

Course of Early-Onset Bipolar Spectrum Disorders during the College Years

A Behavioral Approach System Dysregulation Perspective

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Although bipolar disorder (BD) has a strong genetic predisposition (McGuffin et al., 2003; Merikangas et al., 2002), there is increasing recognition that genetic vulnerability does not fully account for the timing, expression, and polarity of symptoms. Thus, in the past two decades, there has been greater interest in the role of psychosocial, developmental, and neurobiological risk factors that influence the onset, course, and expression of BD (see Alloy et al., 2005; Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006; Alloy, Abramson, Urosevic, Bender, & Wagner, 2009, for general reviews).

BDs are manifested along a continuum or spectrum (cyclothymia, bipolar II, bipolar I), with some disorders in the spectrum less severe and associated with less impairment than others (Akiskal, Djenderedjian, Rosenthal, & Khani, 1977; Akiskal, Khani, & Scott-Strauss, 1979; Cassano et al., 1999; Depue et al., 1981; Goodwin & Jamison, 2007; see Baldessarini, 2000, for criticism of the bipolar spectrum concept). In addition, milder forms of BD sometimes progress to more severe forms (e.g., Akiskal et al., 1977, 1979; Birmaher et al., 2006; Shen, Alloy, Abramson, & Sylvia, 2008) and sometimes exhibit a stable course and do not progress. Moreover, whereas some individuals with a bipolar spectrum disorder exhibit a very negative course with significant impairment in academic, work, and social functioning (e.g., Angst, Stassen, Clayton, & Angst, 2002; Goodwin & Jamison, 2007; Lagace & Kutcher, 2005; Nusslock, Alloy, Abramson, Harmon-Jones,

& Hogan, 2008; Strakowski, DelBello, Fleck, & Arndt, 2000), others experience a more benign course, including high achievement (Andreasen, 1987; Coryell et al., 1989; Kutchner, Robertson, & Bird, 1998; Nusslock et al., 2008).

In this chapter, we consider the course of bipolar spectrum disorders during the late adolescent/early adult years among individuals who had an earlier onset of the disorder. Specifically, in the sections that follow, we discuss a behavioral approach system (BAS) dysregulation perspective for understanding the course of BDs. We then describe and present findings to date from the Longitudinal Investigation of Bipolar Spectrum Disorders (LIBS) Project, a longitudinal study designed to investigate the course of bipolar spectrum disorders from a BAS perspective in college students with earlier onset (mean age of onset for first hypomanic or depressive episode or beginning of cyclothymic pattern, 13 years; median age, 14). However, whether our findings on the course of bipolar spectrum disorders in college students with earlier onset generalize to a sample with bipolar I must be examined directly.

We present descriptive findings on the course of bipolar spectrum disorders in our sample, findings regarding BAS-related risk factors affecting the course of these disorders, potential mediators of those risk factors, transactional processes affecting the course of these disorders, factors that influence differential outcomes and whether or not there is progression to a more severe disorder (multifinality) among individuals with bipolar spectrum disorders, and the role of developmental variables and early adversity in influencing the course of these disorders. We begin with a brief review of some of the literature regarding the course of BD in individuals with adolescent onset.

COURSE OF ADOLESCENT-ONSET BIPOLAR SPECTRUM DISORDERS

Bellivier and colleagues (Bellivier, Golmard, Henry, Leboyer, & Schurhoff, 2001; Bellivier et al., 2003) found that there are three high-risk periods for the onset of BD, with the earliest occurring in midadolescence. Other studies have also found that the first peak in rates of BD is between the ages of 15 and 19 (Burke, Burke, Regier, & Rae, 1990; Kennedy et al., 2005; Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997; Kupfer et al., 2002; Weissman et al., 1996). Recent research indicates that BD may also exhibit prepubertal onset (see Meyer & Carlson, Chapter 2 and Youngstrom, Chapter 3, this volume); however, work on adolescent onset and exacerbation of BD is more relevant to the present chapter.

Evidence suggests that childhood- or adolescent-onset BD is associated with a worse course than adult-onset BD, including more irritability, higher lifetime suicidal ideation, increased comorbidity, and greater familial loading (e.g., Carter, Mundo, Parikh, & Kennedy, 2003; Ernst & Goldberg, 2004; Mick, Biederman, Faraone, Murray, & Wozniak, 2003; Suominen et al., 2007). Childhood- or adolescent-onset BD is also characterized by greater rapid cycling, greater chronicity, and more mixed states than adult-onset BD (Biederman et al., 2005; Geller et al.,

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1995; Leibenluft, Charney, & Pine, 2003; Mick et al., 2003; Strober et al., 1988; Suominen et al., 2007). Moreover, adolescent- (and childhood-) onset BD increases risk for academic, social, and interpersonal problems (see Birmaher & Axelson, 2006, for a review and Birmaher et al., 2006, for contradictory results). These findings provide a context for the results reported later from the LIBS Project.

A BEHAVIORAL APPROACH SYSTEM DYSREGULATION MODEL OF BIPOLAR SPECTRUM DISORDERS

A BAS dysregulation model of bipolar spectrum disorders may provide an overarching, explanatory model for integrating risk factors, etiological, and transactional processes that influence the course of BDs. The BAS dysregulation model integrates specific psychosocial factors and specific neurobiological systems that may combine to affect the onset and course of BD. Moreover, the BAS model provides a single theme—level of approach motivation—to organize a diverse array of symptoms (e.g., motor, affective, cognitive, vegetative) and account for both poles of BD. According to the BAS dysregulation model, individuals with a bipolar spectrum disorder have a single vulnerability—a dysregulated BAS—but polarity-specific triggers for depressive and hypomanic/manic episodes (Urosevic, Abramson, Harmon-Jones, & Alloy, 2008).

The BAS is triggered by incentive cues in reward situations and functions to put an organism in contact with a reward or goal (e.g., Depue & Collins, 1992; Depue & Iacono, 1989; Fowles, 1987; Gray, 1991). At the behavioral level, central components of an activated BAS include locomotor initiation, incentive-reward motivation, positive affect, anger, and complex cognitions (e.g., Depue & Collins, 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001; see also Carver, 2004). Fowles's (1988) hypothesis that obstructed reward is a trigger for BAS-related irritability suggests that environmental cues likely influence whether a high BAS activation state is euphoric or irritable. On the other hand, an individual in a state of low BAS activation should experience anhedonia and decreased energy and exhibit few, if any, approach behaviors. In addition, Fowles (e.g., 1988, 1993) related a high outcome expectancy of success to BAS activation and hopelessness to BAS deactivation or shutdown.

