

FEATURE REVIEW

The phenotypes of bipolar disorder: relevance for genetic investigations

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The search for susceptibility genes for bipolar disorder (BD) depends on appropriate definitions of the phenotype. In this paper, we review data on diagnosis and clinical features of BD that could be used in genetic studies to better characterize patients or to define homogeneous subgroups. Clinical symptoms, long-term course, comorbid conditions, and response to prophylactic treatment may define groups associated with more or less specific loci. One such group is characterized by symptoms of psychosis and linkage to 13q and 22q. A second group includes mainly bipolar II patients with comorbid panic disorder, rapid mood switching, and evidence of chromosome 18 linkage. A third group comprises typical BD with an episodic course and favourable response to lithium prophylaxis. Reproducibility of cognitive deficits across studies raises the possibility of using cognitive profiles as endophenotypes of BD, with deficits in verbal explicit memory and executive function commonly reported. Brain imaging provides a more ambiguous data set consistent with heterogeneity of the illness.

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Bipolar disorder (BD) has a genetic basis with heritability of at least 80%.¹ A number of studies have attempted to map the susceptibility loci giving evidence of linkage in multiple genomic regions. In particular, findings in 4p, 4q, 8q, 10p, 12q24, 13q, 18p, 18q, 21q, and 22q have been supported by more than one study.^{2–19} However, these studies have not identified any specific genes, and a recent meta-analysis of available genome scans showed no regions with a conclusive evidence of linkage.²⁰

The relatively slow progress of gene-mapping efforts is often explained by the ‘complex’ nature of the illness and of the genotype–phenotype relation. The complexity most likely includes heterogeneity, interactions of multiple loci, incomplete penetrance, as well as phenotypes resulting from environmental effects—either alone or in interaction with the genetic predisposition. The goal of psychiatric genetic research is identification of (heritable) variations in DNA sequence or function that influence behaviour or give rise to mental illness. By definition, in complex (multifactorial) traits, this link is not unique and specific. That is, a particular change in gene sequence does not necessarily lead to a specific behaviour, and similar behaviours (symptoms) may be due to distinct (sets of) genes. Moreover, we must

consider the possibility that the path between the genotype and behaviour is not unidirectional. Emerging examples point not only to general effects of environment, for instance stress, on behaviour, but also to specific behaviours influencing gene function that can be transmitted onto the next generation.²¹

No single method is considered clearly superior in identifying susceptibility genes for complex traits such as BD. Most researchers agree that a combination of strategies is most likely to succeed. These include study of homogeneous clinical populations that are well characterized and followed up longitudinally. Proper choice of a phenotype is particularly relevant for several reasons:

1. The clinical manifestation of BD is highly variable, both cross-sectionally (between subjects) and longitudinally (within subjects). Because of this variability, clinical research is needed in order to define the phenotype, either as a clinical category or as a dimensional trait.
2. If effects of individual genes are small, diluting them further due to diagnostic or other imprecisions will decrease statistical power.
3. Accurate and adequate description of the phenotype is relevant for replication efforts to ensure that comparable populations are studied.
4. Once individual susceptibility genes are identified, it will be important to delineate those behavioural manifestations of the illness that are associated with the specific genes.

In this paper, we have selectively reviewed the issues pertinent to phenotype definition in BD. Specifically, we address what psychiatric and neuro-behavioural research can offer genetic research to assist with the task of linking genes to behaviour, signs, and symptoms of psychiatric illness. We discuss clinical diagnosis and phenomenology, issues of diagnostic spectra, and boundaries between diagnostic categories. We then review the most promising endophenotypes in the neuropsychological and brain-imaging domains and discuss their role in genetic research of BD.

Diagnosis of BD

BD is diagnosed using operationalized criteria consisting of lists of symptoms. To meet criteria for a disorder, a patient must have a certain number of symptoms for a certain length of time and must show evidence of impaired function. In the absence of a specific diagnostic test of the illness, this approach has become the gold standard of diagnosis. Thus, biological psychiatry relies on clinical diagnosis, which is then used as a basis for studying biological markers and these are then used to refine the clinical diagnosis in successive iterations.

This reliance on arbitrary (and categorical) criteria has been criticized by several researchers who argued that 'it is sterile' and 'represents an obstacle for research'.^{22,23} The way BD is diagnosed may also at least partially account for some of the observed shifts in population prevalence of the illness, bipolar II disorder (BDII) in particular (Figure 1). In recent years, several authors have argued that BD is more common, that symptoms of (hypo)mania are continually distributed among mood-disorder cases,²⁴ and that the criteria separating BDII from 'softer' conditions are essentially arbitrary.²⁵ These changes in conceptualization of mood disorders, if accepted, are

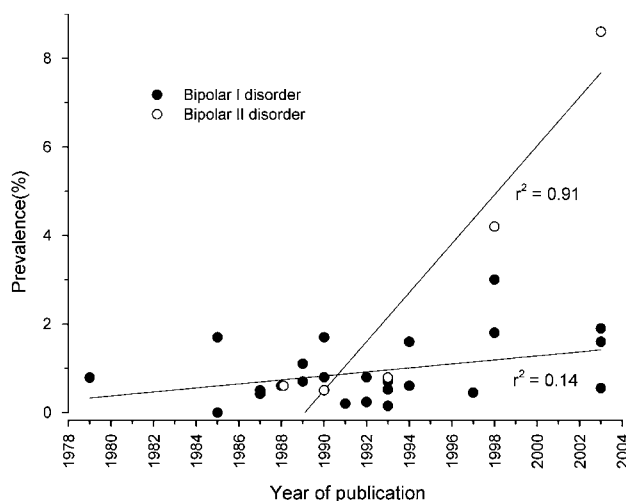


Figure 1 Time trends in reported prevalence of BDI and BDII.

critical for future research of BD. They also raise legitimate concerns about increasing heterogeneity and diminishing the chance of consistent findings in neurobiological or genetic studies.²⁶

Disorders in the bipolar spectrum

Given the variability of its clinical presentation, research is needed to define the diagnostic boundaries of BD and specify what syndromes should be included in its diagnostic spectrum. Current diagnostic criteria already recognize some of this variability and define several 'bipolar' categories such as bipolar I disorder (BDI), BDII, and bipolar disorder not otherwise specified in DSM-IV.

