

Elevated Left Mid-Frontal Cortical Activity Prospectively Predicts Conversion to Bipolar I Disorder

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Bipolar disorder is characterized by a hypersensitivity to reward-relevant cues and a propensity to experience an excessive increase in approach-related affect, which may be reflected in hypo/manic symptoms. The present study examined the relationship between relative left-frontal electroencephalographic (EEG) activity, a proposed neurophysiological index of approach-system sensitivity and approach/reward-related affect, and bipolar course and state-related variables. Fifty-eight individuals with cyclothymia or bipolar II disorder and 59 healthy control participants with no affective psychopathology completed resting EEG recordings. Alpha power was obtained and asymmetry indices computed for homologous electrodes. Bipolar spectrum participants were classified as being in a major/minor depressive episode, a hypomanic episode, or a euthymic/remitted state at EEG recording. Participants were then followed prospectively for an average 4.7-year follow-up period with diagnostic interview assessments every 4 months. Sixteen bipolar spectrum participants converted to bipolar I disorder during follow-up. Consistent with hypotheses, elevated relative left-frontal EEG activity at baseline (a) prospectively predicted a greater likelihood of converting from cyclothymia or bipolar II disorder to bipolar I disorder over the 4.7-year follow-up period, (b) was associated with an earlier age-of-onset of first bipolar spectrum episode, and (c) was significantly elevated in bipolar spectrum individuals in a hypomanic episode at EEG recording. This is the first study to our knowledge to identify a neurophysiological marker that prospectively predicts conversion to bipolar I disorder. The fact that unipolar depression is characterized by decreased relative left-frontal EEG activity suggests that unipolar depression and vulnerability to hypo/mania may be characterized by different profiles of frontal EEG asymmetry.

Keywords: bipolar disorder, EEG, reward, biomarker, hypo/mania

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Bipolar disorder is one of the 10 most debilitating illnesses worldwide, involving high rates of divorce, suicide, alcohol and substance abuse, and erratic work performance (Ayuso-Mateos,

2006; Goodwin & Jamison, 2007). However, bipolar disorder is frequently either misdiagnosed, or there is a lengthy time period from illness onset to correct diagnosis (Hirschfeld, Lewis, & Vornik, 2003). The research agenda for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* emphasizes the importance of identifying neural or neurophysiological markers of psychiatric disorders to better understand their pathophysiology and facilitate accurate and timely diagnosis (Phillips & Frank, 2006). This article is the first investigation to our knowledge of whether a neurophysiological marker of approach-related emotion and mood disorders—relative left-frontal electroencephalographic (EEG) activity—prospectively predicts conversion from a milder bipolar spectrum disorder (cyclothymia or bipolar II) to a more severe bipolar I diagnosis.

The bipolar spectrum comprise different diagnoses—cyclothymia, bipolar II, and bipolar I disorder (American Psychiatric Association, 2000). All diagnoses are characterized by hypo/manic and depressive symptoms (except for instances of pure mania), but differ in severity and illness course. Bipolar I is the most, and

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cyclothymia the least, severe bipolar spectrum diagnosis. Growing evidence indicates that having a “softer” bipolar spectrum diagnosis (cyclothymia, bipolar II) increases risk for developing full-blown bipolar I disorder among both children/adolescents (Birmaher et al., 2006; Kochman et al., 2005) and adults (Coryell et al., 1995; Joyce et al., 2004). A 10-year follow-up study of adult patients with bipolar II disorder reported that 7.5% converted to bipolar I disorder (Joyce et al., 2004). The rates of conversion are even higher among children and adolescents with a bipolar spectrum diagnosis. Birmaher and colleagues’ (Birmaher et al., 2009) Course and Outcome of Bipolar Illness in Youth (COBY) study reported that 25% of individuals with child/adolescent onset bipolar II disorder converted to a bipolar I diagnosis (i.e., manic episode onset) during a 4-year follow-up. As part of our Longitudinal Investigation of Bipolar Spectrum (LIBS) project, we recently reported that 15% of college-age participants with child or adolescent onset of cyclothymia or bipolar II disorder converted to bipolar I disorder over a 4.7-year prospective follow-up (Alloy, Urosevic, et al., 2012). Finally, early age-of-onset of first bipolar spectrum episode has been identified as a primary risk factor for heightened impairment and a more severe course (Alloy, Urosevic, et al., 2012; Birmaher et al., 2009; Coryell et al., 1995; Nusslock & Frank, 2011).

To date, research on predictors of progression to a worse diagnosis along the bipolar spectrum has been largely atheoretical, focusing on demographic and clinical predictors of progression. The Behavioral Approach System (BAS) hypersensitivity model proposes that vulnerability to bipolar spectrum disorders may stem from a hypersensitivity of the BAS, which facilitates approach-related affect and behavior to attain rewards and goals (Alloy & Abramson, 2010; Johnson, 2005; Urosevic, Abramson, Harmon-Jones, & Alloy, 2008). This hypersensitivity is posited to lead to an excessive increase in approach or reward-related affect to reward-relevant cues, which may be reflected in hypo/manic symptoms. Support for this perspective comes from psychosocial research indicating that both reward-striving (Nusslock, Abramson, Harmon-Jones, Alloy, & Hogan, 2007) and reward-attainment (Johnson et al., 2000) relevant life events trigger hypo/manic episodes among bipolar individuals. Compared with relevant control groups, bipolar individuals display elevated scores on self-report measures of both BAS sensitivity and sensitivity to reward-relevant cues (Alloy & Abramson, 2010; Alloy et al., 2006; Gruber & Johnson, 2009; Johnson & Carver, 2006; Meyer, Johnson, & Carver, 1999; Meyer, Johnson, & Winters, 2001; Salavert et al., 2007). Among bipolar spectrum individuals, elevated self-reported BAS sensitivity prospectively predicts shorter time to onset of hypo/manic episodes (Alloy et al., 2008) and a greater likelihood of converting from cyclothymia/bipolar II disorder to bipolar I disorder (Alloy, Urosevic, et al., 2012). We recently extended these findings to adolescents aged 14–19, reporting that elevated self-reported BAS and reward-sensitivity was associated with a greater likelihood and shorter time to first onset of a bipolar spectrum diagnosis (Alloy, Bender, et al., 2012).

