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Validity of the Bipolar Spectrum in Depression

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Abbreviations

ANOVA	Analysis Of Variance
AUDIT	Alcohol Use Disorders Identification Test
BADDS	Bipolar Affective Disorder Dimension Scale
BDI	Beck Depression Inventory
BMQ	Beliefs About Medicines Questionnaire
BD	Bipolar disorder
BSD	Bipolar Spectrum Disorder
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI	Clinical Global Impression Of Illness Scale
crMDD	Chronic Recurrent MDD
CTL	Control
DAST-20	Drug Abuse Screening Test
DS	Digit Symbol Substitution Test
DSM	Diagnostic And Statistical Manual
E	Extraversion
ECA	Epidemiologic Catchment Area
EPQ-RSF	Eysenck Personality Questionnaire – Revised (Short Form)
FIGS	Family Interview For Genetic Studies
GAF	Global Assessment Of Functioning
GHQ	General Health Questionnaire
GPCR	G Protein-Coupled Receptor
GWAS	Genome Wide Association Study
HCL	Hypomania Checklist
HDRS	Hamilton Depression Rating Scale
HWE	Hardy-Weinberg Equilibrium
ICD	International Classification Of Disease
LTE-Q	List Of Threatening Experiences – Questionnaire
LM	Logical Memory
MADRS	Montgomery And Åsberg Depression Rating Scale
MARS5	Medication Adherence Report Scale
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDQ	Mood Disorder Questionnaire
MHV	Mill Hill Vocabulary Test
N	Neuroticism
NART	National Adult Reading Test

NCS	National Comorbidity Survey
NICE	National Institute Of Clinical Excellence
NOS	Not Otherwise Specified
PAL	Paired Associates Learning
PD	Personality Disorder
rMDD	recurrent MDD
RTI	Five-Choice Reaction-Time
SADS-L	Schedule for Affective Disorders and Schizophrenia – Lifetime version
SCID	Structured Clinical Interview for DSM Disorders
SD	Standard Deviation
seMDD	Single Episode MDD
SF-12	Short Form Health Survey
SNP	Single-Nucleotide Polymorphism
SOC	Stockings Of Cambridge
SPQ	Social Problem Questionnaire
SRM	Spatial Recognition Memory
SS	Spatial Span
SWM	Spatial Working Memory
TCI-125	Temperament And Character Inventory
TEMPS-A	Temperament Evaluation Of The Memphis, Pisa, Paris And San Diego – Autoquestionnaire
TR	Text Revision
UHC	University Health Centre
UKU	Udvalg For Kliniske Undersøgelser
UP	Unipolar
VF	Verbal Fluency
VRM	Verbal Recognition Memory
WHO	World Health Organisation
YMRS	Young Mania Rating Scale

Abstract

It is recognised that mood disorder diagnostic categories are simplifications with limited validity, and while dimensional measures may be more valid than categories, their utility is uncertain. It has been argued that the criteria for bipolar disorder (BD) are too narrow, and that a 'bipolar spectrum' should be recognised. The validity and utility of a dimensional measure of mania, the Mood Disorder Questionnaire (MDQ), was investigated in a cohort (n = 68) of young adults being treated for an episode of major depressive disorder (MDD). MDQ score was higher in men and correlated positively with number of depressive episodes, personality measures, and negatively with reaction time. In those on antidepressants at three month follow up (n = 36), MDQ correlated moderately with restlessness (r = .39, p = .01) and suicidal thoughts (r = .34, p = .02). A genetic study of MDD, BD and categorically defined bipolar spectrum disorder (BSD) found an association with a single nucleotide polymorphism (rs1202874) in *GPR50*, on Xq28. When BD and BSD groups were combined, the association strengthened (p = .0014; OR 1.97, 95% CI 1.26-3.06). The MDQ was investigated in a sample (n=2942), from the population-based Generation Scotland biobank. The MDQ showed high internal reliability, and in a subset with MDD (n=620), a three component structure. MDQ was higher in men, and in those with recurrent depression, and correlated negatively with age of onset (r = -.191, p = 2×10^{-6}). A trimodal distribution of age-of-onset was observed in those with chronic or highly recurrent MDD. Controlling for age, gender and current distress, MDQ correlated negatively with general intelligence (r = -.100, p = 1×10^{-8}) in controls. Overall there was reasonable evidence that the MDQ had antecedent, concurrent and predictive validity. There was less evidence to support the reliability or validity of BSD. The findings suggested that in those with MDD (particularly with risk factors such as male gender, early age of onset and recurrence) the MDQ may be useful to (1) identify those who may require more intensive monitoring and (2) inform treatment decisions. Thirdly, classifying mood disorders on the basis of prior course, and including dimensional measures, may be more clinically useful.

Declaration

This thesis is my work, except where stated. No part has been submitted for any other degree or professional qualification.

Donald James MacIntyre

25th April 2012

Chapter 1: Introduction

The Scope of Mood Disorders

Mood disorders are an international public health problem (Moussavi *et al*, 2007). The World Health Organisation (WHO) Global Burden of Disease study created a league table of 107 major causes of disability and early mortality worldwide. Unipolar depression came fourth (Murray & Lopez, 1997), above heart disease and stroke. Bipolar disorder was ranked (at number 22) above diabetes, asthma and schizophrenia.

Epidemiological studies estimate that more than 1 in 6 individuals are afflicted by mood disorders at some point in their lives (Kessler *et al*, 1994, 2005) but current treatments are suboptimal for many patients: WHO studies found that about half of treated primary care attenders with depression are still depressed at the end of a year (Goldberg *et al*, 1998; Üstün & Kessler, 2002); a recent Dutch study showed that only were 43% of patients remitted at 6 months and did not suffer a recurrence over the next 3 years, while 17% remained chronically depressed (Stegenga *et al*, 2010).

Mood disorders usually have their onset during working age (Jacobi *et al*, 2004), and tend to run a recurrent or chronic course (Piccinelli & Wilkinson, 1994; Kessler *et al*, 1997; Simpson *et al*, 1997; Spijker *et al*, 2002; Perlis *et al*, 2006b; Eaton *et al*, 2008; Kessing, 2008; Rhebergen *et al*, 2009) with commensurate economic impact: In the UK, recent evaluations suggest that annual direct costs of depression may be as high as £1.7bn, while indirect annual costs of unipolar disorder was estimated to be £7.5bn and bipolar disorder £5.2bn. (Thomas & Morris, 2003; McCrone *et al*, 2008).

A key difficulty in the clinical management of mood disorders is accurate diagnosis (NICE, 2010, pp. 23–24). The evidence that many patients currently diagnosed as ‘unipolar’ will go on to suffer from mania (Akiskal, 1983; Goldberg *et al*, 2001a), and the longstanding recognition that our diagnostic concepts have poor validity

(Kendell, 1976; Farmer & McGuffin, 1989; Cole *et al*, 2008) have led to efforts to refine them. Proposals to recognise a dimensional spectrum of mood disorder (Akiskal, 1983; Ghaemi *et al*, 2008) may be more valid than current categories, but would increase the proportion of patients receiving a bipolar diagnosis (Smith *et al*, 2011) and are the subject of heated debate (Baldessarini, 2000; Spence, 2011).

A Brief Review of the Development of Mood Disorder Classification

Approaches to classification of mental disorders have evolved many times since the first surviving descriptions, which were categorical in nature. Early accounts from the school of Hippocrates of Cos (ca. 460-380 BC) describe three distinct and mutually exclusive categories: phrenitis (which corresponds roughly to our conception of delirium), and two mood disorders: mania and melancholia, which were seen as separate and distinct ailments, with remorselessly deteriorating courses (Jackson, 1986).

This distinction of separateness was challenged five centuries later, when Aretaeus the Cappadocian ('The Clinician of Mania', ca. 100AD) asserted: “Melancholia is the beginning part of mania … The development of a mania is really a worsening of the disease (melancholia) rather than a change into another disease.” (Angst & Marneros, 2001). Although other writers acknowledged a close relationship between melancholia and mania, the orthodox view (that these conditions were distinct, separate and remorselessly deteriorating in course) predominated over much of the next two millennia.

In 1759, the physician Anders Piquer published a monograph about his most famous patient: King Ferdinand VI of Spain, who was afflicted by “melancholic-manic affect”. Piquer believed that melancholia and mania were “one and the same illness” (Goodwin & Jamison, 2007, p. 5). In France an explicitly unitary conception of manic-depressive illness was asserted by Falret (who emphasised the cyclical nature

of mood disorders when he described ‘la folie circulaire’) and, simultaneously in 1854, by Baillarger who described ‘la folie à double forme’. Hypomania was first defined by Mendel in 1881, and the following year, Kahlbaum recognised an attenuated form of alternating mood disorder that today we might classify as cyclothymia (Jackson, 1986).

Kraepelin & Bleuler

Emil Kraepelin (1856 – 1926) finally put the classification of mental illness onto a scientific footing when he began systematically collecting and analysing clinical data on hundreds of his patients. He revised his ideas over his lifetime, but by the eighth edition of his Textbook of Psychiatry (published in 1913) he conceived “manic-depressive insanity” as a single disease entity encompassing all mood disorders, but separate from dementia praecox (schizophrenia), and distinguished by its recurrent course, family history, and its more benign prognosis. His concept of manic-depressive insanity, a diagnosis which he applied to patients who had never experienced manic episodes (Kraepelin, 1921, p. 187) also included “slight colourings of mood” that “pass over without sharp boundary into the domain of personal disposition” (Kraepelin, 1921, p. 1), an observation that presaged contemporary spectrum concepts (Angst, 2002).

Bleuler’s view that “Except in the rare extreme cases we now no longer have to ask, is it manic-depressive or schizophrenia? but to what extent manic-depressive and to what extent schizophrenia?”, placed “affective” illness (as he termed it) and schizophrenia on a spectrum of disorder, without a point of rarity, determined by the number of schizophrenic features (Bleuler, 1924, p. 175). This essentially unitary view of mood disorder and psychosis remains controversial (Craddock & Owen, 2005, 2010; Lawrie *et al*, 2010).

The Unipolar/Bipolar distinction

In 1959 Leonhard proposed that those with recurrent mood disorder be divided into two groups: with bipolar (alternating mania and depression) or monopolar (recurrent mania or recurrent depression) courses (Leonhard, 1959). Angst and Perris in independent family studies (Angst, 1966; Perris, 1966) supported this unipolar-bipolar distinction. However, the observation that relatives of patients with unipolar mania tend to suffer from both depression and mania, argued for the inclusion of unipolar mania in the 'bipolar' category (Abrams & Taylor, 1974; Pfohl *et al*, 1982) - and so it was the presence or absence of mania which became the key feature incorporated into DSM-III (Spitzer, 1981) and, later, DSM-IV and ICD-10.
With this change in emphasis, the hitherto key feature of recurrence was discarded, significantly lowering the diagnostic threshold, particularly for unipolar disorder. A further result was that subsequent studies of 'bipolar' illness tended to focus only on those patients who had been hospitalised for mania, excluding those with more subtle manic symptoms and systematically (mis)classifying them as 'unipolar' (Zimmermann *et al*, 2009).

The situation was partially redressed by the proposal, supported by family history evidence, to designate patients with depression (sufficient to require hospitalisation) and troublesome hypomania not requiring admission, as 'bipolar II' (Dunner *et al*, 1976). Subsequent studies broadened the depressive criterion, dropping the need for admission, further expanding the concept of bipolar disorder (Baldessarini, 2000).

Current Concepts of Mood (Affective) Disorder

Diagnostic categories

These classifications are detailed in ICD-10 (WHO, 1992) and DSM-IV-TR (American Psychiatric Association, 2000). The list of DSM-IV-TR mood disorders captures the difficulty of imposing a categorical system on a patient population in

whom proportions of symptoms vary, in a continuous fashion. See Table 1.

Major Depressive Disorder
Bipolar I Disorder (includes unipolar mania)
Bipolar II Disorder
Cyclothymic Disorder
Dysthymic Disorder
Bipolar Not Otherwise Specified (NOS)
Mood disorder NOS
Depression NOS

Table 1 DSM-IV-TR Mood Disorders

Not only in the first category (in which patients can show modest manic symptoms), but also in the remaining seven categories, a mixture of manic and depressive symptoms may be present. It should be noted that five of the eight (*italics*) are residual 'catch all' NOS or 'sub-threshold' categories (dysthymia and cyclothymia). Attempts to reduce the proportion of patients in residual categories by creating new categories such as bipolar III, IV, V & VI (Klerman, 1981; Akiskal & Pinto, 1999) have not been enthusiastically adopted. A further indication of the poor validity of categorical approaches is that, in both clinical practice and in population samples, individuals usually fulfil criteria for more than one putatively distinct disorder (Kendell, 1975), or sometimes none (Welner *et al*, 1973). Attempts to validate mood disorder diagnoses rest on external validating criteria (Akiskal, 1980).

Validity: External Criteria

As Kendell stated, "validity is concerned with external correlates of class membership – the more important correlates a class has over its defining characteristics, the less likely its validity is to be questioned" (Kendell, 1989). Several strategies for establishing the validity of a clinical syndrome were outlined in a classic paper (see Table 2), initially applied to schizophrenia, in which family history and follow-up studies were used to make a distinction between 'good' and 'poor' prognosis schizophrenia (Robins & Guze, 1970).

1. Identification and description of the syndrome, either by ‘clinical intuition' or by cluster analysis.
2. Demonstration of boundaries or "points of rarity' between related syndromes by discriminant function analysis, latent class analysis, etc.
3. Follow-up studies establishing a distinctive course or outcome.
4. Therapeutic trials establishing a distinctive treatment response.
5. Family studies establishing that the syndrome ‘breeds true’.
6. Association with some more fundamental abnormality - histological, psychological, biochemical or molecular.

Table 2 Strategies for establishing the validity of a clinical syndrome, after Robins & Guze, 1970.

The features of ‘good prognosis schizophrenia’ in this study included depressive symptoms, guilt, thoughts of death and a strong family history of mood disorder, so arguably these patients may have been more appropriately diagnosed with a mood disorder. Other than follow up and family studies, methods for establishing validity include examining biological markers or ‘endophenotypes’ (Gottesman & Gould, 2003), pharmacological response, and demonstration of points or zones of rarity. Validators may be considered as either antecedent, concurrent or predictive. Predictive validity is associated with clinical utility.

Point of Rarity

If categories are valid, it should be possible to demonstrate natural boundaries; zones or “points of rarity” between illness and normality, and between categories (Sneath, 1957; Kendell, 1969); see Figure 1.

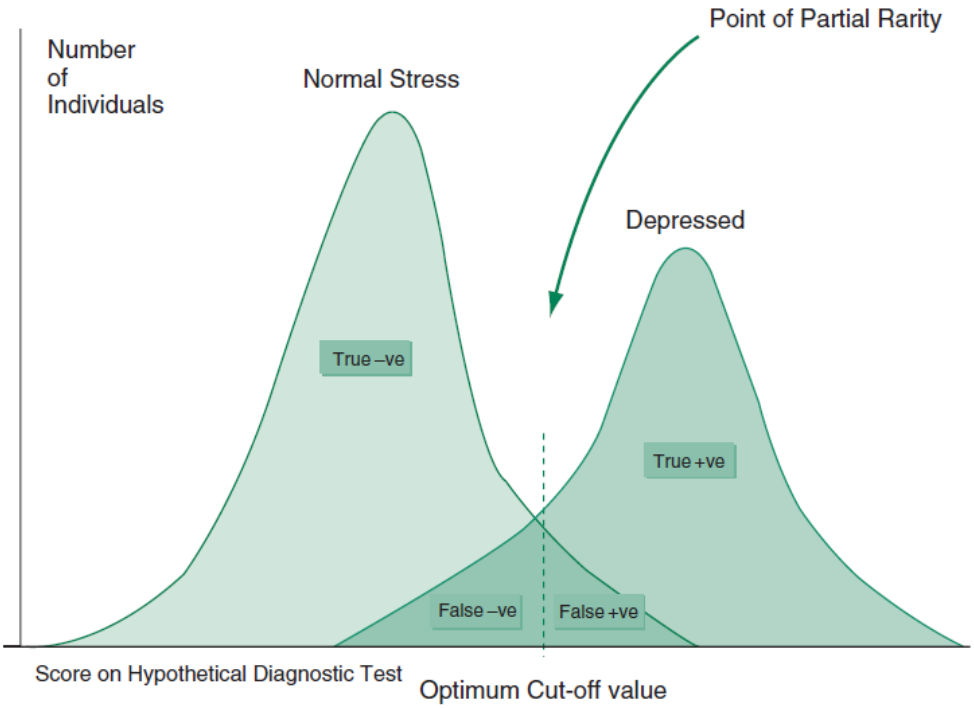


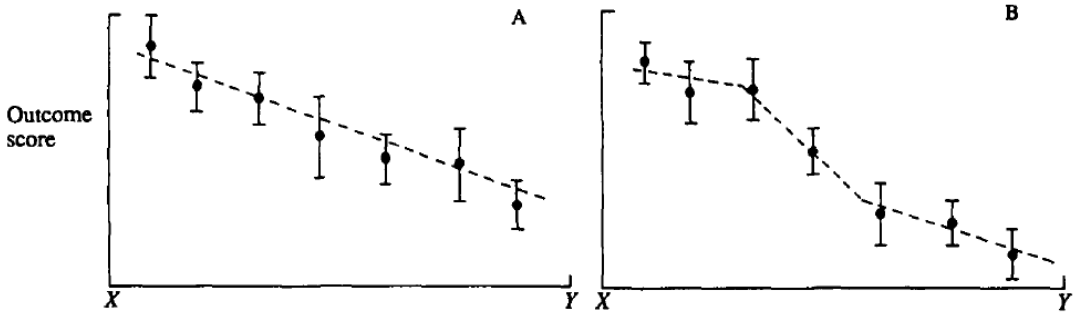
Figure 1 Hypothetical distribution of test scores in two related conditions; Mitchell, 2010.

However, symptoms of common mental disorders are continuously distributed in the consulting population (Goldberg, 2000; Thompson *et al*, 2001; Benazzi, 2003; Cassano *et al*, 2004; Mitchell, 2010), as is disability (Broadhead *et al*, 1990; Judd *et al*, 1996; Hermens *et al*, 2004; Backenstrass *et al*, 2006; Ayuso-Mateos *et al*, 2010), and no "point of rarity" allows mood disorders to be divided from 'normality'. Nevertheless, present diagnostic systems are based on a check-list approach, and make arbitrary distinctions about threshold for 'caseness' based on criteria such as: number of symptoms (for example 5, or more, out of 9 depressive symptoms) (Kendler & Gardner, 1998); duration (for example at least 4 days duration of for hypomania) (Angst, 1998; Judd *et al*, 2003a) or level of impairment (again, for example, in hypomania (Goodwin, 2002))

Outcome Studies

Predicting and altering the future is one of the primary functions of medicine, and a more or less distinctive course is inherent in the concept of a syndrome. However, to prove a qualitative rather than a quantitative difference, it is necessary to demonstrate that the relationship between outcome and symptomatology is non-linear (Kendell, 1989). See Figure 2

Figure 2 Relationship between symptomatology and outcome when symptomatology is converted to a linear variable



X axis: discriminant function or other linear variable expressing variation in symptomatology; Y-axis: outcome score. A, Linear relationship; B, Non-linear relationship; Kendell, 1989.

Endophenotypes

The recognition that psychiatric syndromes represent heterogeneous groups of conditions (of limited utility for genetic dissection), and the hope that more intermediate or fundamental deficits might have simpler, perhaps Mendelian, genetic aetiology, led to the proposal to define phenotypes for genetic analysis by features not visible to the naked eye: so-called ‘endophenotypes’ (Gottesman & Shields, 1973; Gottesman & Gould, 2003), also termed “biological markers”, “subclinical traits” and “intermediate phenotypes”. Endophenotypes may prove useful for clarifying classification systems and, it is hoped, ultimately for aiding diagnosis itself. Explicit criteria for identifying an endophenotype have been described (see *Table 3*)

1. It is associated with illness in the population.
2. It is heritable.
3. It is primarily state-independent (manifests in an individual whether or not illness is active).
4. Within families, it co-segregates with illness.
5. It is found in non-affected family members at a higher rate than in the general population.

Table 3 Characteristics of an Endophenotype; after Gottesman & Shields, 2003

Personality features (such as neuroticism) and cognitive features (such as memory) largely fulfil the stated criteria, and while they are subject to state effects (Kendell & DiScipio, 1968), these are probably not of sufficient magnitude to invalidate them as endophenotypes.

Necessity and benefit of categories

Although it has long been argued that a dimensional classification system of psychiatric disorder would be more valid that a categorical one (Helzer *et al*, 2006), clinicians still need to make categorical decisions about treatment and, to a lesser extent, about diagnosis for wider social and legal purposes. Furthermore, the adoption of explicit diagnostic criteria and rule-based classification of mental disorders has had many benefits, including better diagnostic agreement and communication between clinicians and researchers, and better comparison of groups and outcomes (Lawrie *et al*, 2010). Despite these benefits, significant 'boundary' problems hamper both research and clinical practice (Kendell, 1982).

Utility: Boundary Difficulties in Practice

At the unipolar/bipolar boundary there are at least six significant difficulties that complicate clinical practice and research, namely: poor diagnostic sensitivity to hypomania; so called "false unipolars"; an uncertain duration threshold for hypomania; the uncertain status of mixed episodes; the uncertain status of antidepressant induced mania; and the uncertain status of abnormal personality traits.

