Bipolar Spectrum – Substance Use Co-occurrence: Behavioral Approach System (BAS) Sensitivity and Impulsiveness as Shared Personality Vulnerabilities

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Abstract

Bipolar disorders and substance use disorders (SUDs) show high co-occurrence. One explanation for this co-occurrence may be common personality vulnerabilities involved in both. We tested whether high Behavioral Approach System (BAS) sensitivity and impulsiveness are shared personality vulnerabilities in bipolar spectrum disorders and substance use problems and their co-occurrence in a longitudinal study of 132 bipolar spectrum and 153 normal individuals. At Time 1, participants completed the BIS/BAS Scales and the Impulsive Nonconformity Scale. Substance use problems were assessed via the Michigan Alcoholism Screening Test and the Drug Abuse Screening Test at 4 month intervals for one year. Bipolar participants had higher rates of lifetime SUDs and substance use problems during the follow-up, relative to normal controls. In line with hypotheses, higher BAS sensitivity and impulsiveness predicted bipolar status and increased substance use problems prospectively. BAS Total, BAS Fun-seeking, and impulsiveness mediated the association

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[1]During the end of the recruitment period of the LIBS Project sample, it was becoming difficult to complete the recruitment of normal controls matched to the bipolar participants on age, sex, and ethnicity, who had no history of any Axis I disorders. We found that some of the normal participants who matched the bipolar participants on demographics had a prior history of a single specific phobia (e.g., of spiders). Thus, we decided to allow normal participants with a history of one specific phobia into the control group. Control participants with a specific phobia represented a small proportion (about 5%) of the total control group. From an RST perspective, the presence of some control participants with specific phobia could lead the control group to score higher than the bipolar group on BIS sensitivity. However, this was not the case; the two groups did not differ on BIS sensitivity (see Table 1).

between bipolar spectrum status and prospective substance use problems, with impulsiveness as the most important mediator. High BAS sensitivity and impulsiveness may represent shared personality vulnerabilities for both disorders, and may partially account for their co-occurrence.

Keywords

Bipolar Spectrum; Substance Use; Behavioral Approach System (BAS) Sensitivity; Impulsiveness

Theory and evidence has accumulated on the role of long-term personality differences in vulnerability to clinical disorders. The hypothesized behavioral functions of neurobiological systems has provided a way of conceptualizing associations between personality traits and various forms of psychopathology. For example, the Reinforcement Sensitivity Theory (RST) of personality is a broad theory of personality rooted in research and theory on the biological bases of learning and motivation. In Gray's 1982 version, RST posited three systems: (1) the Fight-Flight System (FFS), (2) the Behavioral Approach System (BAS), and (3) the Behavioral Inhibition System (BIS). The FFS was posited to be sensitive to unconditional aversive stimuli; the BAS was posited to be sensitive to conditioned appetitive stimuli; and the BIS was posited to be sensitive to conditioned aversive stimuli, extreme novelty, high intensity stimuli, and innate fear stimuli. In 2002, Gray and McNaughton revised RST. Now, the FFS was referred to as the Fight-Flight-Freeze System (FFFS) and it was posited to be sensitive to all aversive stimuli; BAS was posited to mediate reactions to all appetitive stimuli; and the BIS was now posited to not mediate reactions to conditioned aversive stimuli, but to resolve goal conflicts between BAS-approach and FFFS-avoidance as well as BAS-BAS and FFFS-FFFS conflicts. In addition to providing a broad theory of personality, RST suggests new ways of thinking about the causes and consequences of clinical disorders. Extreme FFFS sensitivity is posited to underlie disorders such as phobia and panic; extreme BIS sensitivity is posited to underlie disorders such as generalized anxiety and obsessive-compulsive disorder. Extreme BAS sensitivity is posited to underlie addictive behaviors and the appetitive component of mania (Corr, 2008), which is part of bipolar disorder.

Considerable evidence documents high co-occurrence ("comorbidity") between bipolar spectum disorders and substance use disorder (SUDs), even controlling for substance-induced mood disorders and the presence of other Axis I disorders (e.g., Conway, Compton, Stinson, & Grant, 2006; Regier et al., 1990; Wilens et al., 2004). Moreover, SUDs may exhibit even higher co-occurrence with bipolar disorder than with other mood or anxiety disorders (Conway et al., 2006; Grant et al., 2004). For example, in a recent nationally representative sample of U.S. adults, the lifetime prevalence of any SUD was 37.5% among participants with mania vs. 20.7% among participants with unipolar major depression and 19.1% among participants with any anxiety disorder (Conway et al., 2006). Such bipolar – substance use co-occurrence is mutually detrimental to the course, consequences, and treatment of each condition (Dalton, Cate-Carter, Mundo, Parikh, & Kennedy, 2003; Salloum & Thase, 2000; Strakowski et al., 2007). The high co-occurrence between bipolar disorders and SUDs could reflect: 1) attempts to self-medicate bipolar mood symptoms with substance use (e.g., Raimo & Schuckit, 1998); 2) changes in brain functioning leading to mood symptoms as a consequence of repeated substance use; and 3) common vulnerabilities or risk factors involved in both disorders. The present study is designed to examine this last possibility. Specifically, this study investigates the idea that the bipolar spectrum and substance use share common personality vulnerabilities of enhanced BAS sensitivity and impulsiveness.

BAS Hypersensitivity Theory of Bipolar and Substance Use Disorders

As briefly noted above, RST posits that in regulating approach behavior to attain rewards and goals, the BAS is activated by external (e.g., an attractive goal object) or internal (e.g., expectancies of goal attainment) signals of reward (e.g., Depue & Collins, 1999; Fowles, 1987; Gray, 1991). When these cues activate the BAS, the person increases movement toward attaining goals and cognitive activity (e.g., hope, self-efficacy, planning) aimed at promoting goal attainment. Hope, elation, and happiness are hypothesized to be associated with BAS activation (Depue & Iacono, 1989; Gray, 1994). Recent work also documents a link between anger and activation of the BAS (Carver, 2004; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001), particularly when people have a high expectancy of success for rectifying the anger-provoking situation (Harmon-Jones, Sigelman, Bohlig, & Harmon-Jones, 2003). The underlying neural substrate of BAS has been hypothesized to involve dopaminergic systems, particularly the mesolimbic dopaminergic pathways with projections from the ventral tegmental area to the nucleus accumbens, amygdala, and prefrontal cortex. This is also one of the critical pathways hypothesized to underlie the positively reinforcing effects of drugs of abuse (e.g., Chambers, Taylor, & Potenza, 2003; Chiara, 1995; Goldstein & Volkow, 2002; Jentsch & Taylor, 1999). In addition, diverse work has converged on the conclusion that activation of the left frontal cortex is a key component of the neural circuitry implementing BAS function (e.g., Coan & Allen, 2004; Davidson, Jackson & Kalin, 2000; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997; Sobotka, Davidson & Senulis, 1992).

Depue and colleagues (Depue & Iacono, 1989; Depue, Krauss & Spoont, 1987) proposed a BAS hypersensitivity theory of bipolar disorder (see also Urosevic, Abramson, Harmon-Jones & Alloy, 2008 for an update and review of evidence for this theory). According to the BAS theory, individuals vulnerable to bipolar disorder exhibit an overly sensitive BAS that is hyper-reactive to relevant cues. A hyper-responsive BAS can lead to excessive BAS activity in response to BAS activation-relevant events involving themes of reward incentive, goal striving and attainment, and anger-evocation. Excessive activation of the BAS in vulnerable individuals is hypothesized to be reflected in (hypo)manic symptoms such as euphoria, excessive goal seeking, decreased need for sleep, distractibility, irritability, excessive self-confidence, and optimism (Depue & Iacono, 1989; Fowles, 1993; Urosevic et al., 2008). According to this view, the high co-occurrence between SUDs and bipolar disorder may be due, in part, to bipolar individuals' excessive pursuit of rewarding stimuli such as drug-induced highs. In contrast, according to the theory, depressive symptoms such as sadness, low energy, anhedonia, psychomotor retardation, hopelessness, and low self-confidence reflect a shutdown of behavioral approach or excessive deactivation of the BAS in response to BAS deactivation-relevant events such as definite failure or non-attainment of goals (Depue et al., 1987; Fowles, 1993). A key prediction, then, from the BAS hypersensitivity model is that individuals who have a highly sensitive BAS should be vulnerable to both (hypo)mania and depressive states, that is, to bipolar spectrum disorders.

