

Effect of Bipolar Disorder on Left Frontal Cortical Responses to Goals Differing in Valence and Task Difficulty

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Background: The behavioral activation system (BAS) dysregulation theory of bipolar disorder predicts that bipolar individuals will show an excessive increase in approach motivation during reward striving. Building on past research showing that the left frontal cortical region is involved in approach motivation, we predicted that individuals with bipolar disorder would evidence increased relative left frontal cortical activity in response to goal striving, particularly in response to positive challenges.

Methods: Right-handed individuals (age 18–24) with a bipolar spectrum diagnosis ($n = 41$) and individuals with no major affective psychopathology ($n = 53$) were presented with cues indicating that, on a given trial, an easy, medium, or hard anagram (scrambled word) would be presented in 7 seconds and that they would receive money or avoid losing money for the correct solution (10 anagrams of each of the 6 types). During this preparation period, electroencephalogram (EEG) alpha power was measured and hemispheric asymmetry indexes were computed.

Results: Compared with the nonbipolar individuals, individuals with bipolar disorder showed greater relative left frontal cortical activation in preparation for the hard/win trials. Whereas nonbipolar individuals showed a decrease in left frontal cortical activation from medium to hard win trials, bipolar individuals did not. In addition, among bipolar individuals, current self-reported activation related to greater left frontal activation to the hard/win trials.

Conclusions: These results provide support for an integrative biopsychosocial model of bipolar disorder, BAS dysregulation theory, and suggest that relative left frontal activity, which may be involved in mania, is triggered by challenging and potentially rewarding events.

Key Words: Approach motivation, asymmetrical frontal cortical activity, behavioral approach sensitivity, bipolar disorders, EEG alpha power, rewards

The behavioral activation system (BAS) regulates approach behavior to attain rewards and goals, whereas the behavioral inhibition system (BIS) inhibits behavior in response to threat and punishment (1). The BAS is activated by signals of reward and escape from or avoidance of punishment. Activation of the BAS is hypothesized to be associated with hope, anger, and approach motivational tendencies (2). Activation of the left frontal cortex has been implicated as a neurobiological index of BAS (3,4). Theory and research (5–7) suggest that the BAS is important in the bipolar spectrum disorders.

Consistent with the concept by Akiskal (8) of an “affectively dysregulated temperament” as a psychobiological vulnerability for bipolar disorder, Depue *et al.* (5,6) proposed a BAS dysregulation theory of bipolar disorder. According to this theory, bipolar individuals demonstrate an excessive increase in BAS activity in response to rewards, goal striving, and anger evocation and an excessive decrease in BAS activity in response to events such as definite failure. Excessive BAS activity is predicted to be reflected in hypomanic and manic symptoms. Consistent with this hypothesis are results that, compared with control

groups, individuals with bipolar I disorder (9) and individuals prone to hypomanic symptoms (10) show elevated scores on self-report measures of BAS sensitivity (11), activation (12), and achievement motivation (13). Also, goal-striving (14) and goal-attainment (4) life events have been associated with an increase in hypomanic/manic, but not depressive, episodes. According to the BAS perspective, if an event is perceived as a challenge and elicits approach-motivated perceptions of successful coping, the BAS should be activated and hypomania/mania symptoms may ensue.

Support for the idea that left frontal cortical regions are involved in bipolar disorder originates with research with lesion patients with secondary mood disorder. The proximity of left hemisphere lesions to the frontal pole is related to the severity of depressive symptoms, suggesting that deactivation of left prefrontal cortex (PFC) is related to depression. Similarly, right hemisphere lesions, specifically lesions of the structures implicated in the reward system (e.g., orbitofrontal cortex, basotemporal cortex, thalamus, and caudate), have been related to secondary mania (15,16). The increase in mania may have resulted because of increased, unregulated left frontal activation as a consequence of the right hemisphere lesions.