Relative left versus right frontal EEG activity at rest may serve as a neurophysiological index of BAS sensitivity and approach/reward-related affect (Coan & Allen, 2004; Davidson, 1998; Harmon-Jones, Gable, & Peterson, 2010). Increased relative left-frontal cortical activity indicates a propensity to approach or engage a stimulus, whereas decreased relative left-frontal activity

indicates a propensity toward reduced approach-related motivation or increased withdrawal motivation. In line with this perspective, increased relative left-frontal cortical activity has been associated with heightened self-reported BAS sensitivity (Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997), state and trait-related anger (Harmon-Jones, 2003), positive activation (Tomarken, Davidson, Wheeler, & Doss, 1992), and a response bias toward reward-relevant stimuli (Pizzagalli, Sherwood, Henriques, & Davidson, 2005). Consistent with the perspective that unipolar depression is characterized by a blunted sensitivity to reward cues (Kasch, Rottenberg, Arnow, & Gotlib, 2002), a recent meta-analysis reported that individuals with unipolar depression show moderately less relative left-frontal cortical activity at rest during both depressive and euthymic states (Thibodeau, Jorgensen, & Kim, 2006). This meta-analysis also highlights, however, certain failures to replicate the relationship between relative left-frontal cortical activity and unipolar depression, which may be partially attributable to differences across studies in how depression was operationalized.

In line with the perspective that bipolar disorder is characterized by a hypersensitivity to reward-relevant cues and a propensity to experience an excessive increase in approach-related affect, growing evidence suggests that bipolar spectrum disorders are characterized by increased relative left-frontal cortical activity during laboratory tasks designed to elicit approach-related affect (Harmon-Jones et al., 2008; Harmon-Jones et al., 2002). These data suggest that bipolar disorder and unipolar depression may be characterized by differential patterns of relative left-frontal activity. Further, bipolar I individuals in a manic episode at EEG recording displayed elevated left-frontal cortical activity at rest relative to healthy controls (Kano, Nakamura, Matsuoka, Iida, & Nakajima, 1992). Additional support for the involvement of left-frontal cortical areas in bipolar disorder come from both lesion and neuroimaging based research (Narushima, Kosier, & Robinson, 2003). Employing fMRI, we and others reported that both remitted (Nusslock et al., 2012) and manic (Berpohl et al., 2010) bipolar I individuals displayed elevated reward-related brain function, including left-ventrolateral prefrontal cortical activation, during reward-anticipation, relative to healthy controls.

The present study extends this work by examining the relationship between resting relative left-frontal cortical activity and both bipolar course and state-related variables. Participants, drawn from the LIBS project (Alloy, Urosevic, et al., 2012), had either a cyclothymia or bipolar II diagnosis at study entry, or no history of affective psychopathology (healthy controls). Participants were recruited between ages 18 to 24 because this has been defined as a period of risk for bipolar I disorder onset (Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997). After completing baseline EEG recording, participants were followed prospectively for 4.7 years with semistructured diagnostic interview assessments every four months. In line with the BAS hypersensitivity perspective, we made the following two predictions: (a) Among bipolar spectrum participants, elevated relative left-frontal cortical activity (i.e., alpha power suppression) at baseline would prospectively predict a greater likelihood of converting from cyclothymia or bipolar II disorder to a bipolar I diagnosis (i.e., first manic-episode) over the 4.7-year follow-up; (b) there will be meaningful state-related variation in resting relative left-frontal cortical activity, such that bipolar spectrum individuals in a hypomanic episode at EEG

recording will have higher relative left-frontal activity at rest compared with bipolar spectrum individuals in either a depressive or euthymic/remitted state, as well as healthy control participants. Exploratory analyses examined the relationship between relative left-frontal cortical activity and age-of-onset of first bipolar spectrum episode to determine whether these two proposed markers of bipolar course and severity are related or independent. Analyses of conversion to bipolar I disorder and age-of-onset of first bipolar spectrum episode controlled for lifetime comorbid diagnostic status, depressive and hypo/manic symptoms at EEG recording, medication status, and participant age at EEG recording, given that prefrontal maturation extends into early 20's (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). Analyses of state-related variation in relative left-frontal activity controlled for lifetime comorbid diagnostic status, as well as medication status and participant age at EEG recording.