Much evidence supports the BAS hypersensitivity model of bipolar spectrum disorders. Individuals with bipolar spectrum disorders or exhibiting or prone to hypomanic symptoms show elevated scores on self-reported BAS sensitivity (Alloy et al., 2008; Carver & White, 1994; Meyer, Johnson & Carver, 1999; Meyer, Johnson, & Winters, 2001). In addition, high self-reported BAS sensitivity predicted: levels of positive affect and hypomanic symptoms among students over 17 days in a daily diary study (Meyer & Hofmann, 2005), increases in manic symptoms over 6 months in a recovered bipolar I sample (Meyer et al., 2001), a 6 times greater likelihood of a lifetime bipolar spectrum disorder diagnosis among students (Alloy et al 2006), and a shorter time to onset of hypomanic and manic episodes over 3.5 years in a prospective follow-up of a bipolar spectrum sample (Alloy et al., 2008). Also consistent with the theory, low levels of BAS activation have distinguished individuals with current and

recovered major depression from controls (Campbell-Sills, Liverant & Brown, 2004; Kasch, Rottenberg, Arnow, & Gotlib, 2002; Pinto-Meza et al., 2006) and predicted a worse course of depression (Kasch et al., 2002; Mcfarland, Shankman, Tenke, Bruder, & Klein, 2006).

Life events hypothesized to be BAS activation-relevant, such as goal-attainment (Johnson et al., 2000; 2008) and goal-striving (Nusslock Abramson, Harmon-Jones, Alloy & Harmon-Jones, 2007) events, triggered (hypo)manic symptoms or episodes, respectively, in individuals with bipolar disorders. Further, BAS-relevant cognitive styles involving goal-striving, perfectionism, and autonomy characterize individuals with bipolar disorders (Alloy et al., in press; Lam, Wright & Smith, 2004; Scott, Stanton, Garland, & Ferrier, 2000) and in a bipolar spectrum sample, prospectively predicted increases in hypomanic symptoms in combination with congruent positive events and increases in depressive symptoms in combination with congruent negative events (Francis-Raniere, Alloy & Abramson, 2006). Similarly, the BAS-relevant personality trait of achievement-striving predicted increases in manic symptoms over a 6-month follow-up in a bipolar I sample (Lozano & Johnson, 2001). Finally, relative left frontal cortical activity (as measured by EEG), a neurobiological index of BAS activity, is increased in mania or proneness to hypomania (Harmon-Jones et al., 2002; Kano et al., 1992) and decreased in unipolar and bipolar depression (Allen, Iacono, Depue & Arbisi, 1993; Gotlib, Ranganath & Rosenfeld, 1998; Henriques & Davidson, 1990; 1991). Moreover, increased left frontal cortical activity in response to reward incentives in a challenging task distinguished individuals with bipolar spectrum disorders from normal controls (Harmon-Jones et al., 2008).

Similarly, several theorists (Dawe & Loxton, 2004; Dawe, Gullo, & Loxton, 2004; Franken & Muris, 2006; Franken Muris & Georgieva, 2006) hypothesized that heightened reward sensitivity/drive (i.e., BAS) contributes to substance use and addiction. For example, it has been suggested that individuals with "reward deficit syndrome," who have lower levels of dopamine concentration in neural pathways, are more responsive to the reinforcing effects of rewarding stimuli including drugs and thus, are more prone to abuse drugs (Blum et al., 2000). Given that high BAS activation leads to approach behavior in situations involving potentially rewarding stimuli, and drugs of abuse have rewarding properties, high BAS activation should lead to greater substance use. High BAS sensitivity should also be associated with greater responsiveness to conditioned cues associated with substance use (Kambouropoulos & Staiger, 2001; 2004) and to using drugs in order to enhance positive affect/ euphoria (Colder & O'Conner, 2002). Thus, a second prediction from the BAS hypersensitivity model is that individuals with a hypersensitive BAS should be vulnerable to greater problems with substance use. Moreover, BAS hypersensitivity should contribute, at least in part, to the high co-occurrence found between bipolar disorders and substance use.

Although less extensive than the work on BAS and bipolar disorders, growing evidence also supports the BAS hypersensitivity theory for substance use. Cross-sectional and retrospective studies show consistent associations between high self-reported BAS sensitivity and increased substance use and SUDs (Franken & Muris, 2006; Franken et al., 2006, Johnson, Turner & Iwata, 2003; Knyazev, 2004; Loxton & Dawe, 2001; 2006). Behavioral task measures of BAS sensitivity also differentiate heavy or binge drinkers from light drinkers (Colder & O'Conner, 2002, Palfai & Ostafin, 2003) and drinking for enhancement reasons from drinking for coping or social reasons (Colder & O'Conner, 2002). High BAS sensitivity as measured by self-report or behavioral task is also predictive of greater cravings, intention to drink, and positive affective responses in alcohol cue reactivity paradigms (Franken, 2002; Kambouropoulos & Staiger, 2001). Few studies have examined EEG frontal cortical asymmetry in association with substance use and these studies have been mixed (Hayden et al., 2006; Zinser, Fiore, Davidson & Baker, 1999). However, an important limitation of most of these studies is that they only examined EEG cortical activity in the resting state. According to the BAS perspective,

increased left frontal cortical activity, as an index of BAS, should be observed particularly when approach/incentive motivation is engaged. Thus, consistent with the BAS theory, anticipation of reward (smoking) was associated with increased relative left frontal EEG cortical activity among smokers and this BAS activation was most pronounced in smokers with the greatest motivation to smoke (those recently withdrawn from nicotine; Zinser et al., 1999).

Thus, much empirical work is consistent with the BAS theory. However, a major shortcoming of this work is that all of the studies on the BAS – substance use association and most of the studies on the BAS – bipolar disorder association are cross-sectional or retrospective. Such designs are not ideal for testing whether BAS sensitivity provides vulnerability to bipolar mood episodes and substance use. Moreover, to our knowledge, no study has examined whether BAS sensitivity mediates the co-occurrence between bipolar disorder and substance use.

Impulsiveness: A Second Common Personality Vulnerability for Substance Use and Bipolar Disorders

One of the strongest and most consistent personality predictors of substance use is impulsiveness, a tendency toward behavior that is rash, lacks planning and foresight, and occurs without reflection or deliberation (Dawe & Loxton, 2004). Individual differences in impulsiveness and related behavioral tendencies (e.g., sensation seeking) are associated concurrently with substance misuse and prospectively predict SUDs (Acton, 2003; Dawe et al., 2004). Consistent with recent RST discussions of BAS and impulsiveness (Corr, 2008; Pickering & Smillie, 2008), investigators have emphasized that impulsiveness is not a unidimensional construct and contains at least two important and separable, but correlated, dimensions (Dawe & Loxton, 2004; Dawe et al., 2004): BAS or reward sensitivity (discussed above) and rash impulsiveness (RI) or rash, unplanned impulsive behavior without consideration of the consequences. Indeed, recent factor analytic studies show that questionnaire measures of RI (e.g., Eysenck Impulsiveness Scale [Eysenck & Eysenck, 1991], Barrett Impulsivity Scale [Patton, Stanford, & Barratt, 1995], Cloninger Novelty-Seeking Scale [Cloninger, Przybeck, Svrakic. & Wetzel, 1994], Zuckerman Sensation-Seeking Scales [Zuckerman, 1994] load with each other on a separate factor from measures of BAS and reward sensitivity (e.g., BAS from BIS/BAS Scales [Carver & White, 1994], Sensitivity to Reward [SR] scale from the Sensitivity to Punishment Sensitivity to Reward Questionnaire [SPSRQ; Torrubia, Avila, Molto & Caseras, 2001], although the two factors are correlated. This RI component is associated with deficits in executive functions of the PFC that underlie inhibitory control (Chambers et al., 2003; Dawe et al., 2004) and such PFC executive dysfunction has also been linked to substance misuse (e.g., Bechara & Damasio, 2002; Bechara, Dolan & Hindes, 2002).

Recent integrative models of addiction (Chambers et al., 2003; Dawe & Loxton, 2004; Dawe et al., 2004; Goldstein & Volkow, 2002; Jentsch & Taylor, 1999) suggest that BAS sensitivity and RI act in tandem to contribute to substance use. RI and its associated executive dysfunction lead to inability to curb substance use once reward (drug)-cued approach behavior (mediated by BAS reward sensitivity/drive) has been initiated. Individuals with high BAS sensitivity may find it particularly difficult to control goal-striving and reward-seeking including substance use, and this may be even more likely if they are also high in RI with its concomitant poor inhibitory control. Thus, RI may be a second risk factor for problematic substance use that enhances the effects of heightened BAS sensitivity.

Impulsiveness has also been found to relate to bipolar disorders. Self-report measures of RI are elevated in bipolar participants and stable across phases of illness (Swann, Anderson, Dougherty, & Moeller, 2001; Swann, Dougherty, Pazzaglia, Pham & Moeller, 2004). In

addition, behaviorally assessed RI is high during manic states (Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003) and even further elevated in manic individuals with co-occurring SUDs (Swann et al., 2004). Thus, impulsiveness may be a second common vulnerability factor for both substance use and bipolar disorder and may also mediate their co-occurrence.

RI and BAS sensitivity may also interact to affect bipolar disorders. Individuals with hypomanic personality who were low on impulsiveness were least likely to develop bipolar disorder and experienced better outcomes (e.g., fewer arrests) in a longitudinal follow-up (Kwapil, Miller, Zinser, Chapman, & Eckblad, 2000). Similarly, although students with bipolar spectrum disorders exhibited academic impairment relative to controls, the subgroup high on BAS-Drive but low on impulsiveness was protected from such impairment (Nusslock, Alloy, Abramson, Harmon-Jones, & Hogan, 2008).