Further support for the idea that left frontal cortical areas are involved in bipolar disorder comes from electroencephalogram (EEG) studies of frontal asymmetry. Increased relative right frontal activity, as measured in EEG resting baseline measurements, has been observed in bipolar depression (17), whereas increased relative left frontal activity has been observed in mania (18). Other data support the antidepressant effects of repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex in unipolar and bipolar depressed individuals (19). Also, currently manic patients show increased glutamine levels in the left dorsolateral prefrontal cortex (DLPFC) suggestive of glu-

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taminergic dysfunction (20). Finally, neuronal abnormalities in the DLPFC have been observed in individuals with bipolar disorder (21–24), and some evidence suggests that neuronal dysfunction is localized to the left DLPFC (25). Overall, data are consistent with the idea that the left frontal cortical region is involved in bipolar disorder.

Following from the above research, BAS dysregulation theory, and other research showing that anger-evoking events activate the BAS (26), one study has found that proneness to hypomania/mania symptoms, as measured by the General Behavior Inventory (GBI) (27,28), is related to increased relative left frontal cortical activity in response to an anger-evoking event (29). These results support a biopsychosocial approach to bipolar disorder and BAS dysregulation that integrates research on the neural circuitry implementing BAS with work on psychosocial factors. However, the individuals in this study were not clinically diagnosed with bipolar spectrum disorders.

The current study examined whether bipolar spectrum individuals evidence exaggerated approach motivational tendencies in response to a proposed BAS activation relevant event (goal striving). Specifically, bipolar spectrum individuals and nonbipolar individuals participated in a laboratory session in which relative left frontal cortical activity was assessed using regional EEG as individuals prepared to solve tasks that varied in difficulty (i.e., easy, medium, and hard) and whether a potential reward was approached or a potential punishment was avoided. Given the heightened BAS sensitivity (13,14) and achievement motivation (30) observed in bipolar individuals, relative left frontal activation differences between bipolar and nonbipolar participants may be most likely to occur in the hard block because bipolar participants may be especially responsive to such a challenge. Consequently, the easy task block was always first, followed by the medium and then hard task block to avoid confounding task difficulty with task switching and to enhance ecological validity (i.e., often in life, tasks begin easy and become progressively harder). Following much research in motivation (31), nonbipolar individuals should disengage when the task becomes more difficult than the effort or outcome is worth. In contrast, we predict that bipolar individuals may not show this adaptive, energy-conserving response but continue to be motivated even when confronted with very difficult or impossible tasks. In addition, although both potential reward/punishment theoretically involve BAS activation, bipolar participants may be even more reactive to the reward condition, especially when it is hard and positively challenging. This prediction is predicated on past research that suggests that bipolar individuals are especially sensitive to reward (32) and research that suggests that punishment cues often evoke both BIS and BAS (33).

We also examined the effects of current self-reported state (hypomania/mania vs. depression vs. euthymia) to test whether current state exerts an effect in addition to diagnostic category. By testing the effects of current state among the individuals with bipolar disorder, we will be in a position to evaluate whether the predicted effect of a bipolar diagnosis on relative left frontal activation to difficult tasks is driven by a putative biobehavioral vulnerability to bipolar disorder, state, or both.

Methods and Materials

Participants

Undergraduate and graduate students were recruited through announcements around campus. At stage I, participants completed the GBI (28). At stage II, participants who met the GBI

Table 1. Descriptive Information on Participants

	No Affective Disorders	Bipolar Disorder	F/z and p
Age (years)	21.74 (.21)	21.63 (.24)	.11, .74
Caucasian	90.57%	87.80%	.43, .67
Female	49.06%	60.98%	1.14, .32
GBI-D at Screening	1.49 (.98)	24.93 (1.11)	249.16, .001
GBI-HB at Screening	2.42 (.54)	17.83 (.61)	359.74, .001
ISS Active	7.06 (.35)	9.00 (.39)	13.93, .001
ISS Depressed	2.08 (.19)	3.32 (.21)	19.74, .001
ISS Well-Being	9.29 (.28)	8.88 (.32)	0.93, .34
ISS Conflict	7.31 (.31)	8.93 (.34)	12.38, .001

Note: Standard errors are in parentheses.

