Physiological Correlates of Bipolar Spectrum Disorders and their Treatment

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Abstract Bipolar spectrum disorders (BSDs) are associated with great personal and socioeconomic burden, with patients often facing a delay in detection, misdiagnosis when detected, and a trial-and-error approach to finding the most appropriate treatment. Therefore, improvement in the assessment and management of patients with BSDs is critical. Should valid physiological measures for BSDs be identified and implemented, significant clinical improvements are likely to be realized. This chapter reviews the physiological correlates of BSDs and treatment,

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and in doing so, examines the neuroimaging, electroencephalogram, and event-related potential, and peripheral physiological correlates that both characterize and differentiate BSDs and their response to treatment. Key correlates of BSDs involve underlying disturbances in prefrontal and limbic network neural activity, early neural processing, and within the autonomic nervous system. These changes appear to be mood-related and can be normalized with treatment. We adopt an "embodied" perspective and propose a novel, working framework that takes into account embodied psychophysiological mechanisms in which the physiological correlates of BSD are integrated. This approach may in time provide the objective physiological measures needed to improve assessment and decision making when treating patients with BSDs. Future research with integrative, multimodal measures is likely to yield potential applications for physiological measures of BSD that correlate closely with diagnosis and treatment.

Keywords Bipolar disorder · Bipolar spectrum disorders · Physiology · Psychophysiology · Treatment · Heart rate and its variability · EEG · FMRI · GSR · Embodied cognition

Contents

1 Introduction

Determining the physiological correlates of psychiatric disorders and assessing the potential clinical utility of physiological measures are major pursuits in biological psychiatry research (Insel et al. 2010, 2013). The impetus for such research is the promise of objective measures for assessment and predicting response to

treatments, which would improve diagnostic validity and inform treatment selection (Insel et al. 2010, 2013). To facilitate this goal, the National Institute of Mental Health has proposed Research Domain Criteria (or RDoC), which provide researchers with a novel framework in which research can be presented (Morris and Cuthbert 2012). In this context, physiological measures provide an important tool through which diagnosis could be improved and treatment options tailored. Currently, the assessment and management of bipolar spectrum disorders (BSDs) often entails misdiagnosis following a significant delay in detection (Hirschfeld et al. 2003; Suppes et al. 2001), the inability to predict course (Crowe et al. 2012; Malhi et al. 2012, 2013), trial and error in treatment selection (Malhi et al. 2009; Sachs 2013), and a failure to implement long-term management strategies (Keck 2006; Malhi et al. 2009). Therefore, improvement in the assessment and treatment of those with BSDs is critical given the great personal (Bonnín et al. 2012; Merikangas et al. 2007) and socioeconomic burden associated with BSDs (Merikangas et al. 2007). Critically, these disorders are associated with the highest risk of suicide of any mental disorder (Nock et al. 2009), highlighting the need for early and accurate detection with improved diagnosis and a more personalized approach to effective treatment. Initiation of successful treatment early in the course of the disorder will undoubtedly reduce morbidity (Baldessarini et al. 2003; Post et al. 2010) and improve treatment outcomes (Berk et al. 2011; Ketter et al. 2006; Malhi 2012). Given the potential for these needs to be met with the translation of physiological measures into clinical practice (Morris and Cuthbert 2012), identification of physiological markers that could be employed in assessment and treatment selection remains an ambitious but worthy goal.

BSDs represent a cluster of disorders characterized by extreme changes in mood (Malhi et al. 2012). Depression, mania, hypomania, and euthymia (periods of remission) are phases of illness that are subjectively experienced by patients, and objectively determined by clinicians (Tohen et al. 2009). These include cyclothymia, Bipolar I disorder, Bipolar II disorder, and Bipolar Disorder Not Elsewhere Classified (NEC) and are partitioned from major depression on the basis of cycling into mood elevation such as (hypo)mania. The spectrum is conceptualized as increasing in severity and burden from Bipolar Disorder NEC, Cyclothymia, Bipolar II Disorder, through to Bipolar I Disorder (Merikangas et al. 2007), but in reality, this does not always hold true. Currently, there are no physiological tests that can be employed to assist with the detection, assessment, and diagnosis of BSDs. The physiological correlates implicated in cognitive and emotional disturbances underlying BSDs and the different phases of illness have thus far been investigated using neuroimaging and peripheral physiology techniques. Studies have revealed disturbances in prefrontal and limbic network neutral activity (see Strakowski et al. 2012), neural activity states and early neural processing (see Degabriele and Lagopoulos 2009), and within the autonomic nervous system (ANS; Gruber et al. 2011; Lee et al. 2012), respectively. Understandably, most studies have considered these neural and autonomic activation characteristics separately. Hence we now consider the neural and autonomic characteristics of BSDs in the context of an embodied (see Craig 2009; Niedenthal 2007; Price et al. 2011) disturbance affecting

both the brain and body so as to develop a novel framework (see Fig. 1) in which the physiological correlates of the disorder can be investigated.

In addition to characterizing the physiological correlates of the BSDs, we further characterize the correlates—or markers—of treatment effect, and predictors of response to treatment. Patients with BSDs are typically prescribed pharmacological treatment (including lithium, antipsychotics [e.g., olanzapine, risperidone, quetiapine], and anticonvulsants [e.g., valproate, carbazepine lamotrigine)] either alone or in combination) but first-line treatment is often ineffective (Malhi et al. 2009) reflecting the fact that information gained from clinical assessment alone is insufficient for planning and implementing treatment. If physiological measures could anticipate treatment efficacy, then the trial and error involved in first-line treatment strategies may be diminished or subsided altogether. Therefore, the need to identify potential physiological markers of BSDs and to ascertain their clinical utility is imperative.

2 Measuring the Physiological Correlates of Bipolar Spectrum Disorders

Studies on BSDs have most often utilized neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) and findings from studies using these neuroimaging methods have been largely consistent (Strakowski et al. 2005). The next most employed measures have been electroencephalography (EEG) and event-related potential (ERP). While neuroimaging methods enable localization of regional responses to cognitive and emotional tasks across the whole brain (Friston et al. 1998), EEG and ERP have higher temporal resolution such that fluctuations in neural activity states (Davidson 1998, 2004) and early information processing can be examined (Donchin and Coles 1988), respectively. In terms of peripheral physiological measures, cardiovascular measures including heart rate (HR) and heart rate variability (HRV) gathered using electrocardiography (ECG), and galvanic skin response (GSR) have been widely employed. Within these, HR is a measure of overall ANS arousal (see Duschek et al. 2013; Lopes and White 2006) under tonic inhibitory control by the parasympathetic nervous system (PNS; Saul 1990; Thayer et al. 2009), high frequency HRV measures PNS activity (see Duschek et al. 2013; Lopes and White 2006), and galvanic skin response (GSR) measures reflect sympathetic nervous system (SNS) activity (see Dawson et al. 2007). Notably, only GSR has been employed in combination with other measures for multimodal investigations. Building toward a more embodied perspective of BSDs, we delineate, examine, and then integrate the cognitive neuropsychological (brain; fMRI and EEG, and ERP) "neurocorrelates" and the peripheral physiological (body; HR and HRV, and GSR) correlates.

A methodological issue that has been discussed in most physiological studies of BSDs is heterogeneity with respect to previous and current treatment effects,

clinical course, and comorbidities. Though it is often not feasible to exclude or stratify patients on all these bases, future research should report and, where possible, take these factors into account. Another self-evident issue that has challenged researchers is the difficulty in recruiting and testing manic bipolar patients in laboratory settings, explaining why there are relatively fewer studies of this phase of illness (Small et al. 1999). With technological advances, future research will likely take advantage of less invasive, ambulatory sensors including smartphone (Heathers 2013) and sensorized clothing (e.g., Mariani et al. 2012; Quintana et al. 2012; Siegel 2013), which will enable the collection of longitudinal physiological data across illness and treatment phases within BSD patients.

3 Neurocorrelates of Bipolar Spectrum Disorders and Their Treatment

3.1 Functional Neuroimaging Correlates

3.1.1 Characterization and Differentiation

Characterization

Characterization of the functional neuroanatomy of BSDs has been extensive, systematic, and consistent for the last two decades (see Table 1). The results and conclusions obtained across neuroimaging modalities—including fMRI, PET, and SPECT—have been largely consistent and non-modality specific (see Strakowski et al. 2005). Overall, BSDs display prefrontal cortex (PFC) hypoactivity and limbic hyperactivity during emotional and cognitive tasks, and these findings correlate with trait and state emotional lability and mood disturbances in BSDs (see Strakowski et al. 2012). In addition, bipolar disorder is characterized by dysfunctional connectivity among ventral prefrontal networks and limbic brain regions, particularly the amygdala (Blond et al. 2012; Chen et al. 2011; Houenou et al. 2011; Strakowski et al. 2012; Townsend et al. 2012) indicating both difficulty in regulating mood alongside a dysfunction of emotion processing. Impaired PFC regulation subsequently leads to a loss of neurological emotional homeostasis, emotional lability, and mood disturbances (Strakowski et al. 2012). It is posited that a disruption of frontal regulatory networks allows for extreme mood states, switching among mood states, and mixed states (Strakowski et al. 2012). These abnormalities have been conceptualized as dysfunction within oscillatory mechanisms, which perhaps worsen over time, and result in the many manifestations of the illness (Schneider et al. 2012).

Interestingly, bipolar patients have consistently decreased frontal activation across the ventrolateral PFC (VLPFC), a region critical for emotional processing and mood regulation (Blond et al. 2012; Chen et al. 2011; Houenou et al. 2011;

Table 1 Meta-review of fMRI assessment in BSD characterization and differentiation

Study	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation
Chen et al. (2011)	fMRI meta-analysis of 65 adult studies Bipolar patients, $n = 1{,}040$ Controls, $n = 1{,}074$	Yes, no test of effects	Emotional tasks Cognitive tasks	✔/✔	Bipolar patients had decreased IFG and putamen and increased parahippocampus, hippocampus, and amygdala and basal ganglia activation, relative to controls. Decreased IFG activity was seen in both cognitive and emotional processing, while increased limbic activation was seen in emotional processing. Inferior frontal activity was decreased in manic but not in euthymic and depressed states. Limbic activation increases were not associated with mood states	Bipolar disorder can be characterized by abnormal frontal-limbic activation Manic state can be differentiated from depressed and euthymic states by decreased IFG activity Bipolar disorder fMRI studies are largely consistent

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Table 1 (continued)

Study	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation
Houenou et al. (2011)	fMRI meta-analysis of 13 emotion processing studies Bipolar versus control Bipolar patients, $n = 130$ Controls, $n = 141$ Euthymic versus control Bipolar patients, $n = 68$ Controls, $n = 73$ Manic versus control Bipolar patients, $n = 35$ Controls, $n = 40$	Yes, no test of effects	Emotion processing tasks Explicit and implicit affect recognition tasks Emotional go/no-go Emotional Stroop task Emotional Sternberg memory task Emotional face-matching paradigm	✔/✔	Bipolar patients had increased parahippocampus, amygdala, caudate, thalamus, and right MFG activation, and decreased right IFG, right precuneus, right MFG, right thalamus and right cerebellum activation, relative to controls Euthymic patients had increased L parahippocampus and amygdala activation, and decreased right precuneus, right thalamus and right cerebellum activation, compared to controls Manic patients had increased parahippocampus, amygdala, L thalamus, and right MFG activation, and decreased right IFG activation, compared to controls	Bipolar disorder can be characterized by dysfunction in the emotional networks involved in voluntary regulation and cognitive control of emotion. However, the specificity of these network characteristics to bipolar disorder versus major depressive disorder is unknown