With regard to neurobiology, Depue and colleagues (e.g., Depue & Collins, 1999; Depue & Iacono, 1989) hypothesized that the BAS involves the dopaminergic (DA) system, particularly the DA activity in the central nucleus accumbens and several frontal cortex regions. Much research in humans has focused on left frontal cortical activity as a neurobiological index of the BAS (for a review, see Davidson, 1994; Urosevic et al., 2008). Studies have found a significant positive relationship between increased relative left frontal cortical activity as measured by electroencephalogram (EEG) and higher self-report measures of BAS sensitivity (Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997), experimentally manipulated reward motivational states (Miller & Tomarken, 2001; Sobotka, Davidson,

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& Senulis, 1992), and a positive dispositional affective style (see Davidson, Jackson, & Kalin, 2000, for a review).

From a BAS dysregulation perspective, normal developmental changes that occur in the DA system at puberty (Chambers, Taylor, & Potenza, 2003; Spear, 2000) may be relevant to why BDs often develop or worsen during adolescence. In early adolescence, there is a significant increase in functional DA activity in the prefrontal cortex (PFC) (Rosenberg & Lewis, 1995; Sisk & Foster, 2004; Sisk & Zehr, 2005). This increase in circulating PFC dopamine levels may lead to greater sensitivity and efficiency of the brain's reward circuitry and thus to greater behavioral reward seeking and responsiveness (Steinberg, 2008). Indeed, behavioral sensation seeking and reward sensitivity were found to increase in youth from age 10 to midadolescence, peaking somewhere between ages 13 and 16 (Steinberg et al., 2009). Thus, some of the neurobiological circuitry implementing BAS functioning is enhanced beginning in early adolescence and may lead to increased BAS sensitivity.

According to the BAS dysregulation model of BD (Depue & Iacono, 1989; Depue, Krauss & Spoont, 1987; Johnson, 2005; Urosevic et al., 2008), individuals vulnerable to bipolar spectrum disorders exhibit an overly sensitive BAS that is hyperreactive to relevant cues and thus becomes dysregulated easily. Such BAS hypersensitivity should lead to great variability in state levels of BAS activation over time and across situations in response to BAS activating and deactivating stimuli. Thus, in response to BAS activation-relevant events involving goal striving and attainment, reward incentive, and anger evocation, a hypersensitive BAS can lead to excessive BAS activity. In vulnerable individuals, this excessive BAS activation, in turn, is hypothesized to lead to hypomanic/manic symptoms. In contrast, in response to BAS deactivation-relevant events involving definite failure and nonattainment of goals, excessive BAS deactivation or shutdown of behavioral approach should occur, leading to depressive symptoms. Such BAS vulnerability to dysregulation may be an endophenotype that mediates the effects of the genetic predisposition to BD. Moreover, according to Depue and colleagues (1987), individuals with bipolar spectrum disorders have genetically predetermined mean trait levels of BAS that predict which type of episode (depressive vs. hypomanic/manic) will predominate in the course of their BD.

In their expansion of the BAS dysregulation model of BDs, Urosevic and colleagues (2008) added a transactional component. In general, models including transactional processes allow bidirectional influences between various causal factors in the model. In Urosevic and colleagues' expanded BAS model, an individual's level of BAS activation before the occurrence of relevant environmental cues (i.e., pre-event BAS state) can result in selection or creation of environmental events (i.e., dependent BAS-relevant events) through a process of "stress generation" (Hammen, 1991) that affects subsequent changes in BAS activation. Thus, individuals with a highly sensitive BAS may be more likely to actually generate BAS activation and deactivation events in addition to being more emotionally and behaviorally responsive to such events when they occur.

THE LONGITUDINAL INVESTIGATION OF BIPOLAR SPECTRUM DISORDERS PROJECT

The LIBS Project is a two-site (University of Wisconsin [UW], Temple University [TU]) longitudinal study that investigates the psychosocial, cognitive, and neurobiological predictors of the course of bipolar spectrum disorders among 18- to 24-year-olds with earlier onset of their disorder. It primarily examines predictors of bipolar spectrum course from a BAS dysregulation model perspective. In the following sections, we describe the LIBS Project and many of its findings to date.

Participant Selection

Participants in the LIBS Project were selected via a two-phase screening process. In Phase I, approximately 20,500 18- to 24-year-old students at UW and TU were administered the revised General Behavior Inventory (GBI; Depue, Krauss, Spont, & Arbisi, 1989), a first-stage case identification procedure for bipolar spectrum disorders, to identify potential bipolar spectrum and healthy comparison participants. Using the GBI case-scoring method and cutoffs recommended by Depue and colleagues (1989), which were also validated against diagnostic interviews in a pilot study, participants who scored 11 or higher on the Depression (D) scale and 13 or higher on the Hypomanic-Biphasic (HB) scale of the GBI were identified as potential bipolar spectrum individuals (high GBI), whereas those who scored below these cutoffs on the D and HB scales were identified as potential healthy controls (low GBI). Individuals who met these GBI criteria were invited for Phase II of screening, involving an expanded Schedule for Affective Disorders and Schizophrenia—Lifetime (exp-SADS-L; Endicott & Spitzer, 1978) diagnostic interview. High-GBI participants who met DSM-IV (American Psychiatric Association, 1994) or Research Diagnostic Criteria (RDC; Spitzer, Endicott & Robins, 1978) for bipolar II, cyclothymia, or BD not otherwise specified (BD NOS; see Axelson et al., 2006, for validation of the bipolar NOS diagnosis in children and adolescents), but having no lifetime history of mania or mixed episode, were invited to participate in the main longitudinal study. Control participants invited into the longitudinal study exhibited low GBI scores and, based on the exp-SADS-L interview, had no lifetime history of any mood disorder or any other Axis I disorder (except that they could have a specific phobia) and no family history of BD. The comparison participants were matched to the participants with BD on age, sex, and ethnicity.