Relation between bipolar I and bipolar II disorders

Judged by the severity of manic symptoms, BDII appears to be intermediate between unipolar depression and BDI. Similarly, some studies reported distinct differences in rates of recovery,^{27,28} clinical features, and number of episodes.²⁹ Other aspects of illness course, such as age of onset, may³⁰ or may not differentiate patient groups, as one study found no differences in age of onset between 45 BDI and 141 BDII outpatients.³¹ We examined data from 138 patients with BDI or BDII and did not find differences in age of onset, symptom levels, or outcome during 1–4 years of follow-up.³² The tendency towards a mild or more severe expression of mania may run true in families,^{33,34} but may not translate into substantive differences in the expression or frequency of depressions or in overall functional outcome associated with the illness. The familial nature of hypomania has raised questions whether BDII is a distinct category.^{33,35} Congruent with this view are the findings of McMahon *et al*³⁶ showing that families with BDII cases had the strongest evidence of linkage to chromosome 18q21–23 markers.

Bipolar spectrum

The results of family studies indicate that it is not only BD that is more common among relatives of BD probands, but also other psychiatric conditions. These are usually milder forms of BD not meeting the full criteria as well as other psychiatric conditions. Together they are regarded as bipolar spectrum, a set of ... 'several psychopathological states that may share genetic basis'.³⁷ The concept of diagnostic spectra appears throughout the history of psychiatry; in modern psychiatry, it was discussed, for instance, by Rosenthal³⁸ and specifically in relation to mood disorders by Akiskal *et al*.³⁹

The one disorder most commonly recognized as related genetically to BD is unipolar depression. For instance, Blacker and Tsuang have estimated that at least two-thirds of unipolar relatives of bipolar probands may, in fact, be suffering from a variant of BD.^{40,41} Indeed, some authors view the relation between unipolar and BDs as a continuum with a unimodal distribution of numbers of manic

symptoms.²⁴ Similarly, at least some cases of schizoaffective disorder are considered genetically related to BD.⁴² Diagnosing a typical case of BD is usually not difficult, but arguably the severe forms of BD, especially with psychotic symptoms, may pose difficulties differentiating from disorders in the schizophrenia spectrum. There are also debates regarding to what extent BDII, particularly, is overdiagnosed at the expense of personality disorders. Some authors consider other psychiatric conditions such as ADHD, eating disorders, dysthymia, or substance abuse as part of the bipolar spectrum, but these are not accepted unequivocally.

Refining the phenotype

Many psychiatric disorders are heterogeneous. Mapping genes in more homogeneous subgroups has been already effective in other complex traits where such groups were defined by age of onset, biological markers, or clinical characteristics.^{43–50} In a comprehensive review, Nurnberger⁵¹ suggested that homogeneous groups could be defined by age of onset, presence or absence of comorbid conditions, familial patterns of illness, treatment response, gender of transmitting parent, or clinical course of illness in major psychiatric disorders. Such groups might be, in theory, associated with more or less distinct loci. However, it is also possible that BD is a syndrome arising from multiple aetiologic factors but with a common, genetically based underlying pathophysiology. Thus, the first approach would look at differences between individual cases, while the latter strategy emphasizes commonalities, for example, of biological markers or treatment response. In this model, differences between groups of patients are not viewed as a reflection of the underlying causes, but rather a nonspecific 'noise'. For instance, non-response to a specific treatment could be due to various factors such as substance abuse or noncompliance, which are less likely related to the aetiology and pathophysiology of the illness. In either case, delineation of the bipolar spectrum against other conditions is important, but the latter approach is less concerned about the internal differentiation of the bipolar phenotype.

Psychotic symptoms in BD

While typical forms of schizophrenia and BD are not difficult to differentiate clinically, there is some degree of overlap between the two and schizophrenia must be considered in the differential diagnosis of BD. The relation between these disorders has been a subject of intense debate. An increasing number of authors are leaning towards the possibility of shared genetic basis.^{52,53}

Ketter *et al*⁵⁴ have examined whether the presence of psychotic symptoms defines a subgroup of BD or whether these symptoms constitute one of psychopathological dimensions of the illness. The authors

propose that a combination of dimensional and categorical views is most compatible with the existing data.

It appears that individuals with symptoms of psychosis, specifically delusions and hallucinations, are not distributed uniformly in families of bipolar probands, but tend to cluster.^{55,56} Similarly, Schurhoff *et al*⁵⁷ found a familial aggregation of proneness to delusions in a combined sample of families of schizophrenic and bipolar probands and O'Mahony *et al*⁵⁸ found correlation of 'psychotic dimension' in an analysis of affected sib pairs from 160 families of bipolar probands. Using the presence of psychotic symptoms during affective episodes as a means to stratify linkage results, positive lod scores on 13q31 (region containing the locus G72/G30) and 22q12 were obtained from a subset of 10 families with three or more members with a history of psychotic symptoms.⁵⁹ These findings replicate and further clarify previous linkage findings in BD in these two chromosomal regions.^{12,13,19,20,60–62} They are especially interesting as the same regions may encompass susceptibility genes for schizophrenia.^{63–70} Park *et al*⁷¹ made similar conclusions in a study of psychotic BD in which most areas of linkage overlapped with those reported in previous investigations of schizophrenia.

