

## Original Article

## Behavioral Approach System and Behavioral Inhibition System sensitivities and bipolar spectrum disorders: prospective prediction of bipolar mood episodes

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**Objectives:** Research has found that bipolar spectrum disorders are associated with Behavioral Approach System (BAS) hypersensitivity and both unipolar and bipolar depression are associated with high Behavioral Inhibition System (BIS) sensitivity, but prospective studies of these relationships are lacking. We tested whether BAS and BIS sensitivities prospectively predicted the time to new onsets of major depressive and hypomanic and manic episodes in bipolar spectrum individuals.

**Methods:** We followed 136 bipolar II or cyclothymic and 157 demographically matched normal control individuals prospectively for an average of 33 months. Participants completed the BIS/BAS scales and symptom measures at Time 1 and semi-structured diagnostic interviews every four months of follow-up.

**Results:** The bipolar spectrum group exhibited higher Time 1 BAS, but not BIS, scores than the normal controls, controlling for Time 1 symptoms. Among bipolar spectrum participants, high BAS sensitivity prospectively predicted a shorter time to onset of hypomanic and manic episodes, whereas high BIS sensitivity predicted less survival time to major depressive episodes, controlling for initial symptoms.

**Conclusions:** Consistent with the BAS hypersensitivity model of bipolar disorder, a highly responsive BAS provides vulnerability to onsets of (hypo)manic episodes. In addition, a highly sensitive BIS increases risk for major depressive episodes.

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Bipolar disorder (BD) is often a severe, recurrent, or unremitting illness involving significant impairment in many areas of functioning, including erratic work performance and high rates of divorce and suicide (1, 2). During their lifetime, approxi-

mately 1.5% of the US population (3) and 0.5–3.5% of the world population (4) will experience BD and up to 5% will experience a bipolar spectrum condition (5). Research has provided support for a continuum or spectrum of severity within the bipolar category ranging from the milder, subsyndromal cyclothymia, to bipolar II disorder, to full-blown bipolar I disorder (2, 6–10). BD is the sixth leading cause of disability among both physical and psychiatric disorders worldwide (11); however,

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it is understudied compared to other mental health disorders (3).

In the last two decades, two broad neurobiologically-based motivational systems, the Behavioral Approach System<sup>1</sup> (BAS) (12, 13), and the Behavioral Inhibition System (BIS) (13), as well as comparable approach and withdrawal systems (14), has been related to many forms of psychopathology (14–16). The BAS is hypothesized to underlie elation and facilitate goal-seeking in response to incentives and cues for reward, whereas the BIS is proposed to promote inhibition and withdrawal, as well as anxiety, in response to cues of threat and punishment (12, 13, 17–19). Individuals vary in their responsiveness of the BAS and BIS (20) and different patterns of extreme sensitivity of these neurobiological systems may provide vulnerability to various psychiatric syndromes (14–16). This integrative psychobiological approach to understanding psychopathology is highly relevant to BD. Indeed, several theorists (12, 15, 21–23) have suggested that a BAS hypersensitivity model may explain both the depressive and (hypo)manic episodes of individuals with bipolar spectrum disorders. In the present study, we test whether self-reported sensitivity of the BAS (and BIS) predicts time to new prospective onsets of (hypo)manic and depressive episodes among individuals with bipolar spectrum disorders.

### BAS and BD

In its regulation of appetitive motivation and goal-directed behavior, the BAS is activated by external (e.g., an attractive goal object) or internal (e.g., expectancies of goal attainment) signals of reward. BAS activation is hypothesized to be associated with positive affect, such as happiness and elation, and causes the individual to increase movement toward goals as well as cognitive activity designed to promote goal attainment (e.g., hope, self-efficacy, planning) (12, 24). Recent research (25–29) also supports an association between BAS activation and anger and irritability. Along these lines, Bauer et al. (30) argued that heightened activation or drive is a core feature of both euphoric and irritable (hypo)mania. In contrast, deactivation of the BAS has been linked with depression and anhedonia (14, 22, 31–35). Finally, much evidence indicates that relative left versus right frontal cerebral activation [as assessed by

electroencephalography (EEG)] is a neurobiological index of BAS activity (26, 36–38).

According to a BAS hypersensitivity model of BD (12, 21), vulnerability to BD may be reflected in an overly sensitive BAS that is hyper-reactive to relevant cues. Such trait hypersensitivity of the BAS leads individuals to experience great variability in their state levels of BAS activation across situations and over time. A hyper-responsive BAS can lead to excessive BAS activation in response to relevant events involving themes of reward incentive, goal striving and attainment, and anger-evocation. This excessive BAS activation in vulnerable individuals is hypothesized to lead to (hypo)manic symptoms of euphoria, irritability, optimism, excessive self-confidence and goal-seeking, decreased need for sleep, and distractibility (12, 15). Alternatively, excessive BAS deactivation or shutdown of behavioral approach/engagement in response to BAS deactivation-relevant events such as definite failure and non-attainment of goals should lead to depressive symptoms such as sadness, anhedonia, hopelessness, low self-confidence, low energy, and psychomotor retardation (15, 21, 22). In essence, according to the BAS hypersensitivity theory, individuals vulnerable to BD are unable to effectively regulate their emotions and behavior because their proneness to BAS dysregulation renders them excessively responsive to BAS-relevant events. Thus, a core prediction of the BAS hypersensitivity model is that individuals with a highly sensitive BAS should be vulnerable to both hypomanic and depressive states (i.e., bipolar spectrum disorders).

