

Published in final edited form as:

*Bipolar Disord.* 2012 August ; 14(5): 565–570. doi:10.1111/j.1399-5618.2012.01035.x.

## Trait impulsivity as an endophenotype for bipolar I disorder

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### Abstract

**Objective**—Impulsivity, conceptualized as impairment in planning and poor attentional and inhibitory control, is a key feature of bipolar disorder. Familial risk for bipolar disorder is known to affect inhibitory control but its impact on the attentional and planning dimensions of impulsivity is still unclear.

**Methods**—We administered the Barratt Impulsiveness Scale, version 11 (BIS-11) to 54 euthymic individuals with DSM–IV bipolar I disorder, 57 of their clinically unaffected siblings, and 49 healthy comparison subjects. Groups were compared on the attentional (rapid shifts in attention/impatience with complexity), motor (acting impetuously), and non-planning (absence of weighing upon long-term consequences of actions) subscales of the BIS-11, and on total BIS-11 score. To investigate functional implications of trait impulsivity, total BIS-11 score was examined in relation to current psychosocial functioning and criminal history.

**Results**—Individuals with bipolar I disorder had elevated scores compared to healthy comparison subjects on BIS-11 total score and all three subscales ( $p < 0.0001$ ). Unaffected siblings had elevated BIS-11 total score ( $p = 0.0037$ ), motor ( $p = 0.0027$ ), and non-planning ( $p = 0.0379$ ) subscales in comparison to unrelated healthy controls. Total BIS-11 score was negatively associated with global assessment of functioning (GAF) score ( $\beta = -0.32$ ,  $p < 0.0001$ ).

**Conclusions**—Our results suggest that impulsivity is sensitive to familial liability for the illness, making it a potential endophenotype for bipolar disorder.

### Keywords

bipolar disorder; BIS-11; endophenotype; impulsivity; siblings

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### Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

Impulsivity is a multifaceted construct that can be conceptualized as a predisposition to react toward stimuli in a rapid and unplanned manner without regard to negative consequences (1). Increased impulsivity is considered a dimension of mania (2) and may underlie a number of behaviors commonly observed in symptomatic individuals with bipolar disorder, including risky sexual behaviors, indiscriminant spending, reckless driving, and increased suicidal ideation (3). Although the degree of impulsivity is associated to some degree with acute manic symptomatology (4), several studies report persistent elevation of impulsive traits in remitted or minimally symptomatic patients (5–8), raising the possibility that impulsivity may be a trait marker for the illness. In addition, family, twin and adoption studies show that increased impulsivity is heritable (9–12), suggesting that impulsive behavior is under genetic control. Unaffected relatives of patients with bipolar disorder have impairment in cognitive tasks thought to involve aspects of impulsivity, particularly response inhibition (13, 14), which is also reflected in shared abnormalities between bipolar disorder patients and their relatives in brain function (15) and functional connectivity (16) within neural networks involved in inhibitory control. Collectively, these findings suggest that increased impulsivity may be part of familial risk for the illness. However, familial resemblance in self-reported impulsivity in family members discordant for bipolar disorder has not yet been investigated.

We used the Barratt Impulsiveness Scale, version 11 (BIS-11) (17) to examine self-reported attentional, motor, and non-planning dimensions of impulsivity in bipolar probands and their clinically unaffected siblings [see Stanford et al. (18) for a review]. The BIS-11 differs from performance-based or cognitive measures of impulsivity as scores reflect self-rated behaviors rather than discrete cognitive processes and thus may be closer to psychiatric symptomatology. Our primary aim was to test whether familial risk for bipolar disorder impacts on attentional, non-planning and response inhibition scales of the BIS-11. A secondary aim was to examine the real-world implications of increased impulsivity in bipolar disorder patients and their unaffected relatives. There are severe clinical and public health ramifications of impulsive behavior; for example, impulsivity is associated with early experimentation with drugs and liability to developing a substance use disorder (19), and its behavioral manifestations include violent criminality (20). To the extent that behavioral measures of impulsivity can be shown to be risk factors or endophenotypes for bipolar disorder, it is possible that these measures can be used to help disentangle the complex genetic architecture of bipolar disorder.

