HHS Public Access

Author manuscript

Mol Psychiatry. Author manuscript; available in PMC 2015 August 01.

Published in final edited form as:

Mol Psychiatry. 2015 February ; 20(1): 23–31. doi:10.1038/mp.2014.71.

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

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Abstract

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.

Keywords

bipolar disorder; clinical staging; diagnosis; genetics; neuroimaging

Introduction

Recently a number of reviews on bipolar disorders have sought to update key aspects of diagnosis, genetics, neurobiology and treatment. All of these reviews have treated bipolar disorders in the traditional categorical DSM and ICD fashion; 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. Bipolar disorders represent an excellent example of current dilemmas that present barriers to scientific progress.

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In this report we do not review comprehensively all aspects of the bipolar disorders; however, we do direct the reader to specific reports for certain areas. Instead, we will utilize recent data and promising research directions to argue the following. Whatever framework we have been using to understand bipolar disorders has generally been limited by several key factors: 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 life span has been given scant attention, especially beyond puberty. Third, we view our patients as having a primary disorder (in this case, bipolar disorder) and occasionally concern ourselves with psychiatric comorbidities such as anxiety, addictive behaviors. Rarely, however, have we viewed bipolar disorders as multisystem disorders. For example, the presence of early medical conditions as asthma, childhood obesity, and early signs of cardiovascular disease may simply 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 life span, independent of the course of the bipolar disorder, has not been fully appreciated. Recently several of us have proposed that bipolar disorder should be viewed a multisystem inflammatory disease.[1,2] Applying this strategy would allow us to integrate the so-called concurrent medical problems of those with bipolar disorder more directly into our understanding of the longitudinal course or stages of this illness over the life span. Such an approach would be especially important in aligning our understanding of cardiovascular risk factors with the bipolar disorder process and potentially in providing insight as to why a patient whose bipolar disorder 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 biological 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 bipolar disorder

To date, our perspective on diagnosis in bipolar disorder 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 diagnosis, treatment, and research on bipolar disorders. In Table 1 we delineate the clinical presentations associated with a four-stage model of bipolar disorder developed over the past several years along with genetic and neuroimaging correlates.[3-5] This model reconceptualizes bipolar disorder as an evolving condition with changing manifestations over the course of its development from early, pre-risk status, through mild, non-specific symptoms, first fully syndromal episode onset, and then 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 bipolar disorder.

Diagnostic Considerations

The precise form that the diagnostic criteria for bipolar disorders 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 bipolar disorder 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. [6] Part of the difficulty in the accurate diagnosis of bipolar disorders – multiple studies suggest that that the average patient waits seven to ten years for a correct diagnosis[7] - 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 bipolar disorder 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 hour cycles, etc.

It is when one begins to think about diagnosis of the various bipolar disorders from a clinical staging perspective that the longitudinal view becomes particularly critical. Although many clinicians believe that there is "only one bipolar disorder," others might argue that there are many forms with different developmental trajectories. For example, is an individual whose initial diagnosis as a pre-adolescent is 'other specified bipolar disorder' by virtue of the fact that his hypomanic symptoms have never lasted more than two or three 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 20's 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 50's, but never experiences an episode of mania? These are questions that a staging framework for bipolar disorders could help us to resolve.

Perhaps most relevant to a staging perspective of bipolar disorders, 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 bipolar disorder. 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 bipolar disorder that responds more poorly to conventional treatment,[8] 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.[9] Finally, it would not be surprising if this subgroup of patients were found to be neurobiologically or genetically distinct.

Traditionally, in thinking about bipolar disorders, 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 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 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 bipolar disorder and vice versa.[10-13]

Here the concept of allostatic load, a term coined by McEwan and Stellar more than 20 years ago[14] 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 HPA 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 bipolar disorders.

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 Bipolar Disorder

Evidence from twin, family and adoption studies indicates a substantial genetic contribution to the etiology of bipolar disorder (BD), with heritability estimates in excess of 70%.[15] Like many other highly prevalent disorders, the etiologic architecture of BD is complex. Most family based analyses support a multi-factorial polygenic threshold (MFPT) model. The MFPT 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.[16] 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.[17] Early gene mapping studies of BD have been unsuccessful, fueling speculation that there may be hundreds, if not thousands of risk variants.[18] 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 SNPs localized to *CACNAIC*, *ODZ4* and *ANK3* that are statistically associated with BD.[19] Efforts are in progress to muster additional samples for ‘mega analyses’.[20] This incremental approach has been used successfully in schizophrenia (SZ).[21] 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 bipolar disorders

The clinical staging scheme outlined here ostensibly classifies BD patients based on the natural history of the disorder. However, the sub-groups 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 progressively ‘carve’ BD at its ‘joints,’ i.e., identify biologically meaningful sub-groups, while iteratively modifying the clinical stages. In turn, such sub-groups may yield

more refined results for linkage analyses. Indeed, Fears and colleagues have recently combined family, genetic, neuropsychological and imaging studies to produce very interesting results concerning heritable characteristics in two large pedigrees that are and are not associated with bipolar disorder.[22] Epigenetics is another highly relevant avenue of research in this context. Though it has been difficult to identify epigenetic markers that are relevant from the staging perspective for bipolar disorder 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 bipolar disorder, no symptoms currently; Stage 1a; Mild or non-specific 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.[23] 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.[24]

Stage 2. First Episode of bipolar disorder; 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, so 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.[25] Additionally, such groups could supplement ongoing GWAS mega analyses.