Method

Participants

Participants were a subgroup of individuals from whom EEG data were collected in the LIBS Project (see Table 1 for demographic information). All data for the present study were collected at the University of Wisconsin-Madison site. Fifty-eight bipolar spectrum individuals ages 18–24 at recruitment (mean age = 20.24; $SD = 1.65$, male/female = 27/31) participated in the present study. Bipolar spectrum individuals (a) met General Behavior Inventory (GBI; Depue et al., 1981) cutoff criteria for cyclothymia (Hypomania-Biphasic [HB] > 13 and Depression [D] > 11), and (b) had a diagnosis of either cyclothymia ($n = 16$) or bipolar II disorder ($n = 42$) at initial recruitment. Diagnoses were determined by an expanded-Schedule for Affective Disorders

and Schizophrenia-Lifetime interview (exp-SADS-L) (Endicott & Spitzer, 1978). Among bipolar participants, the average age of first bipolar spectrum episode was 12.34 ($SD = 4.32$) years. Eighty-four percent of bipolar spectrum participants had a lifetime comorbid psychiatric illness, and 55% were taking at least one psychotropic medication at EEG recording. Baseline EEG recordings occurred on average 14 months following initial recruitment into the LIBS Project. Bipolar participants in the LIBS project who completed EEG recording were excluded from the present study ($n = 6$) if they (a) did not provide at least 2 years worth of diagnostic data following baseline EEG recordings, or (b) converted to bipolar I disorder prior to baseline EEG recording. This resulted in our final sample of 58 bipolar spectrum participants. Bipolar participants excluded from analyses did not differ from those included in analyses on any relevant demographic variables ($p > .29$).

Fifty-nine healthy control individuals participated in the present study (mean age = 19.72; $SD = 3.92$, male/female = 33/26). At recruitment, healthy controls had no history of psychopathology, as indexed by the GBI (HB < 13 and D < 11), and an exp-SADS-L interview. Healthy controls with only a specific phobia diagnosis, however, were included. Healthy controls were gender-ratio-matched with bipolar participants, $\chi^2(1) = 1.03$, $p = .36$, and age-matched, $t(115) = -0.93$, $p = .35$. All participants were right-handed [>30 , Chapman & Chapman Handedness Scale (Chapman & Chapman, 1987)] and provided written, informed consent.

To examine state-dependent variation in relative left-frontal cortical activity, bipolar spectrum participants were classified according to their current clinical state (hypomanic episode, depressive episode, euthymic) on the day of EEG recording (because of missing data, state-related diagnostic data were available for 51

Table 1
Demographic and Clinical Variables

	Bipolar spectrum disorder ($N = 58$)		Healthy control ($N = 59$)		Statistic	p
	Mean or percentage	SD	Mean or percentage	SD		
Age at EEG	20.24	1.65	19.72	3.92	$t(115) = -.93$.35
Female	53%	—	44%	—	$\chi^2(1) = 1.03$	0.36
Caucasian	78%	—	89%	—	$\chi^2(1) = 2.49$	0.13
GBI-D at screening	24.35	9.60	1.55	1.98	$t(115) = 17.4$.001
GBI-HB at Screening	17.44	3.69	2.57	2.81	$t(115) = 24.0$.001
ISS depression at EEG	1.60	0.62	1.20	0.27	$t(115) = 4.41$.001
ISS activation at EEG	1.86	0.51	1.59	0.46	$t(115) = 3.7$.001
Diagnostic status at EEG						
Bipolar II	73%	—	—	—	—	—
Cyclothymia	27%	—	—	—	—	—
Lifetime anxiety disorder	64%	—	4%	—	$\chi^2(1) = 48.02$.001
Lifetime alcohol disorder	38%	—	—	—	—	—
Lifetime substance use disorder	36%	—	—	—	—	—
Psychotropic medication use at EEG	55%	—	—	—	—	—
Antidepressant	50%	—	—	—	—	—
Lithium/depakote	7%	—	—	—	—	—
Antipsychotic	2%	—	—	—	—	—
Anxiolytic	12%	—	—	—	—	—

Note. EEG = electroencephalogram; GBI-D = General Behavioral Inventory–Depression; GBI-HB = General Behavioral Inventory–Hypomania/Biphasic; ISS = Internal State Scale.

of 58 bipolar participants). Current clinical state was determined by an expanded SADS-Change diagnostic interview (exp-SADS-C) (Spitzer & Endicott, 1978). Hypomanic episodes were diagnosed according to *DSM-IV-TR* criteria. To increase variance for depression related analyses, participants were classified as depressed at EEG recording if they were in either a *DSM-IV-TR* major depressive episode (MDE) or a Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) minor depressive episode. Nine bipolar spectrum participants were in either a *DSM-IV-TR* MDE ($n = 5$) or RDC minor depressive episode ($n = 4$) at EEG recording, 21 were in a *DSM-IV-TR* hypomanic episode, and 21 were euthymic.¹

Procedure

At baseline, participants completed resting EEG recordings, the Internal State Scale (ISS; Bauer et al., 1991) to assess current depressive and hypo/manic symptoms, and the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales (Carver & White, 1994). Participants then were followed prospectively for an average of 4.7 years with diagnostic interview assessments every 4 months using the exp-SADS-C interview (Spitzer & Endicott, 1978). Similar to prior epidemiological research (Kendler, Gardner, & Prescott, 2006), the exp-SADS-C that most closely followed the baseline EEG recording date was used to determine diagnostic status at the time of baseline recording.

Measures

Behavioral Inhibition System/Behavioral Activation System Scales (BIS/BAS) (Carver & White, 1994). The 13-item BAS-Total scale assesses self-reported appetitive motivation and sensitivity to potential reward. The 7-item BIS scale assesses self-reported sensitivity to punishment. In the present study, $\alpha_s = .81$ for BAS-Total and $.74$ for BIS. In line with existing research on the relationship between relative left-frontal cortical activity and BAS sensitivity (Sutton & Davidson, 1997), we calculated a BAS Total-BIS difference score by subtracting the z -transformed BIS scale from the z -transformed BAS-Total scale score to create a unidimensional scale of the strength of BAS sensitivity relative to BIS sensitivity.