The Present Study

Thus, the goal of the present one-year longitudinal study was to examine BAS sensitivity and impulsiveness as predictors of bipolar disorder status and substance use (alcohol and drugs) and their co-occurrence in a sample of late adolescents/young adults with bipolar spectrum disorders and demographically matched normal controls. Despite the high prevalence of comorbidity between bipolar spectrum disorders and substance use, studies have yet to examine the potential role of BAS sensitivity and impulsiveness in their co-occurrence. We hypothesized that both high self-reported BAS sensitivity and impulsiveness would be associated with 1) lifetime bipolar spectrum and SUD diagnosis, 2) would predict substance use problems prospectively, and 3) would mediate the co-occurrence of bipolar disorder and substance use. We also explored whether high impulsiveness mediated or moderated the association of high BAS sensitivity with bipolar disorder status, substance use, and their co-occurrence.

Materials and Methods

Participants

Participants were part of a larger prospective longitudinal study of the psychosocial, cognitive, and biological predictors of the course of bipolar spectrum disorders. They were selected via a two stage screening process. In Phase I, approximately 20,500 18–24-year-old students at a large northeastern and a large midwestern university completed the revised General Behavior Inventory (Depue et al., 1981). Those who met the GBI cut-off scores recommended by Depue and colleagues (1981; see Measures section) to identify bipolar spectrum and normal control participants were invited to participate in Phase II, which involved an interview with the expanded Schedule for Affective Disorders and Schizophrenia-Lifetime (exp-SADS-L; Endicott & Spitzer, 1978) diagnostic interview. Diagnoses were assigned based on the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (American Psychiatric Association, 1994) and/or Research Diagnostic Criteria (RDC; Spitzer, Endicott & Robins, 1978). Those receiving a diagnosis of Bipolar II disorder or Cyclothymia were invited to participate in the longitudinal study. Participants with a lifetime history of mania were excluded from the final sample, as a goal of the larger project was to assess risk factors for the development of full-blown Bipolar I disorder in those with milder bipolar spectrum conditions. During Phase II, lifetime history of alcohol and substance abuse and dependence was also assessed via the exp-SADS-L.

Normal controls were recruited and matched with bipolar spectrum participants on age, sex, and ethnicity. Only those normal participants with no lifetime history of Axis I psychopathology (with the exception of specific phobia),[1] and no family history of mood

disorders were included in the final sample. Informed consent was obtained from all participants prior to their participation in the study.

The final sample consisted of 149 Bipolar II participants (56 male, 93 female) and 57 Cyclothymic participants (23 male, 34 female), with a mean age of 19.6 (+ 1.6 years). Among bipolar participants, the ethnic composition was 68.9% Caucasian, 13.1% African American, 5.1% Hispanic, 3.6% Asian, 0.5% Native American, and 8.2% Other. Only 31 of the Bipolar participants (15%) had sought treatment (medication or psychotherapy) prior to their entry into the study, while 63 (30.6%) sought treatment during follow-up. Of those who sought treatment after inclusion in the study, 32 (15.5%) received medication, 26 (12.6%) received psychotherapy only, and 7 (3.4%) were hospitalized (of these, 2 received other treatment as well). The final normal control sample consisted of 208 participants (86 males, 122 females) with a mean age of 19.7 (+ 1.5 years). The ethnic composition of the normal participants was 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 on impulsivity and BAS sensitivity were included in the present analyses, resulting in a final sample for this study of 132 Bipolar (98 Bipolar II; 34 Cyclothymia) and 153 Normal participants. Demographic and clinical characteristics of the current sample are presented as a function of diagnosis in Table 1. Overall, 59.6% (N=170) were female. Participant ages ranged from 18 to 24 with a mean age of 19.65 (+=1.74). Gender, age, and ethnicity did not differ significantly by diagnosis (χ^2(1)=.094, p=.760; t(211)=-.095, p=.924; and χ^2(5)=3.40, p=.639, respectively).

Procedure

At Time 1, participants completed the Beck Depression Inventory (Beck, Rush, Shaw & Emery, 1979), the Halberstadt Mania Inventory (Alloy, Reilly-Harrington, Fresco, Whitehouse & Zechmeister, 1999), the BIS/BAS Scales (Carver & White, 1994), and the Impulsive Nonconformity Scale (IN; Chapman et al., 1984). Approximately every 4 months over the prospective follow-up period, participants were interviewed with an expanded SADS-Change diagnostic interview to assess the occurrence of major depressive, hypomanic, and manic episodes over the 4 months. In addition, at each 4-month interval, participants completed the Michigan Alcoholism Screening Test (MAST; Selzer, 1971) and the Drug Abuse Screening Test (DAST; Skinner, 1992). The present study was based on data from the first three follow-up periods (1 year). All participants were reimbursed for their time.

Measures

General Behavior Inventory—(*GBI*; Depue et al., 1981; Depue, Krauss, Spoont & Arbisi, 1989). The GBI is a 73-item self-report questionnaire designed as a cost-effective and rapid first-stage screening method for identifying individuals with bipolar spectrum disorders. Items assess intensity, duration, and frequency of bipolar symptoms. The inventory has two subscales: a Depression subscale (GBI-D) and a combined Hypomanic and Biphasic subscale (GBI-HB). Participants rate the frequency with which each symptom occurs on a 4-point scale, with 1 representing "never" and 4 representing "very often or almost constantly." In line with Depue and colleagues (1981; 1989), we used a case scoring method, in which one point was added to the total score for all items rated 3 (often) or 4 (very often). Participants who exceeded Depue and colleagues' (1981) recommended cut-off scores (GBI-D > 11; GBI-HB > 13) were considered potential bipolar participants and those who scored below these cut-offs were considered potential normal controls; both of these groups were invited for Phase II. In past research (Depue et al., 1989), the GBI has shown good internal consistency (α's = .90-.96), high specificity (*r* = .99), and adequate sensitivity (*r* = .78) and test-retest reliability (*r* = .71–.74). In addition, it has shown good discriminant validity, correctly identifying those with

affective disorders among those with non-affective disorders (Mallon, Klein, Bornstein & Slater, 1986) and has been validated in a variety of samples, including university students, individuals with a parental history of bipolar disorder, and outpatients (Depue et al., 1981; 1989; Klein, Depue & Slater, 1986).

Expanded SADS-Lifetime—(*exp-SADS-L*; Endicott & Spitzer, 1978). The exp-SADS-L is a semi-structured diagnostic interview that assesses current and lifetime history of Axis I disorders, including lifetime history of alcohol and substance abuse and dependence. To increase reliability and accuracy in diagnosing bipolar spectrum disorders, the SADS-L and SADS-C (see below for overview of SADS-C) interviews were expanded in consultation with experts on bipolar disorders: Drs. Akiskal, Angst, Clayton, Endicott, and Gruenberg. The following alterations were made to the exp-SADS-L: (1) additional probes were included to allow for the assignment of *DSM-IV* in addition to RDC diagnoses; (2) In the Depression, Mania, Hypomania, and Cyclothymia sections, the number of items were expanded and additional probes were incorporated to capture details regarding episodes and frequency and duration of symptoms; (3) Additional probes were added to assess the precise number of days and percentage of waking hours participants felt depressed or euphoric/irritable in the Depression and Mania/Hypomania sections, respectively; (4) Probes in the Depression, Mania/ Hypomania, and Cyclothymia sections were improved based on Depue's (1985) Behavioral Variability Interview; (5) In the Cyclothymia section, items were added to assess the frequency, duration, and switch rapidity of the depressive and hypomanic periods; (6) Probes were added to examine the extent to which participants' changes in behavior were noted by people in their lives; (7) For each symptom item, a 5 point scale was used (0–4), with a rating of 3 representing the cut-off score for the clinical presence of the symptom; (8) Sections assessing past episodes of depression and mania/hypomania were placed immediately following their corresponding current sections to enhance clarity and facilitate comprehension; (9) Sections were added assessing eating disorders, ADHD, and acute stress disorder; (10) additional probes were included in the anxiety disorders section; (11) and an organic rule-out module and a medical history section were appended. The exp-SADS-L interview has demonstrated good inter-rater reliability for diagnoses of Major Depressive Episodes (κ'$s > .95$) and all unipolar diagnoses (κ'$s > .90$) based on 80 jointly rated interviews in a previous study (Alloy et al., 2000) and for Bipolar spectrum diagnoses (k'$s > .96$) in the current project based on 105 jointly rated interviews. Interviews were conducted by research assistants who had completed over 200 hours of training and were blind to participants' Phase I GBI scores, BIS/BAS, and IN scores. Consensus *DSM-IV* and RDC diagnoses were determined by a 3-tiered standardized diagnostic review procedure involving senior diagnosticians and an expert psychiatric diagnostic consultant, Dr. Alan Gruenberg.

