

## EXPERT REVIEW

# All the world's a (clinical) stage: rethinking bipolar disorder from a longitudinal perspective

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Psychiatric disorders have traditionally been classified using a static, categorical approach. However, this approach falls short in facilitating understanding of the development, common comorbid diagnoses, prognosis and treatment of these disorders. We propose a 'staging' model of bipolar disorder that integrates genetic and neural information with mood and activity symptoms to describe how the disease progresses over time. From an early, asymptomatic, but 'at-risk' stage to severe, chronic illness, each stage is described with associated neuroimaging findings as well as strategies for mapping genetic risk factors. Integrating more biologic information relating to cardiovascular and endocrine systems, refining methodology for modeling dimensional approaches to disease and developing outcome measures will all be crucial in examining the validity of this model. Ultimately, this approach should aid in developing targeted interventions for each group that will reduce the significant morbidity and mortality associated with bipolar disorder.

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## INTRODUCTION

Recently, a number of reviews on bipolar disorders (BDs) have sought to update key aspects of diagnosis, genetics, neurobiology and treatment. All of these reviews have treated BDs in the traditional categorical DSM (Diagnostic and Statistical Manual) and ICD (International Classification of Diseases) manner; however, the reliance on categorical approaches as the primary approach for research studies has been criticized extensively as too constraining and, more important, unlikely to capture the underlying biology. Furthermore, the categorical approach may not help in finding new treatments or altering the prognosis of these disorders. What has emerged from the recent debates in the literature is the need to rethink our diagnostic system and its potential applications. BDs represent an excellent example of current dilemmas that present barriers to scientific progress.

In this report, we do not review comprehensively all aspects of the BDs; however, we do direct the reader to specific reports for certain areas. Instead, we will use the recent data and promising research directions to argue the following. Whatever framework we have been using to understand BDs has generally been limited by several key factors: first, the diagnostic discussion has been dominated by a static cross-sectional view of the patient, with limited attention to the long-term view. In a similar manner, development across the lifespan has been given scant attention, especially beyond puberty. Third, we view our patients as having a primary disorder (in this case, BD) and occasionally concern ourselves with psychiatric comorbidities such as anxiety and addictive behaviors. Rarely, however, have we viewed BDs as multisystem disorders. For example, the presence of early medical conditions such as asthma, childhood obesity and early signs of cardiovascular disease may simply be other manifestations of a multisystem disorder involving both psychiatric and non-

psychiatric 'comorbidities'. In short, the importance of medical risk factors and medical disease with concurrent chronic inflammatory factors that may accumulate over the lifespan, independent of the course of the BD, has not been fully appreciated. Recently, several of us have proposed that BD should be viewed as a multisystem inflammatory disease.<sup>1,2</sup> Applying this strategy would allow us to integrate the so-called concurrent medical problems of those with BD more directly into our understanding of the longitudinal course or stages of this illness over the lifespan. Such an approach would be especially important in aligning our understanding of cardiovascular risk factors with the BD process and potentially in providing insight as to why a patient whose BD is in 'remission' continues to progress along a chronic disease course.

We have chosen, as a most promising direction for understanding the complex interaction among biologic and psychosocial factors, the framework of 'staging' of the illness so that we could pose the following questions: What are the key biomarkers (genetic, neural) at each stage that have been identified or could be identified? What are the relevant psychosocial risk and protective factors at each stage? What might protect some individuals from reaching 'end stage' in whatever model we choose?

## STAGING BD

To date, our perspective on diagnosis in BD has been a relatively static one, still based largely on truly ancient notions of mind-body separation and on largely cross-sectional descriptions of illness phenomena. In this review, we argue that the kind of staging model of disease progression, similar to that used in other areas of medicine, might serve us better in terms of our approach to

**Table 1.** Clinical presentation of the staging model of bipolar disorder, strategies for genetic analysis and neuroimaging findings