GBI (Depue et al., 1981). The GBI contains 73-items that assess core bipolar experiences and their intensity, duration, and frequency in two subscales: Depression (D) and Hypomania/Biphasic (HB). The GBI uses a 4-point frequency scale for each item (1 = *never or hardly ever*, 4 = *very often or almost constantly*) and a case-scoring method in which only items rated a 3 (*often*) or 4 (*very often or almost constantly*) contribute toward the total score. Thus, high GBI scores indicate not only high intensity of cyclothymic symptoms, but also high frequency. In the present study, $\alpha_s = .95$ and $.87$ for the D and HB scales, respectively.

Internal State Scale (ISS) (Bauer et al., 1991). The activation and depression subscales of the ISS were used to assess current bipolar symptoms at baseline EEG recording. The Activation scale (ISS-A) is highly correlated ($r = .60$) with the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and the Altman Self-Report Mania Inventory (Altman, Hedeker, Peterson, & Davis, 2001) and has been used as an index of state-related hypo/manic symptoms previously (Alloy et al.,

2008; Alloy et al., 2006; Meyer et al., 1999). The Depression scale (ISS-D) correlates highly ($r = .84$) with the Hamilton Depression Rating Scale (HDRS). In the present study, $\alpha_s = .87$ and $.85$ for the Activation and Depression scales, respectively.

Expanded SADS-L interview (Endicott & Spitzer, 1978). The exp-SADS-L is a semistructured diagnostic interview that assesses current and lifetime Axis I disorders. The original SADS-L was expanded in several ways for the LIBS Project: (a) probes were added to allow derivation of both *DSM-IV-TR* and RDC diagnoses; (b) questions were added to better capture the frequency and duration of symptoms for depression, hypomania, mania, and cyclothymia sections; (c) probes were expanded to assess whether participants' behavioral changes were observable by others; (d) the order of questions was changed to increase the interview's efficiency and comprehension; and (e) additional probes were added to the anxiety disorders section and organic rule-out and medical history sections were added. To gain further specificity than provided by *DSM-IV-TR*, diagnosis of cyclothymia was operationalized as fulfilling all *DSM-IV-TR* criteria plus: (a) at least two ≥ 2 -day episodes of hypomanic mood with at least two hypomanic symptoms per year; (b) at least two ≥ 2 -day episodes of depressed mood with at least two depressive symptoms per year; (c) presence of hypomanic and depressed mood for at least 50% of the day during the respective mood episodes; and (d) presence of this pattern for at least 2 years if older than age 18 or at least 1 year if younger than age 18. Information regarding age-of-onset of bipolar spectrum diagnoses was obtained from the exp-SADS-L and was operationalized as the earliest age at which the participant met criteria for either an MDE or hypomanic episode (for those with bipolar II diagnoses) or the earliest age at which the participant exhibited at least one depressive *and* at least one hypomanic period within a 1-year period (for those with cyclothymia). For both SADS-L and SADS-C, consensus *DSM-IV-TR* and RDC diagnoses were determined by a three-tiered standardized review procedure involving project interviewers, senior diagnosticians, and an expert psychiatric diagnostic consultant. An interrater reliability study based on 105 jointly rated exp-SADS-L interviews yielded $\kappa_s \geq .96$ for bipolar spectrum diagnoses.

Expanded SADS-C interview (Spitzer & Endicott, 1978). The SADS-C was administered at 4-month intervals during prospective follow-up to diagnose episode onset of Axis I disorders and track treatment status. Exp-SADS-C interviewers were blind to participants' diagnostic status at Stage II screening. We expanded the original SADS-C in the same ways as the exp-SADS-L described above. MDEs were defined according to *DSM-IV-TR* criteria as (a) depressed mood or loss of interest $\geq 90\%$ of waking hours, (b) ≥ 4 additional major depressive symptoms, and (c) significant distress or impairment. A MDE-Definite met these criteria for at least 2 weeks and a MDE-Probable for at least 1-week. Minor Depressive Episodes were defined according to RDC criteria as (a) depressed mood or loss of interest $\geq 50\%$ of waking hours, (b) ≥ 2 additional depressive symptoms, and (c) significant distress/impairment for at least 1 week. Manic and hypomanic episodes were defined according to *DSM-IV-TR* cri-

¹ There were no bipolar spectrum participants in a manic episode on the day of EEG recording.

teria. A manic episode required an abnormally and persistently elevated, expansive, or irritable mood lasting ≥ 1 week or any duration if hospitalized, whereas a hypomanic episode required any of these moods lasting at least 4 days. Persistence of manic mood must be $\geq 75\%$ of waking hours in each manic day accompanied by either 3 (if euphoric) or 4 (if irritable) additional manic symptoms, whereas persistence of hypomanic mood must be $\geq 50\%$ of waking hours in each hypomanic day accompanied by 3 additional hypomanic symptoms. Consistent with *DSM-IV-TR*, a manic episode must be characterized by either the presence of psychotic symptoms, cause marked impairment in social or occupational functioning (e.g., serious legal consequences stemming from risky behavior during manic episode), or lead to hospitalization, whereas a hypomanic episode did not require such impairment, but must be associated with an unequivocal change in mood or functioning observable to others. Manic or hypomanic episodes were not due to the effects of a substance or medical condition. Joint ratings of 60 exp-SADS-C interviews for the LIBS Project yielded good interrater reliability for major/minor depressive episodes and hypo/manic episodes ($\kappa_s \geq .88$).

