressants, although this has yet to be proven. Future studies assessing treatment response across mood disorder diagnoses may benefit from such dimensional measures.

10.4 Final Conclusions

Affective disorders are relatively common and highly morbid. These illnesses can cause a great deal of suffering and, although there are treatments such

as medication and psychotherapy that may be helpful to some people, there are a large number of individuals who do not respond adequately or who suffer adverse effects from treatment.

Research investigating the aetiology of affective disorders will increase public awareness of these disorders, and hopefully help in reducing the stigma associated with mental illness. Such research will also increase our understanding about the causes of these illnesses and the complex interplay between genes and environment. This knowledge may facilitate the development of improved preventative strategies aimed at reducing the risk of mood episodes, as well as improving treatment regimes, both pharmacological and psychological.

The studies in this thesis demonstrate the complexity of the mood disorders phenotype and illustrate how if future studies are to understand the aetiology of these disorders it will be necessary to dissect the heterogeneity within the mood disorders phenotype. The findings of these studies provide examples of ways in which the phenotype may be usefully dissected.

References

ABKEVICH, V., CAMP, N. J., HENSEL, C. H., NEFF, C. D., RUSSELL, D. L., HUGHES, D. C., PLENK, A. M., LOWRY, M. R., RICHARDS, R. L., CARTER, C., FRECH, G. C., STONE, S., ROWE, K., CHAU, C. A., CORTADO, K., HUNT, A., LUCE, K., O'NEIL, G., POARCH, J., POTTER, J., POULSEN, G. H., SAXTON, H., BERNAT-SESTAK, M., THOMPSON, V., GUTIN, A., SKOLNICK, M. H., SHATTUCK, D. & CANNON-ALBRIGHT, L. (2003) Predisposition locus for major depression at chromosome 12q22-12q23.2. *Am J Hum Genet,* 73, 1271-81.

AGRAWAL, A., JACOBSON, K. C., GARDNER, C. O., PRESCOTT, C. A. & KENDLER, K. S. (2004) A population based twin study of sex differences in depressive symptoms. *Twin Res,* 7, 176-81.

AKISKAL, H. S. (2003) Validating 'hard' and 'soft' phenotypes within the bipolar spectrum: continuity or discontinuity? *J Affect Disord,* 73, 1-5.

ALLEN, M. G., COHEN, S., POLLIN, W. & GREENSPAN, S. I. (1974) Affective illness in veteran twins: a diagnostic review. *Am J Psychiatry,* 131, 1234-9.

ALMASY, L. & BLANGERO, J. (1998) Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet,* 62, 1198-211.

ALTMAN, E. G., HEDEKER, D., PETERSON, J. L. & DAVIS, J. M. (1997) The Altman Self-Rating Mania Scale. *Biol Psychiatry,* 42, 948-55.

ANGST, J. (1966) [On the etiology and nosology of endogenous depressive psychoses. A genetic, sociologic and clinical study]. *Monogr Gesamtgeb Neurol Psychiatr,* 112, 1-118.

ANGST, J. (2007) The bipolar spectrum. *Br J Psychiatry,* 190, 189-91.

ANGST, J., ADOLFSSON, R., BENAZZI, F., GAMMA, A., HANTOUCHE, E., MEYER, T. D., SKEPPAR, P., VIETA, E. & SCOTT, J. (2005a) The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord,* 88, 217-33.

ANGST, J., GAMMA, A., BENAZZI, F., AJDACIC, V., EICH, D. & ROSSLER, W. (2003) Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord,* 73, 133-46.

ANGST, J., SELLARO, R., STASSEN, H. H. & GAMMA, A. (2005b) Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord,* 84, 149-57.

ANGUELOVA, M., BENKELFAT, C. & TURECKI, G. (2003) A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders. *Mol Psychiatry,* 8, 574-91.

APA (2000) Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) Washington, DC American Psychiatric Association (APA).

ARNOLD, L. M. (2003) Gender differences in bipolar disorder. *Psychiatr Clin North Am,* 26, 595-620.

BADNER, J. A. & GERSHON, E. S. (2002) Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry,* 7, 405-11.

BECK, A. & STEER, R. (1987) *The Beck Depression Inventory,* San Antonio, TX, Harcourt Brace.
BECK, A. T., WEISSMAN, A., LESTER, D. & TREXLER, L. (1974) The measurement of pessimism: the hopelessness scale. *J Consult Clin Psychol,* 42, 861-5.
BERTELSEN, A., HARVALD, B. & HAUGE, M. (1977) A Danish twin study of manic-depressive disorders. *Br J Psychiatry,* 130, 330-51.
BIERUT, L. J., HEATH, A. C., BUCHOLZ, K. K., DINWIDDIE, S. H., MADDEN, P. A., STATHAM, D. J., DUNNE, M. P. & MARTIN, N. G. (1999) Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women? *Arch Gen Psychiatry,* 56, 557-63.
BLACKER, D. & TSUANG, M. T. (1993) Unipolar relatives in bipolar pedigrees: are they bipolar? *Psychiatr Genet,* 3, 5-16.
BLOCH, M., SCHMIDT, P. J., DANACEAU, M., MURPHY, J., NIEMAN, L. & RUBINOW, D. R. (2000) Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry,* 157, 924-30.
BOWDEN, C. L. (2005) A different depression: clinical distinctions between bipolar and unipolar depression. *J Affect Disord,* 84, 117-25.
BRESLAU, N., DAVIS, G. C., ANDRESKI, P. & PETERSON, E. (1991) Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch Gen Psychiatry,* 48, 216-22.
BRESLAU, N. & MELTZER, H. Y. (1988) Validity of subtyping psychotic depression: examination of phenomenology and demographic characteristics. *Am J Psychiatry,* 145, 35-40.
BROWN, C., SCHULBERG, H. C., MADONIA, M. J., SHEAR, M. K. & HOUCK, P. R. (1996) Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. *Am J Psychiatry,* 153, 1293-300.
BRUGHA, T., BEBBINGTON, P., TENNANT, C. & HURRY, J. (1985) The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med,* 15, 189-94.
BRUGHA, T. S. & CRAGG, D. (1990) The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatr Scand,* 82, 77-81.
CAMP, N. J., LOWRY, M. R., RICHARDS, R. L., PLENK, A. M., CARTER, C., HENSEL, C. H., ABKEVICH, V., SKOLNICK, M. H., SHATTUCK, D., ROWE, K. G., HUGHES, D. C. & CANNON-ALBRIGHT, L. A. (2005) Genome-wide linkage analyses of extended Utah pedigrees identifies loci that influence recurrent, early-onset major depression and anxiety disorders. *Am J Med Genet B Neuropsychiatr Genet,* 135, 85-93.
CARDNO, A. G., MARSHALL, E. J., COID, B., MACDONALD, A. M., RIBCHESTER, T. R., DAVIES, N. J., VENTURI, P., JONES, L. A., LEWIS, S. W., SHAM, P. C., GOTTESMAN, II, FARMER, A. E., MCGUFFIN, P., REVELEY, A. M. & MURRAY, R. M. (1999) Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch Gen Psychiatry,* 56, 162-8.
CARDNO, A. G., RIJSDIJK, F. V., SHAM, P. C., MURRAY, R. M. & MCGUFFIN, P. (2002) A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry,* 159, 539-45.

CASPI, A., SUGDEN, K., MOFFITT, T. E., TAYLOR, A., CRAIG, I. W., HARRINGTON, H., MCCLAY, J., MILL, J., MARTIN, J., BRAITHWAITE, A. & POULTON, R. (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science,* 301, 386-9.

CASSANO, G. B., RUCCI, P., FRANK, E., FAGIOLINI, A., DELL'OSSO, L., SHEAR, M. K. & KUPFER, D. J. (2004) The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. *Am J Psychiatry,* 161, 1264-9.

CHARNEY, D. S., BARLOW, D. H., BOTTERON, K., COHEN, J. D., GOLDMAN, D. & GUR, R. E. (2002) Neuroscience research agenda to guide development of a pathophysiologically based classification system. IN KUPFER, D. J., FIRST, M. B. & REGIER, D. A. (Eds.) *A research agenda for DSM-V.* Washington, DC, American Psychiatric Association.

CHEN, Y. S., AKULA, N., DETERA-WADLEIGH, S. D., SCHULZE, T. G., THOMAS, J., POTASH, J. B., DEPAULO, J. R., MCINNIS, M. G., COX, N. J. & MCMAHON, F. J. (2004) Findings in an independent sample support an association between bipolar affective disorder and the G72/G30 locus on chromosome 13q33. *Mol Psychiatry,* 9, 87-92; image 5.

CHEN, Y. W. & DILSAVER, S. C. (1995) Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. *Am J Psychiatry,* 152, 280-2.

COHEN, J. (1960) A coefficient of agreement for nominal scales. *Educational and Psychological Measurement,* 20, 37-46.

COHEN, J. (1988) *Statistical Power Analysis for the Behavioral Sciences,* New Jersey, Lawrence Erlbaum Associates.

COOPER, P. J. & MURRAY, L. (1995) Course and recurrence of postnatal depression. Evidence for the specificity of the diagnostic concept. *Br J Psychiatry,* 166, 191-5.

CORYELL, W., ENDICOTT, J., KELLER, M. & ANDREASEN, N. C. (1985) Phenomenology and family history in DSM-III psychotic depression. *J Affect Disord,* 9, 13-8.

CORYELL, W., ENDICOTT, J., MASER, J., D , KELLER, M., B, LEON, A., C & AKISKAL, H., S (1995) Long-term stability of polarity distinctions in the affective disorders. *American Journal of Psychiatry,* 152, 385-390.

CORYELL, W., LEON, A., WINOKUR, G., ENDICOTT, J., KELLER, M., AKISKAL, H. & SOLOMON, D. (1996) Importance of psychotic features to long-term course in major depressive disorder. *Am J Psychiatry,* 153, 483-9.

CORYELL, W. & TSUANG, M. T. (1982) Primary unipolar depression and the prognostic importance of delusions. *Arch Gen Psychiatry,* 39, 1181-4.

COYLE, N., JONES, I., ROBERTSON, E., LENDON, C. & CRADDOCK, N. (2000) Variation at the serotonin transporter gene influences susceptibility to bipolar affective puerperal psychosis. *Lancet,* 356, 1490-1.

CRADDOCK, M., ASHERSON, P., OWEN, M. J., WILLIAMS, J., MCGUFFIN, P. & FARMER, A. E. (1996) Concurrent validity of the OPCRIT

diagnostic system. Comparison of OPCRIT diagnoses with consensus best-estimate lifetime diagnoses. *Br J Psychiatry,* 169, 58-63.
CRADDOCK, N. & JONES, I. (2001) Molecular genetics of bipolar disorder. *Br J Psychiatry Suppl,* 41, s128-33.
CRADDOCK, N., JONES, I., KIROV, G. & JONES, L. (2004) The Bipolar Affective Disorder Dimension Scale (BADDS)--a dimensional scale for rating lifetime psychopathology in bipolar spectrum disorders. *BMC Psychiatry,* 4, 19.
CRADDOCK, N., KHODEL, V., VAN EERDEWEGH, P. & REICH, T. (1995) Mathematical limits of multilocus models: the genetic transmission of bipolar disorder. *Am J Hum Genet,* 57, 690-702.
CRADDOCK, N., O'DONOVAN, M. C. & OWEN, M. J. (2005) The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet,* 42, 193-204.
CRADDOCK, N. & OWEN, M. J. (2007) Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry,* 6, 20-7.
DABAN, C., COLOM, F., SANCHEZ-MORENO, J., GARCIA-AMADOR, M. & VIETA, E. (2006) Clinical correlates of first-episode polarity in bipolar disorder. *Compr Psychiatry,* 47, 433-7.
DICK, D. M., FOROUD, T., FLURY, L., BOWMAN, E. S., MILLER, M. J., RAU, N. L., MOE, P. R., SAMAVEDY, N., EL-MALLAKH, R., MANJI, H., GLITZ, D. A., MEYER, E. T., SMILEY, C., HAHN, R., WIDMARK, C., MCKINNEY, R., SUTTON, L., BALLAS, C., GRICE, D., BERRETTINI, W., BYERLEY, W., CORYELL, W., DEPAULO, R., MACKINNON, D. F., GERSHON, E. S., KELSOE, J. R., MCMAHON, F. J., MCINNIS, M., MURPHY, D. L., REICH, T., SCHEFTNER, W. & NURNBERGER, J. I., JR. (2003) Genomewide linkage analyses of bipolar disorder: a new sample of 250 pedigrees from the National Institute of Mental Health Genetics Initiative. *Am J Hum Genet,* 73, 107-14.
DILSAVER, S. C. & CHEN, Y. W. (2003) Social phobia, panic disorder and suicidality in subjects with pure and depressive mania. *J Affect Disord,* 77, 173-7.
DINDO, L. & CORYELL, W. (2004) Comorbid major depression and panic disorder: significance of temporal sequencing to familial transmission. *Journal of Affective Disorders,* 82, 119-123.
DOUGHTY, C. J., WELLS, J. E., JOYCE, P. R., OLDS, R. J. & WALSH, A. E. (2004) Bipolar-panic disorder comorbidity within bipolar disorder families: a study of siblings. *Bipolar Disord,* 6, 245-52.
EATON, W. W., KESSLER, R. C., WITTCHEN, H. U. & MAGEE, W. J. (1994) Panic and panic disorder in the United States. *Am J Psychiatry,* 151, 413-20.
ENDICOTT, J., SPITZER, R. L., FLEISS, J. L. & COHEN, J. (1976) The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry,* 33, 766-71.
EWALD, H., FLINT, T., KRUSE, T. A. & MORS, O. (2002) A genome-wide scan shows significant linkage between bipolar disorder and chromosome 12q24.3 and suggestive linkage to chromosomes 1p22-21, 4p16, 6q14-22, 10q26 and 16p13.3. *Mol Psychiatry,* 7, 734-44.