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Table 1 (continued)

Study	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation
Townsend et al. (2012)	Adult bipolar patients—mania, depression, euthymia	Yes, tested for effects. Some studies test for effects No effects Few studies have used medication-free subjects, and have results consistent with other studies	Emotion activation tasks Emotion processing tasks Emotion regulation task Stimuli: Faces Pictures Emotional Go/No-go words Emotional Stroop Emotional distracters	✔/✔	Amygdala activation varies as a function of mood state. Hyperactivity in mania, valence-related activation in depression, and normal activation in euthymia VLPFC is hypoactivated across mood states	Emotional dysregulation and lability in mania and depression may reflect disruption of a frontal-limbic functional network. There is not enough evidence for classifying state using fMRI

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Table 1 (continued)

Study	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation
Blond et al. (2012)	Adult bipolar patients—mania, depression Euthymia Adolescent samples	Yes, tested for effects Despite medication differences within and between studies, there is still convergence of findings	Resting state Emotion activation tasks with Faces or Pictures Go/No-go tasks Stroop Working memory	✔/✔	Dysfunctional connectivity between the amygdala and the ventral PFC, insula, and temporopolar cortex have been shown in bipolar disorder across mood states, suggesting that they may be trait features of the disorder that are developmental	Bipolar disorder may be characterized by dysfunction in the amygdala–anterior paralimbic neural system. Connectivity within the system is highlighted key to state changes, and may be key to bipolar disorder development. These abnormalities may distinguish bipolar from major depressive disorder. There has been no work to attempt to classify based on this circuit

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Table 1 (continued)

Study	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation
Schneider et al. (2012)	Adult bipolar patients Adolescent samples "At risk" adolescent samples	Yes, some studies test for medication effects. Some effects may be related to medication exposure	*N*-back Parametric sentence completion Stroop tasks Emotional processing tasks with faces or pictures Working memory Go/No-go tasks Reward tasks Dominant hand motor task	✔/×	Studies suggest a pattern of abnormalities in neural development early in the appearance of bipolar disorder that gives way to progressive neuropathic changes at least influenced by the course of illness leading to an iterative process in which functional changes drive clinical symptoms and are in turn exacerbated by the consequences of these symptoms	The few studies characterizing developmental aspects of functional neuroanatomy involved in bipolar disorder are limited There have been no longitudinal studies of functional abnormalities in bipolar disorder

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Table 1 (continued)

Study	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation
Whalley et al. (2012)	Adult bipolar patients compared against Adults schizophrenia patients	Yes, no test of medication effects	Emotional prosody Reward task Associative memory task Emotional memory Verbal fluency Verbal tasks Working memory Comprehension task Auditory oddball, ICA, and temporal network Resting state, default mode	✔/✔	Over-activation in the medial temporal lobe and associated structures was found in bipolar relative to schizophrenia patients in tasks involving emotion or memory. Differences between the disorders in prefrontal regions were not as consistent. Differentiation of diagnosis with fMRI is less accurate in bipolar than schizophrenia patients. Few studies that report symptom associations implicate limbic regions with manic symptoms	Limited number of studies to show ability to classify bipolar and schizophrenia using fMRI

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Table 1 (continued)

Study	Subjects	Medication	Stimuli	Char/Diff	Principle findings	Interpretation
Strakowski et al. (2012)	A consensus view on the functional neuroanatomy bipolar disorder based on reviews conducted by separate groups	Bipolar disorder is characterized by dysfunctional connectivity among ventral prefrontal networks and limbic brain regions, particularly the amygdala. Dysfunction is associated the abnormal development of the component brain regions. Dysregulation of the limbic brain then leads to loss of emotional homeostasis, resulting in mood instability. Due to disruption of networks that can restore this homeostasis, extreme mood states, switching among mood states, and mixed states occur as different unregulated systems oscillate in the absence of homeostatic control. During euthymia, recovery of prefrontal control, along with compensation from other brain regions, temporarily restores homeostasis. However, the underlying functional abnormalities leave the bipolar disorder individual at risk for disruption of this fragile homeostasis under even minor stress				With more evidence, fMRI may be able to discriminate bipolar disorder states and other diagnoses based on the function of these networks
Hajek et al. (2013)	fMRI meta-analysis of 30 response inhibition studies Bipolar patients, $n = 635$ Controls, $n = 667$	Yes, no test of effects in most of the studies	Response inhibition tasks Go/no go Stop signal response task Stroop test Hayling Sentence Completion task	✔/✔	Bipolar patients had decreased R IFG activation regardless of current mood state, relative to controls. Euthymic patients had increased L superior temporal and right MFG and decreased basal ganglia activation. Manic patients had increased bilateral basal ganglia activation and reduced right inferior and MFG activation. Changes in euthymia were associated with normal cognitive performance, whereas manic patients had more errors during response inhibition	Bipolar disorder is characterized by decreased response inhibition and associated R IFG hypoactivation. Euthymic patients subjects may compensate with hyperactivations of adjacent cortical areas, yielding comparable performance in inhibitory functions

Note Char/Diff = the review differentiates between studies that attempt to (1) characterize BSDs (✔/×) or (2) characterize and, differentiate BSDs or differentiate BSDs from other diagnoses (✔/✔); *L* left; *R* right

Strakowski et al. 2012; Townsend and Altshuler 2012), and consistently decreased inferior frontal gryus (IFG) activity, specifically the right IFG (R IFG), a region associated with regulatory inhibition (Hajek et al. 2013). Furthermore, bipolar patients have also increased activity within limbic regions including parahippocampus, hippocampus, and amygdala and basal ganglia (Blond et al. 2012; Chen et al. 2011; Houenou et al. 2011; Strakowski et al. 2012; Townsend and Altshuler 2012), which may underpin abnormalities of primary emotion processing. Hence, decreased IFG activity in bipolar disorder which is seen during both cognitive and emotional processing, and increased limbic activation that is seen during emotional processing (Chen et al. 2011; Hajek et al. 2013; Houenou et al. 2011; Strakowski et al. 2012) may reflect trait-based correlates of BSDs.

With respect to the manic phase of bipolar disorder, IFG activity is decreased in mania but not in euthymic or depressed states, and limbic activation increases are not associated with mood states (Chen et al. 2011; Houenou et al. 2011; Strakowski et al. 2012). However, amygdala activation varies as a function of mood state and the valence of the emotional stimuli: hyperactivity to emotional stimuli in mania; hyperactivity to negative stimuli and hypoactivity to positive stimuli in depression, and normalized activations in euthymia (Townsend and Altshuler 2012). However, it is important to note that many of these findings are preliminary and may be contingent on additional factors such as the tasks used and disorder phenotype, but they do suggest that manic and depressed phases of bipolar disorder can be differentiated on the basis of altered IFG activity and valence-mood congruent activation of the amygdala (Strakowski et al. 2012; Townsend and Altshuler 2012). With respect to response inhibition, the manic phase is associated with reduced performance, associated with decreased R IFG and medial frontal gyrus (MFG) activation and increased bilateral basal ganglia activation (Hajek et al. 2013; Houenou et al. 2011; Strakowski et al. 2012). In the euthymic phase, response inhibition is not dysfunctional, although activity in left superior temporal and right MFG is increased and basal ganglia activation decreased (Hajek et al. 2013; Houenou et al. 2011; Strakowski et al. 2012). Therefore, euthymic patients compensate for reduced inhibitory IFG activity with increased activation of adjacent cortical areas, thereby yielding normalized inhibitory functions (Hajek et al. 2013). During euthymia, recovery of frontal control, along with compensation from other brain regions, temporarily restores neurological emotional homeostasis (Strakowski et al. 2012). However, the underlying functional abnormalities in the VLPFC networks leave the risk for emotional and cognitive disruption, leading to manic, depressed, or mixed phases, even under minor stress (Strakowski et al. 2012).

Differentiation

Over-activation in the medial temporal lobe during tasks involving emotion or memory may differentiate patients with bipolar disorder from patients with schizophrenia (Whalley et al. 2012). However, differential diagnosis with fMRI has been less accurate with bipolar disorder than schizophrenia (Whalley et al. 2012).

While promising preliminary findings have been reported suggesting that BSDs may be distinguished from unipolar major depression in small samples (Diler et al. 2013; Grotegerd et al. 2013; Marchand et al. 2013), large-scale studies are needed to determine the sensitivity and specificity of these findings.

3.1.2 Treatment

Effective treatment would be expected to normalize the state-based and trait-based VLPFC-limbic network disturbances correlated with BSDs using fMRI. In comparison to the fMRI correlates characterizing and differentiating BSDs, fMRI correlates of treatment are understudied. In the last decade, eight controlled studies examining the impacts of treatment administration in BSDs on cognitive and emotional stimuli have been published, with each demonstrating some sort of normalization effect (Table 2). Lithium appears to have prophylactic effects on cognition after 14 days' treatment and acts on frontal regions in the euthymic phase of BSDs with little impact during the depressed phase (Silverstone et al. 2005). After 12 weeks of lamotrigine administration during the euthymic phase, there are increases in the prefrontal and cingulate regions, thereby normalizing the activity of circuitry involved in emotion regulation (Haldane et al. 2008; Jogia et al. 2008). In the depressed phase, 8 weeks of lamotrigine administration reduces amygdala reactivity to negative stimuli, with greater reductions in reactivity being correlated with reductions in depression symptoms after 8 weeks (Chang et al. 2008). When patients are given a 4-week course of antipsychotics and then a 14-week course of lamotrigine, decreases in mania symptoms following treatment are associated with increased VLPFC and dorsolateral (DLPFC) activity during cognitive-emotional (Pavuluri et al. 2010b) and response inhibition tasks (Pavuluri et al. 2010a). In subsyndromal patients, there are no consistent differences after 12 weeks of valproate treatment (Chang et al. 2009). Finally, a study investigating the effect of psychotherapy showed normalization of IFG hypoactivity after 12 weekly sessions (Favre et al. 2013); however, it was difficult to differentiate the effect of psychotherapy from improvement with the medication patients were already receiving (Favre et al. 2013).

In sum, there appears to be normalization of the cognitive and emotional neural networks implicated in BSDs with treatment when patients present in the depressed or manic phases of illness. Additionally, prophylactic treatment appears to affect these networks. However, the majority of investigations thus far have small sample sizes (less than 20 patients) and many did not have a control group for comparison (e.g., Chang et al. 2008; Haldane et al. 2008). Additionally, some studies investigated adolescents (e.g., Chang et al. 2008, 2009; Pavuluri et al. 2010a, b), who are likely to have fundamentally different responses compared to adults. Nevertheless, there are promising findings from this relatively new line of research that should encourage future research with larger samples, across different treatments. In doing so, clinically useful fMRI treatment markers for predicting treatment response and treatment monitoring may be determined.