BIS/BAS Scales—(Carver & White, 1994). The BIS/BAS Scales are the self-report measures most widely used to assess sensitivity of the BIS and BAS. The scales consist of 20 items on a 4-point Likert scale (1 = strongly disagree, 4 = strongly agree) and are comprised of three BAS subscales and one BIS subscale. The BAS Reward Responsiveness (RR) subscale has 5 items designed to assess positive response to reward stimuli. The BAS Drive (D) subscale has 4 items indicative of persistence in pursuit of reward. The BAS Fun-Seeking (FS) subscale contains 4 items indicative of willingness to approach novel and rewarding stimuli. All subscales have adequate internal consistency (α's = .66 -.76) and test-retest reliability (r's =. 59–.69; Carver & White, 1994). The BIS/BAS scales have demonstrated construct validity; they have been associated with prefrontal cortical activity, affect, personality traits, and performance on reaction-time and learning tasks involving incentives (Colder & O'Conner, 2004; Harmon-Jones & Allen, 1997; Kambouroupolis & Staiger, 2004; Sutton & Davidson, 1997; Zinbarg & Mohlman, 1998). The items on the BAS scales did not overlap in content with the items from the SADS-L and SADS-C interviews used to assess the (hypo)manic

symptom criteria for a bipolar spectrum disorder diagnosis or with items on our self-report measure of (hypo)manic symptoms (Halberstadt Mania Inventory [HMI] – see below). Moreover, Alloy et al. (2008; Table 2) reported that the correlations between the HMI and the BAS-Total and BAS subscales ranged from $r = .038 – .214$, corresponding to a maximum of 4.6% of shared variance. Thus, the BAS scales appear to measure a distinct construct of behavioral approach, sufficiently distinct from (hypo)manic symptoms themselves.

Impulsive Nonconformity Scale—(IN; Chapman et al., 1984). The IN scale consists of 51 true/false items that tap impulsive behavior. Items include, "When I want something, delays are unbearable" and "I avoid trouble whenever I can" (reverse-scored). The IN scale has good internal consistency ($\alpha's = .79–.84$; Alloy et al., 2006; Chapman et al., 1984) and 6 week retest reliability ($r = .84$; Chapman et al., 1984). Chapman et al. (1984) found that individuals who scored high on the IN were more likely to endorse antisocial, psychotic, depressive, and hypomanic/manic symptoms than a control group. Moreover, Alloy et al. (2006) found that individuals high in BAS sensitivity exhibited higher IN scores than individuals with moderate BAS sensitivity.

Beck Depression Inventory—(*BDI*; Beck et al., 1979). The BDI is a 21-item self-report scale that assesses affective, motivational, cognitive, and somatic symptoms of depression. Participants select among 4 statements graded in severity, which are weighted from 0 to 3, with 3 representing the highest level of symptom severity. Total scores range from 0 to 63. The BDI has demonstrated good internal consistency, retest reliability, and concurrent validity with clinical depression ratings in both clinical ($r = .72$) and nonclinical ($r = .60$) samples. Furthermore, it has been validated in samples of undergraduates (Beck, Steer & Garbin, 1988).

Halberstadt Mania Inventory—(*HMI*; Alloy et al., 1999). The HMI is a 28-item self-report questionnaire, modelled after the BDI, designed to assess current affective, motivational, cognitive, and somatic symptoms of hypomania/mania. As with the BDI, participants select one of 4 statements representing differing degrees of symptom severity (e.g., "I do not feel particularly happy," I feel happy," "I feel so happy and cheerful it's like a high," and "I am bursting with happiness and I'm on top of the world"). In the LIBS project, the HMI demonstrated construct validity and was correlated ($r = .46$) with hypomanic symptoms reported on the exp-SADS-C interview (Alloy et al., 2008). Moreover, as would be expected, cyclothymic individuals reported HMI scores consistent with their current mood state, reporting significantly more hypomanic symptoms on the HMI when they were in hypomanic states ($M = 23.9$) than when they were in depressed ($M = 15.7$) or euthymic states ($M = 18.8$). In a sample of 1,282 undergraduates (Alloy et al., 1999), the HMI showed high internal consistency ($\alpha = .82$), adequate convergent validity with the mania scale of the MMPI ($r = .32, p < .001$), and adequate discriminant validity both with the MMPI-Depression Scale ($r = −.26, p < .001$) and with the BDI ($r = −.12, p < .001$).

Expanded SADS-Change Interview—(*exp-SADS-C*; Spitzer & Endicott, 1978). The exp-SADS-C interview was administered at 4-month intervals over the prospective follow-up period. It was used to assess onset, duration, and severity of symptoms and episodes of Axis I psychopathology, including major depressive, manic, and hypomanic episodes. Interviewers were blind to diagnostic status of participants, as well as to their GBI, BIS/BAS, and IN scores. The SADS-C was expanded in the same manner as the SADS-L. In addition, it also incorporated features of the Longitudinal Interval Follow-up Evaluation (Shapiro & Keller, 1979). This allowed detailed tracking of the course of symptoms and episodes over each 4-month period. In the current project, the exp-SADS-C demonstrated good inter-rater reliability ($\kappa > .80$) in joint ratings of 60 interviews. Moreover, in a validity study, participants reported the dates of

their symptoms on the exp-SADS-C with at least 70% accuracy relative to daily symptom ratings made over a 4-month interval.

The Michigan Alcoholism Screening Test—(*MAST*; Selzer, 1971). The MAST is a commonly used self-report questionnaire designed to screen for alcohol use problems. It has 24 items assessing symptoms of alcohol abuse and dependence. Items are given a score of 0, 1, 2, or 5, and are summed to yield total MAST scores ranging from 0 to 53, with higher scores indicating greater alcohol use problems. The MAST has shown good reliability (Marion, Fuller, Johnson, Michels & Diniz, 1996) and sensitivity (Maisto, Connors & Allen, 1995), adequate internal consistency (Conley, 2001), construct validity (Conley, 2001), and good concurrent validity with *DSM-IV* diagnostic criteria (Watson, Detra, Fox & Ewing, 1995). The MAST was administered regularly at 4-month intervals, and participants were asked to provide separate responses for each individual month. Cronbach's *a* for dichotomized initial MAST scores in the present sample was .64, which falls within the range reported in a recent reliability meta-analysis of the MAST (Shields, Howell, Potter & Weiss, 2007).

The Drug Abuse Screening Test—(*DAST*; Skinner, 1992). The DAST is a self-report questionnaire designed to assess drug use problems. It consists of 28 yes/no items indicative of symptoms of drug use and dependence. Items are weighted 0 or 1, and responses are summed to yield a total score ranging from 0 to 28, with higher scores indicating higher levels of drug use problems. The DAST has shown good validity and reliability (Cocco & Carey, 1998; El-Bassel et al., 1997; Lin, Lee, Pan, & Hu, 2003; McCann, Simpson, Ries, & Roy-Byrne, 2000). Furthermore, it has been validated for use in both psychiatric and community settings (Cocco & Carey, 1998; El-Bassel et al., 1997; Klamen & Miller, 1997; Lin et al., 2003). As with the MAST, the DAST was administered at each follow-up assessment and yielded monthly ratings of drug use problems. Cronbach's *a* for dichotomized initial DAST scores in the present sample was .65.

Given that we were interested in the prediction of general substance use problems, rather than of any one particular substance, MAST and DAST scores were combined to obtain an overall measure of substance use problems. Specifically, we calculated mean MAST scores across the first three follow-up assessments and mean DAST scores across the same three follow-up assessments. We then averaged MAST and DAST scores to create a composite score representing general substance use problems over the 1-year follow-up period.

Results

Diagnostic Group Differences in BAS Sensitivity, Impulsiveness, and Substance Use Problems

Table 1 presents means and standard deviations of BAS Total, BAS subscale, BIS, IN, and average MAST and DAST composite scores. Bipolar participants evidenced significantly higher BAS Total ($t(278)=-4.95$, $p<.001$), BAS Drive ($t(280)=-4.06$, $p<.001$), BAS Reward ($t(281)=-2.41$, $p=.017$), and BAS Fun-seeking ($t(283)=-5.20$, $p<.001$) scores than did normal controls. Bipolar participants also scored significantly higher on the IN Scale than did normal controls ($t(283)=-8.76$, $p<.001$). There were no significant group differences on BIS scores ($t(283)=-1.67$, $p=.097$). Finally, bipolar participants had significantly higher average MAST and DAST composite scores over the one-year follow-up ($t(275)=-4.79$, $p<.001$).

Associations among BAS Sensitivity, BIS Sensitivity, and Impulsiveness

Pearson correlations were conducted to examine whether the BAS and IN scales assess unique or overlapping constructs. Intercorrelations between BAS Total, BAS subscales, BIS, and IN scores are presented in Table 2. BAS Total and IN scores were significantly positively

correlated ($r = .41$, $p<.001$), but the correlation was moderate and corresponds to only 16.81% shared variance. Thus, consistent with their theoretical origins, these instruments appear to measure overlapping, but distinct constructs. Likewise, IN scores were significantly positively correlated with BAS Drive ($r = .35$, $p < .001$) and BAS Fun-seeking ($r = .49$, $p < .001$), but again these correlations were moderate and correspond to only 12.25% and 24.01% shared variance respectively. BIS was negatively correlated with IN ($r = −.14$, $p = .018$), but was not correlated with BAS Total ($r = .03$, $p = .637$) or any of the BAS subscales, except for BAS Reward ($r = .275$, $p < .001$).