FARAONE, S. V., GLATT, S. J., SU, J. & TSUANG, M. T. (2004) Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. *Am J Psychiatry,* 161, 625-30.
FARMER, A., BREEN, G., BREWSTER, S., CRADDOCK, N., GILL, M., KORSZUN, A., MAIER, W., MIDDLETON, L., MORS, O., OWEN, M., PERRY, J., PREISIG, M., RIETSCHEL, M., REICH, T., JONES, L., JONES, I. & MCGUFFIN, P. (2004) The Depression Network (DeNT) Study: methodology and sociodemographic characteristics of the first 470 affected sibling pairs from a large multi-site linkage genetic study. *BMC Psychiatry,* 4, 42.
FARMER, A., HARRIS, T., REDMAN, K., SADLER, S., MAHMOOD, A. & MCGUFFIN, P. (2000) Cardiff depression study. A sib-pair study of life events and familiality in major depression. *Br J Psychiatry,* 176, 150-5.
FARMER, A. & MCGUFFIN, P. (1989) The classification of the depressions. Contemporary confusion revisited. *Br J Psychiatry,* 155, 437-43.
FAWCETT, J., SCHEFTNER, W. A., FOGG, L., CLARK, D. C., YOUNG, M. A., HEDEKER, D. & GIBBONS, R. (1990) Time-related predictors of suicide in major affective disorder. *Am J Psychiatry,* 147, 1189-94.
FEIGHNER, J. P., ROBINS, E., GUZE, S. B., WOODRUFF, R. A., JR., WINOKUR, G. & MUNOZ, R. (1972) Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry,* 26, 57-63.
FESKE, U., FRANK, E., MALLINGER, A. G., HOUCK, P. R., FAGIOLINI, A., SHEAR, M. K., GROCHOCINSKI, V. J. & KUPFER, D. J. (2000) Anxiety as a correlate of response to the acute treatment of bipolar I disorder. *Am J Psychiatry,* 157, 956-62.
FLEISS, J. L. (1981) Statistical methods for rates and proportions. Second Edition. New York, John Wiley.
FORTY, L., JONES, L., JONES, I., COOPER, C., RUSSELL, E., FARMER, A., MCGUFFIN, P. & CRADDOCK, N. (2009a) Is depression severity the sole cause of psychotic symptoms during an episode of unipolar major depression? A study both between and within subjects. *J Affect Disord,* 114, 103-109.
FORTY, L., JONES, L., JONES, I., SMITH, D. J., CAESAR, S., FRASER, C., GORDON-SMITH, K., HYDE, S. & CRADDOCK, N. (2009b) Polarity at illness onset in bipolar I disorder and clinical course of illness. *Bipolar Disord,* 11, 82-8.
FORTY, L., JONES, L., MACGREGOR, S., CAESAR, S., COOPER, C., HOUGH, A., DEAN, L., DAVE, S., FARMER, A., MCGUFFIN, P., BREWSTER, S., CRADDOCK, N. & JONES, I. (2006) Familiality of postpartum depression in unipolar disorder: results of a family study. *Am J Psychiatry,* 163, 1549-53.
FORTY, L., SMITH, D., JONES, L., JONES, I., CAESAR, S., COOPER, C., FRASER, C., GORDON-SMITH, K., HYDE, S., FARMER, A., MCGUFFIN, P. & CRADDOCK, N. (2008) Clinical differences between bipolar and unipolar depression. *Br J Psychiatry,* 192, 388-9.
FORTY, L., SMITH, D., JONES, L., JONES, I., CAESAR, S., COOPER, C., FRASER, C., GORDON-SMITH, K., HYDE, S., FARMER, A., MCGUFFIN, P. & CRADDOCK, N. (In Press) Clinical Characteristics of Unipolar Disorder and Bipolar Disorder According to the Lifetime Presence of Recurrent Panic Attacks. *J Affect Disord.*

FORTY, L., SMITH, D., JONES, L., JONES, I., CAESAR, S., FRASER, C., GORDON-SMITH, K. & CRADDOCK, N. (2009c) Identifying hypomanic features in major depressive disorder using the hypomania checklist (HCL-32). *J Affect Disord,* 114, 68-73.

FRANCHINI, L., SERRETTI, A., GASPERINI, M. & SMERALDI, E. (1998) Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. *J Psychiatr Res,* 32, 255-9.

FRANK, E., CYRANOWSKI, J. M., RUCCI, P., SHEAR, M. K., FAGIOLINI, A., THASE, M. E., CASSANO, G. B., GROCHOCINSKI, V. J., KOSTELNIK, B. & KUPFER, D. J. (2002) Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. *Arch Gen Psychiatry,* 59, 905-11.

FRANK, E., SHEAR, M. K., RUCCI, P., CYRANOWSKI, J. M., ENDICOTT, J., FAGIOLINI, A., GROCHOCINSKI, V. J., HOUCK, P., KUPFER, D. J., MASER, J. D. & CASSANO, G. B. (2000) Influence of panic-agoraphobic spectrum symptoms on treatment response in patients with recurrent major depression. *Am J Psychiatry,* 157, 1101-7.

GELDER, M., COWEN, P. & HARRISON, P. (2006) *Shorter Oxford textbook of psychiatry. Fifth edition.,* Oxford, Oxford University Press.

GELLER, B., BADNER, J. A., TILLMAN, R., CHRISTIAN, S. L., BOLHOFNER, K. & COOK, E. H., JR. (2004) Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry,* 161, 1698-700.

GERSHON, E. S., HAMOVIT, J., GUROFF, J. J., DIBBLE, E., LECKMAN, J. F., SCEERY, W., TARGUM, S. D., NURNBERGER, J. I., JR., GOLDIN, L. R. & BUNNEY, W. E., JR. (1982) A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry,* 39, 1157-67.

GHAEMI, S., KO, J. & GOODWIN, F. (2002) "Cades Disease" and Beyond: Misdiagnosis, Antidepressant Use, and a Proposed Definition for Bipolar Spectrum Disorder. *Canadian Journal of Psychiatry,* 47, 125-134.

GILLESPIE, N. A., WHITFIELD, J. B., WILLIAMS, B., HEATH, A. C. & MARTIN, N. G. (2005) The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. *Psychol Med,* 35, 101-11.

GLASSMAN, A. H. & ROOSE, S. P. (1981) Delusional depression. A distinct clinical entity? *Arch Gen Psychiatry,* 38, 424-7.

GOODWIN, F. K. & JAMISON, K. R. (2007) *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression, 2nd edition,* New York, Oxford University Press.

GREEN, E. K., RAYBOULD, R., MACGREGOR, S., GORDON-SMITH, K., HERON, J., HYDE, S., GROZEVA, D., HAMSHERE, M., WILLIAMS, N., OWEN, M. J., O'DONOVAN, M. C., JONES, L., JONES, I., KIROV, G. & CRADDOCK, N. (2005) Operation of the schizophrenia susceptibility gene, neuregulin 1, across traditional diagnostic boundaries to increase risk for bipolar disorder. *Arch Gen Psychiatry,* 62, 642-8.

GREEN, E. K., RAYBOULD, R., MACGREGOR, S., HYDE, S., YOUNG, A. H., O'DONOVAN, M. C., OWEN, M. J., KIROV, G., JONES, L., JONES, I. & CRADDOCK, N. (2006) Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. *Br J Psychiatry,* 188, 21-5.

GROF, P., DUFFY, A., CAVAZZONI, P., GROF, E., GARNHAM, J., MACDOUGALL, M., O'DONOVAN, C. & ALDA, M. (2002) Is response to prophylactic lithium a familial trait? *J Clin Psychiatry,* 63, 942-7.

HAMILTON, S. P., FYER, A. J., DURNER, M., HEIMAN, G. A., BAISRE DE LEON, A., HODGE, S. E., KNOWLES, J. A. & WEISSMAN, M. M. (2003) Further genetic evidence for a panic disorder syndrome mapping to chromosome 13q. *Proc Natl Acad Sci U S A,* 100, 2550-5.

HATTORI, E., LIU, C., BADNER, J. A., BONNER, T. I., CHRISTIAN, S. L., MAHESHWARI, M., DETERA-WADLEIGH, S. D., GIBBS, R. A. & GERSHON, E. S. (2003) Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series. *Am J Hum Genet,* 72, 1131-40.

HEALY, D. (2002) *Psychiatric Drugs Explained. Third Edition*, Churchull Livingstone: Elsevier Science Limited.

HOLMANS, P., WEISSMAN, M. M., ZUBENKO, G. S., SCHEFTNER, W. A., CROWE, R. R., DEPAULO, J. R., JR., KNOWLES, J. A., ZUBENKO, W. N., MURPHY-EBERENZ, K., MARTA, D. H., BOUTELLE, S., MCINNIS, M. G., ADAMS, P., GLADIS, M., STEELE, J., MILLER, E. B., POTASH, J. B., MACKINNON, D. F. & LEVINSON, D. F. (2007) Genetics of recurrent early-onset major depression (GenRED): final genome scan report. *Am J Psychiatry,* 164, 248-58.

HOLMANS, P., ZUBENKO, G. S., CROWE, R. R., DEPAULO, J. R., JR., SCHEFTNER, W. A., WEISSMAN, M. M., ZUBENKO, W. N., BOUTELLE, S., MURPHY-EBERENZ, K., MACKINNON, D., MCINNIS, M. G., MARTA, D. H., ADAMS, P., KNOWLES, J. A., GLADIS, M., THOMAS, J., CHELLIS, J., MILLER, E. & LEVINSON, D. F. (2004) Genomewide significant linkage to recurrent, early-onset major depressive disorder on chromosome 15q. *Am J Hum Genet,* 74, 1154-67.

HONG, C. J., HUO, S. J., YEN, F. C., TUNG, C. L., PAN, G. M. & TSAI, S. J. (2003) Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology,* 48, 186-9.

JARDINE, R., MARTIN, N. G. & HENDERSON, A. S. (1984) Genetic covariation between neuroticism and the symptoms of anxiety and depression. *Genet Epidemiol,* 1, 89-107.

JELLIFFE, S. E. (1931) Some historical phases of the manic-depressive synthesis. . *Association for Research in Nervous and Mental Health Disease,* 11, 3-47.

JESTE, D. V., HEATON, S. C., PAULSEN, J. S., ERCOLI, L., HARRIS, J. & HEATON, R. K. (1996) Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. *Am J Psychiatry,* 153, 490-6.