The final LIBS Project sample included 200 participants with bipolar spectrum disorder (78 men, 122 women; 157 with bipolar II and 43 with cyclothymic or BD NOS; age range = 18–24 years [$M = 19.6 \pm 1.6$]). 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. The final healthy comparison sample included 86 men and 122 women ages 18 to 24 years (mean 19.7 ± 1.5 years); 72.8% were

Caucasian, 12.1% African American, 3.4% Hispanic, 4.4% Asian, 0.5% Native American, and 6.8% other.

Project Assessments and Design

After agreeing to participate in the longitudinal study, all participants completed a time 1 assessment that included self-report measures of depressive and hypomanic/manic symptoms; BAS sensitivity, impulsivity, and trait aggressiveness; cognitive and coping styles; and social rhythm regularity. At time 1, participants also completed a set of tasks designed to assess self-referent information processing and Axis II personality dysfunction. In addition, at time 1, participants completed a number of measures assessing developmental factors, including their parents' inferential feedback and parenting styles, their own childhood stressful life events, and childhood emotional, physical, and sexual maltreatment.

A subset of participants also completed two EEG sessions. In one session, EEG was recorded both in the resting state and in response to monetary reward and punishment trials on an anagram task (Harmon-Jones et al., 2008). The anagrams were divided into easy, medium, and hard difficulty blocks, with half of the anagrams in each difficulty block assigned to the reward condition and half to the punishment avoidance condition. After each anagram block, participants completed a questionnaire to assess current affective state. EEG was recorded from 14 (12 homologous and two midline) electrodes, placed on the midfrontal, lateral frontal, central, anterior temporal, posterior temporal, and parietal regions of the scalp. As in previous research (e.g., Harmon-Jones & Allen, 1998), a frontal asymmetry index was computed (for each anticipatory period [7 seconds prior to each anagram]), using midfrontal and lateral frontal sites. For comparison purposes, asymmetry indexes for the other sites were also computed. In the other session, EEG was recorded in the resting state and in response to an anger-induction scenario (a radio editorial proposed a tuition increase and the participants paid at least 33% of their own tuition).

Following time 1, participants were followed longitudinally for up to 7 years (average 4.54 years, $SD = 2.74$ years), with assessments occurring approximately every 4 months. At time 1 and each 4-month follow-up, interviewers were blind to participants' diagnostic group (bipolar spectrum vs. healthy control). During each 4-month assessment, participants were assessed for depressive and hypomanic/manic symptoms and diagnosable episodes, symptoms and diagnoses of other disorders, life events, inferences about those events, and social rhythms (patterns of daily activity and sleep-wake cycles). Symptoms and diagnosable episodes of depression, hypomania/mania, and other disorders were assessed at each 4-month follow-up with self-report measures and an expanded SADS-Change diagnostic interview (exp-SADS-C; Spitzer & Endicott, 1978; see Alloy et al., 2008, for expansion). The exp-SADS-C assessed onset, offset, duration, and severity of symptoms and episodes of Axis I disorders throughout the longitudinal phase.

To assess the occurrence of positive and negative life events over the past 4 months, participants were administered a combination of a self-report questionnaire (expanded Life Events Scale [LES]; Francis-Raniere, Alloy, & Abramson, 2006) and a semistructured interview (Life Events Interview [LEI]; Francis-Raniere et al., 2006). The LEI served as a reliability and validity check on the LES (Francis-Raniere et al., 2006) by providing explicit definitional criteria for what experiences counted as each event and a priori probes to determine whether the event definition criteria were met. If the event did not meet the definitional criteria, the event was designated as "does not qualify" and was not counted in final event totals. The interviewer also dated the occurrence of each event that did qualify and rated the objective impact of the event and the degree to which it disrupted social rhythms (social rhythm disruption [SRD] events).

DESCRIPTIVE FINDINGS ON THE COURSE OF BIPOLAR DISORDER IN THE LONGITUDINAL INVESTIGATION OF BIPOLAR SPECTRUM DISORDERS PROJECT

In this section, we present some general descriptive information about the course of bipolar spectrum disorders in the LIBS Project bipolar spectrum sample. The mean age of first onset of bipolar spectrum disorder (i.e., either bipolar II, cyclothymia, or BD NOS) for the entire bipolar sample was 13.12 ($SD = 4.51$) and the median age was 13.82. Of 43 participants with a cyclothymia or BD NOS diagnosis at the outset of the project (who already had exhibited at least one DSM-IV or RDC hypomanic episode), 32 (74.4%) converted to either a DSM-IV or an RDC bipolar II diagnosis (had a first onset of major depressive episode) over the longitudinal follow-up, whereas 5 (11.6%) converted to a bipolar I diagnosis (had a first onset of manic episode). Note that conversion to a bipolar II and bipolar I diagnosis among individuals with cyclothymia or BD NOS at the outset was not mutually exclusive. Of 157 participants with a DSM-IV or RDC bipolar II diagnosis at the outset of the project, 26 (16.6%) converted to a bipolar I diagnosis (had a first onset of manic episode) over the follow-up period. Combining the participants with a cyclothymia/BD NOS and a bipolar II diagnosis, 31 of 200 (15.4%) converted to a bipolar I diagnosis. The participants who progressed to bipolar I disorder had a significantly younger age at onset ($M = 11.11$, $SD = 4.91$) than those who did not progress to bipolar I ($M = 13.48$, $SD = 4.35$), whereas participants diagnosed with cyclothymia and BD NOS who progressed to bipolar II did not differ on age at onset ($M = 13.87$, $SD = 4.89$) with those who did not ($M = 13.91$, $SD = 5.95$). There were no differences in the likelihood of seeking treatment for mood-related issues between participants who did and did not progress to a more severe diagnosis; 70% of the bipolar spectrum group sought treatment for mood-related problems.