1. Poor sensitivity

It is difficult to reliably establish a history of hypomania, particularly in currently depressed patients (Andreasen *et al*, 1981; Dunner & Tay, 1993). However, systematic enquiry by adequately trained clinicians, interviewing family members and repeated interviewing can all increase sensitivity (Simpson *et al*, 2002; Benazzi & Akiskal, 2003a).

2. "False Unipolars"

Patients initially classified as unipolar often later develop an episode of hypomania or mania: Angst showed in a study of 406 patients with major mood disorders hospitalised at some time between 1959 and 1963 and followed-up until 1985, that about half the 'unipolar' patients, initially admitted with a depressive episode, convert to bipolar I or II disorder, while about half the 'bipolar II' patients progressed to bipolar I (Angst *et al*, 2005b). This conversion rate is in line with that of other studies (Akiskal *et al*, 1979, 1983b, 1995; Rao *et al*, 1995; Kovacs, 1996; Goldberg *et al*, 2001a). See Figure 3.

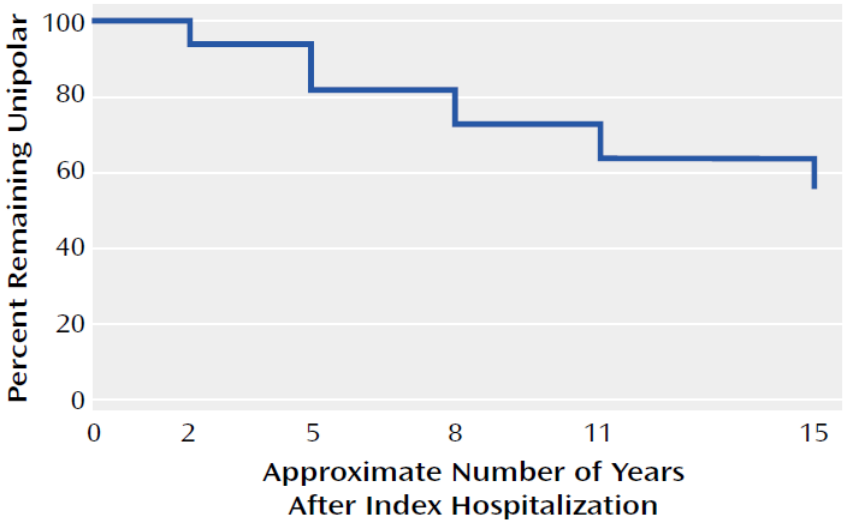


Figure 3 Proportion of patients who remain 'unipolar'; Goldberg, 2001.

3. Uncertain Duration Threshold

Current DSM-IV criteria for hypomania stipulate a minimum duration of 4 days, but epidemiologic data shows that most hypomanias are 1-3 days in duration (Wicki & Angst, 1991) and, on the basis of age of onset, depressive recurrence and familial bipolarity, a 2 day threshold is probably more appropriate (Cassano *et al*, 1992; Manning *et al*, 1997; Angst, 1998; Benazzi & Akiskal, 2001; Angst *et al*, 2003; Judd *et al*, 2003a). Technically these patients can be classified as "bipolar NOS", but most research studies do not mention this group, and in practice they are often misclassified as 'unipolar' (Zimmermann *et al*, 2009). In 153 children and adolescents with bipolar NOS, as a result of short (hypo)manic episodes, 40% went on to meet standard duration criterion within 2.5 years of follow up, and neither family history nor disability distinguished them from youth with BP I disorder (Axelson *et al*, 2006; Birmaher *et al*, 2009). DSM-5 work groups have stated that this finding will inform a recommendation to change the duration criterion (Mood Disorders Work Group, 2010).

4. Mixed Episodes

Kraepelin recognised depressive states with intercurrent manic symptoms. Non-

euphoric manic symptoms, particularly irritability, distractibility and racing thoughts (Serretti & Olgiati, 2005) are frequently present during depressive episodes in patients with bipolar disorder (Akiskal, 1996; Akiskal & Pinto, 1999); however, "Unipolar" depressed patients with intercurrent manic symptoms tend to have a lower age of onset, more recurrence, stronger family histories of bipolar disorder and a poorer response to antidepressants, than those without (Benazzi & Akiskal, 2001; Sato *et al*, 2003; Balázs *et al*, 2006; Smith *et al*, 2009; Angst *et al*, 2011), suggesting they may be better classified as bipolar. It has been proposed that DSM-5 will eliminate the mixed-episode category (currently part of bipolar I disorder in DSM-IV), in favour of a mixed features specifier - that can be applied to depressive, hypomanic and manic episodes (Mood Disorders Work Group, 2012a).

5. Antidepressant induced mania

DSM-IV currently excludes antidepressant-induced manic episodes from contributing to a diagnosis of bipolar disorder, despite family studies which indicate this may be part of a bipolar diathesis (Akiskal *et al*, 2003b; Akiskal & Benazzi, 2003). It could be argued that a patient with a history of anti-depressant induced mania should be treated as if they had a bipolar disorder. It has been proposed that in DSM-5 current criteria should change, so that: "A full [hypo]manic episode emerging during antidepressant treatment (medication, ECT, etc) and persisting beyond the physiological effect of that treatment is sufficient evidence for a [hypo]manic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess or agitation following antidepressant use) are not taken as sufficient for diagnosis of a [hypo]manic episode." (Mood Disorders Work Group, 2012b)

6. Abnormal personality traits

One of the most vexatious difficulties in clinical practice is differentiating between mood and personality disorder (PD) (Akiskal *et al*, 1983a). Studies of remitted inpatients with mood disorder detect PD in about 40% patients (Kay *et al*, 1999; Brieger *et al*, 2003), but during mood episodes this rises to around 60%, with

borderline PD the most prevalent Axis II diagnosis (Peselow *et al*, 1995; Schiavone *et al*, 2004), reflecting the overlap of affective symptoms in both categories. Borderline symptomatology in early-onset depression is predictive of later bipolar outcome (Akiskal *et al*, 1983b).

"Atypical" depressive episodes (with features such as mood reactivity, interpersonal sensitivity and hypersomnia) are common in cyclothymia (Perugi *et al*, 2003), borderline PD (Skodol *et al*, 2002) but also in 'unipolar' patients who ultimately develop bipolar disorders (Akiskal *et al*, 1983b; Perugi *et al*, 1998). To complicate matters further, many episodes of hypomania lack classical euphoria, and are instead characterised by dysphoria and irritability (Akiskal *et al*, 2003a), while tension, restlessness, dysphoria and irritability are common in borderline PD (Coid, 1993).

Summary

Compelling longstanding theoretical objections to current mood disorder categories are accompanied by routine difficulties in their application. A dimensional conception may be more valid and/or useful.

The Bipolar Spectrum

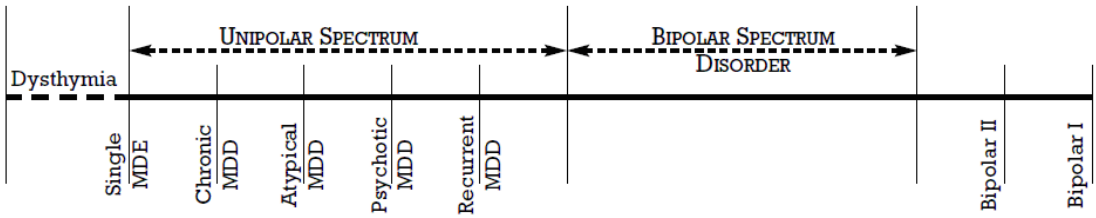
Several Neo-Kraepelinian proposals for a dimensional or 'spectrum' approach to mood disorders have been advanced over the last three decades (Akiskal, 1983; Ghaemi *et al*, 2002, 2004a; Akiskal & Benazzi, 2006; Smith *et al*, 2008).

In theory, any feature of manic-depressive illness could form the basis of a dimension (Goodwin & Jamison, 1990, p. 75), for example, duration or severity of episodes.

Importantly, discrete clinical disorders and continuous dimensions are not mutually exclusive concepts; both are compatible with a threshold model of disease (Kendell & Jablensky, 2003), and analysis of continuous variables increases power to detect relationships (Royston *et al*, 2006)

Models

If the assumption is made that manic symptoms are more severe than depressive symptoms, this allows one-dimensional proposals such as that by Ghaemi and Goodwin (Ghaemi *et al*, 2001). In this conception, bipolar NOS is replaced by "Bipolar Spectrum Disorder" (BSD) - that range of presentations with less manic symptoms than bipolar II disorder (see Figure 4). However this proposal does not address abnormal personality traits or mixed episodes, and it is hard to see how chronic MDD is less severe than atypical MDD, or that psychotic MDD is less severe than recurrent MDD. Furthermore, patients with MDD may be just as disabled as those with bipolar II disorder (Judd *et al*, 2008).



MDE: Major depressive episode
Figure 4 Ghaemi and Goodwin's affective spectrum; Ghaemi, 2001.

A more recent two dimensional model places proportions of depressive and manic symptoms on one axis, and severity on another (Angst, 2007). This model includes subsyndromal disturbance and has face validity; see Figure 5.

Two-dimensional mood/affective spectrum (does not include schizoaffective disorder, as a transition to the schizophrenic spectrum). The precise relationship of personality disorders to the disease spectra is uncertain and an unsolved general problem of psychiatric classification. BP-I (-II), bipolar-I disorder type I (II); D, major depression, d, minor depression; M, mania; m, hypomania; MDD, major depressive disorder; RBD, recurrent brief depression; sx, symptoms

SEVERITY SPECTRUM (MAJOR → MINOR)	PROPORTIONALITY SPECTRUM: DEPRESSION → MANIA				
Psychotic major mood disorders (mood congruent or mood incongruent)	MDD **D**	BP-II **Dm**	BP-I **MD**	**Md**	Mania **M**
Non-psychotic major mood disorders	MDD **D**	BP-II **Dm**	BP-I **MD**	**Md**	Mania **M**
Minor mood disorders (sub-threshold)	Dysthymia RBD Minor depression **d**		Minor BP Cyclothymic disorder **md**		Hypomania **m**
Affective personality disorders[1]	Depressive personality disorder		Borderline/cycloid personality disorder		Hyperthymic personality disorder
Temperament (normal)	Depressive temperament		Cyclothymic temperament		Hyperthymic temperament
Symptoms (normal)	**dsx**		**mdsx**		**msx**
No symptoms (supernormal)	–		–		–

1. The precise relationship of personality disorders to the disease spectra is uncertain and an unsolved general problem of psychiatric classification.

Figure 5 Angst's two dimensional mood spectrum; Angst, 2007.

Craddock proposed the use of four dimensions (Craddock *et al*, 2004) for measuring psychopathology (depression, mania, incongruence and psychosis) as an adjunct to categorical diagnosis. The Bipolar Affective Disorder Dimension Scale (BADDS) takes a lifetime historical approach, and generates an ordinal measure of severity (rather than a measure of symptoms per se) up until the time of the rating. The time required to administer the instrument probably restricts its use to research settings.

Whilst no mood spectrum model has met with widespread acceptance, a two-dimensional proposal by Angst appears to be superior, but is unlikely to help decision making in clinical practice. Those patients who are not at the extremes are likely to represent a sizeable proportion of patients.

Clinical Significance

Reanalysis of the Epidemiologic Catchment Area (ECA) (Judd & Akiskal, 2003) and National Comorbidity Survey (NCS) databases (Merikangas *et al*, 2007) suggested that lifetime prevalence of BSD may be several times that of strictly defined bipolar I & II disorders. Recent re-analysis of the NCS replication sample indicates that BSD accounts for about a third of all patients with mood disorder (Angst *et al*, 2010, 2011).

In clinical practice, misdiagnosing a unipolar disorder in a patient on the bipolar spectrum can have serious consequences (Dunner, 2003) – the standard pharmacological treatment for unipolar disorder (anti-depressant monotherapy) is not recommended for the treatment of bipolar depression: not only is it poorly effective (Ghaemi *et al*, 2004b; Sidor & Macqueen, 2011), but there are risks of triggering mania (Wehr & Goodwin, 1987; Goldberg & Truman, 2003); precipitating treatment resistance (Sharma *et al*, 2005); and increasing suicidal behaviours (Akiskal *et al*, 2005b).

Failure to make the correct diagnosis also delays treatment. International studies

observe an average delay of eight years (see Figure 6) between the onset of a bipolar illness and the initiation of appropriate treatment (Baldessarini *et al*, 1999; Ghaemi *et al*, 1999, 2000; Baldessarini *et al*, 2003). Earlier age of onset is associated with longer delays in diagnosis (Berk *et al*, 2007), and the more years from symptom onset to first mood stabiliser use, the poorer the social functioning of the individual (Goldberg & Ernst, 2002).

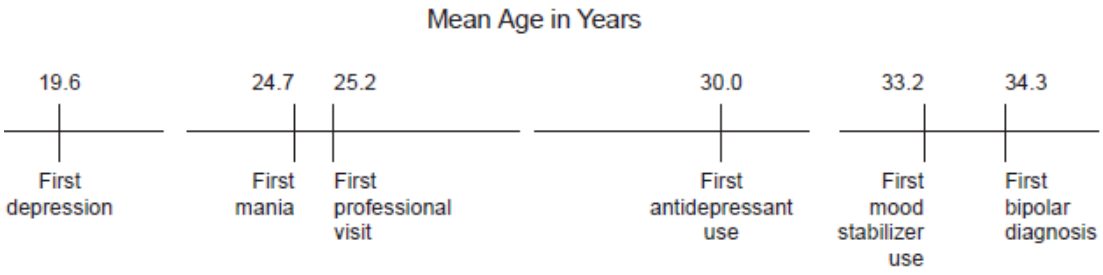


Figure 6 Delay in diagnosis of bipolar patients, from Ghaemi *et al*, 1999.

Nevertheless, misdiagnosis is inevitable, particularly when treating high risk groups like young adults with recurrent depression (Smith *et al*, 2005b). Although up to half may go on to develop a frank bipolar disorder (Goldberg *et al*, 2001b), when seen, they are too early on in the course of their illness to establish a definitive diagnosis. However, there are some features which may predict bipolar outcome in apparently unipolar patients.

Differentiating Unipolar and Bipolar Spectrum Depression.

Neuropsychological, personality, genetic and clinical variables can in theory contribute towards the diagnosis of mood disorder.

Neuropsychology

Neuropsychological research of mood disorders is complicated by many confounding factors – not only boundary problems, but also for example: state (vs. trait) effects,

illness severity and duration, polarity of the episode and presence or absence of psychosis, drug effects and substance abuse.

Nevertheless it has been consistently demonstrated that subtle but widespread cognitive impairments of attention, learning, memory & executive function are a feature of both unipolar and bipolar disorders (Burt *et al*, 1995; Quraishi & Frangou, 2002), in both symptomatic (Wolfe *et al*, 1987; Ravnkilde *et al*, 2002; Porter *et al*, 2003; Martínez-Arán *et al*, 2004; Gruber *et al*, 2007) and remitted states (Cavanagh *et al*, 2002; Clark *et al*, 2002; Thompson *et al*, 2005; Goswami *et al*, 2006; Robinson *et al*, 2006; Hasselbalch *et al*, 2011).

Cognitive deficits show a spectrum of severity, with most impairment in symptomatic bipolar I patients, and least in remitted unipolar depression. Deficits tend get worse with longer duration of illness (Robinson & Nicol Ferrier, 2006). Examination of patients with bipolar II (Torrent *et al*, 2006; Xu *et al*, 2011) and BSD demonstrated intermediate levels of impairment (Smith *et al*, 2006b).

Cognitive impairment in the unaffected first degree relatives of patients with bipolar disorder, compared to controls, indicates that these deficits represent endophenotypes (risk traits), not just scarring or state effects (Gourovitch *et al*, 1999; Nicol Ferrier *et al*, 2004; Clark *et al*, 2005; Frantom *et al*, 2008).

Whilst these cognitive differences are statistically significant across groups, they are of insufficient magnitude to be diagnostically useful, however as endophenotypes they may assist in validation of diagnostic concepts (Gottesman & Gould, 2003).

Personality

Kraepelin's manic-depressive insanity included not only the continuum between bipolar and unipolar disorders, but also the relationship between the most severe forms of mood disorder and those that "pass over without sharp boundary into the

domain of personal disposition". Kraepelin identified four "fundamental states" that he saw as constitutional or temperamental "rudiments of manic-depressive insanity" (Kraepelin, 1921, p. 118), namely depressive (dysthymic), manic (hyperthymic), cyclothymic, and irritable (which has no official contemporary analogue).

Family and cohort evidence argued for the inclusion of cyclothymia within the group of mood disorders (Akiskal *et al*, 1977). The advent of DSM-III (Spitzer, 1981) led to the official recognition of cyclothymia and dysthymia as designated disorders (Akiskal, 2001) on Axis I (mental illness). As a result, previously poorly recognised groups of patients began receiving effective treatment (Silva de Lima *et al*, 2005; Baldessarini *et al*, 2011). "Hyperthymia" is not officially considered a clinical disorder; however there is evidence that patients with depressive disorders, that arise out of a hyperthymic temperament, tend to have stronger family histories of mania than those that do not (Cassano *et al*, 1992, 1999).

How these threshold mood disorders relate to disturbances in personality or temperament is not clear, nor has consensus yet been reached on the number or content of dimensions needed to describe personality (Matthews *et al*, 2003). Eysenck has described three dimensions (Eysenck, 1959, 1967), the most studied being neuroticism (N) and extraversion-introversion (E). Previous studies of E and N in mood disorder have tended to be small and focus on highly selected groups (like in-patients or those attending tertiary referral clinics), fail to control for affective state and use a variety of different personality scales. Their results have often been contradictory. A recent Finish study (which assessed personality using the 57-item Eysenck Personality Inventory, whilst trying to control for affective state) found higher levels of N and lower levels of E in patients with BD and MDD compared to controls, but no statistically significant differences between patients with BD and MDD (Jylhä *et al*, 2010). Similarly, a recent UK study, using the Eysenck Personality Questionnaire – Revised Short Form (*q.v.* Chapter 4, page 65), distinguished cases from controls on N & E but, likewise, these measures did not differentiate bipolar from unipolar subjects (Smillie *et al*, 2009). One explanation for this failure might be that these studies did not consider recurrence.

Akiskal and colleagues have developed a temperamental evaluation tool which can be administered by questionnaire (Akiskal *et al*, 2005a, 2005c). When the temperaments of currently depressed bipolar and unipolar patients were compared, bipolar patient scored higher on measures of cyclothymic temperament (Mendlowicz *et al*, 2005), however a larger study of patients across the bipolar spectrum, using the same instrument, failed to find evidence of a gradient of temperament when confounders such as current mood state were taken into account (Di Florio *et al*, 2010).

A combination of inherited temperamental factors (harm avoidance, novelty seeking, reward dependence, persistence) and character factors (self-directedness, cooperativeness, self-transcendence) which arise during development (Cloninger *et al*, 1993), map onto Kraepelin's fundamental states (Cloninger *et al*, 1998). In one study of depressed young adults, these factors did not distinguish those with and without BSD (Smith *et al*, 2005a).

In summary, assessment of temperament/personality is feasible in currently depressed patients, but so far its role in distinguishing mood disorders is uncertain. It may be a viable endophenotype (Savitz & Ramesar, 2006).

Genetics

Whilst early family studies of mood disorder (before the mid-1960s) did not make the unipolar/bipolar distinction, they nevertheless provided strong evidence of familial aggregation of the broad phenotype of mood disorder (Tsuang, 1990). More recent twin and adoption studies (Craddock & Forty, 2006) clarify the relative importance of genetic and environmental influences (see Table 4).

	Bipolar disorder	*Unipolar depression*
Recurrence risk in sibling of a proband (λ_S)	5–10	2.5–3.5
Proband-wise MZ twin concordance (%)	45–70	40–50
Heritability estimate (%)	80–90	33–42

Table 4 Genetic Epidemiology of Mood Disorders; Craddock and Forty, 2006.

The heritability of unipolar depression (Sullivan, 2000) has been estimated at 31-42%, and that of bipolar disorder (Craddock & Jones, 1999) may be as high as 80-90%. How this genetic risk is transmitted is the subject of considerable controversy. If genes of large effect were commonly implicated, it is expected that linkage studies should have produced more consistent results.

Candidate-gene association studies (which examine one or a few putatively involved genes) have been conducted on about 1% of those genes active in the brain during development and thereafter, but these studies have shown inconsistent results. More recently thousands of DNA samples, gathered by researchers from many centres, have been subjected to genome-wide association studies (GWAS) in both unipolar (Sullivan *et al*, 2008; Wray *et al*, 2012) and bipolar disorder (Sklar *et al*, 2008; Ferreira *et al*, 2008).

Genetic studies are hampered by the nature of psychiatric disorder: clinical syndromes likely represent a heterogeneity of conditions with multiple genetic causes (Ginsburg *et al*, 1996). Furthermore, genetic abnormalities can have pleomorphic expression and are variably penetrant: for example, Huntington's Disease, a disorder caused by a dominantly-inherited single-gene defect, can manifest with a wide variety of neuro-psychiatric presentations including anxiety, mood disorders and even psychosis, or no psychiatric symptoms at all (Jauhar & Ritchie, 2010). Furthermore, chromosomal abnormalities which segregate with psychiatric disorder (Blackwood *et al*, 2001; MacIntyre *et al*, 2003), and the

candidate genes identified in these families show associations that do not respect traditional diagnostic boundaries: for example, increasing risk for anxiety, mood and psychotic disorders (Knight *et al*, 2009).