Table 2 Literature review findings of fMRI assessment in BSD treatment

Study	Modality measure	Subjects	Treatment	Principal findings	Interpretation	Comment
Silverstone et al. (2005)	fMRI 1.5 Tesla BOLD Working memory task Word generation task	5 bipolar disorder patients—depressed Bipolar II, $n = 3$ Taking other medication, $n = 2$ Five bipolar disorder—euthymic Bipolar II, $n = 4$ Taking antidepressants, $n = 2$	Lithium, 14 days	After lithium, euthymic bipolar patients had decreased L precentral, Broca's aera, and supplementary motor area activation during the word generation task. No change in the depressed group. No group effect for the working memory task	Lithium has effects on brain activation that are task, region, and state-dependent	
Haldane et al. (2008)	fMRI 1.5 Tesla BOLD *N*-back task Angry Facial Affect Recognition Task	12 bipolar disorder—euthymic Titrated off medications	Lamotrigine, 12 weeks	After lamotrigine, patients had increased activation in the superior and medial PFC and cingulate gyrus during both tasks	Lamotrigine may impact the neural circuits involved in memory and emotion regulation	No control group to show that practice effects did not cause the changes
Jogia et al. (2008)	fMRI 1.5 Tesla BOLD Sad facial affect recognition task	12 bipolar disorder—euthymic Titrated off medications 12 controls	Lamotrigine, 12 weeks	At baseline, patients had increased temporal and dorsomedial and right VLPFC, and dorsal cingulate gyrus, relative to controls. After lamorigine, patients had reduced temporal and increased prefrontal activation	Lamotrigine may normalize the dysfunctional circuits involved in affect recognition	No treated control group to show that, perhaps differential, practice effects in the patients did not cause the changes

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Table 2 (continued)

Study	Modalitymeasure	Subjects	Treatment	Principal findings	Interpretation	Comment
Chang et al. (2008)	fMRI 3 Tesla BOLD Emotional pictures task Negative Neutral	8 bipolar patients—depressed, adolescents (aged 13–17) Bipolar I, Bipolar II, Bipolar NOS, Previous medication was tapered and discontinued for 2–4 week washout. Other mood stabilizers, antipsychotics, and ADHD treatments with no dose changes within 1 month. Did not test for effects	Lamotrigine, 8 weeks	After lamotrigine, clinical improvement in depression was correlated with decreased right amygdala activation with treatment. After lamotrigine, depression symptoms were positively correlated with bilateral amygdala activation. DLPFC activation was not correlated with clinical improvement in depression	Lamotrigine reduces reactivity to negative stimuli, which is related to clinical improvement in depression	No control group to show that practice effects did not cause the changes
Chang et al. (2009)	fMRI 3 Tesla BOLD Emotional pictures task Negative Positive Neutral (also sMRI, spectroscopy)	Six subsyndromal children, with parent with bipolar disorder (aged 9–18) Two patients previously medicated Antidepressant, $n = 1$ Stimulant, $n = 1$ Five controls	Valproate semisodium, 12 weeks	There were no differences in amygdala or DLPFC activation between groups at baseline or after valproate treatment. Clinical improvement in depression was positively correlated with decreased DLPFC activation	Clinical change may predate neurobiological change that was detectable by the methods employed	Small sample. Perhaps there is large heterogeneity in subsyndromal groups

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Table 2 (continued)

Study	Modalitymeasure	Subjects	Treatment	Principal findings	Interpretation	Comment
Pavuluri et al. (2010b)	fMRI 3 Tesla BOLD Affective color matching task	17 bipolar disorder patients—manic, hypomanic, or mixed, adolescent (aged 10–18) Unmedicated 14 controls	Initially treated with atypical psychotics, four weeks Lamotrigine, 14 weeks	After treatment, the VLPFC and DLPFC hypoactivity between patients and controls was partially normalized. In the patient group, mania symptom improvement was correlated with the increased VLPFC activity	Pharmacotherapy results in amelioration of cognitive and affective circuitry dysfunction, which improves symptoms of mania	Cannot differentiate the impacts of the two different medications. No treated control group to show that, perhaps differential, practice effects in the patients did not cause the changes
Pavuluri et al. (2010a)	fMRI 3 Tesla BOLD Go/No-go Task	17 bipolar disorder patients—manic, hypomanic, or mixed, adolescent (aged 10–18) Unmedicated 14 controls	Initially treated with atypical psychotics, four weeks Lamotrigine, 14 weeks	After treatment, the prefrontal hypoactivity between patients and controls was partially normalized. In the patient group, mania symptom improvement was correlated with the increased VLPFC activity	Pharmacotherapy normalizes dysfunction in cognitive circuitry function supporting voluntary behavioral inhibition	Cannot differentiate the impacts of the two different medications. No treated control group to show that, perhaps differential, practice effects in the patients did not cause the changes
Favre et al. (2013)	fMRI 3 Tesla BOLD Word-Face emotional Stroop Task	16 bipolar patients—euthymic Bipolar I, $n = 11$ Bipolar II, $n = 5$ Lithium, $n = 9$ Anticonvulsants, $n = 10$ Antidepressant, $n = 8$ Atypical antipsychotics, $n = 1$ Drug-free, $n = 1$ Medication was stable between phases. Did not test for effects 16 controls	Psychoeducation therapy, including stress and symptoms management, weekly session for 12 weeks with a psychiatrist and a psychologist	After treatment, the inferior frontal gyrus hypoactivity between patients and controls was partially normalized	Treatment improved dysfunctional cognitive control and emotional regulation mechanisms	Specificity of psychoeducation-related improvement, particularly in relation to medication effects, should be evaluated by comparing it to non-structured interventions

Note *L* left; *R* right

3.2 EEG and ERP Correlates

3.2.1 Characterization and Differentiation

Within the EEG and ERP literature, there has been one systematic review on the correlates that characterize and differentiate BSDs (Degabriele and Lagopoulos 2009). Here, we updated this review (Table 3). There have been 22 studies examining the BSD characteristics with EEG and ERP measures. Overall, there appears to be measurable correlates in frequency band, ERP component, and sleep EEG characteristics (see Degabriele and Lagopoulos 2009), and network properties (Kam et al. 2013; Kim et al. 2013) that can characterize and differentiate BSD phases and BSDs from unipolar depression and schizophrenia. Single electrode EEG (see Iacono et al. 1983), clinical EEGs (see Cook et al. 1986; Small et al. 1999), and associating EEG data with neuroanatomical abnormalities from computerized tomography images (see Dewan et al. 1988) are yet to produce in measurable correlates characterizing and differentiating BSDs.

BSD studies employing EEG data show that differential power at specific frequency bands, which are associated with different activity states, are correlated with traits and states of BSDs. Specifically, differential activity in the alpha band between the frontal lobe hemispheres, frontal alpha asymmetry—an index associated with behavioral motivation (Davidson 1998, 2004)—correlates with BSD phases. In the depressed phase, increased right-dominant, withdrawal-related, frontal alpha asymmetry, relative to controls, is characteristic at rest (Nusslock et al. 2012). Additionally, bipolar disorder patients with decreased functional network integration and decreased optimal balance of network segregation in functional fronto-central and centro-parietal networks had higher depression scores (see Kim et al. 2013). In the manic phase, various frequency characteristics can be observed during rest (see Clementz et al. 1994; Kano et al. 1992), with increased 'busy thinking' related, beta activity correlating with increased mania symptoms (Kam et al. 2013). Increased left-dominant, goal striving frontal alpha asymmetry, relative to controls, appears to be characteristic of mania (Harmon-Jones et al. 2008; Nusslock et al. 2012), opposing the activity characterizing the depressed phase. In the hypomanic phase, increased left-dominant frontal alpha asymmetry at rest is also observed (Harmon-Jones et al. 2008; Nusslock et al. 2012), an effect that also correlates with hypomanic personality (Peterson and Harmon-Jones 2008; Wyczesany et al. 2010). In the euthymic phase, bipolar patients appear to have more normalized frequency characteristics and frontal alpha asymmetry relative to controls (Nusslock et al. 2012), though some residual frequency characteristics remain suggesting some trait-based cognitive dysfunction (El-Badri et al. 2001).

ERP components, such as the commonly reported P300, provide an opportunity to determine whether early information-processing is impaired in patient samples (see Degabriele and Lagopoulos 2009; Donchin and Coles 1988; Kemp et al. 2009). In studies with bipolar patients in no specific phase, results show ERP

Table 3 Literature review findings of EEG assessment in BSD characterization and differentiation

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
Iacono et al. (1983)	Single Au electrode EEG at Cz site Phi, Alpha, Kappa (also cardiac measures and GSR, reported in Tables 1 and 7, respectively)	24 bipolar affective disorder—euthymic 26 Unipolar 46 controls	Yes, tested for effects Imipramine only, not lithium for at least one month, $n = 13$ Lithium only, not imipramine for at least one month, $n = 6$ Imipramine + Lithium = 26 Drug-free for at least 3 months, $n = 5$	Resting state, 5 min, eyes closed	✔/✔	No patient group differences. No impact of medication	Euthymic bipolar patients cannot be differentiated from other groups using EEG	No spatial resolution from one Cz electrode
Cook et al. (1986)	16-channel EEG "EEG abnormalities"	23 bipolar patients with 'abnormal' EEGs 23 bipolar patients with 'normal' EEGs	Unmedicated, 48 h washout period	Clinical EEG	✔/×	"EEG abnormalities" were related to less family history of bipolar disorder	Aetiology of bipolar disorder is unclear	Perhaps clinical EEG abnormalities may not characterize bipolar disorder
Dewan et al. (1988)	EEG Details not reported	26 Euthymic bipolar patients Nine with CT abnormalities 17 without CT abnormalities	Yes, no test of effects Lithium, $n = 24$ Some on carbamazepine and antipsychotics	Two periods of eyes opening and closing Hyperventilation, 3 min	✔/×	EEG could not differentiate between bipolar patients with or without CT abnormalities	CT abnormalities may have no clinical relevance to bipolar disorder	

(continued)

Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Muir et al. (1991)	Single Ag/AgCl electrode at Cz site P300	99 bipolar patients—mixed phases 48 MDD patients 32 in-patient controls 213 controls	Yes, tests of effects Bipolar patients Drug-free, $n = 28$ Neuropeptics, $n = 34$ Antidepressants, $n = 9$ Hypotics, $n = 3$ Lithium, $n = 32$	Covertly counting infrequent tones	✔/✔	P300 latency was greater in bipolar than MDD patients, and controls. No impact of medication on these effects	P300 latency might characterize bipolar disorder, and differentiate bipolar from MDD	No spatial resolution from one Cz electrode
Kano et al. (1992)	16-channel EEG Alpha1 Alpha2 Beta1	7 patients with bipolar disorder—mania 44 controls (also 21 MDD and melancholia. 16 MDD without melancholia)	Yes, no test of effects Across patient sample TCA, $n = 21$ TeCA, $n = 4$ Tranquilizers, $n = 8$ Lithium, $n = 6$ No medication, $n = 6$	Resting state, eyes closed	✔/×	In bipolar patients, Alpha1 was increased in P3 and O1 and decreased at C3. Alpha2 was decreased at F7. Beta2 was increased at F8, relative to controls	Dysfunctional relationships between frontal areas are associated with mood changes	Need to compare patients in different mood states to show that frontal dysfunction is related to mood changes
Clementz et al. (1994)	3-channel EEG Au electrodes at Cz, C3, C4 sites Delta Theta Alpha Beta1 Beta2 Beta3 Total Phi	31 first-episode bipolar patients 35 patient relatives 113 controls 42 relatives 50 first-episode schizophrenia and 55 relatives	Yes, tested for effects Bipolar patients Antipsychotic, $n = 19$ Antidepressant, $n = 4$ Anticholinergic, $n = 9$ Lithium, $n = 12$	Resting state, eyes closed	✔/✔	Bipolar patients had increased delta, increased right alpha, and theta activity compared with controls. Bipolar patients and their relatives had decreased peak alpha frequencies Bipolar patients were differentiable from schizophrenia patients on Cz delta and C4 delta, theta, and alpha	Bipolar patients have a hemispheric dominance in regulation of mood, which is differentiable from schizophrenia	Thorough analysis of medication effects

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Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Koles et al. (1994)	8-channel EEG at F7, T3, T4, P3, P4, T6, T4, and F8 sites. Spatial pattern analysis	22 manic patients 33 depressed patients 113 control 31 schizophrenic patients	No. drug washouts	Resting state, eyes open and eyes closed Vocabulary and oral word Fluency Block design	✔/✔	Spatial patterns can differentiate all groups. Bipolar patients had increased left temporal activity and bilateral frontal hyperactivity The depressed group had right-sided hyperactivity and the manic group had left temporal and bilateral frontal hyperactivity	Resting state, spatial patterns rather than temporal, may provide the best diagnostic differentiation using EEG	Shows spatial resolution is important in EEG in BSDs
Souza et al. (1995)	5-channel EEG at Fz, Cz, Pz, T3, T4 sites P300	19 bipolar patients—mixed 27 controls 26 Schizophrenia	Yes, tested effects of medication Bipolar patients Drug-free, $n = 3$ Neuroleptics, $n = 4$. TCAs, $n = 3$ Benzodiazepines, $n = 1$ Lithium, $n = 8$ MAOI, $n = 2$ Carbamazepine, $n = 4$	Covertly counting target tones	✔/✔	Bipolar patients, like schizophrenia patients had increased P300 latency, but bipolar patients had greater P300 amplitude. No effects of medication	P300 may characterize dysfunction in bipolar disorder, but P300 amplitude differentiates bipolar from schizophrenia	
Small et al. (1999)	22-channel EEG Clinical EEG qEEG (previously reported and described in Table 4)	202 bipolar patients—mania	No. washout 10–14 days	Resting state Photic stimulation Hyperventilation Natural or sedative drowsiness Light Sleep Clinical EEG	✔/×	Abnormal EEGs in 16 % of patients Left-lateralized abnormalities were more common than right	Clinical EEG abnormalities are uncommon in bipolar patients	Perhaps clinical EEG is not useful in bipolar disorder. Different states should be examined

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Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
El-Badri et al. (2001)	9-channel EEG Delta Theta Alpha Beta	29 euthymic bipolar patients 26 control	Yes, tested for effect of lithium Lithium, $n = 20$ Anticonvulsants, $n = 8$ Antipsychotics, $n = 11$ Antidepressants, $n = 9$ Polypharmacy, $n = 18$ With detailed patient breakdown of specific medications	Resting state, eyes closed and neurocognitive tasks	✔/×	Bipolar patients had greater power in all wave bands than controls. Greatest differences were for right temporal theta and left occipital beta No effect of lithium Neurocognitive deficits in patients	EEG differences in visuospatial areas may related to neurocognitive deficits in bipolar disorder	
Rao et al. (2002)	Standard poly-somnography EEG	28 adolescent (mean age = 15.4) unipolar patients At 6–8 year follow-up: 26 patients 5 bipolar patients 21 unipolar patients 35 controls	No, 2-week washout.	Poly-somnography study	✔/✔	Patients that converted to bipolar disorder had greater Stage 1 sleep and REM latency and less REM density and duration at baseline than unipolar patients	EEG sleep profile may relate to clinical course of bipolar disorder	Small sample of bipolar-course patients

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Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
O'Donnell et al. (2004)	32-channel Ag/AgCl EEG N100 P200 N200 P300	13 bipolar patient—manic or mixed 12 schizophrenia patients 35 controls	Yes, tested for effects Bipolar patients Atypical antipsychotics, $n = 3$ Benzodiazepines, $n = 5$ Unmedicated, $n = 5$ Schizophrenia patients Atypical antipsychotics, $n = 12$	Auditory oddball	✔/✔	Bipolar patients had reduced P300 amplitude and latency relative to controls. Schizophrenia patients had additional N100, P200, and N200 reductions	While both patient groups have attentional and working memory deficits, schizophrenia patients also have disturbances in earlier auditory processing	
Hall et al. (2007)	17-channel EEG P300 P50 Mismatch negativity	Six twin pairs concordant for bipolar disorder 10 twin pairs disconcordant for bipolar disorder 78 control twin pairs	Yes Antipsychotics + mood stabilizers and/or antidepressants, $n = 11$ Antidepressant + Mood stabilizers, $n = 3$ Mood stabilizers, $n = 2$ Antidepressant, $n = 1$ Unmedicated, $n = 5$	Auditory Oddball Conditioning-testing paradigm	✔/✘	Bipolar disorder patients had reduced P300 amplitude and decreased P50 suppression. Genetic not environmental factors, accounted for variance in P300 and P50 heritability. MMN and P300 latency were not associated with bipolar disorder	P300 amplitude and P50 suppression ratio may be endophenotypes for bipolar disorder	
Harmon-Jones et al. (2008)	14-channel EEG Alpha frontal asymmetry	41 BSD patients 53 controls	Yes, tested effects. Antidepressant, $n = 7$ Two antidepressants, $n = 1$ Mood stabilizer + anxiolytic, $n = 1$ No information, $n = 2$	Goal-striving task	✔/✘	Bipolar patients had greater relative left frontal activity in preparation for winning hard trials. This effect was driven by hypomanic state. No effects of medication	Relative left frontal activity may be involved in mania and triggered by challenging and potentially rewarding events	

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Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
Peterson and Harmon-Jones (2008)	27-channel EEG Alpha coherence Hypomanic personality scale	36 controls	Not assessed	Squeeze ball contraction and relaxation	✔/×	During right-hand contractions, increased left mid-frontal (F3-F4) and frontal-central (Fc3-Fc4) coherences were related to increased hypomanic personality scores	Proneness to hypomania may be related to the connectivity of the left motor cortex and the left PFC, priming approach-related motor responses	
Lahera et al. (2009)	3-channel EEG Ag/AgCl electrodes at Fz, Cz, Pz sites. P300	21 euthymic bipolar patients 38 controls	Yes, did not test for effects Mood stabilizers, 29.1 % Mood stabilizers + antipsychotics, 20.8 % Other combinations, 50 %	Auditory oddball	✔/×	No differences between patients and controls on P300 latency and amplitude	Refutes the hypothesis that P300 latency reduction in bipolar disorder is state independent, and than P300 response is driven by symptoms	Did not test for mediation effects. It could be that the medication is normalizing P300
Bestelmeyer et al. (2009)	4-channel EEG Ag/AgCl electrodes at Fz, Cz, Pz, Oz electrode sites P300	19 bipolar disorder patients 21 schizophrenia patients 35 controls	Yes, did not test for effects Lithium, $n = 11$ Carbamazepine, $n = 2$ Other, $n = 6$	Auditory oddball Visual oddball	✔/✔	Auditory both bipolar and schizophrenia patients had decreased P300 amplitude at Pz, relative to controls The bipolar patients could not be differentiated from the schizophrenia patients with P300	Auditory P300 amplitude at Pz may be an endophenotype for psychosis in general rather than specifically for schizophrenia	

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Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Wyczesany et al. (2010)	32-channel EEG Alpha1 Alpha2 Beta1 Beta1 Beta3 Laterality coefficients Activation Deactivation Adjective CheckList Energy-Tiredness (ET), Tension-Calmness (TC)	31 hospitalized patients 13 MDD 5 bipolar disorder—mania 13 without mood disorders	Yes, did not test for effects Did not report medications taken	Resting state, eyes open	✔/×	The high-energy group showed right shift of activity in frontocentral and posterior areas visible in alpha and beta range, respectively. High tension was related to right prefrontal dominance and right posterior activation in beta1 band. Also, overall alpha2 decrease and beta2 increase	An increase of right frontocentral cortical activation may be related to conditions of energetic arousal	
Degabriele et al. (2011)	34-channel EEG P100 N170	18 bipolar disorder patients 18 controls	Yes, no test of effects Most patients receiving combination including antipsychotics, antidepressants and anticonvulsants such as sodium valproate or lithium	Emotional face go/no-go inhibition task	✔/×	Bipolar patients had larger P100 amplitudes in response to this happy compared to sad faces. Reaction time was significantly reduced in the happy compared to sad faces. Controls did not have significant differences	Responses to positive emotion is facilitated in bipolar patients. Potentiation of positive stimuli at the early stage of emotion processing may result in bipolar mania	Need to confirm across affective states and medications

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Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
Nusslock et al. (2012)	14-channel EEG Alpha Frontal alpha asymmetry at F3/F4 and F7/F8 electrode sites	58 BSD patients depressed, $n = 9$ hypomanic, $n = 21$ euthymic, $n = 21$ no data, $n = 7$ 16 converted to bipolar I after 4.7-year follow-up 59 control	Yes, controlled for medication status Medicated, 55 % Antidepressant, 50 % Lithium/Depakote, 7 % Antipsychotic, 2 % Anxiolytic, 12 %	Eyes open-eyes closed trials	✔/✔	Hypomanic patients had greater relative left F3/F4 than depressed and euthymic patients, and controls. Increased relative left F3/F4 was associated with a greater probability of converting to bipolar I disorder. Increased relative left F3/F4 classified 76 % of individuals with cyclothymia or bipolar II disorder based on whether they did or did not convert to bipolar I disorder	Mid-frontal cortical activity differentiates bipolar affective states and can predict clinical course	Unable to examine conversion to bipolar II disorder from small number of cyclothymia patients
Kim et al. (2013)	29-channel Ag AgCl EEG Synchronization likelihood Delta Theta Alpha Beta Gamma Graph theory functional connectivity analysis	57 bipolar I patients Current episode, $n = 43$ Depressed, $n = 19$ Manic, $n = 10$ Mixed, $n = 14$ Euthymic, $n = 14$ 87 control	Yes, no test of effects 53 medicated Antipsychotic Atypical, $n = 37$ Typical, $n = 8$ Anticonvulsant, $n = 26$ Antidepressant, $n = 24$ Benzodiazepine, $n = 16$ Lithium, $n = 14$ Buspirone, $n = 3$ Stimulant, $n = 2$ Anticholinergic, $n = 4$ No medication, $n = 4$	Resting state, eyes closed	✔/×	Bipolar I patients had decreased mean alpha synchronization, with largest decreases in F4-FC4-Cz-C4 and Cz-C4-CPz connections. Network properties were different in patients relative to controls. Network properties were correlated with depression scores in patients	Bipolar I patients show impaired neural synchronization at rest and a disruption of resting-state functional connectivity n fronto-central and centro-parietal regions	First network-based analysis of bipolar disorder with EEG Need to apply networks to different states and medication status