GBI-D, General Behavior Inventory-Depression Scale; GBI-HB, General Behavior Inventory-Hypomania-Biphasic Scale; ISS, Internal State Scale.

cutoff criteria for cyclothymia (hypomania-biphasic [HB] score > 13 and depression [D] score > 11) or for the absence of affective psychopathology (HB < 13 and D < 11), as specified by Depue *et al.* (28), were administered an expanded Schedule for Affective Disorders and Schizophrenia-Lifetime (exp-SADS-L) diagnostic interview (34). Based on the exp-SADS-L interview and the GBI, two groups were formed: 1) individuals with bipolar spectrum disorder (i.e., cyclothymia, bipolar II disorder; $n = 41$) according to the DSM-IV and/or Research Diagnostic Criteria (RDC) (34); and 2) individuals with no lifetime diagnosis of psychopathology ($n = 53$).

Of participants in the bipolar spectrum group, 78% met criteria for bipolar II disorder, while 22% met criteria for cyclothymic disorder. Of the bipolar participants, nine were on psychotropic medications (seven on one antidepressant, one on two antidepressants, and one on both a mood stabilizer and an anxiolytic). Medication information was unavailable for two participants. Of bipolar participants, 25 had comorbid diagnoses—15 anxiety disorder, 15 substance use disorder, and 6 eating disorder. See Table 1 for demographic information.

Participants were strongly right-handed (score > 37 on Chapman and Chapman (35) inventory). Only right-handed individuals participated because research suggests that right- and left-handed persons may differ in hemispheric specialization of emotion. Experimenters were blind to participants' group status. Participants were paid \$40 (\$25 + approximately \$15 in earnings).

Procedure

After providing consent, participants completed questionnaires and were prepared for EEG recording. Participants were given oral and onscreen instructions explaining the upcoming word game. Two trial types were described: the chance to win 50 cents for the correct solution with no loss for incorrect solutions or the chance to lose 50 cents for an incorrect solution with no gain or loss for a correct solution. Seven seconds prior to the presentation of each anagram, the computer indicated the anagram's difficulty and whether it was a possible win or loss trial. Participants were informed they would start the game with \$10 in quarters; a jar containing quarters was on a nearby table.

The anagrams were divided into three difficulty blocks—easy, medium, and hard. Each block included 20 anagrams and began with four practice trials. For easy anagrams (e.g., aws), participants had 10 sec to solve; for medium anagrams (e.g., iumcs), 30 sec to solve; and for hard anagrams (e.g., ssoia), 50 sec to solve. All trials had 5-sec intertrial intervals. The anagrams were assigned to the difficulty blocks according to the median solution

times, determined in a pilot study and elsewhere (36). The easy anagram block was always first, followed by the medium and then hard blocks, to enhance ecological validity. Latency to solve anagrams and number correctly solved were collected, as in past research (37,38), to assess how the predictor variables affected these. Half of the anagrams in each difficulty block belonged to the reward condition; the other half belonged to the punishment condition. After each anagram block, participants completed a questionnaire to assess current affective state, to explore the subjective state of the task performance.

EEG Recording and Processing

Electroencephalogram was recorded after trial information was presented and during a 7-sec period as participants viewed a fixation point. The collection of EEG during this period occurred because approach motivation should be activated by the anticipation of action (39). Electroencephalogram was recorded from 14 (12 homologous and 2 midline) electrodes mounted in a stretch-lycra electrode cap (Electro-Cap, Eaton, Ohio). Electroencephalogram was recorded from the midfrontal, lateral frontal, central, anterior temporal, posterior temporal, and parietal regions of the scalp. The ground electrode was mounted in the cap on the midline between the frontal pole and the frontal site. The reference electrode was placed on the left ear and data were also acquired from an electrode placed on the right ear, so that an offline digitally derived, averaged ears' reference could be computed. Eye movements (electro-oculogram [EOG]) were recorded to facilitate artifact scoring of the EEG. Electro-oculogram was recorded from the supraorbit and suborbit of the left eye. All electrode impedances were under 5000 ohms, and homologous sites (e.g., F3 and F4) were within 1000 ohms of each other. Electro-Gel (Eaton, Ohio) was used as the conducting medium. Electroencephalogram and EOG were amplified with a Contact Precision Instruments (Boston, Massachusetts) amplifier, bandpass filtered (.1 to 100 Hz; 60 Hz notch filter enabled), digitized at 500 Hz onto a computer hard drive. Prior to each participant, a low-impedance .5 Hz 100 μ V square wave signal was run and inspected.