<i>Clinical stage</i>	<i>Clinical presentation</i>	<i>Strategies for genetic analysis</i>	<i>Neuroimaging findings</i>
0	Increased risk of bipolar disorder; no symptoms currently	Evaluate endophenotypes using GWAS confirmed SNPs; risk prediction studies	<i>Resilience markers:</i> abnormal prefrontal cortical activity increases during cognitive control of emotion and cognitive control tasks; abnormal volumetric increases in right-sided vIPFC and left-sided subcortical regions <i>Risk markers:</i> Abnormally increased amygdala activity; abnormal prefrontal WM
1a	Mild or nonspecific symptoms	Evaluate putative endophenotypes using GWAS confirmed SNPs	<i>Resilience markers:</i> Abnormally increased prefrontal cortical activity during cognitive control of emotion and cognitive control tasks; abnormally increased prefrontal cortical volume <i>Risk markers:</i> Abnormally decreased prefrontal cortical volumes; left-sided subcortical volume increases; abnormally decreased WM volume
1b	Ultra-high-risk: moderate but subthreshold symptoms, with neurocognitive changes and functional decline to caseness	Discovery of rare variants and <i>de novo</i> mutations	
2	First episode of bipolar disorder; full threshold disorder with moderate to severe symptoms, neurocognitive deficits and functional decline	Mapping endophenotypes, biomarker studies	<i>Theme 1:</i> Abnormally decreased prefrontal cortical activity (especially right-sided vIPFC activity) during cognitive control of emotion and cognitive control tasks; abnormally increased amygdala activity during these tasks; abnormally decreased prefrontal cortical volumes and decreased prefrontal WM; altered subcortical volumes <i>Theme 2:</i> Abnormally increased left-sided striatal and prefrontal cortical activity during reward processing
3a	Incomplete remission from first episode (could be linked or fast-tracked to Stage 4)	Contribute to GWAS mega analyses	<i>Markers of disease progression:</i> A negative association between prefrontal cortical volumes (especially right vIPFC gray matter volume) and illness duration; reductions in amygdala, striatal and hippocampal volumes with illness progression
3b	Recurrence or relapse of psychotic or mood disorder which stabilizes with treatment, residual symptoms or neurocognition below the best level achieved following remission from first episode	Pleiotropy analysis, examine longitudinal trajectories	
4	Severe, persistent illness as judged on symptoms, neurocognition and disability criteria	Pleiotropy analysis, examine longitudinal trajectories	

Abbreviations: GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism; vIPFC, ventrolateral prefrontal cortex; WM, white matter. Adapted from Scott *et al.*<sup>3</sup>

diagnosis, treatment and research on BDs. In Table 1, we delineate the clinical presentations associated with a four-stage model of BD developed over the past several years along with genetic and neuroimaging correlates.<sup>3–5</sup> This model reconceptualizes BD as an evolving condition with changing manifestations over the course of its development from early, pre-risk status to mild, nonspecific symptoms, to first fully syndromal episode onset, to recurrence and finally to end-stage chronic illness. Within this context, we use the term ‘high risk’ to refer to those individuals whose risk of the illness is significantly greater than that in the general population and the term ‘ultra-high-risk’ to refer to individuals who have a first-degree relative with early-onset BD.

## DIAGNOSTIC CONSIDERATIONS

The precise form that the diagnostic criteria for BDs will take in ICD-11, which will not be published for several years, remains to be seen; however, the changes made to the diagnostic considerations for BD in DSM-5 are now known. Although the DSM remains largely a cross-sectional nomenclature, several of

these changes are, in fact, quite compatible with the longitudinal, staging model of the disorder that we propose here.<sup>6</sup> Part of the difficulty in the accurate diagnosis of BDs—multiple studies suggest that that the average patient waits 7–10 years for a correct diagnosis<sup>7</sup>—is that the typical patient first presents in Stage 3a or 3b during an episode of depression and receives a cross-sectional diagnosis of unipolar depression. Indeed, this may happen on multiple occasions before the bipolarity is identified. In an effort to enhance the probability of early, *retrospective* diagnosis of mania and hypomania, perhaps as early as Stage 1b and to emphasize that BD is as much a disorder of energy as it is one of mood, the DSM-5 includes now *changes in activity and energy*, as well as changes in mood in the A Criterion for mania and hypomania. Because prior episodes of mood elevation are less clearly observable and less likely to be remembered than changes in activity and energy, this addition to what are considered the key symptoms of mania and hypomania should have the effect of improving identification of bipolarity at an earlier stage in the illness and may have relevance for neurobiologic strategies focusing on fatigue, 24 h cycles, etc.

