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Objective and biological markers in bipolar spectrum presentations

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Abstract (197/200)

Introduction: Subthreshold presentations of bipolarity (BSPs) pose a diagnostic conundrum, in terms of whether they should be conceptualized and treated similarly as traditionally defined bipolar disorders (BD). While it has been argued that BSPs are on a pathophysiologic continuum with traditionally defined BDs, there has been limited examination of biological and objective markers in these presentations to validate this assertion.

Areas covered: The authors review studies examining genetic, neurobiological, cognitive and peripheral markers in BSPs, encompassing clinical and non-clinical populations with subthreshold hypo/manic symptoms. Results are placed in the context of previously identified markers in traditionally defined BDs.

Expert commentary: There have been few studies of objective and biomarkers in subthreshold presentations of BD, and results are mixed. While abnormalities in brain structure/functioning, peripheral inflammatory and cognitive markers have been reported, it is unclear whether these findings are specific to BD or indicative of broad affective pathology. However, some studies suggest that increased sensitivity to reward and positive stimuli are shared between subthreshold and traditionally defined BDs, and may represent a point of departure from unipolar major depression. Further examination of such markers may improve understanding of subthreshold bipolar presentations, and provide guidance in terms of therapeutic strategies.

Keywords: bipolar disorder; bipolar spectrum disorders; subthreshold bipolar disorder; biomarker; cognition; inflammatory cytokine; neuroimaging; genetic

Article highlights:

- Patients with subthreshold presentations of bipolar disorder have been proposed to form part of a 'bipolar spectrum' continuous with bipolar I (BDI) and bipolar II (BDII) disorders

- This subset of patients share demographic and clinical similarities with BDI and II, lending support to the bipolar spectrum model and leading some to suggest that these presentations should be treated similarly to traditionally defined BD
- However, there has thus far been limited examination of biological and objective markers in proposed bipolar spectrum presentations (BSPs)
- In this review of the literature, we find BSPs to be variably defined, with variable thresholds applied for symptom number/duration, and variable tools used to assess subthreshold presentations.
- In addition to the variability such heterogeneity introduces, studies specifically investigating genetic, neurobiological, peripheral or cognitive markers in BSPs have been sparse
- Although abnormalities in brain structure/functioning, inflammatory/peripheral markers and cognition in BSPs are reported, results are inconsistent, and it is unclear whether these findings are specific to bipolar disorders versus indicative of broad affective dysfunction
- Previous studies however have identified markers of increased sensitivity to reward and positive stimuli as potentially specific to BD, and some studies find evidence for similar markers in BSPs
- Further investigation of markers of increased sensitivity to reward and positive stimuli in BSPs may help establish pathophysiologic continuity with BD, and guide in determining the most effective treatment strategy in these presentations.

1. Introduction

Symptom clusters form the basis for diagnostic schemes in psychiatry; however, this approach does not necessarily result in the creation of valid diagnostic categories [1]. In recognition of this, there has been increasing interest in incorporating biological and objective indices into diagnostic formulations. An example of this is the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP), which aims to identify cognitive, electrophysiologic and brain imaging biomarkers in patients within the psychosis spectrum (i.e. schizophrenia, schizoaffective and bipolar disorder with psychosis) [2]. Characterization of patients based on such biomarkers resulted in three distinct 'biotypes' which did not respect DSM diagnostic criteria, and showed better correspondence to external validators such as functional and clinical data compared to traditional diagnostic categories [3]. Such results illustrate the potential use of biomarkers to generate more meaningful disease classifications.

The diagnostic classification of bipolar disorders is one area which requires greater clarity. In the DSM- III, bipolar disorders (defined by the presence of a manic episode) were formally separated from unipolar depressive disorders [4]. The DSM III also specified duration and symptom thresholds for mood episodes, thus introducing criteria for categorical diagnoses. This conception – that bipolar and unipolar disorders are fundamentally distinct, and that symptom thresholds are required to make these diagnoses – has informed understanding and research around affective disorders to the present day. The most recent version of the DSM includes three defined bipolar disorders (BDs) - bipolar I (BDI), bipolar II (BDII) and cyclothymia – and three adult

unipolar disorders – major depressive disorder (MDD), persistent depressive disorder and premenstrual dysphoric disorder [5].

However, some researchers and clinicians see this conceptualization as flawed [6,7]. They argue that MDD and BDI form the endpoints of a spectrum, with various gradations and combinations of depressive, hypomanic and manic symptoms in between [7]. The proposals for operationalizing criteria for this bipolar spectrum have been varied (Table 1). In its most limited scope, proponents argued for loosening the time requirements and symptom thresholds needed to diagnose hypomania [8]. This was based on the observation that patients presenting with subthreshold versus strictly defined hypomania did not appear to differ in demographic characteristics or clinical outcomes [8,9]. This is to a certain extent addressed in the DSM-5, which includes short duration or subthreshold hypomania in the category of 'other specified' bipolar disorders [5]. Some, however, advocate for even further expansions of the bipolar concept. Highly recurrent depressive episodes in MDD, for example, are argued to be manifestations of BD related mood cycling, and certain clinical factors such as early age of onset and family history of BD (Table 1) are proposed as bipolarity indicators to be incorporated into diagnostic formulations [7]. Cyclothymic and hyperthymic temperaments have also been put forward as subclinical presentations of BDs, with the most severe manifestations of these temperaments underlying clinically apparent mood disturbances (Figure 1) [10].

The bipolar spectrum concept has major clinical implications. Using more permissive criteria for hypo/manic symptoms, the prevalence of bipolar spectrum disorders was calculated to be around 5%, significantly higher than the previously cited 1% for BDI

and II, respectively [11]. Thus, it is argued that many patients who have an underlying bipolar diathesis are incorrectly classified as and treated for MDD. These patients may respond poorly to these treatments, and may also experience mood destabilization as a result of unopposed antidepressant therapy [12]. Conversely, there is concern that expanding the bipolar concept could result in over diagnosis of BD [4]. For instance, the French EPIDEP study found that using more permissive criteria resulted in more than one half of patients presenting with major depressive episodes being diagnosed with a bipolar spectrum disorder [13]. By the arguments above, these patients should be treated for bipolar rather than unipolar depression. Clearly, strong evidence is needed to justify such a radical shift in diagnostic and treatment approaches. The clarification that treatment trials may provide is unfortunately lacking; there have been no randomized trials assessing outcomes with antidepressants versus mood stabilizers in patients who display bipolar spectrum features.

Establishing that subthreshold presentations share underlying pathophysiologic mechanisms with traditionally defined BD would provide support for adopting a similar treatment approach; objective and biological indices may be helpful in determining whether such continuity exists. There is an extensive literature on biomarkers in BDI, with multiple candidate genetic, peripheral and neurobiological markers [14,15]. The International Society for Bipolar Disorders (ISBD) Biomarker Task Force identified genetic markers of neuronal development and calcium metabolism, as well as peripheral markers such as decreased brain-derived neurotrophic factor (BDNF), increased inflammatory cytokines and indices of mitochondrial dysfunction/oxidative stress as biomarkers of promise in BDs [14]. Functional imaging and EEG markers of

abnormal emotional processing and reward sensitivity have also been reported in BD [14-17]. Objective cognitive deficits are also now recognized as a core feature of BD [14,18], and cognitive functioning has been identified as an important objective measure across multiple psychiatric disorders [1]. However, there has thus far been little systematic investigation of the above markers in patients with 'soft' or 'subthreshold' bipolar spectrum presentations (hereafter termed 'BSPs') [19].