Stages 3 and 4. 3a, 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 co-morbidity. The co-morbidity 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/sub-groups of BD. This phenomenon, also called pleiotropy was harnessed to

identify novel risk variants for schizophrenia (SZ).[26] Using novel empirical Bayesian statistical approaches, Andreassen et al found genetic overlap between SZ and cardiovascular risk factors such as obesity, hypertension and dyslipidemia.[27,28] They next leveraged available GWAS results for these traits to identify several new SZ risk variants that were undetected using conventional SZ GWAS approaches.[29] Arguably, the Bayesian analyses could be harnessed more extensively for BD gene mapping efforts (Andreassen and Thompson, personal communication, December 3, 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 bipolar disorder and bipolar disorder at-risk individuals: evidence for a staging model of bipolar disorder?

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 bipolar disorders 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 bipolar disorders 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 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/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 Bipolar Disorder (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, i.e. emotion dysregulation, emotional liability, and reward sensitivity.[30] These two themes are processing domains include: 1) cognitive control of emotion during emotion regulation, inhibitory control processes (cognitive and inhibitory) during emotion regulation 2) reward processing.[31,32] Neural circuitry important for the first theme include the amygdala, implicated in emotion processing[33,34]; ventrolateral prefrontal cortex (vlPFC) implicated in inhibitory control processes[31]; and regions such as the orbitofrontal cortex,

OFC, anterior cingulate cortex, ACC, mediodorsal prefrontal cortex, mdPFC, and hippocampus important for automatic emotion regulation.[31] Neural regions important for the second theme include the ventral striatum (VS), important for processing reward cues and outcomes[35,36]; vlPFC, supporting both inhibitory processes and arousal in the context of emotional stimuli[37,38]; OFC, which encodes reward value,[39] and medial prefrontal cortex (mPFC, a larger region including both the ACC and mdPFC), regulating appetitive behaviors in potentially rewarding contexts.[40,41]

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 fronto-limbic 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.[42-54] 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 VS-vlPFC over-reactivity to reward anticipation,[55-59] although see Abler et al.[60] 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,[61-63] and bilateral abnormalities in prefrontal WM[64-76] in adults with BD that may represent structural correlates of the functional abnormalities described above. Studies reporting reduced volumes in subcortical regions, e.g. 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.[62,77-85] Studies suggesting larger volumes of the amygdala in adults with BD may be confounded by potential neurotrophic effects of lithium on these structures.[86]

Individuals at future risk of Bipoar 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 dlPFC) and in the amygdala[87] and decreased right frontal (vlPFC-amygdala) functional connectivity.[88,89]

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.[59] The main pattern observed in structural studies is abnormally *increased* gray matter (GM) volume in several areas including right vlPFC,[87] left parahippocampal gyrus,[91] and left caudate[92-94]

Reductions in left anterior insular GM volumes have also been observed.[63] There are null findings, however.[92,95-98] DI studies indicate abnormal, predominantly right-sided, decreases in fractional anisotropy (FA) and volume in white matter (WM) tracts connecting prefrontal cortical and subcortical regions.[63,75,99,100]

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, and abnormal prefrontal WM, as these patterns are similar to findings from studies of adults with BD.

Psychiatrically affected individuals at future risk of bipolar disorder (Stage 1a-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 bipolar disorder, neuroimaging studies indicate abnormally increased bilateral dlPFC activity (right>left) and increased left vlPFC-bilateral amygdala functional connectivity in youth with milder-level behavioral and emotional dysregulation symptoms,[101] and abnormally increased activity in left frontal pole in first-degree relatives of individuals with BD who currently have depression or substance abuse diagnoses.[102,103] 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.[104,105]

Theme 2: Reward processing and structural abnormalities

One study reported increased left vlPFC/middle prefrontal cortical activity to reward with increasing magnitude of non-specific behavioral and mood dysregulation symptoms in youth.[106] 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.[107]

Genetic risk for BD is associated with abnormally decreased volumes in the right DLPFC,[73] OFC,[73] insula,[73] ACC,[108] VS,[108] and bilateral frontal[108] and left temporoparietal regions.[108] Increased volumes are observed in the right VLPFC,[90] left insula,[109] and left caudate.[92-94] However, some findings are mixed.[110-112] DI studies report that genetic risk for BD is associated with decreased WM volume and white matter integrity, particularly in the frontal regions.[71,73,94,108,113] Again, some findings are mixed.[114]

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 (Stage 3a, b, 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.[115] Focusing on the main themes described above in adults with BD, the most consistent finding is smaller right vlPFC GM volumes in adults with BD with long-term illness and minimal lifetime exposure to lithium compared to healthy adults. By contrast, larger right vlPFC volumes are observed in younger adults in early stages of BD.[90] Prefrontal cortical gray matter volumes in general may decrease with illness progression and number of manic episodes[116-119] but normalize (or even increase) with lithium treatment.[90,120] Several studies report no associations between illness progression and prefrontal cortical GM volume[115]; or even increased prefrontal cortical GM volumes with illness progression.[86,121,122] In parallel, GM reductions in amygdala, striatum and hippocampus may be associated with increasing illness duration and age,[83,84,123-125] but may be normalized, or increased, by lithium.[85] The latter finding may explain some of the inconsistent findings of increased subcortical volume with illness duration in adults.[86,126,127] Several studies, however, reported no association between illness course and amygdala or hippocampal volume.[115] DI studies suggest a progression of WM tract abnormalities in illness progression in adults with BD [65,128] but the majority of studies indicate no change in WM with illness course. [115,125,129,130]

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 bipolar disorder?