Psychiatric comorbidity

In addition to core mood symptoms, bipolar patients commonly present with other symptoms such as anxiety or substance abuse. The type of symptoms and their number are often sufficient to diagnose these patients with comorbid diagnoses.

Clinical and population studies of patients with BD find point prevalence rates of anxiety disorders (ADs) between 30 and 40%^{72–74} and lifetime prevalence rate of any AD in patients with BD approximate 90%. The Epidemiological Catchment Area study reported the lifetime prevalence for panic disorder in bipolar illness to be 20.8%, twice that of unipolar patients.^{73,75,76} The extant literature examining anxiety in patients with BD suggests that patients with anxiety have longer, more frequent, and more difficult to treat mood episodes and greater functional impairment.^{74,77–79} Others have noted an association between ADs and mixed as opposed to euphoric mania.^{80,81} BD patients with high levels of anxiety symptoms experience more substance abuse and chronic suicidal ideation and these patients are less responsive to treatment with lithium,^{77,82,83} and may have an earlier onset of mood illness.^{72,74}

Rates of comorbidity are another aspect of illness that has appeared to differentiate BDII from BDI. High rates of comorbid disorders have been reported with BDII,^{73,84} including substance abuse or dependence,^{34,85} ADs,⁸⁶ and personality disorders.^{87,88} Young *et al*⁸² noted high rates of comorbid anxiety in BD patients, including a sample of BDII patients, but whether this association was an artefact of referral to a tertiary care centre could not be ascertained.

Angst *et al*⁸⁹ subsequently found a similarly high association between BDII and anxiety in a community-based sample. Some investigators proposed that understanding the temperamental dysregulation underlying BDII⁹⁰ may provide a framework for understanding why ADs such as social phobia and obsessive compulsive disorder occur at high rates in BD type II.⁹¹ Consistent with data from Himmelhoch,⁹² they suggest that the temperamental inhibition or constraint that characterizes social phobia and obsessive-compulsive disorder exists on a continuum with the disinhibited behaviour of BDII. Rates of comorbidity may account for much of the reported variance in course and outcome, as a number of studies have found that differences between BDI and BDII patients diminish when comorbidity is excluded.^{30,86,93,94}

Bipolar patients with comorbid panic disorder often have relatives with the same condition. MacKinnon *et al*^{95–98} found in a series of studies that these patients are characterized by rapid mood switching and they are more likely to be diagnosed with BDII. The same group found that these families had higher lod scores for markers on chromosome 18q.⁹⁹ These findings indicate that the subgroup of patients with BDII, comorbid panic disorder, and mood lability may share a susceptibility gene on the long arm of chromosome 18q, with a possible parent-of-origin effect. In family studies of lithium-responsive probands, we found little evidence of linkage to chromosome 18 markers,^{100,101} which is consistent with the observation of very low rates of comorbid conditions and mood lability among responders to lithium.¹⁰² Such traits, on the other hand, are common among responders to the anticonvulsant lamotrigine.¹⁰³

Substance abuse also occurs at high rates in BD. This association could arise from a shared genetic basis, but substance use can also be a consequence of psychiatric symptoms (impulsivity, disinhibition) or response to them—'self-medication'. On the other hand, it can lead to manifestation of illness in vulnerable individuals and can be associated not with the mood disorder, but with its comorbid conditions. The available literature provides arguments for and against each of these possibilities. Only careful history and longitudinal observations may clarify which of these factors play the most prominent role in individual patients. For instance, Preisig *et al*¹⁰⁴ found no evidence of crossaggregation between alcoholism and BD and they suggested that the independent familial aggregation of BD and alcoholism, and the finding that the onset of BD usually preceded that of alcoholism, was compatible with a self-medication hypothesis as the explanation for the frequent co-occurrence of BD and alcohol abuse. Importantly, presence of substance abuse influences the clinical presentation, course, outcome, and treatment response.¹⁰⁵ Thus, it is an important factor to consider in clinical and genetic research, but perhaps more to control for than to take advantage of.

Clinical course and outcome

The clinical course of BD is highly variable and some of this variability may be influenced by heritable factors. Particularly, promising findings have emerged in studies of age of onset, and pattern of clinical course, including rapid cycling. Both characteristics are also associated with other clinical features.

Age of onset of BD ranges from childhood to the late stages of life, but most commonly reported values extend from late 20 to 30s in older studies, and from late teens to early 20s in more recent reports. Early onset correlates with genetic loading. Affected relatives appear to have similar onset.⁵⁸ Bellivier *et al*¹⁰⁶ analysed the distribution of age of onset and concluded that age of onset was correlated in affected family members. When Faraone *et al*¹⁰⁷ investigated age of onset as a quantitative trait in linkage analysis of BD, they found that the onset of mania was heritable ($h^2=0.41$) and using it as a phenotype provided suggestive lod scores on chromosomes 12p, 14q, and 15q, in regions not implicated by traditional linkage analyses of that or other data sets.