JOHNSON, J., HORWATH, E. & WEISSMAN, M. M. (1991) The validity of major depression with psychotic features based on a community study. *Arch Gen Psychiatry,* 48, 1075-81.
JOHNSON, M. R. & LYDIARD, R. B. (1998) Comorbidity of major depression and panic disorder. *J Clin Psychol,* 54, 201-10.
JONES, I. & CRADDOCK, N. (2001a) Candidate gene studies of bipolar disorder. *Ann Med,* 33, 248-56.
JONES, I. & CRADDOCK, N. (2001b) Familiality of the puerperal trigger in bipolar disorder: results of a family study. *Am J Psychiatry,* 158, 913-7.
JONES, I. & CRADDOCK, N. (2002) Do puerperal psychotic episodes identify a more familial subtype of bipolar disorder? Results of a family history study. *Psychiatr Genet,* 12, 177-80.
JONES, I., HAMSHERE, M., NANGLE, J. M., BENNETT, P., GREEN, E., HERON, J., SEGURADO, R., LAMBERT, D., HOLMANS, P., CORVIN, A., OWEN, M., JONES, L., GILL, M. & CRADDOCK, N. (2007) Bipolar affective puerperal psychosis: genome-wide significant evidence for linkage to chromosome 16. *Am J Psychiatry,* 164, 1099-104.
JONES, I., KENT, L. & CRADDOCK, N. (2002) Genetics of Affective Disorders. IN MCGUFFIN, P., OWEN, M. J. & GOTTESMAN, I. I. (Eds.) *Psychiatric Genetics and Genomics.* New York, Oxford University Press.
JONES, L., SCOTT, J., HAQUE, S., GORDON-SMITH, K., HERON, J., CAESAR, S., COOPER, C., FORTY, L., HYDE, S., LYON, L., GREENING, J., SHAM, P., FARMER, A., MCGUFFIN, P., JONES, I. & CRADDOCK, N. (2005) Cognitive style in bipolar disorder. *Br J Psychiatry,* 187, 431-7.
JUDD, L. L., AKISKAL, H. S., SCHETTLER, P. J., CORYELL, W., MASER, J., RICE, J. A., SOLOMON, D. A. & KELLER, M. B. (2003) The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *J Affect Disord,* 73, 19-32.
KASSEM, L., LOPEZ, V., HEDEKER, D., STEELE, J., ZANDI, P. & MCMAHON, F. J. (2006) Familiality of polarity at illness onset in bipolar affective disorder. *Am J Psychiatry,* 163, 1754-9.
KAUFMAN, J., YANG, B. Z., DOUGLAS-PALUMBERI, H., HOUSHYAR, S., LIPSCHITZ, D., KRYSTAL, J. H. & GELERNTER, J. (2004) Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A,* 101, 17316-21.
KENDELL, R. E. (1987) Diagnosis and classification of functional psychoses. *Br Med Bull,* 43, 499-513.
KENDELL, R. E., CHALMERS, J. C. & PLATZ, C. (1987) Epidemiology of puerperal psychoses. *Br J Psychiatry,* 150, 662-73.
KENDLER, K. S. (1997) The diagnostic validity of melancholic major depression in a population-based sample of female twins. *Arch Gen Psychiatry,* 54, 299-304.
KENDLER, K. S. (1998c) Major depression and the environment: a psychiatric genetic perspective. *Pharmacopsychiatry,* 31, 5-9.
KENDLER, K. S., EAVES, L. J., WALTERS, E. E., NEALE, M. C., HEATH, A. C. & KESSLER, R. C. (1996) The identification and validation of

distinct depressive syndromes in a population-based sample of female twins. *Arch Gen Psychiatry,* 53, 391-9.
KENDLER, K. S. & GARDNER, C. O., JR. (1998) Twin studies of adult psychiatric and substance dependence disorders: are they biased by differences in the environmental experiences of monozygotic and dizygotic twins in childhood and adolescence? *Psychol Med,* 28, 625-33.
KENDLER, K. S., GARDNER, C. O. & PRESCOTT, C. A. (1999) Clinical characteristics of major depression that predict risk of depression in relatives. *Arch Gen Psychiatry,* 56, 322-7.
KENDLER, K. S., GATZ, M., GARDNER, C. O. & PEDERSEN, N. L. (2006) A Swedish national twin study of lifetime major depression. *Am J Psychiatry,* 163, 109-14.
KENDLER, K. S., KARKOWSKI, L. M. & WALSH, D. (1998) The structure of psychosis: latent class analysis of probands from the Roscommon Family Study. *Arch Gen Psychiatry,* 55, 492-9.
KENDLER, K. S., KESSLER, R. C., WALTERS, E. E., MACLEAN, C., NEALE, M. C., HEATH, A. C. & EAVES, L. J. (1995a) Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry,* 152, 833-42.
KENDLER, K. S., KUHN, J. & PRESCOTT, C. A. (2004) The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *Am J Psychiatry,* 161, 631-6.
KENDLER, K. S., KUHN, J. W., VITTUM, J., PRESCOTT, C. A. & RILEY, B. (2005) The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry,* 62, 529-35.
KENDLER, K. S., NEALE, M., KESSLER, R., HEATH, A. & EAVES, L. (1993a) A twin study of recent life events and difficulties. *Arch Gen Psychiatry,* 50, 789-96.
KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C. & EAVES, L. J. (1992) Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Arch Gen Psychiatry,* 49, 716-22.
KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C. & EAVES, L. J. (1993b) The lifetime history of major depression in women. Reliability of diagnosis and heritability. *Arch Gen Psychiatry,* 50, 863-70.
KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C. & EAVES, L. J. (1993c) A longitudinal twin study of personality and major depression in women. *Arch Gen Psychiatry,* 50, 853-62.
KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C. & EAVES, L. J. (1994) Parental treatment and the equal environment assumption in twin studies of psychiatric illness. *Psychol Med,* 24, 579-90.
KENDLER, K. S., PEDERSEN, N., JOHNSON, L., NEALE, M. C. & MATHE, A. A. (1993d) A pilot Swedish twin study of affective illness, including hospital- and population-ascertained subsamples. *Arch Gen Psychiatry,* 50, 699-700.
KENDLER, K. S., WALTERS, E. E., NEALE, M. C., KESSLER, R. C., HEATH, A. C. & EAVES, L. J. (1995b) The structure of the genetic and

environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Arch Gen Psychiatry,* 52, 374-83.
KENNEDY, N., BOYDELL, J., KALIDINDI, S., FEARON, P., JONES, P. B., VAN OS, J. & MURRAY, R. M. (2005) Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *Am J Psychiatry,* 162, 257-62.
KESSLER, R. C., MCGONAGLE, K. A., ZHAO, S., NELSON, C. B., HUGHES, M., ESHLEMAN, S., WITTCHEN, H. U. & KENDLER, K. S. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry,* 51, 8-19.
KIESEPPA, T., PARTONEN, T., HAUKKA, J., KAPRIO, J. & LONNQVIST, J. (2004) High concordance of bipolar I disorder in a nationwide sample of twins. *Am J Psychiatry,* 161, 1814-21.
KIROV, G., MURPHY, K. C., ARRANZ, M. J., JONES, I., MCCANDLES, F., KUNUGI, H., MURRAY, R. M., MCGUFFIN, P., COLLIER, D. A., OWEN, M. J. & CRADDOCK, N. (1998) Low activity allele of catechol-O-methyltransferase gene associated with rapid cycling bipolar disorder. *Mol Psychiatry,* 3, 342-5.
KLERMAN, G. L. & WEISSMAN, M. M. (1989) Increasing rates of depression. *Jama,* 261, 2229-35.
KRAEPELIN, E. (1921) *Manic-Depressive Insanity and Paranoia.,* Edinburgh, E. & S. Livingstone.
KRINGLEN, E. (1967) *Heredity and Environment in the Functional Psychoses.,* London, William Heinemann.
LAMBERT, D., MIDDLE, F., HAMSHERE, M. L., SEGURADO, R., RAYBOULD, R., CORVIN, A., GREEN, E., O'MAHONY, E., NIKOLOV, I., MULCAHY, T., HAQUE, S., BORT, S., BENNETT, P., NORTON, N., OWEN, M. J., KIROV, G., LENDON, C., JONES, L., JONES, I., HOLMANS, P., GILL, M. & CRADDOCK, N. (2005) Stage 2 of the Wellcome Trust UK-Irish bipolar affective disorder sibling-pair genome screen: evidence for linkage on chromosomes 6q16-q21, 4q12-q21, 9p21, 10p14-p12 and 18q22. *Mol Psychiatry,* 10, 831-41.
LASKY-SU, J. A., FARAONE, S. V., GLATT, S. J. & TSUANG, M. T. (2005) Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. *Am J Med Genet B Neuropsychiatr Genet,* 133, 110-5.
LATTUADA, E., SERRETTI, A., CUSIN, C., GASPERINI, M. & SMERALDI, E. (1999) Symptomatologic analysis of psychotic and non-psychotic depression. *J Affect Disord,* 54, 183-7.
LECKMAN, J. F., WEISSMAN, M. M., PRUSOFF, B. A., CARUSO, K. A., MERIKANGAS, K. R., PAULS, D. L. & KIDD, K. K. (1984) Subtypes of depression. Family study perspective. *Arch Gen Psychiatry,* 41, 833-8.
LEONARD, B. E. (2007) Psychopathology of depression. *Drugs Today (Barc),* 43, 705-16.
LEONHARD, K. (1959) *Aufteilung der endogenen Psychosen.,* Berlin, Akademie Verlag.
LEWIS, A. J. (1934) Melancholia:A historical review. *Journal of Mental Science,* 80, 1-42.

LISH, J. D., GYULAI, L., RESNICK, S. M., KIRTLAND, A., AMSTERDAM, J. D., WHYBROW, P. C. & PRICE, R. A. (1993) A family history study of rapid-cycling bipolar disorder. *Psychiatry Res,* 48, 37-46.
LYONS, M. J., GOLDBERG, J., EISEN, S. A., TRUE, W., TSUANG, M. T., MEYER, J. M. & HENDERSON, W. G. (1993) Do genes influence exposure to trauma? A twin study of combat. *Am J Med Genet,* 48, 22-7.
MACGREGOR, S., CRADDOCK, N. & HOLMANS, P. A. (2006) Use of phenotypic covariates in association analysis by sequential addition of cases. *Eur J Hum Genet,* 14, 529-34.
MACKINNON, D. F., MCMAHON, F. J., SIMPSON, S. G., MCINNIS, M. G. & DEPAULO, J. R. (1997) Panic disorder with familial bipolar disorder. *Biol Psychiatry,* 42, 90-5.
MACKINNON, D. F., ZANDI, P. P., COOPER, J., POTASH, J. B., SIMPSON, S. G., GERSHON, E., NURNBERGER, J., REICH, T. & DEPAULO, J. R. (2002) Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry,* 159, 30-5.
MAIER, W., MINGES, J. & LICHTERMANN, D. (1995a) The familial relationship between panic disorder and unipolar depression. *J Psychiatr Res,* 29, 375-88.
MAIER, W., MINGES, J. & LICHTERMANN, D. (1995b) The familial relationship between panic disorder and unipolar depression. *Journal of Psychiatric Research,* 29, 375-388.
MCGUFFIN, P., COHEN, S. & KNIGHT, J. (2007) Homing in on depression genes. *Am J Psychiatry,* 164, 195-7.
MCGUFFIN, P., FARMER, A. & HARVEY, I. (1991) A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Arch Gen Psychiatry,* 48, 764-70.
MCGUFFIN, P. & KATZ, R. (1989) The genetics of depression and manic-depressive disorder. *Br J Psychiatry,* 155, 294-304.
MCGUFFIN, P., KATZ, R. & BEBBINGTON, P. (1987) Hazard, heredity and depression. A family study. *J Psychiatr Res,* 21, 365-75.
MCGUFFIN, P., KATZ, R. & BEBBINGTON, P. (1988) The Camberwell Collaborative Depression Study. III. Depression and adversity in the relatives of depressed probands. *Br J Psychiatry,* 152, 775-82.
MCGUFFIN, P., KATZ, R., WATKINS, S. & RUTHERFORD, J. (1996) A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Arch Gen Psychiatry,* 53, 129-36.
MCGUFFIN, P., KNIGHT, J., BREEN, G., BREWSTER, S., BOYD, P. R., CRADDOCK, N., GILL, M., KORSZUN, A., MAIER, W., MIDDLETON, L., MORS, O., OWEN, M. J., PERRY, J., PREISIG, M., REICH, T., RICE, J., RIETSCHEL, M., JONES, L., SHAM, P. & FARMER, A. E. (2005) Whole genome linkage scan of recurrent depressive disorder from the depression network study. *Hum Mol Genet,* 14, 3337-45.
MCGUFFIN, P., OWEN, M., O'DONOVAN, M., THAPAR, A. & GOTTESMAN, I. (1994) *Seminars in Psychiatric Genetics*
London, Royal College of Psychiatrists.
MCGUFFIN, P., RIJSDIJK, F., ANDREW, M., SHAM, P., KATZ, R. & CARDNO, A. (2003) The heritability of bipolar affective disorder and

the genetic relationship to unipolar depression. *Arch Gen Psychiatry,* 60, 497-502.