Overall, the rates of lifetime comorbid diagnoses among participants with bipolar spectrum disorder were as follows: 11% generalized anxiety disorder, 11%

TABLE 6.1. Predictors of Progression to a More Severe Bipolar Disorder among LIBS Project Participants During Prospective Follow-Up

Conversion to bipolar II diagnosis	Conversion to bipolar I diagnosis
<u>Clinical predictors</u>	<u>Clinical predictors</u>
No age-of-onset differences Comorbid alcohol abuse	Earlier age of onset Comorbid alcohol abuse Comorbid substance abuse Comorbid eating disorder not otherwise specified
<u>Temperament/personality predictors</u>	<u>Temperament/personality predictors</u>
Higher BAS sensitivity	Higher BAS sensitivity Higher impulsiveness Higher physical aggression

Note. This table summarizes predictors discovered to date. Further predictors of progression to more severe bipolar disorders may yet be found in further analyses of the LIBS Project data. BAS, behavioral approach system.

panic disorder, 28% specific and social phobia, 9% obsessive-compulsive disorder, 19% posttraumatic stress disorder, 10% anxiety disorder NOS, 24% alcohol abuse, 9% alcohol dependence, 29% substance abuse, 6% anorexia, 2% bulimia, and 6% eating disorder NOS. Participants with bipolar spectrum disorder who progressed to bipolar I had significantly higher rates of comorbid alcohol abuse (39% vs. 21%), substance abuse (45% vs. 26%), and eating disorder NOS (16% vs. 5%) than those who did not convert to bipolar I. Similarly, participants diagnosed with cyclothymia and BD NOS who progressed to bipolar II had marginally significantly higher rates of comorbid alcohol abuse (25% vs. 0%) than those who did not progress to bipolar II (the SADS-Change interviewers ruled out mood episodes that were specifically substance induced). Table 6.1 summarizes the predictors of progression to more severe BDs discovered in the LIBS Project sample to date.

RISK FACTORS INFLUENCING THE COURSE OF BIPOLAR SPECTRUM DISORDERS

In this section, we review findings from the LIBS Project regarding risk factors and transactional processes in the course of bipolar spectrum disorders (see Table 6.2 for a summary of these findings). Our review focuses on risk factors primarily from a BAS dysregulation model perspective.

Behavioral Approach System-Related Risk Factors

Directly relevant to the BAS dysregulation model, as part of the LIBS Project, Alloy and colleagues (2008) found that at time 1, controlling for depressive and hypomanic/manic symptoms, the bipolar spectrum group exhibited higher levels of

TABLE 6.2. Risk Factors, Mediators, and Moderators of Outcomes in the Course of Bipolar Spectrum Disorders in the LIBS Project

Risk factors	Outcomes
<u>BAS-related risk factors</u>	
High BAS sensitivity	Higher likelihood of lifetime BD diagnosis Higher likelihood and shorter time to onset of Hyp/Ma episodes (and of MD episodes for BAS-RR) Progression to BD II among participants with Cyc or BD NOS Progression to BD I among participants with BD II or Cyc Higher rates of BAS activation and deactivation life events Greater substance abuse problems
BAS-relevant cognitive styles	Higher likelihood of lifetime BD diagnosis Higher likelihood of Hyp/Ma episode onset (autonomy, self-criticism) and lower likelihood of MD episode onset (autonomy)
<u>BAS-relevant life events</u>	
BAS-activation life events	Higher likelihood of Hyp/Ma episode onset Increased relative left frontal cortical activation on EEG
BAS-deactivation life events	Higher likelihood of MD episodes Decreased relative left frontal cortical activation on EEG
Relative left frontal cortical activity (EEG)	Higher likelihood of lifetime BD diagnosis Higher likelihood of Hyp/Ma and MD episode onset
<u>Social rhythm-related risk factors</u>	
Low social rhythm regularity	Higher likelihood of lifetime BD diagnosis Shorter time to onset of Hyp/Ma and MD episodes
Social rhythm disruption events	Higher likelihood of MD episode onsets and symptoms
<u>Developmental risk factors</u>	
Childhood stressful life events	Higher likelihood of lifetime BD diagnosis Earlier age of first onset of BD
"Affectionless control" or critical parenting	Higher likelihood of lifetime BD diagnosis BAS-relevant cognitive styles
Childhood maltreatment	Higher likelihood of lifetime BD diagnosis
<u>Moderators</u>	
<u>BAS-relevant life events</u>	
BAS-activation life events	Higher likelihood of Hyp/Ma episode onsets (in interaction with high BAS sensitivity or BAS-relevant cognitive styles)
BAS-deactivation life events	Higher likelihood of MD episode onsets (in interaction with high BAS sensitivity or BAS-relevant cognitive styles)

(cont.)

TABLE 6.2. (cont.)

Risk factors	Outcomes
Low impulsivity	Higher academic achievement (in interaction with high BAS-Drive) Lower likelihood of progression to BD I (in interaction with high BAS sensitivity)
Mediators	
High impulsivity	Higher substance abuse problems (impulsivity mediates BD diagnosis and high BAS sensitivity)

Note. This table summarizes findings discovered to date. Further risk factors, moderators, and mediators may yet be found in further analyses of the LIBS Project data. Please see the text for more detailed description of these findings. BAS, behavioral approach system; RR, Reward Responsiveness subscale; BD, bipolar disorder; Cyc, cyclothymia; NOS, not otherwise specified; MD, major depressive; Hyp/Ma, hypomanic/manic; EEG, electroencephalogram.

self-reported BAS sensitivity on the BAS total and BAS Drive and Fun-Seeking subscales than the matched healthy comparison group. Other cross-sectional studies have also obtained higher self-reported BAS sensitivity as well as greater reward responsiveness on behavioral tasks, in both symptomatic and euthymic bipolar spectrum individuals compared with controls (for a review, see Alloy et al., 2008; Alloy, Abramson, Urosevic, et al., 2009). Using a behavioral high-risk design in an adjunctive part of the LIBS Project, Alloy, Abramson, Walshaw, and colleagues (2006) selected 18- to 24-year-old participants with high versus moderate levels of BAS sensitivity based on two self-report measures (behavioral inhibition system [BIS]/BAS Scales [Carver & White, 1994] and Sensitivity to Punishment Sensitivity to Reward Questionnaire [Torrubia, Avila, Molto, & Caseras, 2001]), blind to their symptom levels. These high- and moderate-BAS sensitivity individuals were administered the exp-SADS-L diagnostic interview used in the LIBS Project (Endicott & Spitzer, 1978) and measures of bipolar symptoms, hypomania proneness, and impulsivity. Alloy, Abramson, Walshaw, and colleagues found that the high-BAS sensitivity group was six times more likely to meet diagnostic criteria for a lifetime bipolar spectrum disorder than the moderate-BAS sensitivity group (50% vs. 8%), but the groups did not differ in their likelihood of a lifetime unipolar depression diagnosis (14% vs. 29%). The high-BAS group also had higher impulsivity and marginally higher GBI Hypomanic/Biphasic scores than the moderate BAS group. Higher BAS Reward Responsiveness subscale scores were also associated with higher hypomania proneness. The two groups did not differ on concurrent depressive or hypomanic symptoms. Finally, in the main LIBS Project, controlling for time 1 depressive and hypomanic symptoms, Alloy and colleagues (2008) reported that higher time 1 BAS total scores significantly predicted a greater likelihood and a shorter time to onset of hypomanic/manic episodes, but not depressive episodes, among the bipolar spectrum group over an average of 3 years of follow-up. Both time 1 BAS Reward Responsiveness and BIS scores

marginally predicted ($p < .10$) shorter time to onset of major depressive episodes over the follow-up. Similarly, two other longitudinal studies (Meyer, Johnson, & Winters, 2001; Salavert et al., 2007) also found that initial higher BAS sensitivity predicted manic episode/symptom relapse over time.