Here, we review the literature on biological and objective markers associated with BSPs, and whether there is evidence to suggest that BSPs are indeed continuous with traditional BDs. As a wide range of clinical features have been proposed as part of the bipolar spectrum, we focus on studies reporting on populations displaying subthreshold hypomanic or manic symptoms. We include studies of cyclothymic and hyperthymic temperaments, which have been proposed as milder symptomatic manifestations of hypo/mania [10]. We did not review all proposed indicators of bipolarity in depression, such as early onset, highly recurrent episodes, or atypical/mixed/psychotic features (see [20] for review of biomarkers in depression with some of these features). As discussed in a 2013 review of neuroimaging markers across the bipolar spectrum, markers of general affective pathology would have little value in supporting a specific pathophysiologic relation between BSPs and currently defined BD [19]. Thus, we briefly review the literature comparing each candidate marker between MDD and traditionally defined BDs to highlight those which may be specific to BD, and then examine whether such markers have been associated with BSPs [19]. Our aim is to ascertain whether there is currently enough evidence to suggest that BSPs are indeed related to BD proper, and identify further avenues of investigation.

2. Genetic Markers

Several candidate genes regulating diverse neurobiological processes have been proposed as markers in BD (Table 2)[21-28]. Pooled analyses of genome wide association studies (GWAS) suggest that the ANK3 and CACNA1C polymorphisms may be the most robust [22,23,25]. However, like most psychiatric disorders, BD is mediated by multiple genes of small effect, and even the most promising polymorphisms only contribute to a small proportion of variance [29]. This has led to the formulation of BD specific polygenic scores, which uses risk alleles identified from GWAS to quantify an individual's risk allele burden. However, these scores still only account for an estimated 2-3% of phenotypic variance [29].

Genes implicated in BDI partially overlap with those associated with MDD and other psychiatric disorders, suggesting a shared genetic diathesis for affective disorders as well as broader domains of psychopathology. An analysis of polygenic risk scores derived for BD, MDD and schizophrenia (SCZ) found that common genetic markers account for 1% of the variance in risk for each diagnosis, and thus are not clinically useful in discriminating between diagnoses [30]. The CACNA1C loci implicated in BD is also associated with recurrent MDD, SCZ, autism spectrum disorder and ADHD [31], while polymorphisms in 5HTTLPR, DRD4, and COMT alleles contribute to risk of both BD and MDD [24].

However, despite evidence of overlap, there is some preliminary evidence for genetic markers that are unique to BD. Susceptibility to BD has been linked to genes regulating circadian rhythms, most notably T to a C nucleotide substitution in the 3' region of the CLOCK (3111T/C) gene which has been associated with delay in preferred sleep time

in humans [33]. While some studies and meta-analyses have concluded that there is no evidence for an association between this individual CLOCK allele and BD [33,34], a GWAS study found evidence that variation in a network of related 'core' genes involved in regulating circadian rhythms is associated with BD [35]. An examination of single nucleotide polymorphisms (SNPs) in 19 circadian genes identified differential associations with MDD versus BD: MDD was associated with SNPs in clock genes CRY1 and NPAS2, while BD was associated with the 3111 T/C CLOCK SNP discussed above and VIPR2 [36]. Another study found that two polymorphisms of the CLOCK gene were associated with BDII, while two polymorphisms of TIM were associated with MDD [37]. While this provides preliminary evidence that different circadian genes may serve as markers distinguishing MDD from BD, a GWAS found that variation within 18 core clock genes was distributed across diagnostic categories BD, ADHD, MDD and SCZ [35]. Thus, while there is some indication that different circadian rhythm genes may serve as markers of polarity, specific genes and SNPS have yet to be definitively identified and validated.

2.1. BSPs

Some studies have examined whether putative bipolarity indicators are associated with BD polygenic risk scores. Subclinical hypo/manic symptoms, along with recurrent episodes, early onset, and atypical symptoms, in a sample of MDD patients were associated with higher BD polygenic risk scores [38]. The strongest contributors were presence of at least one manic symptom and early onset. These results, however, did not replicate in a re-test cohort. Using data from the STAR-D study, Casamassima et al. (2009) attempted to determine whether 'soft' bipolar features were associated with

the presence of high risk BD SNPs in the CACNA1C gene. These high risk SNPs were in fact associated with decreased potential baseline subsyndromal symptoms such as irritability and sleep disturbance. Emerging suicidality during antidepressant treatment, a proposed bipolarity indicator, was associated with these SNPs [39]. However, these results were not corrected for multiple comparisons.

Cyclothymic/hyperthymic temperaments have been found to be heritable, and more common in first degree relatives of BD [40]. However, there has been limited examination of whether these temperaments share genetic markers with BD. Cyclothymic temperament in unaffected relatives of BD probands was associated with 18p11, which has been consistently linked with BD [41,42]. One study also found that cyclothymic temperament was associated with the s allele of 5HTTLPR [43]. However, this was not replicated in a larger cohort [44], and, as described above, this polymorphism is non-specifically associated with affective disorders. The 4R polymorphism of the DRD4 gene was associated with cyclothymic/irritable temperaments in Korean males; however, previous meta-analyses have linked the 2R polymorphism in DRD4 with MDD and BD, and the 4R polymorphism with ADHD [24,45]. These findings may therefore be more indicative of an association between cyclothymic/irritable temperaments and ADHD.

Cyclothymic and hyperthymic temperaments may be linked with circadian rhythm genes. Amongst 383 university students, an ARNTL allele was associated with cyclothymic temperament, and TIM allele was associated with hyperthymic temperament [46]. This same ARNTL polymorphism (in an epistatic interaction with anther clock gene polymorphism) had previously been linked to bipolar versus unipolar

disorder [37], lending credence to a relationship between cyclothymic temperaments and BD. However, neither of the associations between ARNTL and TIM with affective temperaments in the study by Jankowski et al. survived correction for multiple comparisons.

2.2. Summary

While numerous candidate genes have been proposed in BD, it is unclear which, if any, are specific markers of bipolarity. Individual polymorphisms and aggregate polygenic risk scores only account for a fraction of the phenotypic variance in affective disorders. Additionally, while some studies have found differential associations between circadian rhythm gene variants and BD versus MDD, no reliable variants distinguishing BD and MDD have been established. Genetic investigations in populations with BSPs has been extremely limited. One study reported that subclinical hypo/manic symptoms in patients with MDD was associated with higher BD polygenic risk scores, but this did not replicate in a retest cohort. Specific genetic markers linking cyclothymic/hyperthymic temperaments with BD have also not been conclusively established; while one study associated cyclothymic and hyperthymic temperaments with clock gene variants that are possibly related to BD, these associations did not survive correction for multiple comparisons. Thus it remains unclear whether BSPs share a genetic diathesis with BD.