MCQUEEN, M. B., DEVLIN, B., FARAONE, S. V., NIMGAONKAR, V. L., SKLAR, P., SMOLLER, J. W., ABOU JAMRA, R., ALBUS, M., BACANU, S. A., BARON, M., BARRETT, T. B., BERRETTINI, W., BLACKER, D., BYERLEY, W., CICHON, S., CORYELL, W., CRADDOCK, N., DALY, M. J., DEPAULO, J. R., EDENBERG, H. J., FOROUD, T., GILL, M., GILLIAM, T. C., HAMSHERE, M., JONES, I., JONES, L., JUO, S. H., KELSOE, J. R., LAMBERT, D., LANGE, C., LERER, B., LIU, J., MAIER, W., MACKINNON, J. D., MCINNIS, M. G., MCMAHON, F. J., MURPHY, D. L., NOTHEN, M. M., NURNBERGER, J. I., PATO, C. N., PATO, M. T., POTASH, J. B., PROPPING, P., PULVER, A. E., RICE, J. P., RIETSCHEL, M., SCHEFTNER, W., SCHUMACHER, J., SEGURADO, R., VAN STEEN, K., XIE, W., ZANDI, P. P. & LAIRD, N. M. (2005) Combined analysis from eleven linkage studies of bipolar disorder provides strong evidence of susceptibility loci on chromosomes 6q and 8q. *Am J Hum Genet,* 77,

□ MENDLEWICZ, J. & RAINER, J. D. (1977) Adoption

MENDLEWICZ, J. & RAINER, J. D. (1977) Adoption study supporting genetic transmission in manic--depressive illness. *Nature,* 268, 327-9.

MEYER, T., HAMMELSTEIN, P., NILSSON, L., SKEPPAR, P., ADOLFSSON, R. & ANGST, J. (2007) The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples. *Compr Psychiatry,* 48, 79-87.

MIDDLETON, F. A., PATO, M. T., GENTILE, K. L., MORLEY, C. P., ZHAO, X., EISENER, A. F., BROWN, A., PETRYSHEN, T. L., KIRBY, A. N., MEDEIROS, H., CARVALHO, C., MACEDO, A., DOURADO, A., COELHO, I., VALENTE, J., SOARES, M. J., FERREIRA, C. P., LEI, M., AZEVEDO, M. H., KENNEDY, J. L., DALY, M. J., SKLAR, P. & PATO, C. N. (2004) Genomewide linkage analysis of bipolar disorder by use of a high-density single-nucleotide-polymorphism (SNP) genotyping assay: a comparison with microsatellite marker assays and finding of significant linkage to chromosome 6q22. *Am J Hum Genet,* 74, 886-97.

MITCHELL, P., GOODWIN, G., JOHNSON, G. & HIRSCHFELD, R. (2008) Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar Disorders,* 10, 144-52.

MITCHELL, P., PARKER, G., JAMIESON, K., WILHELM, K., HICKIE, I., BRODATY, H., BOYCE, P., HADZI-PAVLOVIC, D. & ROY, K. (1992) Are there any differences between bipolar and unipolar melancholia? *J Affect Disord,* 25, 97-105.

MITCHELL, P. B., SLADE, T. & ANDREWS, G. (2004) Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychol Med,* 34, 777-85.

MITCHELL, P. B., WILHELM, K., PARKER, G., AUSTIN, M. P., RUTGERS, P. & MALHI, G. S. (2001) The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. *J Clin Psychiatry,* 62, 212-6; quiz 217.

NAKATA, K., UJIKE, H., SAKAI, A., UCHIDA, N., NOMURA, A., IMAMURA, T., KATSU, T., TANAKA, Y., HAMAMURA, T. & KURODA, S. (2003)

Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder. *Neurosci Lett,* 337, 17-20.
NEALE, M. C., BOKER, S. M., XIE, G. & MH, H. (2003) *Mx: Statistical Modeling.* , VCU Box 900126, Richmond, VA 23298, Department of Psychiatry.
NELSON, W. H., KHAN, A. & ORR, W. W., JR. (1984) Delusional depression. Phenomenology, Neuroendocrine function, and tricyclic antidepressant response. *J Affect Disord,* 6, 297-306.
NEVES-PEREIRA, M., MUNDO, E., MUGLIA, P., KING, N., MACCIARDI, F. & KENNEDY, J. L. (2002) The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am J Hum Genet,* 71, 651-5.
NICE (2006a) National Institute for Health and Clinical Excellence. Clinical Guideline 38. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. London, NICE.
NICE, N. I. F. H. A. C. E. (2006b) Clinical Guideline 38. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. London, NICE.
NOLEN-HOEKSEMA, S. (2001) *Abnormal Psychology. Second edition,* New York, McGraw Hill.
NURNBERGER, J., JR., GUROFF, J. J., HAMOVIT, J., BERRETTINI, W. & GERSHON, E. (1988) A family study of rapid-cycling bipolar illness. *J Affect Disord,* 15, 87-91.
NURNBERGER, J. I., JR., FOROUD, T., FLURY, L., SU, J., MEYER, E. T., HU, K., CROWE, R., EDENBERG, H., GOATE, A., BIERUT, L., REICH, T., SCHUCKIT, M. & REICH, W. (2001) Evidence for a locus on chromosome 1 that influences vulnerability to alcoholism and affective disorder. *Am J Psychiatry,* 158, 718-24.
O'HARA, M. & SWAIN, A. (1996) Rates and risk of postpartum depression- a meta-analysis. *International Review of Psychiatry,* 8, 37-54.
O'MAHONY, E., CORVIN, A., O'CONNELL, R., COMERFORD, C., LARSEN, B., JONES, R., MCCANDLESS, F., KIROV, G., CARDNO, A. G., CRADDOCK, N. & GILL, M. (2002) Sibling pairs with affective disorders: resemblance of demographic and clinical features. *Psychol Med,* 32, 55-61.
O'REILLY, R. L., BOGUE, L. & SINGH, S. M. (1994) Pharmacogenetic response to antidepressants in a multicase family with affective disorder. *Biol Psychiatry,* 36, 467-71.
OHAYON, M. M. & SCHATZBERG, A. F. (2002) Prevalence of depressive episodes with psychotic features in the general population. *Am J Psychiatry,* 159, 1855-61.
OSWALD, P., DEL-FAVERO, J., MASSAT, I., SOUERY, D., CLAES, S., VAN BROECKHOVEN, C. & MENDLEWICZ, J. (2004) Non-replication of the brain-derived neurotrophic factor (BDNF) association in bipolar affective disorder: a Belgian patient-control study. *Am J Med Genet B Neuropsychiatr Genet,* 129, 34-5.
PARKER, G., HADZI-PAVLOVIC, D., BRODATY, H., AUSTIN, M. P., MITCHELL, P., WILHELM, K. & HICKIE, I. (1995) Sub-typing depression, II. Clinical distinction of psychotic depression and non-psychotic melancholia. *Psychol Med,* 25, 825-32.

PAYKEL, E. S. (1978) Contribution of life events to causation of psychiatric illness. *Psychol Med,* 8, 245-53.
PERALTA, V. & CUESTA, M. J. (2007) A dimensional and categorical architecture for the classification of psychotic disorders. *World Psychiatry,* 6, 100-1.
PERLIS, R. H., DELBELLO, M. P., MIYAHARA, S., WISNIEWSKI, S. R., SACHS, G. S. & NIERENBERG, A. A. (2005) Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. *Biol Psychiatry,* 58, 549-53.
PERRIS, C. (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. IV. A multidimensional study of personality traits. *Acta Psychiatr Scand Suppl,* 194, 68-82.
PERUGI, G., AKISKAL, H. S., RAMACCIOTTI, S., NASSINI, S., TONI, C., MILANFRANCHI, A. & MUSETTI, L. (1999) Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection? *J Psychiatr Res,* 33, 53-61.
PERUGI, G., MICHELI, C., AKISKAL, H. S., MADARO, D., SOCCI, C., QUILICI, C. & MUSETTI, L. (2000) Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. *Compr Psychiatry,* 41, 13-8.
PINI, S., CASSANO, G. B., SIMONINI, E., SAVINO, M., RUSSO, A. & MONTGOMERY, S. A. (1997) Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. *J Affect Disord,* 42, 145-53.
PLOMIN, R., LICHTENSTEIN, P., PEDERSEN, N. L., MCCLEARN, G. E. & NESSELROADE, J. R. (1990) Genetic influence on life events during the last half of the life span. *Psychol Aging,* 5, 25-30.
POTASH, J. B., CHIU, Y. F., MACKINNON, D. F., MILLER, E. B., SIMPSON, S. G., MCMAHON, F. J., MCINNIS, M. G. & DEPAULO, J. R., JR. (2003) Familial aggregation of psychotic symptoms in a replication set of 69 bipolar disorder pedigrees. *Am J Med Genet B Neuropsychiatr Genet,* 116, 90-7.
POTASH, J. B., WILLOUR, V. L., CHIU, Y. F., SIMPSON, S. G., MACKINNON, D. F., PEARLSON, G. D., DEPAULO, J. R., JR. & MCINNIS, M. G. (2001) The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. *Am J Psychiatry,* 158, 1258-64.
PREISIG, M., BELLIVIER, F., FENTON, B. T., BAUD, P., BERNEY, A., COURTET, P., HARDY, P., GOLAZ, J., LEBOYER, M., MALLET, J., MATTHEY, M. L., MOUTHON, D., NEIDHART, E., NOSTEN-BERTRAND, M., STADELMANN-DUBUIS, E., GUIMON, J., FERRERO, F., BURESI, C. & MALAFOSSE, A. (2000) Association between bipolar disorder and monoamine oxidase A gene polymorphisms: results of a multicenter study. *Am J Psychiatry,* 157, 948-55.
RAYBOULD, R., GREEN, E. K., MACGREGOR, S., GORDON-SMITH, K., HERON, J., HYDE, S., CAESAR, S., NIKOLOV, I., WILLIAMS, N., JONES, L., O'DONOVAN, M. C., OWEN, M. J., JONES, I., KIROV, G.

& CRADDOCK, N. (2005) Bipolar disorder and polymorphisms in the dysbindin gene (DTNBP1). *Biol Psychiatry,* 57, 696-701.
RICE, J., REICH, T., ANDREASEN, N. C., ENDICOTT, J., VAN EERDEWEGH, M., FISHMAN, R., HIRSCHFELD, R. M. & KLERMAN, G. L. (1987) The familial transmission of bipolar illness. *Arch Gen Psychiatry,* 44, 441-7.
RIHMER, Z., SZADOCZKY, E., FUREDI, J., KISS, K. & PAPP, Z. (2001) Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. *J Affect Disord,* 67, 175-9.
ROTONDO, A., MAZZANTI, C., DELL'OSSO, L., RUCCI, P., SULLIVAN, P., BOUANANI, S., GONNELLI, C., GOLDMAN, D. & CASSANO, G. B. (2002) Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. *Am J Psychiatry,* 159, 23-9.
ROY, M. A., NEALE, M. C., PEDERSEN, N. L., MATHE, A. A. & KENDLER, K. S. (1995) A twin study of generalized anxiety disorder and major depression. *Psychol Med,* 25, 1037-49.
RUSH, A. J. & WEISSENBURGER, J. E. (1994) Melancholic symptom features and DSM-IV. *Am J Psychiatry,* 151, 489-98.
SAUNDERS, E. H., SCOTT, L. J., MCINNIS, M. G. & BURMEISTER, M. (2007) Familiality and diagnostic patterns of subphenotypes in the National Institutes of Mental Health Bipolar sample. *Am J Med Genet B Neuropsychiatr Genet.*
SCHATZBERG, A. F. & ROTHSCHILD, A. J. (1992) Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? *Am J Psychiatry,* 149, 733-45.
SCHULZE, T. G., HEDEKER, D., ZANDI, P., RIETSCHEL, M. & MCMAHON, F. J. (2006) What is familial about familial bipolar disorder? Resemblance among relatives across a broad spectrum of phenotypic characteristics. *Arch Gen Psychiatry,* 63, 1368-76.
SCHUMACHER, J., JAMRA, R. A., FREUDENBERG, J., BECKER, T., OHLRAUN, S., OTTE, A. C., TULLIUS, M., KOVALENKO, S., BOGAERT, A. V., MAIER, W., RIETSCHEL, M., PROPPING, P., NOTHEN, M. M. & CICHON, S. (2004) Examination of G72 and D-amino-acid oxidase as genetic risk factors for schizophrenia and bipolar affective disorder. *Mol Psychiatry,* 9, 203-7.
SEGURADO, R., DETERA-WADLEIGH, S. D., LEVINSON, D. F., LEWIS, C. M., GILL, M., NURNBERGER, J. I., JR., CRADDOCK, N., DEPAULO, J. R., BARON, M., GERSHON, E. S., EKHOLM, J., CICHON, S., TURECKI, G., CLAES, S., KELSOE, J. R., SCHOFIELD, P. R., BADENHOP, R. F., MORISSETTE, J., COON, H., BLACKWOOD, D., MCINNES, L. A., FOROUD, T., EDENBERG, H. J., REICH, T., RICE, J. P., GOATE, A., MCINNIS, M. G., MCMAHON, F. J., BADNER, J. A., GOLDIN, L. R., BENNETT, P., WILLOUR, V. L., ZANDI, P. P., LIU, J., GILLIAM, C., JUO, S. H., BERRETTINI, W. H., YOSHIKAWA, T., PELTONEN, L., LONNQVIST, J., NOTHEN, M. M., SCHUMACHER, J., WINDEMUTH, C., RIETSCHEL, M., PROPPING, P., MAIER, W., ALDA, M., GROF, P., ROULEAU, G. A., DEL-FAVERO, J., VAN