Recent evidence is consistent with the BAS hypersensitivity model of BD. Whereas mania and proneness to hypomania are associated with an increase in relative left frontal cortical activity, a neurobiological index of BAS activity (29, 39), unipolar and bipolar depression are associated with a decrease in relative left frontal cortical activity (40–44). Two studies found that life events involving goal-striving (45) or goal attainment (23), hypothesized to be BAS activation-relevant, triggered diagnosable hypomanic episodes or (hypo)manic symptoms, respectively, in individuals with BD. In addition, cognitive styles with distinctive BAS-relevant features of goal-striving, autonomy, and perfectionism appear to characterize individuals with bipolar spectrum disorders (46–48) and such BAS-relevant cognitive styles prospectively predicted increases in hypomanic symptoms in combination with congruent positive events and increases in depressive symptoms in combination with congruent negative events in a bipolar spectrum sample (49). Similarly, among bipolar I individuals, the BAS-relevant personality trait of

<sup>1</sup> The Behavioral Approach System has also been referred to as the Behavioral Activation System and Behavioral Facilitation System.

achievement-striving predicted increases in manic symptoms over a six-month follow-up (50).

The development of the BIS-BAS scales (20), reliable and well-validated self-report measures of BIS and BAS sensitivities, has aided the empirical testing of the BAS hypersensitivity model of BD. Consistent with the model, individuals with bipolar I (51), bipolar II and cyclothymia (S. Urosevic, unpublished data), and exhibiting or prone to hypomanic symptoms (20, 52) show elevated scores on the BAS total score and subscale scores (Reward Responsiveness, Drive, and Fun-seeking). In addition, high self-reported BAS sensitivity predicted levels of positive affect and hypomanic symptoms over 17 days in a daily diary study of students (53) and predicted an increase in manic symptoms over six months in a recovered bipolar I sample (51). Using a retrospective behavioral high-risk design, Alloy et al. (54) found that individuals selected on the basis of high self-reported BAS sensitivity were six times more likely to obtain a lifetime diagnosis of a bipolar spectrum disorder and exhibited higher impulsivity and proneness to hypomanic symptoms than individuals with moderate BAS sensitivity. The two groups did not differ in their likelihood of a unipolar depression diagnosis. Low levels of BAS have also been related to unipolar depression. Hypoactive BAS distinguished individuals with current and recovered major depression from controls (33, 35, 55) and predicted a worse course of depression over follow-up (33, 34).

Most studies have examined the association between self-reported BAS sensitivity or BAS-relevant cognitive and neurobiological correlates and current or past history of bipolar symptoms and disorders. To date, only one study (51) has examined self-reported BAS sensitivity as a predictor of worsening of symptoms among 59 recovered bipolar I individuals prospectively. The present study expands on this prior work and is the first to test whether self-reported BAS sensitivity predicts the development of new prospective episodes of diagnosed (hypo)mania and major depression in a large, non-clinical sample with bipolar spectrum disorders. It is important to test the applicability of the BAS vulnerability hypothesis to the 'soft' bipolar conditions given that these conditions are on a continuum with more severe BD (e.g., 6), are often precursors to a more severe course (56), and are associated with significant impairment (57).

### **BIS and BD**

The BIS regulates inhibition of behavior or withdrawal in response to punishment (13, 22) and, thus, has been linked to anxiety and depression (22, 24).

Consistent with this theorizing, high levels of self-reported BIS sensitivity have been associated with both unipolar and bipolar depressive states and diagnosed episodes (16, 33, 35, 51, 52, 54, 55). The sole existing prospective study (51) did not find that BIS sensitivity predicted worsening of depressive symptoms in a small, clinical sample of recovered bipolar I patients. Thus, we further examined whether self-reported BIS sensitivity prospectively predicts development of new major depression episodes in a large bipolar spectrum sample.

### **The present study**

The present study investigated the BAS vulnerability hypothesis of BD, as well as the role of BIS vulnerability, using a prospective design in a large, non-clinical sample with bipolar spectrum disorders. Participants were selected based on a two-stage screening process including lifetime structured diagnostic interviews. Those who qualified for either the bipolar spectrum or normal control group completed Carver and White's (20) BIS/BAS scales at Time 1 and were followed prospectively for an average of 33 months with structured diagnostic interview assessments of depressive and (hypo)manic episodes every 4 months.

Based on the BAS hypersensitivity theory of BD, we hypothesized that (i) the bipolar spectrum group would show higher levels of self-reported BAS sensitivity than the normal control group at Time 1; and (ii) higher Time 1 BAS sensitivity would predict prospectively a shorter time to onset of new episodes of (hypo)mania and major depression among the bipolar participants. In addition, based on the associations previously obtained between high BIS sensitivity and unipolar and bipolar depression, we also hypothesized that (iii) the bipolar spectrum group would exhibit higher Time 1 BIS scores than the normal controls; and (iv) higher Time 1 BIS sensitivity would predict prospectively a shorter time to onset of new major depressive episodes in the bipolar group. In order to insure that any concurrent and prospective associations between BAS and BIS sensitivities and bipolar status or development of new mood episodes were not attributable to current symptom levels, all hypotheses were tested controlling for depressive and (hypo)manic symptom scores at Time 1.