3. Neurobiological Markers

Imaging studies in BD have consistently found aberrant structure/functioning in frontal regions, such as the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) [16].

Additionally, limbic areas such as the amygdala (AMY), insula and hippocampus/parahippocampal gyrus (PHG), and striatal structures such as the caudate, putamen and ventral striatum (VS), have emerged as areas with a potential role in the pathogenesis of BD. EEG markers of increased reward sensitivity are also reported in BDs [17]. Thus structural and functional changes in regions involved in emotional processing/regulation and reward processing are believed to be neurobiological contributors to BD [16,19]. The following sections review imaging and EEG studies in BSPs, with attention to regions and measures involved in emotional and reward processing.

3.1. Structural Markers

BD is associated with structural changes in frontal and limbic areas. In addition to global grey matter loss and enlarged lateral ventricles [47], meta-analyses have found grey matter reductions in specific regions such as the dorsomedial PFC, ventromedial PFC and insula [47-49]. Cortical thinning in frontal and temporal regions similar to what is seen in BDI, as well as decreased PFC volumes, have also been reported in BDII, although these changes appear to be less pronounced than what is seen in BDI [50] [51]. Importantly, however, meta-analyses have found that MDD is also characterized by similar reductions in prefrontal, insular and limbic regions [47-49], making it unclear the degree to which such volumetric changes can be used to distinguish between the two.

Some potential differences in striatal and limbic volumes between BD and MDD have emerged. Meta-analyses of structural studies comparing MDD and BD found the former to have smaller hippocampi, and BD to have larger basal ganglia and thalamus volumes

compared to MDD and healthy participants [47-49]. This suggests that subcortical volumes may be a potential marker distinguishing BD and MDD. However, mega-analysis of BD imaging studies found decreased, rather than increased, hippocampi, amygdala and thalamic volumes compared to healthy participants [52]. Medication, particularly lithium and antipsychotic, use has been associated with increased total grey matter and subcortical volumes, and may account for the enlarged subcortical volumes observed in BD [52,53]. Interestingly, some studies have found that subcortical volumes may be a differentiating feature of BD subgroups. One study reported larger left putamen volumes in BDII compared to BDI [54]. Another study comparing patients with cyclothymia, BDII and BDI found that the cyclothymia group had reduced putamen and thalamic volumes compared to BDI and healthy participants. However, BDI patients in this sample were all on mood stabilizers and/or antipsychotics, both of which could potentially enlarge basal ganglia volumes [55].

Widespread white matter abnormalities are also present in BD and MDD. Deep white matter hyperintensities (WMH) is one of the most commonly replicated neuroimaging findings in BD [56]. Multiple meta-analyses have reported decreased fractional anistotrophy (FA – a measure of the organization of white matter tracts) in the cingulate cortex and PHG of patients with BD [57,58], as well as lower white matter volumes in the inferior longitudinal fasciculus and superior corona radiata [48]. White matter abnormalities are also seen in MDD, with decreased FA in the corpus callosum, frontal lobes, and anterior limb of the internal capsule [59]. However, WM changes may be more marked in BD compared to MDD, with higher numbers of deep WMH, smaller

corpus callosum volumes, and decreased FA in the posterior cingulum reported in meta-analyses of comparative studies [49,59].

3.1.1. BSPs

Few studies have specifically examined volumetric changes in BSPs. One study of 30 adolescents found that those with subthreshold BD (defined as a distinct period of abnormally elevated, expansive or irritable mood associated with one or more hypo/manic symptoms, but below criteria threshold in number and duration of symptoms) had significantly decreased left anterior cingulate volumes compared to healthy age matched controls. They also showed lower FA in the superior and inferior longitudinal fasciculi, corpus callosum, and cingulum [60]. Similarly, young, medication naive BDII and BD-NOS (defined via DSM-IV-TR criteria) patients displayed decreased FA in the corpus callosum and widespread white matter tracts compared to healthy controls. No significant differences were found in FA or grey matter volumes between BDII and BD-NOS [61].

One study investigated volumetric differences associated with cyclothymic temperament in healthy participants, and found that higher cyclothymic scores were associated with larger grey matter volume of the left middle frontal gyrus. The largest volumes were found in those having both high cyclothymic and hyperthymic scores [62].

3.1.2. Summary

Grey and white matter changes in frontal and subcortical regions are seen in BD and MDD, and while there is some evidence that BD and MDD may differ in subcortical volumes, this is not supported in all studies and may be confounded by medication

effects. Thus, while the few studies of volumetric abnormalities in BSPs report altered frontal volumes and widespread white matter alterations, this appears to be a finding that is non-specific to affective disorders in general.

3.2. Functional Markers

3.2.1. Emotional processing and regulation

Emotional dysregulation is a core feature of BD. Overactivation of subcortical/limbic structures involved in emotional processing, including the AMY, PHG and basal ganglia, is consistently seen (Table 3) [16,63] [64]. BD is also characterized by decreased activity in the dlPFC, vlPFC, and ACC, as well as dysfunctional connectivity between prefrontal and limbic regions [65]. This pattern is seen both in response to emotional stimuli and while completing cognitive tasks, indicating a lack of top-down cognitive control even in non-emotional contexts [64]. BDII appears to be characterized by similar functional abnormalities, with a resting state FDG-PET study finding that both euthymic BDI and BDII showed reduced glucose uptake in dlPFC, ACC, insula and striatum, and increased uptake in the left PHG, compared to healthy participants. These abnormalities, however, were significantly more pronounced in the BDI group [66]. Euthymic BDII patients also demonstrate greater activity in the dlPFC, amygdala and accumbens in response to negative distractors during an emotional regulation task compared to healthy participants [67].

These findings are not specific to BD, as MDD is associated with a similar pattern of brain activation [63]. However, brain activation in response to positive stimuli may differentiate BD from MDD [16]. MDD studies have consistently reported that limbic

activity is decreased in response to positive stimuli [68]. Conversely, multiple studies have found increased limbic/striatal activation in response to positive stimuli in BDI [69], and a meta-analysis of fMRI studies found significantly increased limbic/striatal activation to positive stimuli in BD compared to MDD [63]. This pattern of activation has been detected across all mood states in BD - although some studies have reported no or decreased activation in remitted and depressed BD - and is seen in unaffected first degree relatives [70]. This pattern has also been reported in individual studies of BDII patients, with euthymic BDII patients showing increased AMY response to positive distractors compared to healthy participants [67]. BDII however showed greater negative functional connectivity between the dlPFC and AMY, suggesting that BDII patients are better able to engage emotional regulation strategies in response to positive stimuli compared to BDI.