**Table 2.** Diagnostic criteria for the 'with mixed features' specifiers

<i>Mania</i>	<i>Depression</i>
<p>Full criteria are met for a manic or hypomanic episode, and at least three of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania:</p> <ol style="list-style-type: none"> <li>1. Prominent dysphoria or depressed mood as indicated by either subjective report or observation made by others</li> <li>2. Diminished interest or pleasure in all, or almost all activities</li> <li>3. Psychomotor retardation nearly every day</li> <li>4. Fatigue or loss of energy</li> <li>5. Feelings of worthlessness or excessive or inappropriate guilt</li> <li>6. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide</li> </ol>	<p>Full criteria are met for a major depressive episode, and at least three of the following symptoms are present during the majority of days of the current or most recent episode of depression:</p> <ol style="list-style-type: none"> <li>1. Elevated, expansive mood</li> <li>2. Inflated self-esteem or grandiosity</li> <li>3. More talkative than usual or pressure to keep talking</li> <li>4. Flight of ideas or subjective experience that thoughts are racing</li> <li>5. Increase in energy or goal-directed activity</li> <li>6. Increased or excessive involvement in activities that have a high potential for painful consequences</li> <li>7. Decreased need for sleep</li> </ol>
<p>Mixed symptoms are observable by others and represent a change from the person's usual behavior. For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features, owing to the marked impairment and clinical severity of full mania. The mixed symptoms are not attributable to the physiological effects of a substance. Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright © 2013). American Psychiatric Association. All rights reserved.</p>	

It is when one begins to think about diagnosis of the various BDs from a clinical staging perspective that the longitudinal view becomes particularly critical. Although many clinicians believe that there is 'only one BD', others might argue that there are many forms with different developmental trajectories. For example, is an individual whose initial diagnosis as a preadolescent is 'other specified BD' by virtue of the fact that his hypomanic symptoms have never lasted more than 2 or 3 days (Stage 1b), but who then progresses to a diagnosis of bipolar II disorder as an adolescent and finally to bipolar I disorder upon experiencing a first manic episode in his early 20s is different—either in terms of psychiatric symptomatology and functioning or in terms of non-psychiatric comorbidities—from the individual who continues to cycle between depression and hypomania well into his 50s, but never experiences an episode of mania? These are questions that a staging framework for BDs could help us to resolve.

Perhaps, most relevant to a staging perspective of BDs, the DSM-5 has identified a new set of *specifiers* for the mood disorders that imply an at least partially longitudinal rather than strictly cross-sectional perspective. The first of these is the 'with mixed features' specifier that includes the notion that even those whose diagnosis to date is unipolar disorder may experience mixed symptoms, thus acknowledging the importance of spectrum conditions including unipolar depressions that evidence some aspects of bipolarity and may, in fact, be reflective of Stage 1b of a BD. The 'with mixed features' specifier can be applied to any episode of depression, mania or hypomania in which at least three non-overlapping symptoms of the opposite pole are present (see Table 2). From a staging perspective, this specifier can have clear prognostic significance as the disorder develops over time, with a high proportion who present with early signs of mixed features being likely to 'progress' to a bipolar diagnosis.

The list of new specifiers in DSM-5 also includes a 'with anxious distress' option (see Table 3). This specifier may prove useful in identifying a subtype of BD that responds more poorly to conventional treatment,<sup>8</sup> especially of bipolar depression, and that may require a different approach to pharmacotherapy and/or a psychotherapeutic approach that addresses the anxiety component of the disorder. Most relevant to the present discussion, this kind of anxious distress seen in young people with a current diagnosis of unipolar depression may be a key harbinger of a subsequent manic or hypomanic episode.<sup>9</sup> Finally, it would not be surprising if this subgroup of patients were found to be neurobiologically or genetically distinct.