Neuroimaging findings provide some support of a staging model of BD, with findings indicating: 1) similar functional, structural and white matter 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 bipolar disorders?

First, support for or rejection of a staging model of bipolar disorder will clearly require the inclusion of other biologic measures related to the concept that bipolar disorder 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 bipolar disorders. 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’ bipolar disorder 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 bipolar disorder 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 bipolar disorders.

Acknowledgements

This work was partially supported by NIMH grants MH63480, TW008302, and MH09375, awarded to Dr. Nimgaonkar; and MH092221-03, MH0922250, MH073953, and MH060952-12S1, awarded to Dr. Phillips; MH081003 awarded to Drs Kupfer and Frank, and a bequest from the Mueller family. The authors wish to thank Fiona C. Ritchey, B.A. for her editorial assistance in preparing this manuscript. Drs. Frank and Kupfer are consultants to the American Psychiatric Association and each has an equity interest in Psychiatric Assessments, Inc. Dr. Frank receives royalties from Guilford Press and the American Psychological Association and has received honoraria from Servier and Lundbeck. Drs. Kupfer, Nimgaonkar, and Phillips have no further conflicts to declare.

References

1. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neuroscience and Biobehavioral Reviews. 2011; 35(3):804–817. [PubMed: 20934453]
2. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease. Journal of Affective Disorders. 2012; 141(1):1–10. [PubMed: 22497876]
3. Scott J, Leboyer M, Hickie IB, Berk M, Kapczinski F, Frank E, Kupfer DJ, McGorry PD. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. The British Journal of Psychiatry. 2013; 202(4):243–245. [PubMed: 23549937]

4. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer, and more effective interventions. Australia and New Zealand Journal of Psychiatry. 2006; 40(8):616–622.
5. Berk M, Conus P, Lucas N, Hallam K, Malhi GS, Dodd S, et al. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disorders. 2007; 9(7):671–678. [PubMed: 17988356]
6. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed.. American Psychiatric Publishing, Inc.; Arlington, VA: 2013.
7. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: A naturalistic study. Journal of Clinical Psychiatry. 2000; 61(10):804–808. [PubMed: 11078046]
8. Frank E, Cyranowski JM, Rucci P, Shear MK, Fagiolini A, Thase ME, et al. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. Archives of General Psychiatry. 2002; 59(10):905–912. [PubMed: 12365877]
9. Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. Journal of Affective Disorders. 2010; 121(1-2):127–135. [PubMed: 19541368]
10. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and Mortality in Bipolar Disorder: A Swedish National Cohort Study. Archives of General Psychiatry. 2013; 70(9):931.
11. Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, Miller DD, Haynes WG. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Annals of Clinical Psychiatry. 2008; 20(3):131–137. [PubMed: 18633739]
12. Fiedorowicz JG, Solomon DA, Endicott J, Leon AC, Li C, Rice JP, et al. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosomatic Medicine. 2009; 71(6):598–606. [PubMed: 19561163]
13. Hickie IB, Scott EM, Hermens DF, Naismith SL, Guastella AJ, Kaur M, et al. Applying clinical staging to young people who present for mental health care. Early Intervention in Psychiatry. 2013; 7(1):31–43. [PubMed: 22672533]
14. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Archives of Internal Medicine. 1993; 153(18):2093–2101. [PubMed: 8379800]
15. Tsuang, MT.; Faraone, SV. The genetic epidemiology of bipolar disorder. In: Marneros, A.; Angst, J., editors. Bipolar Disorders: 100 Years After Manic-Depressive Insanity. Kluwer Academic; Zurich: 2000.
16. Gottesman II, Shields J. A polygenic theory of schizophrenia. International Journal of Mental Health. 1972; 1(1-2):107–115.
17. Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, et al. Genome Scan Meta-Analysis of Schizophrenia and Bipolar Disorder, Part II: Schizophrenia. The American Journal of Human Genetics. 2003; 73(1):34–48. [PubMed: 12802786]
18. Genome-wide association studies: History, rationale, and prospects for psychiatric disorders. The American Journal of Psychiatry. 2009; 166(5):540–556. [PubMed: 19339359]
19. Craddock N, Sklar P. Genetics of bipolar disorder. The Lancet. 2013; 381(9878):1654–1662.
20. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nature Genetics. 2013; 45(9):984–994. [PubMed: 23933821]
21. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nature Genetics. 2013; 45(10): 1150–1161. http://www.nature.com/ng/journal/v45/n10/pdf/ng.2742.pdf. [PubMed: 23974872]
22. Fears SC, Service SK, Kremeyer B, et al. Multisystem Component Phenotypes of Bipolar Disorder for Genetic Investigations of Extended Pedigrees. JAMA Psychiatry. 2014; 71(4):375–387. doi: 10.1001/jamapsychiatry.2013.4100. [PubMed: 24522887]
23. Bamne MN, Ponder CA, Wood JA, Mansour H, Frank E, Kupfer DJ, et al. Application of an ex vivo cellular model of circadian variation for bipolar disorder research: A proof of concept study. Bipolar Disorders. 2013; 15(6):694–700. [PubMed: 23782472]

24. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature. 2012; 485(7397):237–241. [PubMed: 22495306]
25. Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK. Toward Constructing an Endophenotype Strategy for Bipolar Disorders. Biological Psychiatry. 2006; 60(2):93–105. [PubMed: 16406007]
26. Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR, et al. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. PLoS Genetics. 2013; 9(4)
27. Andreassen OA, Thompson WK, Dale AM. Boosting the Power of Schizophrenia Genetics by Leveraging New Statistical Tools. Schizophrenia Bulletin. 2013
28. Efron, B. Large-scale inference: empirical Bayes methods for estimation, testing, and prediction. Cambridge University Press; Cambridge, UK: 2012.
29. Andreassen Ole A, Djurovic S, Thompson Wesley K, Schork Andrew J, Kendler Kenneth S, O'Donovan Michael C, et al. Improved Detection of Common Variants Associated with Schizophrenia by Leveraging Pleiotropy with Cardiovascular-Disease Risk Factors. American Journal of Human Genetics. 2013; 92(2):197–209. [PubMed: 23375658]
30. Goodwin, FK.; Jamison, KR.; Ghaemi, SN. Manic-depressive illness: bipolar disorders and recurrent depression. 2nd edn.. Vol. xxvi. Oxford University Press; New York, N.Y.: 2007. p. 1262
31. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry. 2008; 13(9):829, 833–857. [PubMed: 18574483]
32. Caseras X, Lawrence NS, Murphy K, Wise RG, Phillips ML. Ventral striatum activity in response to reward: differences between bipolar I and II disorders. Am J Psychiatry. 2013; 170(5):533–541. [PubMed: 23558337]
33. Swanson LW. The amygdala and its place in the cerebral hemisphere. Ann N Y Acad Sci. 2003; 985:174–184. [PubMed: 12724158]
34. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry. 2001; 6(1):13–34. [PubMed: 11244481]
35. Knutson B, Wimmer GE. Splitting the difference: how does the brain code reward episodes? Ann N Y Acad Sci. 2007; 1104:54–69. [PubMed: 17416922]
36. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 2004; 5(6):483–494. [PubMed: 15152198]
37. Dolcos F, LaBar KS, Cabeza R. Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. Neuroimage. 2004; 23(1):64–74. [PubMed: 15325353]
38. Schmidt L, Clery-Melin ML, Lafargue G, Valabregue R, Fossati P, Dubois B, et al. Get aroused and be stronger: emotional facilitation of physical effort in the human brain. J Neurosci. 2009; 29(30):9450–9457. [PubMed: 19641108]
39. Grabenhorst F, Rolls ET. Value, pleasure and choice in the ventral prefrontal cortex. Trends Cogn Sci. 2011; 15(2):56–67. [PubMed: 21216655]
40. Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, et al. Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. Biol Psychiatry. 2004; 55(6):594–602. [PubMed: 15013828]
41. Pedroni A, Koeneke S, Velickaite A, Jancke L. Differential magnitude coding of gains and omitted rewards in the ventral striatum. Brain Res. 2011; 1411:76–86. [PubMed: 21831362]
42. Foland-Ross LC, Bookheimer SY, Lieberman MD, Sugar CA, Townsend JD, Fischer J, et al. Normal amygdala activation but deficient ventrolateral prefrontal activation in adults with bipolar disorder during euthymia. Neuroimage. 2012; 59(1):738–744. [PubMed: 21854858]
43. Townsend JD, Torrisi SJ, Lieberman MD, Sugar CA, Bookheimer SY, Altshuler LL. Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder. Biol Psychiatry. 2013; 73(2):127–135. [PubMed: 22858151]

44. Altshuler L, Bookheimer S, Townsend J, Proenza MA, Sabb F, Mintz J, et al. Regional brain changes in bipolar I depression: a functional magnetic resonance imaging study. Bipolar Disord. 2008; 10(6):708–717. [PubMed: 18837865]
45. Strakowski SM, Eliassen JC, Lamy M, Cerullo MA, Allendorfer JB, Madore M, et al. Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. Biol Psychiatry. 2011; 69(4):381–388. [PubMed: 21051038]
46. Townsend JD, Bookheimer SY, Foland-Ross LC, Moody TD, Eisenberger NI, Fischer JS, et al. Deficits in inferior frontal cortex activation in euthymic bipolar disorder patients during a response inhibition task. Bipolar Disord. 2012; 14(4):442–450. [PubMed: 22631623]
47. Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, et al. Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. Eur Neuropsychopharmacol. 2012; 22(2):100–113. [PubMed: 21820878]
48. Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, et al. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol Psychiatry. 2004; 55(6):578–587. [PubMed: 15013826]
49. Blumberg HP, Donegan NH, Sanislow CA, Collins S, Lacadie C, Skudlarski P, et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology (Berl). 2005; 183(3):308–313. [PubMed: 16249909]
50. Keener MT, Fournier JC, Mullin BC, Kronhaus D, Perlman SB, LaBarbara E, et al. Dissociable patterns of medial prefrontal and amygdala activity to face identity versus emotion in bipolar disorder. Psychol Med. 2012; 42(9):1913–1924. [PubMed: 22273442]
51. Surguladze SA, Marshall N, Schulze K, Hall MH, Walshe M, Bramon E, et al. Exaggerated neural response to emotional faces in patients with bipolar disorder and their first-degree relatives. Neuroimage. 2010; 53(1):58–64. [PubMed: 20595014]
52. Almeida JR, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ, et al. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. Biol Psychiatry. 2009; 66(5):451–459. [PubMed: 19450794]
53. Versace A, Thompson WK, Zhou D, Almeida JR, Hassel S, Klein CR, et al. Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder. Biol Psychiatry. 2010; 67(5):422–431. [PubMed: 20159144]
54. Almeida JR, Mechelli A, Hassel S, Versace A, Kupfer DJ, Phillips ML. Abnormally increased effective connectivity between parahippocampal gyrus and ventromedial prefrontal regions during emotion labeling in bipolar disorder. Psychiatry Res. 2009; 174(3):195–201. [PubMed: 19910166]
55. O'Sullivan N, Szczepanowski R, El-Deredy W, Mason L, Bentall RP. fMRI evidence of a relationship between hypomania and both increased goal-sensitivity and positive outcome-expectancy bias. Neuropsychologia. 2011; 49(10):2825–2835. [PubMed: 21703286]
56. Nusslock R, Almeida JR, Forbes EE, Versace A, Frank E, Labarbara EJ, et al. Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. Bipolar Disord. 2012; 14(3):249–260. [PubMed: 22548898]
57. Chase HW, Nusslock R, Almeida JRC, Forbes EE, Phillips ML. Dissociable patterns of of abnormal frontal cortical activation during activation during activation during anticipation of an uncertain reward or loss in bipolar versus major depression. Bipolar Disord. In Press.
58. Bermpohl F, Kahnt T, Dalanay U, Hagele C, Sajonz B, Wegner T, et al. Altered representation of expected value in the orbitofrontal cortex in mania. Hum Brain Mapp. 2010; 31(7):958–969. [PubMed: 19950195]
59. Linke J, King AV, Rietschel M, Strohmaier J, Hennerici M, Gass A, et al. Increased medial orbitofrontal and amygdala activation: evidence for a systems-level endophenotype of bipolar I disorder. Am J Psychiatry. 2012; 169(3):316–325. [PubMed: 22267184]
60. Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. Neuropsychopharmacology. 2008; 33(9):2217–2227. [PubMed: 17987058]