3.2.1.1. BSPs

Though again few in number, imaging studies of BSPs broadly indicate dysfunction in frontal and subcortical regions. In a resting state comparison of MDD patients scoring high versus low on the Hypomania Checklist (a screening tool for lifetime hypomanic symptomatology), differences in regional homogeneity were found in the superior frontal and middle temporal cortices between the two groups [71]. Two studies also associated dimensional measures of bipolarity to changes in striatal/limbic activation and connectivity. The bipolarity index (a dimensional measure of bipolar traits) was correlated with increased putamen/insula resting state activity in a mixed sample of youth with BDI and MDD diagnoses [72]. In adolescents with diagnoses of ADHD,

bipolar spectrum (DSM-IV-TR defined BDI, BDII or BD-NOS), MDD, and anxiety, increased mania scores across all groups was associated with decreased connectivity between the amygdala and insula/putamen [73]. Contrastingly, in a study using the same population as above, no association was found between amygdala-vlPFC connectivity and dimensional measures of mania in youth with ADHD and bipolar spectrum diagnoses [74].

Functional studies have found some evidence for increased response to positive stimuli in BSPs. In comparison to healthy controls, MDD patients demonstrated increased amygdala activation in response to angry and happy faces; activation in response to happy faces was specifically correlated with level of lifetime subthreshold manic psychopathology [75]. However, in a study involving BDI and BD-NOS (defined as elated/irritable mood with at least two associated symptoms, associated with a clear change in functioning and present for at least 4 cumulative life time days, 4 hours a day) youth, the latter group did not display altered activation to positive stimuli. Rather, while BDI patients displayed higher amygdala, VMPFC, and DLPFC activation to happy faces, the BD-NOS group showed reduced activation in these regions in response to neutral faces compared to BDI and healthy participants [76]. BD-NOS did have higher vmPFC activity at trend level significance, and greater VMPFC-DLPFC coupling, in response to happy faces, which the authors postulated represented increased recruitment of cognitive control regions.

Imaging studies of emotional processing in relation to cyclothymic and hypomanic traits in non-clinical samples have yielded varying results. In a study of first degree unaffected relatives of BDI patients and healthy controls, abnormal amygdala activation while

completing a cognitive task was specific to unaffected relatives. However, scores of cyclothymic temperament were negatively associated with vlPFC recruitment regardless of group. This suggests that, consistent with meta-analyses in first degree BD relatives, limbic overactivation may represent a genetic vulnerability factor to BD, while additional frontal hypoactivation is seen in those displaying possible subclinical symptoms regardless of genetic risk [77]. However, another study did not find any significant differences in frontal activation in a non-clinical group with high hypomanic personality traits compared to healthy participants when completing a cognitive task in the presence of emotional distractors [78].

Two studies associated cyclothymic temperament scores in non-clinical samples with decreased lingual gyrus activation during a task involving esthetic judgement of paintings, and increased activation during a working memory task [79,80]. Lingual gyrus activity was previously found to be increased while completing a cognitive task in unaffected BD relatives and decreased in meta-analyses of BD patients completing cognitive tasks [64,81]. Cyclothymic temperament was also associated with greater glucose metabolism in the right superior parietal lobule in the resting state, and hyperthymic temperament with changes in left inferior orbitofrontal cortex activation (both increased and decreased activation reported in two studies) in response to a brightness judgement task [62,82,83]

3.2.1.2. Summary

Limbic hyperactivation and frontal hypoactivation is characteristic of affective disorders. Increased activation in response to positive stimuli may differentiate BD and MDD; these changes may represent an underlying vulnerability towards mood instability and

pathological mood elevation. One study associated life time subsyndromal hypomanic pathology in MDD to greater amygdala activation to positive stimuli, although another found that BD-NOS youth had reduced amygdala activation to neutral faces, rather than increased activation to happy faces. Cyclothymic temperament may be associated with frontal hypo-activity to emotional stimuli, but another study did not find any differences in participants with high hypomanic personality traits in engagement of frontal regions. Overall, though response to positive stimuli may represent a useful biological marker in investigating the affective spectrum, results in BSPs are inconsistent and further studies are required.

3.2.2. Reward sensitivity and processing

Abnormalities in reward processing is a replicated finding in BD [84]. The 'reward hypersensitivity model' of BD postulates that the neurobiological system mediating goal directed behavior is overactivated by possible reward [84], leading to increased mood, energy and goal directed activity. The resulting elevated mood may cause subsequent rewarding outcomes to be perceived as being of even higher value, resulting in a 'positive feedback loop' wherein rewarding outcomes drive mood elevation and vice versa [85]. Conversely, BD patients may experience an aberrant downregulation of the reward system in response to failures, leading to the development of anhedonia and amotivation [84]. MDD patients, however, show a reduced sensitivity to reward independent of mood state [17]. Thus, imbalances in reward processing and sensitivity may be an important mediator of mood instability in BD, and may be a distinguishing feature between MDD and BD.

Functional imaging studies of BD in euthymic and manic states have found over activity in structures mediating reward anticipation and encoding reward value [70], including the VS, vlPFC and OFC [16]. BD also demonstrates increased connectivity between VS and OFC, ACC, insula and ventral tegmental area [86], as well as decreased prefrontal regulation of response to reward [87]. Studies in BDII have also found increased resting state metabolism in the VS and OFC, and higher VS activity during reward anticipation [54,88]. Indeed, one study found that VS activity during reward anticipation was higher in BDII patients compared to BDI [54]. EEG has also been used to assess reward processing, as increased reward sensitivity has been associated with increased left frontal cortical activation and attenuated feedback related negativity (FN) [70]. A mixed sample of patients with cyclothymia and BDII displayed greater relative left frontal cortical activation on EEG in preparation for difficult/high reward trials vs healthy participants [89]. Elevated relative left frontal EEG at baseline is also associated with a greater likelihood of cyclothymia or BDII converting to BDI over 5 years [70]. Remitted and symptomatic patients with MDD, conversely, consistently show decreased activation in reward related subcortical and frontal regions [17].

Consistent with the reward hypersensitivity model– which postulates excessive downregulation of the reward system in response to loss -– depression in BD may be characterized by a greater attenuation of reward processing compared to unipolar depression [17]. Decreased activation in VS, basal ganglia and prefrontal areas in reward tasks is seen in BD depression compared to MDD and healthy controls, although one study still detected increased vlPFC activity to reward in BD depression

[90,91]. Additionally, depression symptom severity has been inversely correlated with VS, ACC, and OFC activation in BD depression [86,92].

3.2.2.1. BSPs

Some, but not all, studies have found BSPs to be associated with increased activity in reward processing areas. Healthy participants with high scores on the Hypomania Personality Scale (HPS) had increased VS activity when anticipating reward, and increased insula activation in response to expected rewards [93]. Similarly, increased structural connectivity between the VS and OFC/amygdala was seen in community participants who scored high on the HPS [94]. In a group of 85 adolescents with diagnoses of ADHD, disruptive behavior disorders and/or bipolar spectrum disorders (encompassing DSM-IV defined BDI, BDII, cyclothymic disorder or BD-NOS), increased mania scores were dimensionally associated with increased left mPFC activity during a reward task regardless of diagnosis [95]. Similarly, non-clinical samples displaying high hypomanic traits showed increased left frontal cortical activation in response to an anger-evoking event [96], as well as attenuated FN in a reward task [97]. However, one study of 20 euthymic, antipsychotic and mood stabilizer naive BDII/BD NOS (not meeting symptom criteria for previous mood episodes) adults found decreased ventral/dorsal striatum activity during reward anticipation compared to healthy participants [98].