(continued)

Table 3 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Kam et al. (2013)	32-channel Ag/ AgCl EEG Delta Theta Alpha1 Alpha2 Beta1 Beta2 Gamma Intra-hemispheric coherence Inter-hemispheric coherence	76 bipolar patients 132 schizophrenia 136 controls	Yes, tested for and then co-varied effects Medicated, $n = 55$ Atypical antipsychotics, $n = 31$ Typical antipsychotics, $n = 6$ Antidepressants, $n = 20$ Anticonvulsants, $n = 27$ Anticholinergics, $n = 2$ Benzodiazepine, $n = 17$ Lithium, $n = 15$ Antiparkinsonians, $n = 1$	Resting state, eyes closed	✔/✔	Bipolar patients had greater beta and gamma power than schizophrenia patients across regions Intra- and Inter-hemispheric coherence was different between bipolar and schizophrenia patients, varying differently across bands Mania symptoms were related to bipolar patients' increase in beta	Bipolar patients had increased high frequency power with few disruptions in neural synchronization. Whereas schizophrenia patients had enhanced synchronization within and across hemispheres	Resting EEG synchronization may differentiate bipolar disorder from schizophrenia

Note Char/Diff = the review differentiates between studies that attempt to (1) characterize BSDs (✔/×) or (2) characterize and, differentiate BSDs or differentiate BSDs from other diagnoses (✔/✔)

component differences characteristic of disturbance in early executive functions (Hall et al. 2007; Muir et al. 1991; O'Donnell et al. 2004; Souza et al. 1995) and accentuation of the early processing of positive stimuli (Degabriele et al. 2011). Furthermore, some ERP components appear to be heritable, endophenotypes for bipolar disorder (Hall et al. 2007). Therefore, early processing deficits appear to be measureable BSD traits.

Clinical course from unipolar to bipolar disorder has been predicted using EEG sleep components (Rao et al. 2002), a finding that may be associated with increasing or differential chronobiological disturbances in BSDs (see Malhi and Kuiper 2013). Bipolar I conversion from cyclothymia and bipolar II is reliably classified by increased manic-related, left-dominant frontal asymmetry at rest (Nusslock et al. 2012). Finally, bipolar disorder can be differentiated from unipolar disorder with specific ERP components (Muir et al. 1991) and network properties (Koles et al. 1994), and from schizophrenia with specific ERP components (O'Donnell et al. 2004; Souza et al. 1995) and network properties (Kam et al. 2013).

In summary, there are identifiable EEG and ERP characteristics that correlate with the states and symptoms of depression and mania that may differentiate the two poles of the illness: withdrawal or negative valence-related right-hemispheric dominance for the depressed phase and approach or positive valence-related left-hemispheric dominance for the manic phase, each related to changes in network properties. In addition, frequency band and early processing disturbances consistently appear to be trait-based characteristics of bipolar disorder, which can differentiate it from unipolar disorder. Furthermore, early processing and network disturbances differentiate bipolar disorder from schizophrenia. Given that classification and predicting clinical course using EEG has been successfully examined, future directions in EEG and ERP research should concern classification of different phases and differential diagnosis using the aforementioned characteristics.

3.3 Treatment

Within the EEG and ERP literature, there has been one review examining correlates of lithium treatment effect (Ikeda and Kato 2003). Here, we updated this review and review other treatments (Table 4). The EEG and ERP characteristics that correlate with the phases and symptoms and trait-based early processing characteristics of BSDs would be expected to normalize with effective treatment. Indeed, all six studies reviewed show that EEG and ERP can detect treatment-related changes with commonly prescribed treatment. Although clinical EEG did not appear to be a useful measure for characterizing BSDs, it appears that existing EEG abnormalities (including, spikes and irregular beta, theta, and slow alpha activity) is a predictor of 3-month lithium treatment non-response (Ikeda et al. 2002). Additionally, clinical EEG and ERP changes with anticonvulsant medication predict treatment response (Gerez and Tello 1992).

Table 4 Literature review findings of EEG assessment in BSD treatment

Study	Modality measure	Subjects	Treatment	Finding	Interpretation	Comment
Small et al. (1989)	22-channel EEG Waking, hyperventilation, photic stimulation and, in some cases, drowsiness and sleep Delta Theta Alpha Beta1 Beta2	14 drug-free mania patients 14 controls 15 drug-free depression patients 15 controls (also 16 schizophrenia, 6 OCD, and controls	Carbamazepine Lithium	EEG changes detected during treatments in mania and depression patients Carbamazepine increased delta activity in the anterior regions, more right-sided increases, and decreased theta; response/non-response could not be differentiated Lithium increased beta1 and increase left in delta, theta, and beta2; treatment response was correlated with increases in delta EEG could not differentiate between disorders	EEG might be useful for treatment monitoring	Cannot determine treatment responses to a particular treatment or treatment combination in this study
Gerez and Tello (1992)	19-channel EEG Resting state, 30 mins P300 Visual evoked potentials P300 Auditory oddball	90 mixed sample of patients, including bipolar disorder patients	Anticonvulsants Treatment as usual	Focal and P300 changes predicted treatment response to anticonvulsants, regardless of diagnosis	EEG might be useful for monitoring anticonvulsant treatment	Cannot determine treatment responses to a particular treatment or treatment combination in this study

(continued)

Table 4 (continued)

Study	Modality measure	Subjects	Treatment	Finding	Interpretation	Comment
Small et al. (1998)	28-channel EEG Slow delta Fast delta Slow theta Fast theta Slow alpha Fast alpha Slow beta Fast beta Total power Eyes closed	37 hospitalized manic patients, newly medicated after washout	Lithium, $n = 5$ or Carbamazepine, $n = 6$ Or Lithium + Carbamazepine, $n = 10$ Lithium + Halopediol, $n = 8$ Lithium + Risperidone, $n = 8$	In the whole sample, non-responders to treatment had higher left fronto-temporal amplitudes (F1, T1, T3, and T5) than responders in the fast delta, theta, and beta bands. Treatment groups were differentiable	Treatment response to commonly prescribed medication for bipolar disorder can be determined from EEG	
Schulz et al. (2000)	8-channel EEG Eyes closed Delta Theta Alpha Beta	12 patients with affective disorders, including bipolar affective disorders (ICD-10, F31) with and without previous medication use Antidepressant, $n = 9$ Neuroleptics, n = 3 No medication, n = 3	Lithium treatment for 4.4 months	After lithium treatment, relative theta power was increased. Lithium plasma level was correlated with increased theta power. Lithium also decreased relative alpha power in the right centro-parietal region. There was a general slowing of the dominant alpha frequencies	Change in theta power was induced by lithium	No control group. Did not examine the laterality of the effects

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Table 4 (continued)

Study	Modality measure	Subjects	Treatment	Finding	Interpretation	Comment
Ikeda et al. (2002)	20-channel EEG Clinical EEG	27 bipolar patients Lithium responders, $n = 5$ Lithium non-responders, $n = 17$	Retrospective investigation to impact of lithium treatment response	All of the lithium responders had normal EEGs. Five of the lithium non-responders had abnormal EEGs	Abnormal EEG may be a predictor of lithium treatment non-response in bipolar disorder	
Howells et al. (2012)	6-channel EEG (F3, F4, C3, C4, P3, P4 electrode sites) Resting state, eyes open, and eyes closed Theta Alpha Beta P300 Visual oddball	12 euthymic bipolar patients, medicated Mood stabilizers, $n = 12$ Lithium, $n = 8$ Antipsychotics, $n = 8$ Antidepressants, $n = 2$ Anxiolytics, $n = 1$ 9 controls	Mindfulness-based cognitive therapy, 8 weeks. Bipolar participants only, tested before and after treatment	Bipolar patients had decreased theta and increased beta at F3 and C3 during eyes closed, relative to controls Post treatment, beta was decreased at F4 during eyes closed No significant differences between groups in P300. P300-like wave components were different between groups at F3 and F4. Therapy normalized this difference	Treatment slightly improved attentional readiness, and attenuated activation of non-relevant information processing	Cannot determine treatment responses to a particular treatment or treatment combination in this study. No treated control group

Note Char/Diff = the review differentiates between studies that attempt to (1) characterize BSDs (*/*) or (2) characterize and, differentiate BSDs or differentiate BSDs from other diagnoses (*/*); *L* left; *R* right.

On the one hand, studies (Schulz et al. 2000; Small et al. 1989, 1998) that show frequency band component changes with treatment do not interpret these changes in the context of changes in neural activity or cognitive-emotional processing, correlating with normalization of symptoms. Instead, these studies discuss the potential utility of frequency band component changes as a tool to monitor and measure treatment responses. On the other hand, studies (Howells et al. 2012; Schulz et al. 2000; Small et al. 1989, 1998) showing laterality effects suggest that the greater left-dominant frontal approach-related activity characterizing mania may be normalized in treatment responders, relative to treatment non-responders. After 20 weeks of lithium treatment, relative alpha power in the right centro-parietal region is decreased (Schulz et al. 2000). Lithium, carbamazepine, and risperidone treatment non-response are correlated with higher left fronto-temporal amplitudes than responders in the fast delta, theta, and beta bands at baseline (Small et al. 1998). After lithium treatment, beta1 and left delta, theta, and beta2 increase, and treatment response correlates with increases in delta (Small et al. 1989). Lithium plasma level is correlated with increased theta power.

After carbamazepine administration, delta activity in the anterior regions is increased, with more right-sided increases, and theta is decreased (Small et al. 1989). Mindfulness-based cognitive therapy appears to decrease right frontal beta at rest and normalize P300-like ERP components in already medicated euthymic patients (Howells et al. 2012). Although the specificity of changes due to the therapy is uncertain, this was interpreted as improvement in attentional readiness and attenuation of non-relevant information processing (Howells et al. 2012). Although network disturbances appear to characterize and differentiate BSDs (as described in the previous section), the impacts of treatment on these networks are yet to be investigated.

Overall, there appears to be measurable EEG and ERP correlates of general treatment response that normalize phase and symptom-based characteristics of BSDs; however, the specificity of these effects to a particular medication or phase remains uncertain. Future directions would be to examine the specificity of medication effects and consequent treatment responses on EEG, ERP components, and network properties at each illness phase. Additionally, the relationships between frequency band component changes and cognitive-emotional changes with treatment should be determined. These developments would lay the foundations for investigation into the clinical utility of EEG and ERP components as markers of treatment response in BSDs.