61. Foland-Ross LC, Thompson PM, Sugar CA, Madsen SK, Shen JK, Penfold C, et al. Investigation of cortical thickness abnormalities in lithium-free adults with bipolar I disorder using cortical pattern matching. Am J Psychiatry. 2011; 168(5):530–539. [PubMed: 21285139]
62. Rimol LM, Hartberg CB, Nesvag R, Fennema-Notestine C, Hagler DJ Jr. Pung CJ, et al. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry. 2010; 68(1):41–50. [PubMed: 20609836]
63. Matsuo K, Kopecek M, Nicoletti MA, Hatch JP, Watanabe Y, Nery FG, et al. New structural brain imaging endophenotype in bipolar disorder. Mol Psychiatry. 2012; 17(4):412–420. [PubMed: 21321565]
64. Emsell L, Leemans A, Langan C, Van Hecke W, Barker GJ, McCarthy P, et al. Limbic and callosal white matter changes in euthymic bipolar I disorder: an advanced diffusion magnetic resonance imaging tractography study. Biol Psychiatry. 2013; 73(2):194–201. [PubMed: 23158457]
65. Versace A, Almeida JR, Hassel S, Walsh ND, Novelli M, Klein CR, et al. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Arch Gen Psychiatry. 2008; 65(9):1041–1052. [PubMed: 18762590]
66. Versace A, Andreazza AC, Young LT, Fournier JC, Almeida JR, Stiffler RS, et al. Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. Mol Psychiatry. 2013
67. Mahon K, Burdick KE, Szeszko PR. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev. 2010; 34(4):533–554. [PubMed: 19896972]
68. Wang F, Jackowski M, Kalmar JH, Chepenik LG, Tie K, Qiu M, et al. Abnormal anterior cingulum integrity in bipolar disorder determined through diffusion tensor imaging. Br J Psychiatry. 2008; 193(2):126–129. [PubMed: 18669996]
69. Wang F, Kalmar JH, Edmiston E, Chepenik LG, Bhagwagar Z, Spencer L, et al. Abnormal corpus callosum integrity in bipolar disorder: a diffusion tensor imaging study. Biol Psychiatry. 2008; 64(8):730–733. [PubMed: 18620337]
70. Benedetti F, Absinta M, Rocca MA, Radaelli D, Poletti S, Bernasconi A, et al. Tract-specific white matter structural disruption in patients with bipolar disorder. Bipolar Disord. 2011; 13(4):414–424. [PubMed: 21843281]
71. Chaddock CA, Barker GJ, Marshall N, Schulze K, Hall MH, Fern A, et al. White matter microstructural impairments and genetic liability to familial bipolar I disorder. Br J Psychiatry. 2009; 194(6):527–534. [PubMed: 19478293]
72. Versace A, Almeida JR, Quevedo K, Thompson WK, Terwilliger RA, Hassel S, et al. Right orbitofrontal corticolimbic and left corticocortical white matter connectivity differentiate bipolar and unipolar depression. Biol Psychiatry. 2010; 68(6):560–567. [PubMed: 20598288]
73. van der Schot AC, Vonk R, Brouwer RM, van Baal GC, Brans RG, van Haren NE, et al. Genetic and environmental influences on focal brain density in bipolar disorder. Brain. 2010; 133(10): 3080–3092. [PubMed: 20837502]
74. Benedetti F, Yeh PH, Bellani M, Radaelli D, Nicoletti MA, Poletti S, et al. Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. Biol Psychiatry. 2011; 69(4):309–317. [PubMed: 20926068]
75. Mahon K, Burdick KE, Ikuta T, Braga RJ, Gruner P, Malhotra AK, et al. Abnormal temporal lobe white matter as a biomarker for genetic risk of bipolar disorder. Biol Psychiatry. 2013; 73(2):177–182. [PubMed: 23036958]
76. Bruno S, Cercignani M, Ron MA. White matter abnormalities in bipolar disorder: a voxel-based diffusion tensor imaging study. Bipolar Disord. 2008; 10(4):460–468. [PubMed: 18452442]
77. Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, et al. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry. 2003; 60(12):1201–1208. [PubMed: 14662552]
78. Wijeratne C, Sachdev S, Wen W, Piguet O, Lipnicki DM, Malhi GS, et al. Hippocampal and amygdala volumes in an older bipolar disorder sample. Int Psychogeriatr. 2013; 25(1):54–60. [PubMed: 22929183]