### **Methods**

#### **Participants and procedure**

Participants in this study were from the Longitudinal Investigation of Bipolar Spectrum Disorders

(LIBS) Project, a two-site prospective study investigating psychosocial, cognitive, and biological predictors of the course of bipolar spectrum disorders. Participants were selected using a two-stage screening process. In Phase I, approximately 20,500, 18–24-year-old students at Temple University and the University of Wisconsin were administered the revised General Behavior Inventory (GBI) (58) to identify potential bipolar spectrum and normal control participants. Students who met the initial GBI screening criteria (see Measures) were invited for Phase II of screening, involving an expanded Schedule for Affective Disorders and Schizophrenia – Lifetime (exp-SADS-L) (59) diagnostic interview. Informed consent was obtained from participants. All interviews were tape-recorded to obtain consensus diagnoses and interrater reliability checks. Students who met DSM-IV (60) and/or Research Diagnostic Criteria (RDC) (61) criteria for bipolar II (Bi II), cyclothymia (Cyc), or bipolar not otherwise specified (BiNOS)<sup>2</sup>, but having no lifetime history of mania (or major depression if diagnosed with Cyc or BiNOS), were invited to participate in the longitudinal study. Normal controls were recruited and matched to bipolar participants on age, sex, and ethnicity. Based on the exp-SADS-L interview, normal participants had no lifetime history of major depression (MD), manic (Ma) or hypomanic (Hyp) episodes, Cyc, or of other Axis I psychopathology, with the exception that they could have a specific phobia. In addition, normal participants with a family history of mood disorders were excluded from the study. Participants who met all of the above criteria were invited to participate in the longitudinal phase of the LIBS Project and provided informed consent.

The final LIBS Project bipolar sample included 149 Bi II participants (56 male, 93 female) and 57 Cyc or BiNOS participants (23 male, 34 female) aged 18–24 years (mean age of 19.6 ± 1.6 years). The ethnic composition of the bipolar sample was 68.9% Caucasian, 13.1% African-American, 5.1% Hispanic, 3.6% Asian, 0.5% Native American, and

8.2% Other. Of the 206 bipolar participants, only 31 (15.0%) had sought treatment (medication or psychotherapy) prior to the start of the LIBS Project and 63 (30.6%) sought treatment during the follow-up phase of the study. Of these 63, 32 (15.5%) were treated with medications (with or without psychotherapy), 26 (12.6%) received psychotherapy only, and 7 (3.4%) were hospitalized (including 2 who also received other treatment). The final normal sample included 86 males and 122 females aged 18–24 years (mean age of 19.7 ± 1.5 years), with 72.8% Caucasian, 12.1% African-American, 3.4% Hispanic, 4.4% Asian, 0.5% Native American, and 6.8% Other. Only participants with complete data for this study were included in the present analyses, resulting in a final sample for this study of 136 bipolar (100 Bi II, 36 Cyc or BiNOS) and 157 normal participants. The present sample did not differ from other LIBS Project participants who were not included in these analyses on demographics, diagnosis, treatment history, or GBI scores. Table 1 presents the demographic data for the sample included in the present analyses. The bipolar spectrum and normal groups did not differ from each other on age, gender or ethnicity.

At Time 1 of the project, participants completed the BIS/BAS scales and depressive and (hypo)man-

Table 1. Demographic information, Behavioral Inhibition System (BIS)/Behavioral Approach System (BAS), and initial symptom scores as a function of diagnostic group

	Bipolar spectrum (n = 136)	Normal control (n = 157)
Age (years)	19.83 (1.67)	19.98 (1.62)
Sex	60.7% Female	57.1% Female
Ethnicity	76.7% Caucasian 11.3% African-American 5.3% Hispanic 2.0% Asian 0.7% Native American 4.0% Other	77.4% Caucasian 10.1% African-American 3.0% Hispanic 3.6% Asian 0.6% Native American 5.4% Other
BIS	20.86 (3.71)	20.11 (3.12)
BAS Total	41.08 (5.32)	37.95 (5.15)***
BAS Drive	11.60 (2.34)	10.48 (2.41)**
BAS Fun-seeking	12.45 (2.37)	11.01 (2.25)***
BAS Reward Responsiveness	17.03 (1.97)	16.44 (1.93)
BDI	10.73 (8.31)	2.20 (2.67)***
HMI	13.69 (6.89)	12.59 (5.42)

Means are reported with standard deviations in parentheses. BDI = Beck Depression Inventory; HMI = Halberstadt Mania Inventory.

\*\*p < 0.01; \*\*\*p < 0.001.

<sup>2</sup> The bipolar NOS diagnosis included individuals who exhibited recurrent hypomanic episodes without diagnosable depressive episodes, individuals who exhibited a cyclothymic pattern but with hypomanic and depressive periods that did not meet minimum duration criteria for hypomanic and depressive episodes, and individuals with hypomanic and depressive periods that were too infrequent to qualify for a cyclothymia diagnosis. Participants who met criteria for bipolar I disorder were excluded because an aim of the LIBS Project was to predict conversion to bipolar I status over time.

ic symptom measures (as well as other measures not relevant to the current study). Although bipolar spectrum participants had a lifetime bipolar diagnosis, most (90.4%) were not in either a depressive or (hypo)manic episode at Time 1. An exp-SADS-Change interview was administered to assess MD, Hyp, and Ma episodes at each four-month assessment during the follow up. The present study was based on an average of  $33.10 \pm 16.89$  months of follow-up. All participants were paid for their time.