Similar to other studies of individuals diagnosed as euthymic bipolar and individuals at risk for BD based on exhibiting hypomanic personality (for a review, see Alloy, Abramson, Urosevic, et al., 2009; Urosevic et al., 2008), Alloy, Abramson, Walshaw, and colleagues (2009) found that, controlling for time 1 depressive and hypomanic symptoms, the bipolar group in the LIBS Project exhibited a unique profile of BAS-relevant maladaptive cognitive styles (measured by the Dysfunctional Attitudes Scale [Weissman & Beck, 1978]; Sociotropy Autonomy Scales [Beck, Epstein, Harrison, & Emery, 1983]; and Depressive Experiences Questionnaire [Blatt, D'Afflitti, & Quinlan, 1976]) characterized by perfectionism, autonomy, and self-criticism relative to the healthy controls. However, the bipolar group did not show maladaptive dependency, sociotropy, or approval-seeking attitudes typically observed among unipolar depressed individuals. Moreover, time 1 BAS-relevant autonomous and self-critical cognitive styles, but not styles involving approval seeking, dependency, and sociotropy, predicted prospective onsets of hypomanic/manic and depressive episodes during an average of 3 years of follow-up among the bipolar spectrum group (Alloy, Abramson, Walshaw, et al., 2009). Lozano and Johnson (2001) also reported that the BAS-relevant trait of achievement-striving predicted increases in manic symptoms over 6 months in a sample with bipolar I disorder.

In line with the BAS dysregulation model, longitudinal studies found that life events involving goal striving or goal attainment that are hypothesized to activate the BAS specifically trigger hypomanic/manic symptoms and episodes among individuals with BD. In two studies, Johnson and colleagues (2000, 2008) found that events involving goal attainment predicted increases in manic, but not depressive, symptoms among patients with bipolar I disorder over follow-up, whereas general positive life events did not. In the LIBS Project, Nusslock, Abramson, Harmon-Jones, Alloy, and Hogan (2007) examined the effects of a goal-striving event (studying for and taking final exams) on the course of bipolar spectrum disorders. Bipolar symptoms were assessed during the final exam period and a control period in the bipolar spectrum and control groups, with each group further subdivided into those currently taking or not taking final exams. Individuals with BD taking exams, unlike those not taking exams and the whole control group, exhibited more onsets of new hypomanic episodes in the final exam period compared with the control period. Indeed, a full 42% of the bipolar spectrum individuals experienced onset of a new hypomanic episode during the final exam period. This pattern of results was not found for depressive episodes. In addition, consistent with the BAS model, over the first year of follow-up, we found that among the participants with bipolar spectrum disorder, controlling for initial depressive and hypomanic symptoms, BAS activation-relevant events (e.g.,

goal striving and attainment events) prospectively predicted increases in hypomanic symptoms, whereas BAS deactivation-relevant events (e.g., definite failures and losses) prospectively predicted increases in depressive symptoms.

In the LIBS Project, we found that BAS-relevant events also combined with BAS sensitivity and BAS-related maladaptive cognitive styles to predict prospective bipolar mood symptoms. In preliminary analyses, controlling for initial depressive and hypomanic symptoms, higher time 1 BAS sensitivity interacted with BAS activation-relevant events to prospectively predict increases in hypomanic symptoms, whereas it interacted with BAS deactivation-relevant events to prospectively predict increases in depressive symptoms over the first year of follow-up. Similarly, Francis-Raniere and colleagues (2006) reported that, controlling for initial symptom levels, time 1 BAS-relevant, self-critical, perfectionistic cognitive styles interacted with BAS-relevant negative events to predict prospective increases in depressive symptoms and with BAS-relevant positive events to predict prospective increases in hypomanic symptoms at the next 4-month assessment among participants with bipolar spectrum disorder.

In sum, BAS sensitivity, BAS-related cognitive styles, and the occurrence of BAS-relevant life events each predict prospectively a greater likelihood of mood symptoms or episodes or a shorter time to onset of mood episodes and thus a worse course among individuals with bipolar spectrum disorder. Moreover, BAS-activating and deactivating life events combined with BAS sensitivity and BAS-relevant cognitive styles to predict mood symptoms and episodes, suggesting that the BAS dysregulation model may be very promising for understanding processes that contribute to the course of BD.

Behavioral Approach System–Related Transactional Processes

An important component of the expanded BAS model of BDs discussed by Urosevic and colleagues (2008) is the transactional, bidirectional influences between BAS-related life events and bipolar symptoms. In the LIBS Project, Urosevic and colleagues (2009) found that individuals with bipolar spectrum disorder reported both BAS-activating and deactivating events at significantly greater rates than controls over the follow-up. Among the bipolar spectrum group, rates of BAS activation-relevant and deactivation-relevant events were significantly positively related to each other, suggesting that the same individuals with BD were experiencing high rates of both types of events. Thus, our participants with early-onset bipolar spectrum disorders may actually experience more BAS-activating and -deactivating life events through processes of stress generation (Hammen, 1991), which, in turn, trigger onsets of additional hypomanic/manic and depressive symptoms and episodes, respectively, as our findings described previously show.