EEG recording and reduction. Eight 60-s eyes-open/eyes-closed trials were collected in counterbalanced sequence using 14-electrodes (F3/F4, F7/F8, C3/C4, T3/T4, T5/T6, P3/P4, Cz, Pz) grounded near Fz. The online reference was the left ear lobe (A1) and data were recorded from the right ear lobe (A2), enabling computation of an off-line averaged-ears reference (impedances < 5 k Ω ; homologs < 1 k Ω). Data were filtered (0.1–100 Hz; 60 Hz notch-filter enabled), amplified, and digitized (500 Hz).

The EEG and electro-oculogram (EOG) signals were visually scored and portions of data containing clearly defined aberrant eye movements, pronounced muscle movements, or other sources of clearly defined artifacts were removed (data from all channels were removed at that point in time). Vertical EOG was then used in a regression-based artifact correction of the EEG (Semlitsch, Anderer, Schuster, & Presslich, 1986), and a second visual inspection insured no aberrations remained. Derived averaged-ears reference data were used for further data reduction. Artifact-free epochs (1.024-s) were Hamming windowed (75%–overlap) and power spectral density ($\mu V^2/Hz$) computed. Total power in the alpha (8–13 Hz) frequency range was obtained across eyes-open/closed for each channel given evidence that greater alpha power at a given scalp electrode reflects less cortical activity (Allen, Coan, & Nazarian, 2004; Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998; Pizzagalli et al., 2005).² Power densities were log-transformed and, as in previous research (Coan & Allen, 2004), asymmetry indices [$\ln(\text{right}) - \ln(\text{left})$ alpha power] were computed for homologous electrodes with higher scores reflecting greater relative left-hemisphere activity. In line with existing research (Coan & Allen, 2004), hypothesis testing focused on mid-frontal (F3/F4) and lateral-frontal (F7/F8) asymmetry indices. Across electrode pairs, mean Cronbach's alpha for the eight 1-min resting recordings was .93.

Data Analysis Plan

Conversion to bipolar I disorder. Rates of conversion to bipolar I disorder were calculated for bipolar spectrum participants. Two hierarchical logistic regression analyses were conducted to examine whether relative left-frontal EEG activity at

baseline prospectively predicted conversion to a bipolar I diagnosis among individuals with a diagnosis of cyclothymia or bipolar II disorder. The first examined whether mid-frontal asymmetry scores (F3/F4) predicted conversion to a bipolar I diagnosis among bipolar spectrum participants and the second examined whether lateral-frontal asymmetry scores (F7/F8) predicted conversion. Medication status, ISS-D, and ISS-A scores at EEG recording were included as covariates, and mid- or lateral-frontal asymmetry scores were entered in the second step. Analyses were also conducted controlling for lifetime comorbid alcohol, substance, and anxiety diagnoses, as well as participant age at EEG recording.

Age-of-onset of first bipolar spectrum episode. Two hierarchical multiple regression analyses were conducted to test whether either mid-frontal (F3/F4) or lateral-frontal (F7/F8) asymmetry scores was associated with age-of-onset of first bipolar spectrum episode. Medication status, ISS-D, and ISS-A scores at the time of EEG recording were included as covariates, and mid- or lateral-frontal asymmetry scores were entered in the second step. Analyses were also conducted controlling for lifetime comorbid alcohol, substance, and anxiety diagnoses, as well as participant age at EEG recording.

State-dependent variation in relative left-frontal cortical activity. Analyses of covariance (ANCOVAs) were used to examine group differences in mid- and lateral-frontal asymmetry scores for bipolar spectrum individuals in either a major or minor depressive episode ($n = 9$), a hypomanic episode ($n = 21$), or a euthymic state ($n = 21$), and healthy controls, on the day of EEG recording, controlling for medication status. Analyses were also conducted controlling for lifetime comorbid alcohol, substance, and anxiety diagnoses, as well as participant age at EEG recording. Fisher's protected t tests (Cohen, Cohen, West, & Aiken, 2003) were employed to minimize familywise error rate which requires a significant omnibus ANOVA F test in to proceed to pairwise comparisons.

Correlation analyses. We examined correlations between both mid- and lateral-frontal asymmetry scores and demographic, clinical, medication, and mood-related variables, among bipolar spectrum participants. To minimize familywise error rates we used a Bonferroni corrected statistical threshold to correct for 15 variables included in the correlation matrix ($p < .003$). For descriptive purposes, we also denote correlations at $p < .05$ and $p < .01$.

Hemispheric specificity. Our primary interest was the relative difference in alpha power over the frontal cortex between the right and left hemispheres [that is, the asymmetry index $\ln(\text{right}) - \ln(\text{left})$ alpha power]. When a significant relationship was observed between an outcome variable and either the mid- or lateral

² There are three sources of data supporting the claim that alpha power is inversely related to cortical activity. (a) Research has documented that sensory input shows modality-specific blocking of alpha activity at cortical regions involved in processing such input (see Allen et al., 2004, for review). (b) Studies employing both positron emission tomography and EEG have shown a negative relationship between alpha power at a specific electrode and cerebral perfusion in tissue underlying that electrode (Cook et al., 1998). (c) Source-localization studies have localized the neuronal generators of frontal EEG asymmetry to frontal cortical regions (Pizzagalli et al., 2005). It is important to note, however, research suggests the thalamus also plays an important role in synchronizing cortical EEG activity (Larson et al., 1998).

frontal asymmetry index, we conducted follow-up analyses to examine the relationship between the particular outcome variable and alpha power at both the right and left mid or lateral-frontal electrodes separately. To accomplish this we separately regressed left and right mid- and lateral-frontal alpha power onto the arithmetic average of alpha power at all recording sites, and saved the unstandardized residuals (Allen et al., 2004). We then ran the aforementioned analyses, replacing the relevant asymmetry index with the appropriate left or right mid- or lateral-alpha power residuals.