Lifetime and Prospective Associations between Bipolar Spectrum Diagnosis and Substance Use

We first examined the association between lifetime history of SUDs and bipolar spectrum diagnosis. In line with previous research, we expected higher rates of lifetime SUDs among those with bipolar spectrum disorders compared to normal controls. Because lifetime history of SUD was an exclusion criterion for normal controls in the longitudinal study, we were unable to compare rates of lifetime SUDs by diagnostic status in our analysis sample. Instead, we examined lifetime prevalence rates of SUDs among those who completed our Phase II diagnostic interview. Specifically, from the Phase II sample, we compared rates of lifetime SUDs among bipolar participants (Bipolar I, II, or Cyclothymia; N=204), those with a history of major depressive episode(s) but no mania/hypomania (N=251), and those without a history of either mania/hypomania or major depression (N=449). Consistent with results reported in the literature, rates of lifetime SUDs differed significantly among those with bipolar spectrum disorder (28.4%), those with a history of major depressive episode(s) but no mania/hypomania (21.1%), and those without a history of any mood disorder (14.5%), $\chi^2(2)=18.02$, $p<.001$. Pairwise comparisons revealed that bipolar spectrum participants had significantly higher rates of SUDs than those without a history of mania/hypomania or major depression ($\chi^2(1)=17.87$, $p<.001$). Bipolar participants also showed higher rates of SUDs than individuals with histories of major depression only, and this effect was marginally significant ($\chi^2(1)=3.27$, $p=.07$).

We also examined the association between bipolar spectrum status and prospective substance use problems (as measured by the combined average of monthly MAST and DAST scores) over the follow-up period. Given that a lifetime SUD diagnosis predicted greater prospective substance use problems over the follow-up (see Table 5), we controlled for lifetime SUD diagnosis in our analyses. Despite gender differences in mean combined MAST-DAST scores, gender was not a significant predictor of prospective substance use problems in any of our regression models, and therefore, was not included as a covariate in final analyses. A linear regression revealed that bipolar spectrum status significantly predicted prospective substance use problems ($\beta = .164$, $p = .005$), controlling for lifetime history of SUD. Thus, compared with normal controls, bipolar spectrum individuals exhibited elevated rates of substance use, both lifetime SUDs and prospective substance use problems. Given the demonstrated association between bipolar spectrum disorders and substance use problems in this sample, we next tested our remaining hypotheses, namely, whether BAS sensitivity and IN represent shared vulnerabilities for both and whether they can account for their co-occurrence.

Associations of BAS Sensitivity and Impulsiveness with Bipolar Spectrum Status

Logistic regression analyses were conducted to examine the hypothesis that BAS sensitivity and IN would be related to bipolar diagnostic status. Results are presented in Table 3. We did not control for any demographic variables, as none were predictive of bipolar spectrum status. BAS total scores were associated significantly with diagnostic status, with higher levels of BAS sensitivity among those with bipolar spectrum disorder relative to normal controls. We also examined the contribution of each of the three BAS subscales (Reward, Drive, and Fun-Seeking) to the prediction of bipolar spectrum status and found that all three were associated

significantly with diagnostic status, with higher levels of sensitivity among those with a bipolar spectrum disorder relative to normal controls. Controlling for initial depressive (BDI) and hypomanic (HMI) symptom levels, BAS Total and BAS Fun- Seeking continued to be associated significantly with bipolar spectrum status (B=.084, S.E. B=.038, p=.028 and B=.202, S.E. B=.081, p=.012, respectively). However, BAS Drive became marginally associated with bipolar diagnostic status (B=.142, *S.E. B*=.082, p=.083), and BAS Reward was no longer associated (B=.065, S.E. B=.090, p=.470). BIS was associated with diagnostic status and became nonsignificant after controlling for initial symptom levels (B=.016, *S.E. B*=.055, p=.774). Logistic regression analyses also revealed that IN was associated significantly with diagnostic status, with higher levels of IN among bipolar participants than normal controls. This finding remained significant even after controlling for initial symptom levels (B=.078, *S.E. B*=.545, p<.001).

BAS Sensitivity and Impulsiveness as Predictors of Prospective Substance Use Problems

Next, we conducted a series of hierarchical linear regression analyses to examine whether BAS sensitivity and IN predicted prospective substance use problems over the 1-year follow-up period. Again, we controlled for lifetime SUD diagnosis in our analyses. Results are presented in Table 5. As hypothesized, BAS total scores and IN each significantly predicted prospective substance use problems over the follow-up, controlling for lifetime SUD diagnosis. With regard to the BAS subscales, BAS Fun-seeking significantly predicted prospective substance use problems; however, the BAS Reward subscale, BAS Drive subscale, and BIS scores did not.

Examination of the Interaction between BAS Sensitivity and Impulsiveness

Given that BAS and IN scores do represent distinct constructs in our data, we explored whether IN moderated the association between BAS and 1) bipolar spectrum status or 2) prospective substance use problems. Each of the previously tested models predicting to bipolar status or prospective substance use problems was reanalyzed with predictors entered into the model in the following order: lifetime history of SUD diagnosis entered in Step 1 (when prospective substance use problems was the dependent variable), BAS, a BAS subscale, or BIS entered in Step 2, IN entered in Step 3, and the interaction term (BAS x IN, a BAS subscale x IN, or BIS x IN) entered in Step 4. Results for these tests of moderation are presented in Table 4 and Table 6, with results predicting bipolar spectrum status presented in Table 4 and results predicting prospective substance use presented in Table 6. In no case were any of the interaction terms significant, indicating that BAS and IN did not interact to predict either bipolar spectrum status or substance use problems, over and above the prediction afforded by either construct alone.

Shared Vulnerability: Test of a Mediation Model

In summary, the findings above suggest (1) that bipolar spectrum status is associated with prospective substance use, (2) that BAS sensitivity and impulsiveness both are associated with bipolar spectrum status, and (3) that BAS sensitivity and impulsiveness both are associated with prospective substance use. Therefore, we were able to test our final hypothesis that the positive association between bipolar spectrum status and prospective substance use problems might be attributable in part to the shared personality factors of BAS sensitivity and impulsiveness. Such mediation hypotheses are often tested using the causal steps approach popularized by Baron and Kenny (Baron & Kenny, 1986), or the product-of-coefficients approach developed by Sobel (Sobel, 1982, 1986). Both procedures employ parametric techniques that assume multivariate normality of the sampling distribution of total and specific indirect effects, which can be problematic except in very large samples (MacKinnon, Rose, Chassin, Presson, & Sherman, 2000; Preacher & Hayes, 2008). The present study used a bootstrapping approach to multiple mediation that does not impose such an assumption, a process that simultaneously increases power and maintains reasonable control over the Type

I error rate (Preacher & Hayes, 2008). Bootstrapping is a nonparametric resampling technique that empirically generates an approximation of the sampling distribution. In the case of multiple mediation models, sampling distributions of total and indirect effects are empirically generated by selecting a subsample, with replacement, of the full data set and then calculating indirect effects in the repeated subsamples. The procedure yields point estimates and percentile confidence intervals for indirect and total effects. In the present study, bootstrap percentile confidence intervals were further improved using bias-correction and acceleration, as recommended by Preacher and Hayes (2008). Lifetime history of SUD was entered as a covariate in each model. Controlling for lifetime history of SUD represents a conservative test of our hypothesis, because BAS sensitivity and/or IN may represent vulnerabilities to lifetime SUDs as well as to prospective substance use problems.

Table 7 presents point estimates and bias-corrected and accelerated bootstrap confidence intervals based on 5,000 bootstrap samples, for both simple and multiple mediator models of our hypotheses. Tests of simple indirect effects (Table 7, top part) indicated that the relationship between bipolar spectrum diagnosis and prospectively assessed substance use problems was significantly mediated by BAS Total, BAS Fun-Seeking, and IN scores, but not by BAS Drive, BAS Reward, or BIS. Conclusions drawn from an examination of the bias corrected and accelerated confidence intervals were consistent with results of a traditional product-of-coefficients approach: the Sobel test statistic was 1.81 for BAS Total (p =.07), 2.86 for BAS Fun-Seeking (p =.004), and 3.21 for IN (p =.001), Sobel tests for all other simple mediation models were nonsignificant.