The EEG and EOG signals were visually scored and portions of the data that contained aberrant eye movements, muscle movements, or other sources of artifact 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 (40). Derived averaged-ears reference data were used for data reduction (41). All artifact-free epochs that were 1.024 sec in duration were extracted through a Hamming window, which was used to prevent spurious estimates of spectral power. Contiguous epochs were overlapped by 75% to minimize loss of data due to Hamming window extraction. A fast Fourier transform (FFT) was used to calculate the power spectra. These power values were averaged across the epochs of a given trial. Because alpha power is inversely related to cortical activity (42,43), total power within the alpha (8–13 Hz) frequency range was obtained. The power values were log transformed to normalize the distributions.

As in previous research (44,45), a frontal asymmetry index (natural log right minus natural log left alpha power) was computed for each anticipatory period, using midfrontal and lateral frontal sites (F34, F78); past research has found stronger effects at F78, so our primary predictions concerned this region (46). For comparison purposes, asymmetry indexes for the other sites (T34, T56, C34, P34) were also computed. Anticipatory anagram EEG responses were averaged across trials within each task difficulty type; all participants had at least 80 usable EEG

epochs. Because alpha power is inversely related to cortical activity, higher scores on the indexes indicate greater relative left hemisphere activity.

Measures

General Behavior Inventory depression and hypomania scores were calculated using recommended methods (28). The GBI has good internal consistency, test-retest stability, and overall classification accuracy.

The exp-SADS-L (32) is a semistructured diagnostic interview to assess current and lifetime history of RDC/DSM-IV diagnoses. Aided by consultations with experts, we expanded the SADS-L to enable greater accuracy in diagnosis of bipolar conditions, including additional probes to allow DSM-IV diagnoses and greater precision in assessing the precise number of days an individual was symptomatic. Based on 105 jointly rated interviews, the exp-SADS-L has good interrater reliability (kappas > .96) for bipolar disorder diagnoses. An average interrater correlation for hypomanic symptoms was .93 and for depressive symptoms also was .93. The exp-SADS-L interviewers were blind to GBI scores. Diagnoses were determined by a three-tiered consensual procedure involving review of audiotaped interviews by project interviewers and senior diagnosticians and consultations with an expert psychiatric diagnostic consultant.

Prior to the anagram-solving task, a questionnaire assessed their experience with and expectations/motivation toward the anagrams. Participants also indicated whether or not they were native English speakers and how long they had been speaking English.

The Internal State Scale (ISS) (12) was used to assess current bipolar state. The questionnaire instructed participants to indicate to what extent each statement applied to them today (5-point scale, with labels “very slightly or not at all,” “a little,” “moderately,” “quite a bit,” and “extremely”). The scale consists of four factors: activation (e.g., I feel sped up inside); perceived conflict (e.g., I feel argumentative); well-being (e.g., I actually feel great inside); and depression (e.g., I feel depressed). Each subscale was internally consistent (Cronbach's alphas > .70).

The affect questionnaire instructed participants to “indicate to what extent you felt this way during the last block of anagrams.” Feelings of anger (angry, frustrated, mad), sadness (sad, depressed, hopeless), and hyperactivity (elated, energized, invincible, sped-up, hyper, activated) were assessed. Each subscale was internally consistent (Cronbach's alphas > .66).

Results

Preexisting Group Differences and Manipulation Checks

A multivariate analysis of variance (MANOVA) revealed that the bipolar individuals, as compared with nonbipolar individuals, scored higher on ISS activation and ISS depression, Wilks lambda = .77, $F(2,107) = 16.07$, $p < .001$ (Table 1).

For questionnaire responses concerning anagrams (experience, motivation, etc.), the groups did not differ, Wilks lambda = .87, $F(9,84) = 1.41$, $p = .20$. Also, the groups did not differ in whether or not they were native English speakers, $p > .20$.