So far, a number of genes are implicated in mood disorder, including *DISC1*, *CACNA1C*, *ANK3* (Barnett & Smoller, 2009; Gaysina *et al*, 2009; Sklar *et al*, 2011) and *GPR50* (Thomson *et al*, 2004). Few clear findings have been replicated, suggesting that most genes involved are of modest effect size, and that even larger clinical samples may be required. Novel ways of defining phenotypes may aid genetics research (Craddock *et al*, 2004; Cross-Disorder Phenotype Group of the Psychiatric GWAS Consortium *et al*, 2009).

Although psychiatric genetics may eventually clarify the pathogenesis of mental disorders, it is not yet useful in routine clinical practice. However, genetic analysis may help validate novel bipolar phenotypes.

Clinical

Cross-sectional and cohort studies have reliably identified clinical characteristics more common in bipolar than unipolar depression (Forty *et al*, 2008): male gender, early age of onset (Perris & D' Elia, 1964; Weissman *et al*, 1996), bipolar and 'loaded' family history, substance abuse, psychosis, diurnal variation, and shorter but greater number of depressive episodes (see Table 5).

	Bipolar	Unipolar
History of mania or hypomania (definitional)	Yes	No
Temperament	Cyclothymic	Dysthymic
Sex ratio	Equal	Women>men
Age at onset	Teens, 20s, and 30s	30s, 40s, 50s
Onset of episode	Often abrupt	More insidious
Number of episodes	Numerous	Fewer
Duration of episodes	3–6 months	3–12 months
Postpartum episodes	More common	Less common
Psychotic episodes	More common	Less common
Psychomotor activity	Retardation >agitation	Agitation >retardation
Sleep	Hypersomnia >insomnia	Insomnia >hypersomnia
Family history		
Bipolar disorder	High	Low
Unipolar disorder	High	High

Table 5 Differentiating bipolar and unipolar disorders by clinical characteristics; Akiskal, 2005.

Excessive self-reproach, loss of energy and diminished libido are more common in unipolar depression (Akiskal, 2005; Bowden, 2005; Perlis *et al*, 2006a). Poor response to anti-depressant treatment may predict eventual bipolarity (Li *et al*, 2012).

Recently published guidelines from the International Society for Bipolar Disorders Diagnostic Task Force have argued (Ghaemi *et al*, 2008) for a dimensional rather a categorical distinction between unipolar depression and bipolar disorder, and a 'probabilistic' approach to diagnosis has been advocated (Mitchell *et al*, 2008), and had some early validation (Mitchell *et al*, 2011).

Although clinical features may be suggestive, and probabilistic approaches are promising, they do not yet allow a definitive diagnosis. Neuropsychological features are too subtle, and our current understanding of genetics cannot aid clinical decision making. However, analysis of these features may provide external validation of novel

bipolar phenotypes.

The Mood Disorder Questionnaire

It has been argued that dimensional assessment of clinical features will aid diagnosis and research (Angst *et al*, 2005a; Nassir Ghaemi *et al*, 2005; Forty *et al*, 2008).

The use of questionnaires to develop dimensional measures is well established. The Mood Disorder Questionnaire (MDQ) is a 15 item self-report checklist based on DSM-IV manic criteria, initially designed as a screening instrument for bipolar disorder (Hirschfeld *et al*, 2000) in a psychiatric outpatient population (Figure 7, overleaf).

Extension of the use of the MDQ in large population samples (Hirschfeld *et al*, 2003b, 2003a) has been criticised, mainly because, like all screening tools, its sensitivity is dependent on the base rate of the disorder in the sample (Zimmerman *et al*, 2004). The final item of the checklist was designed to elicit from the patient if the manic experiences caused any problems. This item reduced sensitivity in patients with poor insight; removing it increased sensitivity, without adversely reducing specificity (Miller *et al*, 2004).

The main focus of this thesis was the assessment of the validity and utility of a dimensional measure of mania, the MDQ.

MOOD DISORDER QUESTIONNAIRE (MDQ)

INSTRUCTIONS:

Please answer each question as best you can.

		Yes	No
1	Has there ever been a period of time when you were not your usual self and ...		
	– you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	☐	☐
	– you were so irritable that you shouted at people or started fights or arguments?	☐	☐
	– you felt much more self-confident than usual?	☐	☐
	– you got much less sleep than usual and found that you didn't really miss it?	☐	☐
	– you were more talkative or spoke much faster than usual?	☐	☐
	– thoughts raced through your head or you couldn't slow your mind down?	☐	☐
	– you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
	– you had much more energy than usual?	☐	☐
	– you were much more active or did many more things than usual?	☐	☐
	– you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
	– you were much more interested in sex than usual?	☐	☐
	– you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
	– spending money got you or your family in trouble?	☐	☐
2	If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	☐	☐
3	How much of a problem did any of these cause you–like being unable to work; having family, money or legal trouble; getting into arguments or fights?		

☐ No problem ☐ Minor problem ☐ Moderate problem ☐ Serious problem

Figure 7 Mood Disorder Questionnaire (Hirschfeld *et al*, 2000)

Outline

1. A prospective clinical, cognitive and psychological follow-up study of young adults with an episode of DSM-IV major depressive disorder was conducted to determine the validity and the utility of the MDQ.

2. Genetic samples, collected from the participants of the clinical study, were pooled with other samples collected locally, and a candidate-gene association study was conducted to test the validity of the BSD category.

3. A cross-sectional population-based study to determine the validity of the MDQ was conducted using data from the Generation Scotland: Scottish Family Health Study.

Chapter 2: A Prospective Clinical, Cognitive And Psychological Study

Introduction

Bipolar disorder is often initially misdiagnosed (Zimmermann *et al*, 2009), with an average of around 8 years delay in making the correct diagnosis (Ghaemi *et al*, 1999). Earlier age-of-onset is associated with longer delays in diagnosis (Berk *et al*, 2007) and delayed treatment results in poorer outcomes (Goldberg & Ernst, 2002). Young adults with a major depressive episode are at high risk of misdiagnosis (Smith *et al*, 2005b). Furthermore, the boundary between unipolar and bipolar disorders is uncertain and failures to find zones of rarity between different disorders or even between 'normality' and 'disorder' (Kendell & Jablensky, 2003) have led to disease 'spectrum' models (Angst, 2007). Dimensional measures of mania like the Mood Disorder Questionnaire (MDQ) (Hirschfeld *et al*, 2000) may help clarify the validity of the bipolar spectrum concept, and ultimately improve our ability to detect important clinical differences. The validity and utility of the MDQ in young adults presenting with an episode of major depression depressive disorder was unknown. It was hypothesised that in those with a DSM-IV diagnosis of Major Depressive Disorder, the MDQ would correlate with external validators of bipolar disorder. To be clinically useful, the MDQ would require predictive validity (Kendell, 1989). A clinical, cognitive and psychological study was conducted.

Method

Recruitment of participants

Patients

All patients (n=64) were recruited from the psychiatry clinic serving the University Health Centre (UHC). Over 90% of students at Edinburgh university are registered with a general practitioner at the UHC.

Over a twenty-one month period, between May 2005 and January 2007, 314 referrals were made by General Practitioners (GPs) at the UHC of patients with a working diagnosis of depression. All patients were clinically assessed by the author and eligibility was determined.

Controls

Study participants were asked to volunteer friends who had no personal history of depression to act as controls. Thirteen controls were recruited in this way. Additional controls were recruited from medical students attending teaching at the Royal Edinburgh Hospital (14) and their non-medical friends (5). In total there were 32 control subjects.

Ethical Approval

The work was approved by Lothian Research Ethics Committee and participants gave informed consent in writing.

Eligibility Assessment

Patients were determined to be eligible if:

1. they were currently suffering from an episode of DSM-IV major depressive disorder, with either a Hamilton Depression Rating Score of at least 15 or a Beck Depression Inventory of at least 20.

and

2. they were younger than 25 or had had at least one previous episode of DSM-IV major depression before the age of 25.

Patients were excluded if they had poor English or a previous serious head injury.

These criteria are slightly broader than a previous study in this population (Smith *et al*, 2005b), which excluded those with a single episode of depression, and used a lower maximum age-of-onset, at 22 years.

From the original 314 referrals to the clinic, 217 (69%) attended and were assessed. Of those who were assessed, 72 (33%) were eligible. Of those seventy-two, 8 declined to participate, but 64 (89%) agreed, gave written informed consent, and provided baseline data. All patients were given treatment as usual and followed up at least monthly by the author.

Forty-eight (75%) patients stayed in follow up at 3 months and provided outcome data.

All data were collected by the author.

Clinical Assessment

The core diagnostic assessment was made using the Structured Clinical Interview for DSM-IV-TR (First *et al*, 2002).

Overall severity of current episode was recorded according to the Clinical Global Impression of Illness scale (CGI) (Guy, 1976). Current mood state was assessed using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), the Young Mania Rating Scale (YMRS) (Young *et al*, 1978), and the Beck Depression Inventory (BDI) (Beck *et al*, 1961).

'Bipolarity' was assessed by: Ghaemi's novel diagnostic criteria (Ghaemi *et al*, 2002) for bipolar spectrum disorder; a 15-item hypomania checklist (Angst *et al*, 2003; Smith *et al*, 2005b) and the first thirteen items of the MDQ (Hirschfeld *et al*, 2000).

Family history was elicited using the structure of the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992).

Substance use was assessed using the Drug Abuse Screening Test (DAST-20) (Skinner, 1982) and the Alcohol Use Disorders Identification Test (AUDIT) (Saunders *et al*, 1993).

The Global Assessment of Functioning (GAF) component of DSM-IV-TR (ibid), the social problem questionnaire (SPQ) (Corney, 1988), and the 12-item version of the Short Form Health Survey (SF-12) (Ware *et al*, 1996) were used to assess psychosocial functioning. Life events during the preceding 6 months were elicited using a modified version of the List of Threatening Experiences – Questionnaire version (LTE-Q) (Brugha & Cragg, 1990).

Physical symptoms were elicited using a modified version of the UKU [Committee On Clinical Investigations] side effect rating scale (Lingjaerde *et al*, 1987).

Beliefs about medicines were elicited using the Beliefs about Medicines Questionnaire (BMQ) (Horne *et al*, 1999), while adherence was estimated using the Medication Adherence Report Scale (MARS5) (Horne & Weinman, 1999).

Cognition

Intelligence was estimated using the National Adult Reading Test (NART) (Nelson & Willison, 1991). The NART is a measure of pre-morbid verbal IQ, and is highly correlated with full-scale IQ.

As noted in Chapter 1, impairments of attention, learning, memory & executive function are a feature of both unipolar and bipolar disorders, and show a spectrum of severity, with most impairment in symptomatic bipolar I patients, and least severity in remitted unipolar depression. Patients with bipolar II and "bipolar spectrum disorder" demonstrate intermediate levels of impairment. Attention has a widespread impact on cognitive function.

In the present study the domains of executive function, memory and attention were assessed, using a fixed-order series from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins *et al*, 1994, 1998): Spatial recognition memory (SRM) is predominantly a test of visual memory. Paired associates learning (PAL) is a test of visual memory and learning. Verbal recognition memory (VRM) is a test of verbal memory. Five-Choice Reaction Time (RTI) is a test of sustained attention and psychomotor speed. Spatial Span (SS), Spatial Working Memory (SWM) and Stockings of Cambridge (SoC) are test of executive function, working memory, and planning. The tests were administered in the following order: SRM, PAL, VRM – immediate, RTI, SSP, SWM, SOC and finally VRM – delayed. All testing was done in a quiet room, at around 11am, to control for any diurnal variation in performance.

Personality

Personality was evaluated with the Temperament Evaluation of the Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) (Akiskal *et al*, 2005c) and the 125 item Temperament and Character Inventory (TCI-125) (Cloninger, 1994).

The timing of data collection at recruitment and at follow up are tabulated in *Table 6*.

Measure	t=0	t=3/12
SCID	x	
HDRS	x	x
MADRS	x	x
YMRS	x	x
BDI	x	x
MDQ	x	
FIGS	x	
DAST-20	x	
AUDIT	x	
GAF	x	x
SPQ	x	
SF-12	x	x
LTE-Q	x	
UKU-SE	x	x
BMQ	x	x
MARS-5		x
NART	x	
CANTAB	x	x
TEMPS-A	x	
TCI-125	x	x

Table 6 Timing of data collection

Data Analysis

An alpha level of .05 was used for all statistical tests. Where stated, when there was prior evidence of a relationship, one-tailed tests were used; otherwise 2-tailed tests were used. Change in GAF, BDI and HDRS were assessed by calculating proportional change.

Differences between means were assessed by independent-sample t-test, or one-way

independent analysis of variance (ANOVA) as appropriate. Non-parametric data were analysed with the Mann-Whitney test, or Kruskal-Wallis test as appropriate. Continuous data were subject to bivariate Pearson's correlation.

Cohen's conventions for effect size (Cohen, 1992) were used throughout. Analysis was conducted using SPSS version 19.

Results

Demographics

The demographic characteristics and substance use history of the whole sample are displayed in Table 7, along with the depressive symptoms and severity measures of the patients.

	patients n = 64	controls n = 32
female n(%)	39 (60.9)	19 (59.4)
Caucasian n(%)	56 (87.5)	26 (81.3)
age: *M* (*SD*)	22.6 (3.76)	23.3 (3.99)
age at onset: *M* (*SD*)	16.7(2.85)	
in a relationship n(%)	29 (45.3)	22 (68.8)
SE class n(%)		
1	42 (65.6)	22 (68.8)
2	9 (14.1)	7 (21.9)
3-8	13 (20.3)	5 (9.4)
yrs education: *M* (*SD*)	16.5 (2.33)	16.5 (2.01)
accommodation n(%)		
in halls	5 (7.8)	---
sharing	42 (65.6)	20 (62.5)
own flat	14 (21.9)	9 (28.1)
with relatives	3 (4.7)	3 (9.4)
IQ: *M* (*SD*)	117.0 (5.22)	117.9 (3.70)
AUDIT: *M* (*SD*)	7.92 (5.35)	6.19 (3.35)
DAST-20: *M* (*SD*)	1.23 (2.08)	0.34 (0.70)
HDRS: *M* (*SD*)	21.7 (5.21)	
BDI: *M* (*SD*)	27.9 (9.18)	
CGI: *M* (*SD*)	4.44 (0.53)	
GAF: *M* (*SD*)	44.5 (11.0)	

Table 7 Demographics, substance use and symptom severity

The distribution of total scores of the first thirteen items of the MDQ, by gender, is displayed in Figure 8.

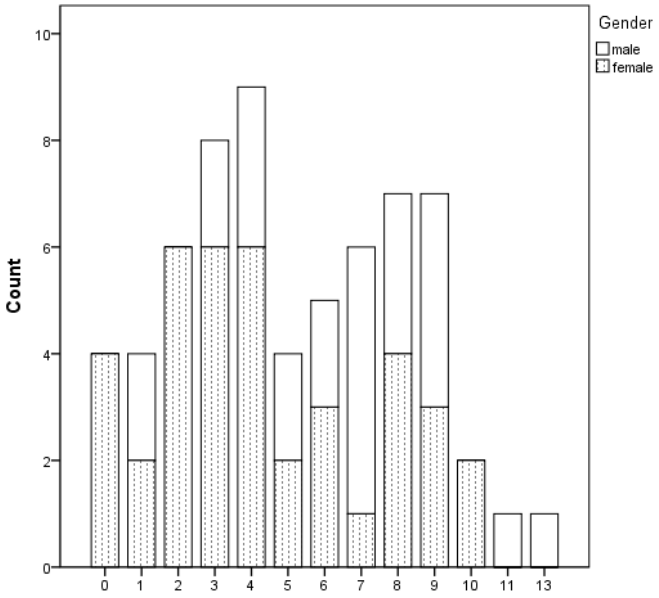


Figure 8 Histogram: MDQ total score by gender

Clinical Characteristics

Clinical characteristics of the sample are displayed in Table 8.

	seMDD n = 7	rMDD n = 57	combined n = 64		
				MDQ	HCL
			n(%)	*M*(*SD*)	
Subtype: Melancholic	2	28	30(46.9)	5.33(3.11)	5.97(3.16)
Atypical	2	10	12(18.8)	5.50(2.74)	6.50(3.48)
Neither	3	19	22(34.3)	4.77(3.39)	5.05(3.76)
MDD FHx nil	4	13	17(20.3)	5.53(2.98)	5.88(3.77)
2nd degree	3	5	8(12.5)	4.00(2.39)	5.50(4.11)
1st degree	---	16	16(25.0)	5.00(3.76)	5.69(3.28)
1st & 2nd degree	---	23	23(35.9)	5.43(3.03)	5.78(3.23)
"loaded" FHx no	7	41	48(75.0)	5.10(3.08)	5.71(3.54)
yes	---	16	16(25.0)	5.38(3.30)	5.88(3.16)
History DSH No	4	27	31(48.4)	5.03(2.67)	5.23(3.44)
Yes	3	30	33(51.6)	5.31(3.52)	6.24(3.38)
Adverse reaction No	6	46	52(81.2)	4.92(2.90)	5.63(3.33)
to antidepressant Yes	1	11	12(18.8)	6.25(3.86)	6.25(3.93)
Antidepressant Yes	5	33	38(59.4)	4.92(3.05)	5.37(3.24)
No	2	24	26(40.6)	5.54(3.23)	6.31(3.66)

seMDD – single episode; rMDD – recurrent; FHx: family history

Table 8 Baseline clinical characteristics and the MDQ and HCL

Novel Criteria for BSD

Novel criteria for bipolar spectrum disorder were applied to the sample and the results are shown in Table 9.

	seMDD	rMDD	comb n(%)	MDQ	HCL	test *df* = 62	*r*
n(%)	7(10.9)	57(89.1)	64(100)	*M* (*SD*)			
BSD: yes	---	3	3 (4.7)	7.33(2.08)	11.3(0.58)		
no	7	54	61(95.3)	5.07(3.13)	5.48(3.26)		
MDQ +ve	---	14	14(21.9)	**---**	**8.43(1.95)**	***t* = 4.84**	**.52**
-ve	7	43	50(78.1)		**5.00(3.38)**	***p* < .001**	
MDQ7 +ve	1	23	24(37.5)	**---**	**8.42(2.77)**	***t* = 6.03**	**.61**
-ve	6	32	40(62.5)		**4.15(2.72)**	***p* < .001**	
HCL≥8 +ve	1	21	22(34.4)	**7.59(2.56)**		***t* = 5.41**	**.57**
-ve	6	36	42(65.6)	**3.90(2.60)**		***p* < .001**	

p (two-tailed) < .001 in **bold**; equal variances not assumed;
seMDD – single episode; rMDD – recurrent; comb – combined sample

Table 9 Prevalence of BSD

Clinical and psychological correlations

To further explore the validity of the use of the MDQ as a continuous measure of bipolarity, Pearson's correlations were conducted with continuous clinical variables, temperament and personality measures, and symptoms measures suggestive of adverse reaction to antidepressant treatment; see Table 10.

Pearson's correlations at t = 0		MDQ		HCL	
n = 64		*r*	*p*	*r*	*p*
Clinical	Age of Onset	-.077	.273‡	-.143	.129
	Number of episodes	**.259**	**.019‡**	**.226**	**.036**
	Length of episode (n=37)	.050	.767‡	-.235	.162
TCI-125	**Novelty Seeking**	**.338**	**.003‡***	**.270**	**.015‡**
	Harm Avoidance	.084	.512	-.006	.965
	Self Transcendence	**.453**	**<.001***	**.352**	**.004***
	Cooperativeness	.013	.918	.026	.839
	Persistence	.107	.201‡	**.221**	**.040‡**
	Reward Dependence	-.163	.197	-.120	.345
	Self-Directedness	-.128	.313	-.130	.307
TEMPS-A	Anxious	.110	.387	.140	.272
	Cyclothymic	**.427**	**<.001***	**.369**	**.003***
	Depressive	.000	.998	.021	.868
	Hyperthymic	.200	.057‡	.163	.099‡
	Irritable	**.316**	**.005*‡**	.092	.235
adverse	restlessness	.102	.271	.163	.164
effects‡	agitation	-.116	.244	-.054	.373
	decreased sleep	-.085	.306	-.048	.387
n = 38	DSH thoughts	-.178	.146	-.076	.327
	suicidal thoughts	-.098	.283	.013	.471
		‡one-tailed test; ***p* < .05 in bold**; **p* < .01			

Table 10 Clinical, personality, temperament, and side-effect correlations

Case-control cognitive differences

Case-control comparisons are displayed in Table 11.