#### Measures

*Phase I: Self-report screening measure.* The revised GBI (9, 58) is a time-efficient, economical self-report screening measure to assess affective disorders in large populations. It was used to identify potential bipolar and normal participants to invite for the Phase II diagnostic screening interview. The revised GBI contains 73 items that assess core bipolar experiences and their frequency, intensity, and duration on two subscales: Depression (D) and Hypomania and Biphasic (HB) items combined. We used the case-scoring method of Depue et al. (9, 58) to identify potential bipolar and normal participants. Only items rated as a '3' ('often') or '4' ('very often or almost constantly') on the GBI 4-point frequency scale contributed a point toward the total score on each subscale. Based on the cut-offs recommended by Depue et al. (58), those participants who scored  $\geq 11$  on the D scale and  $\geq 13$  on the HB scale were identified as potential bipolar spectrum participants (Hi GBI group), whereas those who had a D score  $< 11$  and an HB score  $< 13$  formed a potential normal control (Lo GBI) group. These criteria were based on the findings of Depue et al. (58) and a pilot study for the LIBS Project in which Hi and Lo GBI students, using these cut-offs, were validated against diagnoses derived from exp-SADS-L interviews. The GBI has good internal consistency ( $\alpha = 0.90\text{--}0.96$ ), test-retest reliability ( $r = 0.71\text{--}0.74$ ), high specificity (0.99) and adequate sensitivity (0.78) for bipolar spectrum conditions (9, 58). In addition, it has been validated extensively in college, psychiatric outpatient, and offspring of bipolar I patient samples (9, 10, 58).

*Phase II: Diagnostic interview.* The exp-SADS-L (59) is a semi-structured diagnostic interview that assesses current and lifetime history of Axis I disorders. To ensure the clinical validity of our diagnostic procedures for assessing bipolar spectrum disorders, we consulted with experts on BD (Drs. H. S. Akiskal, J. Angst, P. J. Clayton,

J. Endicott, and A. Gruenberg). Aided by these consultations, we expanded both the SADS-L and SADS-C interviews (see below for overview of SADS-C) to enable greater accuracy and reliability in diagnosis of bipolar conditions, including: (i) additional probes to allow for the assignment of DSM-IV as well as RDC diagnoses; (ii) expansion of the number of items and improvements in the probes in the Depression, Mania/Hypomania, and Cyclothymia sections; (iii) additional probes to assess the precise number of days participants felt depressed or euphoric/irritable and for what percentage of waking hours of each day they felt depressed or euphoric/irritable in the Depression and Mania/Hypomania sections, respectively; (iv) improvements of the probes in the Depression, Mania/Hypomania, and Cyclothymia sections based on Depue's Behavioral Variability Interview (62); (v) addition of items in the Cyclothymia section that assess the frequency, duration, and switch rapidity of depressive and hypomanic periods; (vi) addition of probes to examine the extent to which changes in participants' behavior were noticeable to people in their lives; (vii) for each symptom item, we utilized a 5-point scale (0–4) to make ratings in which 3 was the cut-off for presence of the symptom; (viii) Past Depression and Mania/Hypomania sections were placed immediately after the corresponding current sections to increase participants' understanding; and (ix) sections were added to assess eating disorders, attention-deficit hyperactivity disorder, and acute stress disorder, additional probes were added in the anxiety disorders section, and an organic rule-out module and medical history section were appended. The exp-SADS-L interview has yielded  $\kappa \geq 0.95$  for MD diagnoses and  $> 0.90$  for all unipolar depressive diagnoses based on 80 jointly rated interviews (63). An inter-rater reliability study based on 105 jointly rated exp-SADS-L interviews for the LIBS Project yielded  $\kappa \geq 0.96$  for bipolar spectrum diagnoses. Extensively trained research assistants, blinded to participants' Phase I GBI status and scores, conducted the interviews. Consensus DSM-IV and RDC diagnoses were determined by a three-tiered standardized diagnostic review procedure involving senior diagnosticians and an expert psychiatric diagnostic consultant (Dr. A. Gruenberg).

*Prospective diagnostic measure.* An expanded SADS-Change interview (exp-SADS-C) (64) was administered approximately every four months during the prospective follow-up period. The exp-SADS-C was used to assess onsets, remissions, and relapses and recurrences of diagnosable episodes of

Axis I psychopathology, including DSM-IV and RDC MD, Hyp and Ma episodes, during each four-month interval. Interviewers were blinded to participants' BIS/BAS scores, as well as their Phase I GBI scores and Phase II diagnostic status. The SADS-C was expanded in the same way as the SADS-L interview. In addition, features of the Longitudinal Interval Follow-up Evaluation (LIFE II) (65) were added to the exp-SADS-C in order to systematically track the course of symptoms and episodes during the follow-up. Although the LIFE II tracks symptoms on a weekly basis, the exp-SADS-C inquired about the presence of each symptom on a daily basis during the four-month interval. Inter-rater reliability (49) for the exp-SADS-C in joint ratings of 60 interviews for the LIBS Project was good ( $\kappa > 0.80$ ). In a validity study, participants dated their symptoms on the exp-SADS-C with at least 70% accuracy compared to daily symptom ratings made over a four-month interval.

*Criteria for bipolar spectrum disorders.* DSM-IV and RDC criteria were used for both the diagnosis of bipolar spectrum disorders and bipolar spectrum episodes. Bipolar II disorder was operationalized by the occurrence of one or more DSM-IV or RDC MD episodes accompanied by at least one DSM-IV or RDC Hyp episode (for episode definitions, see below). The presence of a Ma or Mixed Episode precluded a bipolar II diagnosis. The symptoms of bipolar II disorder must have caused clinically significant distress or impairment in social, occupational, or other areas of functioning. However, consistent with DSM-IV, Hyp episodes themselves did not need to cause impairment, but must have been associated with an unequivocal change in mood and functioning that is observable to others.