Regarding the manipulation check for perceived task difficulty, a significant effect emerged, $F(2,184) = 746.15$, $p < .001$. The easy task was rated as least difficult (mean [M] = 1.31, SE = .05), the medium task was rated as moderately difficult (M = 4.52; SE = .16), and the hard task was rated as very difficult (M = 7.05; SE = .12), all p 's < .001. Groups did not differ in their perceptions of task difficulty, as expected.

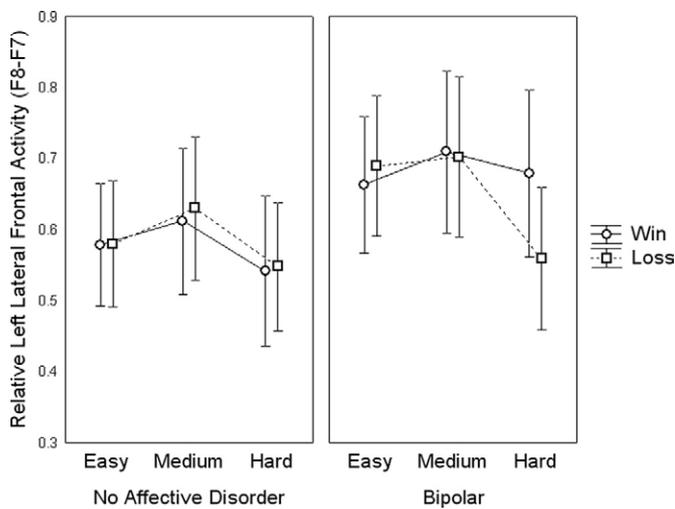


Figure 1. Relative left lateral frontal activity as a function of diagnostic group, task difficulty, and goal.

Effect of Diagnostic Group, Task Difficulty, and Goal on Asymmetrical Cortical Activations

Our primary hypotheses concerned asymmetrical frontal cortical activations during the anagram task and whether diagnostic group status, task difficulty, and potential reward versus punishment interacted to affect these activations. To examine these hypotheses, three-way analyses of variance (ANOVAs) were conducted. For asymmetrical activity at lateral frontal sites, a significant main effect of task difficulty and a significant task difficulty by goal interaction emerged, all *F*'s > 3.15, *p*'s < .05. Finally, a significant diagnostic group by task difficulty by goal interaction emerged, *F*(2,180) = 3.17, *p* < .05 (Figure 1). It indicated that the diagnostic groups differed in their relative left frontal activations to the goals in the very difficult task. Whereas the normal participants evidenced a significant reduction in left frontal activation from the moderately difficult to the extremely difficult task for both types of goals, the bipolar participants only showed the significant reduction in left frontal activation to the extremely difficult task when confronting a potential punishment but not when confronting a potential reward (*p*'s < .05). This divergent response to win versus loss trials in the hard task was greater for bipolar participants (*M* = .1202; *SE* = .02801) than normal participants

(*M* = -.0008; *SE* = .0424), *t*(92) = 2.47, *p* < .02. A three-way interaction with a similar pattern of means emerged for midfrontal sites, but it was not significant, *p* = .20. No other asymmetry indexes produced significant effects.

Additional analyses were performed with participants who were not on psychotropic medications. The three-way interaction was significant with these participants, *F*(2,158) = 3.66, *p* < .03, and the critical divergent response to win versus loss hard trials remained, *t*(81) = 2.54, *p* < .02. Other analyses found no differences between bipolar II and cyclothymic participants in this critical divergent response, *p* > .68, but both groups differed from normal participants, *p*'s < .05.

Effects of Current Clinical State on Asymmetrical Frontal Cortical Responses

To examine whether current clinical state emerged as a predictor of lateral frontal asymmetrical activations during the hard task, correlations of ISS scales and lateral frontal asymmetry were examined for bipolar individuals. Internal State Scale activation correlated positively with relative left frontal activity to most trial types (Table 2). These results suggest that among bipolar individuals, those currently experiencing more activated states evidenced greater relative left frontal cortical responses to the tasks. The same correlations were computed for nonbipolar participants and none were significant (for activation, all positive *r*'s < .06, *p*'s > .68; all negative *r*'s > -.24, *p*'s > .08).