Results

Conversion to Bipolar I Disorder

Conversion rates from cyclothymia or bipolar II to bipolar I disorder for the full LIBS project sample are reported in Alloy, Urosevic, et al. (2012). Of the 58 individuals with cyclothymia or bipolar II disorder in the present study, 16 converted to bipolar I during the 4.7 year follow-up (i.e., manic episode onset). The mean number of months to manic episode onset was 29 (range = 3 to 61). Table 2 summarizes the two hierarchical logistic regression findings for mid-frontal (F3/F4) and lateral-frontal asymmetry scores (F7/F8) predicting conversion to a bipolar I diagnosis among individuals with a diagnosis of cyclothymia or bipolar II disorder. In line with prediction, elevated relative left mid-frontal cortical activity (F3/F4) was associated with a greater probability of converting to bipolar I disorder over the follow-up period ($\beta = .67$, $SE = .34$), Wald $\chi^2(1, N = 58) = 3.90$, (odds ratio [OR] = 2.00), $p < .05$, controlling for medication status, ISS-D, and ISS-A scores at EEG recording (Table 2). Relative left mid-frontal cortical activity correctly classified 76% of individuals with a diagnosis of cyclothymia or bipolar II disorder based on whether they did or did not convert to bipolar I disorder over the follow-up period. No relationship was observed between relative left lateral-frontal cortical activity (F7/F8) and conversion to bipolar I ($\beta = .27$, $S.E = .33$), Wald $\chi^2(1, N = 58) = .70$, (OR = 1.32), $p = .40$. The relationship between relative left mid-frontal cortical activity and conversion status was maintained after controlling for lifetime comorbid alcohol, substance, and anxiety diagnoses, as well as participant age at EEG recording ($ps < .22$). None of the non-

frontal asymmetry indices (C3/C4, T3/T4, T5/T6, P3/P4) predicted conversion to bipolar I ($ps > .52$), indicating the relationship between EEG asymmetry and conversion status was specific to the mid-frontal region.

Age-of-Onset of First Bipolar Spectrum Episode

Table 3 summarizes the two hierarchical multiple regression findings for the association between mid-frontal (F3/F4) and lateral-frontal (F7/F8) asymmetry scores and age-of-onset of first bipolar spectrum episode among individuals with a diagnosis of cyclothymia or bipolar II diagnosis. In line with prediction, both elevated relative left mid- (F3/F4) ($B = -.38$, $t = -2.90$, $p < .005$, $partial r = -.37$) and lateral- (F7/F8) ($B = -.37$, $t = -3.00$, $p < .005$, $partial r = -.38$) frontal cortical activity were associated with a younger age-of-onset of first bipolar spectrum episode, controlling for medication status, ISS-D, and ISS-A scores at EEG recording (Table 3). These relationships were maintained after controlling for lifetime comorbid alcohol, substance, and anxiety diagnoses, as well as participant age at EEG recording ($ps < .03$). None of the nonfrontal asymmetry indices (C3/C4, T3/T4, T5/T6, P3/P4) were related to age-of-onset of first bipolar spectrum episode ($ps > .30$), indicating the relationship between EEG asymmetry and age-of-onset was specific to the mid- and lateral-frontal regions.

State-Dependent Variation in Relative Left-Frontal Cortical Activity

In line with prediction, an ANCOVA indicated a significant difference in relative left mid-frontal cortical activity (F3/F4) across the four groups of bipolar spectrum individuals in a major or minor depressive episode, hypomanic episode, or euthymic state, and healthy controls, on the day of EEG recording, controlling for medication status, $F(3, 105) = 3.83$, $p < .05$, $\eta_p^2 = .10$ (Figure 1). Pairwise comparisons revealed that bipolar individuals in a hypomanic episode at the time of EEG recording had significantly greater relative left mid-frontal cortical activity ($M = .17$, $SD = .11$) than bipolar individuals in a depressive episode ($M = .04$, $SD = .08$), $t(28) = 2.89$, $p < .01$, $d = 1.30$, or a euthymic state ($M = .10$, $SD = .09$), $t(40) = 2.13$, $p < .05$, $d = .70$, and

Table 2
Hierarchical Logistic Regression Analyses of Relative Left-Frontal Cortical Activity as a Predictor of Conversion to Bipolar I Disorder Among Participants With a Diagnosis of Cyclothymia or Bipolar II Disorder (n = 58) Controlling for Medication Status and State-Related Depressive and Hypomanic Symptoms

Predictor	B (SE)	Wald χ^2	p	OR
ISS-D	.11 (.30)	.13	.72	1.11
ISS-A	.40 (.31)	1.67	.20	1.40
Medication Status	.36 (.32)	1.27	.26	1.43
Relative left mid-frontal activity [‡] (F3/F4)	.67 (.34)	3.90	.04	2.00
Relative left lateral-frontal activity (F7/F8)	.27 (.33)	.70	.40	1.32

Note. ISS-D = Internal State Scale-Depression score; ISS-A = Internal State Scale-Activation score. Odds ratios (ORs) greater than 1.0 indicate a positive association between the predictor and conversion to bipolar I disorder.