Cyclothymic disorder was operationalized as recurrent periods of depression (not meeting criteria for MD episodes) and of Hyp (not meeting criteria for Ma episode) that occurred over at an least two-year period. During this two-year period, any symptom-free interval lasted no longer than two months. Given that DSM-IV and RDC Criterion A for cyclothymic disorder does not specify the minimum duration of depressive or hypomanic periods required for the diagnosis, we required a two-day minimum duration for both kinds of periods based on the RDC for Hyp and Depue et al. (9). We also required at least 2 hypomanic and 2 depressive periods within one year for a cyclothymic diagnosis. Based on consultation with Dr. J. Endicott, Criterion A symptoms for both depression (sadness or loss of interest) and hypomania (elevated, expansive, irri-

table) needed to be present at least 50% of the day, and participants needed at least two additional symptoms, for both kinds of periods. Significant distress or impairment in important areas of functioning must have been reported as a result of cyclothymic disorder for DSM-IV diagnosis, but not for RDC diagnosis. Cyclothymic disorder was diagnosed only if the initial two-year period of cyclothymic symptoms was free of MD episodes. After the initial two-year period, MD episodes could have been superimposed on the cyclothymic disorder, in which case both cyclothymic and bipolar II disorder are diagnosed.

*Criteria for bipolar spectrum episodes.* For both exp-SADS-L and exp-SADS-C, full-blown Hyp episodes were defined according to DSM-IV or RDC criteria. Hyp episode required an abnormally and persistently elevated, expansive, or irritable mood that lasts at least 4 days for DSM-IV and 2 days for RDC diagnosis. Persistence of hypomanic mood must be  $\geq 50\%$  of waking hours in each hypomanic day accompanied by either 2 (RDC) or 3 (DSM-IV) additional hypomanic symptoms (note that Dr. J. Endicott suggested that we operationalize persistence as  $\geq 50\%$  of waking hours). If the mood is irritable rather than elevated or expansive, one more additional symptom must be present for both DSM-IV and RDC. Consistent with DSM-IV, the episode must be associated with an unequivocal change in mood and functioning that is observable to others; however, a Hyp episode is not severe enough to cause marked impairment in social or occupational functioning, or necessitate hospitalization, and there are no psychotic features present (as this is the criteria for Ma). Indeed, research suggests that hypomanic symptoms among bipolar spectrum individuals sometimes may even enhance functioning (57). The hypomanic symptoms are not due to the effects of a substance or medical condition. MD episodes also were defined according to DSM-IV or RDC criteria requiring persistence of depressed mood or pervasive loss of interest to be  $\geq 90\%$  of waking hours in each depressed day and accompanied by 4 (DSM-IV) or 5 (RDC) additional depressive symptoms (note that Dr. J. Endicott suggested that we operationalize the persistence requirement of 'most of the day' as  $\geq 90\%$  of waking hours). This depression had to be present for at least two weeks, cause clinically significant distress or impairment, and not be the result of a substance or medical condition.

*BIS/BAS scales.* The BIS/BAS scales were developed by Carver and White (20) to quantify

individual differences in sensitivity of the BIS and BAS and they are the most frequently used self-report measures for this purpose. The scales include 20 items, on 4-point Likert scales, ranging from 'strongly disagree' to 'strongly agree,' and consist of 1 BIS subscale, and 3 BAS subscales: Reward Responsiveness (RR), Drive (D), and Fun-seeking (FS). All subscales have demonstrated adequate internal consistencies ( $\alpha$  is in the range 0.59–0.74) (20, 54) and good test–retest reliabilities and stabilities in both bipolar spectrum and normal control samples (S. Urosevic, unpublished data). Confirmatory factor analyses of the BIS/BAS scales have confirmed the latent structure of 1 BIS scale and 3 correlated BAS subscales (20, 55). Numerous studies support the construct validity of the BIS/BAS scales, including their relation to prefrontal cortical activity, affect, personality traits, and performance on reaction-time and learning tasks involving incentives (e.g., 26, 38, 44, 54, 55, 66, 67). The BIS/BAS scales were administered to participants in the final sample at Time 1 of the study.

*Self-report symptom measures.* Initial levels of depressive symptoms at Time 1 were measured with the Beck Depression Inventory (BDI) (68). The BDI is a 21-item self-report questionnaire that assesses the severity of affective, motivational, cognitive, and somatic symptoms of depression. The BDI has been validated in student samples (69) and the internal and test–retest reliabilities are good in both clinical and non-clinical samples (69).

Initial levels of (hypo)manic symptoms at Time 1 were assessed with the Halberstadt Mania Inventory (HMI) (70). This 28-item self-report measure was modelled after the BDI, and similar to the BDI, it assesses the affective, motivational, cognitive, and somatic symptoms of (hypo)mania. Like the BDI, it asks participants to choose 1 of 4 statements graded in severity (e.g., 'I do not feel particularly happy', 'I feel happy', 'I feel so happy and cheerful it's like a high', or 'I am bursting with happiness and I'm on top of the world'). The HMI has good internal consistency ( $\alpha = 0.82$ ), and it has demonstrated convergent validity with the MMPI-Mania scale ( $r = 0.32$ ,  $p < 0.001$ ), as well as discriminant validity with the MMPI-Depression scale ( $r = -0.26$ ,  $p < 0.001$ ) and the BDI ( $r = -0.12$ ,  $p < 0.001$ ) (70). In the LIBS Project, the HMI correlated ( $r = 0.46$ ) with hypomanic symptoms rated from the exp-SADS-C interview. The HMI also shows expected changes as cyclothymic individuals cycle through hypomanic, euthymic, and depressed mood states (70). That

is, cyclothymic participants' HMI scores were significantly higher when they were in a Hyp period (mean score of 23.9) than when they were in a euthymic period (mean score of 18.8) or a depressed period (mean score of 15.7) (70).