79. Foland-Ross LC, Brooks JO, Mintz J, Bartzokis G, Townsend J, Thompson PM, et al. Mood-state effects on amygdala volume in bipolar disorder. J Affect Disord. 2012; 139(3):298–301. [PubMed: 22521854]
80. Foland LC, Altshuler LL, Sugar CA, Lee AD, Leow AD, Townsend J, et al. Increased volume of the amygdala and hippocampus in bipolar patients treated with lithium. Neuroreport. 2008; 19(2): 221–224. [PubMed: 18185112]
81. Pfeifer JC, Welge J, Strakowski SM, Adler CM, DelBello MP. Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2008; 47(11):1289–1298. [PubMed: 18827720]
82. Hajek T, Kopecek M, Hoschl C, Alda M. Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. J Psychiatry Neurosci. 2012; 37(5): 333–343. [PubMed: 22498078]
83. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 2011; 69(4):326–335. [PubMed: 21030008]
84. Javadapour A, Malhi GS, Ivanovski B, Chen X, Wen W, Sachdev P. Hippocampal volumes in adults with bipolar disorder. Journal of Neuropsychiatry & Clinical Neurosciences. 2010; 22(1): 55–62. [PubMed: 20160210]
85. Ong D, Walterfang M, Malhi GS, Styner M, Velakoulis D, Pantelis C. Size and shape of the caudate nucleus in individuals with bipolar affective disorder. Aust N Z J Psychiatry. 2012; 46(4): 340–351. [PubMed: 22368240]
86. Lisy ME, Jarvis KB, DelBello MP, Mills NP, Weber WA, Fleck D, et al. Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. Bipolar Disord. 2011; 13(4):396–405. [PubMed: 21843279]
87. Ladouceur CD, Diwadkar VA, White R, Bass J, Birmaher B, Axelson DA, et al. Fronto-limbic function in unaffected offspring at familial risk for bipolar disorder during an emotional working memory paradigm. Dev Cogn Neurosci. 2013; 5:185–196. [PubMed: 23590840]
88. Kim P, Jenkins SE, Connolly ME, Deveney CM, Fromm SJ, Brotman MA, et al. Neural correlates of cognitive flexibility in children at risk for bipolar disorder. J Psychiatr Res. 2012; 46(1):22–30. [PubMed: 22024484]
89. Whalley HC, Sussmann JE, Chakirova G, Mukerjee P, Peel A, McKirdy J, et al. The neural basis of familial risk and temperamental variation in individuals at high risk of bipolar disorder. Biol Psychiatry. 2011; 70(4):343–349. [PubMed: 21601834]
90. Hajek T, Cullis J, Novak T, Kopecek M, Blagdon R, Propper L, et al. Brain structural signature of familial predisposition for bipolar disorder: replicable evidence for involvement of the right inferior frontal gyrus. Biol Psychiatry. 2013; 73(2):144–152. [PubMed: 22818781]
91. Ladouceur CD, Almeida JR, Birmaher B, Axelson DA, Nau S, Kalas C, et al. Subcortical gray matter volume abnormalities in healthy bipolar offspring: potential neuroanatomical risk marker for bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2008; 47(5):532–539. [PubMed: 18356765]
92. Hajek T, Gunde E, Slaney C, Propper L, MacQueen G, Duffy A, et al. Striatal volumes in affected and unaffected relatives of bipolar patients--high-risk study. J Psychiatr Res. 2009; 43(7):724–729. [PubMed: 19046588]
93. Noga JT, Vladar K, Torrey EF. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. Psychiatry Res. 2001; 106(1):25–34. [PubMed: 11231097]
94. van der Schot AC, Vonk R, Brans RG, van Haren NE, Koolschijn PC, Nuboer V, et al. Influence of genes and environment on brain volumes in twin pairs concordant and discordant for bipolar disorder. Arch Gen Psychiatry. 2009; 66(2):142–151. [PubMed: 19188536]
95. Hajek T, Gunde E, Bernier D, Slaney C, Propper L, Grof P, et al. Subgenual cingulate volumes in affected and unaffected offspring of bipolar parents. J Affect Disord. 2008; 108(3):263–269. [PubMed: 18037495]
96. Hajek T, Bernier D, Slaney C, Propper L, Schmidt M, Carrey N, et al. A comparison of affected and unaffected relatives of patients with bipolar disorder using proton magnetic resonance spectroscopy. J Psychiatry Neurosci. 2008; 33(6):531–540. [PubMed: 18982176]

97. Mondelli V, Dazzan P, Gabilondo A, Tournikioti K, Walshe M, Marshall N, et al. Pituitary volume in unaffected relatives of patients with schizophrenia and bipolar disorder. Psychoneuroendocrinology. 2008; 33(7):1004–1012. [PubMed: 18640787]

98. Hajek T, Novak T, Kopecek M, Gunde E, Alda M, Hoschl C. Subgenual cingulate volumes in offspring of bipolar parents and in sporadic bipolar patients. Eur Arch Psychiatry Clin Neurosci. 2010; 260(4):297–304. [PubMed: 19812886]

99. Versace A, Ladouceur CD, Romero S, Birmaher B, Axelson DA, Kupfer DJ, et al. Altered development of white matter in youth at high familial risk for bipolar disorder: a diffusion tensor imaging study. J Am Acad Child Adolesc Psychiatry. 2010; 49(12):1249–1259. [PubMed: 21093774]

100. Sprooten E, Sussmann JE, Clugston A, Peel A, McKirdy J, Moorhead TW, et al. White matter integrity in individuals at high genetic risk of bipolar disorder. Biol Psychiatry. 2011; 70(4):350–356. [PubMed: 21429475]

101. Bertocci MA, Bebko G, Olino T, Fournier J, Hinze AK, Bonar L, et al. Behavioral and emotional dysregulation trajectories marked by prefrontal-amygdala function in symptomatic youth. Psychological Medicine. 2014 Forthcoming.