We hypothesized that both euthymic individuals with bipolar disorder and their clinically unaffected siblings would have higher levels of trait impulsivity compared to healthy subjects, and that siblings would evidence impulsivity levels intermediate between those of healthy controls and bipolar I disorder probands. Additionally, in order to assess the functional implications of impulsiveness, we examined the association of BIS-11 scores with psychosocial functioning and criminal history in bipolar I disorder patients, their siblings, and controls.

## Methods

### Participants

The protocol was approved by the Institutional Review Boards at Hartford Hospital and Yale University, and written informed consent was obtained from all participants prior to enrollment. Participants were recruited through online advertisements and flyers placed throughout the state of Connecticut. Fifty-four individuals with bipolar I disorder, 57 of their non-bipolar full siblings, and 49 healthy comparison subjects participated in the study. Inclusion criteria for individuals with bipolar disorder were: (i) age range of 18–70 years, (ii) a diagnosis of bipolar I disorder based on the *Diagnostic and Statistical Manual of*

*Mental Disorders, 4th edition* (DSM–IV) (21) with onset before age 50, and (iii) at least one non-bipolar sibling willing to participate in the study. Siblings were included if they were: (i) within 10 years of the age of the bipolar proband, and (ii) did not have a diagnosis of bipolar disorder or bipolar spectrum disorder (i.e., bipolar disorder type II, bipolar disorder not otherwise specified, or cyclothymia), while other affective diagnoses (anxiety disorders, and one past major depressive episode) were allowed. Unrelated healthy comparison subjects were included if they: (i) were free of any lifetime personal history of Axis I psychiatric disorders (with the exception of history of drug or alcohol abuse/dependence,  $n = 3$ ), and (ii) had no family history (first degree relative) of any Axis I disorder or bipolar spectrum disorder.

Participants were excluded for: (i) alcohol or drug abuse/dependence within the past six months, (ii) history of neurodegenerative disorder, (iii) traumatic head injury, and/or (iv) mental retardation (IQ less than 70). Traumatic head injury was defined as any head trauma resulting in medical treatment/hospitalization or loss of consciousness for more than 5 min.

### Assessment procedure

All participants were screened for DSM–IV diagnoses using the Structured Clinical Interview for DSM–IV-TR Axis I Disorders (SCID), administered by trained clinical research staff (inter-rater reliability for all Axis I disorders,  $\kappa > 0.85$ ) (21). Bipolar disorder subjects were assessed during a period of symptom remission, as indicated by scores below 10 on both the Hamilton Depression Scale (HAMD) (22) and the Young Mania Rating Scale (YMRS) (23). All subjects completed the Barratt Impulsiveness Scale, version-11 (BIS-11), a 30-item self-report questionnaire that measures three components of impulsiveness: attentional (tendency to make rapid decisions), motor (acting without thinking), and non-planning (lacking forethought) (17). A global assessment of functioning (GAF) score was determined for each subject by DSM–IV criteria, and data on arrest and conviction history were collected using a standardized legal history questionnaire.

### Hypothesis testing

Statistical analyses addressed the following predictions:

- i. Subjects with bipolar I disorder will have increased self-reported impulsivity, as evidenced by higher scores on the BIS-11, compared with their non-bipolar siblings and healthy subjects.
- ii. BIS-11 scores in unaffected siblings will be higher than those in healthy control subjects, but lower than those in their affected sibling with bipolar I disorder.
- iii. There will be an inverse correlation between GAF and BIS-11 total scores across the sample, and within each group individuals with a criminal history will have higher BIS-11 total scores than those without a history, indicating that lower impulsivity is associated with better functioning.

Prior to statistical analysis, all outcomes were assessed for normality using normal probability plots and Kolmogorov test statistics. All data were sufficiently normally distributed. Each of the four BIS-11 variables was compared between diagnostic groups using linear mixed models that included group (control, bipolar disorder, and sibling) as a between-subjects factor and random family effects (Hypotheses 1 and 2). Thus, the non-independence between the proband and their sibling was accounted for as a random effect. Significant group effects were followed by Tukey's multiple comparisons test, and effect sizes (Cohen's  $d$ ) were calculated for each analysis. Examination of psychosocial functioning/criminal history and impulsivity was limited to BIS-11 total score to minimize the number of analyses. A mixed model analysis adjusting for family effects was used to

determine the correlation between BIS-11 total score and GAF across the entire sample. Independent samples *t*-tests were used to examine the relationship between criminal history (includes arrest and conviction history, coded categorically as *yes* and *no* for each) and impulsivity for each of the groups separately (Hypothesis 3). All tests were two-tailed and considered significant at the 0.05 level.