3.2.2.2. Summary

BD appears to be distinct from MDD in hypersensitivity to reward in euthymia and mania, and possibly decreased reward sensitivity in acute depression (Table 4). This

may be an important mediator of mood instability in BD, and is associated with increased prospective risk of developing more severe BD pathology. Consistent with this, higher levels of hypomanic traits in non-clinical samples have been associated with higher sensitivity to reward, as demonstrated via neuroimaging and EEG measures. However, one study reported decreased striatal activation in a euthymic BDII/BD-NOS sample. While measures of increased reward sensitivity may be promising biological markers in BSPs, further studies are needed.

4. Cognitive Markers

Cognitive deficits are a well replicated finding in BD, with widespread impairments in multiple cognitive domains detectable in acutely symptomatic and euthymic states [18]. It appears that BDI and BDII demonstrate a similar degree of impairment; a meta-analysis comparing cognition between BD subgroups found BDI to be associated with poorer global cognition, verbal memory, processing speed and executive functioning compared to BDII, but with small effect sizes for differences between the two groups [99]. Another meta-analysis of executive functioning in euthymic BDI and BDII found both to display a similar degree of impairment when compared to healthy controls [100]. MDD is also characterized by cognitive deficits, and a meta-analysis of comparative studies (including both BDI and II subtypes) found that both are similarly impaired when depressed. BD patients, however, demonstrated worse verbal memory than MDD in euthymia, suggesting that trait verbal memory impairment might be a distinguishing feature of BD [101]. Individual studies reporting on exclusive samples of BDII however are less clear on how BDII might be distinguished from MDD on the basis of cognition. One study found that depressed BDII patients displayed worse performance in verbal

memory and executive functioning compared to MDD [102], while another found that depressed BDII patients performed equally to MDD in cognitive tests [103]. Two studies using unmedicated patients, however, found that depressed BDII patients actually had better cognitive performance than MDD [104,105]. Another large study of participants with a family history of BDI and II found that, after controlling for childhood trauma, participants with diagnoses of BDII and MDD did not differ significantly from unaffected relatives in cognitive performance. Participants with BDI, however, remained significantly impaired in verbal memory after controlling for childhood trauma and medication use, suggesting that verbal memory deficits may be specific to BDI [106].

4.1. BSPs

One study of cognition in BSPs found that these patients demonstrate similar cognitive performance to patients with BDII. Lin et al. compared currently depressed patients with BDI, BDII, MDD and BSP, as defined by Akiskal and Pinto criteria (see Table 1). BSP patients in this study met criteria for 'bipolar II ½' (MDEs with subthreshold hypomanias), 'bipolar III' (antidepressant induced hypomanias) and 'bipolar IV' (MDEs superimposed on hyperthymic temperament). The BSP group performed equally to BDII and better than BDI in set shifting and visuospatial memory [107]. Another study also reported that BSP adolescents showed similar cognitive deficits as traditionally defined BD. In this study, youth with BDI, BDII, and BD-NOS (defined as a distinct period of abnormally elevated, expansive or irritable mood plus at least 2 associated DSM-IV manic symptoms and clear change in functioning, with symptoms present for a

significant part of the day for at least 4 cumulative lifetime days) performed cognitive testing. All BD subtypes showed impairments in sustained attention and processing of emotional words compared to healthy controls [108]. However, the BDI/II group (largely comprised of BDI) had additional executive functioning deficits. Another study found that high risk youths (aged 8-28) with subthreshold symptoms showed greater cognitive deficits than their high risk counterparts without subthreshold symptoms. Children with a BD parent and displaying subthreshold symptoms (defined as ≥2 hypomania symptoms lasting ≥4 days but not meeting DSM-IV hypomanic criteria, and/or ≥2 depressive episodes lasting for at least 1 week but not meeting DSM-IV MDE criteria, and/or attenuated psychotic symptoms, or >2 hyperactivity/impulsivity symptoms of ADHD) had additional deficits in verbal learning/memory, working memory, visuospatial memory, and cognitive planning compared to what was seen in high risk children without subthreshold symptoms [109]. Children with subthreshold symptoms but no family history, however, did not show any deficits, although this sample was small (n=17).

There have been mixed results regarding cognition in BSPs compared to MDD. Smith et al. (2006) recruited 63 remitted patients with recurrent MDD, 21 of whom met bipolar spectrum criteria as defined by Ghaemi et al (2001) (see Table 1) [110]. This group scored significantly lower than healthy controls and 'pure' MDD on executive functioning and verbal memory. However, Lin et al. found that currently depressed BSP patients (as per Akiskal and Pinto criteria) performed better than MDD in processing speed, visuospatial memory and verbal working memory [107].A recent study by Wu et al. (2017) used machine learning to determine distinct 'phenotypes' within a mixed sample

of BDI, BDII and DSM-IV defined BD-NOS based on neurocognitive performance [111]. Phenotype I was characterized by reduced response accuracy in executive functioning and response inhibition tests, as well as greater negative affective bias. Phenotype II had slower reaction times but improved accuracy and problem solving, and had distinct white matter abnormalities. Notably, patients with BDI, II and NOS were equally distributed between these two phenotypes.

4.2. Summary

Cognitive dysfunction is a core feature of BD, and verbal memory may be an endophenotype of the disorder. Studies that have examined cognition in BSPs have found evidence for impairment compared to healthy controls which is lesser in magnitude compared to BDI. It is unclear how, if at all, BSPs differ from MDD in cognitive performance, with one study finding that patients with BSPs performed better in verbal memory than patients with MDD. Notably, one study which used neurocognitive performance to create subgroups in a mixed sample of BDI/II/NOS patient did not find any correspondence between diagnostic category and objective cognitive/neurobiological markers.

5. **Peripheral Markers**

5.1. Inflammatory

Increases in peripheral inflammatory markers (PIMs) are seen across all mood states in BD, and may contribute to adverse neurobiological changes and the burden of physical comorbidities [112]. Meta-analyses have found elevations in multiple inflammatory and anti-inflammatory cytokines such as IL-2, IL-4, IL-6 TNF-alpha, IL 10, as well as soluble

TNF receptor-1 (sTNFR1), soluble IL-6 receptor (sIL6-R), soluble IL-2 receptor (sIL-2R) and IL1 receptor antagonist (IL-1Ra) [112].

MDD has also been associated with increased PIMs, particularly IL-6, TNF-alpha and sIL-2R [113,114] . Although there are few direct comparisons, one study found euthymic BD to have significantly higher levels of PIMs compared to MDD, after controlling for smoking and BMI, suggesting that BDI is associated with higher levels of systemic inflammation [115]. Similarly, although still displaying higher PIMs than healthy participants, BDII had lower levels of some inflammatory markers compared to BDI [116].

