Risk and resilience in bipolar disorder: rationale and design of the Vulnerability to Bipolar Disorders Study (VIBES)

Sophia Frangou
Section of Neurobiology of Psychosis, Institute of Psychiatry, King’s College London, De Crespigny Park, London SE5 8AF, U.K.

Abstract
BD (bipolar disorder) is among the ten most significant causes of disability worldwide. Neuroscientists and clinicians have yet to meet the challenge of reducing this disability burden. The main obstacle to date has been our incomplete understanding of the pathophysiology of BD which thwarts primary prevention and early diagnosis and hinders effective treatment. There is a need to move beyond diagnostic approaches based purely on behavioural observation, as they lack reliability and biological validity. The present article reviews the evidence for cognitive, brain structural and functional correlates of genetic predisposition to BD and highlights biological markers of risk as well as factors that might protect against disease expression. It also outlines the rational and design of the Vulnerability to Bipolar Disorders Study (VIBES), which exemplifies a promising approach to delineating biological mechanisms mediating risk, resilience and disease expression in BD.

Introduction
BD (bipolar disorder) is characterized by repeated episodes mania or hypomania intermingled with episodes of depression [1]. It is now recognized that most patients will have a recurrent illness associated with significant disability in terms of social, marital or occupational function. It is therefore not surprising that the World Health Organization has listed BD among the 30 leading causes of global burden of disease [2].

Defining the neural circuitry involved in mood regulation is fundamental to understanding the pathophysiology of BD. Several brain regions are involved in emotional processing and in the integration of emotion with cognition and visceral functions. These include the PFC (prefrontal cortex), the ACC (anterior cingulate cortex), the amygdala, the parahippocampal gyrus and the hippocampus. These regions are heavily interconnected and are also connected with other brain structures, particularly the thalamus, hypothalamus and striatum.

The extended phenotype of BD
It is now widely accepted that BD is associate with changes in cognition, brain structure and function even during periods of complete illness remission.

Cognitive changes
The pattern of trait cognitive changes in BD is still under investigation, since small sample sizes and large variability in the tests used to assess cognition have resulted in significant heterogeneity between studies. Several reviews and meta-analyses have attempted to overcome these problems [3–5]. The emerging consensus is that BD patients are impaired in most cognitive domains during acute mood episodes, whereas abnormalities in memory and aspects of executive control of attention, response initiation and inhibition may persist during inter-episode intervals.

Brain structural changes
Kempton et al. [6] have published the most recent meta-analysis of available brain structural studies \((n = 141)\) comparing BD patients with healthy individuals. They found lateral ventricular volume to be significantly increased \((+17\%)\) in BD patients, whereas differences in other brain regions, including total grey and total white matter, prefrontal and temporal volume, the amygdala and hippocampus, basal ganglia and cerebellum (vermis and hemispheres), were of small to modest effect (effect size less than 0.5). Neither demographic nor illness characteristics influenced these results.

Brain functional changes
During depressive episodes, a decrease in the activity of the DLPFC (dorsolateral prefrontal cortex) and increases in the amygdala [7,8] have been reported in resting state functional imaging studies. Manic states have been associated with decreased activity in the VPFC (ventral prefrontal cortex) [9] and increased activity in the ACC [10]. In contrast with resting state studies, fMRI (functional magnetic resonance imaging) investigation of brain function...
employs a variety of activation paradigms. Trait-related decreases in brain activation within the left VPFc (Brodman area; BA47) have been reported in BD patients compared with healthy participants [10] during response-inhibition paradigms; conversely, abnormalities within the DLPFC, suggestive of decreased engagement, have been reported in fMRI studies of working memory [11–14]. The facial affect discrimination task has been widely used to probe the neural correlates of emotional processing in BD. Yurgelun-Todd et al. [15] were among the first to use the facial affect discrimination paradigm to compare brain activation with fearful and happy expressions in BD patients and controls. BD patients showed reduced activation in the DLPFC and increased in the amygdala in response to fearful facial affect, a pattern that has been confirmed in subsequent studies.

The phenotypic spectrum of individuals with genetic predisposition to BD

Genetic factors are important in the aetiology of BD [16]. However, the spectrum of behavioural and psychiatric abnormalities associated with the predisposition to BD is very wide.

Clinical phenotypes

First-degree relatives of probands with BDI (BD type I) are at increased risk of not only BD, but also MDD (major depressive disorder); morbidity risk estimates range between 1.1 and 4.9% for BDI and 5.8 and 14% for MDD [17]. There is little evidence of specificity in familial aggregation for the clinical phenotype of BD, suggesting that the relationship between genetic predisposition and clinical phenotypes is complex even when heritability is very high, as is the case with BD [16].