Bootstrapped tests of simultaneous multiple indirect effects were conducted in order to determine the unique ability of each putative mediator to account for the effects of bipolar diagnosis on prospective substance use problems. In other words, we examined whether the relationship between bipolar disorder and substance use problems was significantly mediated by (1) BAS Total, BAS subscales, or BIS, even after controlling for IN, and (2) IN, even after controlling for the effects of BAS Total, BAS subscales or BIS. Results are presented in Table 7. When entered simultaneously with IN, BAS Total and BAS Fun-Seeking no longer significantly mediated the bipolar spectrum – prospective substance use relationship. Impulsiveness, however, remained as a significant mediator even when controlling for the simultaneous specific indirect effects through BAS, BAS Reward, BAS Drive, and BIS. The sum of the specific indirect effects (i.e., total indirect effects) was significant in all multiple mediation models.

When contrasting specific indirect effects within each model, no significant differences were found between BAS Total or BAS subscales and impulsiveness. A contrast of the specific indirect effects of BIS and impulsiveness did indicate a significant difference between the two effects. Of note, all confidence intervals constructed for interaction terms between BIS/BAS (BAS Total, BAS subscales, or BIS) and IN contained zero, indicating nonsignificant interactions (consistent with the nonsignificant interaction effects shown in Table 4 and Table 6). Moreover, inclusion of interaction terms in the multiple mediation models did not change the significance or direction of relationships between other variables.

Discussion

The aim of the present study was to examine whether high BAS sensitivity and/or impulsiveness represent shared vulnerabilities to bipolar spectrum disorders and substance use problems. Consistent with prior evidence of high co-occurrence between bipolar disorders and SUDs (e.g., Conway et al., 2006; Grant et al., 2004), our initial analyses revealed that individuals with bipolar spectrum disorders were at elevated risk for lifetime SUDs, and exhibited higher levels of prospective substance use problems. Specifically, in the large

screening sample, individuals diagnosed with bipolar disorder (I, II, or cyclothymia) exhibited higher rates of lifetime SUDs than did those with either a history of unipolar major depression, or no history of mood episodes. In addition, in the main analysis sample, bipolar spectrum status (II or cyclothymia) also prospectively predicted increased substance use problems over the one-year follow-up, even after controlling for lifetime history of SUDs. Thus, the consistently reported association between bipolar disorder and SUD was conceptually replicated in our sample and extended with the more powerful prospective design. These results also allowed us to test the shared vulnerability hypothesis.

Consistent with hypothesis 1, RST (Gray, 1982; Gray & McNaughton, 2002), and the BAS dysregulation model (Depue & Iacono, 1989; Depue et al., 1987; Urosevic et al., 2008), individuals with bipolar spectrum disorders exhibited significantly higher self-reported BAS sensitivity, as measured by BAS Total, Drive, Fun-seeking, and Reward scores. This finding is consistent with prior results of Alloy et al. (2008); in that study, high self-reported BAS sensitivity also predicted shorter time to onset of hypomanic/manic episodes among individuals with bipolar spectrum disorders. Our analyses revealed that BAS sensitivity (specifically, BAS Total and Fun-seeking scores) continued to significantly predict bipolar spectrum diagnosis, even after controlling for initial symptom levels. High self-reported impulsiveness also predicted bipolar spectrum status, controlling for initial symptom levels. Thus, results are consistent with the hypothesis that both BAS sensitivity and impulsiveness may confer vulnerability to bipolar spectrum disorders.

Consistent with hypothesis 2 and RST, both high self-reported BAS sensitivity and impulsiveness predicted greater substance use problems over the follow-up. As with bipolar spectrum status, it was again BAS Total and Fun-seeking scores that specifically predicted prospectively assessed substance use problems, after controlling for lifetime SUD. It is important to note that controlling for lifetime history of SUDs represents a conservative test of our hypotheses, in that BAS sensitivity and/or impulsiveness may represent vulnerabilities to lifetime SUDs as well as to prospective substance use problems. Thus, results support our second hypothesis that BAS sensitivity and impulsiveness confer vulnerability to substance use problems. That the same BAS scale scores predicted both bipolar diagnosis and substance use further underscores a possible shared personality vulnerability between the two disorders.

In contrast with findings on BAS, findings on the role of BIS in bipolar disorder and SUD expression have been mixed (Alloy et al., 2008). In the present sample, BIS sensitivity did not predict either bipolar spectrum status or substance use problems over the follow-up. Our results add to research suggesting that BIS may not play a critical role in the expression of bipolar disorder and SUD. However, it is important to note that our measure of BIS (Carver & White, 1994) was based on the 1982 version of RST and probably best assesses punishment sensitivity. It will be interesting to assess whether yet-to-be developed measures of the revised RST's BIS may explain variance in bipolar disorder and SUDs.

With respect to our mediational hypotheses, BAS Total, BAS Fun-seeking, and impulsiveness each predicted increased prospective substance use problems after controlling for lifetime history of SUD and bipolar spectrum status. Both bootstrapping methods and Sobel tests of mediation indicated that BAS Total, BAS Fun-seeking, and impulsiveness all mediated the association between bipolar spectrum status and substance use problems. Thus, all three study hypotheses received support. Moreover, our bootstrapped tests of simultaneous multiple indirect effects indicated that BAS Total and Fun-seeking no longer mediated the bipolar – substance use association controlling for impulsiveness, whereas impulsiveness continued to mediate bipolar – substance use co-occurrence controlling for BAS and BIS. BAS sensitivity (Total or subscales) and impulsiveness did not interact to predict bipolar spectrum status, substance use problems, or their co-occurrence. Our mediational findings are consistent with

the idea that although existing theory and research and the correlations between the BAS and IN instruments used in this study suggest that BAS sensitivity and impulsiveness are separate, but overlapping, constructs, it is the component of BAS sensitivity shared with impulsiveness that appears to be most important in mediating the co-occurrence of bipolar disorder with substance use.

It is of interest that in most analyses, BAS Fun-seeking scores were the strongest predictor among BAS Total and subscale scores. Whereas BAS-Drive assesses persistence in striving for goals and BAS-Reward Responsiveness assesses responsiveness to obtained rewards (or consummatory, post-goal positive affect), the BAS Fun-seeking subscale assesses specifically the component of BAS sensitivity relating to willingness to approach new and potentially rewarding experiences (items include "I'm always willing to try something new if I think it will be fun" and "I crave excitement and new sensations"). Of the three BAS subscales, perhaps the BAS Fun-seeking subscale best captures anticipatory, pre-goal positive affective processes that activate the nucleus accumbens (Knutson & Wimmer, 2007), a structure rich in dopamine, a neurochemical implicated in BAS sensitivity (Depue & Collins, 1999). Importantly, the accumbens and dopamine have been found to be involved in drug addiction in animal research (Berridge, 2007).

To our knowledge, this is the first study to demonstrate that impulsiveness and BAS sensitivity mediate the association between bipolar spectrum disorders and prospectively assessed substance use problems. Findings are consistent with the hypothesis that high BAS sensitivity and impulsiveness represent shared vulnerabilities to both bipolar disorder and substance use problems, with the component of BAS sensitivity that overlaps with impulsiveness (i.e., BAS Fun-seeking) being most important in this shared vulnerability. Though the strength of association between the tested variables was modest, it is important to note that the shared vulnerability hypothesis likely explains only a portion of bipolar spectrum – substance use co-occurrence. As noted earlier, other potential explanations include the self-medication hypothesis, and the neuropsychological effects of repeated substance use over time.

Notable study strengths include the prospective assessment of substance use problems, large sample, interviewers blinded to BIS/BAS and impulsivity scores, and a unique contribution to the literatures on both RST and bipolar spectrum – substance use co-occurrence. Several study limitations should be noted as well. First, this study relied on self-report measures of BAS, impulsiveness and substance use problems; future research should adopt a multi-method, multi-measure approach to the assessment of these constructs. In particular, it may be beneficial to assess additional dimensions of substance use, such as frequency and amount of use over the follow-up. A second limitation is that associations between bipolar spectrum diagnosis and BAS sensitivity and impulsiveness were examined cross-sectionally, although we previously demonstrated that BAS sensitivity predicted time to onset of prospectively assessed manic and hypomanic episodes (Alloy et al., 2008). Further studies are needed to determine whether BAS sensitivity and impulsiveness prospectively predict first lifetime onsets of bipolar disorder and SUD, in order to more precisely test the shared vulnerability hypothesis. Finally, the present study examined prospective prediction of general substance use problems in an undergraduate sample. Participants experienced relatively low levels of mood symptomatology and substance use problems. Although it is noteworthy that shared vulnerability effects were demonstrated even in this relatively high functioning sample, further research is needed to replicate findings in other samples.

In conclusion, the present study adds to a growing body of research implicating both BAS sensitivity and impulsiveness in bipolar and SUDs. Results support the central importance of heightened impulsiveness and components of BAS sensitivity that overlap with impulsiveness in both bipolar disorders and SUDs. Moreover, findings are consistent with the shared

personality vulnerability hypothesis and indicate that the hypothesis warrants further evaluation. Understanding the role of these personality vulnerabilities may be especially important, as they represent potential points of behavioral intervention.