Despite differences in methodology for the ascertainment of patients, length and timing of follow-up, and definition of outcome, studies consistently find that 30–60% of patients with BD have poor psychosocial functioning in interepisode intervals. Some studies report a positive association between clinical course, measured as number of prior admissions^{108,109} or past episodes,¹¹⁰ and interepisode level of functioning. Others have failed to find such relations.^{111–113} One explanation for the discrepancies in studies examining the role of episode number in outcome may be that this relation may be nonlinear. We found that nonlinear logarithmic and power functions best described the association between number of past episodes and functioning in a group of 64 euthymic bipolar patients.¹¹⁴ It is not known whether a subset of patients with BD develop a syndrome analogous to the deficit syndrome of schizophrenia or whether instead, low levels of residual symptoms account for the persistent dysfunction despite the fact that patients fall into the euthymic range on formal assessment. A number of studies have identified interepisode symptoms as a factor that could contribute to poor outcome; yet outcome was not appreciably better in studies in which patients had documented low levels of residual symptoms.^{108,115} The qualitative and quantitative characteristics of clinical course appear similar in affected family members. A modest correlation in frequency of episodes among affected siblings has been observed.⁵⁸ In a study of children of bipolar parents, Duffy *et al*¹¹⁶ found a strong association between the quality of remission in affected parents and children.

Suicide in BD

Rihmer and Pestalicy¹¹⁷ summarized studies in which lifetime rates of suicide attempts were analysed

separately for patients with BDI, BDII, and unipolar disorder. Risk of suicide was highest in patients with BD compared to unipolar patients, and the risk was significantly higher for BDII (24%) compared to BDI (17%) when all studies were combined. Suicide behaviour may constitute a partly independent genetic trait, however. In a study of 3372 twins, Fu *et al*¹¹⁸ reported that suicidal ideation was influenced by genetic (36%) and nonshared environmental (64%) effects, while suicide attempt was affected by additive genetic (17%), shared environmental (19%), and nonshared environmental (64%) effects. Cavazzoni *et al*¹¹⁹ found that the risk of suicidal behaviour was not distributed uniformly in families of bipolar probands and it correlated with the degree of genetic loading for BD. Another group reported that in a group of over 300 BDI and BDII patients, 42% had made at least one suicide attempt in their life; suicide attempts were associated with history of suicidal behaviour in first-degree relatives but not with history of mood disorder.¹²⁰ In contrast, however, another recent study of bipolar patients and their family members failed to find that a suicide attempt by a proband was associated with any increase in suicide attempts by relatives.¹²¹ Thus, while suicide may have a genetic contribution, the proposition that patients with BD and suicide attempts constitute a valid subgroup for genetic studies remains to be better established.

Response to long-term treatment

Several lines of evidence suggest that response to maintenance treatment identifies distinct subgroups of BD. These subgroups differ in other clinical characteristics such as family histories, clinical course, or comorbid conditions. Responders to lithium treatment are the most extensively studied group in this respect. Their clinical features correspond to the BD 'core phenotype', with an episodic course of the illness, low rates of comorbid conditions, and absence of rapid cycling.^{26,122–125} Most family studies support the association of lithium response and family history of BD,^{102,126–131} and the response to lithium prophylaxis itself appears to have a familial component.¹³² In studies of three independent populations, we found that lithium responders were a more homogeneous subgroup of BD, characterized by a stronger genetic loading for BD, and with a familial transmission compatible with a major-gene effect.^{102,103,133,134} Similar support for a major-gene effect was found in other study of lithium responders¹³¹ and in typical BD.¹³⁵ Nonaffective psychiatric disorders among relatives of lithium responders are uncommon.^{101–103}

Treatment outcome findings in BD also define lithium responders as a distinct, more uniform subgroup. Responders to lithium differ from responders to other mood stabilizers and the treatment response appears to be specific;^{103,136–139} the antimanic responses to valproate and lithium are present in

different patient groups.¹³⁷ In the MAP Study, Greil *et al*¹³⁸ found that in contrast to lithium responders, patients who benefited from long-term treatment with carbamazepine had atypical clinical features. As well, a study comparing responders to lithium and lamotrigine identified robust differences with respect to clinical course, comorbid conditions, and family history;¹⁰³ and patients nonresponsive to lithium may respond well to olanzapine.^{140,141}

Finally, genetic research may benefit from growing knowledge of the mechanisms of action of mood-stabilizing drugs. This includes the possibility of biochemical endophenotypes as well as informed selection of candidate genes.^{142,143}

Familial transmission of BD

The pattern of transmission of BD in families is another feature that may prove useful in searching for susceptibility genes. The possibility of preferential transmission from the paternal or maternal side of the family has been raised in the context of two genetic theories. One of them is *imprinting*, which suggests that there is a differential expression of maternally or paternally transmitted genes with a resulting difference in the clinical presentation; the other is *mitochondrial inheritance*. It does not appear that either theory applies to most families. BD type I is about equally prevalent among men and women and the same seems to apply to prevalence of affected relatives on maternal and paternal sides of families. In fact, there is strong evidence for bilineal transmission.¹⁴⁴ However, differences in prevalence between men and women are well established in BDII, and some studies find preferential transmission from mother compared to father as well as parent-of-origin effects in linkage data, especially data on chromosome 18.^{15,145} Moreover, several intriguing findings with respect to mitochondrial mechanisms have been published, some of them linking these with the chromosome 18p results.^{146,147}

Anticipation refers to the phenomenon of increased severity and/or earlier age at onset in successive generations. These characteristics have been sometimes observed in families of BD probands. As anticipation in some other conditions has been associated with unstable repeats in the human genome, most typically trinucleotide repeats, several studies tested for these in BD with equivocal results at best.¹⁴⁸ The lack of consistent findings may further support the argument that anticipation observed in families of psychiatric patients is an artefact of ascertainment bias.