[‡] Separate regression analyses were conducted to examine the association between relative left mid- and lateral-frontal cortical activity and conversion to a bipolar I diagnosis.

healthy controls ($M = .09$, $SD = .11$), $t(78) = 2.75$, $p < .01$, $d = .72$. These effects were maintained after controlling for lifetime comorbid alcohol, substance, and anxiety diagnoses, as well as participant age at EEG recording ($ps < .02$). No difference in relative left mid-frontal cortical activity was observed between bipolar individuals in a depressive episode, bipolar individuals in a euthymic state, and healthy control participants ($ps > .23$). No significant difference between the four groups was observed in relative left lateral-frontal cortical activity, $F(3, 105) = 2.51$, $p = .07$, or any of the nonfrontal asymmetry scores ($ps > .17$), suggesting the relationship between EEG asymmetry and diagnostic status at EEG recording was specific to the mid-frontal region.³

Fn3

Correlational Analyses

Within the bipolar spectrum group, no significant correlations occurred between resting relative left mid- or lateral-frontal EEG activity and the following variables: gender, comorbid psychiatric diagnosis, medication status, and taking versus not taking each of the main psychotropic medication subclasses: antidepressants, Lithium/Depakote, antipsychotics, benzodiazepines (Supplemental Table 1). In line with prediction, greater relative left lateral-frontal cortical activity was associated with increased self-reported BAS sensitivity among bipolar spectrum participants. Self-reported BAS sensitivity was also positively associated with lifetime comorbid alcohol diagnosis, and negatively associated with lifetime comorbid anxiety diagnosis, among bipolar spectrum participants. None of these relationships, however, met the conservative Bonferroni corrected statistical threshold of $p < .003$.

Hemispheric Specificity

None of the analyses of individual hemispheric alpha power were significant, indicating it was the relative relationship between right and left frontal cortical activity (the asymmetry index) that was related to the variables examined in this study.

Table 3

Hierarchical Multiple Regression Analyses of the Relationship Between Relative Left-Frontal Cortical Activity and Age-of-Onset of First Bipolar Spectrum Episode Among Participants With a Diagnosis of Cyclothymia or Bipolar II Disorder (n = 58) Controlling for Medication Status and State-Related Depressive and Hypomanic Symptoms

Predictor	β	t	p	partial r
ISS-D	.07	.53	.60	.07
ISS-A	.13	.99	.33	.13
Medication status	.24	1.84	.07	.24
Relative left mid-frontal activity [‡] (F3/F4)	-.38	-2.90	.005	-.37
Relative left lateral-frontal activity (F7/F8)	-.37	-3.00	.005	-.38

Note. ISS-D = Internal State Scale-Depression score; ISS-A = Internal State Scale-Activation score.

[‡] Separate regression analyses were conducted to examine the relationship between relative left mid- and lateral-frontal cortical activity and age-of-onset of first bipolar spectrum episode.

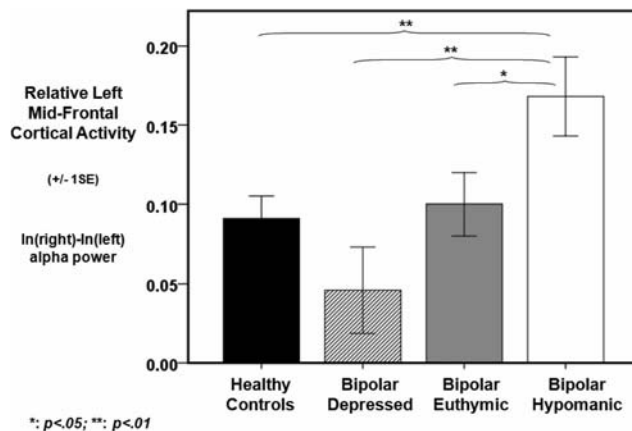


Figure 1. Relative left mid-frontal cortical activity (F3/F4 asymmetry index) as a function of clinical state at the time of electroencephalographic (EEG) recording.

Discussion

Research indicates that bipolar disorder may be characterized by a hypersensitivity to reward-relevant cues and a propensity to experience an excessive increase in approach-related affect, which may be reflected in hypo/manic symptoms (Alloy & Abramson, 2010; Johnson, 2005). The present study extends this research by examining the relationship between resting relative left-frontal cortical activity, a proposed neurophysiological index of approach-system sensitivity and approach-related affect, and bipolar course and state-related variables. Consistent with prediction, elevated relative left mid-frontal cortical activity prospectively predicted a greater likelihood of converting from cyclothymia or bipolar II disorder to a more severe bipolar I diagnosis over the 4.7-year follow-up. It is important to note that this is the first study to identify either a neural or neurophysiological marker that prospectively predicts conversion from a "soft" bipolar diagnosis to bipolar I disorder. Furthermore, and also in line with prediction, elevated relative left mid- and lateral-frontal cortical activity at rest was associated with a younger age-of-onset of a first bipolar spectrum episode. Research has consistently identified early age-of-onset of a first bipolar spectrum episode as a primary risk factor for heightened impairment and poor outcome among bipolar individuals (Alloy, Urosevic, et al., 2012; Birmaher et al., 2009; Coryell et al., 1995; Nusslock & Frank, 2011). Thus, at multiple levels of analysis (conversion to bipolar I disorder and age-of-onset), elevated relative left-frontal cortical activity was associated with a more severe course of bipolar disorder. The fact that the relationship between elevated relative left-frontal cortical activity and both conversion status and age-of-onset was observed after controlling for mood state and medication status at the time of EEG recording, as well as lifetime comorbid diagnoses and participant age at EEG recording, highlights the strength of the

³ There was no significant relationship between current clinical state (hypomanic episode, depressive episode, euthymic) of bipolar spectrum individuals on the day of EEG recording and the likelihood of converting to a bipolar I diagnosis during the 4.7-year follow-up period ($\beta = .47$, $SE = .35$), Wald $\chi^2(1, N = 58) = 1.79$, (OR = 1.60), $p = .20$.

relationship between relative left-frontal cortical activity and bipolar course-related variables.