Cognitive phenotypes

The high rates of psychiatric morbidity in first-degree relatives of BD have prompted researchers to examine potential expressions of genetic predisposition to BD in terms of cognitive function. There have been four recent reviews and meta-analyses of cognitive studies in unaffected first-degree relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20]. Arts et al. [5] identified verbal learning and verbal working memory impairment as relatives of BD patients [5,18–20].

Surprisingly in BD, only one study to date has compared the cognitive profile of individuals with BD with that of patients with other affective disorders from bipolar pedigrees. Savitz et al. [21] examined the effect of diagnosis on verbal fluency, memory, interference and abstraction/set shifting in 230 relatives from 47 families; these comprised 49 individuals with BDI, 19 with BD type II, 77 with depressive illness, 20 with miscellaneous diagnosis and a group of 65 psychiatrically healthy relatives. They reported that BDI patients performed less well than their MDD counterparts as well as all of their other relatives in memory (recall and recognition) and learning.

Structural phenotypes

Several neuroimaging studies have attempted to define the pattern of brain structural changes associated with genetic predisposition in BD, but the results have generally been inconsistent.

McDonald et al. [22] collected structural MRI (magnetic resonance imaging) data from 37 patients with BD and 50 first-degree relatives. Through the use of a genetic liability scale, they inferred that genetic risk of BD was negatively correlated with grey matter volume in the right medial frontal gyrus, anterior cingulate gyrus, caudate nucleus and anterior putamen (BA9, BA11, BA24, BA25 and BA32). Despite using a similar study design, McIntosh et al. [23] failed to replicate these findings. They employed optimized voxel-based morphometry to investigate the effects of genetic liability to BD on white and grey matter volume in 22 well relatives from families affected by BD alone, i.e. unaffected relatives with at least two first- or second-degree relatives with BD. They did not show any significant relationship between a genetic liability to bipolar disorder and either white or grey matter volume. Both research groups conducted further analyses on their samples. McDonald et al. [24] used a hypothesis-based region of interest analysis to assess ventricular and hippocampal volumes; they did not find significant differences between BD relatives and controls, although relatives showed a 2.3% increase in total cerebral volume. Similarly, McIntosh et al. [25] carried out an alternative voxel-based morphometry study on their sample of 22 unaffected individuals with a family history BD. Following small volume correction, they found decreased grey matter density in the bilateral anterior cingulate cortex, caudate nucleus and putamen (BA9, BA11, BA24, BA25 and BA32) respectively in two independent region-of-interest studies of unaffected offspring of BD patients. Taken together, these studies suggest that, in individuals at high risk of BD, brain structural changes are probably of small effect size, whereas the direction of change in cortical and subcortical regions remains unclear.

Brain functional phenotypes

Krüger et al. [29] used H215O positron emission tomography to study a cohort of nine lithium-responsive BD patients and nine healthy siblings. They collected rCBF (regional cerebral blood flow) data during baseline euthymia and during induction of transient sadness using a short autobiographical script, which related to a sad life event. During induced
sadness, patients and their siblings showed rCBF increase in the ACC (BA24), the anterior insula, the premotor cortex (BA4/6) and cerebellum. Both groups showed rCBF decrease in orbitofrontal cortex (BA11) and inferior temporal cortex (BA22/21). However, rCBF in the medial PFC (BA10) was decreased in BD patients and increased in their siblings. Krüger et al. [29] postulate that increased rCBF in siblings represented a compensatory response in an at-risk group, as this pattern was not seen previously in healthy subjects without depression risk factors [30].

Drapier et al. [13] focused on working memory function. They used fMRI to compare patterns of brain activation between 20 BD patients, 20 of their unaffected first-degree relatives and 20 healthy participants while performing the N-back verbal memory task. During this task, participants are presented with a series of stimuli (verbal or non-verbal) and are asked to indicate whether the stimulus they are currently viewing matches the one they saw in the previous one, two or three trials. This task allows for group comparisons within a single condition as well as for the examination of group differences in response to increasing working memory load across conditions. Patients’ performance in the 2-back and 3-back conditions were worse than their relatives and controls. Significant group differences were observed in a left ventral cluster extending from the frontopolar to VLPFC (BA10/47). Relatives showed greater activation in these regions than the other two groups, particularly in the 2-back condition. The authors suggested that the increased activation within PFC regions in the relatives group reflected cortical inefficiency (i.e. recruitment of wider networks to maintain adequate performance).

It would appear that increased prefrontal activation is associated with genetic risk of BD, but not with disease expression. The biological meaning of this finding is still unclear, but it is likely to be associated with aspects of neural functioning that protect against or compensate for disease expression.