**Table 3.** Diagnostic criteria for the 'with anxious distress' specifier

<i>Symptom</i>	<i>Severity</i>
1. Feeling keyed up or tense	Mild: 2 symptoms
2. Feeling unusually restless	Moderate: 3 symptoms
3. Difficulty concentrating because of worry	Moderate-severe: 4–5 symptoms
4. Fear that something awful may happen	Severe: 4–5 symptoms with psychomotor agitation
5. Feeling that the individual might lose control of himself or herself	
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Traditionally, in thinking about BDs, comorbid psychiatric conditions have been discussed separately from what have been considered 'medical' conditions. In this review, however, we take a somewhat different approach based on the increasing evidence that these forms of comorbidity may be strongly linked. For example, anxiety and panic states include symptoms reflected in cardiac regulatory systems and other peripheral systems. Various forms of the so-called psychiatric comorbidity have now been characterized as associated with increased cytokine activity and other chronic inflammatory processes. Sleep disturbances may have equal importance in psychiatric and medical comorbidity. The features of the metabolic syndrome, with accompanying obesity and changes in blood glucose levels, may represent a unique 'bath' for brain circuitry associated with changes in both physiology and behavior that push us to recognize the intimate relationship between the so-called medical and behavioral factors. Specific data are available to show the impact of hypertension, cardiovascular disease, diabetes and cerebrovascular disease on the long-term course of BD and *vice versa*.<sup>10–13</sup>

Here the concept of allostatic load, a term coined by McEwen and Stellar<sup>14</sup> more than 20 years ago may have particular utility. Allostatic load refers to the cost of chronic exposure to fluctuating or heightened neural or neuroendocrine activity resulting from the organism's attempt to deal with repeated or chronic environmental challenge. Allostatic load can be understood at multiple levels. At the population level, it provides a way of understanding both comorbidity of mental disorders and the

association between social class and mental disorders. At the individual level, it helps us to understand the association between hypothalamic-pituitary-adrenal axis and monoamine system (over) activation and comorbidity of psychiatric disorders with one another and of psychiatric disorders with a variety of medical conditions, particularly those associated with the metabolic syndrome. Finally, at the molecular level, the concept of allostatic load encourages thinking about the role of oxidative stress, mitochondrial abnormalities and inflammatory processes, all of which are relevant to our understanding of BDs.

In the next sections of this report, we describe how data from two active areas of research—genetics and neuroimaging—fit well with this illness staging conceptualization.

## RECENT DEVELOPMENTS IN UNDERSTANDING THE GENETICS OF BD

Evidence from twin, family and adoption studies indicates a substantial genetic contribution to the etiology of BD, with heritability estimates in excess of 70%.<sup>15</sup> Similar to many other highly prevalent disorders, the etiologic architecture of BD is complex. Most family-based analyses support a multifactorial polygenic threshold model. The multifactorial polygenic threshold model posits that individuals are diagnosed with BD only when a hypothetical threshold of liability is exceeded; the liability reflects a combined effect of several genetic factors acting against variable environmental backgrounds.<sup>16</sup> The model does not predict how many risk factors contribute to liability nor does it indicate the frequency of such variants in the population. Therefore, psychiatric geneticists have approached the gene hunting problem in stages, assuming initially that BD risk was conferred only by single mutations and subsequently assuming progressively more risk variants.<sup>17</sup> Early gene mapping studies of BD have been unsuccessful, fueling speculation that there may be hundreds, if not thousands of risk variants.<sup>18</sup> Fortunately, genome-wide association studies (GWAS) have been successfully deployed in thousands of other genetically complex disorders (<http://gds.nih.gov/>). GWAS agnostically compare the frequency of known variants in the human genome between cases and controls, but there is an important caveat. As millions of genetic variants can now be assayed across the genome, the statistical penalty for multiple comparisons has increased substantially. If an individual genetic variant does not confer substantial risk (odds ratios ~2), even cohorts numbering in the thousands may lack sufficient power. This may explain why recent GWAS studies have identified only a handful of single-nucleotide polymorphisms (SNPs) localized to *CACNA1C*, *ODZ4* and *ANKK1* that are statistically associated with BD.<sup>19</sup> Efforts are in progress to muster additional samples for 'mega-analyses'.<sup>20</sup> This incremental approach has been used successfully in schizophrenia (SZ).<sup>21</sup> It has much in its favor, although cost for ascertainment of samples and genotype assays for new samples may be limiting factors. Thoughtful analyses based on clinical staging could complement the 'mega-sample' approach and may even uncover additional variants. We advocate this approach, exploiting the staging strategy.