Endophenotypes

While genetic investigations based on a purely positional approach have produced successful results in many conditions, research linking genetic and pathophysiological strategies can be much more powerful, especially in complex traits. For instance,

studies of diabetes, asthma, hypertension, or Alzheimer's disease all benefited from at least partial knowledge of some mechanisms underlying these conditions.^{43,44,47,149–151} Such knowledge can be used to (1) identify illness subtypes to increase homogeneity of clinical samples; (2) define phenotypes better accessible to genetic investigations (endophenotypes); and (3) select candidate genes in linked regions.

As psychiatric diagnoses are made at the level of clinical symptoms (behaviour), it is probable that the path from genotype to phenotype is long and complex with many instances of convergence and divergence. It is, therefore, appealing to study traits that are intermediate between the clinical presentation and its genetic underpinning. Such traits, commonly called endophenotypes, are assumed to be simpler from the genetic point of view, likely associated with fewer loci.¹⁵² Instead of looking for genes coding complex disorders, endophenotypic research looks for genes for simple, ideally monogenic traits that accompany the illness and probably contribute to its pathophysiology. Decreasing the complexity of the marker should also decrease the complexity of its genetic basis. If phenotypes associated with a disorder are very specialized and represent more elementary phenomena, the number of genes required to produce variations in these traits may be fewer than those involved in producing a complex psychiatric diagnostic entity. Endophenotypes are a step towards simplifying extremely complex diseases.

Certain criteria have to be met, however, before a given marker can be used as an endophenotype in genetic analyses. The marker must be associated with the illness in the population, be heritable, and state independent (ie present during remission); it also has to co-segregate with the disease within the family and have higher prevalence in high-risk unaffected subjects than in general healthy population.

Lenox *et al*¹⁴³ examined the most promising endophenotypes in BD. They identified abnormal regulation of circadian rhythms (the sleep/wake cycle, hormonal rhythms, etc), response to sleep deprivation, P300 event-related potentials, behavioural responses to psychostimulants and other medications, response to cholinergics, increase in white matter hyperintensities (WMHs), and biochemical alterations in peripheral mononuclear cells. Therefore, in this paper, we review only those areas that have drawn the most interest in the last few years, namely cognitive dysfunction and structural brain changes.

Cognitive endophenotypes

Glahn *et al*¹⁵³ have elegantly reviewed the evidence supporting the use of cognitive endophenotypes in BD; the data supporting this approach are therefore only briefly summarized below. A number of cognitive domains appear to be highly heritable; as well as the known heritability of general intelligence,

performance on tests assessing information processing, attention, working and declarative memory as well as executive function is strongly genetically influenced. This high heritability increases the likelihood that a search for a cognitive phenotype for BD will be successful.

In addition to heritability, a putative phenotypic marker should be detectable in patients with BD independent of current illness state. A substantial number of studies have now confirmed that many patients with BD have cognitive impairment that persists into the euthymic state.^{154–159} Impairment has been demonstrated in sustained attention,¹⁶⁰ working memory and executive function,¹⁵⁵ global cognitive functioning,¹⁵⁴ visuospatial recognition memory,¹⁶¹ problem-solving strategies,¹⁵⁶ declarative memory,¹⁵⁷ and cognitive processing speed.¹⁶² The fact that such impairment is detectable independent of clinical state is suggestive of a trait marker, but factors such as the neuropsychological deterioration secondary to acute episodes of illness, medication treatment, and/or withdrawal effects, long-term effects of comorbid conditions such as substance abuse, or the effect of unrecognized neurobiological changes such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis could all contribute to performance deficits in the euthymic state. In fact, there is evidence that performance on cognitive tests declines as a function of past illness burden,^{154,162,163} and that a past history of alcohol abuse can impact on cognitive performance in certain domains.¹⁶⁴ Neither the short- nor long-term impact of medication on cognitive performance is known,¹⁶⁵ and evidence is just emerging supporting a recurrent or even chronic dysregulation of HPA axis function in BD.^{166,167} It is important, therefore, that potential cognitive endophenotypes be studied in unaffected family members of BD probands.

In contrast to the now substantive literature on cognitive function in patients with BD, relatively few studies have examined cognitive performance in unaffected family members of BD probands. Most of the data that are available from family studies suggest that verbal memory is the cognitive domain that is most likely to be impaired when unaffected relatives are compared to healthy comparison subjects with no affected relatives. Gourovitch *et al*¹⁶⁸ examined memory in monozygotic twins discordant for BD. They found that unaffected twins of the discordant pairs were impaired relative to control twins (neither affected) on several measures of the California Verbal Learning Test, including immediate recall, short delayed cued recall, long delayed free and cued recall, and recognition. Additionally, they found differences in the Wechsler Memory Scale memory quotient and the intrusion measure of the Brown–Petersen test, in which words must be remembered over short delays during which overt rehearsal is prevented by distracting tasks. In contrast to results on the Brown–Petersen test, working memory measured by forward and backward digit span did not

differ between monozygotic, unaffected twins and control twins.¹⁶⁸ Keri *et al*¹⁶⁹ also examined working memory and verbal explicit memory in siblings of patients with BD and siblings of patients with schizophrenia. Siblings of patients with BD or schizophrenia were impaired relative to controls on the long delay components of a verbal memory test, but performed at control levels on other cognitive domains, including a spatial working memory task.¹⁶⁹ Another group compared working memory and explicit memory of first-degree relatives of patients with BD type I and II and controls unrelated to patients with BD. Although the groups performed at the same level on a picture learning task, the first-degree relatives of patients with BD were impaired on the recall and recognition tasks of a verbal learning task in comparison to controls. In contrast to the verbal learning test results, working memory function was retained in first-degree relative of patients with BD relative to controls. Of note, first-degree relatives of patients with BD type I had more pronounced memory impairment than first-degree relatives of patients with BD type II.^{170,171} Ferrier *et al*,¹⁷² however, did not find verbal declarative memory deficits in a sample of unaffected relatives of BD probands, and they suggest that the discrepancy may be secondary to the use of different tests across studies although they did use a relatively standard list learning procedure.