Cognitive test	cases n=62 *M*(*SD*)	controls n=32 *M*(*SD*)	*t*-test	*p*	*r*
NART IQ	117.0 (5.22)	117.9 (3.70)	0.08‡	.431	
SRM	78.6 (13.1)	79.7 (13.3)	0.40	.692	
PAL	10.1 (7.9)	9.6 (9.4)	0.27	.785	
VRM	8.4 (2.0)	8.9 (1.7)	1.26	.212	
5CRT	**323.0 (52.58)**	**301.3 (34.4)**	**2.11**	**.037**	**.21**
5CMT	**364.4 (136.3)**	**284.9 (53.7)**	**4.03‡**	**.018**	**.39**
SS	7.1 (1.6)	7.7 (1.4)	1.76	.081	
SWM	15.7 (15.7)	13.6 (13.7)	0.63	.530	
SoC-ITT	11617 (6411)	9601 (6084)	1.46	.146	
SoC-PS	10.11 (1.5)	9.81 (1.6)	0.909	.366	

SRM: Spatial Recognition Memory; PAL: Paired Associate Learning;
VRM: Verbal Memory – immediate free recall; 5CRT: 5 Choice Reaction Time;
SS: Spatial Span; SWM: Spatial Working Memory - between errors;
SOC-ITT: Stockings of Cambridge initial thinking time;
SOC-PS: Stockings of Cambridge problems solved.
‡equal variances not assumed; $p < .05$ in **bold**

Table 11 Cognition: cases and controls compared

Cognitive Correlations

Correlations between cognitive measures and the MDQ and HCL were conducted and are displayed in Table 12

Pearson's *r*		MDQ		HCL	
t = 0 (n = 62)		*r*	*p*	*r*	*p*
	SRM	.053	.685	.206	.108
	PAL‡	-.106	.418	-.042	.746
	VRM‡	.011	.932	.116	.372
	5CRT	**-.302**	**.017**	-.223	.082
	5CMT	-.030	.817	-.008	.954
	SS	.157	.223	.172	.181
	SWM	-.114	.337	-.155	.230
	Soc-ITT‡	.086	.510	.008	.953

SRM: Spatial Recognition Memory; PAL: Paired Associate Learning;
VRM: Verbal Memory – immediate free recall;
5CRT: 5 Choice Reaction Time; 5CMT: 5 Choice Movement Time;
SS: Spatial Span; SWM: Spatial Working Memory - between errors;
SOC-ITT: Stockings of Cambridge initial thinking time;
SOC-PS: Stockings of Cambridge problems solved.

‡n=61; $p < .05$ in **bold**

Table 12 MDQ & HCL Cognitive correlations in MDD patients

Outcome at three months

After recruitment the author, along with the patient's usual GP, treated the depressed patients in the usual manner, and followed them up at least monthly. Forty-eight (75%) of the original 64 participants stayed in follow up and donated outcome data. Thirty-six patients (75%) were taking unopposed antidepressant medication (i.e. without a mood stabiliser) at 3 months. Correlations are presented in Table 13.

	t=3/12	MDQ		*HCL*	
		r	*p*	*r*	*p*
clinical	GAF change	.265	.072	.104	.486
n=48	HDRS change	-.138	.351	-.178	.226
	BDI change	-.081	.583	-.176	.230
adverse	**restlessness**	**.393**	**.009***	**.268**	**.057**
effects‡	agitation	.121	.241	.037	.415
n=36	decreased sleep	.205	.115	.266	.059
	DSH thoughts	.237	.082	.218	.100
	suicidal thoughts	**.338**	**.022**	**.391**	**.009***

‡one-tailed test; p < .05 in **bold**; *p < .01

Table 13 Outcome and adverse effects at 3 month follow up

Discussion

Demographics

The clinical sample, drawn from patients registered at the University Health Centre, is fairly affluent. The control sample is well matched in terms of age, years education IQ and social class. Lower scores on measures of alcohol consumption (AUDIT), and drug use (DAST-20), than one would expect from anonymous surveys in this population probably represent under-reporting. In terms of severity measures, the patients were moderately depressed and impaired, as would be expected in a secondary care out-patient clinic.

The sample were predominantly female. As the gender ratio of bipolar disorder is

equal, but females predominate in unipolar disorder, it was hypothesised that men would score higher than women on the MDQ. No patients scored 12. On average, men scored higher (M = 6.44, SD = 2.92) than women (M = 4.36, SD = 3.00) on the MDQ, $t(62) = 2.74$, p (two-tailed) = .008, and gender represented a medium effect, r = .33. This supports the validity of the MDQ as a measure of bipolarity in this sample.

Clinical Characteristics

The majority of patients (89.1%) had a recurrent depressive disorder. Younger age at onset, and greater recurrence has been reported in bipolar patients. In the current sample, the small number of patients 7 (10.9%) with a single depressive episode had a later age of onset (M = 19.9, SD = 3.02), than those with a previous episode (M = 16.4, SD = 2.61). This was a significant $t(62) = 3.30$, p = .002, and moderate effect, r = .39, and is in line with previous findings. The combined sample age of onset (M = 16.7, SD = 2.85) was roughly a year older than that in the previous study (Smith *et al*, 2005b).

Patients with bipolar disorder tend to have higher rates of atypical depressive features, and 12 (18.8%) participants met criteria for DSM-IV atypical subtype at recruitment. It was hypothesised that those with atypical depression would score higher on the MDQ (M = 5.50, SD = 2.75), than those without (M = 5.10, SD = 3.21) however there was no significant difference, $t(62) = .402$, p = .689.

No patients in the sample had a first degree relative with bipolar disorder, but most (79.7%) had a first or second degree relative with depression. Patients with a single episode of depression reported fewer family members with histories of mood disorder, than those with recurrent depression, as expected. Both unipolar and bipolar disorder probands are know to have high familial levels of depression and, across groups of family history, neither MDQ, $F(3, 60) = 0.51$, p = .68, nor HCL, $F(3, 60) = 0.02$, p = .99, varied significantly. Sixteen patients (25%), all with recurrent

depression, had three or more first-degree relatives with mood disorder, or were from families with three successive generations with mood disorder (so called "loaded" pedigrees, more common in bipolar probands), but they did not differ significantly on the MDQ score, $t(62) = .299$, $p = .77$, or HCL, $t(62) = .167$, $p = .87$, from those without a "loaded" family history.

One previous study found a trend for higher levels of deliberate self-harm (DSH) in bipolar patients (Parker *et al*, 2005) and, in the current sample, patients with a history of DSH tended to score slightly higher on the MDQ ($M = 5.30$, $SD = 3.52$), than those without ($M = 5.03$, $SD = 2.66$), but there was no significant effect, $t(62) = 0.345$, $p = .731$.

Adverse reaction to previous antidepressant treatment was reported by 12 (18.8%) patients, who tended to score higher on the MDQ ($M = 6.25$, $SD = 3.86$) than those who had not reported this problem ($M = 4.92$, $SD = 2.90$), but a failure to record which patients were antidepressant naïve prevented further analysis.

Novel Criteria for BSD

Only three patients (4.7%), all with recurrent depression, fulfilled Ghaemi's criteria in this sample. This is significantly fewer than might be expected from a previous study in this population (Smith *et al*, 2005b), which found a prevalence of BSD of 36.9%, however that cohort had an earlier age of onset, and did not include those with single-episode depression.

Patients with bipolar disorder often struggle to recognise their manic symptoms as pathological. The original categorical criteria of the MDQ (score of 7 or more, occurring at the same period of time, impairing function) were found to have low sensitivity, partly because bipolar patients tended not to endorse the impairment criterion, and it has been suggested that this should be removed (Miller *et al*, 2004). Fourteen (21.9%) patients scored positive on the MDQ original criteria, while a

further 10 patients were positive with the impairment criterion removed ("MDQ7" in the table), giving a total of 24 (37.5%). All patients who scored 7 or more also endorsed the "same period of time" criterion, so this was not discriminatory. An alternative measure, the clinician-elicited 15-item hypomania checklist (HCL) has a threshold of 8 or more for a diagnosis of BSD. Twenty-two (34.4%) patients were positive for BSD by this measure. Patients who were positive for the MDQ and "MDQ7" scored significantly higher on the HCL, and conversely those who were HCL positive scored much higher on the MDQ. These were all large effects, $r > .5$.

In the previous study (Smith *et al*, 2005b), 10% of participants had a first degree relative with bipolar disorder, whilst in this sample no patients were in this category. In the current investigation, rates of depressive disorder in 1st degree relatives were also lower, at almost two thirds, compared with over three-quarters in the earlier study. The low prevalence of Ghaemi's BSD in this study could indicate poor inter-rater reliability for Ghaemi's criteria, but the absence of bipolar family history, and lower rates of depression in 1st degree relatives in this sample could reflect broader entry criteria, changes in referral pattern or random fluctuations. However, it should be noted that using the MDQ (with and without the severity criterion) and the HCL, the prevalence of BSD was comparable with the previous study (*ibid*), at between one and two-fifths of the sample.

Clinical and psychological correlations

As the known age-of-onset in bipolar disorder is, on average, lower than in unipolar depression, it was hypothesised that there would be an inverse correlation between MDQ and age-of-onset. There was a small inverse correlation, $r = -.077$, but this was not significant, p (one-tailed) = .27. The relatively young age, and narrow age range ($M = 22.6$, $SD = 3.76$) of the sample may explain the lack of any association.

As bipolar disorder tends to be more highly recurrent than unipolar disorder, it was hypothesised that number of depressive episodes would show a positive correlation

with MDQ. There was a small to medium positive correlation, $r = .259$, and this was significant, p (one-tailed) = .019; a very similar finding was also seen with the HCL.

Brief major depressive episodes (less than 3 months) are one of Ghaemi's criteria for BSD. It was hypothesised that there would be an inverse correlation between MDQ and length of current depressive episode, however there was no significant effect with either the MDQ, $r = .05$, p (one-tailed) = .38, or the HCL. In practice, it was often difficult for patients to recall the duration of their current depressive episode. The lack of any significant correlation may represent the methodological weakness of retrospective collection of this information.

Temperament and Character Inventory: TCI-125

Studies have found that Cloninger's personality dimension, Novelty Seeking (NS), is higher in patients with bipolar compared to unipolar disorder (Young *et al*, 1995; Evans *et al*, 2005). It was hypothesised that there would be a positive correlation between NS and MDQ. There was a highly significant, p (one-tailed) = .003, positive correlation, $r = .34$. This was a moderate effect.

It was predicted (Cloninger *et al*, 1998) that Self Transcendence (ST) would be associated more strongly with bipolar than unipolar depression, and this finding has recently been reported (Harley *et al*, 2011). In the current sample a significant moderate positive correlation was seen between ST and MDQ, $r = .453$, p (one-tailed) <.001, and a very similar correlation was also found with the HCL.

Several studies found higher levels of Harm Avoidance (HA) in bipolar, compared with unipolar patients (Young *et al*, 1995; Evans *et al*, 2005; Harley *et al*, 2011) but these trends were not statistically significant. In the current sample there was no sizeable or significant correlation between HA and MDQ or HCL. The distribution of HA was negatively skewed, with the modal score equal to the maximum possible score of 20. Correction of negative skew by reflection and log transformation did not

materially alter the result (see Appendix 1). In a previous study (Smith *et al*, 2005a), harm-avoidance measured during euthymia in this population was also high, but not statistically different between 'pure' unipolar and BSD groups, but TCI Persistence (P) was higher in the BSD group. It was hypothesised that P would be correlated with MDQ. Although there was a small, significant, correlation between HCL and P, there was no sizeable or significant correlation with MDQ.

It has been predicted that low Cooperativeness (C) and low Self-Directedness (SD) are more unipolar than bipolar (Cloninger *et al*, 1998), and while in one study, a BSD group did show a non-significant trend in that direction (Smith *et al*, 2005a) another found the converse (Evans *et al*, 2005). In the current sample there was no sizeable or significant correlation between C, SD and either the MDQ or HCL.

Several studies (Evans *et al*, 2005; Smith *et al*, 2005a; Harley *et al*, 2011) have found no difference in Reward Dependence (RD) between unipolar and bipolar groups; in the current sample there was no sizeable or significant correlation.

TEMPS-A

The TEMPS-A has been analysed in patients with bipolar and unipolar disorder in several studies recently reviewed by Di Florio (Di Florio *et al*, 2010); in general, bipolar patients tended to score higher than unipolars on the cyclothymia and irritable subscale and, in this large study, patients with bipolar II scored higher than those with bipolar I disorders. As a whole the bipolar group scored higher than unipolars on the hyperthymic scale, and this was consistent with several previous findings (Gassab *et al*, 2008; Mazzarini *et al*, 2009). Analyses of the dysthymic and anxious scales have not shown consistent results.

It was hypothesised that MDQ would positively correlate with the cyclothymia, hyperthymia and irritable scales of the TEMPS-A. There was a highly significant positive correlation of moderate effect with cyclothymia, $r = .427$, p (one-tailed) <

.001; a moderate positive correlation with irritability, $r = .316$, p (one-tailed) = .005; and a small positive correlation with hyperthymia: $r = .200$, p (one-tailed) = .057. These result persisted after controlling for depressive (BDI) and manic symptoms (YMRS) by partial correlation, and the association with hyperthymia increased slightly in size , $r = .240$, and strengthened in significance, p (one-tailed) = .031 (see Appendix 2).

The use of unopposed anti-depressants in unrecognised bipolar disorder may be associated with switch to mania, poor tolerance of antidepressants, increase in suicidal ideation and poor response (McElroy *et al*, 2006). It was hypothesised that in those taking antidepressants at recruitment (n=38), the MDQ would positively correlate with adverse effects of antidepressants, however, there were no sizeable correlations or any approaching one-tailed significance.

Case-control cognitive differences

Patients with bipolar disorder tend to show more severe cognitive deficits than those with unipolar disorder. It was hypothesised that patients would show significant impairment compared to controls on neuropsychological measures administered by the CANTAB touch screen computer, and that, in the patient group, MDQ would correlate with impairment.

Comparison of depressed patients, versus controls, detected moderate differences on five-choice reaction time and small differences on movement time: controls responded and moved more quickly than patients. No other differences were detected. Although cognitive deficits have been detected between similar groups of patients and controls, even in remitted subjects (Smith *et al*, 2006b), these tests were traditional, well validated, paper and pencil tests. Using the CANTAB system in young adults, several authors have failed to show differences between controls and unipolar depressed patients (Purcell *et al*, 1997; Sweeney *et al*, 2000). Another possible confounding factor was the above-average IQ of the sample. During data

collection the author observed that some quite profoundly depressed patients were able to complete the cognitive tasks without error, so ceiling effects may have played a part.

Cognitive Correlations

It was *a priori* hypothesised that, in the patient group, MDQ would correlate with neuropsychological measures administered by the CANTAB touch screen computer. Although there was a moderate negative correlation, r = -.302, p (two-tailed) = .017, with reaction time, there were no other effects that were sizeable or approaching significance, which may not be surprising, given the paucity of case-control differences.

Outcome at three months

The MDQ and HCL were not correlated with outcome at 3 months, but interestingly there was a moderate, highly-significant positive correlation between MDQ and restlessness, and a similar effect approaching significance with HCL. Furthermore, there was a moderate, significant, positive correlation between MDQ and suicidal thoughts, and this was supported by a similar correlation with HCL.

Strengths and limitations

The main potential limitations of this study were a lack of any external biological validator, the relatively small sample size, and the highly selected population from which the sample was drawn. The fact that some patients had been initiated on drug treatment at recruitment reduced the ability of the study to examine drug effects. The relatively high social status of the sample could be seen as a weakness; on the other hand, cases and controls were drawn from the same fairly homogenous population, and this increased the likelihood of detecting real differences. Furthermore, young

adults are a high-risk group for bipolar disorder, and they also have the most to lose if they are diagnosed or treated inappropriately, so the relatively young age of the sample could be seen as a strength.

Implications

This study supports the observation that manic symptoms are continuously distributed in depressive patient populations (Cassano *et al*, 2004), and indicates that young adults presenting with a major depressive episode have sub-DSM-IV threshold manic symptoms which are non-the less of clinical relevance (Smith *et al*, 2009). It emphasises the need to routinely probe for historical manic experiences, and suggests that both structured clinical interviewing and the MDQ are valid approaches.

Summary

A prospective clinical, cognitive and psychological study of young adults, presenting with an episode of DSM-IV Major Depressive Disorder, examined the validity of a questionnaire-based dimensional measure of historical manic symptoms, and compared it to a clinician elicited checklist. The prevalence of BSD in this sample was 4.7% using Ghaemi's criteria, 34% using the checklist and 22% using the questionnaire. Removing the impairment criterion from the MDQ increased the prevalence of BSD to ~37%. The prevalence of Ghaemi's criteria BSD was lower than expected: this could be partially explained by slightly different inclusion criteria, or may indicate poor inter-rater reliability. Higher scores on the MDQ were significantly associated with male gender, recurrence, greater number of episodes, novelty seeking, self-transcendence, cyclothymic and irritable temperament, *faster* reaction time, and (in patients taking unopposed antidepressants) greater restlessness and suicidal thinking at 3-month follow-up. Effect sizes were small or moderate. The checklist was highly correlated with the questionnaire, and they tended to show very similar associations. This provides evidence that the MDQ, and to a lesser extent the

HCL, are valid measures of bipolarity in young adults with a DSM-IV diagnosis of MDD.

An attempt to test the validity of the bipolar spectrum concept by external biological means, in this case genetic analysis, will be examined presently in Chapter 3. The validity of the MDQ in a larger and more representative sample will be described in Chapter 4.

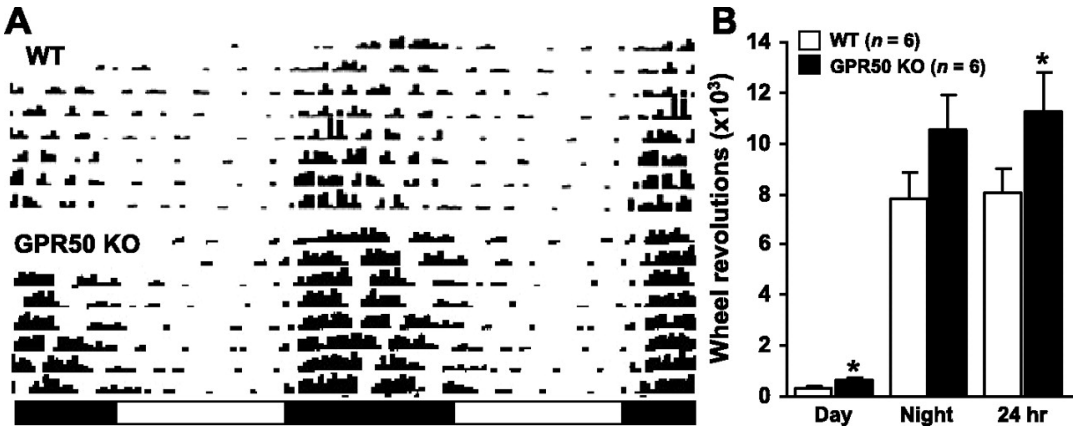
Chapter 3: Genetic association of mood disorder and *GPR50*, an X-linked orphan G protein-coupled receptor.

Introduction

Candidate gene studies, and more recently, genome-wide association studies (GWAS) have identified a number of loci containing variants predisposing to bipolar disorder including: *DISC1*, *CACNA1C*, *ANK3* and *DTNBP1* (Barnett & Smoller, 2009; Gaysina *et al*, 2009; Sklar *et al*, 2011). The melatonin-related G protein-coupled receptor 50 (*GPR50*) is located on Xq28, a region previously implicated in linkage studies for bipolar disorder (Massat *et al*, 2002). RNA in situ hybridisation experiments with human *GPR50* detected expression in the mediobasal hypothalamus (in a region containing the ventromedial and arcuate nuclei), the paraventricular nucleus, and in the infundibular stalk (Reppert *et al*, 1996); expression was also detected in the pituitary gland. The combination of map position on Xq28 and expression pattern makes GPR50 a positional and functional candidate in affective disorder (Thomson *et al*, 2004).

G protein-coupled receptors (GPCRs) mediate transmembrane signal transduction in response to ligand binding, linking interactions between the cell and the environment (Lundstrom, 2006). The *GPR50* gene encodes a protein of 617 amino acids that is 45% identical to the melatonin receptors MT_1 and MT_2. Despite this close relationship, the *GPR50* receptor does not bind to melatonin, and no biological ligand has been identified (i.e. it is an "orphan receptor"). The *GPR50* receptor does however heterodimerise with MT_1 and MT_2, resulting in the inhibition of MT_1 signalling (Levoye *et al*, 2006). *GPR50* is most highly expressed in the paraventricular nucleus, the infundibular stalk and in the mediobasal hypothalamus, in a region containing the ventromedial and arcuate nuclei; it is expressed in foetal

and adult brain (Reppert *et al*, 1996; Drew *et al*, 2001). The expression pattern suggests a role in the neuroendocrine system. However, recent identification of neurite outgrowth inhibitor, Nogo-A, as a protein interaction partner, and subsequent identification of a neurite outgrowth phenotype in neurons over-expressing *GPR50*, suggest that it may have a role in neuronal development (Grünewald *et al*, 2009). A study at the University of Manchester with *GPR50* knockout mice showed a hyperactivity/metabolic phenotype - see Figure 9. (Ivanova *et al*, 2008).



Representative, double-plotted wheel-running activity records from wild-type (top) and *GPR50* knockout (bottom) mice spanning an 8-day period. The white and black bar below the activity records represents the light and dark phases of day, respectively. *GPR50* knockout mice exhibited significantly higher activity (mean wheel revolutions/day) than did the wild-type mice (n = 6/genotype, $*P < 0.05$). Figure 9 Hyperactivity in *GPR50* mice; Ivanova *et al.*, 2008.