## LEVERAGING THE CLINICAL STAGING APPROACH FOR GENE MAPPING STUDIES OF BDs

The clinical staging scheme outlined here ostensibly classifies BD patients based on the natural history of the disorder. However, the subgroups identified by the staging approach may be enriched for different sets of genetic risk variants. Thus, directed searches for specific types of variants may be successful with relatively small samples in particular groups. They could also enable sophisticated statistical analyses based on Bayesian approaches. The Bayesian approach is very relevant to the staging concept, but other statistical approaches could also be used to test this concept. For

example, classical family studies could be used to examine whether the temporal trajectory of the staging concept 'breeds true'. Several of these concepts are illustrated here with specific examples. The goal is to 'carve' BD progressively at its 'joints', that is, identify biologically meaningful subgroups, while iteratively modifying the clinical stages. In turn, such subgroups may yield more refined results for linkage analyses. Indeed, Fears *et al.*<sup>22</sup> have recently combined family, genetic, neuropsychologic and imaging studies to produce very interesting results concerning heritable characteristics in two large pedigrees that are and are not associated with BD. Epigenetics is another highly relevant avenue of research in this context. Although it has been difficult to identify epigenetic markers that are relevant from the staging perspective for BD to date, epigenetic analyses are still in their infancy. Epigenetic research could be a useful tool to evaluate the staging approach. For example, certain epigenetic markers could be associated with the temporal evolution of BP and could thus represent *bona fide* therapeutic targets.

*Stage 0:* Increased risk of BD, no symptoms currently.

*Stage 1a:* Mild or nonspecific symptoms.

Risk variants confirmed through GWAS could be evaluated in these groups for associations with putative endophenotypes such as chronotype or other aspects of circadian function.<sup>23</sup> The individuals in these groups could also be evaluated prospectively to investigate the predictive power of GWAS validated SNPs.

*Stage 1b:* Ultra-high-risk: moderate but subthreshold symptoms, with neurocognitive changes and functional decline to caseness.

This group, particularly individuals from pedigrees with early onset BD may be very useful for identifying rare mutations such as copy number variants. As such individuals are typically ascertained early in their lives, parents and/or siblings are more likely to be available. Thus, family-based samples could be used to detect 'de novo' (non-inherited) mutations, as was successfully implemented for autism spectrum disorders.<sup>24</sup>

*Stage 2:* First episode of BD; full threshold disorder with moderate severe symptoms, subtle neurocognitive deficits and functional decline.

Individuals at an early stage of the illness are less likely to be affected by factors such as medications that may have a role in chronic medical illness; thus, this group would be useful for gene mapping studies of endophenotypes or for validating GWAS-identified SNPs as 'biomarkers' in conjunction with brain imaging studies.<sup>25</sup> Additionally, such groups could supplement ongoing GWAS mega analyses.

*Stages 3 and 4:* Incomplete remission from first episode; 3b, recurrence or relapse of psychotic or mood disorder which stabilizes with treatment, residual symptoms or neurocognition below the best level achieved following remission from first episode; 4, severe, persistent illness as judged on symptoms, neurocognition and disability criteria.

As we note above, individuals with chronic BD frequently experience medical and psychiatric comorbidity. The comorbidity can be a major confounding factor for most clinical research studies, but it may be a boon for gene hunting efforts. For example, many BD patients are diagnosed with hyperlipidemias, hypertension or heart disease. Numerous risk SNPs for these diseases have already been identified through GWAS studies (<http://gds.nih.gov/>). Arguably, the same SNPs could also confer risk for BD or for specific features/subgroups of BD. This phenomenon, also called pleiotropy, was harnessed to identify novel risk variants for SZ.<sup>26</sup> Using novel empirical Bayesian statistical approaches, Andreassen *et al.* found genetic overlap between SZ and cardiovascular risk factors such as obesity, hypertension and dyslipidemia.<sup>27,28</sup> They next leveraged available GWAS results for these traits to identify several new SZ risk variants that were undetected using conventional SZ GWAS approaches.<sup>29</sup> Arguably, the Bayesian analyses could be harnessed more extensively for BD gene mapping efforts (O Andreassen and W Thompson, personal



communication, 3 December 2013). In the future, the pleiotropic SNPs could be used to evaluate predictive value for different longitudinal trajectories of BD; in turn, such analyses could also help to refine the clinical staging proposed here. In Table 1, we illustrate how specific strategies for genetic analysis might fit within this staging framework.