5.1.1. BSPs

Increased PIMs have also been detected in BSPs, but results have been mixed in terms of how these findings compare to other affective disorders. One study found that patients (mood state not specified) with history of short duration hypomania did not differ from BDII in the 4 inflammatory markers measured (TNF-a, CRP, TGF-B1 and IL-8). Both groups were significantly elevated in these markers compared to healthy participants, and both displayed lower levels of IL-8 compared to BDI [117]. However, another study found that currently depressed patients with history of short duration hypomania had significantly lower levels of IL-6, and higher levels of IL-1B, compared to depressed BDII [118]. After 12 weeks of valproic acid treatment, the subthreshold BD group had a greater decrease in TGF-B1 associated with treatment response. Though both subthreshold BD and BDII showed the same level of symptomatic improvement, the authors postulated that it may be more difficult for BDII patients to correct the

underlying imbalance between pro- and anti-inflammatory cytokines. Conversely, another study found no differences in inflammatory markers between depressed men with and without subthreshold manic symptoms [119]. A study in adolescents also did not find differences in TNF-a, IL-6 or CRP levels between DSM-IV defined BDI, BDII and BD-NOS subtypes; rather, levels were associated with variables such as subthreshold mood symptoms, history of self-harm, family history of suicide and substance use [120].

5.1.2. Summary

The extant evidence finds that BSPs are associated with increased systemic inflammation. However, PIMs are non-specifically associated with affective disorders, and results are heterogenous in terms of how PIMs in BSPs compare to other BD subtypes and MDD. Importantly, one study found PIMs to be associated with clinical factors, suggesting that inflammatory marker levels may be more related to variables which supersede diagnostic categories.

5.2. BDNF

Decreased BDNF levels are seen in MD and BD. This is apparent in both when acutely symptomatic, but appears to normalize in euthymic states [121]. One study found that BDNF levels were lower in BDI depression compared to MDD, and proposed a cut-off level which could discriminate between BD and MDD with 88% sensitivity and 90% specificity [122]. However, another study found no significant differences in BDNF between euthymic MDD, BDI, BDII and currently depressed MDD [123]. The stage of illness appears to be related to BDNF levels in BD, with first episode patients having no

alteration in BDNF levels while those that had multiple mood episodes had significantly lower levels [124]. Further, age related decreases in BDNF levels appear to be more pronounced in BD I patients relative to healthy comparators [125].

5.2.1. BSPs

Only two studies, both by Wang et al. and described above, assessed BDNF levels in BSPs. In the first, larger study, there were no differences in BDNF levels (mood state not specified) between BDI, BDII, subthreshold BD (defined by presence of subthreshold hypomania) and healthy participant groups [117]. However, in a second treatment study, Wang et al. (2016b) found that depressed subthreshold BD was associated with lower levels of BDNF compared to BDII [118].

6. Expert Opinion

The delineation of diagnostic categories in psychiatry is moving towards the incorporation of biological and objective indices. As subthreshold/subsyndromal presentations of BD are increasingly recognized as an area of clinical uncertainty, we examined the evidence for biological and objective markers in these proposed BSPs. In particular, we wished to ascertain whether objective markers can establish that such presentations share similar underlying pathophysiologic mechanisms with traditionally defined BD, and therefore may potentially benefit from a similar treatment approach. We find that there has thus far been limited examination of biomarkers in BSPs, and results are inconclusive. One reason for this is the variability in defining BSPs in studies conducted to date. In non-clinical samples, various scales were used to quantify temperaments or 'hypomanic' proneness/traits. In clinical samples, a minority of studies

used previously defined criteria for BSPs, while most set their own thresholds in terms of time and/or symptom number and severity. Some studies also used mixed populations of BDI, II and/or BSPs, included patients in different mood states and who differed in medication status or length of illness. Studies using adolescent samples were also included, which may have been another source of heterogeneity.

Another, more fundamental contributor to inconclusive results is the existing lack of unique markers of bipolarity. The literature is inconsistent in terms of genetic, brain structural, cognitive and peripheral markers which may distinguish traditionally defined BD and MDD. Thus, while most studies of BSPs report some abnormalities in these measures, at this time these can only be taken as evidence of general affective pathology and cannot establish a shared diathesis with traditionally defined BD. Possible exceptions are markers of hypersensitivity to positive stimuli and dysfunctional reward processing. There is reasonable evidence that MDD and BD differ on these two measures; though results are not consistent, some studies have also reported that populations with putative BSPs display markers in these domains consistent with BD (Figure 2). The presence of these features may have treatment implications. Hypersensitivity to positive stimuli and rewarding outcomes is hypothesized to contribute to mood instability in BD, and antidepressants differentially modulate these processes [84]. Agents which increase norepinephrine and/or dopamine activity, such as reboxetine, amisulpride and bupropion, increase frontostriatal response to reward in healthy and clinical populations, and increase memory/recognition for positive stimuli [126-129]. SSRIs, conversely, have been found to decrease VS response to pleasurable experiences [126]. Clinical studies have found that stimulants and

noradrenergic antidepressants are associated with increased risk of treatment emergent affective switching when used in BD depression [130]. Increased sensitivity to reward and positive stimuli may be the pathophysiological mechanism by which these agents destabilize mood in BD. Better understanding of whether antidepressants exacerbate, or mood stabilizers normalize, these abnormalities in BSPs may help formulate safer and more effective treatment plans.

It remains unclear how data regarding genetic, peripheral inflammatory, neurotrophic and cognitive markers may contribute to our understanding of BSPs, as markers which clearly distinguish MDD and BD have not yet been established. This signals the need to pursue avenues of investigation which produce BD specific markers. For example, while serum inflammatory cytokine levels may be non-specific and confounded by environmental factors, more recent studies have suggested that monocyte inflammatory gene expression may produce a specific signature for BD [131]. Other biological markers investigated in BD, such as markers of oxidative stress and mitochondrial dysfunction, as well as epigenetic changes, have not been examined in BSPs. Imaging modalities which examine neurotransmitter and metabolite quantity and functioning, such as PET and MRS, would also provide useful information in characterizing BSPs. There is some, albeit highly inconsistent, literature that unipolar and bipolar disorders may be distinguished by circadian clock genes, which warrant further investigation. Additionally, further examination of objective sleep markers via actigraphy may be useful [84,132]

Lastly, focusing solely on an affective spectrum may falsely exclude other psychiatric disorders which are related to BD [19]. Further studies may also focus on identifying

markers associated with pertinent symptom dimensions, such as impulsivity and mood lability, to further understand the relationship between BD and other disorders which share phenotypic similarities, such as borderline personality disorder and ADHD [19].

6.1. Five-year view

As the field moves away from categorical diagnoses, more work identifying the biological correlates of what are now labeled 'subthreshold' bipolar disorders is required. There are currently studies underway using intermediate phenotypes and candidate biomarkers to generate subgroups within the psychosis spectrum and depression [2], and studies using this 'bottom-up' paradigm in the affective spectrum are needed. Further investigation of reward and emotional processing, may help identify distinct markers which can be integrated to characterize affective presentations on the basis of pathophysiologic similarities. Controlled treatment trials investigating the efficacy and impact of antidepressants versus mood stabilizing medications in BSPs would greatly aid our understanding of how best to treat this patient population.