BROECKHOVEN, C., MENDLEWICZ, J., ADOLFSSON, R., SPENCE, M. A., LUEBBERT, H., ADAMS, L. J., DONALD, J. A., MITCHELL, P. B., BARDEN, N., SHINK, E., BYERLEY, W., MUIR, W., VISSCHER, P. M., MACGREGOR, S., GURLING, H., KALSI, G., MCQUILLIN, A., ESCAMILLA, M. A., REUS, V. I., LEON, P., FREIMER, N. B., EWALD, H., KRUSE, T. A., MORS, O., RADHAKRISHNA, U., BLOUIN, J. L., ANTONARAKIS, S. E. & AKARSU, N. (2003) Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. *Am J Hum Genet,* 73, 49-62.

SERRETTI, A., LATTUADA, E., CUSIN, C., GASPERINI, M. & SMERALDI, E. (1999) Clinical and demographic features of psychotic and nonpsychotic depression. *Compr Psychiatry,* 40, 358-62.

SHARMA, V., KHAN, M. & SMITH, A. (2005) A closer look at treament resistant depression: is it due to a bipolar diathesis? *Journal of Affective Disorders* 84, 251-257.

SHINK, E., MORISSETTE, J., SHERRINGTON, R. & BARDEN, N. (2005) A genome-wide scan points to a susceptibility locus for bipolar disorder on chromosome 12. *Mol Psychiatry,* 10, 545-52.

SIMON, N. M., OTTO, M. W., WISNIEWSKI, S. R., FOSSEY, M., SAGDUYU, K., FRANK, E., SACHS, G. S., NIERENBERG, A. A., THASE, M. E. & POLLACK, M. H. (2004) Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry,* 161, 2222-9.

SIMON, N. M., SMOLLER, J. W., FAVA, M., SACHS, G., RACETTE, S. R., PERLIS, R., SONAWALLA, S. & ROSENBAUM, J. F. (2003) Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. *J Psychiatr Res,* 37, 187-92.

SKIBINSKA, M., HAUSER, J., CZERSKI, P. M., LESZCZYNSKA-RODZIEWICZ, A., KOSMOWSKA, M., KAPELSKI, P., SLOPIEN, A., ZAKRZEWSKA, M. & RYBAKOWSKI, J. K. (2004) Association analysis of brain-derived neurotrophic factor (BDNF) gene Val66Met polymorphism in schizophrenia and bipolar affective disorder. *World J Biol Psychiatry,* 5, 215-20.

SKLAR, P., GABRIEL, S. B., MCINNIS, M. G., BENNETT, P., LIM, Y. M., TSAN, G., SCHAFFNER, S., KIROV, G., JONES, I., OWEN, M., CRADDOCK, N., DEPAULO, J. R. & LANDER, E. S. (2002) Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. *Mol Psychiatry,* 7, 579-93.

SMITH, A. L. & WEISSMAN, M. M. (1992) Epidemiology. IN PAYKEL, E. S. (Ed.) *Handbook of affective disorders.* Edinburgh.

SMITH, D. J., GHAEMI, S. & CRADDOCK, N. (2008) The broad clinical spectrum of bipolar disorder: implications for research and practice *Journal of Psychopharmacology,* 22, 397-400.

SPITZER, R. L., ENDICOTT, J. & ROBINS, E. (1978) Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry,* 35, 773-82.

SPITZER, R. L., KROENKE, K. & WILLIAMS, J. B. (1999) Validation and utility of a self-report version of PRIME-MD: the PHQ primary care

study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Jama,* 282, 1737-44.
STROBER, M. (1992) Relevance of early age-of-onset in genetic studies of bipolar affective disorder. *J Am Acad Child Adolesc Psychiatry,* 31, 606-10.
SULLIVAN, P. F., NEALE, M. C. & KENDLER, K. S. (2000) Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry,* 157, 1552-62.
SURTEES, P. G., WAINWRIGHT, N. W., WILLIS-OWEN, S. A., LUBEN, R., DAY, N. E. & FLINT, J. (2005) Social Adversity, the Serotonin Transporter (5-HTTLPR) Polymorphism and Major Depressive Disorder. *Biol Psychiatry.*
SWANN, A. C., GELLER, B., POST, R. M., ALTSHULER, L., CHANG, K. D., DELBELLO, M. P., REIST, C. & JUSTER, I. A. (2005) Practical Clues to Early Recognition of Bipolar Disorder: A Primary Care Approach. *Prim Care Companion J Clin Psychiatry,* 7, 15-21.
TAPE, T. G. (2004) Interpreting Diagnostic Tests. http://gim.unmc.edu/dxtests.
TERP, I. M. & MORTENSEN, P. B. (1998) Post-partum psychoses. Clinical diagnoses and relative risk of admission after parturition. *Br J Psychiatry,* 172, 521-6.
THAKUR, M., HAYS, J., RANGA, K. & KRISHNAN, R. (1999) Clinical, demographic and social characteristics of psychotic depression. *Psychiatry Res,* 86, 99-106.
TORGERSEN, S. (1986) Genetic factors in moderately severe and mild affective disorders. *Arch Gen Psychiatry,* 43, 222-6.
TORGERSEN, S. (1990) Comorbidity of major depression and anxiety disorders in twin pairs. *Am J Psychiatry,* 147, 1199-202.
TRELOAR, S. A., MARTIN, N. G., BUCHOLZ, K. K., MADDEN, P. A. & HEATH, A. C. (1999) Genetic influences on post-natal depressive symptoms: findings from an Australian twin sample. *Psychol Med,* 29, 645-54.
TURECKI, G., GROF, P., GROF, E., D'SOUZA, V., LEBUIS, L., MARINEAU, C., CAVAZZONI, P., DUFFY, A., BETARD, C., ZVOLSKY, P., ROBERTSON, C., BREWER, C., HUDSON, T. J., ROULEAU, G. A. & ALDA, M. (2001) Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. *Mol Psychiatry,* 6, 570-8.
VIETA, E., SÁNCHEZ-MORENO, J., BULBENA A, C., L, RAMOS, J., ARTAL, J., PÉREZ, F., OLIVERAS, M., VALLE, J., LAHUERTA, J., ANGST, J. & (2007) Cross validation with the mood disorder questionnaire (MDQ) of an instrument for the detection of hypomania in Spanish: the 32 item hypomania symptom check list (HCL-32). *Journal of Affective Disorders,* 101, 43-55.
WEISSMAN, M. M., GERSHON, E. S., KIDD, K. K., PRUSOFF, B. A., LECKMAN, J. F., DIBBLE, E., HAMOVIT, J., THOMPSON, W. D., PAULS, D. L. & GUROFF, J. J. (1984a) Psychiatric disorders in the relatives of probands with affective disorders. The Yale University--National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry,* 41, 13-21.

WEISSMAN, M. M., PRUSOFF, B. A. & MERIKANGAS, K. R. (1984b) Is delusional depression related to bipolar disorder? *Am J Psychiatry,* 141, 892-3.
WEISSMAN, M. M., WICKRAMARATNE, P., ADAMS, P. B., LISH, J. D., HORWATH, E., CHARNEY, D., WOODS, S. W., LEEMAN, E. & FROSCH, E. (1993) The relationship between panic disorder and major depression. A new family study. *Arch Gen Psychiatry,* 50, 767-80.
WENDER, P. H., KETY, S. S., ROSENTHAL, D., SCHULSINGER, F., ORTMANN, J. & LUNDE, I. (1986) Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Arch Gen Psychiatry,* 43, 923-9.
WHIFFEN, V. E. (1991) The comparison of postpartum with non-postpartum depression: a rose by any other name. *J Psychiatry Neurosci,* 16, 160-5.
WHO (1993) The International Classification of Diseases 10 Classification of Mental and Behavioural Disorders.
Diagnostic Criteria for Research. Geneva, World Health Organisation.
WILLIAMS, N. M., GREEN, E. K., MACGREGOR, S., DWYER, S., NORTON, N., WILLIAMS, H., RAYBOULD, R., GROZEVA, D., HAMSHERE, M., ZAMMIT, S., JONES, L., CARDNO, A., KIROV, G., JONES, I., O'DONOVAN, M. C., OWEN, M. J. & CRADDOCK, N. (2006) Variation at the DAOA/G30 locus influences susceptibility to major mood episodes but not psychosis in schizophrenia and bipolar disorder. *Arch Gen Psychiatry,* 63, 366-73.
WING, J. K., BABOR, T., BRUGHA, T., BURKE, J., COOPER, J. E., GIEL, R., JABLENSKI, A., REGIER, D. & SARTORIUS, N. (1990) SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry,* 47, 589-93.
WINOKUR, G., CLAYTON, P. J. & REICH, T. (1969) *Manic Depressive Illness,* St. Louis, C. V. Mosby Company.
WINOKUR, G., SCHARFETTER, C. & ANGST, J. (1985) A family study of psychotic symptomatology in schizophrenia, schizoaffective disorder, unipolar depression, and bipolar disorder. *Eur Arch Psychiatry Neurol Sci,* 234, 295-8.
WINOKUR, G., TSUANG, M. T. & CROWE, R. R. (1982) The Iowa 500: affective disorder in relatives of manic and depressed patients. *Am J Psychiatry,* 139, 209-12.
WTCCC (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature,* 447, 661-78.
WU, Y., ANGST, J., OU, C., CHEN, H. & LU, R. (2008) Validation of the Chinese version of the hypomania checklist (HCL-32) as an instrument for detecting hypo(mania) in patients with mood disorders. *Journal of Affective Disorders,* 106, 133-43.
YOUNG, E. & KORSZUN, A. (1998) Psychoneuroendocrinology of depression. Hypothalamic-pituitary-gonadal axis. *Psychiatr Clin North Am,* 21, 309-23.
ZEGGINI, E. (2007) A new era for Type 2 diabetes genetics. *Diabet Med,* 24, 1181-6.

ZUBENKO, G. S., MAHER, B., HUGHES, H. B., 3RD, ZUBENKO, W. N., STIFFLER, J. S., KAPLAN, B. B. & MARAZITA, M. L. (2003) Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. *Am J Med Genet B Neuropsychiatr Genet,* 123, 1-18.

Appendices

Appendix A

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 B

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 (eg. 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.

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 C

Part 1:

Modified OPCRIT Symptom Checklist

Rating Form

DEPRESSIVE SYMPTOMS		**WE**	**LE**
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**
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**
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**
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	☐	☐

WE Worst Ever Episode
LE Lifetime Ever

Appendix C

Part 2:

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.

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 <u>not</u> 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 <u>not</u> 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.