4 Peripheral Physiological Correlates of Bipolar Spectrum Disorders and their Treatment

4.1 Cardiovascular Correlates

4.1.1 Characterization and Differentiation

A systematic literature review of cardiovascular correlates in BSD is presented in Table 5. Eight studies have examined cardiovascular measures and suggest that BSDs are associated with a higher heart rate (HR), reflecting increased arousal and reduced PNS function (see Duschek et al. 2013; Lopes and White 2006) can characterize BSDs. This is important as high resting HR is associated with an increased risk of suicide (Lemogne et al. 2011), which may be related to high suicidality in BSDs (Nock et al. 2009). Studies further suggest that lower HRV can characterize BSDs under tonic and phasic conditions. High frequency HRV measures reflects activity within the PNS branch of the ANS (see Duschek et al. 2013; Lopes and White 2006). PNS activity at the heart during emotional responding is associated with engagement of executive PFC control on the limbic system, and thus afferent and efferent brainstem nuclei linked to the heart (Duschek et al. 2013). Studies of BSDs suggest that low HRV are correlated with BSD traits. This is important given that low HRV is associated with poor mental and physical health and psychological flexibility in the face of stress, increasing the risk of cardiovascular disease and mental disorder, and overall morbidity and mortality (see Duschek et al. 2013; Kemp and Quintana 2013).

Studies suggest that euthymic patients have higher HR (Iacono et al. 1983) and lower HRV (Cohen et al. 2003; Lee et al. 2012) at rest than controls, reflecting disturbed capacity to adapt and regulate autonomic arousal. Similarly, in manic (Henry et al. 2010) and subsyndromal (Lee et al. 2012) depressed bipolar patients, there appears to be increased HR and decreased HRV at rest, relative to controls. Furthermore, decreases in HRV appear to be related to both mania (Henry et al. 2010) and depression severity (Lee et al. 2012; Migliorini et al. 2011). In controls at risk for mania, however, there have been findings of increased HRV during emotional films, relative to controls at low risk (Gruber et al. 2008). There has been no comparison between, or within patients, differentiating BSD phases, except for one pilot study showing that HRV seemed to differ from controls when a patient was in a depressed state, rather than in a euthymic state (see Migliorini et al. 2011). Studies that compare bipolar to unipolar (Iacono et al. 1983) and schizophrenia (Henry et al. 2010) patients have not revealed any differential findings. However, many studies have encountered measurement problems—including poor consistency of findings across different HRV measures and short recording times—when compared against established guidelines (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology [Task Force] 1996). These issues have been highlighted in the "Comment" column in Table 5. Therefore, the results of these studies should be

Table 5 Literature review findings of cardiovascular assessment in BSD characterization and differentiation

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Iacono et al. (1983)	HR (cardiotachometer coupler R&L arm electrodes) Phasic HR acceleration Phasic HR deceleration (Main measure was GSR; also EEG)	24 Bipolar Affective Disorder—euthymic 26 Unipolar 46 controls	Yes, tested for effects Imipramine only, not lithium for at least one month, $n = 13$ Lithium only, not imipramine for at least one month, n = 6 Imipramine + Lithium = 26 Drug-free for at least three months, $n = 5$	Resting state with controlled breathing, 2 min Dishabituation Auditory Task, for phase HR changes	✔/✔	The affective disorder groups had higher tonic HR and phasic acceleration than controls	Affective disorders have greater cardiovascular reactivity, due to a tonic difference; however, medication status (imipramine) may explain group differences	While a wide range of physiological factors determines heart rate, the heart is under tonic inhibitory control by the PNS
Cohen et al. (2003)	Holter monitor ECG HR HRV (SDNN, VLF, LF, HF, HFn, LF/HF, TP) QTc	39 Bipolar disorder patients—euthymic 39 controls	Yes, tested for effects Lithium only, $n = 18$ Lithium + other, $n = 11$ Other, $n = 10$	Resting state, no controlled breathing, no time period specified	✔/×	Euthymic patients had lower SDNN,TP, LF/HF, and higher HF%. No difference on HR, QTc, HF, LF, VLF. No differences between patients on different treatments, with or without lithium	Euthymic bipolar patients had decreased HRV	Inconsistent results. Inconclusive due to no specification of the time period

(continued)

Table 5 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
Todder et al. (2005)	Holter monitor ECG HRV (MED, LLE, Shenon entropy, SD1, SD2, SD1/SD2)	32 Bipolar disorder patients—euthymic 24 controls	Yes, did not test for medication effects Lithium, $n = 28$ Valporic acid, $n = 4$	Resting state, no controlled breathing, no time period specified	✔/×	No differences	No difference between euthymic bipolar and controls on non-linear HRV measures	Inconclusive due to no specification of the time period
Gruber et al. (2008)	Ambulatory monitor HR HRV (RMSSD) (also GSR, facial expressions,)	36 High risk mania 54 low risk mania	Yes, tested for effects. Antidepressants in the high risk group, $n = 2$. No medication use in the low risk group	Baseline (90 s) Emotional Films (positive, negative, neutral; 50–170 s)	✔/×	At baseline, high risk mania subjects had higher RMSSD than low risk subjects. No difference for HR or GSR High risk mania subject had higher RMSSD regardless of valence. No differences for HR or GSR	Tonic differences between those at risk for mania and those who are at low risk	Inconclusive due to short time period at baseline, and the short, variable, time periods for the emotional images

(continued)

Table 5 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Henry et al. (2010)	Sensorized with 3 lead ECG HR HRV (SDNN, RMSSD, pNN50, LF/HF, LFn, HFn, SampEn, entropy h)	23 Bipolar disorder patients—acute manic 23 controls 14 schizophrenia patients	Yes, tested for effects Bipolar patients on Antipsychotic + mood stabilizer, $n = 17$ Antipsychotic only, $n = 4$ Mood stabilizer only, $n = 1$ On risperidone, $n = 11$ On valproate, $n = 9$ On lithium, $n = 7$ Not medicated, $n = 1$	Resting state, 5 min	✔/×	Acute manic bipolar patients had greater HR, lower RMSSD, pNN50, HFn, LF/HF, SampEn Entropy h than controls. No difference on SDNN, LFn LF/HF, but no other measure, was positively correlated with scores on mania scale No differences between bipolar and schizophrenia patients	Decreased HRV in acute mania. Severity of acute mania is associated with decreased HRV	Decrease in HRV in acute mania appears to be valid; however, conclusions regarding severity and HRV are in doubt due to inconsistent results. However, it is the study with the least methodological issues. Guidelines prescribe reporting of raw LF and HF power

(continued)

Table 5 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
Migliorini et al. (2011)	Sensorized with 3 lead ECG HR HRV (MEANNN,SDNN, RMSSD, VLF, LF, HF, LF/HF, LFn, HFn, SampEn, Lempel–Ziv, DFA a1, DFA a2, 1/f slope) (also three axis accelerometer)	1 bipolar patient—depressed and euthymic, over time Eight controls	The patient had ECT	Sleep studies over 4 nights	✔/×	MEANNN, SDNN, RMSSD was decreased in the bipolar patient, relative to controls. Lempel–Ziv and SampEn seem to correlate with depression level	In the bipolar patient, HRV seemed to differ when they were in a depressed state, rather than euthymic. When they were euthymic, they had similar values as the controls	Pilot, proof-of-concept study into how HRV measures may be used for home monitoring of changes in clinical state. Needs to be replicated

(continued)

Table 5 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principal findings	Interpretation	Comment
Gruber et al. (2011)	2 lead ECG HR HRV (HF) (also GSR, facial expressions,)	26 bipolar disorder patients—euthymic Bipolar I, $n = 24$. Bipolar II, $n = 2$ 23 controls	Yes, poorly reported tests of effects Lithium, $n = 4$ Anticonvulsants, $n = 14$, Antidepressants, $n = 19$ Neuroleptics, $n = 13$ Benzodiazepines ($n = 4$), Stimulants, $n = 1$ Sedative-hypnotics, $n = 1$	Resting baseline 60 s Positive emotional film, 150 or 181 s Resting baseline 60 s Positive emotional memory task. 60 s	✔/×	Bipolar patients had decreased HR during the positive memory No differences on HR for the positive film Bipolar patients had greater HRV in with the film and memory than controls	HRV may be a biomarker for extreme positive emotion in bipolar disorder	Inconclusive results. The recording periods are too short according to guidelines, and are variable. No connection was made between high positive emotion in the bipolar patients and high HRV Medication also may have affected the results

(continued)

Table 5 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/Diff	Principal findings	Interpretation	Comment
Jung-Sun et al. (2012)	2 limb lead ECG HR HRV (HRV index, SDNN, RMSSD, pNN50, TP, VLF, LF, HF)	33 bipolar patients—subsyndromal depressive phase 59 controls	Yes, only tested effect of lithium versus no lithium Lithium only, $n = 3$ Lamotrigine only, $n = 3$ Antipsychotic only, $n = 16$ Polypharmacy, $n = 16$ Lithium, $n = 22$ No Lithium, $n = 10$	Resting state, 5 min	✔/×	Patients had less SDNN, pNN50, Log TP, and VLF. No differences on HR, LF, HF, or RMSSD	The subsyndromal depressive state is associated with reduced HRV, relative to controls. Increased severity is associated with reduced HRV. HRV is a biomarker of clinically remitted depressive state	VLF cannot be reliably measured in a 5 min period. Log TP and SDNN are equivalent measures. HRV index is a cruder, more summative, geometric measure of variability, which is not related to vagal tone specifically. Regardless, established standards prescribe at least 20 mins of recording for geometric HRV Polypharmacy patients may have included those on TCAs

Note HRV (HRV measures) = the different time and frequency domain, and nonlinear HRV measures employed in the studies (Lopes and White 2006); Char/Diff = the review differentiates between studies that attempt to (1) characterize BSDs (✔/×) or (2) characterize and, differentiate BSDs or differentiate BSDs from other diagnoses (✔/✔)

interpreted with caution. Given the resurgence of interest in this type of research, future directions for research into cardiovascular measures in the characterization and differentiation of BSDs should replicate findings across phases of illness between, and within, patients and other diagnostic groups, in accordance with established guidelines (Task Force 1996). Furthermore, given that cardiovascular measures are some of the least costly, time-consuming, invasive, and most mobile (see Heathers 2013; Mariani et al. 2012; Quintana et al. 2012) of commonly employed measures, the potential clinical utility of HR and HRV in BSD assessment and monitoring should be explored.

4.1.2 Treatment

A review of the cardiovascular literature focusing on the treatment of BSDs is presented in Table 6. The cardiovascular findings of the increased HR and decreased HRV characterizing BSD phases would expect to be normalized with effective treatment. For example, lithium is known to decrease depolarization at the sinoatrial node of the heart (Chong et al. 2001); thus, it could be predicted that lithium administration increases HRV, in the context of the wider literature (Duschek et al. 2013; see Lopes and White 2006). However, no study has directly investigated this possibility. Decreased depolarization at the sinoatrial node could be a direct effect of lithium or a more indirect, neural-ANS integration effect.