There is a growing recognition of the importance of identifying neural or neurophysiological markers of psychiatric disorders (Phillips & Frank, 2006). Such markers can facilitate accurate and timely diagnosis, increase understanding of the pathophysiology of psychiatric illness, and help identify individuals at heightened risk for a particular disorder (Gottesman & Gould, 2003). Results from this study suggest that elevated relative left-frontal cortical activity may reflect an important neurophysiological marker of risk for bipolar I disorder. Furthermore, the fact that unipolar depression is characterized by decreased, as opposed to increased, relative left-frontal cortical activity [although see (Reid, Duke, & Allen, 1999) for contrary findings] suggests that unipolar depression and vulnerability for mania may be characterized by different profiles of relative left-frontal cortical activity. Future research is needed directly comparing individuals with bipolar disorder and unipolar depression on both resting and task-related EEG.

In line with research indicating that current state accounts for approximately 40% of the variance in relative left-frontal cortical activity (Hagemann, Naumann, Thayer, & Bartussek, 2002), bipolar spectrum individuals in a hypomanic episode at EEG recording had significantly elevated relative left mid-frontal activity compared with bipolar depressed, bipolar euthymic, and healthy control participants. This finding extends existing research demonstrating that bipolar I individuals in a manic episode display elevated left-frontal cortical activity (Kano et al., 1999), suggesting this elevation is also observed among individuals in a hypomanic episode. We did, not however, find that bipolar depressed participants displayed decreased relative left-frontal cortical activity compared to healthy controls. This may be attributable in part to the relatively small number of bipolar depressed participants in the present study. Future research is needed to more fully examine the relationship between frontal EEG asymmetry and bipolar depression.

Results from the present study support a BAS hypersensitivity perspective of bipolar disorder. Over the past decade there has been growing evidence that bipolar disorder is characterized by elevated scores on self-report measures of both BAS sensitivity and sensitivity to reward-relevant cues (Alloy & Abramson, 2010; Johnson, 2005; Urosevic et al., 2008). Moreover, elevated scores on these dimensions are associated with a greater likelihood of developing a bipolar spectrum diagnosis (Alloy, Bender, et al., 2012) and converting to a more severe bipolar diagnosis (Alloy, Urosevic, et al., 2012). This study extends this work by showing that a neurophysiological index of BAS/approach-system activity predicts bipolar course and is related to current mood state. The present study also compliments fMRI-based research demonstrating that both remitted (Nusslock et al., 2012) and manic (Bermppohl et al., 2010) bipolar I individuals display elevated reward-related brain function, including left-ventrolateral prefrontal cortical activation, during reward-anticipation, relative to healthy controls.

Participants were recruited between ages 18–24 because this has been defined as a period of risk for conversion to bipolar I disorder (Kessler et al., 1997). Epidemiological research, however, suggests multiple risk periods for onset of bipolar I disorder, including late adolescence, early to midtwenties, and late thirties to early forties (Bellivier et al., 2003). Furthermore, growing evidence documents the presence of childhood onset or pediatric bipolar I disorder,

which tends to be associated with higher rates of rapid cycling and irritability than adult bipolar disorder (Birmaher et al., 2009). Future research is needed examining whether relative left-frontal cortical activity is a risk factor for mania onset across the developmental spectrum. The potential importance of this research is highlighted by data indicating that adult and pediatric bipolar disorder may be characterized by different neural profiles, particularly in the amygdala (Chang et al., 2005). Examining relative left-frontal cortical activity in children and adults with bipolar disorder not only has the potential of identifying neurophysiological markers of risk, but informing our understanding of the biological similarities and differences across childhood onset and adult bipolar disorder.

Diagnostic-Related Issues and Study Limitations

The high number of bipolar spectrum participants in a hypomanic episode at EEG recording is likely related to our use of the GBI as a first-stage screening measure, requiring a person to indicate they experience hypomanic symptoms “often” or “very often or almost constantly” to obtain a high score. It is noteworthy, however, that minimal epidemiological research has examined the frequency of hypomanic episodes among bipolar spectrum individuals. Thus, it is unclear whether rates of hypomanic episodes in the present study are comparable to the general bipolar spectrum population. Future research is needed to address this issue.

There were limitations of the present study. Given the small number of participants with cyclothymia, we were unable to examine whether relative left-frontal cortical activity predicted conversion to bipolar II disorder. Future research on this topic is warranted. Future research is also needed with larger sample sizes examining the interaction between relative left-frontal activity and life events in the onset of first manic episode to more explicitly test a vulnerability-stress perspective of bipolar disorder. Finally, quantitative EEG has relatively poor spatial resolution and is unable to provide detailed information or make causal inferences on the neuronal generator of the signal recorded at a particular electrode. Future research using other neuroscience techniques is warranted.

Conclusions

The present study aimed to integrate psychosocial and neurophysiological perspectives on bipolar disorder and to take a theoretical approach to investigate predictors of progression along the bipolar spectrum. The growing evidence that bipolar disorder may be characterized by a hypersensitivity to reward-relevant cues at both the psychosocial and neurophysiological level of analysis has important implications for understanding the pathophysiology of the illness and treatment development (Johnson & Fulford, 2009; Nusslock, Abramson, Harmon-Jones, Alloy, & Coan, 2009). The fact that unipolar depression and vulnerability to mania may be characterized by differential profiles of relative left-frontal cortical activity suggests that frontal cortical activity may serve as a useful neurophysiological marker to differentiate vulnerability to depression and bipolar I disorder (e.g., mania).

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