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

Reliability Ratings Sheet for Mood Disorder Research Study Subjects

STUDY ID _____ INITIALS _____ DOB _____

RATER _____ DATE _____

DSM-IV	ICD-10	RDC	PN CYCLOID

DIMENSION SCORES: M ___ ___ ___
D ___ ___ ___
P ___ ___ ___
I ___ ___ ___

GAS SCORES: **LIFETIME WORST (IN DEP EPISODE)** _____
LIFETIME WORST (IN MANIC EPISODE) _____
PAST WEEK _____

SECTION 2 (LE)____ **MOOD CONGRUENCE (LE)** ____ **NEAR SECTION 2 (LE)** ____

PREDOMINANT MAN AFFECT (LE) ____ **DYSPHORIC MAN (LE)** ____

NO. EPISODES: **MANIA** ____ **DEPRESSION** ____

LONGEST DURATION: **MANIA** ____ **DEPRESSION** ____

AGE ONSET:

SYMPTOM ____ **IMPAIRMENT** ____ **CONTACT** ____ **ADMISSION** ____

FIRST SYMPTOMS **MANIA** _____ **DEP** _____
FIRST IMPAIRMENT **MANIA** _____ **DEP** _____
FIRST PSYCHIATRIC CONTACT _____
FIRST ADMISSION **MANIA** _____ **DEP** _____
MOST RECENT ADMISSION **MANIA** _____ **DEP** _____

NO. ADMISSIONS: _____

AGE OF FIRST PSYCHOSIS (HALLUCINATION OR DELUSION): _____

FIRST EPISODE POSTPARTUM? Y / N / UK

PUERPERAL EPISODE ____ **MENSTRUAL** ____ **RAPID CYCLING** ____

SUICIDAL IDEATION (LE) ____

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		

Appendix E

The Beck Depression Inventory (BDI)

(Beck and Steer, 1987)

On this questionnaire are groups of statements. Please read each group of statements carefully, circle the number (0, 1, 2 or 3) next to the one statement in each group which ***best*** describes how you feel ***today.*** If several statements within a group seem to apply equally well, circle each one. ***Be sure to read all the statements in each group before making your choice.***

1
0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2
0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3
0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4
0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5
0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7
0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8
0 I don't feel I am worse than anyone else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11
0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14
0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19
0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes No (please circle)

20
0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Appendix F

The Altman Self-Rating Mania Scale (ASRM)

(Altman et al., 1997)

1. On this questionnaire are groups of five statements. Please read each group of statements carefully.
2. Choose one statement in each group that ***best*** describes how you feel ***today***.
3. Circle the number next to the statement you have picked.
4. Please not the word '*occasionally*' when used here means once or twice. '*Often*' means several times or more. '*Frequently*' means most of the time.

1 0 I do not feel happier or more cheerful than usual.
1 I occasionally feel happier or more cheerful than usual.
2 I often feel happier or more cheerful than usual.
3 I feel happier or more cheerful than usual most of the time.
4 I feel happier or more cheerful than usual all of the time.

2 0 I do not feel more self-confident than usual.
1 I occasionally feel more self-confident than usual.
2 I often feel more self-confident than usual.
3 I feel more self-confident than usual most of the time.
4 I feel more self-confident than usual all of the time.

3 0 I do not need less sleep than usual.
1 I occasionally need less sleep than usual.
2 I often need less sleep than usual.
3 I frequently need less sleep than usual.
4 I can go all day and night without any sleep and still do not feel tired.

4 0 I do not talk more than usual.
1 I occasionally talk more than usual.
2 I often talk more than usual.
3 I frequently talk more than usual.
4 I talk constantly and cannot be interrupted.

5 0 I have not been more active (either socially, sexually, at work, home or school) than usual.
1 I have occasionally been more active than usual.
2 I have often been more active than usual.
3 I have frequently been more active than usual.
4 I am constantly active or on the go all the time.

Appendix G

The Hypomania Checklist (HCL-32)

(Angst et al., 2005a)

At different times in their lives everyone experiences changes or swings in energy, activity and mood ("highs and lows" or "ups and downs").

This questionnaire asks about any periods of "high mood" or "elation" that you feel you may have experienced during your life. These periods may last for hours, days, weeks or months.

The aim of this questionnaire is to assess the characteristics of the "high" periods.

Q1. First of all, how are you feeling today compared to your usual state? (Please cross only ONE of the following)

Much worse than usual ☐

Worse than usual ☐

A little worse than usual ☐

Neither better nor worse than usual ☐

A little better than usual ☐

Better than usual ☐

Much better than usual ☐

Q2. How are you usually compared to other people?

Independently of how you feel today, please tell us how you are normally compared to other people, by crossing which of the followings statements describes you best.

Compared to other people, my level of activity energy and mood…

(Please cross only ONE of the following)

….is always rather stable and even ☐

….is generally higher ☐

….is generally lower ☐

….repeatedly shows periods of ups and downs ☐

No box for each of the statements below.

In such a state:	**Yes**	**No**
1. I need less sleep	☐	☐
2. I feel more energetic and more active	☐	☐
3. I am more self-confident	☐	☐
4. I enjoy my work more	☐	☐
5. I am more sociable (make more phone calls, go out more)	☐	☐
6. I want to travel and/or do travel more	☐	☐
7. I tend to drive faster or take more risks when driving	☐	☐
8. I spend more money/too much money	☐	☐
9. I take more risks in my daily life (in my work and/or other activities)	☐	☐
10. I am physically more active (sport etc.)	☐	☐
11. I plan more activities or projects.	☐	☐
12. I have more ideas, I am more creative	☐	☐
13. I am less shy or inhibited	☐	☐
14. I wear more colourful and more extravagant clothes/make-up	☐	☐
15. I want to meet or actually do meet more people	☐	☐
16. I am more interested in sex, and/or have increased sexual desire	☐	☐
17. I am more flirtatious and/or am more sexually active	☐	☐
18. I talk more	☐	☐
19. I think faster	☐	☐
20. I make more jokes or puns when I am talking	☐	☐
21. I am more easily distracted	☐	☐
22. I engage in lots of new things	☐	☐
23. My thoughts jump from topic to topic	☐	☐
24. I do things more quickly and/or more easily	☐	☐
25. I am more impatient and/or get irritable more easily	☐	☐
26. I can be exhausting or irritating for others	☐	☐
27. I get into more quarrels	☐	☐
28. My mood is higher, more optimistic	☐	☐
29. I drink more coffee	☐	☐
30. I smoke more cigarettes	☐	☐
31. I drink more alcohol	☐	☐
32. I take more drugs (sedatives, anti-anxiety pills, stimulants...)	☐	☐

Q4. Did the questions (Q3, 1-32) above, which characterise a "high", describe how yo are.... (Please cross only ONE of the following)

..sometimes (if you cross this box please answer all questions, 5-9 below) ☐

..most of the time (if you cross this box please answer only questions, 5 and 6 below)

☐

..I have never experienced such a "high" (if you cross this box this questionnaire is now complete)

☐

Q5. Impact of your "highs" on various aspects of your life: (Please cross only ONE box for each aspect)

	Positive & Negative	Positive	Negative	No Impact
1. Family Life	☐	☐	☐	☐
2. Social Life	☐	☐	☐	☐
3. Work	☐	☐	☐	☐
4. Leisure	☐	☐	☐	☐

Q6. Other people's reactions and comments to your "highs".

How did people close to you react to or comment on tour "highs"?
(Please cross only ONE of the following)

Positively (encouraging and supportive) ☐
Neutral ☐
Negatively (concerned, annoyed, irritated, critical) ☐
Positively & Negatively ☐
No reactions ☐

Q7. Length of your "highs" as a rule (on average): (Please cross only ONE of the following)

1 day ☐
2-3 days ☐
4-7 days ☐
Longer than 1 week ☐
Longer than 1 month ☐
I can't judge/ don't know ☐

Q8. Have you experienced such "highs" in the past twelve months?

Yes ☐
No ☐

Q9. If yes, please estimate how many days you spent in "highs" during the last twelve months:

_ _ _ days

Appendix H

Panic Attacks Questionnaire

[Questions taken from the Patient Health Questionnaire (PHQ) (questions 2a to 2e and question 3 of the PHQ) (Spitzer et al., 1999)].

Q1. Have you ever had an anxiety attack- suddenly feeling fear or panic?

Yes □ No □

If no, this questionnaire is now complete.
If yes, please complete Q2-6 below.

Q2. Has this happened on more than one occasion?

Yes □ No □

Q3. Do some of these attacks come out of the blue-that is, in situations where you do not expect to be nervous or uncomfortable?

Yes □ No □

Q4. Do these attacks bother you a lot or are you worried about having another attack?

Yes □ No □

Q5. During these attacks do you have symptoms like shortness of breath, sweating, your heart racing or pounding, dizziness, tingling or numbness, or nausea or upset stomach?

Yes □ No □

Q6. If you answered yes to any of the five questions above, how difficult do these problems make it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all □

Somewhat difficult □

Very difficult □

Extremely difficult □

Appendix I

The Brief Life Events Questionnaire (BLEQ)

(Brugha et al., 1985)

We have established that your **first** episode of FEELING DEPRESSED began on __ / __/ ____. I would like to ask you about events or problems which may have happened to you during the 6-months prior to that date.

*[For the worst ever episode of depression, "**first**" was replaced with "**worst**"]*

1. In the 6 months prior to your first episode of depression, did you suffer from a serious illness, injury or an assault?		Yes	No
If yes, at the time, how bad was that for you?	Very bad	Moderately bad	Not too bad
2. In the 6 months prior to your first episode of depression, did a serious illness, injury or assault happen to a close relative?		Yes	No
If yes, at the time, how bad was that for you?	Very bad	Moderately bad	Not too bad
3. In the 6 months prior to your first episode of depression, did a parent, spouse (or partner), child, brother or sister of yours die?		Yes	No
If yes, at the time, how bad was that for you?	Very bad	Moderately bad	Not too bad
4. In the 6 months prior to your first episode of depression, did a close family friend or relative die, such as an aunt, cousin or grandparent?		Yes	No
If yes, at the time, how bad was that for you?	Very bad	Moderately bad	Not too bad
5. In the 6 months prior to your first episode of depression, did you have a separation due to marital difficulties or break off a steady relationship?		Yes	No
If yes, at the time, how bad was that for you?	Very bad	Moderately bad	Not too bad

6. In the 6 months prior to your first episode of depression, did you have a serious problem with a close friend, neighbour or relatives? Yes No

If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad

7. In the 6 months prior to your first episode of depression, were you made redundant or sacked from your job? Yes No

If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad

8. In the 6 months prior to your first episode of depression, were you seeking work without success for more than one month? Yes No

If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad

9. In the 6 months prior to your first episode of depression, did you have a major financial crisis such as losing the equivalent of three months income? Yes No

If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad

10. In the 6 months prior to your first episode of depression, did you have problems with the police involving a court appearance? Yes No

If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad

11. In the 6 months prior to your first episode of depression, was something you valued lost or stolen? Yes No

If yes, at the time, how bad was that for you? Very bad Moderately bad Not too bad

12. In the 6 months prior to your first episode of depression, did you/ your wife or partner give birth to a child? Yes No

If yes, do you think this contributed to your becoming depressed? Probably not Perhaps yes Probably yes

Appendix J

Histograms showing the distributions of scores in the unipolar and bipolar samples for the scales used throughout the thesis.