## NEUROIMAGING STUDIES IN BD AND BD AT-RISK INDIVIDUALS: EVIDENCE FOR A STAGING MODEL OF BD?

Next, we review findings from neuroimaging studies in adults with BD, and adults and youth who are at genetic and/or subsyndromal symptomatic risk of BD to determine the extent to which these findings support a staging model of the illness. While the current cost of imaging studies makes the use of imaging to stage BDs infeasible on any broad scale, given the remarkable speed of technological development at present and the concomitant reduction in cost of procedures that were strictly limited to research just a decade or two ago, it is not unreasonable to imagine that in the foreseeable future such studies could be used as commonly to stage BDs as complex genotyping studies unthinkable 20 years ago are now routinely used to stage cancers.

We first evaluate data from imaging studies of individuals with established BD, irrespective of current mood state, to determine persistent functional, structural and white matter (WM) abnormalities in neural circuitries underlying information processing domains relevant to the illness. We then examine the extent to which findings from studies of individuals at risk of future BD indicate abnormalities in these neural circuitries that would be consistent with early clinical stages of BD. Finally, we determine whether extant findings from neuroimaging studies of individuals with recurrent and/or more persistent BD illness support a staging model of progressive worsening of abnormalities in these neural circuitries with increasing illness severity (see Table 1).

### Adults with BD (Stage 2)

Main findings from functional neuroimaging studies of adults with established BD can be broadly categorized into two main themes, based on abnormalities in neural circuitry supporting information processing domains relevant to the characteristic symptom profiles of BD, that is, emotion dysregulation, emotional lability and reward sensitivity.<sup>30</sup> These two themes are processing domains that include: (1) cognitive control of emotion during emotion regulation, inhibitory control processes (cognitive and inhibitory) during emotion regulation and (2) reward processing.<sup>31,32</sup> Neural circuitry important for the first theme include the amygdala, implicated in emotion processing;<sup>33,34</sup> ventrolateral prefrontal cortex (vLPFC) implicated in inhibitory control processes;<sup>31</sup> and regions such as the orbitofrontal cortex (OFC), anterior cingulate cortex, mediodorsal prefrontal cortex and hippocampus important for automatic emotion regulation.<sup>31</sup> Neural regions important for the second theme include the ventral striatum, important for processing reward cues and outcomes;<sup>35,36</sup> vLPFC, supporting both inhibitory processes and arousal in the context of emotional stimuli;<sup>37,38</sup> OFC, which encodes reward value,<sup>39</sup> and medial prefrontal cortex (a larger region including both the anterior cingulate cortex and mediodorsal prefrontal cortex), regulating appetitive behaviors in potentially rewarding contexts.<sup>40,41</sup>

Neuroimaging studies of adults with BD indicate the following patterns of abnormalities in the neural circuitries associated with the two information processing domain themes outlined above.

**Theme 1. Emotion processing and regulation:** Studies indicate dysfunction in frontolimbic circuitry evidenced by amygdala and striatal over-reactivity, vLPFC under-reactivity and decreased

OFC–amygdala functional connectivity during a variety of cognitive inhibitory and emotional control tasks.<sup>42–54</sup> This may represent an inefficient attempt to top-down regulate response to emotionally distracting stimuli.

**Theme 2. Reward processing and structural abnormalities:** Studies indicate left-sided ventral striatum–vLPFC over-reactivity to reward anticipation,<sup>55–59</sup> although see Abler et al.<sup>60</sup> This may represent an increased feed-forward, bottom-up responsivity to rewarding stimuli. Structural and diffusion imaging (DI) findings indicate predominantly right-sided vLPFC gray matter (GM) volume reductions,<sup>61–63</sup> and bilateral abnormalities in the prefrontal WM<sup>64–76</sup> in adults with BD that may represent structural correlates of the functional abnormalities described above. Studies reporting reduced volumes in subcortical regions, for example, amygdala, striatum and hippocampus suggest a possible neurotoxic effect of the elevated activity in these structures during emotion and reward processing; however, findings to date are mixed.<sup>62,77–85</sup> Studies suggesting larger volumes of the amygdala in adults with BD may be confounded by potential neurotrophic effects of lithium on these structures.<sup>86</sup>

### Individuals at future risk of bipolar disorder (Stage 0)

**Theme 1. Emotion processing and regulation:** During cognitive control of emotion and cognitive control tasks in psychiatrically healthy but at-risk individuals, neuroimaging studies indicate abnormally elevated, predominantly right-sided activity in frontal control regions (vLPFC and dorsolateral PFC) and in the amygdala<sup>87</sup> and decreased right frontal (vLPFC–amygdala) functional connectivity.<sup>88,89</sup>