#### Data analyses

Initial descriptive analyses using Pearson correlations were conducted to examine the associations between BIS/BAS scores and initial symptom levels (BDI and HMI scores). In addition, the likelihood of onset of prospective episodes of MD, Hyp, and Ma were calculated. To test Hypotheses 1 and 3, analyses of covariance (ANCOVA) was used to examine group differences in BIS and BAS scores, controlling for initial BDI and HMI symptom scores to insure that relationships between BIS and BAS and bipolar status were not due to current symptomatic state. Cox proportional hazard regression (survival) analyses were used to examine the relationship between Time 1 BAS and BIS sensitivities and time (in days) to bipolar participants' first prospective onset of MD and Hyp/Ma episodes (Hypotheses 2 and 4). We utilized this analytic technique because it allows for varying length of follow-up in longitudinal studies and, thus, minimizes bias due to attrition (71, 72). In addition, survival analysis utilizes all available data at each time point and accounts for censored, or missing, data. Bipolar participants who were already in an affective episode at Time 1 were excluded from the survival analyses. We entered BIS or BAS scores as the predictors and time to first MD or Hyp/Ma episode as the outcome variables. BDI and HMI scores at Time 1 were included as covariates. When the BAS total score was a significant predictor of time to mood episode onset, we also examined which BAS subscales contributed to this significant prediction.

## Results

### Correlations between BIS/BAS and initial symptoms

Table 2 presents the correlations between the BIS and BAS scores and BDI and HMI scores in the entire sample at Time 1. Higher BIS scores were associated with higher depressive symptoms (BDI) and lower (hypo)manic symptoms (HMI). In addition, higher BAS and higher BAS-D and BAS-FS were related to higher (hypo)manic symptoms. Finally, BIS and BAS scores were unrelated to each other, with the exception that BIS was correlated positively with higher BAS-RR.

Table 2. Pearson correlations of Behavioral Inhibition System (BIS)/Behavioral Approach System (BAS) scales and symptom scores

	BDI T1	HMI T1	BIS	BAS-Tot	BAS-D	BAS-FS	BAS-RR
BDI T1	1						
HMI T1	-0.065	1					
BIS	0.208***	-0.192**	1				
BAS-Tot	0.108	0.177**	0.028	1			
BAS-D	0.052	0.214***	-0.092	0.827***	1		
BAS-FS	0.138*	0.160**	-0.077	0.824***	0.511***	1	
BAS-RR	0.071	0.038	0.276***	0.735***	0.420***	0.411***	1

BDI T1 = Beck Depression Inventory Time 1; HMI T1 = Halberstadt Mania Inventory Time 1; BAS-Tot = Behavioral Approach System – total from the BIS/BAS scales; BAS-D = BAS-Drive subscale; BAS-FS = BAS-Fun-seeking subscale; BAS-RR = BAS-Reward Responsiveness subscale.

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001.

Diagnostic group differences in BIS/BAS

Table 1 displays the respective mean and SD of the BIS/BAS scores as a function of diagnostic group<sup>3</sup>. Controlling for initial symptom levels, bipolar participants exhibited higher total BAS scores [ $F(1,257) = 12.44, p < 0.001$ ], as well as higher BAS-D [ $F(1,257) = 7.14, p < 0.01$ ] and BAS-FS [ $F(1,257) = 15.04, p < 0.001$ ] subscale scores, than did normal controls. The two groups did not differ on BAS-RR [ $F(1,257) = 2.42, p < 0.12$ ]. In addition, the groups did not differ on BIS sensitivity [ $F(1,257) = 0.20$ , not significant], although the group difference was marginally significant ( $p < 0.06$ ) when the BDI and HMI were not covaried.

Rates of mood episodes

For the subsample of LIBS Project participants included in the present analyses, we examined the proportion that experienced various affective episodes during the average of 33 months of follow-up. At least one MD episode occurred in 70.6% of the bipolar spectrum and 9.6% of the normal controls, whereas at least one Hyp episode was experienced by 85.3% of bipolar and 1.9% of normal participants. No normal controls experienced onset of a Ma episode, whereas 12.5% of bipolar participants did.

BIS/BAS as a prospective predictor of time to mood episodes

BAS total and BAS-RR significantly predicted the time to bipolar spectrum participants' first Hyp/

<sup>3</sup> In previous articles (45, S. Urosevic, unpublished data), we reported on BIS and BAS score differences in subsets of our bipolar spectrum and normal control groups. The present findings are based on the entire sample with BIS and BAS scores available at both sites.

Table 3. Summary of Cox regression models predicting time to first major depression (MD) and hypomanic (Hyp)/manic (Ma) onset in bipolar spectrum participants

Predictor	B	SE	Wald	OR	CI
Dependent variable: time to Hyp/Ma onset					
BIS	0.04	0.03	2.22	1.04	0.98–1.10
BAS-Tot	0.05	0.02	4.77**	1.05	1.01–1.09
BAS-D	0.07	0.05	2.22	1.08	0.98–1.18
BAS-FS	0.06	0.04	1.95	1.06	0.98–1.16
BAS-RR	0.11	0.05	4.48**	1.12	1.01–1.24
Dependent variable: time to MD onset					
BIS	0.05	0.03	2.81*	1.05	0.99–1.12
BAS-Tot	-0.02	0.02	1.14	0.98	0.94–1.02
BAS-D	-0.03	0.05	0.27	0.97	0.88–1.08
BAS-FS	-0.02	0.05	0.10	0.98	0.90–1.08
BAS-RR	-0.09	0.05	2.77*	0.92	0.83–1.02

Data are shown for the last step of the analyses after controlling for the variance accounted for by the Beck Depression Inventory and the Halberstadt Mania Inventory.

BIS = Behavioral Inhibition System from the BIS/BAS scales; BAS-Tot = Behavioral Approach System Total score from the BIS/BAS scales; BAS-D = BAS-Drive subscale; BAS-FS = BAS-Fun-seeking subscale; BAS-RR = BAS-Reward Responsiveness subscale; OR = odds ratio; CI = confidence interval.