UP: Unipolar Sample
BP: Bipolar Sample

i) **BADDS (Bipolar Affective Disorder Dimension Scale)**

Depression Dimension (UP & BP), Mania Dimension (UP & BP), Psychosis Dimension (UP & BP), Congruence Dimension (BP)

ii) **GAS (Global Assessment Scale)**

Life Time Worse in Depressive Episode (UP & BP)
Life Time Worse in Manic Episode (BP)

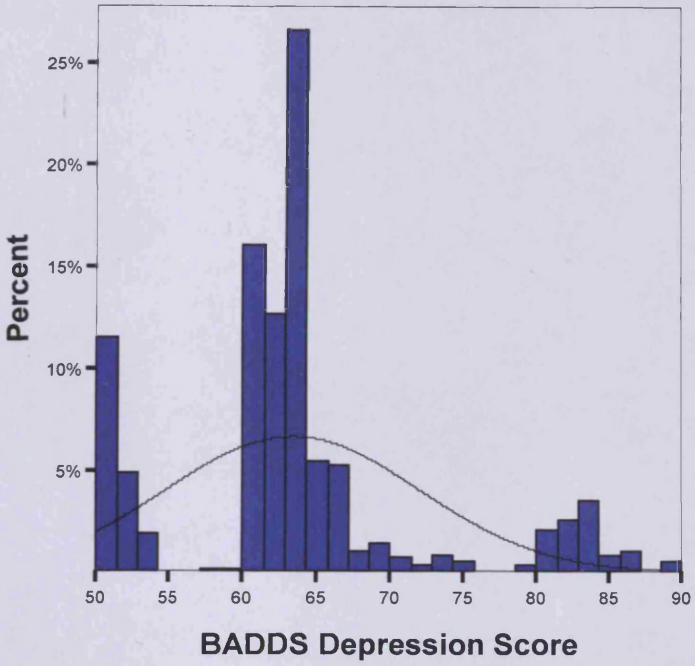
iii) **BDI (Beck Depression Inventory)** (UP & BP)

iv) **ASRM (Altman Self-Rating Mania Scale)** (UP & BP)

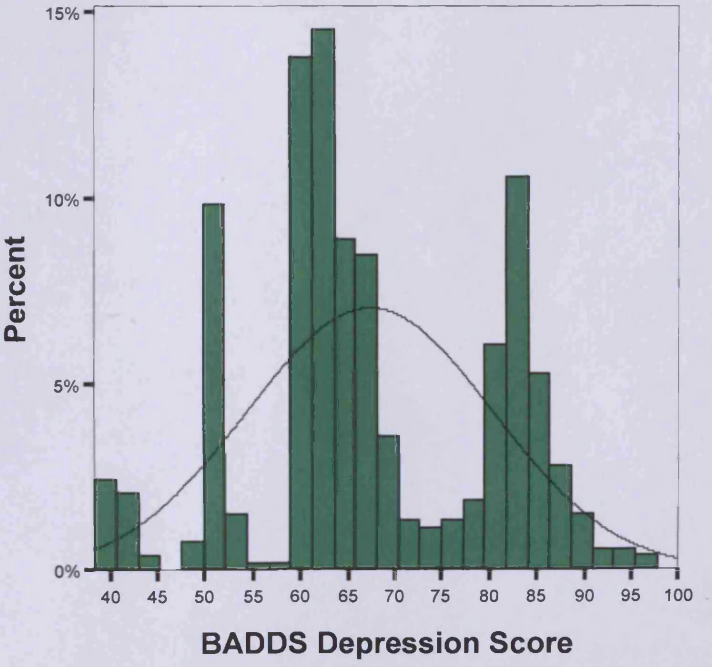
v) **BLEQ (Brief Life Events Questionnaire)** (UP sibling pairs)

Six months prior to worst ever episode of depression
Six months prior to first ever (onset) episode of depression

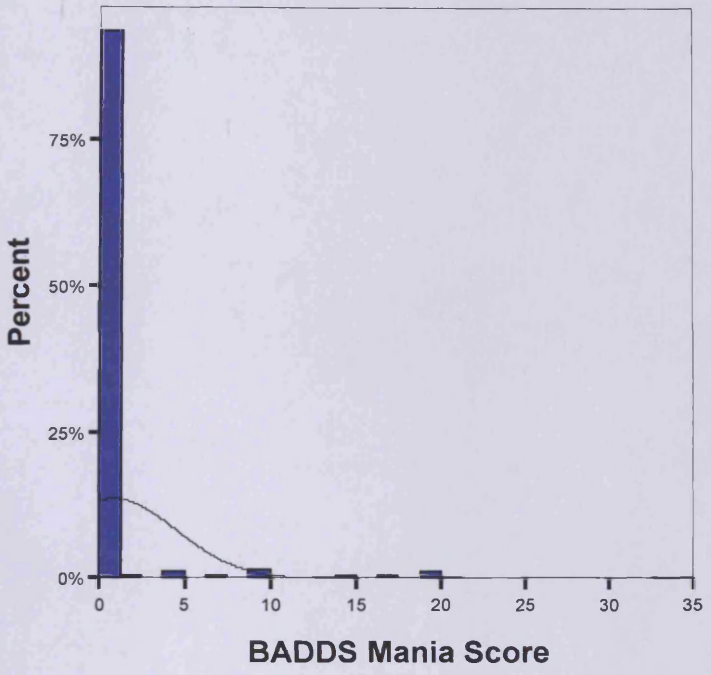
UP N=593



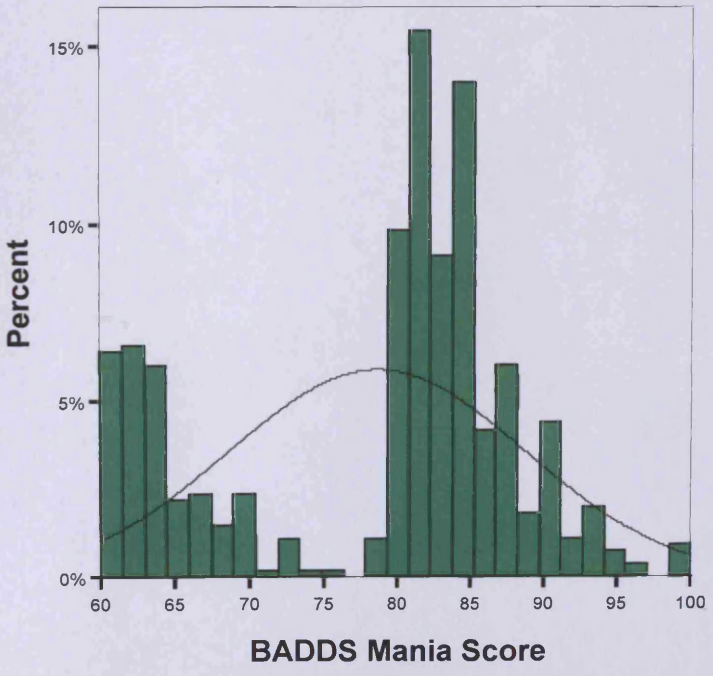
BP N=530



UP N=589



BP N=550



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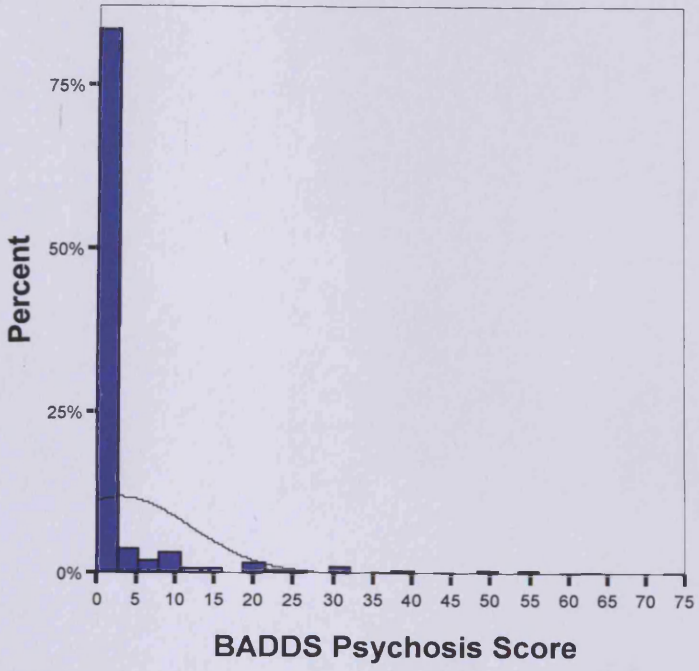

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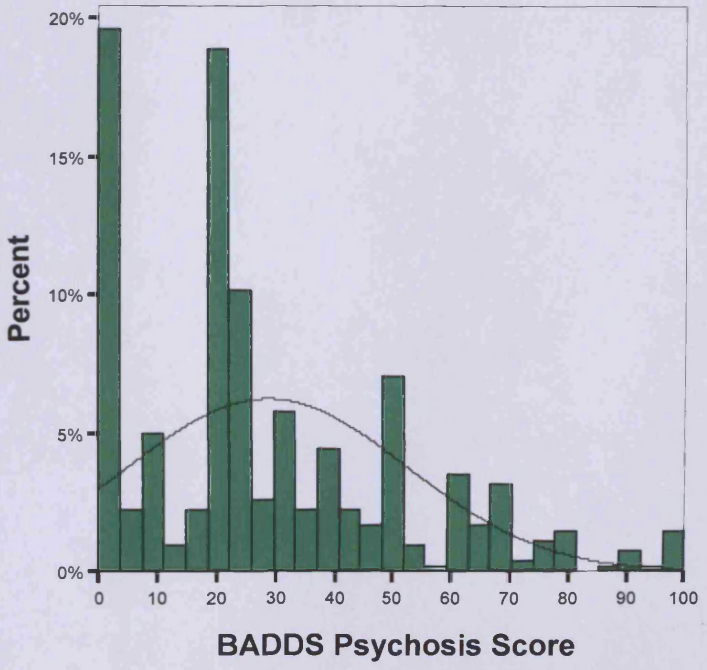
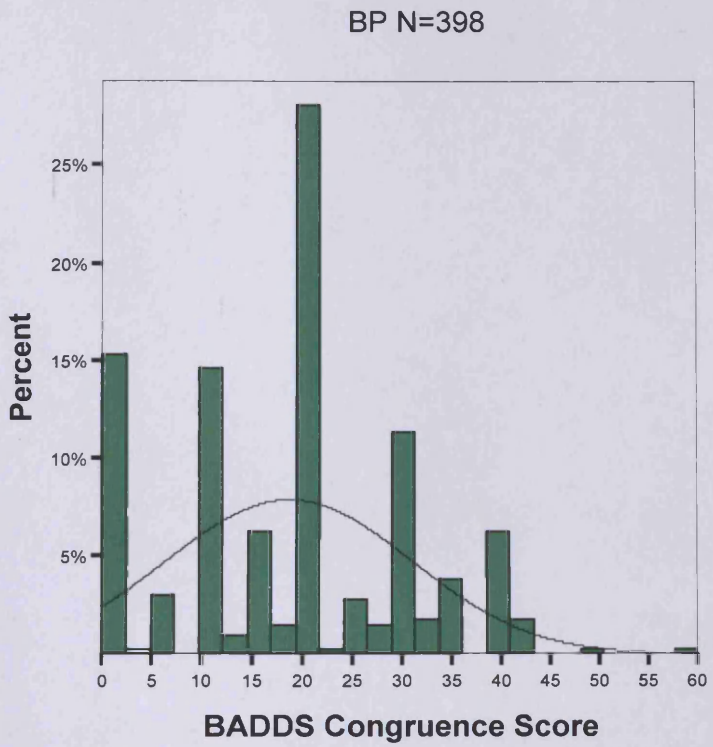
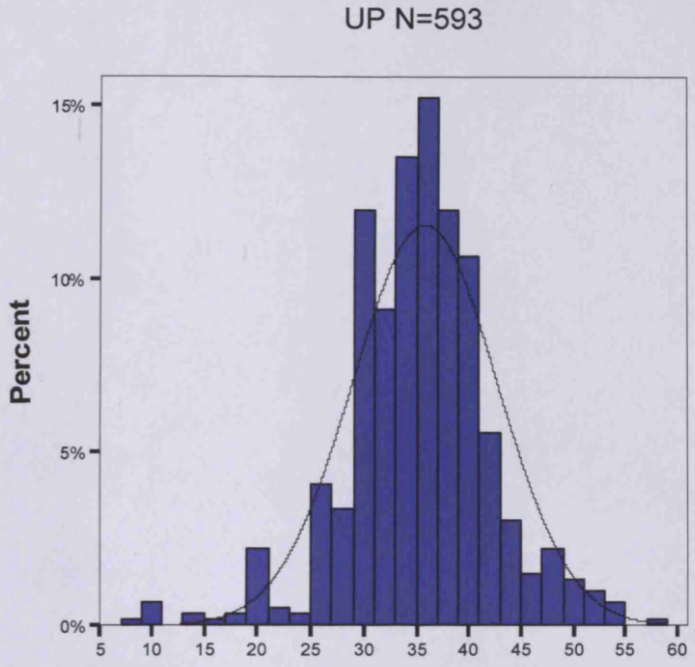
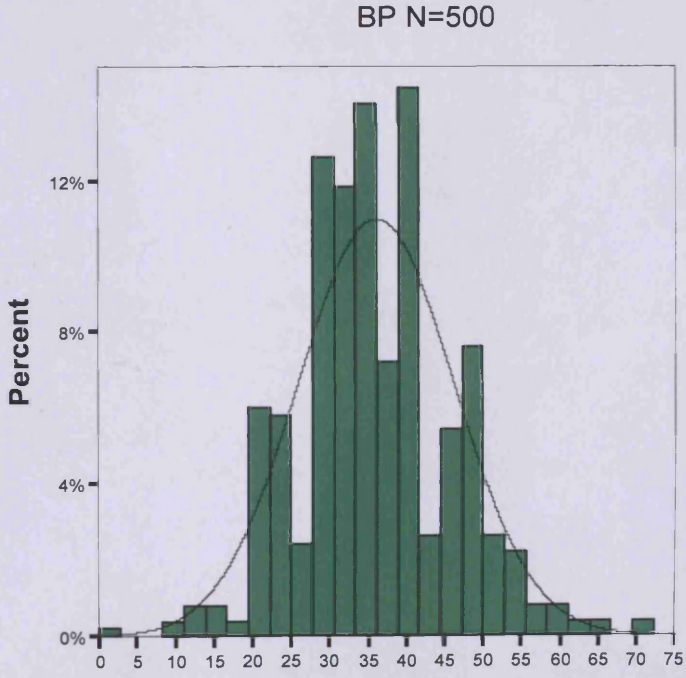