In addition, Bender, Alloy, Sylvia, Urosevic, and Abramson (2009) further examined stress-generation processes using data from the first year of follow-up in the LIBS Project. Bender and colleagues found that higher time 1 hypomanic

symptoms predicted greater subsequent occurrence of BAS-related positive and negative achievement events among males, whereas higher time 1 depressive symptoms predicted greater occurrence of positive and negative interpersonal events among females. These gender differences in stress-generation processes among individuals with bipolar spectrum disorder may contribute to the gender differences typically seen in the course of BD, in which men typically show a predominance of hypomania/mania, whereas women typically show a predominance of depression (e.g., Leibenluft, 1996; Rasgon et al., 2005).

Biopsychosocial Behavioral Approach System–Related Risk Factors

Findings from the LIBS Project also suggest that a neurobiological index of BAS activation may be a risk factor that could interact with psychosocial stressors to influence the course of BD. In the LIBS Project, our main neurobiological measure of BAS activation was obtained from assessment of participants' EEG in the resting state and in response to reward and punishment trials on an anagrams task and in response to an anger-induction manipulation. Prior work has shown that increased relative left frontal cortical EEG activity is a neurobiological index of BAS activation, whereas decreased relative left frontal EEG activity indicates BAS deactivation (Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997).

According to the BAS dysregulation model, individuals with BD show an excessive increase in BAS activity in response to reward incentives, goal striving, and anger evocation. If an event is perceived as a "challenge" and elicits approach-motivated perceptions of successful coping, the BAS should be activated and hypomanic/manic symptoms may follow. Consistent with this hypothesis, in the LIBS Project, Harmon-Jones and colleagues (2008) obtained a significant three-way interaction between diagnostic group, anagram difficulty level, and type of trial (reward vs. punishment) in the anagram EEG session. Specifically, individuals with bipolar spectrum disorder exhibited greater relative left frontal cortical activation on EEG to a challenging goal-striving task (the difficult anagram trials) compared with healthy controls when they confronted a potential reward but not when they faced a potential punishment. That is, whereas controls disengaged from goal pursuit in response to the most difficult reward trials (and showed decreased relative left frontal cortical activation), individuals with BD maintained a heightened motivational state (and relative increased left frontal cortical activation) in this condition. This effect was specific to frontal EEG sites. These findings may indicate that individuals with BD get "stuck" in a state of goal pursuit and cannot regulate out of this state.

In the anger-induction EEG session, Harmon-Jones and colleagues (2002) reported that individuals with higher proneness to hypomania (on the GBI) exhibited greater relative left frontal cortical EEG activation in response to the anger manipulation, whereas those with higher proneness to depression (on the GBI) showed lower relative left frontal cortical activation in response to this

anger-provoking manipulation. Thus, the same event triggered either increased or decreased BAS activation on EEG, depending on whether the individual was relatively more vulnerable to hypomania/mania or to depression.

Finally, there is preliminary evidence from the LIBS Project that relative left frontal EEG activation predicts prospective onsets of both hypomanic/manic and depressive episodes over the first 3 years of follow-up over and above the self-report BAS sensitivity measure. Future analyses from the LIBS Project could examine whether the EEG indices of BAS activation interact with naturally occurring BAS-activating and -deactivating events to affect onset and other characteristics of prospectively occurring mood episodes among individuals with BD.

Potential Mediators of Behavioral Approach System–Relevant Events: Social Rhythm Disruption

Events that disrupt daily social rhythms (e.g., meal times, sleep–wake times) have been found to trigger bipolar mood episodes in several studies (for a review, see Alloy et al., 2005; Alloy, Abramson, Urosevic, et al., 2009). For example, Malkoff-Schwartz and colleagues (1998, 2000) observed that manic episodes were significantly more likely to be preceded by SRD events than depressive episodes. SRD events are hypothesized to trigger bipolar mood episodes through destabilizing circadian rhythms (see Ehlers, Frank, & Kupfer, 1988; Grandin, Alloy, & Abramson, 2006, for reviews). In the LIBS Project, Sylvia and colleagues (2009) reported that during the first year of follow-up SRD events at each 4-month assessment predicted increased depressive symptoms at the next assessment. In addition, participants with bipolar spectrum disorder were more likely to experience an SRD event before a depressive episode than during a control period without a depressive episode, and they experienced more depressive symptoms after than before an SRD event. Thus, SRD events may increase the likelihood of depressive as well as hypomanic/manic episodes. Moreover, Shen and colleagues (2008) found that individuals with BD in the LIBS Project had less regular social rhythms than healthy controls at time 1 (as measured by the Social Rhythm Metric; Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990) and lower time 1 social rhythm regularity predicted a shorter time to onset of both hypomanic/manic and depressive episodes during an average of 33 months of prospective follow-up.

It is possible that social rhythm disruption may be one of the processes that mediate the effects of BAS dysregulation on BD course. For example, events involving a loss of a goal may trigger a dysregulated BAS response with SRD as one component of this dysregulated response (e.g., a person loses his or her job, responds with BAS deactivation, helplessness, and rumination, and as a result loses hours of sleep, thus disrupting social and circadian rhythms, leading to depressive symptoms). Future work with data from the LIBS Project will need to explicitly assess whether SRD is related to and mediates dysregulated BAS response in predicting bipolar mood symptoms.

DIFFERENTIAL OUTCOMES AMONG INDIVIDUALS WITH BIPOLAR SPECTRUM DISORDERS

It is well known that BD is associated with functional impairment, including erratic work history, divorce, substance abuse, lower academic achievement, and increased suicide (e.g., Angst et al., 2002; Conway, Compton, Stinson, & Grant, 2006; Lagace & Kutcher, 2005; Strakowski et al., 2000). However, paradoxically, BD has also been associated with high levels of accomplishment (e.g., Coryell et al., 1989; Johnson, 2005; Petterson, 1977; Tsuchiya, 2004). There are also reports of high levels of creativity among individuals with bipolar spectrum disorders (Andreasen, 1987; Jamison, 1996; Richards et al., 1988; Simeonova, Chang, Strong, & Ketter, 2005). In addition, as described previously, some individuals in the LIBS Project with an initial cyclothymia or bipolar II diagnosis went on to develop a more severe disorder in the bipolar spectrum (i.e., converted to bipolar II or bipolar I diagnosis), whereas others did not and had a more stable course. These findings demonstrate the developmental concept of multifinality in that an initial diagnosis of a bipolar spectrum disorder can lead to either a stable or a worsening course and high levels of either impairment or achievement.