Human Studies

Of three human studies investigating *GPR50* in psychiatric illness, the first, which examined patients with schizophrenia, bipolar disorder, recurrent major depression and controls (Thomson *et al*, 2004), found a significant association between an insertion-deletion polymorphism (Δ502-505) and bipolar disorder in a sample of 264 patients (with bipolar I or II disorder) and 562 controls (p = .007). As *GPR50* is sex linked, the sample was divided by gender, resulting in a stronger association in females (p = .00023), but no significant association in men. The strength of the association was further increased when the female patients, who fulfilled Ghaemi's

criteria (Ghaemi *et al*, 2002) for bipolar spectrum disorder, were combined with the bipolar I and II sample (p = .000026). In that study, association was also detected between MDD in females and both Δ502-505 (p = 0.044) and a non-synonymous single-nucleotide polymorphism (SNP) rs13440581 (p = 0.018), but those results did not withstand correction for multiple testing (*ibid*).

A second study in a smaller Swedish cohort of patients with bipolar disorder failed to replicate the Δ502-505 findings (Alaerts *et al*, 2006), while in a Hungarian sample of children and adolescents which grouped MDD and BD together, no association was found with three markers (Feng *et al*, 2007), one of which (rs561077) was in complete linkage disequilibrium (LD) with the Δ502-505 polymorphism in the Scottish population. It is possible that the later two studies were unable to detect association due to genetic heterogeneity between populations, or lack of power. Although, the studies appeared to be correctly powered to repeat the initial finding, multiple studies have shown that subsequent replication studies often result in a reduced estimate of the effect size, with fewer than half of primary studies being strongly replicated: the so-called "winner's curse" (Lohmueller *et al*, 2003).

An attempt to replicate the Thomson *et al.* study in an independent sample follows. One additional marker, rs1202874, recently reported to be associated with significantly elevated plasma triglycerides and lowered HDL-cholesterol levels (Bhattacharyya *et al*, 2006). Most studies suggest a closer link between coronary heart disease risk and hypertriglyceridaemia among women than among men (McBride, 2008). Female patients with mood disorder have been found to have elevated triglycerides levels, and low HDL-C to other cholesterol ratios (Sagud *et al*, 2009); in that sample, those with bipolar disorder had significantly higher triglyceride levels than both those with MDD and controls. A similar gradient (bipolar > MDD > controls) of cardiovascular and cerebrovascular disease has also been demonstrated (Baune *et al*, 2006). It was therefore decided that, although we had not previously genotyped rs1202874, we would include it in the current study.

The author collected DNA donated by the patients and controls described in Chapter 2 and, along with others, an additional larger sample. Laboratory analysis of the DNA was performed by others. The author analysed the data and, along with others, wrote the subsequent paper.

The study was designed and carried out in 2008-09, before results of genome wide association studies in bipolar disorder, schizophrenia and depression had been published. However it is relevant to note that the X chromosome has not been adequately analysed in current GWAS, and the association data available on X-linked genes is from relatively small case-control studies, as described here.

Method

Recruitment of Participants

Patients

Out-patients were recruited from those attending general psychiatry clinics in the East of Scotland. Participants were eligible if they fulfilled DSM-IV criteria for MDD or BD. Subjects with a history of head injury or a primary diagnosis of personality disorder were excluded. A currently depressed, early-onset subset (n=56) was recruited as described in Chapter 2. A previously recruited subset of early-onset MDD patients (Smith *et al*, 2005b) including 27 females positive for bipolar spectrum disorder (BSD) by Ghaemi's criteria were included. In total, 365 subjects with BD, and 379 with MDD were recruited.

Controls

Eight hundred and eighty four unscreened (population) blood samples were obtained from the Scottish Blood Transfusion Service and from general practices in the East of Scotland. Twenty-nine controls were recruited as described in Chapter 2.

Ethical Approval

All subjects gave informed consent in writing before participating. The project was conducted in accordance with the Declaration of Helsinki.

Clinical Assessment

The additional patients had diagnostic assessment performed by the author and other experienced psychiatrists using the SADS-L (Schedule for Affective Disorders and Schizophrenia – Lifetime version (Endicott & Spitzer, 1978)) along with case note review. Diagnoses were made according to DSM-IV-TR criteria. Blood was taken for genotyping. Age at onset was defined as the age when the subject first consulted a professional with symptoms.

Genotyping

To investigate this gene further, and because GWAS generally have not included sufficient coverage of single-nucleotide polymorphisms (SNPs) in this region of poor linkage disequilibrium (LD), four SNPs used in the previous study (Thomson *et al*, 2004) were genotyped, spanning the *GPR50* gene region: rs561077, rs13440581, rs2072621 and rs529386. For the Δ502-505 polymorphism, Taqman technology was used. Genotyping was performed by others at the Wellcome Trust Clinical Research Facility, Genetics Core in Edinburgh. In the initial association study (Thomson *et al*, 2004) the Δ502-505 polymorphism was genotyped using fluorescently labelled polymerase chain reaction (PCR) products, separated on an automated laser fluorescence DNA sequencer, ABI 3730. To validate the methodology, 40 samples used in the original study were genotyped using the Taqman method. This gave 100% concordance. In addition, the SNP rs561077 is in very high (complete) LD with the Δ502-505 polymorphism (D' = 1, $r^2 = 0.998$), providing a second validation method for the Δ502-505 genotype call. One additional marker, rs1202874, recently reported to be strongly associated with abnormal lipid metabolism (Bhattacharyya *et al*, 2006), was also included.

Data Analysis

Case-control association analyses were performed using Haploview (Barrett *et al*, 2005) and χ^2 goodness of fit test for single markers and BD, MDD and subgroup. 100,000 permutation were used to correct for multiple testing. Linkage disequilibrium analysis showed that SNP, rs1202874, was not in LD with any of the five remaining polymorphisms ($r^2 < 0.05$). All markers were tested for Hardy-Weinberg equilibrium (HWE) using a χ^2 goodness of fit test. All markers were in HWE ($p > 0.05$) in the control sample.

Clinical phenotype and treatment response were subjected to ANOVA for continuous variables and Fisher's exact test for categorical variables. Significant associations were examined post-hoc with Tukey's *t*-test. Two-tailed test and an alpha level of .05 were used. Analysis was conducted with SPSS, version 19.

Results

The association analysis results are displayed in Table 14 Associations that might have been expected between rs13440581 or Δ502-505 and mood disorder were not replicated, even when females were considered alone.

The intronic SNP rs1202874 (which had not been genotyped in the original study, but had been added because of its association with abnormal lipid metabolism) showed nominally significant association with BD in females ($p = .0035$; OR 1.9, 95% CI 1.2-3.0), which remained significant after correction for multiple testing (permuted $p = .037$). When 29 female MDD patients, who fulfilled Ghaemi's criteria for BSD were included in a joint analysis with the female bipolar cases, as previously performed (Thomson *et al*, 2004), this association became stronger, giving a highly significant result ($p = .0014$; OR 1.97, 95% CI 1.26-3.06) which remained significant after correction for multiple testing (permuted $p = .0035$). Initial associations were also observed ($p = 0.037$) in females with MDD, and in the combined male and

female BD sample (p = .0157) with the same SNP, but these were no longer significant (p > 0.05) after correction for multiple testing.

As mentioned above, there was no significant association between the Δ502-505 polymorphism and any disorder, regardless of gender. Access to the original sample, yielding a combined sample size of 336 females with BD, and 542 female controls allowed a joint analysis. In the combined sample (Pippa Thompson, 2008, personal communication), significant association between females with bipolar disorder and the deletion polymorphism of Δ502-505, gave p = .0006 (permuted p = .0024) but with reduced effect size (OR 1.41, 95%CI 1.16-1.71).

		All			Male			Female					
Marker[a]	Group	*p*[c]	frequency	n[b]	*p*[c]	frequency	n[b]	*p*[c]	frequency	n[b]	χ^2	OR	95%CI
Deletion/Insertion	CTL		40.0	1206		41.5	620		38.4	586			
	BD	ns	41.6	531	ns	38.6	145	ns	42.7	386			
	MDD	ns	43.4	574	ns	49.3	144	ns	41.0	430			
rs529386 (A/G)	CTL		64.0	1167		61.9	599		66.2	568			
	BD	ns	60.7	532	ns	62.5	144	0.052	60.1	388			
	MDD	ns	64.9	562	ns	66.2	136	ns	64.6	426			
rs561077 (A/G)	CTL		60.1	1187		59.0	607		61.2	580			
	BD	ns	58.3	511	ns	62.6	139	ns	56.7	372			
	MDD	ns	55.8	556	0.054	50.0	138	ns	57.7	418			
rs1202874 (C/T)	CTL		9.0	1194		10.8	614		7.1	580			
	BD	**0.0157**	12.0	533	ns	13.1	145	**0.0035**	12.6	388	8.52	1.9	1.20 - 3.01
	MDD	ns	9.9	558	ns	7.0	142	**0.0370**	10.8	416	4.31	1.59	1.00 - 2.54
	BD+BSD	na	na	na	na	na	na	**0.0014**	13.0	446	10.19	1.97	1.26 - 3.06
rs2072621 (A/C)	CTL		44.2	1174		42.4	602		46.2	572			
	BD	ns	45.8	528	ns	42.4	144	ns	47.1	384			
	MDD	ns	42.8	561	ns	41.0	139	ns	43.4	422			
rs13440581 (A/G)	CTL		40.3	1173		40.1	609		40.6	564			
	BD	ns	41.8	512	ns	38.2	144	ns	43.2	368			
	MDD	ns	37.6	550	ns	37.1	140	ns	37.8	410			

[a]Allele listed first has frequency shown; [b]Number of chromosomes; [c]uncorrected *p* value
CTL: control; BD: bipolar disorder; BSD: bipolar spectrum disorder; MDD: major depressive disorder

Table 14 Association study between *GPR50* markers and mood disorder

Genotype data was successfully acquired for 53 of the patients described in Chapter 2. Thirty-five (66%) were female, and their associations with the minor allele of the rs1202874 SNP and the deletion polymorphism are displayed in Table 15, overleaf. Group number were small. Patients carrying the deletion had, on average, a younger age of onset, and reported more episodes of depression, but these differences were of marginal statistical significance. Patients carrying the minor C allele of rs1202874 had, on average, a longer reaction time. No association remained statistically significant after Bonferroni's correction for multiple testing.

Discussion

An association between BD and an intronic SNP, rs1202874, in *GPR50* was detected. As in the previous study of the Scottish population (Thomson *et al*, 2004), association was restricted to females ($p = 0.0035$, OR = 1.9, 95%CI 1.2-3.0), and increased when a subgroup of MDD meeting Ghaemi's criteria for BSD were included ($p = 0.0014$, OR 1.97, 95% CI 1.3-3.1), providing some predictive validity for the concept of bipolar spectrum disorder.

Rs1202874 was not tested in the original study of the Scottish population, and due to a lack of LD across *GPR50*, it could not be imputed. This SNP has previously been associated with significantly elevated plasma triglycerides and lowered HDL-cholesterol levels (Bhattacharyya *et al*, 2006). Most studies suggest a closer link between coronary heart disease risk and hypertriglyceridaemia among women than among men (McBride, 2008). Female patients with mood disorder have been found to have elevated triglycerides levels, and low HDL-C to other cholesterol ratios (Sagud *et al*, 2009); in that sample, those with bipolar disorder had significantly higher triglyceride levels than both those with MDD and controls. A similar gradient (bipolar > MDD > controls) of cardiovascular and cerebrovascular disease has also been demonstrated (Baune *et al*, 2006).

female university health service sample	ins/ins n=9 *M* (*SD*)	del carrier n=26 *M* (*SD*)	*t*	*p*	RS C carrier n=9 *M* (*SD*)	RS T/T n=26 *M* (*SD*)	*t*	*p*
age at onset	**17.4(2.2)**	**15.42(2.4)**	**2.19**	**.036**	16.0(2.00)	15.9(2.71)	0.08	.938
episodes MDD	**2.78(1.56)**	**5.69(4.19)**	**2.02**	**.052**	4.22(1.72)	5.19(4.41)	0.64	.528
MDQ	3.11(1.54)	4.73(3.41)	1.92	.064	3.44(3.05)	4.62(3.12)	0.98	.337
HCL	3.67(2.40)	5.58(3.33)	1.58	.124	4.11(3.22)	5.42(3.18)	1.06	.295
Novelty seeking	7.67(4.18)	7.81(3.20)	0.11	.917	6.67(2.34)	8.15(3.67)	1.13	.266
Self Transcendence	2.56(2.74)	3.31(2.26)	0.82	.421	2.56(1.74)	3.31(2.56)	0.82	.421
Persistence	1.67(1.80)	1.94(1.79)	0.40	.694	1.56(1.59)	1.98(1.85)	0.62	.543
Cyclothymia	5.67(2.83)	4.50(2.96)	1.03	.310	3.78(2.59)	5.15(3.00)	1.32	.206
Irritability	0.89(0.93)	1.69(1.64)	1.38	.176	1.11(0.78)	1.62(1.70)	0.85	.400
five-choice RT	315.9(55.6)	334.7(62.2)	0.80	.429	**374.9(66.4)**	**314.2(50.6)**	**2.86**	**.007**
five-choice MT	353.9(101.6)	386.9(163.5)	0.57	.575	387.1(112.2)	375.4(162.1)	0.20	.843
MDD: major depressive disorder; MDQ: mood disorder questionnaire; HCL hypomania checklist; RT: Reaction Time; MT: Movement Time; RS: rs1202874; C: cytosine; T thymine; uncorrected $p < .05$ in **bold**								

Significant differences were found between those homozygous for the Δ502-505 insertion polymorphism, compared to ins-del and del-del combined on age-of-onset, and number of episodes. Five-choice reaction time was significantly shorter in those homozygous for thymine at rs1202875, compared with heterozygotes and the individual homozygous for cytosine.

Table 15 Clinical, personality and neuropsychological features, by genotype

The reported association with the Δ502-505 insertion/deletion polymorphism and bipolar disorder was not replicated in this sample. However, combining the Δ502-505 data from both studies did detect significant association with a nominal *p* value in combined data, $p = .0006$, and permuted $p = .0024$, but with a reduced effect size compared to the original report (OR 1.41 and 95% CI 1.16-1.71). The lack of replication in the smaller follow-up studies by others may be due to population differences, or to a lack of power; both had low power to detect modest effects. Likewise the difference in signal between the two Scottish samples, as with other attempts to look at association between this locus and affective disorders, may be as a result of ascertainment bias, genetic heterogeneity between individuals with BD, or the relatively small sample sizes.

Despite the lack of any overall association between the Δ502-505 deletion and bipolar disorder, analysis of the early onset depression subset, described in Chapter 2, detected an earlier age of onset of illness ($p = 0.036$), and a greater number of episodes of depression ($p = 0.052$) in deletion carriers. Reaction-time was significantly slower in carriers of the C allele at rs12012875, and slower in deletion carriers, but this latter difference was not statistically significant. Had the overall study found an association, the subset results would have provided evidence of predictive validity for the BSD category. In the current circumstances, the subset result is difficult to interpret. Deletion carriers also scored, on average, higher on the MDQ and HCL, but this finding was not statistically significant. In any case, the very small sample size suggests these findings must be treated with caution.

Overall, the failure to replicate an association between a Δ502-505 deletion and bipolar disorder makes it difficult to interpret findings in the highly phenotyped subset. Until the genetics of bipolar disorder is more firmly established, association studies will not be able to provide convincing validation or refutation of the bipolar spectrum concept (Kelsoe, 2003); conversely, genetic analysis of phenotype across traditional diagnostic boundaries studies may provide the insight needed to understand these highly complex phenomena (Hamshere *et al*, 2011).

The new finding of an association between bipolar disorder and a SNP implicated in abnormal lipid metabolism is biologically attractive, and may warrant further investigation in other populations.

Chapter 4: A Dimensional Measure Of Mania, In A Large Population-Derived Sample

Introduction

In Chapter 2, an analysis of a traditionally defined unipolar out-patient sample provided some clinical and psychological evidence of concurrent and predictive validity of two dimensional mania measures (one interview–based and the other questionnaire–based), in a moderate sized sample of young adults. It was uncertain if these finding would be replicated in more representative sample of the population.

The Generation Scotland: Scottish Family Health Study (GS:SFHS) is population-based family cohort (n≅24 000) which was in recruited over the 7 years from 2004 to 2011 (www.generationscotland.org). The aim was to create a resource for genetic studies of common disorders of public health importance (Smith *et al*, 2006a). One of the three main themes of the biobank is 'mental health', which includes mood disorder and cognition.

In this chapter, the validity the MDQ was examined in a group of participants from GS:SFHS with and without lifetime diagnoses of MDD. It was hypothesised that if the MDQ was a valid measure of bipolarity, higher scores on the MDQ would be associated with features more common in bipolar than unipolar disorder, such as an earlier age of onset, greater recurrence, and more cognitive impairment.

Two major dimensions of personality have been extensively investigated in mood disorder: neuroticism and extraversion-introversion. Eysenck described neuroticism as a "largely inherited" general measure of emotionality (Goodwin & Jamison, 2007, 329) and this construct has been studied as a potential indicator of bipolar disorder. Results have been contradictory: some studies have indicated that unipolar patients score higher on levels of neuroticism (Hirschfeld & Klerman, 1979), but studies

designed to show differences between unipolar and bipolar disorders failed to show differences between groups (Perris, 1971; Matussek P, 1983). Nevertheless, both dimensions were measured in the Generation Scotland cohort and this provided an opportunity to examine their relationship with the MDQ.

The analysis also offered the opportunity to examine the reliability and internal structure of the MDQ in the Scottish population. Analysis of the MDQ has been conducted using principal component analysis (PCA) followed by orthogonal (varimax) rotation (Harman, 1976) in recovered outpatients with mood disorder (Benazzi & Akiskal, 2003b), in community samples (Mangelli *et al*, 2005), in stable mood disorder patients in Hong Kong (Chung *et al*, 2008) and Spain (Sanchez‐Moreno *et al*, 2008), in pregnant Iranian women without severe depression (Barekatain *et al*, 2008), Polish patients with major depressive disorder (MDD), half of whom were treatment-resistant (Kiejna *et al*, 2010) and in depressed out-patients in Brazil (Leão & Del Porto, 2012). These studies have described fairly similar internal structures: two factors[§] have been identified repeatedly: 'energised-activity' and 'irritable-thought racing'. However these studies could be criticised for using arbitrary cut-off eigenvalues to determine the number of factors. Furthermore it may not be appropriate to assume *a priori* that the factors do not correlate, and if so, oblique rotation may be more appropriate (Field, 2005, 637).

Method

Participants

Participants were recruited at random from primary care patient lists (initially in Glasgow and Tayside, but latterly from Ayrshire, Arran and North-East Scotland), and were eligible to participate if they were aged between 35 and 65 and had at least one first degree relative, age 18 or over, who would also participate. As each

[§] The term "factor" is widely used in the literature to describe components, and the terms are used interchangeably throughout this text, however this is not strictly correct: PCA and factor analysis are both linear models, and often give similar results, but they have significant methodological differences.

participant was enrolled, they were invited to indicate a further first-degree relative who might be prepared to participate, with the aim of "snowballing" recruitment to maximise family size.

Ethical framework

The methods of participant identification, recruitment, access and commercialisation policies were developed with wide-spread public consultation (Haddow *et al*, 2008). Ethical approval was given by Tayside NHS Committee on Research Ethics (reference 05/S1401/89).

Data collection

Participants completed a multiple-choice questionnaire, including the MDQ (Hirschfeld *et al*, 2000), before visiting a clinic. At the clinic visit they underwent a session lasting about 2 hours which included physical measurements, biological sampling and personality and cognitive tests.

Trained researchers administered the screening questions of a structured diagnostic interview and, if the screen was positive, the mood sections of the SCID-I (First *et al*, 2002), slightly modified by the author. The SCID elicited presence or absence of lifetime history of MDD, age of onset, and number of depressive episodes.

Scales Used

Extraversion and neuroticism were measured with the Eysenck Personality Questionnaire-Revised, Short Form (EPQ-RSF) (Eysenck *et al*, 1985). Verbal declarative memory was assessed with the Logical Memory (LM) test, immediate and delayed, from the Wechsler Memory Scale III (Wechsler, 1998a). Information processing speed was tested with the Digit Symbol (DS) substitution test from the Wechsler Adult Intelligence Scale III (Wechsler, 1998b). Executive function was assessed with a letter-based Verbal Fluency (VF) test (Lezak, 1995). Verbal ability was measured with the Mill Hill Vocabulary (MHV) Test (Raven *et al*, 1977).

Current levels of psychological distress were assessed with the 28-item General Health Questionnaire (GHQ-28), which consists of 4 subscales designed to assess: (A) somatic symptoms, (B) anxiety and insomnia, (C) social dysfunction and (D) 'severe depression' (Goldberg & Hillier, 1979).