The impacts of commonly prescribed pharmacological treatment have been documented as manipulation checks in studies that characterize BSDs using cardiovascular measures. Additionally, there are some other potentially relevant findings from pharmacological HRV studies. Both these types of findings are provided in Table 6. Tricyclic antidepressants are known to decrease HRV in unipolar patients (Kemp et al. 2010) and in a mixed sample of bipolar and unipolar patients (Paclt et al. 2003). Promisingly, there appears to be some effect of lithium on HRV (Henry et al. 2010), consistent with decreased depolarization at the sinoatrial node. This finding should be followed up in trials that investigate the impact of lithium, along with other commonly prescribed medications, on tonic and phasic changes in HR and HRV across BSD phases and in healthy controls. The potential clinical utility of these HR and HRV measures for treatment monitoring in BSDs should be explored. This is important given cardiovascular measures provide insights into suicidality (Lemogne et al. 2011), health and wellbeing (Duschek et al. 2013; Kemp and Quintana 2013), and morbidity and mortality (Kemp and Quintana 2013).

Table 6 Literature review findings of cardiovascular assessment in BSD treatment

Study	Modality measure	Subjects	Finding	Interpretation	Comment
No trials of commonly prescribed treatment on cardiovascular measures in BSD					
Lithium is known to decrease depolarization at the sinoatrial node (Chong et al. 2001). Thus, it is likely that lithium administration increases HRV					
Examples of relevant exploratory results that have been reported					
Iacono et al. (1983)	Cardiotachometer coupler R&L arm electrodes Tonic HR Phasic HR acceleration Phasic HR deceleration (Main measure was GSR; also EEG)	Mixed bipolar and unipolar sample. Imipramine only, not lithium for at least one month, $n = 13$ Lithium only, not imipramine for at least one month, $n = 6$ Imipramine + Lithium = 26 Drug-free for at least 3 months, $n = 5$	Medication status impacted tonic HR and phasic HR acceleration There were no differences between patients taking lithium and those who were not Patients taking imipramine had increased tonic HR and smaller phasic HR deceleration	Tricyclics may have some effect on tonic heart rate and/or cardiac reactivity	Suggests that use of tricyclics may impact cardiovascular tone and reactivity, and should be taken into account when comparing patient groups; consistent with Kemp et al. (Kemp et al. 2010) (below)
Jung-Sun et al. (2012)	2 limb lead ECG HR HRV (HRV index, SDNN, RMSSD, pNN50, TP, VLF, LF, HF)	22 bipolar patients on lithium 10 bipolar patients not on lithium	Reduced LF in patients on lithium, no differences on any other measure	No effect of lithium on HR or HRV due to inconsistent results	Inconsistent results, yet fits with (Chong 2001wf) (above)
Cohen et al. (2003)	Holter monitor ECG HR HRV (SDNN, VLF, LF, HF, HFn, LF/HF, TP) QTc	Euthymic bipolar patients Lithium only, $n = 18$ Lithium + Other, $n = 11$ Other, $n = 10$	No differences between treatments, with or without lithium	Medications have no effects	The "Other" medication category is undefined, so result is inconclusive

(continued)

Table 6 (continued)

Study	Modality measure	Subjects	Finding	Interpretation	Comment
Paclt et al. (2003)	ECG HR RR (also PQRST characteristics, vectorcardiogram, and body surface potential maps)	Bipolar and depressed patients, mixed sample Patients taking dosulepine only, $n = 43$ Patients taking lithium only, $n = 30$ Patients taking citalopram only, $n = 40$ Controls, $n = 21$	HR increased and RR was decreased in patients treated with dosulepine, relative to controls	Tricyclics decrease HRV in a mixed sample	There may be an effect of diagnosis. Cannot differentiate the effects between the bipolar and depressed patients
Henry et al. (2010)	Sensorized with three lead ECG HR HRV (SDNN, RMSSD, pNN50, LF/HF, LFn, HFn, SampEn, entropy h)	23 acute manic bipolar patients Antipsychotic + mood stabilizer, $n = 17$ Antipsychotic only, $n = 4$ Mood stabilizer only, $n = 1$ On risperidone, $n = 11$ On valproate, $n = 9$ On lithium, $n = 7$ Not medicated, $n = 1$ 23 Controls	No different effects of risperidone or valproate on HRV. No effects of antipsychotic medication alone compared to combination of antipsychotic and mood stabilizer. Patients treated with lithium had decreased LF/HF ratio compared to all other groups	Lithium may blunt sympathetic activation	No consistent results. Inconclusive
Kemp et al. (2010)	Meta-analysis of six treatment studies. Mixed methods and analysis techniques HRV (TD, RSA, HF)	Not a study on bipolar patients Meta-analysis of 186 major depressive disorder patients treated with tricyclic, selective noradrenaline inhibitors, and selective serotonin reuptake inhibitors 407 controls	No effect of commonly prescribed antidepressants (SSRIs, SNRIs) in depressed patients, but TCAs decrease HRV	Tricyclic antidepressants decrease HRV	

Note HRV (HRV measures) = the different time and frequency domain, and nonlinear HRV measures employed in the studies (Lopes and White 2006)

4.2 GSR and Multimodal Correlates

4.2.1 Characterization and Differentiation

Here, we present the first review of multimodal methods to study the physiological correlates of BSDs (Table 7). If BSDs can be characterized and differentiated by embodied dysfunction in brain-body integrated systems, multimodal studies would be expected to show this dysfunction. GSR has been employed only in the context of multimodal physiology measurement. In contrast to the parasympathic HRV measures, GSR is used as a measure of tonic SNS activation at rest or during experimental tasks, whereby task-related phasic changes in skin conductance can be compared from a baseline (see Dawson et al. 2007 for full explanation). Increased magnitude of GSRs—associated with the strength of SNS activation—but not the number of responses has been shown in BSDs relative to controls (Iacono et al. 1983; Malhi et al. 2005). Given that studies employing GSR phasic responses in response to brief emotional stimuli could not make this differentiation (Gruber et al. 2008, 2011), GSR magnitude appears to be a trait marker of bipolar disorder. Though simultaneous GSR, EEG, and HR and HRV measures (Iacono et al. 1983)—along with measurement of positive facial emotion expression (Gruber et al. 2008, 2011)—have been utilized, results from these simultaneous measures have been largely inconsistent within studies and thus have not provided complementary information. However, this may be due to methodology (see "Comment" column in Table 7), including lack of spatial resolution using single electrode EEG (e.g., Iacono et al. 1983) and short recording times for HRV measures (e.g., Gruber et al. 2008, 2011).

With the improvement of MR-compatible GSR systems and techniques, preliminary research on BSD with simultaneous fMRI and GSR measurement in BSDs has been conducted (e.g., Malhi et al. 2005). This work suggests that bipolar patients may have cognitive deficits related to arousal and appraisal of emotional stimuli given simultaneous VLPFC hypoactivity and increased SNS activity during an emotional stroop task (Malhi et al. 2005). The future research should examine whether simultaneous and integrative neurological and peripheral physiological measurement provides further insight into BSDs. Should integrative measurements be employed, the neural responses when the central and peripheral ANSs (both PNS and SNS) are concurrently active could be measured (see Gray et al. 2009), and thus embodiment of cognitive and emotional processes can be observed.

With GSR-fMRI integration, for example, neural activity during periods of SNS activity can be partitioned (Gray et al. 2009). This is promising given that PFC activity—the disturbances of which are implicated in BSDs—is positively associated with GSR amplitude (Critchley et al. 2000). Future work will employ these methods given that BSDs may be characterized by a lack of inhibition of the VLPFC on increased amygdala activity which relates to increased SNS activity, which then may be related to the disengagement of the PFC regions involved in appraisal during emotional stimuli, in accordance with aforementioned neural-ANS

Table 7 GSR and multimodal assessment in BSD characterization and differentiation

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation	Comment
Iacono et al. (1983)	Single Au electrode EEG at Cz site Phi, Alpha, Kappa GSR HR (cardiotachometer coupler R & L arm electrodes) Phasic HR acceleration Phasic HR deceleration	24 Bipolar Affective Disorder—in remission 26 Unipolar 46 controls	Yes, tested for effects Imipramine only, not lithium for at least one month, $n = 13$ Lithium only, not imipramine for at least one month, $n = 6$ Imipramine + Lithium = 26 Drug-free for at least three months, $n = 5$	Resting state with controlled breathing (2 min) Dishabituation Auditory Task, for phase HR changes	✔/✔	On average, electrodermal activity was decreased across patient groups for each task Five bipolar patients and one unipolar patient had increased activity There were no differences on EEG. HR findings might be explained by medication effects	Decreased electrodermal activity may serve as a marker of affective disorder	No spatial resolution from one Cz electrode HR and phasic HR measures do not reflect activity of the PNS or SNS, only indices of arousal and changes in arousal
Malhi et al. (2005)	fMRI 3 Tesla BOLD GSR	12 Bipolar disorder patients—euthymic 12 controls	Yes, did not test for effects Lithium only, $n = 3$ Valporate only, $n = 4$ Lithium + Valporate, $n = 1$ Drug-free, $n = 4$	Emotional stroop	✔/×	Bipolar patients had greater electrodermal arousal, relative to controls. Mean GSR responses between groups were equal across valence Bipolar patients had decreased amygdala and VLPFC activity	Cognitive deficit in bipolar disorder might be a due to arousal differences	Concurrent, rather than integrative, illustration of SNS-related arousal differences PNS activity may also play a role

(continued)

Table 7 (continued)

Study	Modality measure	Subjects	Medication	Stimuli	Char/ Diff	Principle findings	Interpretation	Comment
Gruber et al. (2008)	GSR HR HRV Facial expressions	36 High risk mania 54 low risk mania	Yes, tested for effects Antidepressants in the high risk group, $n = 2$. No medication use in the low risk group	Baseline (90 s) Emotional films (positive, negative, neutral; 50–170 s)	✔/×	High-risk group reported elevated positive emotion in response to all film clips, but were equally facially expressive High-risk group had higher resting vagal tone than did the low-risk group High-risk group exhibited higher HRV across all film clips No group differences were found for HR or GSR	Mania is associated with elevated tonic positive emotion	Inconclusive results. The recording periods are too short according to guidelines, and are variable No integration between high positive emotion in the bipolar patients and HRV or GSR
Gruber et al. (2011)	GSR HR HRV Facial expressions	26 bipolar patients Bipolar I, $n = 24$. Bipolar II, $n = 2$ 23 control	Yes, under-reported tests of effects Lithium, $n = 4$ Anticonvulsants, $n = 14$, Antidepressants, $n = 19$ Neuroleptics, $n = 13$ Benzodiazepines ($n = 4$), Stimulants, $n = 1$ Sedative-hypnotics, $n = 1$	Resting baseline 60 s Positive emotional film, 150 or 181 s Resting baseline 60 s Positive emotional memory task. 60 s	✔/×	Bipolar patients had greater HRV in with the film and memory than controls Bipolar patients had increased positive facial expression and decreased HR during the positive memory No differences on HR, GSR, affect, or facial expressions for the positive film	HRV may be a biomarker for extreme positive emotion in bipolar disorder	Inconclusive results. The recording periods are too short according to guidelines, and are variable No integration between high positive emotion in the bipolar patients and HRV or GSR Medication also may have affected the results

Note Char/Diff = the review differentiates between studies that attempt to (1) characterize BSDs (✔/×) or (2) characterize and, differentiate BSDs or differentiate BSDs from other diagnoses (✔/×); *L* left; *R* right

integration accounts (see Damasio 1996; Porges 2007; Thayer et al. 2009) and preliminary findings (e.g., Malhi et al. 2005). In addition to neural-SNS integration, dysfunctional prefrontal engagement of the inhibitive PNS might be involved in BSDs. Thus, the future work in BSDs should explore the integration of the PNS with integrative measurement (e.g., fMRI-HRV measurement; see Thayer et al. 2012). Finally, in order to provide a complete account of the neutral-autonomic integration, longitudinal integrative measurement (e.g., fMRI-GSR-HRV; EEG-GSR-HRV) should be employed. A more complete embodied account and multimodal measurement techniques may provide objective measures of the mechanisms through which emotional lability and mood disturbance occurs in BSDs. Consideration of an embodied psychophysiological mechanism, not just examining individual physiological correlates, may provide the clinically useful, objective physiological measures needed to characterize and differentiate BSDs.