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Table 1: Proposed criteria for bipolar spectrum presentations

Table 2: Proposed genetic markers of BD

Table 2 footnotes: Bolded indicates evidence from multiple meta-analyses

Table 3: Studies of emotional processing in BSPs

Table 3 footnotes: Summary of functional neuroimaging studies examining regions involved in emotional processing/regulation in BSPs. Each arrow represents one study; large arrows indicate results from meta-analysis or from more than three studies. Grey arrows indicate studies which specifically reported results for brain activation in response to positive stimuli; black indicates negative, neutral (e.g. cognitive task or resting state) or unspecified valence. 'Dimensional' row specifies association between continuous measures of bipolarity/mania and brain activity.

*increased vmPFC activity in response to positive stimuli at trend level significance.

ACC, anterior cingulate cortex; AMY, amygdala; dlPFC, dorsolateral prefrontal cortex; PHG, parahippocampal gyrus; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex

Table 4: Studies of reward processing in BSPs

Table 4 footnotes: Summary of functional neuroimaging and EEG studies examining reward processing in BSPs. Each arrow represents one study; large arrows indicate results from meta-analysis or from more than three studies. Grey arrows indicate studies which used acutely depressed BD patients. 'Dimensional' row specifies association between continuous measures of bipolarity/mania and markers of reward processing.

*Indicative of increased reward processing

ACC, anterior cingulate cortex; AMY, amygdala; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex; VS, ventral striatum

Figure 1: The bipolar spectrum

Figure 1 footnotes: Visual summary of the proposed bipolar spectrum, which spans from subthreshold depression to bipolar I disorder. Recurrent MDDs, with the features listed, are proposed to be more closely related to BD than single major depressive episodes. Cyclothymic/hyperthymic temperaments and genetic loading for BD are proposed vulnerability factors for BD, which may be present in non-clinical populations (i.e. within the 'subclinical' range of symptom presentations), or which may underlie clinically significant mood disturbances.

Figure 2: Proposed markers in bipolar spectrum presentations

Figure 2 footnotes: Previous functional studies have reported decreased sensitivity to reward and positive stimuli in major depressive disorder, and increased sensitivity to reward and positive stimuli in bipolar I and II disorders. Some studies have reported similar neurobiological markers in subthreshold presentations of BD. It is possible that increased response to reward and positive stimuli may be the mechanism by which antidepressants contribute to further mood destabilization in those with an underlying bipolar diathesis, while mood stabilizers attenuate abnormalities in these measures. Thus, markers of increased sensitivity to reward and positive stimuli may have utility in generating diagnostic subtypes within the affective spectrum, and guide further investigation of effective pharmacological treatments.

Table 1: Proposed criteria for bipolar spectrum presentations

Ghaemi, Ko and Goodwin (2002) [7]	
A. At least one major depressive episode	
B. No spontaneous hypomanic/manic episodes	
C. Either of the following, plus >2 from criteria D/both of the following plus >1 from D/ none of the following and ≥6 from D 1. Family history of BD in first degree relative 2. Antidepressant induced mania/hypomania	
D. 1. Hyperthymic personality at baseline 2. Recurrent major depressive episodes (>3) 3. Brief major depressive episodes (<3 months) 4. Atypical depressive symptoms 5. Psychotic major depressive episodes 6. Age of onset <25 years old 7. Post-partum depression 8. Antidepressant "wear off" 9. Non response to ≥ 3 antidepressant treatments	
Akiskal and Pinto (1999) [13]	
Bipolar I: Mania Bipolar I1/2: Depression with protracted hypomania Bipolar II: Depression with hypomania Bipolar II1/2: Depression with cyclothymic temperament Bipolar III: Antidepressant induced hypomania Bipolar III1/2: bipolarity associated with stimulant abuse Bipolar IV: MDEs superimposed on hyperthymic temperament	
Angst (2003) [8]	
Hypomanic syndrome: 1. euphoria, irritability or overactivity 2. subsequent problems or comments that something must be wrong 3. presence of at least 3/7 associated signs/symptoms	
Hypomanic symptoms: above, but without functional consequences	
BDI: mania plus MDEs	
BDII: Hypomanic syndrome or symptoms plus MDEs	
Minor BD: dysthymia, minor depression, recurrent brief depressions with hypomanic syndrome or symptoms	
DSM-IV TR (2000) [133]	
Bipolar disorder not otherwise specified	Disorders with bipolar features that do not meet criteria for any specific bipolar disorder (i.e. bipolar I, bipolar II or cyclothymic disorder). *Includes very rapid alterations between manic and depressive symptoms that meet symptom threshold criteria but not duration criteria, recurrent hypomanic episodes without intercurrent depressive symptoms, hypomanic episodes with chronic depressive symptoms too infrequent to qualify for diagnosis of cyclothymic disorder.*
DSM-5 (2013) [5]	
Other specified bipolar and related disorders	1. Short duration hypomanic episodes and MDEs 2. Hypomanic episodes with insufficient symptoms and MDEs 3. Hypomanic episode without prior MDE 4. Short-duration cyclothymia
Unspecified bipolar and related disorders	Symptoms characteristic of a bipolar and related disorder causing clinically significant distress or impairment, but not meeting full criteria for of the disorders in the bipolar and related disorders diagnostic class.

Table 2: Proposed genetic markers of BD

Gene	Gene function	Polymorphism	Associated disorders
Neuronal functioning/structure			
ANK3 [22-24][134]	Encodes ankyrin proteins, connecting membrane proteins to underlying cytoskeleton. Involved in cell motility, activation and contact; modulates neuronal sodium channels	rs10994336 rs1938526	BD
BDNF Val66Met [24]	Encodes brain derived neurotrophic factor.	Val allele; increased synaptic plasticity and growth	BD, SCZ
CACNA1C [23][25][31]	Encodes a-1 subunit of L-type calcium channels; regulates dendritic calcium influx	rs1006737	BD, SCZ, recurrent MDD
DISC1 [135,136]	Multifunctioning scaffolding protein; protein interaction partners involved in neuronal migration, neurosignalling and synaptic functioning	Multiple haplotypes at 3' and 5' ends	BD, SCZ, recurrent MDD
NCAN [24][137,138]	Encodes neurocan, extracellular matrix glycoprotein involved in cell adhesion and migration; highly expressed in amygdala and hippocampus	rs1064395	BD, SCZ, MDD
ODZ4 [26]	Encodes teneurins, involved in cell surface signaling, neuronal pathfinding and myelination	rs12576775	BD
TRANK1 [139]	Encodes tetratricopeptide repeat and ankyrin repeat containing 1 protein	rs9834970	BD, SCZ
Neurotransmitter regulation			
MAOA [24]	Encodes monoamine oxidase A, which degrades dopamine, norepinephrine and serotonin	5 and 6 CA dinucleotide repeat alleles	BD
DRD4 [24]	Encodes D4 dopamine receptor, G-protein coupled receptor which inhibits adenylyl cyclase	2-repeat of 48 bp VNTR region; reduced coupling of dopamine receptor to adenylate cyclase and reduction in dopamine functioning	BD, MDD
COMT Val158Met [24]	Catechol-O-methyl transferase enzyme, inactivates extraneuronal dopamine	Met allele; 3-4X reduction in COMT activity	BD, AD
5-HTTLPR [24]	Repeat polymorphic region in SLC6A4, gene that codes for serotonin transporter	'Short' allele; decreased serotonin reuptake and expression.	BD, MDD
DAOA [24]	Encodes protein responsible for degrading D-serine, an NMDA type receptor activator. Also involved in dopamine turnover	T variant; disturbed dopamine turnover	BD, SCZ
Circadian rhythm			
CLOCK [34]	Involved in regulation of diurnal pattern	Rs1801260 3111 T to C SNP in 3'-flanking region; associated with	BD, SCZ