102. Drapier D, Surguladze S, Marshall N, Schulze K, Fern A, Hall MH, et al. Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task. Biol Psychiatry. 2008; 64(6):513–520. [PubMed: 18571627]

103. Thermenos HW, Goldstein JM, Milanovic SM, Whitfield-Gabrieli S, Makris N, Laviolette P, et al. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B(1):120–131. [PubMed: 19418510]

104. Pompei F, Jogia J, Tatarelli R, Girardi P, Rubia K, Kumari V, et al. Familial and disease specific abnormalities in the neural correlates of the Stroop Task in Bipolar Disorder. Neuroimage. 2011; 56(3):1677–1684. [PubMed: 21352930]

105. Pompei F, Dima D, Rubia K, Kumari V, Frangou S. Dissociable functional connectivity changes during the Stroop task relating to risk, resilience and disease expression in bipolar disorder. Neuroimage. 2011; 57(2):576–582. [PubMed: 21570470]

106. Bebko G, Bertocci MA, Fournier JC, Hinze AK, Bonar L, Almeida JRC, Perlman SB, Versace A, Schirda C, Travis M, Gill MK, Demeter C, Diwadkar VA, Ciuffetelli G, Rodriguez E, Olino T, Forbes E, Sunshine JL, Holland SK, Kowatch RA, Birmaher B, Axelson D, Horwitz SM, Arnold LE, Fristad MA, Youngstrom EA, Findling RL, Phillips ML. Parsing dimensional versus diagnostic category-related patterns of reward circuitry function in behaviourally and emotionally dysregulated youth in the Longitudinal Assessment of Manic Symptoms (LAMS) study. JAMA Psychiatry. Nov 27.2013 Published online. doi:10.1001/jamapsychiatry.2013.2870.

107. Fusar-Poli P, Howes O, Bechdolf A, Borgwardt S. Mapping vulnerability to bipolar disorder: a systematic review and meta-analysis of neuroimaging studies. J Psychiatry Neurosci. 2012; 37(3):170–184. [PubMed: 22297067]

108. McDonald C, Bullmore ET, Sham PC, Chitnis X, Wickham H, Bramon E, et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. Arch Gen Psychiatry. 2004; 61(10):974–984. [PubMed: 15466670]

109. Kempton MJ, Haldane M, Jogia J, Grasby PM, Collier D, Frangou S. Dissociable brain structural changes associated with predisposition, resilience, and disease expression in bipolar disorder. J Neurosci. 2009; 29(35):10863–10868. [PubMed: 19726644]

110. Singh MK, Delbello MP, Adler CM, Stanford KE, Strakowski SM. Neuroanatomical characterization of child offspring of bipolar parents. J Am Acad Child Adolesc Psychiatry. 2008; 47(5):526–531. [PubMed: 18356766]

111. Takahashi YK, Roesch MR, Wilson RC, Toreson K, O'Donnell P, Niv Y, et al. Expectancy-related changes in firing of dopamine neurons depend on orbitofrontal cortex. Nat Neurosci. 2011; 14(12):1590–1597. [PubMed: 22037501]

112. Karchemskiy A, Garrett A, Howe M, Adleman N, Simeonova DI, Alegria D, et al. Amygdalar, hippocampal, and thalamic volumes in youth at high risk for development of bipolar disorder. Psychiatry Res. 2011; 194(3):319–325. [PubMed: 22041532]

113. Frazier JA, Breeze JL, Papadimitriou G, Kennedy DN, Hodge SM, Moore CM, et al. White matter abnormalities in children with and at risk for bipolar disorder. Bipolar Disord. 2007; 9(8): 799–809. [PubMed: 18076529]

114. Walterfang M, Wood AG, Barton S, Velakoulis D, Chen J, Reutens DC, et al. Corpus callosum size and shape alterations in individuals with bipolar disorder and their first-degree relatives. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33(6):1050–1057. [PubMed: 19500633]

115. Schneider MR, DelBello MP, McNamara RK, Strakowski SM, Adler CM. Neuroprogression in bipolar disorder. Bipolar Disord. 2012; 14(4):356–374. [PubMed: 22631620]

116. Kalmar JH, Wang F, Spencer L, Edmiston E, Lacadie CM, Martin A, et al. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. J Int Neuropsychol Soc. 2009; 15(3):476–481. [PubMed: 19402934]

117. Ekman CJ, Lind J, Ryden E, Ingvar M, Landen M. Manic episodes are associated with grey matter volume reduction - a voxel-based morphometry brain analysis. Acta Psychiatr Scand. 2010; 122(6):507–515. [PubMed: 20712826]

118. Lyoo IK, Kim MJ, Stoll AL, Demopulos CM, Parow AM, Dager SR, et al. Frontal lobe gray matter density decreases in bipolar I disorder. Biol Psychiatry. 2004; 55(6):648–651. [PubMed: 15013835]