Self-Reported Emotions

A 2 (diagnostic group) × 3 (task) × 4 (emotion: capable, anger, sad, hyperactive) mixed repeated measures ANOVA produced significant effects for emotion, *F*(3,276) = 197.37, *p* < .001; a group by emotion interaction, *F*(3,276) = 3.42, *p* < .02; and a task by emotion interaction, *F*(6,552) = 12.92, *p* < .001. The three-way interaction was not significant, *p* > .66. The main effect for emotion indicated participants reported feeling more capable than any other emotion and that the other emotions did not differ from one another. The diagnostic group by emotion interaction revealed that bipolar individuals reported feeling more sadness than the nonbipolar individuals. Finally, the task by emotion interaction revealed that feelings of being capable decreased from the easy to the medium and from the medium to the hard tasks. In contrast, feelings of anger increased from the easy to the medium and from the medium to the hard tasks. Feelings of being hyperactive decreased from easy to medium and hard tasks, and these feelings did not differ between the

Table 2. Correlations Between Lateral Frontal Asymmetry Indexes to Tasks and ISS Scale Scores for Bipolar Individuals

	W/E	L/E	W/M	L/M	W/H	L/H	Act	Dep	WB
Loss/Easy	.81 ^b								
Win/Med	.67 ^b	.83 ^b							
Loss/Med	.74 ^b	.86 ^b	.85 ^b						
Win/Hard	.81 ^b	.79 ^b	.76 ^b	.80 ^b					
Loss/Hard	.60 ^b	.59 ^b	.58 ^b	.59 ^b	.61 ^b				
Act	.31 ^a	.37 ^a	.30	.23	.35 ^a	.20			
Dep	.01	.02	.06	.11	.11	.01	.15		
WB	.02	.08	.21	.08	-.02	.09	.10	-.49 ^b	
Conflict	.03	.05	.03	.06	.11	-.01	.14	.36 ^a	-.05

Win/Easy refers to asymmetrical lateral frontal activity in preparation for possible win trials that were indicated to be easy in difficulty. Loss refers to the same asymmetry variable but to potential loss trials. Medium refers to medium difficulty trials, and Hard refers to hard difficulty trials.

Act, ISS activation; Conflict, ISS perceived conflict; Dep, ISS depression; ISS, Internal State Scale; L/E, Loss/Easy; L/H, Loss/Hard; L/M, Loss/Medium; Med, Medium; WB, ISS well-being; W/E, Win/Easy; W/H, Win/Hard; W/M, Win/Medium.

^a*p* < .05.

^b*p* < .01.

Table 3. Self-Reported Emotional Responses to the Tasks as a Function of Bipolar Disorder

	Capable	Anger	Sad	Hyperactive
Nonbipolar	3.59 (.08) _{a1}	1.43 (.07) _{b1}	1.10 (.16) _{c1}	1.37 (.06) _{b1}
Bipolar	3.38 (.09) _{a1}	1.67 (.07) _{b1}	1.54 (.18) _{b2}	1.49 (.07) _{b1}

Note: Standard errors are shown in parentheses. Within rows, means with different subscript letters differ at $p < .05$. Within columns, means with different subscript numbers differ at $p < .05$.

medium and hard tasks. Sadness did not differ as a function of task. See Table 3 for simple effects tests. These feelings measures did not map exactly onto the measure of relative left frontal activation and consequently suggest that relative left frontal activation is not a direct measure of feelings (2,26).