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Table 1

Sample Demographic and Clinical Characteristics (N=285)

	Normal Control (n=153)	Bipolar Spectrum (n=132)
Age	19.64 (1.84)	19.66 (1.63)
Gender		
Female	58.8%	60.6%
Ethnicity		
Caucasian	77.9%	75.0%
African American	8.8%	14.0%
Hispanic	3.5%	4.0%
Asian	1.8%	1.0%
Native American	0.0%	1.0%
Other	8.0%	5.0%
BAS Total[***]	37.85 (5.12)	40.96 (5.34)
BAS Drive[***]	10.42 (2.38)	11.57 (2.34)
BAS Reward[*]	16.41 (1.93)	19.98 (1.98)
BAS Fun-seeking[***]	10.99 (2.26)	12.42 (2.38)
BIS	20.15 (3.14)	20.83 (3.75)
Impulsive Nonconformity[***]	9.50 (6.56)	17.42 (8.63)
Lifetime Substance Diagnosis (any)[1]		
Yes	--	24.5%
No	--	75.5%
MAST-DAST average[***]	1.91 (0.89)	2.53 (1.26)

Note: Means are presented with standard deviations in parentheses.

[1] Individuals with a lifetime history of substance abuse/dependence were screened out of the normal control group. Thus, lifetime history of substance dependence is not reported for the normal control group.

[*] p<.05

[**] p<.01

[***] p<.001

Table 2

Intercorrelations between BAS, BAS subscales, IN, and BIS

	1	2	3	4	5	6
1. BAS Total	--					
2. BAS Drive	.83**	--				
3. BAS Reward	.74**	0.42**	--			
4. BAS Fun-Seeking	.82**	.51**	.41**	--		
5. Impulsive Nonconformity	.41**	.35**	0.11	.49**	--	
6. BIS	0.03	−0.09	.28**	−0.08	−0.14*	--

*
p<.05

**
p<.001

Table 3

Logistic Regression Models of Associations of BAS Total, BAS Subscales, BIS, and IN with Bipolar Spectrum Status

	β	S.E. β	Wald	OR	95% CI	p
BAS Total	0.12	0.03	21.78	1.12	1.07–1.18	<.001
BAS Fun-seeking	0.27	0.06	24.29	1.31	1.18–1.46	<.001
BAS Drive	0.20	0.05	14.42	1.22	1.10–1.35	<.001
BAS Reward	0.16	0.06	6.44	1.17	1.04–1.32	0.01
BIS	0.07	0.04	3.52	1.07	1.00–1.14	0.06
Impulsive Nonconformity	0.13	0.02	49.17	1.14	1.10–1.18	<.001

Note: *OR* = odds ratio. 95% CI = 95% confidence interval for odds ratio.

Table 4

Logistic Regression Models with BAS, BAS Subscales, IN, and the Interaction of BAS and BAS subscales with IN Predicting Bipolar Spectrum Status.

	β (S.E.)	Wald	OR	95% CI
Model 1				
Step 1				
BAS Total	.114(.025)	20.936	1.121***	1.067–1.177
Step 2				
BAS Total	.052(.028)	3.355	1.053	.996–1.113
IN	.119(.020)	36.188	1.126***	1.083–1.170
Step 3				
BAS Total	0.05(.028)	3.199	1.052	.995–1.111
IN	0.118(.020)	0.02	35.96***	1.083–1.170
BAS x IN	0.002(.004)	0.287	1.002	.995–1.009
Model 2				
Step 1				
BAS Fun-seeking	0.265 .055	23.089	1.303***	1.170–1.452
Step 2				
BAS Fun-seeking	.086(.064)	1.782	1.09	.961–1.236
IN	0.12(.02)	34.206	1.127***	1.083–1.173
Step 3				
BAS Fun-seeking	.087(.064)	1.836	1.09	.962–1.236
IN	.119(.021)	33.487	1.126***	1.082–1.172
Funseeking x IN	.006(.008)	0.593	1.006	.990–1.023
Model 3				
Step 1				
BAS Drive	.205(.053)	14.893	1.228***	1.106–1.363
Step 2				
BAS Drive	.087(.061)	2.064	1.091	.969–1.230
IN	.124(.019)	40.972	1.132***	1.090–1.176
Step 3				
BAS Drive	.086(.061)	1.982	1.09	.967–1.228

	β (S.E.)	Wald	OR	95% CI
Model 4				
Step 1				
BAS Reward	.148(.063)	5.615	1.16*	1.026–1.311
Step 2				
Bas Reward	.118(.070)	2.839	1.125	.981–1.291
IN	.129(.019)	47.584	1.138***	1.097–1.181
Step 3				
BAS Reward	.118(.070)	2.841	1.125	.981–1.289
IN	.130(.019)	47.71	1.139***	1.097–1.181
Reward x IN	.006(.009)	0.371	1.006	.987–1.024
Model 5				
Step 1				
BIS	.058(.035)	2.745	1.06**	1.026–1.311
Step 2				
BIS	.130(.042)	9.381	1.139**	.981–1.291
IN	.144(.020)	53.094	1.155***	1.097–1.181
Step 3				
BIS	.130(.043)	9.371	1.139**	.981–1.289
IN	.144(.020)	52.429	1.155***	1.097–1.181
BIS x IN	.000(.005)	0.021	0.999	.987–1.024

	β (S.E.)	Wald	OR	95% CI	β (S.E.)	Wald	OR	95% CI
IN	0.124(.019)	40.671	1.132***	1.089–1.175				
Drive x IN	.002(.008)	0.086	1.002	.987–1.018				

Note: *OR* = odds ratio. 95% CI = 95% confidence interval for odds ratio. ; BAS = Behavioral Activation Scale; BIS = Behavioral Inhibition Scale. IN = Impulsive Nonconformity. Model 1. Block 1: $\chi^2(1) = 23.657$, $p = .000$; Block 2: $\chi^2(1) = 45.250$, for Step 1 ($p = .000$); $\chi^2(2) = 68.907$, for Model ($p = .000$); Block 3: $\chi^2(1) = .287$ for Step 1 ($p = .592$); $\chi^2(3) = 69.195$ for Model ($p = .000$). Model 2. Block 1: $\chi^2(1) = 42.613$, $p = .000$; Block 2: $\chi^2(1) = 42.613$, for Step 1 ($p = .000$); $\chi^2(2) = 68.413$, for Model ($p = .000$); Block 3: $\chi^2(1) = .597$ for Step 1 ($p = .440$); $\chi^2(3) = 69.010$ for Model ($p = .000$). Model 3. Block 1: $\chi^2(1) = 16.083$, $p = .000$; Block 2: $\chi^2(1) = 52.199$, for Step 1 ($p = .000$); $\chi^2(2) = 68.282$, for Model ($p = .000$); Block 3: $\chi^2(1) = .087$ for Step 1 ($p = .768$); $\chi^2(3) = 68.369$ for Model ($p = .000$). Model 4. Block 1: $\chi^2(1) = 5.785$, $p = .016$; Block 2: $\chi^2(1) = 63.007$, for Step 1 ($p = .000$); $\chi^2(2) = 68.792$, for Model ($p = .000$); Block 3: $\chi^2(1) = .368$ for Step 1 ($p = .544$); $\chi^2(3) = 69.160$ for Model ($p = .000$). Model 5. Block 1: $\chi^2(1) = 2.88$, $p = .095$; Block 2: $\chi^2(1) = 73.762$, for Step 1 ($p = .000$); $\chi^2(2) = 68.792$, for Model ($p = .000$); Block 3: $\chi^2(1) = .021$ for Step 1 ($p = .884$); $\chi^2(3) = 76.572$ for Model ($p = .000$).

***
$p < .001$,

**
$p < .01$,

*
$p < .05$.

Table 5

Summary of Linear Regression Models of BAS, BAS Subscales, BIS and Impulsive Nonconformity Predicting MAST-DAST Average Over the 1-year Follow-up

	B	S.E. B	β	t	p
Model 1					
Step 1					
Lifetime SUD	0.77	0.24	0.22	3.20	<.01
Step 2					
Lifetime SUD	0.73	0.24	0.21	3.07	<.01
BAS Total	0.04	0.01	0.18	2.75	<.01
Model 2					
Step 1					
Lifetime SUD	0.91	0.24	0.25	3.79	<.001
Step 2					
Lifetime SUD	0.82	0.23	0.23	3.50	<.01
BAS Fun-seeking	0.11	0.03	0.24	3.77	<.001
Model 3					
Step 1					
Lifetime SUD					
Step 2					
Lifetime SUD	0.90	0.24	0.25	3.74	<.001
Lifetime SUD	0.89	0.24	0.25	3.69	<.001
BAS Drive	0.04	0.03	0.09	1.40	.16
Model 4					
Step 1					
Lifetime SUD	0.78	0.24	0.22	3.25	<.01
Step 2					
Lifetime SUD	0.77	0.24	0.22	3.21	<.01
BAS Reward	0.06	0.04	0.10	1.55	.12
Model 5					
Step 1					
Lifetime SUD	0.91	0.24	0.25	3.79	<.001
Step 2					
Lifetime SUD	0.92	0.24	0.25	3.82	<.001