119. Lyoo IK, Sung YH, Dager SR, Friedman SD, Lee JY, Kim SJ, et al. Regional cerebral cortical thinning in bipolar disorder. Bipolar Disord. 2006; 8(1):65–74. [PubMed: 16411982]

120. Moore GJ, Cortese BM, Glitz DA, Zajac-Benitez C, Quiroz JA, Uhde TW, et al. A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. Journal of Clinical Psychiatry. 2009; 70(5):699–705. [PubMed: 19389332]

121. Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol Psychiatry. 2002; 52(2): 93–100. [PubMed: 12114000]

122. Li M, Cui L, Deng W, Ma X, Huang C, Jiang L, et al. Voxel-based morphometric analysis on the volume of gray matter in bipolar I disorder. Psychiatry Res. 2011; 191(2):92–97. [PubMed: 21236649]

123. Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, et al. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry. 2000; 48(2):147–162. [PubMed: 10903411]

124. Doty TJ, Payne ME, Steffens DC, Beyer JL, Krishnan KR, LaBar KS. Age-dependent reduction of amygdala volume in bipolar disorder. Psychiatry Res. 2008; 163(1):84–94. [PubMed: 18407469]

125. Brambilla P, Harenski K, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, et al. Anatomical MRI study of basal ganglia in bipolar disorder patients. Psychiatry Res. 2001; 106(2):65–80. [PubMed: 11306247]

126. Usher J, Menzel P, Schneider-Axmann T, Kemmer C, Reith W, Falkai P, et al. Increased right amygdala volume in lithium-treated patients with bipolar I disorder. Acta Psychiatr Scand. 2010; 121(2):119–124. [PubMed: 19573050]

127. Hajek T, Kopecek M, Kozeny J, Gunde E, Alda M, Hoschl C. Amygdala volumes in mood disorders--meta-analysis of magnetic resonance volumetry studies. J Affect Disord. 2009; 115(3): 395–410. [PubMed: 19019455]

128. Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, et al. Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. Bipolar Disord. 2004; 6(3):197–203. [PubMed: 15117398]

129. Sarnicola A, Kempton M, Germana C, Haldane M, Hadjulis M, Christodoulou T, et al. No differential effect of age on brain matter volume and cognition in bipolar patients and healthy individuals. Bipolar Disord. 2009; 11(3):316–322. [PubMed: 19320638]

130. McIntosh AM, Munoz Maniega S, Lymer GK, McKirdy J, Hall J, Sussmann JE, et al. White matter tractography in bipolar disorder and schizophrenia. Biol Psychiatry. 2008; 64(12):1088–1092. [PubMed: 18814861]

Table 1

Clinical Presentation of the Staging Model of Bipolar Disorder, Strategies for Genetic Analysis, and Neuroimaging findings

Clinical Stage	Clinical Presentation	Strategies for Genetic Analysis	Neuroimaging Findings
0	Increased risk of bipolar disorder; no symptoms currently	Evaluate endophenotypes using GWAS confirmed SNPs; risk prediction studies	**Resilience markers:** abnormal prefrontal cortical activity increases during cognitive control of emotion and cognitive control tasks; abnormal volumetric increases in right-sided vlPFC and left-sided subcortical regions **Risk markers:** Abnormally increased amygdala activity; abnormal prefrontal WM
1a	Mild or non-specific symptoms	Evaluate putative endophenotypes using GWAS confirmed SNPs	**Resilience markers:** Abnormally increased prefrontal cortical activity during cognitive control of emotion and cognitive control tasks; abnormally increased prefrontal cortical volume
1b	Ultra high risk: moderate but subthreshold symptoms, with neurocognitive changes and functional decline to caseness	Discovery of rare variants and de novo mutations	**Risk markers:** Abnormally decreased prefrontal cortical volumes; left-sided subcortical volume increases; abnormally decreased WM volume
2	First episode of bipolar disorder; full threshold disorder with moderate to severe symptoms, neurocognitive deficits and functional decline	Mapping endophenotypes, biomarker studies	**Theme 1:** Abnormally decreased prefrontal cortical activity (especially right-sided vlPFC 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 **Theme 2:** 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	**Markers of disease progression:** A negative association between prefrontal cortical volumes (especially right vlPFC 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	

Adapted from Scott J, Leboyer M, Hickie IB, Berk M, Kapczinski F, Frank E, Kupfer DJ, McGorry PD. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. The British Journal of Psychiatry 2013; 202(4): 243-245.

Table 2

Diagnostic Criteria for the "With Mixed Features" Specifiers

Mania	Depression
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: **1** Prominent dysphoria or depressed mood as indicated by either subjective report or observation made by others **2** Diminished interest or pleasure in all, or almost all activities **3** Psychomotor retardation nearly every day **4** Fatigue or loss of energy **5** Feelings of worthlessness or excessive or inappropriate guilt **6** Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	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: **1** Elevated, expansive mood **2** Inflated self-esteem or grandiosity **3** More talkative than usual or pressure to keep talking **4** Flight of ideas or subjective experience that thoughts are racing **5** Increase in energy or goal-directed activity **6** Increased or excessive involvement in activities that have a high potential for painful consequences **7** Decreased need for sleep
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, due to the marked impairment and clinical severity of full mania	
The mixed symptoms are not attributable to the physiological effects of a substance	

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Table 3

Diagnostic Criteria for the “With Anxious Distress” Specifier

Symptom	Severity	
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		