## Results

### Sample characteristics

Demographic data are shown in Table 1. Age, race, and sex were comparable between the groups ( $p > 0.40$ ); however, the control group completed more years of education than the bipolar disorder and sibling groups ( $p = 0.02$ ). Matching samples based on educational attainment may bias results (24) and thus education was not used as a covariate in analyses. After completion of clinical interview where diagnosis was established, three bipolar disorder subjects were unable to complete the study at the time of data analysis, resulting in fewer subjects with bipolar I disorder than unaffected siblings. The average HAMD and YMRS scores for the bipolar disorder participants were  $2.9 \pm 2.6$  (range: 0–9) and  $1.8 \pm 2.3$  (range: 0–8), respectively. Twenty-seven bipolar disorder subjects (50%), seven siblings (12.3%), and three controls (6.1%) met criteria for history of alcohol abuse/dependence, in remission for at least six months. Twenty-six bipolar disorder subjects (48.1%), six siblings (10.5%), and three controls (6.1%) met criteria for a history of drug abuse/dependence, in remission for at least six months. Eighty-nine percent ( $n = 48$ ) of the bipolar disorder group were on at least one psychotropic medication at the time of data collection. Mean GAF scores were  $81.4 \pm 8.9$  (range: 55–93) for the bipolar disorder group,  $90.7 \pm 4.3$  (range: 75–98) for the sibling group, and  $93.1 \pm 3.8$  (range: 80–99) for the healthy comparison group. Data on legal issues were available on 129 subjects (80.6% of the total sample), with 21 (51.2%) bipolar disorder subjects, nine (18.8%) siblings, and four (10.0%) controls arrested at least once during their lifetime. Of those arrested, 12 (29.3%) bipolar disorder subjects were convicted, as were two (4.2%) siblings, and two (5%) controls.

### BIS-11 scores

The mixed model analysis comparing the three diagnostic groups (bipolar disorder, sibling, and controls) yielded significant group effects after covarying for sex and age. Both age and sex were significant covariates, but neither interacted with group. The groups differed significantly on the total score of the BIS-11 [ $F(2,45) = 55.1$ ,  $p < 0.0001$ ] (see Table 1). Post-hoc analyses confirmed that the bipolar disorder subjects had significantly higher scores compared to the healthy controls ( $p < 0.0001$ , Cohen's  $d = 2.02$ ). Additionally, there were significant group effects on all three subscales of the BIS-11: attentional impulsiveness [ $F(2,45) = 40.6$ ,  $p < 0.0001$ ], motor impulsiveness [ $F(2,45) = 34.8$ ,  $p < 0.0001$ ], and non-planning impulsiveness [ $F(2,45) = 36.7$ ,  $p < 0.0001$ ]. Post-hoc analyses revealed that the bipolar disorder group had significantly higher scores on all subscales compared to healthy controls ( $p < 0.0001$ ), with effect sizes ranging from 1.62 to 1.70.

Unaffected siblings had significantly higher scores compared to the healthy controls on the BIS-11 total score ( $p = 0.004$ , Cohen's  $d = 0.67$ ), and on the motor impulsiveness ( $p = 0.0027$ , Cohen's  $d = 0.69$ ) and non-planning impulsiveness ( $p = 0.038$ , Cohen's  $d = 0.50$ ), and trended higher for attentional impulsiveness ( $p = 0.058$ , Cohen's  $d = 0.46$ ) subscales. Yet, siblings had significantly lower scores compared to their bipolar probands on BIS-11 total ( $p < 0.0001$ , Cohen's  $d = 1.34$ ), attentional ( $p < 0.0001$ , Cohen's  $d = 1.23$ ), motor ( $p < 0.0001$ , Cohen's  $d = 0.94$ ), and non-planning ( $p < 0.0001$ , Cohen's  $d = 1.12$ ) subscales.