Quality Control

All new researchers received group training in the administration of the SCID from the author, and ongoing refresher sessions throughout the study. Senior research nurses at each site received extra training from the author and acted as local mentors, and trained researchers discussed borderline cases with the author as they presented. A short local training video (see Appendix) was created to supplement the official SCID videos and training manual. Anonymised digital audio recordings of sequential clinic sessions were made, and were reviewed (blind to database diagnosis) by the author, with the assistance of another trained psychiatrist. Inter-rater reliability for the presence or absence of a lifetime diagnosis of major depressive disorder was good: $\kappa = 0.86$ ($p < .001$), 95% CI (0.7, 1.0) in the quality control sample (n = 58).

Sample

The data available for analysis was from 2942 participants who had completed the MDQ, 610 (20.7%) of whom had received a research diagnosis of major depressive disorder (MDD), and the remaining 2332 who had screened negative for psychiatric disorder. A small number who screened positive, but did not receive a SCID diagnosis were excluded (n = 21).

Data Analysis

Reliability was assessed using Cronbach's α. Principal component analysis (PCA) was conducted with oblique (direct oblimin) rotation. A Monte-Carlo simulation (parallel analysis) using raw data permutation (O'Connor, 2000) was conducted to determine eigenvalues, and draw scree plots.

Group differences between means were assessed by one-way independent analysis of variance (ANOVA) as appropriate. As group sizes were unequal, to avoid type I error, the conservative Welch *F* was calculated. Equal variance could not be assumed, so conservative post-hoc Games-Howell *t*-tests were conducted. Continuous data were subject to Pearson's bivariate and partial correlation as stated.

An alpha level of .01 was used for omnibus tests, and an alpha level of .05 was used for post-hoc tests and the parallel analysis. Two-tailed tests were used. Cohen's conventions for effect size (Cohen, 1992) were used. Analysis was conducted using SPSS, version 19.

Results

Psychometric Properties of the MDQ

Reliability

In terms of the reliability (internal consistency) of the MDQ, a Cronbach's α coefficient of .85 was observed. Individual item – total correlations ranged from .35 to .62, overall very similar to results seen in a US general population study (Hirschfeld *et al*, 2003b). Inter-item correlations are displayed in Table 16.

MDQ item	1	2	3	4	5	6	7	8	9	10	11	12	13
1 hyper	---												
2 irritable	.305	---											
3 confident	.345	.279	---										
4 less sleep	.263	.198	.330	---									
5 talkative	.358	.304	.402	.333	---								
6 racing	.241	.340	.314	.285	.359	---							
7 distracted	.299	.360	.303	.258	.369	.444	---						
8 energy	.333	.241	**.502**	.375	.424	.309	.315	---					
9 active	.310	.247	**.500**	.360	.417	.330	.338	**.721**	---				
10 outgoing	.344	.167	.301	.212	.269	.178	.228	.275	.262	---			
11 sex	.321	.239	.407	.271	.310	.256	.277	.354	.378	.365	---		
12 risky	.381	.267	.319	.238	.274	.270	.299	.254	.289	.356	.402	---	
13 spending	.247	.218	.206	.184	.214	.233	.224	.164	.178	.207	.236	.327	---

r > .3 underlined; *r* > .5 in **bold**

Table 16 *R* – Matrix: MDQ Inter-Item Correlations

Increased energy levels, increased activity, and increased self-confidence were particularly highly correlated.

Internal factor structure

Monte Carlo simulation, using raw data permutation was conducted and scree plots were drawn for the combined sample, controls alone and MDD cases alone (see

Appendix 3). When the combined sample was examined, 3 factors appeared to provide the best fit (initial eigenvalues 4.73, 1.19, 1.08), but when controls and cases were separated, 2 factors appeared more appropriate for controls (initial eigenvalues 4.64, 1,19), and 3 factors more appropriate for cases (initial eigenvalues 4.38, 1.30, 1.10). Principal component analyses are displayed in Table 17, overleaf.

In controls, the first factor comprised increased energy and activity measures, but also included racing thoughts, irritability and distractibility. A second 'disinhibited' factor was found which was comprised of those criteria which asked about taking risks or impulsivity. Previous studies which have included healthy controls (Sanchez‐Moreno *et al*, 2008) or population samples (Mangelli *et al*, 2005) have not analysed controls separately, so no previous data is available for comparison.

In the combined sample, and in participants with MDD, a three factor structure was detected. Again, the largest factor loaded heavily onto energised and activity items, while a second factor loaded predominantly on racing thoughts, distractibility and irritability. A third factor emerged which included risk taking/impulsivity criteria and 'feeling so good or so hyper'. An 'energised-activity' factor has been consistently found in analyses of the MDQ and in other mania self-rating scales (Bauer *et al*, 1991; Forty *et al*, 2010), however previous studies of the MDQ, which have all reduced the scale to two factors, have tended to include irritable/racing thoughts items, or disinhibited/risk-taking items, or a mixture of both in a second factor in an inconsistent manner. It is possible that this inconsistency might be resolved if a 3 factor structure was used.

		Combined n=2942				Controls n=2322			Cases n=620			
			Factor				Factor			Factor		
Item		uC	1	2	3	uC	1	2	uC	1	2	3
8	much more energy	.703	**.871**	-.019	.003	.740	**.825**	-.054	.653	**.842**	.038	.029
9	much more active	.711	**.845**	-.008	.035	.749	**.807**	-.018	.636	**.839**	.080	-.021
3	much more self-confident	.687	**.612**	.205	.044	.715	**.626**	.167	.637	.449	.010	.372
5	much more talkative	.656	.446	.076	.339	.657	**.661**	.044	.612	.382	.355	.135
4	less sleep didn't miss it	.549	.495	.054	.149	.535	**.636**	-.089	.607	.377	.085	.339
6	thoughts raced	.579	.172	-.077	**.724**	.551	**.630**	-.060	.536	.149	**.797**	-.096
7	easily distracted	.602	.135	.032	**.681**	.597	**.554**	.099	.508	.110	**.771**	-.075
2	irritable	.518	-.023	.084	**.690**	.498	.446	.103	.442	-.146	**.562**	.226
12	foolish or risky	.589	-.041	**.732**	.104	.560	-.002	**.758**	.601	-.115	.123	**.728**
10	much more social	.521	.131	**.740**	-.211	.492	-.031	**.703**	.567	.113	-.140	**.692**
11	much more sex	.620	.296	**.571**	-.077	.653	.237	**.554**	.573	.143	-.114	**.653**
1	so good or so hyper	.606	.143	**.535**	.124	.561	.215	.483	.662	.160	-.008	**.591**
13	spending money	.431	-.226	**.543**	.302	.369	-.074	**.592**	.457	-.180	.280	.491
rotated sums of squares loadings			3.57	3.18	2.80		4.28	3.09		2.86	2.53	3.37

rotated principal components loading < .4 in grey > .5 in **bold**
uC: first unrotated component; Factor: rotated component

Table 17 Principal component analysis of the MDQ

Group differences

Of 620 participants with a history of MDD, 317 (51%) had experienced a single depressive episode (seMDD). Of the remainder 206 (33%) had a recurrent course (rMDD), with a range of between 2 and 20 episodes. The SCID interview elicits number of previous depressive episodes but has a residual category within recurrent MDD in which episodes are either 'too numerous or indistinct to count'; ninety-seven (~16%) participants fell into this category, referred to as chronic/recurrent (crMDD) hereafter.

The frequencies with which participants in each group endorsed individual statements of the MDQ are displayed in Table 18 .

		Control n(%)	seMDD n(%)	rMDD n(%)	crMDD n(%)	χ^2 test
		2322 (78.9)	317(10.8)	206 (6.9)	97(3.3)	
1	hyper	137(5.9)	41(12.9)	32(15.5)	32(33.0)	**119.3**
2	irritable	534(23.0)	140(44.2)	109(52.9)	62(63.9)	**191.7**
3	confident	471(20.3)	78(24.6)	59(28.6)	34(35.1)	**20.2**
4	less sleep	424(18.3)	59(18.0)	59(26.7)	35(36.1)	**26.6**
5	talkative	320(13.8)	73(23.0)	67(32.5)	41(42.3)	**104.1**
6	racing	591(25.5)	148(46.7)	132(64.1)	69(71.1)	**243.1**
7	distracted	493(21.2)	141(44.5)	117(56.8)	62(63.9)	**244.0**
8	energy	422(18.2)	68(21.5)	47(22.8)	32(33.0)	**16.1**
9	active	468(20.2)	81(25.6)	58(28.2)	40(41.2)	**32.4**
10	outgoing	67(2.9)	19(6.0)	12(5.8)	19(19.6)	**74.4**
11	sex	197(8.5)	45(14.2)	45(21.8)	17(17.5)	**48.6**
12	risky	157(6.8)	43(13.6)	43(20.9)	35(36.1)	**137.7**
13	spending	93(4.0)	39(12.3)	41(19.9)	28(28.9)	**173.3**
			subset n = 1277			
	n (%)	855 (67.0)	197(15.4)	151(11.8)	74 (5.8)	
B	same time	424(49.6)	137(69.5)	115(76.2)	61(82.4)	**74.0**
						$p < .001$ in **bold**

Table 18 Proportion Endorsing Individual MDQ items

A gradient in score (control < seMDD < rMDD < crMDD), was observed across most individual items: see Figure 10.

Criterion B: “If you ticked YES to more than one of the above, have several of these happened during the same period of time?” could only validly be endorsed by those scoring more than 1 on the MDQ (n=1322), however in 45 individuals data was missing, leaving 1277 subjects. In that subset, the proportion endorsing the ‘same time’ criterion showed a gradient across the groups (control < single episode MDD < recurrent MDD < chronic/highly recurrent MDD). The non-euphoric manic symptoms of irritability, distractibility and racing thoughts (which made up the second factor of the MDQ in the patient group) were most frequently endorsed, in line with previous findings (Hirschfeld *et al*, 2000).

It appeared that the more recurrent the depressive disorder, the more likely individuals were to report manic symptoms, and this could indicate that manic symptoms are a marker of severity of MDD (Cassano *et al*, 2004), however it is also likely that some participants within the MDD category were suffering from unrecognised bipolar II disorder (Angst *et al*, 2011; Smith *et al*, 2011).

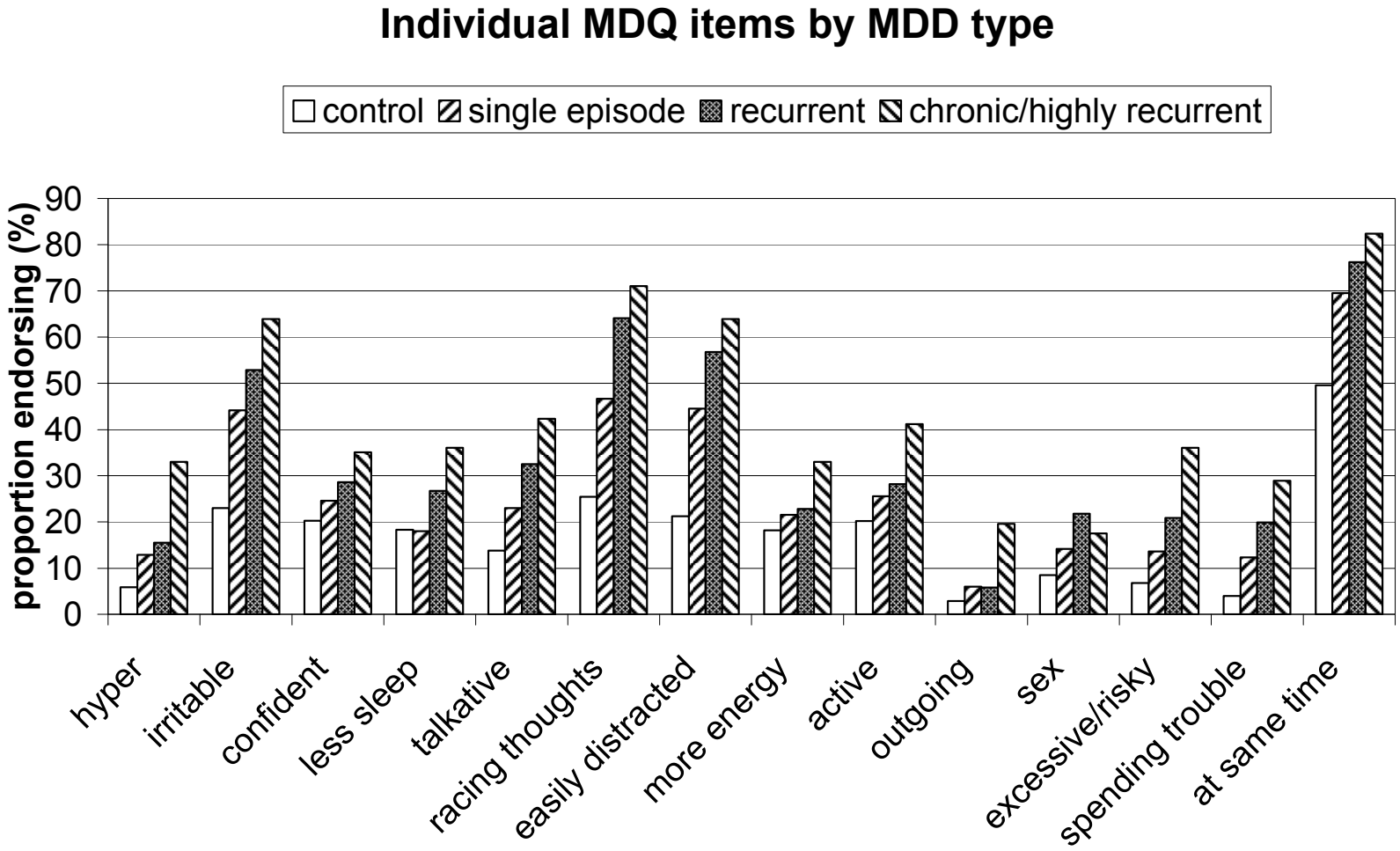


Figure 10 Proportion endorsing individual MDQ items

Clinical, personality and cognitive findings

Clinical

MDQ scores were positively skewed (see Appendix 4). In the recurrent MDD group, mean MDQ was significantly higher in men than in women but there were no significant differences between genders within the seMDD or crMDD groups. Both correction by log transformation, and non-parametric analysis with Mann-Whitney U-test, gave the same material result. MDQ scores by gender are displayed in Table 19.

	male:female	m:f	male *M*(*SD*)	female *M*(*SD*)	*t*	*p*	*r*
control	985:1337	1:1.4	2.28 (2.91)	1.59 (2.35)	6.24	**< .001**	.14
seMDD	111:206	1:1.8	3.27 (3.18)	2.96 (2.60)	0.932	.352	
rMDD	86:120	1:1.4	4.83 (3.29)	3.35 (3.04)	3.27	**.001**	.23
crMDD	35:62	1:1.8	5.09 (3.64)	5.29 (3.61)	0.267	.791	
equal variances not assumed; $p \leq .001$ in **bold**							

Table 19 Mean MDQ scores by gender

As the female to male ratio is lower in bipolar than unipolar disorder, this result provides some evidence of antecedent validity of the MDQ. In the control sample MDQ was higher in men than women. This was a small but highly significant effect. Demographic and psychometric data are displayed in Table 20.

	A Control	B seMDD	C rMDD	D crMDD	omnibus test	*p*	‡post-hoc	*r*
	n(%)							
	2322(78.9)	317(10.8)	206(7.0)	97(3.3)				
female	1337(57.6)	206(65.0)	120(58.3)	62(63.9)				
MDQ≥7	**186(8.0)**	**39(12.3)**	**46(22.3)**	**29(29.9)**	$\chi^2 = 87.9$	**<.001**		
GHQ>4	**264(11.5)**	**66(21.2)**	**96(47.1)**	**49(52.1)**	$\chi^2 = 273.7$	**<.001**		
	M(*SD*)							
age	52.4(13.7)	45.6(13.5)	48.2(12.4)	46.8(12.2)				
age/onset	---	**34.7(11.7)**	**31.0(12.1)**	**24.6(10.2)**	$F(3, 607) = 33.8$	**<.001**	B>C>D	.28
MDQ Total	**1.88(2.6)**	**3.07(2.8)**	**3.97(3.2)**	**5.22(3.6)**	$F(3, 2938) = 64.1$	**<.001**	A<B<C<D	.29
EPQ N	**2.96(2.76)**	**5.07(3.19)**	**6.89(3.22)**	**8.04(3.03)**	$F(3,2929) = 201.8$	**<.001**	A<B<C<D	.44
EPQ E	**7.76(3.48)**	**7.73(3.38)**	**6.22(3.92)**	**5.78(4.00)**	$F(3, 2929) = 16.7$	**<.001**	A,B>C,D	.14
LM-I	15.9(4.03)	16.3(3.59)	16.0(4.19)	14.9(3.91)	$F(3, 2929) = 3.17$	.024		
LM-D	14.7(4.46)	15.2(3.88)	14.8(4.38)	13.7(4.07)	$F(3, 2916) = 3.33$	.020		
VF	40.0(11.7)	40.8(11.6)	41.0(12.4)	40.6(11.6)	$F(3, 2911) = 0.81$	.487		
DS	**70.1(16.6)**	**72.9(16.0)**	**72.2(15.9)**	**68.6(15.2)**	$F(3, 2920) = 4.01$	**.008**	A<B,C,D	.06
MHV	30.6(4.65)	30.2(4.74)	30.8(5.05)	29.8(5.11)	$F(3, 2905) = 1.64$	.181		
GHQ A	**0.64(1.32)**	**1.02(1.65)**	**1.78(1.97)**	**1.96(2.20)**	$F(3, 2904) = 35.8$	**<.001**	A<B<C,D	.25
GHQ B	**0.45(1.14)**	**0.84(1.55)**	**1.75(2.22)**	**2.34(2.61)**	$F(3, 2905) = 43.2$	**<.001**	A<B<C,D	.32
GHQ C	**0.42(1.10)**	**0.77(1.63)**	**1.66(2.17)**	**2.27(2.44)**	$F(3, 2904) = 42.2$	**<.001**	A<B<C,D	.31
GHQ D	**0.07(0.49)**	**0.21(0.90)**	**0.82(1.67)**	**1.75(2.54)**	$F(3, 2903) = 28.5$	**<.001**	A,B<C<D	.15
GHQ Total	**1.51(2.84)**	**2.63(3.92)**	**5.20(5.25)**	**6.56(6.13)**	$F(3, 2903) = 58.8$	**<.001**	A<B<C,D	.35

p < .01 in **bold**; seMDD: single episode MDD; rMDD: recurrent MDD; crMDD: chronic/recurrent MDD;
LM-I: logical memory immediate; LM-D: logical memory delayed; VF: verbal fluency;
DS: digit symbol; MHV: Mill Hill Vocabulary; *F*: Welch *F*; ‡Games-Howell *t*-tests, *p* < .05

Table 20 Demographic and psychometric results by diagnostic group

Age of onset was highest in the single episode group (M = 34.7, SD = 11.7) and, on average, 10 years lower in the chronic/highly recurrent group (M = 24.6, SD = 10.2). Interestingly, although age-of-onset was unimodally distributed in the other groups, in the crMDD group (n = 96) there was a suggestion of a trimodal distribution (Figure 11), and furthermore a trimodal distribution of MDQ scores was seen in this group.

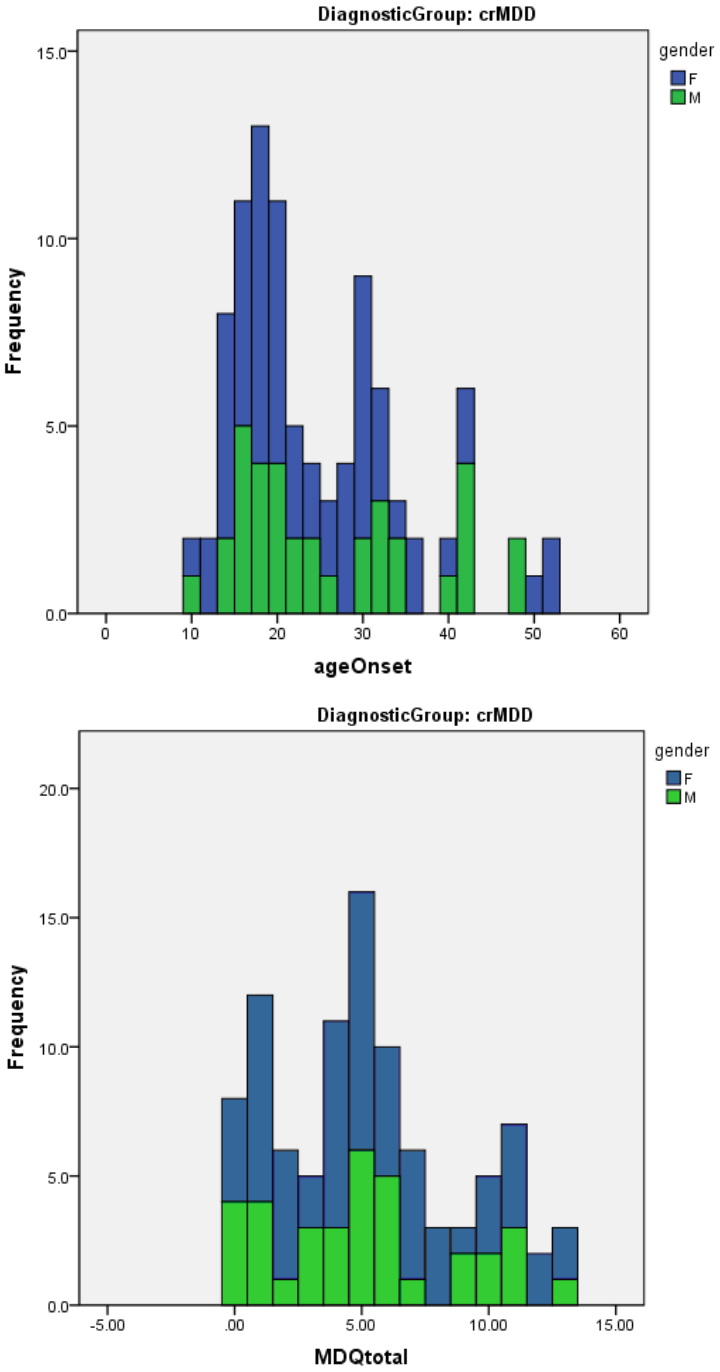


Figure 11 Chronic/recurrent MDD: age of onset and total MDQ by gender

Several studies (Bellivier *et al*, 2001; Bellivier, 2003; Perlis *et al*, 2004; Lin, 2006; Manchia *et al*, 2008) have reported that bipolar I aggregates into three sub-groups on age of onset, broadly speaking 'early' with a mean of 17 years; 'mid' with a mean of about 26, and 'late' with a mean between 35 and 46 years, and these finding have been replicated recently in the UK, in the largest sample to date (n = 1369) (Hamshere *et al*, 2009).