Apart from verbal memory impairment in first-degree relatives of BD probands, there is some evidence for executive function impairment; Zalla *et al*¹⁷³ examined executive function deficits in first-degree relatives of patients with BD, and found impairment on interference trials of the Stroop test. Executive control deficits in unaffected relatives were also recently observed by Ferrier *et al*,¹⁷² but they were limited to deficits in the executive control of working memory and were not apparent on the Stroop test. Interestingly, the executive dysfunction in BD appears to follow bimodal distribution, perhaps suggesting an existence of two subgroups of patients;¹⁷⁴ this suggestion is consistent with findings of a subgroup of elderly patients with depression associated with executive dysfunction. Other cognitive domains have been insufficiently studied in either patient or family studies to confirm or disprove their utility as endophenotypes.

The most consistent finding from studies of cognitive function in unaffected family members, therefore, is that verbal explicit memory is impaired compared to controls. This is consistent with the fact that most studies of cognitive function in euthymic patients report explicit memory impairment. There is also some evidence for executive function deficits in unaffected relatives, but the data are sparse. In contrast, working memory deficits in relatives of patients with BD are less reliably reported and this is consistent with much more variable reports of working memory impairment in euthymic patients with BD. Verbal declarative memory and executive

system dysfunction are unlikely to be highly specific for BD. In fact, deficits in such domains have been well described in other patient groups. This lack of specificity need not reduce the utility of these deficits as endophenotypes; overlap of BD with unipolar depression and psychotic disorders is discussed above, and the use of cognitive endophenotypes in BD may improve identification of genes for psychopathology more generally.

High-risk studies of children of parents with BD are limited, but have reported performance changes that may be indicative of cognitive trait markers.^{175–177} In general, formal neuropsychological assessments of high-risk offspring have not been conducted. We recently conducted a study of offspring of lithium-responsive parents with BD. The study assessed visual backward masking (VBM) performance in affected and unaffected offspring; striking VBM deficits were apparent only in affected offspring, while unaffected offspring performed at control levels.¹⁷⁸ Studies are ongoing to examine declarative memory performance and aspects of executive function in such high-risk groups.

There is little information describing which candidate genes for BD may be associated with the cognitive phenotype observed in patients with BD. A recent report suggested a relation between executive function and a brain-derived neurotrophic factor gene polymorphism.¹⁷⁹ Brain-derived neurotrophic factor is important in learning and memory, is found in high concentration in the hippocampus, and has been implicated in susceptibility to BD.¹⁸⁰ Each of these factors supports the notion that allelic variation in the BDNF gene may be associated with cognitive dysfunction in BD. Recently, a functional polymorphism in the catechol-*o*-methyl transferase (COMT) gene, which appears to selectively impact prefrontal dopamine regulation,¹⁸¹ has been shown to predict performance on prefrontal executive cognition and working memory tasks. Some investigators have postulated that at least some aspects of cognitive dysfunction in BD may be related to changes in dopamine projections¹⁸² although the association of dopamine with other clinical aspects of BD, such as expression of mania, is controversial.¹⁸³

Brain imaging and endophenotypes

Genetic factors contribute to interindividual differences in brain morphology. Cerebral, hemispheric, and ventricular volumes are highly heritable,^{184–187} but heritability of regional brain structures is variable.¹⁸⁷ For example, the size of corpus callosum is largely determined by genetic factors: Scamvougeras *et al*¹⁸⁸ applied a structural equation model to estimate that 94% of the variance in midsagittal size of the corpus callosum is attributable to the genome. Pfefferbaum *et al*¹⁸⁹ recently confirmed the high degree of heritability in corpus callosum. In contrast, when Sullivan *et al*¹⁹⁰ estimated heritability of the hippocampus, they found that it was subject to

substantially less genetic control (40%) than comparison regions. This suggests that imaging studies attempting to use morphological volume as a phenotypic marker must carefully attend to the heritability of the region under examination.

In order to understand what morphological changes might be expected in relatives of patients with BD, the morphological changes in patients themselves should be reasonably established. A number of reviews have summarized the data on structural brain changes in BD. These include grey matter tissue loss, enlarged ventricles, magnetic resonance T2 signal hyperintensities, as well as regional volume abnormalities in basal ganglia, lateral and mesial temporal structures (amygdala, hippocampus, thalamus), and cortical regions (dorsolateral prefrontal cortex, subgenual cingulate). Neuroimaging studies in BD have been recently reviewed,¹⁹¹ and while some consistent findings are beginning to emerge, a recent meta-analysis of 26 carefully selected MRI studies found only significantly larger right lateral ventricles in BD patients. No significant differences were seen in total brain, whole brain grey or white matter volumes, or volumes of individual cortical, subcortical, or limbic structures.¹⁹² Regions of particular interest in BD, including the hippocampus and amygdala, for example, have been reported to be increased, decreased, and not changed. Some segmentation studies report decreased overall grey matter volumes,^{193,194} but others have found no difference compared with control subjects.¹⁹⁵ No decreases in overall white matter volumes were apparent in several studies.¹⁹³ A number of investigators have reported increased occurrence of WMHs in patients with BD, however,^{196–199} including in adolescents with BD.²⁰⁰

Possible explanations for the discrepant nature of the reports are discussed in detail in several reviews and include not only variability in scan parameters, but also heterogeneity of patients along dimensions such as chronicity of illness, comorbidity, and medication exposure.^{191,201,202} Several investigators have attempted to identify subgroups of patients for study, such as those with familial vs nonfamilial BD. Two groups found significant reductions in grey matter volume in the subgenual prefrontal cortex in family history-positive subjects, suggesting that studying more homogenous patient groups may result in more consistent findings as further studies emerge.^{203,204} Some of the changes may constitute primary biological traits associated with the risk of developing mood disorder, while others may represent sequelae of the illness and its burden²⁰⁵ or treatment effects.¹⁹⁵ Primary changes that could be used as endophenotypes should be detectable in a proportion of unaffected relatives, but such studies are less common.