4.2.2 Treatment

Although there have been studies that employ multimodal physiology to characterize BSDs, there are yet to be multimodal investigations of treatment effects and responses. Additionally, treatment studies employing GSR are yet to be conducted. Research has already employed simultaneous fMRI-GSR measurement (e.g., Malhi et al. 2005); thus, determining whether treatment normalizes these correlates is a likely next step. In doing so, researchers may be able to illustrate the manner in which treatment impacts the embodied neural-SNS integration of cognitive and emotional stimuli, which in turn may be related to improvement in depressed and manic symptoms, and prophylaxis in the euthymic phase.

5 An Embodied Framework for the Psychophysiology of Bipolar Spectrum Disorders

Here, we interpret the physiological correlates of BSDs in line with embodied, neural-autonomic integration perspectives (see Craig 2009; Niedenthal 2007), particularly with respect to the crucial role for the body in emotion, motivation, and cognition (see Price et al. 2011). Characterization of BSD as an embodied disturbance is gaining some attention with consideration of molecular biological correlates across circadian, homeostatic, and stress systems (see Malhi et al. 2012; Malhi and Kuiper 2013). A previous review of BSDs (Green et al. 2007) has discussed the potential impact of the neurological dysfunction on autonomic arousal systems; however, the exact disturbance remains to be determined. Initial support for an embodied perspective on BSD psychophysiological correlates originates from preliminary multimodal investigations (e.g., Malhi et al. 2005). These studies may provide the objective physiological measures needed to characterize and differentiate, and make treatment decisions in patients with BSDs.

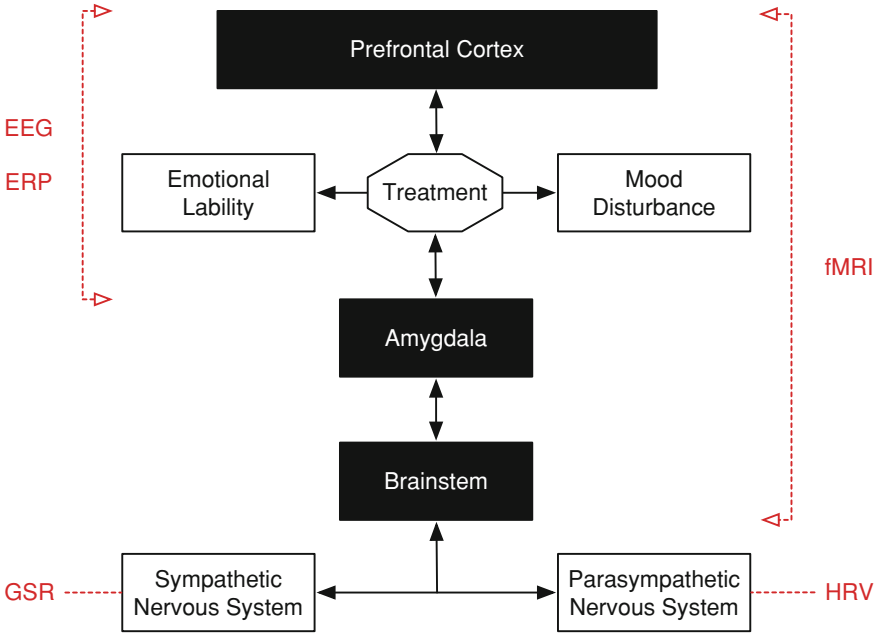

Fig. 1 Embodied framework for the psychophysiology of bipolar spectrum disorders (*BSDs*). This schematic provides a working framework, which enables the characterization of BSDs in an embodied manner. It details the dysfunctional neural-autonomic integration of cognitive and emotional processes and responses, which result in emotional lability and mood disturbances. Within this framework, this dysfunction would be normalized by effective treatment. With respect to noninvasive multimodal measurement of the physiological correlates, cortical neural activity can be measured (but not limited to the measures reviewed; see in red) using electroencephalogram (*EEG*) and functional magnetic resonance imaging (*fMRI*), the temporal information processing stream from the cortex with event-related potential (*ERP*), subcortical neural activity with fMRI, sympathetic nervous system activity with galvanic skin response (*GSR*), and parasympathetic nervous system activity with high frequency heart rate variability (*HRV*)

After having provided overviews of the cardiovascular, EEG and ERP, fMRI, and multimodal literatures that characterize and differentiate BSDs, we incorporated these areas into a simplified, working embodied framework for the physiology of BSDs (see Fig. 1). Accordingly, we suggest that BSDs may be considered as a cluster of disorders characterized by dysfunctional embodied cognitive and emotional neural integration with the ANS, resulting in emotional lability and mood disturbances. In a simplified illustration, dysfunctional VLPFC connectivity between the amygdala impacts the neural-autonomic integration of SNS and PNS activity, through the brainstem, resulting in the core cognitive and emotional dysfunctions of BSDs, which is the target of treatment. Dysfunctional neural-autonomic integration will lead to decreased control over primary visceromotor activity and decreased flexibility for adaptation to stress: SNS hyperactivation and PNS hypoactivation. Dysregulated primary viscerosensory feedback from the

periphery will then be inadequately regulated by hypoactivation of the medial frontal regions involved in the appraisal of the stimuli, resulting in emotional lability and mood disturbance characteristic of BSDs. It is perhaps through bidirectional projections between brain and body that underpin core cognitive and emotional dysfunction in BSDs: VLPFC may fail to regulate the amygdala effectively, increasing SNS activity through visceral efferent pathways, leading to a state of ANS rigidity, which subsequently impacts on the brain through afferent feedback, resulting in the core dysfunctions. An embodied approach to better understanding BSDs may, in time, provide clinically useful physiological measures needed to improve assessment and make treatment decisions in patients with BSDs.

5.1 Novel Predictions Within the Embodied Framework

Within the simple, embodied framework for the physiology of BSDs, novel predictions regarding BSD psychophysiology arise. Within BSD patients during the euthymic phase in comparison to other phases, increased VLPFC activity would be associated with higher PNS and low SNS activity (e.g., greater HRV; lower GSR). However, in comparison to healthy controls, the characteristic decreased VLPFC activity would be associated with lower PNS and higher SNS activity (e.g., lower HRV; greater GSR). We further predict that neural and peripheral responses in response to positive, approach-related stimuli will differ from those in response to negative, withdrawal-related stimuli, and that these responses during mania will differ from those in the depressed phase. We predict that manic phase will be associated with decreased VLPFC and R IFG activity, in addition to increased left-dominant alpha asymmetry, lower PNS and higher SNS activity (e.g., lower HRV; higher GSR), and in turn medial PFC disengagement involved in appraisal of goal-oriented positive stimuli, relative to negative stimuli. By contrast, during the depressed phase, we predict the opposite: decreased VLPFC and R IFG, increased right-dominant alpha asymmetry, low PNS and higher SNS activity (e.g., lower HRV; higher GSR), and in turn medial PFC disengagement from appraisal of withdrawal-oriented negative stimuli, relative to positive stimuli. We predict that effective treatments will act on neural-autonomic integration, thereby normalizing these differences.

6 Conclusions and Future Directions

In conclusion, there are measurable physiological correlates of BSDs and their responses to treatment. Of particular promise, discernible fMRI and EEG and ERP correlates that characterize and differentiate BSDs, and responses to treatment in BSD patients are beginning to emerge. However, the ability to use these correlates to aid classification of BSDs and to improve treatment selection and prediction of

response requires further validation. Additionally, cardiovascular correlates of BSDs and treatment response are still in the initial stages of investigation, but again early findings hold promise especially when considered within the context of the wider literature regarding autonomic disturbances and their relationship with suicidality, and longer term morbidity and mortality. Other than the aforementioned future directions specific to each physiological modality, a number of general future initiatives for research are recommended.

From having developed a simplified integrative embodied framework of BSDs, a major future direction for research into the physiological correlates of BSDs will be to employ simultaneous recording techniques in order to determine dysfunction in the neural-autonomic integration of cognitive and emotional responses. Such an approach will aid our understanding of the adverse impact of BSDs on brain and body function and facilitate the characterization of treatment targets. Building on previous work on neural-autonomic integration in BSDs (e.g., Malhi et al. 2005), future work could partial-out the inhibitory and excitatory neural activation associated with the activity of both the inhibitory PNS and excitatory SNS, respectively. Such work would illustrate the manner in which BSD patients attend to, process, respond to, regulate responses, and recover from cognitive and emotional stimuli, accounting for the bidirectional nature of the central and peripheral ANSs. In doing so, the differential cognitive and emotional inhibition and activation changes associated with the manic and depressed phases may be better integrated and understood. Further, longitudinal and simultaneous multimodal physiological assessment is likely to better differentiate phases of illness, characterize clinical trajectory, and provide insights into the chronobiological changes associated with phase and course in BSDs (see Malhi et al. 2012; Malhi and Kuiper 2013).

With the development of a simplified integrative framework reflecting the current state of the literature, future work may be guided toward examining the embodied, cognitive, and emotional dysfunction that is associated with BSD emotional lability and mood disturbance in accordance with the aforementioned novel predictions. Taking an embodied account of psychophysiological mechanisms, and not just examining the physiological correlates of the dysfunctional parts, is likely to yield more clinical meaningful and objective physiological measures that will in turn improve assessment and therapeutic decision making in patients with BSDs. Given complexity of assessment and the multitude of treatment considerations associated with BSDs, and the fact that they continue to exert an overwhelming burden because of their prevalence and poor response to treatment, there remains a critical need to continue with such endeavors.

7 Conflict of Interest

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