**VIBES (Vulnerability to Bipolar Disorders Study): rationale, design and sample**

Although BD is highly heritable, individuals with genetic predisposition to BD are also at increased risk of a wide spectrum of phenotypes, including a range of psychiatric disorders as well as cognitive and brain functional and structural changes. The mechanisms involved in translating familial risk to BD into specific phenotypes remain largely unknown. The core aims of VIBES are to address the following questions: in individuals at high familial risk of BD (i) what are the genetically mediated traits shared with patients and by at-risk, but non-symptomatic, relatives, and (ii) can we identify disease-specific traits that differentiate BD patients from their relatives with other diagnoses such as MDD? Each of the study modules focuses on characterizing the cognitive, structural or functional brain-related changes associated with familial predisposition to BD. However, the set of biomarkers that best distinguishes between predisposing, protective and disease-related mechanisms will probably include measures from each of these modalities. Hence, we use bioinformatic techniques to determine which variables are uniquely sensitive to the expression of different phenotypes among individuals with a genetic predisposition to BD. This set of biomarkers should provide tools for subsequent neuropsychiatric, pharmacological and genetic research.

**Eligibility criteria**

Inclusion criteria for BD patients are: (i) being aged between 17 and 65 years, (ii) fulfilling Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised (DSM-IV) [1] criteria for BD, (iii) having at least one first-degree relative unaffected by BD, and (iv) no family history (up to second degree) of schizophrenia or schizophrenia spectrum disorders.

Their siblings and offspring were eligible to participate, with the patients’ consent, if (i) aged 17–65, and (ii) had no personal history of bipolar spectrum disorders.

Inclusion criteria for control participant are: (i) being aged between 17–65 and (ii) having no personal or family history of any Axis I or II DSM-IV disorder. Healthy volunteers were selected so that they matched both patients and relatives in age, gender and level of education.

Exclusion criteria for the entire sample are: (i) head trauma resulting in loss of consciousness, (ii) personal history of neurological or medical disorders, (iii) family history of hereditary neurological disorders, and (iv) fulfilling DSM-IV criteria for lifetime drug- or alcohol-dependence and drug or alcohol abuse in the preceding 6 months.

**Clinical assessments**

Diagnostic assessments for all participants were conducted by trained psychiatrists using the Structured Clinical Interview for DSM-IV for Axis I diagnoses. Inter-rater reliability was $k > 0.92$. Where applicable, further information was collected from medical notes. Family history of psychiatric disorders

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**Table 1 | VIBES cognitive test battery**

<table>
<thead>
<tr>
<th>Test</th>
<th>Neuropsychological domain</th>
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<tbody>
<tr>
<td>Wechsler Adult Intelligence Scale-Revised</td>
<td>Full-scale IQ</td>
</tr>
<tr>
<td>Hayling Sentence Completion Test (HSCT)</td>
<td>Response inhibition</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test (WCST)</td>
<td>Rule discovery and perseveration</td>
</tr>
<tr>
<td>Continuous Performance Task (CPT)</td>
<td>Sustained attention</td>
</tr>
<tr>
<td>Wechsler Memory Scale-III (WMS-III)</td>
<td>Auditory and visual immediate and delayed auditory recognition, delayed and working memory</td>
</tr>
<tr>
<td>Stroop Colour Word Test (SCWT)</td>
<td>Interference</td>
</tr>
<tr>
<td>N-Back sequential letter working memory task</td>
<td>Working memory</td>
</tr>
<tr>
<td>Iowa Gambling Task (IGT)</td>
<td>Emotional learning</td>
</tr>
</tbody>
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was assessed using the Family Interview for Genetic Studies. Psychopathology was rated using the HDRS (Hamilton Depression Rating Scale) [31], the YMRS (Young Mania Rating Scale) [32] and the BPRS (Brief Psychiatric Rating Scale) [33]. Before assessment, participation patients’ psychopathology was assessed weekly over a minimum period of 1 month to ensure that they: (i) fulfilled DSM-IV criteria for remission requiring a minimum period of 6 months of remission since the last syndromal episode, (ii) scored below 7 in the HDRS and YMRS, and (iii) had remained on the same type and dose of medication for a minimum period of 6 months.

**Conclusions**

Our understanding of BD, like that of most psychiatric illnesses, lags behind that of other brain disorders in part because of the use of heterogeneous diagnostic constructs and the lack of clear biomarkers. Better delineation of the pathophysiology of BD should improve diagnostic classification including premorbid identification of subjects at risk of disease expression. It could thus facilitate the development of innovative new pharmacological and psychosocial treatments and clarify the role of potential risk conferring genes for BD.

**References**


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