Basal ganglia

Noga *et al*²⁰⁶ measured basal ganglia, the amygdala-hippocampus, and cerebral hemispheres in six discordant monozygotic twin pairs and six control twin

pairs and found larger caudate nuclei and no typical asymmetry of hemispheres among healthy co-twins of bipolar twins compared with control subjects. Right caudate volume was larger only in affected monozygotic twins.²⁰⁶ Imaging studies of caudate in adults with BD have been ambiguous, with some studies also showing an increased volume,²⁰⁷ but other suggesting either a difference in the opposite direction—decreased caudate in older bipolar patients, particularly those with illness onset after 45 years of age²⁰⁸—or no differences in patients with minimal exposure to antipsychotics,²⁰⁹ hospitalized manic patients,²¹⁰ bipolar patients,²¹¹ or first-episode manic patients.²¹²

The heritability of caudate volume is unknown, but enlarged caudate volumes are associated with both genetic^{213,214} and environmental factors,²¹⁵ including antipsychotic use. No association between antipsychotics or mood-stabilizing medications and caudate volume was reported in the above reviewed studies of BD, however.^{209,216}

White matter hyperintensities

Ahearn *et al*¹⁷ examined WMHs in a family of 21 members with a high loading of BD type I and found a high prevalence of findings in both affected and unaffected family members. A total of 15 family members had MRI hyperintensities, including nine bipolar patients and six unaffected subjects. Four bipolar family members had deep white matter changes and eight had lesions of the subcortical grey nuclei. Six out of 10 unaffected family members had lesions in the subcortical grey nuclei and one also in white matter.²¹⁷ T2 hyperintensities in white and grey matter are probably the most replicated structural finding in BD. According to meta-analyses, the risk of WMH in bipolar patients is over three times higher than that found in psychiatrically healthy control subjects,^{218,219} although several studies have reported negative results.^{220–222}

Genetic factors account for the largest proportion of variation in WMH volumes. Heritability of WMHs was 0.73 in community dwelling elderly male subjects and 0.55 in a large population-based sample of stroke- and dementia-free subjects.^{223,224} A high prevalence of WMHs is also found in 22q11-deletion syndrome frequently associated with psychosis,²²⁵ cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, which is caused by mutations in the NOTCH3 gene on chromosome 19 and frequently associated with depression, and other less common genetic conditions.^{226–229} Nongenetic factors are associated with WMHs as well;^{230–238} for example, Moore *et al*²³⁹ reported a correlation between WMH and season of birth in a group of patients with BD. Thus, it appears that WMHs are not specific to BD and their usefulness as an endophenotype remains to be established. One study examined WMH as a phenotype for BD, with NOTCH3 as the candidate gene. Both linkage analysis and mutation screens were negative in this study.²⁴⁰

White matter volume changes

Genetic factors accounted for 88% of the individual differences in white matter volumes in healthy subjects¹⁸⁶ and a number of genetic conditions are associated with white matter volume changes.^{241–243} In a recent study, Kieseppa *et al*²⁴⁴ performed MRI brain scans on 24 twins with BD type I, 15 healthy co-twins, and a demographically balanced sample of control twin subjects. Patients and co-twins showed a significant decrease in left hemispheric white matter volume, and the authors suggested that such alterations of the left hemisphere white matter may reflect genetic factors predisposing to the disorder. Strong support for this hypothesis comes from another study in which genetic risk for both schizophrenia and BD in patients and their first-degree relatives was associated with distributed white matter volume deficits that were anatomically coincident in the left prefrontal and temporoparietal regions.²⁴⁵ Specific for BD were changes in the anterior corpus callosum and right frontal and right parietal regions white matter present both in bipolar patients and their first-degree relatives.²⁴⁵ Significantly smaller bilateral white matter volume within superior temporal gyrus was found also in mostly euthymic bipolar children and adolescents.²⁴⁶ First-episode manic patients exhibited a trend towards reduced total cerebral white matter and significantly larger ratios of grey and white matter relative to healthy controls.²¹² Other studies, including a meta-analysis of available data, reported no change in total or prefrontal white matter, however.^{193–195,247–249}

Anterior cingulate

In a recent study of patients with BD, schizophrenia, and their first-degree relatives, McDonald *et al*²⁴⁵ examined associations between genetic liability and variations in grey or white matter volumes. Genetic risk for BD was specifically related to grey matter deficits in the right anterior cingulate gyrus and ventral striatum. Decreased volume of the subgenual prefrontal cortex (situated on the anterior cingulate gyrus ventral to the anteroventral border of the corpus callosum) has been reported in three^{203,204,250} out of four studies of familial bipolar patients. Abnormalities within this region are also supported by post-mortem,²⁵¹ functional neuroimaging,²⁰³ and MRS findings.²⁵² The heritability of anterior cingulate volume is unknown, but individuals with aniridia and deficits in executive and social cognition, due to heterozygous mutation of the neurodevelopmental control gene PAX6, have structural abnormalities of grey matter in the anterior cingulate cortex.²⁵³