\*p < 0.10; \*\*p < 0.05.

Ma episode (Table 3). Among bipolar participants, higher BAS sensitivities predicted a shorter time to onset of Hyp/Ma. Figure 1 illustrates the survival curves for Hyp/Ma onset as a function of high versus low BAS total scores. BAS total scores did not predict time to MD onset; however, BAS-RR did marginally predict ( $p < 0.10$ ) time to MD onset among bipolar participants (Table 3). Shorter time to first MD onset was also predicted marginally ( $p < 0.10$ ) by higher BIS scores (this relationship was significant,  $p < 0.01$ , when BDI and HMI were not included as covariates). Figure 2 shows the survival curves for MD onset as a function of high versus low BIS.



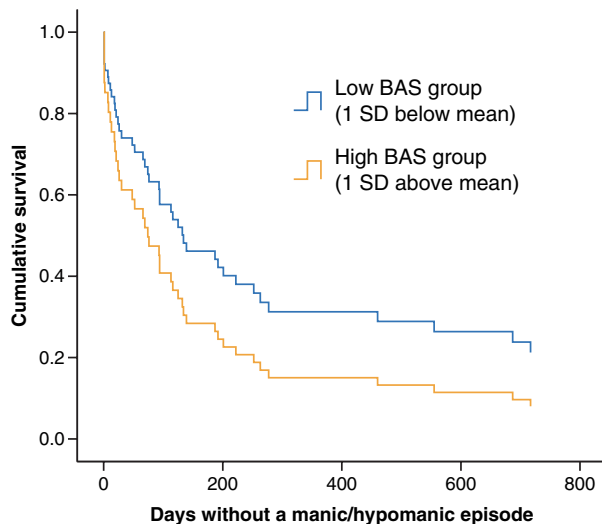


Fig. 1. Time to first (hypo)mania episode as a function of Behavioral Approach System (BAS)-total score.

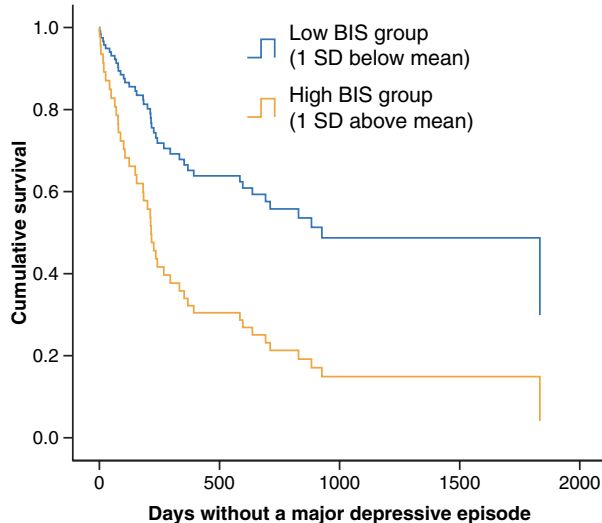


Fig. 2. Time to first major depressive episode as a function of Behavioral Inhibition System (BIS) score.

## Discussion

Diagnostic group differences in BAS and BIS sensitivities

Consistent with Hypothesis 1 and the BAS hypersensitivity model, as well as prior empirical findings (20, 51–54), we found that bipolar spectrum individuals exhibited higher self-reported BAS sensitivity, as measured by BAS Total, BAS Drive, and BAS Fun-seeking, than normal control individuals and that higher BAS scores were concurrently correlated with higher (hypo)manic symptom scores. Thus, the association between high BAS sensitivity and concurrent (hypo)manic symptoms or a history of (hypo)mania appears to

be a reliable finding across the entire continuum of severity of bipolar conditions. In contrast to Hypothesis 3, the bipolar spectrum and normal control groups did not differ on self-reported BIS sensitivity. Although this finding did not support our hypothesis, it is consistent with the similar finding of Meyer et al. (51) showing that a bipolar I sample did not differ from a normative sample on BIS sensitivity. Given that some studies have obtained concurrent associations between high self-reported BIS and bipolar depressive states and episodes (52, 54), further work is needed to understand the conditions under which the high BIS–bipolar depression association is observed.

BAS and BIS sensitivities and prospective onsets of mood episodes

Consistent with part of the BAS vulnerability hypothesis (Hypothesis 2), we found that, based on structured diagnostic interviews and DSM-IV and RDC criteria, high Time 1 BAS sensitivity was associated prospectively with a shorter time to onset of hypomanic and manic episodes among the bipolar spectrum participants. The vulnerability to (hypo)mania episodes was particularly strong for the BAS-RR subscale, which was associated with an 12% shorter time to onset of (hypo)mania during the follow-up period. Our results correspond with the one other prospective study by Meyer et al. (51), in which high self-reported BAS sensitivity predicted worsening of manic symptoms among recovered bipolar I patients, and extend these findings to a bipolar spectrum group, and to the prospective development of diagnosed (hypo)manic episodes. It is important to note that we obtained support for the BAS vulnerability hypothesis of (hypo)mania onset despite controlling for initial hypomanic and depressive symptoms (HMI and BDI scores). Consequently, initial symptomatic state associated with high BAS scores is unlikely to provide a plausible explanation for our BAS effects. Our controls for initial symptoms provide a very (probably overly) conservative test of the BAS vulnerability hypothesis because any variance in time to (hypo)mania episode onset shared between BAS hypersensitivity and initial symptoms is allocated to the initial symptoms, even though the BAS vulnerability hypothesis predicts that such shared variance should exist (12, 15, 21–23). Thus, the magnitude of the BAS effect for onset of (hypo)mania that we obtained may be an underestimate of the true effect size in nature. Our findings suggest that high BAS sensitivity may

indeed confer risk for occurrences of hypomanic and manic episodes.