Perlis and colleagues (Perlis *et al*, 2006a) analysed data from participants in large multicentre trials of major depression and bipolar I disorder, which ascertained episode number using the SCID: 40% of the bipolar I group had episodes that were 'too numerous or indistinct to count', compared with less than 5% of the MDD subjects. In the present study 97 (16%), of those 620 with MDD, were in the crMDD sub-category, and this group also had the earliest age of onset. It was predicted the MDQ would be highest in this group, and this proved to be the case. This provides some concurrent evidence of the validity of the MDQ.

Neuroticism and Extraversion

Neuroticism (N) was highest in the chronic/highly recurrent group (M = 8.04, SD = 3.03), lower in the group with recurrent depression, followed by single episode MDD, with controls showing the lowest levels of N (M = 2.96, SD = 2.76). All differences were statistically significant. N shows a weak relationship with short term (3-6 month) outcome, but more strongly predicts poor 1 year (Scott *et al*, 1995), longer term outcome (Mulder, 2002), and chronicity, when defined as depressed for at least 24 months in the previous 4-5 years (Wiersma *et al*, 2011). In this longitudinal Dutch cohort study, low E was also a strong predictor of chronicity. In the present sample E was lower in the rMDD and crMDD groups, compared to seMDD and controls.

In the current study N, and to a lesser extent E, appear to differentiate cases from controls, but also between single episode, recurrent and chronic/recurrent courses.

Cognition

In terms of cognitive function, no statistically significant differences were found between groups on verbal ability, verbal memory or executive function. The groups showed a small (r = .06) but statistically significant difference on digit symbol substitution test (processing speed); post-hoc comparisons indicated that controls were faster at performing the task than participants with a history of MDD. This finding is in accord with other research (Xu *et al*, 2012).

Psychological Distress

The GHQ-28 is a screening tool designed to detect probable current psychiatric disorder in primary care settings; sensitivity (84%) and specificity (86%) are reasonable in the UK population (Goldberg *et al*, 1997). The threshold for 'caseness' on the GHQ-28 is a total score of 5 or more; by this criterion, over 11% of controls met threshold; this proportion was approximately doubled (21.2%) in participants with a history of a single episode of depression, and more than doubled again (47.1%) in those with a history of recurrent depression. Over half (52.1%) of those in the chronic/recurrent group screened positive on the GHQ-28. Overall, the high total GHQ-28 scores in the participants with a history of MDD emphasise the chronic nature of depression, and the long-term burden of depressive symptoms.

In terms of both the individual sub-scales, and total GHQ-28 score, a gradient of abnormality (control < single episode MDD < recurrent MDD) was observed, with highly statistically significant differences between groups. Only the 'severe depression' subscale (GHQ D) significantly distinguished the chronic/recurrent group, who scored highest on this subscale. These results are consistent with the previous finding that patients with MDD, particularly those with a recurrent disorder, tend to have chronic depressive symptoms (Judd *et al*, 1998), as do patients with bipolar disorder (Judd *et al*, 2002), in which bipolar II disorder may have a more chronic course than bipolar I disorder (Judd *et al*, 2003b).

MDQ correlations

Partial correlations were conducted (controlling for age, gender and GHQ total Likert score) between the MDQ and other psychometric measures in the combined sample and subgroups. Results are detailed in Table 21.

	MDQ total score									
Group	combined		control		seMDD		rMDD		crMDD	
n	2942		2314		317		206		97	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age/onset					**-.146**	**.009**	-.176	.013	.009	.927
Episodes							.095	.181		
EPQ N	**.257**	**<.001**	**.218**	**<.001**	**.238**	**<.001**	**.264**	**<.001**	.030	.777
EPQ E	**.054**	**.004**	**.069**	**.001**	.089	.118	.050	.484	.095	.369
LM-I	**-.061**	**.001**	**-.056**	**.008**	-.014	.803	-.137	.054	-.036	.738
LM-D	**-.052**	**.005**	-.050	.017	-.025	.669	-.109	.126	.030	.782
VF	-.009	.612	-.036	.088	-.038	.513	.072	.311	.118	.269
DS	**-.050**	**.008**	-.050	.018	-.041	.473	-.085	.233	.135	.206
MHV	**-.100**	**<.001**	**-.120**	**<.001**	**-.146**	**.010**	-.055	.439	-.081	.451

p <= .01 in **bold**; EPQ - Eysenck Personality Questionnaire - Revised (Short Form)
N - Neuroticism; E - Extraversion; LM-I: logical memory immediate;
LM-D: logical memory delayed; VF: verbal fluency; DS: digit symbol;
MHV: Mill Hill Vocabulary

Table 21 MDQ, personality and cognitive partial correlations

If age of onset is on average 8 to 10 years lower in BP, compared to MDD, and total MDQ score is a valid dimensional measure of bipolarity, it would be expected to correlate negatively with age-of-onset, as it did in the combined patient group: $r = -.191$, $p = 2 \times 10^{-6}$, but also in the seMDD and rMDD subgroups. This may provide some convergent validity of a dimensional measure of bipolarity in patients with MDD, however some participants may have been 'false unipolars'. More rigorous phenotyping of mania to exclude those with bipolar II and bipolar NOS would be necessary to exclude this possibility.

If MDQ indicated bipolarity in the rMDD sample, it might have been expected to correlate positively with number of depressive episodes (as in Chapter 2), but the small positive correlation seen here was not statistically significant. This may be because the number of depressive episodes was not ascertained systematically in GS:SFHS sample.

Neuroticism and Extraversion

The MDQ showed positive moderate-sized significant correlations with Eysenck's neuroticism in the combined sample, and the seMDD and rMDD groups. There was no correlation with the crMDD group. Extraversion was very weakly correlated with the MDQ in the control group only.

Cognition

A meta-analysis of cognitive deficits in bipolar disorder showed a modest effect on general IQ, $r = .05$, but this persistent association appears to be mainly the result of deficits in performance, rather than verbal IQ (Goodwin & Jamison, 2007, 279). However it should be noted that this is an area of conflicting evidence, probably because of the different definitions of mood disorders used and the difficulties inherent in cognitive testing. One recent cohort study (MacCabe *et al*, 2010) used longitudinal data from over 900 000 individuals in Sweden to examine the relationship between scholastic achievement at age 16 and risk for BP in adulthood, controlling for potential confounders including socioeconomic group and parental education. They detected a U-shaped curve, with the highest achievers at greatest risk.

The Mill Hill Vocabulary test (MHV) of verbal ability correlates highly with Raven's progressive matrices, a performance test of general intelligence. In the current study there was a small negative, but highly significant correlation between the MDQ and MHV in the combined sample. Small negative effects were present but not statistically significant in the individual and combined patient groups. The largest effect was found in the control sample alone ($r = -.120$, $p = 1 \times 10^{-8}$). This subtle but highly significant effect may be evidence of an association between a tendency to experience manic symptoms and subtle impairment of general intelligence in the normal population. If this finding was replicated, it would provide external validation to support Kraepelinian assertion that there is no distinct border between normality and abnormality in mood disorders.

Small negative correlations were seen with the other cognitive measures in most groups, however in general the effects were small and not statistically significant, except for Logical Memory-Immediate (uncorrected $p = .008$) in the control group. This result did not withstand correction for multiple testing. This serves to emphasise the subtle nature of cognitive impairment in mood disorders.

Psychological Distress

The GHQ total score provided an overall measure of current levels of psychological distress. To assess the predictive validity of the MDQ, a multiple regression analysis was conducted, using hierarchical, blockwise entry. Neuroticism correlates highly with psychological distress and was therefore entered into the model first. Dummy variables were created to allow the diagnostic groups (seMDD, rMDD and crMDD – seMDD was the baseline) to be entered, followed finally by the MDQ total score (see Table 22).

	R^2		*B*	*SE B*	*β*	*p*
Model 1	.210	Constant	-0.071	0.375		
		EPQ-N	0.681	0.054	.458	**<.001**
Model 2	.237	Constant	-0.356	0.378		
		EPQ-N	0.591	0.056	.398	**<.001**
		Group1	1.505	0.410	.141	**<.001**
		Group2	2.167	0.545	.156	**<.001**
Model 3	.242	Constant	-0.564	0.391		
		EPQ-N	0.560	0.058	.377	**<.001**
		Group1	1.455	0.410	.137	**<.001**
		Group2	2.014	0.549	.145	**<.001**
		MDQ	0.118	0.060	.075	**.048**

$p < .05$ in **bold**

Table 22 GHQ Total multiple regression model

Using this model, the MDQ accounted for only 0.5% of the variance, compared with 21% for the EPQ-N and 2.7% for the diagnostic group. Nevertheless this was a statistically significant result. This provides modest evidence of the predictive validity of the MDQ.

Discussion

In this Chapter a dimensional measure of mania was examined in a large population-based sample.

The instrument showed very similar internal reliability as it did in a US population-based study. Principal component analysis suggested a 3-factor internal structure, with 'energised-activity', 'racing thoughts-irritability' and 'disinhibition/risk-taking' components.

Early age of onset, and recurrence (chronic/recurrent > recurrent > single) was associated with higher total MDQ score, suggesting that in MDD, manic symptoms are a marker of severity (Cassano *et al*, 2004). Non-euphoric manic symptoms (irritability, racing thoughts and distractibility) were the most commonly experienced, as in other studies (Serretti & Olgiati, 2005). In controls (n = 2252), number of historical manic symptoms, as measured by the MDQ, showed a highly significant ($p = 1 \times 10^{-8}$) but modest negative correlation ($r = -.120$) with a measure of general intelligence, consistent with most findings in bipolar disorder. In participants with MDD, MDQ score showed a trend towards cognitive impairment. Taken together, these finding suggest a continuum of impairment, rather than a distinct boundary between 'normal' and abnormality, or between MDD and BP, and support Angst's 2-dimensional model of affective disorder (Figure 5).

In the early-onset sample (see Table 10), MDQ correlated with Cloninger's Novelty Seeking (NS), but not Harm Avoidance (HA). In the population-based study, MDQ correlated with N but not E, as has been described (Bowen *et al*, 2011). Although E has been found to correlate with NS ($r = .44$), and N correlates with HA ($r = .59$) (Zuckerman & Cloninger, 1996), there is considerable unexplained variance, making it hard to compare these different personality dimensions. It appears that E and N do not differentiate polarity but are more strongly associated with clinical course.

About half of those with more than one episode of MDD were current 'cases' of psychological distress by GHQ-28. This finding serves to emphasise the chronic burden of distress caused by these conditions. MDQ modestly predicted current levels of psychological distress, even after controlling for neuroticism and diagnostic group, indicating that it has divergent and predictive validity.

Clinical Implications

It appears that the use of a dimensional measure of mania has validity in patients with MDD. In patients who are at higher risk of BP, such as males, those with an early age of onset, or a recurrent or chronic depression, it may be clinically useful to rate manic symptoms as this could inform treatment choices, possibly away from antidepressants towards mood stabilisers. Classifying mood disorders on the basis of recurrence or chronicity, and including personality measures, rather than just polarity, may have more predictive validity (clinical utility).

Strengths and Limitations

The large sample size increased power to find small effects. Detailed cognitive phenotyping allowed analysis of MDQ associations in a population-based sample. Diagnostic assessment was not carried out by psychiatrists, but use of a structured instrument, and a continuous training program for researchers, produced reasonable inter-rater reliability. Drug treatment was a potential confounder but this information was not available at the time of analysis. Lack of a traditionally defined bipolar group limited the analysis, and more systematic assessment of hypomania would be necessary to reduce the proportion of MDD participants who may have had unrecognised bipolar disorder. Retrospective collection of age-of-onset and number of episodes is subject to recall bias and is less accurate than prospective ascertainment.

Chapter 5: Conclusions

The introduction of operationally defined categories in psychiatry led to more reliable diagnostic agreement and communication between clinicians and researchers, and more reliable comparison of groups and outcomes (Lawrie *et al*, 2010). However, these categories are difficult to apply in mood disorder (Andreasen *et al*, 1981), of limited validity (Kendell & Jablensky, 2003) and arguably too narrow in bipolar disorder (Angst *et al*, 2010, 2011). Poor diagnostic validity hampers our understanding of the underlying structures and aetiologies of mood disorder (Kendell, 1982), and poor utility impairs patient care (Kendell, 1989).

Although other clinical features can help differentiated mood disorders, current classification is dominated by the necessity to establish the presence or absence of a history of mania (Forty *et al*, 2008), whilst degree of recurrence has been discarded as a diagnostic criterion. Although full-blown manic episodes are easy to identify, most patients with mood disorder experience less extreme, but clinically significant symptoms (Judd & Akiskal, 2003), which are time-consuming to elicit reliably. Mania questionnaires such as the MDQ (Hirschfeld *et al*, 2000) may speed up assessment and improve diagnostic sensitivity, however the validity (Zimmerman *et al*, 2004) and utility of this approach, or novel diagnostic categories such as BSD (Ghaemi *et al*, 2002) are the subject of uncertainty. In the preceding chapters, three studies were conducted in an attempt to address some of these uncertainties.

As was described (see page 6 and Table 2), methods to establish validity - based on finding external correlates outwith defining characteristics - were probably first formally proposed by Robins & Guze, and have since been elaborated by Kendler, and latterly Andreasen (Kendell & Jablensky, 2003). External validators may be considered as antecedent (e.g., familial, personality, genetic), concurrent (e.g., neuropsychological) or predictive (e.g., clinical course, response to treatment).

Antecedent Validity

Genetics

In Chapter 3, a genetic study of mood disorder, a replication of a previous finding (Thomson *et al*, 2004) was attempted. A polymorphism in the region (rs1202874) was associated with mood disorder, particularly BP, but the association was not found with the original markers. As in the previous study, a sub-sample of those with traditionally defined MDD were positive for Ghaemi's criteria for bipolar spectrum disorder. When these cases were combined with the BP group the effect size, and statistical significance increased. It could be argued from this finding provides antecedent biological validity of the BSD category, and that these 'unipolar' patients should be re-classified as 'bipolar'. However, the failure to replicate the association using the original markers made the result hard to interpret. Recent approaches to the elucidation of the genetics of mood disorder involve association studies using hundreds of thousands of genetic markers, and much larger sample sizes (Sklar *et al*, 2011). Newer polygenetic approaches may be informative (Hamshere *et al*, 2011).

Gender

In Chapter 2, males with early onset MDD tended to score higher on dimensional measures of historical manic symptoms. Furthermore, in the larger population-based study, when there were gender differences in total MDQ score, males scored higher. As the female to male ratio in MDD is greater than one, but the gender ratio is equal to one in BP, this provided some antecedent validation of the MDQ.

Clinical Course

Modest but significant correlations were found between MDQ and HCL and number of episodes in the high-risk early-onset sample, and there was also a modest but highly significant negative correlation with age-of-onset and MDQ in the population-based sample (r = -.191, $p = 2 \times 10^{-6}$). The population-based MDD sample was separated into groups according to degree of recurrence. There is evidence that

bipolar disorder tends to be more recurrent than MDD, and a greater proportion of bipolar patients suffer a chronic/recurrent course, compared to those with MDD. MDQ scores showed a significant gradient across groups (crMDD > rMDD > seMDD), with ~30% of patients in the chronic recurrent group meeting threshold (≥ 7) for a positive screen on the MDQ, some of whom could have been 'false unipolars'. Overall, clinical course provided reasonable antecedent validation of the MDQ, and supported the assertion that manic symptoms in depression are markers of severity (Cassano *et al*, 2004).

Familiality

Systematic ascertainment of family history in the early-onset sample allowed comparison of the MDQ and HCL in probands with and without heavily 'loaded' pedigrees. Those with loaded pedigrees scored slightly higher on the MDQ but the difference was not statistically significant. This did not provide clear familial evidence of the validity of the MDQ, however the Generation Scotland cohort is a family study (Smith *et al*, 2012), and analysis of the heritability of the MDQ in this sample could provide familial validation.

Personality

The relationship between personality and affective disorders is complex: for example, personality traits may be conceived of as propensities that predispose individuals to affective disorders; as modifiers of affective states; as attenuated expressions of affective illness; or as orthogonal dimensions (Akiskal *et al*, 1983a). Furthermore some affective states, previously considered personality disorders, have been shown to respond favourably to pharmacological treatment (Silva de Lima *et al*, 2005). Measurement of personality in affective disorders is potentially complicated by state effects (Hirschfeld *et al*, 1983; Morey *et al*, 2010), nevertheless these reservations do not negate the use of personality traits as endophenotypes (Savitz & Ramesar, 2006), and in this work I assessed the relationship between personality traits and the mood disorder questionnaire to determine its validity.

Neuroticism and Extraversion-Introversion

The systematic assessment of personality remains a controversial area: no clear consensus has emerged as to the number or contents of the dimensions that should be used to describe personality (Matthews *et al*, 2003). However Eysenck's Neuroticism (N) and Extraversion-Introversion (E) are probably the most widely studied (Eysenck, 1959, 1967). Previous studies which attempted to differentiate bipolar from unipolar subjects on N and E tended to be small and failed to control for affective state, but more recently, larger studies controlling for affective state (Smillie *et al*, 2009; Jylhä *et al*, 2010) have not been able to differentiate unipolar from bipolar patients on N and E. In the population-based study, Extraversion was higher in controls and in those with single episodes of depression than in those with recurrent or chronic/recurrent depression; Neuroticism showed a gradient across categories with N lowest in controls, and highest in the chronic/recurrent group. This indicates that N is a marker of severity and MDQ was modestly correlated with N, except perhaps surprisingly in the chronic/recurrent group. Overall, a lack of clear published differences between bipolar and unipolar disorder on N and E made these results difficult to interpret, and arguably prevented the drawing of conclusions on the validity of the MDQ based on these personality traits.

Temperament and Character

Personality can be conceived in terms of constitutional or genetic tendencies, referred to as 'temperament' and learned attributes acquired during childhood development, referred to as 'character'. Cloninger's Temperament and Character Inventory (Cloninger *et al*, 1993) and the TEMPS-A (Akiskal *et al*, 2005c) attempt to capture these dimensions and were measured in the early-onset sample. Previous research had shown associations between bipolar disorder and Novelty Seeking (Young *et al*, 1995; Evans *et al*, 2005); associations between bipolar disorder and Self Transcendence had been predicted (Cloninger *et al*, 1998); and compared to unipolars, bipolars have been found to score higher on measures of cyclothymic temperament (Di Florio *et al*, 2010). On these measures, in the early-onset sample, the MDQ showed moderate positive correlations of statistical significance which

persisted after controlling for affective state: this finding supported the validity of the MDQ (and HCL) as a measure of bipolarity in MDD. In mood disorders research, temperamental evaluation may be more useful in distinguishing mood disorders than Eysenck's 'Big Two'.

Concurrent Validity

Criterion validity

Strong and highly significant correlations between the MDQ and the clinician-administered HCL provided some evidence of criterion validity. This indicates that sub-clinical manic symptoms can be reliably elicited by clinical interview or questionnaire. Use of questionnaires may be an efficient way to increase diagnostic sensitivity to historical manic experiences (Forty *et al*, 2010).

Convergent and divergent validity

It has been found that euthymic patients with bipolar disorder have subtle impairments in general intelligence that have not been reliably detected in euthymic unipolar patients (Goodwin & Jamison, 2007). In the population-based sample a modest, but highly significant negative correlation was found between the MDQ and a measure of general intelligence, the Mill Hill Vocabulary test. This was also present to a slightly lesser extent in controls. This finding provides some evidence of the convergent validity of the MDQ in MDD, but it may also indicate that a history of manic symptoms is associated with subtle cognitive impairment in the 'normal' population. In the early-onset study, the absence of any correlation between the MDQ and either Cloninger's Harm Avoidance, or anxious or depressive temperament provided some evidence of divergent validity.