Performance on Anagram Tasks

Next, 2 (group) \times 2 (reward vs. punishment) \times 3 (task difficulty) mixed ANOVAs were conducted on number of anagrams solved correctly and on time to solve correct anagrams. For correct solutions, only a main effect of task difficulty resulted, $F(2,168) = 473.70$, $p < .001$. It indicated that participants solved more of the easy anagrams ($M = 9.85$, $SE = .03$), followed by medium anagrams ($M = 6.52$, $SE = .19$) and then hard anagrams ($M = 3.97$, $SE = .16$). For time to solve correct anagrams, only a main effect of task difficulty resulted, $F(2,168) = 602.08$, $p < .001$. It indicated that participants solved the easy anagrams most quickly ($M = 3188.16$ msec, $SE = 76.55$), followed by the medium anagrams ($M = 11951.40$ msec, $SE = 304.24$) and then the hard anagrams ($M = 23343.02$ msec, $SE = 686.71$). No effect of group emerged on anagram performance. Taken together with the asymmetrical frontal cortical results, these results suggest that bipolar individuals may have been motivationally persisting at the hard/win tasks but this persistence did not manifest in better or worse performance on this relatively complex cognitive task.

Examining Effect of Self-Reports on Asymmetrical Frontal Response

The critical difference between groups was the lateral frontal asymmetrical response to hard tasks. As such, we investigated whether perceived task difficulty, reported emotions, or ISS activation or depression affected the magnitude of this effect. Win minus loss trial for relative left lateral frontal activation was regressed onto group and these variables (in separate regressions). In each analysis, group significantly predicted greater relative left frontal activation to the hard/win task over the hard/loss task, controlling for the variables specified above. Interestingly, anger and hyperactivation independently predicted the asymmetrical response, β 's $> .22$, p 's $< .05$.

Discussion

Consistent with the BAS dysregulation theory, bipolar spectrum individuals exhibited greater relative left than right frontal activation to a challenging goal-striving task (i.e., hard anagram trials) compared with control participants when confronting a potential reward but not when confronting a potential punishment. These results indicate that for bipolar individuals, pursuit of a challenging reward may be a more salient BAS-activation relevant event than active avoidance of punishment. Further, these results suggest that asymmetrical frontal brain activity in response to motivational elicitation may serve as a useful neurophysiological correlate of bipolar disorder (29). Finally, current self-reported hypomanic state predicted increased left frontal activation to the

tasks. This suggests that the effect of a bipolar diagnosis on left frontal activation to a challenging goal-striving task was partly driven by current hypomanic state at the time of recording.

The current study highlights the importance of an integrative biopsychosocial model of bipolar disorder. To date, research on biological and psychosocial models of bipolar disorder has proceeded in relative isolation. Research on biological models has provided evidence implicating genetic and neural factors in the etiology of bipolar disorder (21,47). Research on psychosocial factors has highlighted the important role that environmental variables play in determining the timing, frequency, and polarity of bipolar episodes among vulnerable individuals (48). As speculated by Akiskal (8, p. 671), "... what is transmitted are these affectively dysregulated temperaments and that the progression to full-blown bipolar illness is due to environment." Both biological and psychosocial processes need to be examined in the study of bipolar disorder. The current study is an important step in this endeavor, suggesting that exposure to a BAS-activation relevant event has a differential effect on left frontal cortical activation in bipolar individuals relative to normal individuals. The present study does have limitations, however. It relied on a cross-sectional design and did not include a unipolar depression comparison group, incentive control conditions, or counter-balance difficulty trial order. Future studies should address these and examine the extent to which the findings generalize to bipolar I individuals.

Results from the current study have clinical implications. In line with the BAS involvement in regulating appetitive motivation (49), evidence suggests that manic episodes are characterized by extreme goal setting and heightened expectations of success in the achievement domain (50). Goal striving and goal attainment (4,14) predict increases in (hypo)mania. In the presence of such events, bipolar individuals overinterpret their abilities and become unrealistically confident about achieving their desired goal (13). This unrealistic confidence may fuel excessive goal-striving behaviors and even higher goal setting (30). Increased goal-directed activity is one of the most common prodromes of mania and has been associated with increased rates of manic episodes (51). This phenomenon is consistent with the current findings. That is, where normal individuals had the adaptive response to disengage from goal pursuit in response to the extremely difficult reward trials, bipolar individuals maintained a heightened motivational state. This may be an example of how bipolar individuals get "stuck" in a state of goal pursuit and do not, or cannot, regulate out of this state. Clinicians taking a BAS dysregulation perspective should help their clients understand the relationship between ambitious goal-striving behaviors and the onset of manic episodes (52).

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