In the LIBS Project, we have begun to examine predictors of progression to a more severe bipolar diagnosis over the longitudinal follow-up period among participants with BD who initially had a milder diagnosis in the bipolar spectrum at the outset of the project (see Table 6.1 for a summary of these findings). To date, among participants with an initial cyclothymia (based on DSM-IV or RDC) or BD NOS diagnosis (at least one DSM-IV or RDC hypomanic episode), controlling for length of follow-up time, higher BAS total and Fun-Seeking and Reward Responsiveness subscale scores significantly predicted conversion to a bipolar II diagnosis (first onset of a major depressive episode) on follow-up (odds ratios: 1.75–2.10). Among individuals with a bipolar II, cyclothymia, or BD NOS diagnosis at the outset of the project, controlling for length of follow-up time, higher BAS total, impulsiveness (on the Impulsive Nonconformity Scale [Chapman et al., 1984]) and physical aggression (on the Buss Aggression Questionnaire [Buss & Perry, 1992]) all significantly predicted conversion to a bipolar I diagnosis (first onset of a manic episode) over the follow-up (odds ratio = 1.08). Thus, higher BAS sensitivity, impulsiveness, and physical aggressiveness predicted a worsening of course during early adulthood among individuals with a milder adolescent-onset bipolar spectrum disorder.

What factors may contribute to a course of bipolar spectrum disorder marked by greater impairment versus greater accomplishment? We have begun to address this question in the LIBS Project with respect to substance use problems and academic achievement. Given prior theorizing and research linking heightened reward sensitivity/drive (i.e., BAS sensitivity) to substance use and addiction (see Alloy, Bender, et al., 2009, for a review), and the fact that alcohol and drugs of abuse have rewarding properties, Alloy, Bender, and colleagues (2009) hypoth-

esized that high BAS sensitivity may predict a course marked by greater substance use problems among individuals with bipolar spectrum disorders as well as partially mediate BD–substance use comorbidity. Also, Alloy, Bender, and colleagues predicted that higher impulsiveness, referring to a tendency toward behavior that is rash, lacks planning and foresight, and occurs without reflection or deliberation (Dawe & Loxton, 2004), might predict worse substance use problems among individuals with BD. Indeed, prior research found that high trait impulsivity has been associated with increased substance abuse, suicidal behavior, and higher rates of arrest among individuals with BD (Kwapil, Miller, Zinser, Chapman, & Eckblad, 2000; Swann et al., 2005, 2007). In the LIBS Project, BAS sensitivity and impulsiveness correlated at $r = .41$ with each other, indicating that, although related, they are distinct constructs. Consistent with the hypotheses, Alloy, Bender, and colleagues (2009) found that higher BAS total scores, BAS Fun-Seeking scores, and Impulsiveness scores each significantly predicted increased substance use problems over the first year of follow-up, controlling for lifetime history of substance use. Moreover, BAS total and Fun-Seeking scores partially mediated and Impulsiveness scores fully mediated the association between bipolar spectrum diagnosis and prospective substance use problems (bipolar spectrum diagnosis did not predict substance abuse once impulsiveness was covaried). Thus, lower impulsivity protected against substance use problems among individuals with BD. BAS sensitivity and impulsiveness did not interact to predict prospective substance use problems among the bipolar spectrum group.

Nusslock and colleagues (2008) further examined the role of BAS sensitivity and impulsiveness in predicting academic achievement. Academic transcripts were gathered for a subset of the LIBS Project sample (54 with bipolar spectrum disorder and 66 control participants). Individuals with bipolar spectrum disorder obtained a significantly lower cumulative grade point average (GPA), dropped more classes, and were more likely to withdraw from college either for a semester or permanently than healthy controls, controlling for number of semesters enrolled. In addition, among individuals with bipolar spectrum disorder, there was a significant interaction between BAS Drive subscale scores and impulsivity scores in predicting cumulative GPA. Individuals with BD exhibiting a combination of high BAS Drive and low impulsivity earned higher cumulative GPAs than the remaining participants with BD. Thus, high BAS sensitivity (specifically, BAS Drive), when paired with low impulsivity, may not be impairing and may contribute to the high achievement sometimes observed among individuals with BD.

Taken together, the studies described in this section suggest that differential outcomes (multifinality) for individuals with bipolar spectrum disorders may be at least partially due to their levels of trait BAS sensitivity, impulsivity, and physical aggression. High BAS sensitivity, impulsiveness, and physical aggressiveness may be predictive of a more negative course of BD in the form of greater likelihood of mood episodes (see Alloy et al., 2008), conversion to more severe bipolar

diagnoses, and substance use problems (see Alloy, Bender, et al., 2009). However, when high BAS sensitivity is accompanied by the protective factor of low impulsivity, such high BAS sensitivity may actually contribute to higher achievement (Nusslock et al., 2008) and is associated with a lower likelihood of progression to bipolar I disorder. It makes sense that a tendency to be high in goal striving and approach motivation would be associated with relatively high achievement when combined with low impulsivity, which might prevent goal striving from getting out of control.

DEVELOPMENTAL FACTORS AND EARLY ADVERSITY IN BIPOLAR SPECTRUM DISORDERS

Research and theory suggest that exposure to certain parenting practices, childhood stressors, or maltreatment experiences may increase individuals' risk for onset and a more severe course of BD (see Alloy, Abramson, Smith, Gibb, & Neeren, 2006, for a review). Early adverse experiences and parenting practices may affect a person's development of emotion regulation strategies, which, in turn, may influence the course and expression of BD, given that emotion dysregulation is a central feature of the disorder. In the LIBS Project, we have begun to examine the role of such developmental factors in the onset and course of bipolar spectrum disorders.

Grandin, Alloy, and Abramson (2007) examined the association between childhood stressors that were independent or dependent on an individual's behavior and eventual bipolar spectrum diagnosis. Grandin et al. reasoned that if childhood adversity contributes to the emergence of bipolar symptoms, then independent childhood stressful events occurring before the age of onset of participants' bipolar spectrum disorder would be associated with bipolar versus healthy control status, and a greater number of independent childhood stressors would be associated with an earlier age of onset of BD. Grandin and colleagues found that, controlling for family history of BD, age at BD onset, and depressive and hypomanic symptoms at the time participants reported their childhood stressors (at time 1), a higher number of pre-onset, independent stressful events was associated with a bipolar versus control diagnosis. Moreover, controlling for family history of BD and time 1 depressive and hypomanic symptoms, the more total childhood stressors, as well as independent, dependent, negative emotional, and achievement failure events participants with BD experienced, the younger they were when they had their first bipolar mood episode. Whereas independent events might help to directly bring about an earlier onset of a bipolar mood episode, dependent events may do so through indirect stress-generation processes. Prodromal or early-occurring symptoms of bipolarity or a highly sensitive BAS temperament may lead to the occurrence of the dependent events via stress generation, and then these events, in turn, may have increased the likelihood of an earlier onset of a full-blown affective episode.