	B	S.E. B	β	t	p
BIS	0.02	0.02	0.07	1.03	.31
Model 6					
Step 1					
Lifetime SUD	0.86	0.24	0.24	3.55	.000
Step 2					
Lifetime SUD	0.62	0.25	0.17	2.54	.012
Impulsiveness	0.03	0.01	0.24	3.55	.000

Note: SUD = Substance Use Disorder; BAS = Behavioral Activation Scale; BIS = Behavioral Inhibition Scale. Model 1. $R^2 = .047$, $F(1, 208) = 10.25$ for Step 1 ($p = .002$); $\Delta R^2 = .034$, $\Delta F(1,207) = 7.586$ for Step 2 ($p = .006$). Model 2. $R^2 = .063$, $F(1, 213) = 14.36$ for Step 1 ($p = .000$), $\Delta R^2 = .059$, $\Delta F(1, 212) = 14.24$ for Step 2 ($p = .000$). Model 3. $R^2 = .062$, $F(1, 210) = 13.99$ for Step 1 ($p = .000$); $\Delta R^2 = .009$, $\Delta F(1,209) = 1.953$ for Step 2 ($p = .164$). Model 4. $R^2 = .048$, $F(1, 211) = 10.559$ for Step 1 ($p = .001$), $\Delta R^2 = .011$, $\Delta F(1,210) = 2.402$ for Step 2 ($p = .123$). Model 5. $R^2 = .063$, $F(1, 213) = 14.361$ for Step 1 ($p = .000$); $\Delta R^2 = .005$, $\Delta F(1,212) = 1.059$ for Step 2 ($p = .305$). Model 6. $R^2 = .056$, $F(1, 211) = 12.614$ for Step 1 ($p = .000$); $\Delta R^2 = .053$, $\Delta F(1, 210) = 12.606$ for Step 2 ($p = .000$).

Table 6

Summary of Linear Regression Models of BAS Total, BAS Subscales, BIS, Impulsive Nonconformity and the Interaction of BAS, BAS Subscales, and BIS with Impulsive Nonconformity Predicting MAST-DAST Average over the 1-year Follow-up, Controlling for Lifetime History of Substance Use.

Model 1

	β	T
Step 1		
Lifetime SUD	.201**	2.927
Step 2		
Lifetime SUD	.192**	2.818
BAS	.171*	2.522
Step 3		
Lifetime SUD	.147*	2.112
BAS	.089	1.187
IN	.192*	2.488
Step 4		
Lifetime SUD	.146*	2.096
BAS	.088	1.171
IN	.190*	2.449
BAS x IN	.022	.326

Model 2

	β	t
Step 1		
Lifetime SUD	.238**	3.536
Step 2		
Lifetime SUD	.240**	3.565
BIS	.066	.979
Step 3		
Lifetime SUD	.173*	2.541
BIS	.097	1.465
IN	.252***	3.671
Step 4		
Lifetime SUD	.172*	2.531
BIS	.100	1.496
IN	.250***	3.640
BIS x IN	−.022	.746

Model 3

	β	t
Step 1		
Lifetime SUD	.238**	3.536
Step 2		
Lifetime SUD	.214**	3.245
Funseeking	.232**	3.515
Step 3		
Lifetime SUD	.179**	2.638
Funseeking	.155*	2.062
IN	.159*	2.043
Step 4		
Lifetime SUD	.177*	2.612
Funseeking	.156*	2.066
IN	.155*	1.981
Funseek x IN	.034	.518

Model 4

	β	t
Step 1		
Lifetime SUD	.203**	2.975
Step 2		
Lifetime SUD	.201**	2.065
Reward	.083	1.214
Step 3		
Lifetime SUD	.142*	2.065
Reward	.050	.750
IN	.229**	3.293
Step 4		
Lifetime SUD	.142*	2.050
Reward	.052	.770
IN	.229**	3.277
Reward x IN	.040	.603

Model 5

	β	t
Step 1		
Lifetime SUD	.237**	3.488
Step 2		
Lifetime SUD	.234**	3.455
Drive	.096	1.413
Step 3		
Lifetime SUD	.174*	2.517
Drive	.009	.126
IN	.231**	3.094
Step 4		
Lifetime SUD	.174*	2.505
Drive	.008	.115
IN	.230**	3.059
Drive x IN	.010	.882

Note: SUD = Substance Use Disorder; BAS = Behavioral Activation Scale; BIS = Behavioral Inhibition Scale; IN = Impulsive Nonconformity. Model 1. $R^2 = .041$, $F(1, 203)=8.569$ for Step 1 ($p = .004$); $\Delta R^2=.029$, $\Delta F(1,202)=6.359$ for Step 2 ($p = .012$), $\Delta R^2=.028$, $F(1, 201)=6.188$ for Step 3 ($p = .014$); $\Delta R^2=.000$, $\Delta F(1,200)=.106$ for Step 4 ($p =.745$). Model 2. $R^2 = .057$, $F(1, 208) = 12.505$ for Step 1 ($p =.001$), $\Delta R^2=.004$, $\Delta F(1, 207) = .959$ for Step 2 ($p=.329$), $\Delta R^2=.058$, $F(1, 206) = 13.473$ for Step 3 ($p = .000$), $\Delta R^2=.000$, $\Delta F(1, 205) = .105$ for Step 4 ($p =.746$). Model 3. $R^2 = .057$, $F(1, 208) =12.505$ for Step 1 ($p = .001$); $\Delta R^2=.053$, $\Delta F(1,207)=12.354$ for Step 2 ($p =.001$), $\Delta R^2=.018$, $\Delta F(1,206)=4.176$ for Step 3 ($p =.042$), $\Delta R^2=.001$, $\Delta F(1,205)=.268$ for Step 4 ($p =.605$). Model 4. $R^2=.041$, $F(1, 206)=8.849$ for Step 1 ($p = .003$); $\Delta R^2=.007$, $\Delta F(1,205)=1.473$ for Step 2 ($p =.226$), $\Delta R^2=.048$, $F(1, 204)=10.847$ for Step 3 ($p =.001$); $\Delta R^2=.002$, $\Delta F(1,203)=.364$ for Step 4 ($p =.547$). Model 5. $R^2=.056$, $F(1, 205)=12.163$ for Step 1 ($p = .001$); $\Delta R^2=.009$, $\Delta F(1,204)=1.998$ for Step 2 ($p =.159$); $\Delta R^2=.042$, $\Delta F(1,203)=9.574$ for Step 3 ($p =.002$); $\Delta R^2=.000$, $\Delta F(1,202)=.022$ for Step 4 ($p =.882$).

*** $p < .001$,

** $p < .01$,

* $p < .05$.

Table 7

Simple and Multiple Mediation of the Indirect Effects of Bipolar Spectrum Diagnosis on Prospective Substance Use Problems through BAS, BAS Subscales, Impulsiveness, and BIS

	Point Estimate	BCa[*] 95% CI	
		Lower	Upper
Simple Indirect Effects			
BAS Total**	0.0899	0.0029	0.2194
Funseeking**	0.1391	0.0415	0.2815
Reward	0.0296	−0.0171	0.1168
Drive	0.0264	−0.0317	0.1189
Impulsiveness**	0.1747	0.0418	0.1738
BIS	0.0140	−0.0226	0.0842
Multiple Indirect Effects			
Model 1			
Indirect Effects			
BAS Total	0.0493	−0.0526	0.1636
Impulsiveness**	0.1401	0.0008	0.3525
TOTAL	0.1895	0.0353	0.3993
Contrasts			
BAS Total vs. Impulsiveness	−0.0908	−0.3539	0.1013
Model 2			
Indirect Effects			
Funseeking	0.0966	−0.0039	0.2287
Impulsiveness	0.1118	−0.0282	0.3454
TOTAL	0.2084	0.0587	0.4289
Contrasts			
Funseeking vs. Impulsiveness	−0.0152	−0.2951	0.1905
Model 3			
Indirect Effects			
Drive	0.001	−0.0798	0.0744
Impulsiveness**	0.1748	0.0342	0.397
TOTAL	0.1757	0.0309	0.3916
Contrasts			
Drive vs. Impulsiveness	−0.1738	−0.4178	−0.0016
Model 4			
Indirect Effects			
Reward	0.0151	−0.0341	0.0943
Impulsiveness**	0.1711	0.0372	0.3905
TOTAL	0.1862	0.0364	0.4186
Contrasts			
Reward vs. Impulsiveness	−0.156	−0.362	−0.0121
Model 5			
Indirect Effects			

	Point Estimate	BCa[*] 95% CI	
		Lower	Upper
BIS	0.0248	−0.0058	0.1103
Impulsiveness**	0.1964	0.0523	0.4127
TOTAL	0.2212	0.0622	0.4528
Contrasts			
BIS vs. Impulsiveness**	0.1717	0.0258	0.3829

[*] BCa=Bias corrected and accelerated bootstrapping confidence intervals that include correction for median bias and skew. Confidence intervals containing zero are interpreted as not significant.