		delayed sleep preference	

Bolded indicates evidence from multiple meta-analyses

Table 3: Studies of emotional processing in BSPs

	MDD	Bipolar spectrum		BDII	BDI
		Non-clinical sample	Clinical sample		
Subcortical/ limbic	AMY		AMY	AMY	AMY
	insula				
	PHG				PHG
	striatum			striatum	striatum
		lingual gyrus			lingual gyrus
Frontal	ACC				ACC
		OFC	vmPFC*		
	dlPFC		dlPFC	dlPFC	dlPFC
		vlPFC		vlPFC	vlPFC
Dimensional	putamen/insula resting state activity amygdala-putamen/insula connectivity				

Summary of functional neuroimaging studies examining regions involved in emotional processing/regulation in BSPs. Each arrow represents one study; large arrows indicate results from meta-analysis or from more than three studies. Grey arrows indicate studies which specifically reported results for brain activation in response to positive stimuli; black indicates negative, neutral (e.g. cognitive task or resting state) or unspecified valence. 'Dimensional' row specifies association between continuous measures of bipolarity/mania and brain activity.

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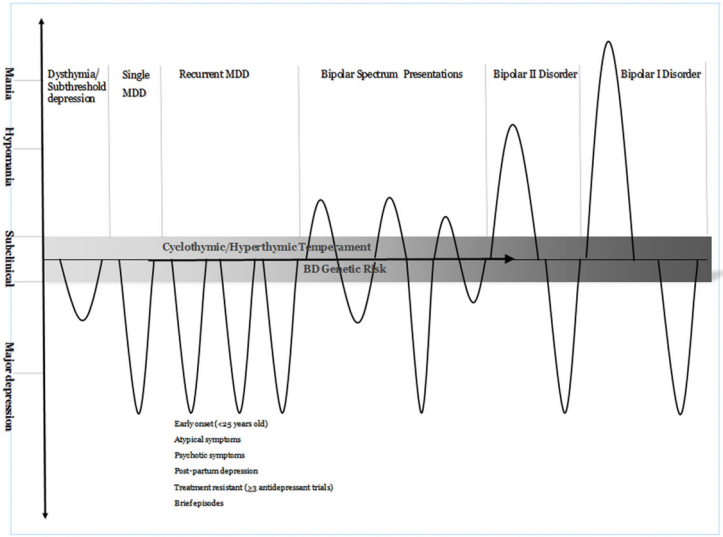
Table 4: Studies of reward processing in BSPs

	MDD	Bipolar spectrum		BDII	BDI
		Non-clinical sample	Clinical sample		
Subcortical/limbic	⬇ VS	↑ VS	↓ VS	↑↑ VS	⬆⬇ VS
	⬇ insula	↑ insula			↓ insula
	⬇ thalamus				↓ thalamus
	⬇ caudate/ putamen				↑↓ caudate/ putamen
Frontal	⬇ ACC	↓ *feedback negativity			↓ ACC
				↑↑ OFC	↑↑↓ OFC
					↑↑ vlPFC
	⬇ L>R frontal cortical activation	↑ *L>R frontal cortical activation		↑ *L>R frontal cortical activation	
Dimensional	↑ left mPFC				

Summary of functional neuroimaging and EEG studies examining reward processing in BSPs. Each arrow represents one study; large arrows indicate results from meta-analysis or from more than three studies. Grey arrows indicate studies which used acutely depressed BD patients. 'Dimensional' row specifies association between continuous measures of bipolarity/mania (red) or depression (blue) and markers of reward processing. *Indicative of increased reward processing

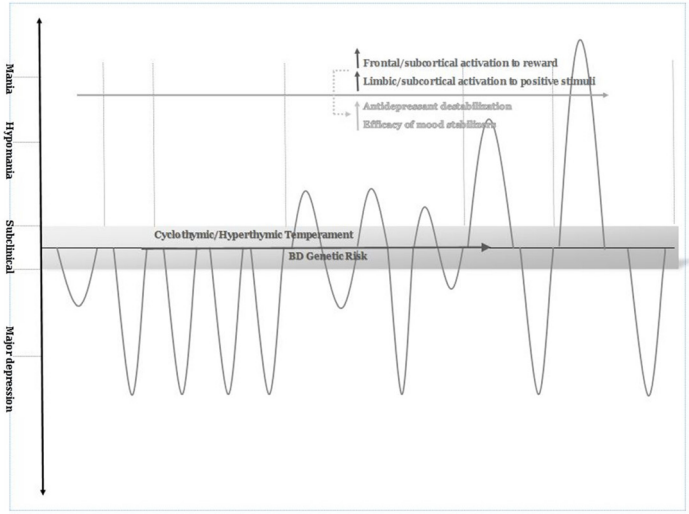
ACC, anterior cingulate cortex; AMY, amygdala; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex; VS, ventral striatum

Figure 1: The bipolar spectrum



Visual summary of the proposed bipolar spectrum, which spans from subthreshold depression to bipolar I disorder. Recurrent MDDs, with the features listed, are proposed to be more closely related to BD than single major depressive episodes. Cyclothymic/hyperthymic temperaments and genetic loading for BD are proposed vulnerability factors for BD, which may be present in non-clinical populations (i.e. within the 'subclinical' range of symptom presentations), or which may underlie clinically significant mood disturbances.

Figure 2: Proposed markers in bipolar spectrum presentations



Previous functional studies have reported decreased sensitivity to reward and positive stimuli in major depressive disorder, and increased sensitivity to reward and positive stimuli in bipolar I and II disorders. Some studies have reported similar neurobiological markers in subthreshold presentations of BD. It is possible that increased response to reward and positive stimuli may be the mechanism by which antidepressants contribute to further mood destabilization in those with an underlying bipolar diathesis, while mood stabilizers attenuate abnormalities in these measures. Thus, markers of increased sensitivity to reward and positive stimuli may have utility in generating diagnostic subtypes within the affective spectrum, and guide further investigation of effective pharmacological treatments.