Neeren, Alloy, and Abramson (2008) examined reported histories of negative parenting and parental maltreatment in the bipolar spectrum and healthy comparison groups. Controlling for family history of mood disorder and concurrent (time 1) depressive and hypomanic/manic symptoms, low levels of maternal warmth/acceptance and high levels of maternal and paternal negative psychological control (the "affectionless control" pattern identified by Parker [1983]) were associated with a bipolar spectrum diagnosis. In addition, controlling for family history of mood disorder and concurrent symptoms, and counting only experiences of maltreatment that occurred before the age of onset of BD, higher levels of emotional maltreatment by mothers and fathers and higher levels of physical maltreatment by mothers were associated with a bipolar spectrum diagnosis.

Wagner, Alloy, and Abramson (2009) followed up on the Neeren and colleagues findings by examining the association of critical parenting with bipolar status, course of illness, and BAS-relevant cognitive styles. Wagner and colleagues reasoned that parenting that is overtly critical may be especially likely to exacerbate BAS sensitivity and contribute to the development of a self-critical, perfectionistic cognitive style in offspring, the type of style that several studies, including our own (Alloy, Abramson, Walshaw, et al., 2009), suggest characterizes individuals with BD. Controlling for family history of mood disorders and time 1 depressive and hypomanic/manic symptoms, higher reported critical parenting by both mothers and fathers was associated with a bipolar versus control diagnosis and with BAS-relevant cognitive styles of higher perfectionism and autonomy but not with the BAS-irrelevant cognitive styles of approval seeking or sociotropy. However, critical parenting did not predict prospective occurrence (yes–no) of major depressive or hypomanic/manic episodes. It may be that parenting is related to vulnerability to BD but not episode recurrence. Alternatively, analyses that examine whether parenting predicts other aspects of BD course such as fluctuations in symptoms, time to onset of episodes, or episode number, severity, or duration might yield different results. It is also possible that critical parenting did not predict episode recurrence during the college years because the college students were no longer exposed to their parents as regularly. In addition, future studies would benefit by assessing parenting styles using behavioral observation rather than relying solely on self-reports of individuals with BD (see Alloy, Abramson, Smith, et al., 2006).

In sum, to date, the LIBS Project findings regarding developmental experiences in BD suggest that early childhood stressors, childhood emotional and physical maltreatment, and parenting characterized by low affection, high psychological control, and high criticism are associated with a bipolar spectrum diagnosis. In addition, critical parenting is specifically associated with greater BAS-relevant cognitive styles. Moreover, higher numbers of childhood stressors predict an earlier age of onset of bipolar spectrum disorder. Further analyses with LIBS Project data will examine whether aspects of parenting or early adversity (childhood stressors or maltreatment experiences) predict characteristics of the course of BD.

CONCLUSION

Much research remains to be conducted regarding the course of adolescent bipolar spectrum disorders. However, work to date from the LIBS Project has yielded much valuable information on risk factors, possible mechanisms, transactional processes, and differential outcomes in BDs from a BAS dysregulation perspective. It should be noted, though, that the findings from the LIBS Project may or may not generalize to clinical samples or to individuals with bipolar I disorder. First, our descriptive findings regarding age at onset (mean = 13.12 years) and rates of progression to more severe disorders (74.4% individuals diagnosed as cyclothymic or BD NOS progressed to bipolar II, and 15.4% of individuals diagnosed as bipolar II, cyclothymic, and BD NOS progressed to bipolar I disorder) in the bipolar spectrum are generally consistent with other findings in the literature (e.g., Akiskal et al., 1977, 1979; Birmaher et al., 2006). Second, as predicted by a BAS dysregulation model of BD, high BAS sensitivity and activation, as assessed by self-report and EEG, greater BAS-relevant cognitive styles, and BAS-relevant life events, each predicts a greater likelihood or shorter time to occurrence of bipolar mood episodes and symptoms, alone and in combination (BAS sensitivity or BAS-relevant cognitive styles in interaction with BAS-relevant life events). High BAS sensitivity also predicts progression to bipolar II disorder among individuals with cyclothymia or BD NOS and progression to bipolar I disorder among individuals with bipolar II or cyclothymia. Third, consistent with the transactional part of the BAS dysregulation model, our findings suggest that individuals with bipolar spectrum disorders may be more likely to actually generate the kinds of BAS activation and deactivation events that, in turn, worsen the course of their disorder. Thus, individuals with BD may be both more likely to experience and more reactive than other individuals to the sorts of environmental triggers that contribute to their symptoms.

Fourth, our developmental findings to date suggest that early BAS-relevant critical parenting along with low affection and early childhood stressors and maltreatment may also contribute to the risk for bipolar spectrum disorder and earlier onset of BD, as well as maladaptive BAS-relevant cognitive styles in offspring. Finally, high BAS sensitivity in combination with high versus low impulsiveness and aggressiveness may help explain which individuals with a bipolar spectrum disorder have a more negative course (progression to bipolar I, greater substance use problems, poor achievement) and which have more positive outcomes (less likelihood of progression to a more severe disorder, fewer substance use problems, high achievement).

In conclusion, the findings reviewed here suggest that the BAS dysregulation model is very promising for integrating psychosocial and neurobiological vulnerability factors and mechanisms involved in the onset and course of bipolar spectrum disorders. Moreover, the BAS dysregulation model suggests strategies for improving the effectiveness of various psychosocial interventions for BD (see Nusslock, Abramson, Harmon-Jones, Alloy, & Coan, 2009), as well as potential novel

interventions that manipulate BAS activation by manipulating left versus right frontal cortical activation (Harmon-Jones, 2006; Peterson, Shackman, & Harmon-Jones, 2008). It is hoped the evidence reviewed here sets the foundation for further research on the onset and course of BDs from a BAS dysregulation perspective.

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