In the early-onset sample, reaction time findings were unexpected, and the results from the genetic study made them harder to interpret: cases were on average slower than controls, as would be expected, but the MDQ correlated negatively with

reaction time: i.e., high scorers on the MDQ reacted faster. Patients carrying the apparent bipolar risk C allele at rs1202875 (n = 9) reacted more slowly, however they also scored lower on the MDQ, HCL, cyclothymia and irritability scales which suggested they had fewer manic features. Given the very small numbers and lack of replication, the genetic results should probably be given less weight. Attempts could be made to replicate the unexpected negative correlation between MDQ and reaction time. The Generation Scotland cohort has reaction time data on around a thousand participants, and this could allow an attempt at replication.

MDQ showed a modest but highly significant correlation with measures of general distress (GHQ-28). Multiple regression allowed diagnostic group and Eysenck's N to be controlled. Over and above these factors, the MDQ total score explained 0.5% of the variance. This provided weak evidence of convergent and predictive validity. From a clinical perspective, predictive validity is the most important feature of a diagnostic entity (Kendell, 1989); the clinical utility of using the MDQ can be determined by follow-up studies in the GS cohort, either by record linkage or by re-contacting participants.

Construct validity

A principal component analysis in population-based sample allowed an exploration of the underlying structure of the MDQ, and comparison of its performance in Scotland, compared to other countries. As in other studies (Hirschfeld *et al*, 2003b), it was internally reliable, and most items loaded strongly onto a single 'energised-activity' component, providing some evidence of construct validity. Two lesser factors, a 'racing thoughts – irritability' and a 'disinhibited' component were also detected, however the steep scree plots demonstrated that the first factor was dominant.

Predictive Validity (Utility)

Patients want to know how their illness is likely to progress, and clinicians need to

make decisions about what treatment to recommend: in clinical practice the most important aspect of the validity of a diagnostic concept is its predictive validity, also know as utility, or usefulness (Kendell & Jablensky, 2003).

In Chapter 2, the early-onset depressed MDD patients were treated as usual and followed up for 3 months. MDQ and HCL showed weak but non-significant negative correlations with change in depressive symptoms. It has been recognised that, in general, bipolar patients are more likely than unipolars to suffer adverse effects from antidepressant treatment. Three-quarters of the patients (n = 36) were receiving unopposed antidepressant treatment at follow up – in these individuals there was moderate and significant positive correlation between MDQ, restlessness and suicidal thoughts. This provided some evidence of predictive validity. If this finding was replicated, it could indicate that those with early-onset MDD who also score highly on the MDQ, may need particularly careful monitoring for suicidality. A more speculative implication is that, as in bipolar depression (Sidor & Macqueen, 2011), unopposed antidepressant therapy may not be the best first-line drug treatment for this group .

Summary

The validity of the MDQ was examined in an early-onset and population-based sample with MDD, and in a large group of controls. On clinical, psychological and cognitive measures the MDQ showed modest or moderate antecedent and concurrent validity. Findings supported a spectrum of severity, with no clear boundaries between 'normality' and MDD or BP. A genetic association study (MacIntyre *et al*, 2010) provided some evidence that Ghaemi's criteria for BSD may identify individuals more appropriately considered bipolar. In the early-onset MDD sample, the MDQ did not predict recovery but, in those on antidepressants, it correlated with subjective restlessness and thoughts of suicide.

Clinical Implications

Clinical implications that may be drawn from this research are threefold. In those with MDD (particularly those with other risk factors for BP such as early age of onset and a recurrent disorder) it may be useful to rate manic symptoms to (1) identify those who may require more intensive monitoring of suicidality, (2) inform treatment decisions, possibly away from antidepressant towards mood stabilisers. Thirdly, classifying mood disorders on the basis of prior course, and including personality measures, along with polarity, may have more clinical utility.

Further research

The longstanding tension between categorical and dimensional classification will perhaps never be resolved, however a pragmatic approach combining both may be useful. Novel diagnostic criteria, and probabilistic approaches (Mitchell *et al*, 2008) should have their utility firmly established by follow up studies before their use is widely promoted. The predictive validity of the MDQ should be assessed by follow-up studies of the Generation Scotland cohort, using record linkage and re-contacting of participants, preferably along with drug treatment data.

A randomised clinical trial in early-onset MDD, comparing antidepressant monotherapy with a treatments usually reserved for bipolar depression may be justified.

Creating rational treatments for mood disorders is likely to depend on understanding their aetiology, and this may rests on carefully phenotyping of patients. As larger population based-samples become available, the use of dimensional measures may become more important in dissecting risk traits.

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Chapters 2 and 3

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Chapter 4

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Appendices

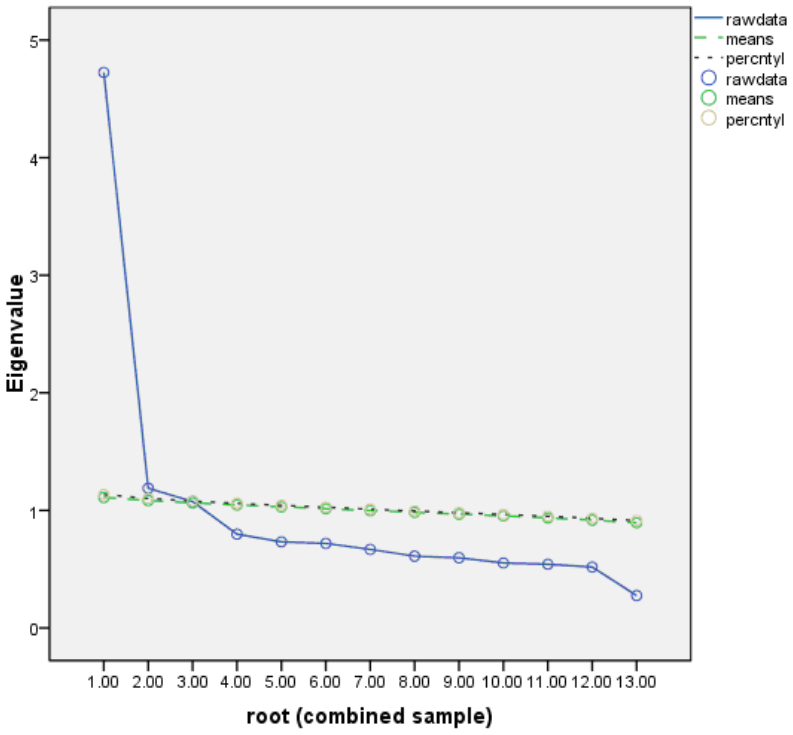
Appendix 1 Log transformed TCI/HA correlations

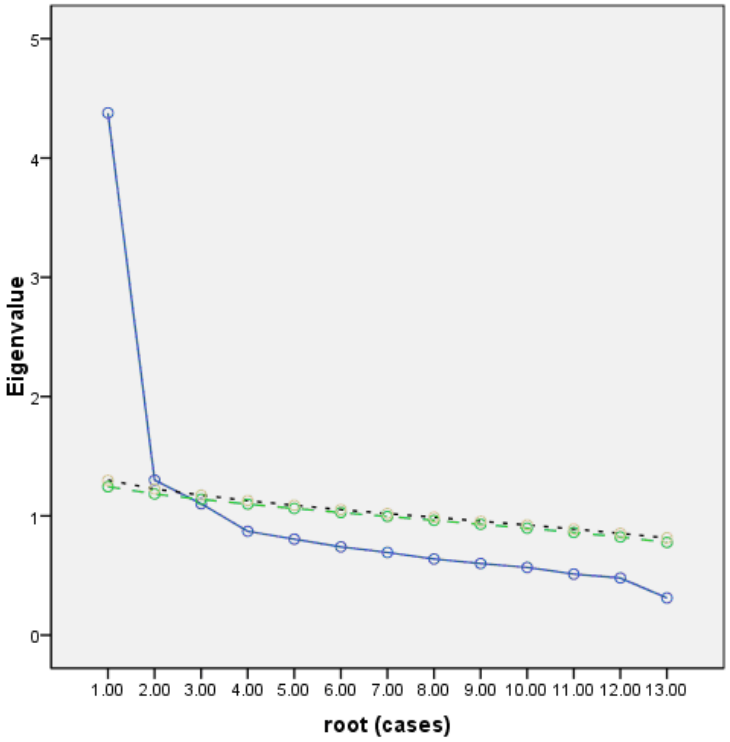
		MDQ_13	TCI_1 HA	rev_log MDQ	rev_log TCI_HA
MDQ_13	Pearson Correlation	1	.084		
	Sig. (2-tailed)		.512		
	N	64	64		
TCI_1 HA	Pearson Correlation	.084	1		
	Sig. (2-tailed)	.512			
	N	64	64		
rev_log MDQ	Pearson Correlation			1	.057
	Sig. (2-tailed)				.657
	N			64	64
rev_log TCI_HA	Pearson Correlation			.057	1
	Sig. (2-tailed)			.657	
	N			64	64

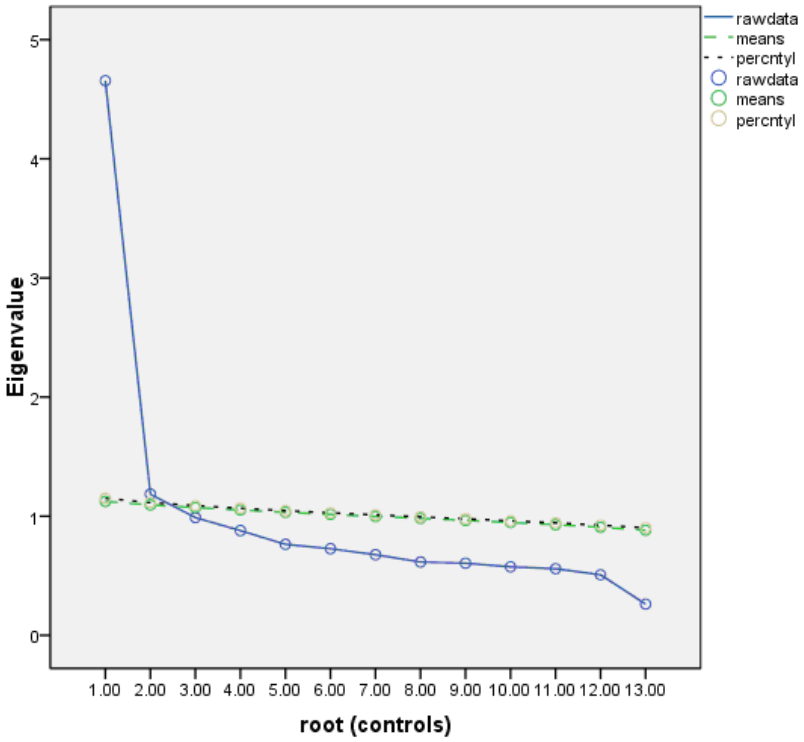
Appendix 2 Partial TEMPS-A correlations

Control Variables			HypomaniaChecklist	MDQ_13
BDI_1 & YMRS1	HypomaniaChecklist	Correlation	1.000	.705
		Significance (2-tailed)	.	.000
		df	0	60
	MDQ_13	Correlation	.705	1.000
		Significance (2-tailed)	.000	.
		df	60	0
	TempsA_1	Correlation	.147	.040
		Significance (2-tailed)	.255	.760
		df	60	60
	TempsC_1	Correlation	.385	.400
		Significance (2-tailed)	.002	.001
		df	60	60
	TempsD_1	Correlation	.018	-.071
		Significance (2-tailed)	.892	.585
		df	60	60
	TempsH_1	Correlation	.179	.240
		Significance (2-tailed)	.164	.061
		df	60	60
	TempsI_1	Correlation	.091	.271
		Significance (2-tailed)	.484	.033
		df	60	60

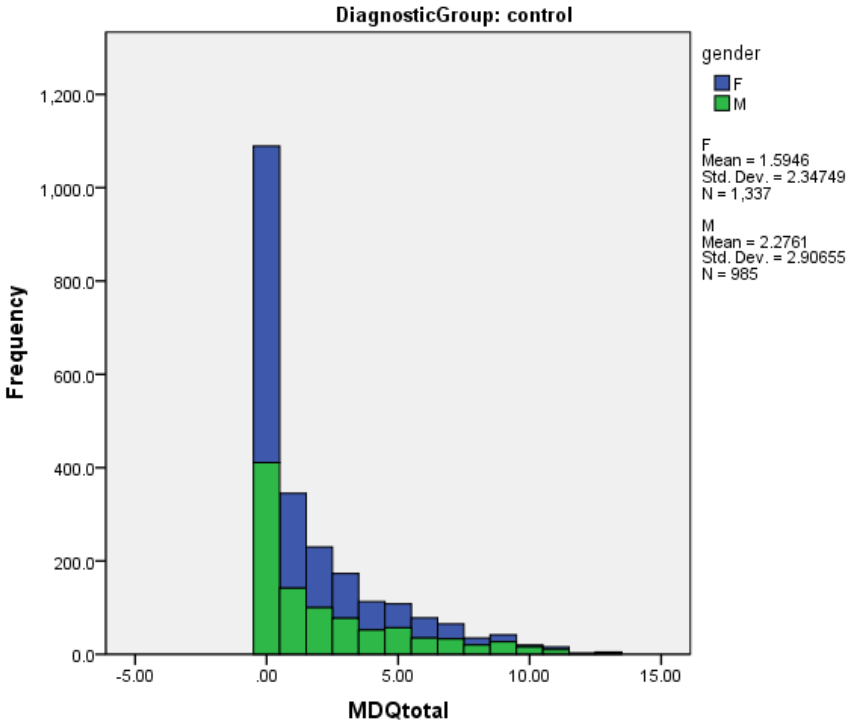
Appendix 3 Monte Carlo simulation (raw data) permutation scree plots

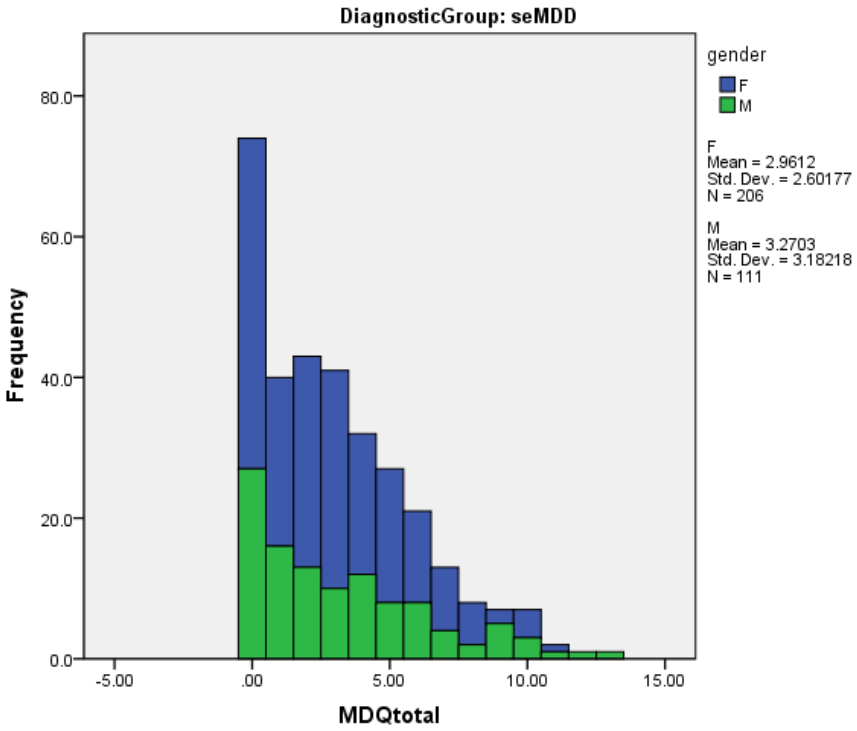


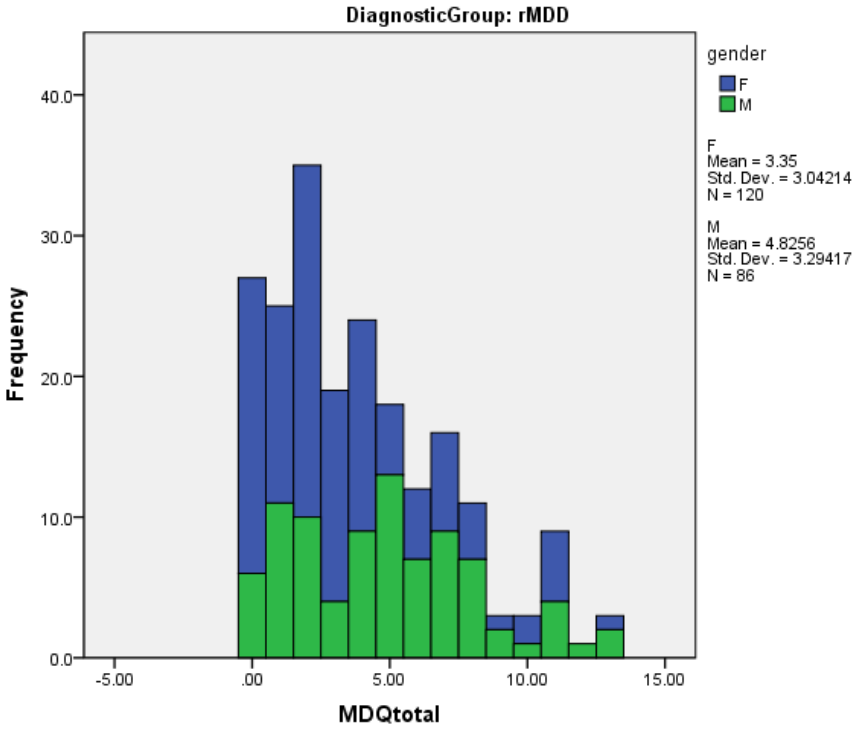


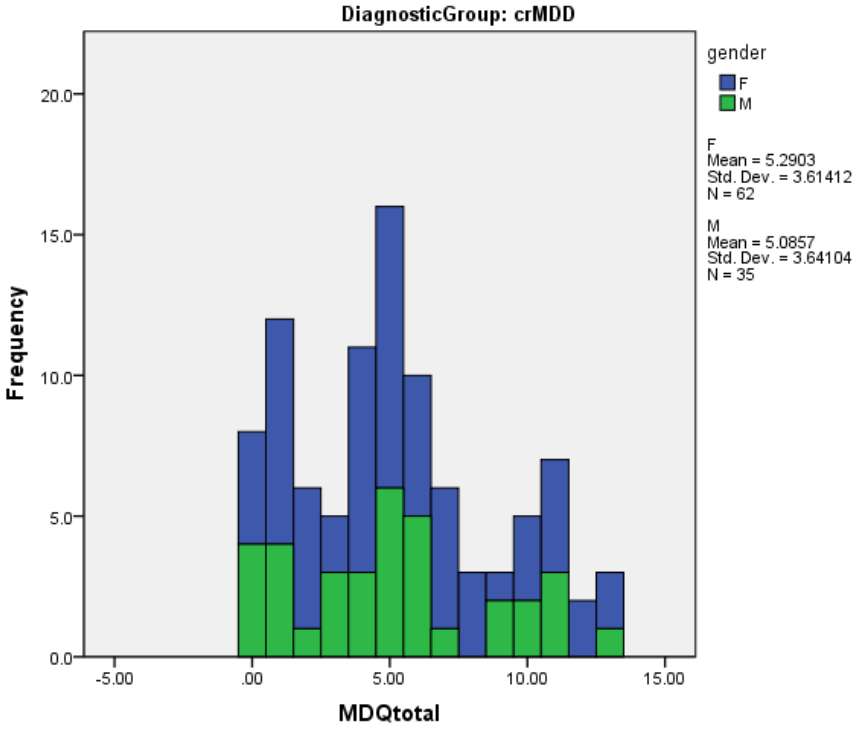

rawdata
means
percntyl
rawdata
means
percntyl
Eigenvalue
0
1
2
3
4
5
1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00
root (controls)

Appendix 4 MDQ histograms






DiagnosticGroup: rMDD
gender
F
M
F
Mean = 3.35
Std. Dev. = 3.04214
N = 120
M
Mean = 4.8256
Std. Dev. = 3.29417
N = 86
Frequency
40.0
30.0
20.0
10.0
0.0
-5.00
.00
5.00
10.00
15.00
MDQtotal


DiagnosticGroup: crMDD
gender
F
M
F
Mean = 5.2903
Std. Dev. = 3.61412
N = 62
M
Mean = 5.0857
Std. Dev. = 3.64104
N = 35
Frequency
20.0
15.0
10.0
5.0
0.0
-5.00
.00
5.00
10.00
15.00
MDQtotal

Publications Arising From This Work

MacIntyre, D.J., McGhee, K.A., MacLean, A.W., Afzal, M., Briffa, K., Henry, B., Thomson, P.A., Muir, W.J. & Blackwood, D.H.R. (2010) Association of GPR50, an X-linked orphan G protein-coupled receptor, and affective disorder in an independent sample of the Scottish population. *Neuroscience Letters*, **475**, 169–173.

Smith, B.H., Campbell, A., Linksted, P., McGilchrist, M., Wisely, L., Fitzpatrick, B., Ford, I., Hocking, L., Jackson, C., Kerr, S., Lindsay, R., Morton, R., Palmer, C.N.A., Deary, I.J., MacIntyre, D.J., Campbell, H., Dominiczak, A.F., Porteous, D. & Morris, A.D. (2012) Generation Scotland: Scottish Family Health Study. A profile of the study, its participants, and their potential for genetic research on health and illness. *International Journal of Epidemiology*, In press.