The use of regional morphological changes as an endophenotype in BD is currently limited by the lack of consistent data in patients with BD, and may remain limited by the fact that some regions of particular interest in mood disorders, such as the hippocampus, are not highly heritable. The few morphological studies to date of relatives of BD patients have not consistently identified changes in

particular brain regions that could be utilized as endophenotypes, and studies of relatives will continue to be hampered by the fact that patient studies do not suggest specific regions that might form a focus of detailed study. Thus, while some investigators have recently asserted that computational methods from brain imaging and genetics can inform studies of the inheritance of diseases that affect the human brain,¹⁸⁵ refinement of studies in BD appears necessary before genetics and structural neuroimaging are likely to be successfully combined in the elucidation of endophenotypes for BD.

At this time, caudate enlargement, white matter volume decrease, WMHs, and anterior cingulate changes define the most suitable phenotypes for linkage studies; further studies in unaffected relatives of bipolar patients are needed to identify other potential endophenotypes.

Functional neuroimaging studies complement the neuroanatomical data. For most regions identified by structural and functional neuroimaging, there is substantial agreement, including the distinction of state and trait abnormalities (if available). A study examining affect discrimination in stable outpatients with bipolar disorder found increased amygdala and reduced dorsolateral prefrontal cortex activation in response to fearful facial affect.²⁵⁴ Blunted activation of the left ventral prefrontal cortex during colour-naming Stroop task, independent of current mood status (depression, mania, euthymia) was reported in another study.²⁵⁵ Euthymic, unmedicated bipolar patients exhibited more activation in emotional brain regions (parahippocampus/amygdala, ventrolateral prefrontal cortex) than healthy controls during the continuous performance task.²⁵⁶ Malhi *et al* studied depressed bipolar²⁵⁷ and hypomanic patients²⁵⁸ during cognitive generation of affect. In contrast with healthy or unipolar depressed patients, bipolar subjects recruited subcortical brain regions (caudate, thalamus, amygdala) during emotional evaluation. Affective and attentive processing deficits may occur because of diminished frontal cortical functioning, which seem to be a trait abnormality. Increased subcortical activation may be an attempt to compensate when advanced prefrontal cognitive processing is no longer sufficient.

FMRI studies provide additional details suggesting neurodevelopmental abnormalities. Adolescents with BD relative to healthy controls show overactive subcortical regions (thalamus, putamen) on the Stroop task in the absence of the dysfunction in ventromedial prefrontal cortices (VMP) observed in adults. VMP activation correlated with age in healthy subjects, but this association was missing in bipolar patients. The absence of the prefrontal abnormalities in bipolar adults and the absence of the age-related increases in prefrontal activity observed in normal comparison subjects suggest that a developmental disturbance in prefrontal function may emerge over the course of adolescence in bipolar patients.²⁵⁹ While there is a shift from reliance on subcortical structures

to reliance on prefrontal regulatory regions in healthy subjects, this switch is impaired in bipolar patients. Abnormalities in regulation of prefrontal-subcortical circuits in adolescents with BD during cognitive and affective tasks were confirmed also in another study.²⁶⁰ The extent to which the changes observed in functional imaging studies of patients with BD will be apparent in high-risk groups remains to be established, as does the stability of activation patterns in response to specific behavioural challenges within healthy subjects across development. More data on these aspects of functional studies would enhance our ability to elucidate the long-term value of functional studies in revealing endophenotypes appropriate for BD.

Conclusion

The available clinical and genetic data on BD are converging on several consistent findings. Patients with comorbid panic disorder appear to represent a subtype of BD characterized by rapid mood switching, and by clinical picture of BDII. It is this subgroup where linkage to 18q may be the strongest. Another subtype of BD is characterized by presence of (familial) psychotic symptoms as well as suggestive linkage to chromosomes 13q and 22q, regions implicated in linkage studies of schizophrenia. A third subgroup may be represented by 'classical' BD often associated with response to lithium and low rates of comorbidity. Yet, it is also possible that some of the genomic regions emerging from linkage studies are shared by two or all three subgroups. This is consistent with the view that a combination of dimensional and categorical models can be useful to reconcile the reality of variable clinical presentation of BD with defined diagnostic categories.^{54,261,262}

An important task for future phenotypic studies of BD will be to integrate findings from molecular, structural, cognitive, and clinical domains. For instance, we do not know if the heterogeneity of clinical and molecular-genetic findings is paralleled by similar differences at the cognitive or functional level. Is it possible that the subgroup with psychotic symptoms will show mainly executive-function deficits, while the group with mood lability might have prominent attention problems? Such heterogeneity may partially account for the variability of the existing findings. Other relevant questions concern the phenomenological description of mood symptoms and clinical diagnosis. The current diagnostic criteria have been developed as a pragmatic consensus to facilitate communication among clinicians and to allow a reliable diagnosis in absence of a specific test. But the symptoms chosen as criteria may not best represent the underlying pathophysiology of the illness and other dimensions such as mood refractoriness vs lability, or clinical course may become more relevant for research. The best strategies for advancing the field are probably those that include a comprehensive assessment of several domains:

thorough clinical assessment that accounts for illness subtypes, course, treatment responsiveness, and comorbidity; cognitive and functional assessment that documents discrete domains of impairment and performance preservation; and structural, molecular, and genetic studies that can eventually link the behavioural profiles with the neurobiological dysregulation underlying BD. Such integrative studies, while difficult, are required for our understanding of BD to advance.

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