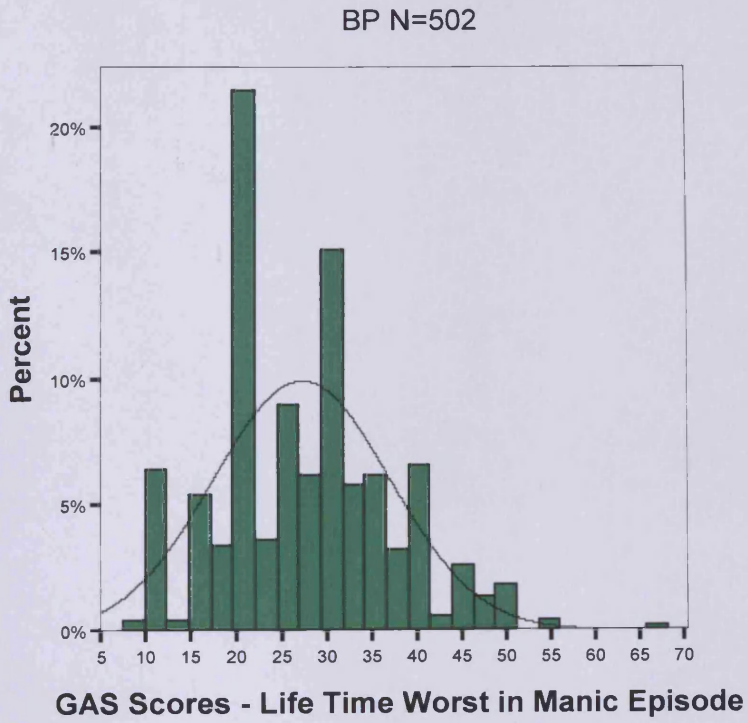

BP N=398
Percent
25%
20%
15%
10%
5%
0
5
10
15
20
25
30
35
40
45
50
55
60
BADDS Congruence Score

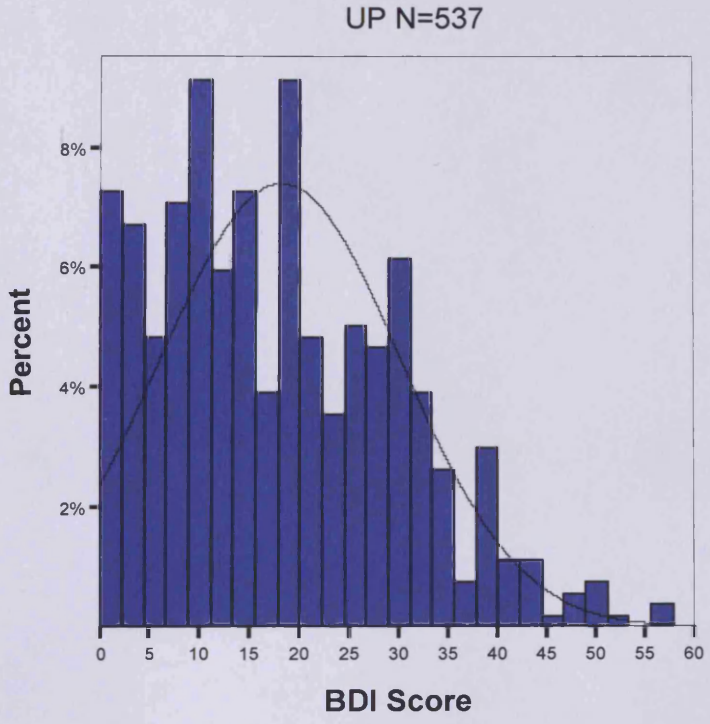


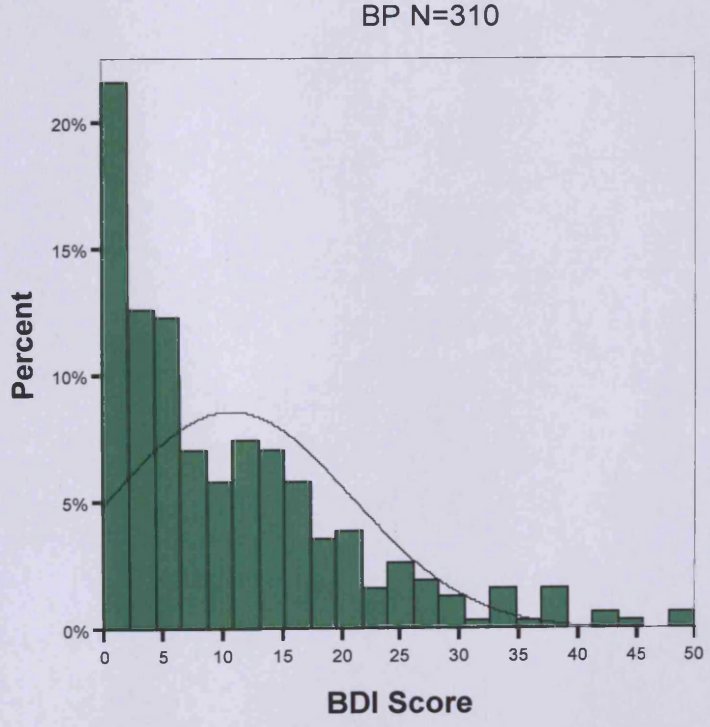
GAS Scores - Life Time Worst in Depressive Episode



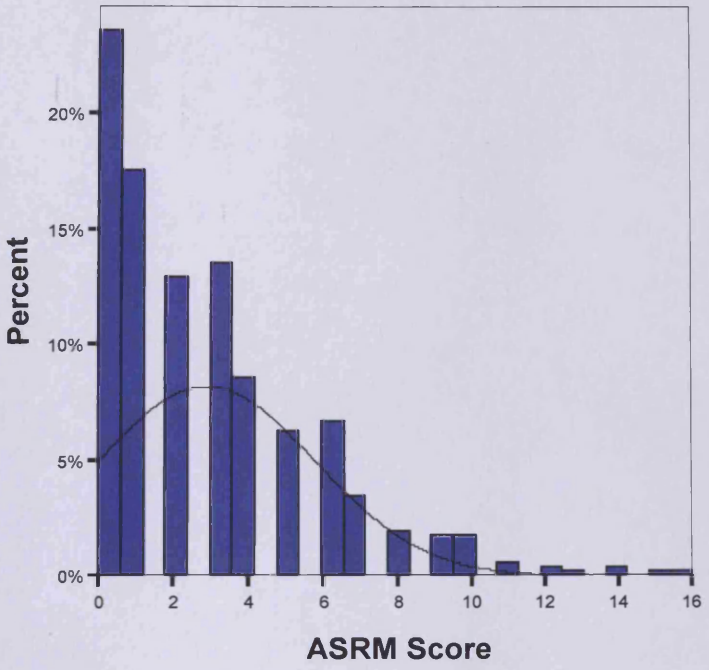
GAS Scores - Life Time Worst in Depressive Episode


BP N=502
Percent
20%
15%
10%
5%
0%
5
10
15
20
25
30
35
40
45
50
55
60
65
70
GAS Scores - Life Time Worst in Manic Episode


UP N=537
Percent
8%
6%
4%
2%
0
5
10
15
20
25
30
35
40
45
50
55
60
BDI Score


BP N=310
Percent
20%
15%
10%
5%
0%
0
5
10
15
20
25
30
35
40
45
50
BDI Score

UP N=524



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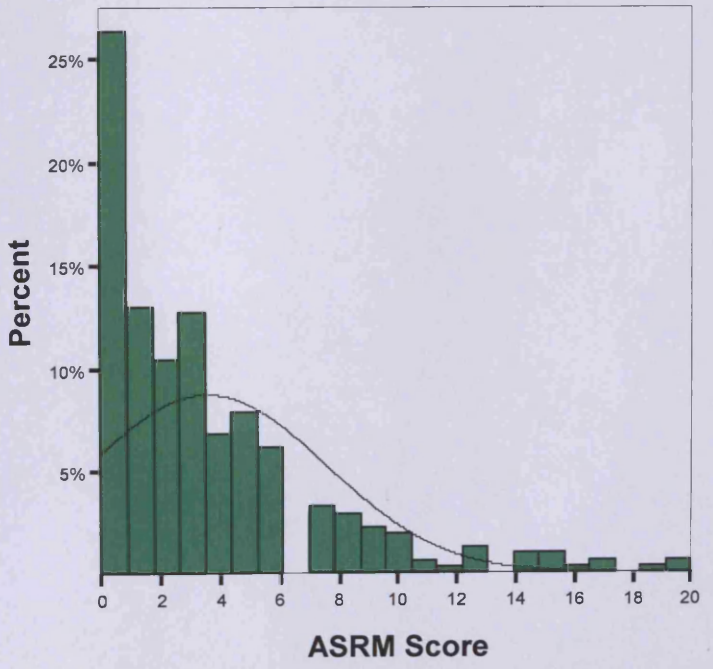
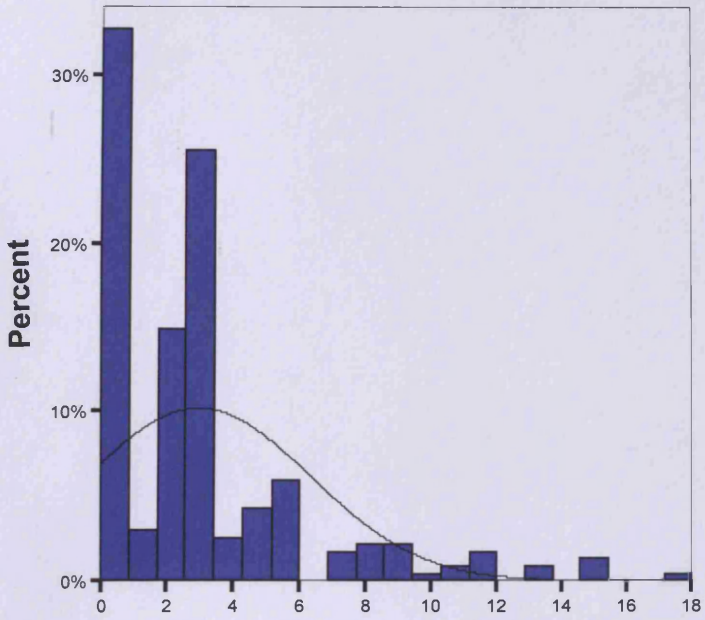
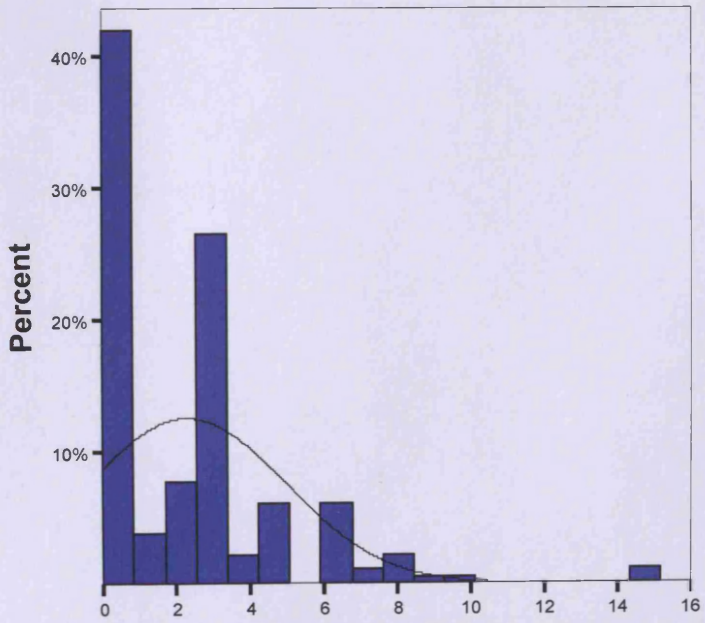


UP Sibling Pairs N=236



BLEQ Score: Six months prior to the worst ever episode of depression

UP Sibling Pairs N=181



BLEQ Score: Six months prior to the first ever (onset) episode of depression