In contrast to the second part of the BAS vulnerability hypothesis of BD (Hypothesis 2), BAS sensitivity did not predict significantly the time to onset of major depressive episodes in the present study (although BAS-RR marginally predicted time to major depression). This is similar to the finding of Alloy et al. (54) showing that, compared to a moderate BAS sensitivity group, a high BAS sensitivity group only exhibited an increased lifetime history of (hypo)manic, but not depressive, episodes. One possible explanation is that BD actually consists of two distinct, but frequently comorbid, syndromes, (hypo)mania and depression, and excessive BAS sensitivity provides risk for the former, whereas other processes increase vulnerability to the latter; a discussion of the 'one-illness' versus 'two-illness' debate for BD is provided elsewhere (73, 74).

Alternatively, our findings may be the result of methodological limitations. According to the BAS hypersensitivity theory of BD, individuals vulnerable to both poles of BD should exhibit excessive sensitivity to both BAS activation-relevant and deactivation-relevant stimuli. The BIS/BAS scales of Carver and White (20), used both in the present study and previously (54), directly measure sensitivity to BAS activation-relevant cues, such as the prospect of and presence of rewards, but do not directly assess responses to clear BAS deactivation-relevant stimuli, such as irreconcilable failures and losses. Although Carver (25) found that the BAS Fun-seeking subscale did predict feelings of frustration and sadness in response to a failure on a laboratory task, the failure in Carver's study was potentially remediable and may not have been perceived as final. As such, it would be expected to lead to a BAS activation response (frustration and intensified efforts to obtain the incentive) that could be predicted by the BAS activation-relevant items of the BAS scales. Major depressive episodes, theoretically involving large-scale deactivation of the BAS, should only be triggered by losses and failures that cannot be remediated, and may require direct BAS deactivation-relevant items on the BAS scale to be predicted. A third possibility is that BAS sensitivity assessed with the BIS/BAS scales would predict onsets of major depressive episodes in combination with the actual occurrence of BAS deactivation-relevant life events (actual definite failures and losses). Two important directions for future research on the BAS hypersensitivity model may be further development of instruments that can assess sensitivity to both BAS activation-relevant and deactivation-relevant

cues directly, as well as studies that include assessments of BAS-relevant life events.

Given that BIS sensitivity is thought to be involved in regulating inhibition of behavior in response to punishments, and has been theorized and found to be associated with depression, we also tested whether self-reported BIS sensitivity would prospectively predict time to major depressive episodes. Consistent with Hypothesis 4, we found that high Time 1 BIS sensitivity was marginally predictive of a shorter time to onset of major depressive episodes, controlling for initial depressive and (hypo)manic symptoms (BDI and HMI scores), and predicted major depressive episodes significantly when initial symptoms were not statistically controlled. Thus, some of the association between BIS sensitivity and prospective onset of major depression may be attributable to the BIS's shared variance with initial depressive symptoms, but such overlap with concurrent depressive symptoms does not completely account for the prospective association with major depression onset that we obtained. Further prospective studies are needed to confirm the role of high BIS sensitivity as a vulnerability factor for onsets of major depressive episodes in the context of bipolar spectrum disorders.

As noted in the introduction (p. 311), individual differences in BAS and BIS sensitivity have been related to various forms of psychopathology in addition to mood disorders (14–16). For example, high BAS (and low BIS) sensitivity has been suggested to underlie psychopathy and high levels of externalizing behavior (16, 75), whereas high BIS sensitivity has been related to anxiety disorders and internalizing behaviors more generally (25, 76). Perhaps common neurobiological and behavioral processes related to BAS and BIS may account for comorbidities between BD and these other forms of psychopathology.

#### Study strengths and limitations

The most notable strength of this study is the use of a prospective, longitudinal design that provides a more adequate test of the BAS and BIS vulnerability hypotheses for bipolar spectrum disorders. Other important strengths include the use of standardized diagnostic interviews and criteria, interviewers blinded to BIS/BAS scores, and extension of prior findings to a non-clinical, bipolar spectrum sample.

However, the study sample was limited by the fact that it consisted solely of undergraduates, which although ethnically and socio-economically diverse, may not be representative of a community

sample. A second limitation is that BAS and BIS sensitivities were assessed with a single self-report instrument, the BIS/BAS scales (20). As noted above, this questionnaire may be more sensitive to assessing responses to BAS (and BIS) activation-relevant cues than to deactivation-relevant cues. Thus, further instrument development is needed to more powerfully test the BAS hypersensitivity model of BD. Moreover, although the BIS/BAS scales have been validated against both behavioral (66, 67) and neurobiological (26, 38, 44) indices of BAS activity, future tests of this model would benefit from the use of behavioral and neurobiological (e.g., EEG) indicators of BAS sensitivity as well.

### Conclusion

In summary, consistent with the vulnerability hypothesis of the BAS hypersensitivity model of BD (12, 15, 21–23), the present study provides strong evidence that bipolar spectrum individuals exhibit higher self-reported BAS sensitivity than normal controls and that high BAS sensitivity prospectively predicts faster time to onset of hypomanic and manic episodes among individuals with bipolar spectrum disorders. In addition, high self-reported BIS sensitivity may increase risk for major depressive episode onset. Thus, the BAS hypersensitivity model of BD is promising for prediction of (hypo)mania and warrants continued investigation. Whether BAS sensitivity also increases vulnerability to depressive episodes requires further examination.

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