**Theme 2. Reward processing and structural abnormalities:** One study in unaffected relatives of BD adults reported abnormally elevated right OFC activity to reward, but abnormally elevated left OFC activity to loss.<sup>59</sup> The main pattern observed in structural studies is abnormally increased gray matter (GM) volume in several areas including right vLPFC,<sup>87</sup> left parahippocampal gyrus<sup>90</sup> and left caudate.<sup>91–93</sup> Reductions in left anterior insular GM volumes have also been observed.<sup>63</sup> There are null findings, however.<sup>91,94–97</sup> DI studies indicate abnormal, predominantly right-sided, decreases in fractional anisotropy and volume in WM tracts connecting prefrontal cortical and subcortical regions.<sup>63,75,98,99</sup>

The findings described above may represent two separate kinds of markers: those representing resilience and those representing risk. The resilience markers might include increased prefrontal activity and increased frontal and subcortical volumes, given that the at-risk individuals who demonstrated these patterns were psychiatrically healthy at the time of study. The risk markers might include increased amygdala activity, as well as abnormal prefrontal WM, as these patterns are similar to findings from studies of adults with BD.

### Psychiatrically affected individuals at future risk of BD (Stages 1a and b)

**Theme 1. Emotion processing and regulation:** During cognitive control of emotion and cognitive control tasks in at-risk individuals who currently carry a psychiatric diagnosis other than BD, neuroimaging studies indicate abnormally increased bilateral dorsolateral PFC activity (right > left) and increased left vLPFC–bilateral amygdala functional connectivity in youth with milder-level behavioral and emotional dysregulation symptoms,<sup>100</sup> and abnormally increased activity in left frontal pole in first-degree relatives of individuals with BD who currently have depression or substance abuse diagnoses.<sup>101,102</sup> Such individuals also show abnormally decreased activity in cognitive control regions (mainly

parietal cortical regions), and abnormally decreased functional connectivity between frontal control and limbic regions.<sup>103,104</sup>

**Theme 2. Reward processing and structural abnormalities:** One study reported increased left vIPFC/middle prefrontal cortical activity to reward with increasing magnitude of nonspecific behavioral and mood dysregulation symptoms in youth.<sup>105</sup> A meta-analysis concluded that high-risk individuals (both those with and without a current psychiatric diagnosis) showed abnormally increased neural response in *left-sided* prefrontal cortical and insula (the left superior frontal gyrus, medial frontal gyrus and left insula) activity, regardless of task.<sup>106</sup>

Genetic risk for BD is associated with abnormally decreased volumes in the right dorsolateral PFC,<sup>73</sup> OFC,<sup>73</sup> insula,<sup>73</sup> anterior cingulate cortex,<sup>107</sup> ventral striatum,<sup>107</sup> and bilateral frontal<sup>107</sup> and left temporoparietal regions.<sup>107</sup> Increased volumes are observed in the right VLPFC,<sup>108</sup> left insula<sup>109</sup> and left caudate.<sup>91–93</sup> However, some findings are mixed.<sup>110–112</sup> DI studies report that genetic risk for BD is associated with decreased WM volume and WM integrity, particularly in the frontal regions.<sup>71,73,93,107,113</sup> Again, some findings are mixed.<sup>114</sup>

Abnormally increased prefrontal cortical activity during cognitive control of emotion and cognitive control tasks may represent resilience factors in non-BD affected at-risk individuals. Similarly, findings of abnormally increased prefrontal cortical volume may also present resilience factors, while findings of abnormally decreased prefrontal cortical volumes parallel findings in adults with BD. Risk factors include left-sided subcortical volume increases that may be associated with the left-sided increases in prefrontal cortical and subcortical activity during reward and other task performance observed across at-risk individuals and individuals with BD. DI studies reporting decreased WM volume in these at-risk individuals may also represent risk factors as they, too, parallel findings in adults with BD.

Individuals with recurrent episodes, and/or severe, persistent illness (Stages 3a, b and 4)

Few studies have specifically examined the extent to which there is progression of neural circuitry abnormalities with increasing severity of BD. In adults, these studies have been largely retrospective and cross-sectional, and focused mainly upon structural neuroimaging findings.<sup>115</sup> Focusing on the main themes described above in adults with BD, the most consistent finding is smaller right vIPFC GM volumes in adults with BD with long-term illness and minimal lifetime exposure to lithium compared with healthy adults. By contrast, larger right vIPFC volumes are observed in younger adults in early stages of BD.<sup>108</sup> Prefrontal cortical gray matter volumes in general may decrease with illness progression and number of manic episodes<sup>116–119</sup> but normalize (or even increase) with lithium treatment.<sup>108,120</sup> Several studies report no associations between illness progression and prefrontal cortical GM volume,<sup>115</sup> or even increased prefrontal cortical GM volumes with illness progression.<sup>86,121,122</sup> In parallel, GM reductions in amygdala, striatum and hippocampus may be associated with increasing illness duration and age,<sup>83,84,123–125</sup> but may be normalized, or increased, by lithium.<sup>85</sup> The latter finding may explain some of the inconsistent findings of increased subcortical volume with illness duration in adults.<sup>86,126,127</sup> Several studies, however, reported no association between illness course and amygdala or hippocampal volume.<sup>115</sup> DI studies suggest a progression of WM tract abnormalities in illness progression in adults with BD,<sup>65,128</sup> but the majority of studies indicate no change in WM with illness course.<sup>115,125,129,130</sup>

Given the paucity of longitudinal neuroimaging studies of BD, further research is needed to determine whether the magnitude of the functional and structural abnormalities in neural circuitry associated with BD, and risk for future BD, continues to increase

with increasing number of illness episodes, failure to achieve remission, and whether some of the inconsistencies in existing findings can be explained by differential pharmacotherapy.

## DO NEUROIMAGING STUDIES SUPPORT A STAGING MODEL OF BD?

Neuroimaging findings provide some support of a staging model of BD, with findings indicating: (1) similar functional, structural and WM abnormalities in prefrontal cortical-subcortical emotion processing, emotion/cognitive control and reward processing neural circuitry in adults with BD and individuals at risk of BD, and (2) increased magnitude of these abnormalities in adults with BD relative to at-risk individuals. Emerging findings also suggest that the magnitude of abnormalities in these neural circuitries is greater in those at-risk individuals who currently carry a non-bipolar diagnosis than in those who are currently psychiatrically healthy.

## WHAT ADDITIONAL RESEARCH IS NEEDED TO FURTHER SUPPORT OR DISCONFIRM A STAGING MODEL OF BDS?

First, support for or rejection of a staging model of BD will clearly require the inclusion of other biologic measures related to the concept that BD is a multisystem disorder. For example, at what stage should we incorporate the tracking of inflammatory markers or ascertain specific risk factors for various medical diseases including diabetes, asthma, and other chronic illnesses. Such an approach may require the application of the allostatic load models referred to above and consideration of both exogenous factors in the form of life stress and factors endogenous to bipolar illness itself. For example, what are the costs to the endocrine and neural circuitry and even to cellular mechanisms of the chronic shifting from one pole of the illness to the other with attendant changes in activity, appetite, weight and sleep/wake patterns? Second, we need to refine the methodology for modeling and incorporating dimensional approaches to the description of BDs. The nomenclature makes relatively arbitrary distinctions among bipolar I, bipolar II and other forms of the illness, but there is great variation within each of these categories and, in some respect, substantial overlap between some of these categories. And, particularly relevant for staging models, is the fact that what may first appear as an 'other specified' BD in an early adolescent, may progress to a bipolar II disorder by later adolescence and to a bipolar I disorder in early adulthood. Third, precise outcome measures need to be developed and applied to the various stages, both in the domain of symptomatology and in the domain of functioning. Finally, as all of the previous points imply, a staging approach to BD explicitly points to the need for targeted stage-appropriate interventions. Work on such targeted treatments is in its infancy, but does exist and, in some cases, has begun to incorporate genetic, neuroimaging and other biologic data collection that may eventually lead to a fuller understanding of the stages of BDs.

## CONFLICT OF INTEREST

Drs Frank and Kupfer are consultants to the American Psychiatric Association and each has an equity interest in Psychiatric Assessments. Dr Frank receives royalties from Guilford Press and the American Psychological Association and has received honoraria from Servier and Lundbeck. The other authors have no conflict of interest to declare.

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