### Associations with GAF and criminal history

Across the sample ( $n = 160$ ), the BIS-11 total score was negatively associated with GAF scores ( $\beta = -0.32$ ,  $p < 0.0001$ ). However, the differences in slopes between the bipolar disorder and healthy control groups did not differ ( $p = 0.19$ ), nor did the slopes between the unaffected siblings and controls ( $p = 0.47$ ), suggesting that the relationship between impulsivity and functional outcomes was not substantively different between groups. Within the bipolar I disorder group, the BIS-11 total score was negatively associated with GAF score ( $\beta = -0.29$ ,  $p < 0.0001$ ), and this correlation was similar but attenuated in the sibling and healthy control groups. There was not a difference in BIS-11 total score between bipolar disorder subjects with ( $n = 20$ ) and without ( $n = 21$ ) a criminal history ( $p > 0.4$ ). Due to the small sample size of siblings ( $n = 9$ ) and controls ( $n = 4$ ) with a criminal history, analyses were not completed for these groups.

### Effects of co-occurring diagnoses

Bipolar disorder subjects with a history of an alcohol use disorder ( $n = 27$ , 50%) had significantly higher scores on the motor subscale compared to bipolar disorder subjects without a history ( $p = 0.023$ ). There were no differences in BIS-11 total and subscale scores between bipolar disorder subjects with and without a history of a drug use disorder ( $p > 0.1$ ). To determine whether elevations in BIS-11 scores were due to a co-occurring alcohol use disorder, we removed these subjects from analyses. However, the bipolar disorder subjects without an alcohol abuse/dependence history still exhibited significantly elevated BIS-11 total and subscale scores compared to healthy controls ( $p < 0.0001$ ).

### Discussion

To our knowledge, this is the first study to examine trait impulsivity using the BIS-11 in sibling pairs discordant for bipolar I disorder. Our data support previous findings of increased trait impulsivity in individuals with bipolar I disorder in a state of euthymia compared to healthy controls (5–8), and extends these findings by demonstrating that impulsivity is also increased in the unaffected full siblings of bipolar probands. Our results suggest that the BIS-11 is a candidate endophenotype for bipolar I disorder and suggest that increased impulsivity is associated with familial liability for developing bipolar disorder.

The GAF score, coded using information from psychological, social and occupational functioning, was negatively correlated with trait impulsivity. Increased impulsivity is associated with a more severe course of illness (25), and the consequences of impulsive behavior may have a maladaptive effect on personal relationships and careers that results in a lower GAF score. However, the relationship between the GAF and BIS-11 scores did not differ across groups, suggesting that the increased impulsivity observed in the bipolar disorder group did not strongly impact psychosocial functioning in this group. Yet, all three groups had good to superior functioning on the GAF scale. Individuals in the bipolar disorder group were selected to be euthymic at the time of assessment, and the majority of patients were medicated (89%), perhaps resulting in overall higher psychosocial functioning. Thus, additional studies examining the relationship between impulsivity and psychosocial functioning in bipolar disorder are warranted.

Individuals with bipolar disorder and a criminal history did not differ in terms of BIS-11 scores from patients without criminality. Criminal acts, including events that lead to an arrest, may be mediated by state rather than trait impulsivity. Swann and colleagues (26) showed that while BIS-11 scores were not related to conviction history in bipolar disorder, reduced inhibitory control, measured by commission errors and accelerated reaction times in a laboratory measurement of impulsivity, was associated with criminal history. Together

with the current data, this may suggest that self-reported measures of impulsiveness may not accurately reflect the tendency to engage in impulsive behavior that results in criminal acts. A larger sample size of individuals in the sibling and control groups with a criminal history would be needed to assess the relationship between criminal history and trait-impulsivity in non-patient samples.

Limitations of this study include the overrepresentation of females, which may have an effect on the number of subjects with an arrest history and comorbid alcoholism. Bipolar disorder with a comorbid substance abuse diagnosis has been shown to have a greater effect on criminal behavior in women than in men (27) and to have additional negative consequences for women (28). Nevertheless, the current findings suggest minimal evidence of elevated BIS-11 scores due to a co-occurring drug or alcohol use disorder. Indeed, our finding of increased motor impulsivity in bipolar I disorder individuals with an alcohol use disorder versus bipolar I disorder individuals without a history supports a previous study (29), which also found that this elevation does not account for overall increased impulsivity in individuals with bipolar I disorder versus controls. An additional limitation is the self-report nature of the BIS-11, which depends on the veracity of an individual's responses and may be liable to bias. However, the BIS-11 is a widely used measure that is internally consistent across populations (17), and has been linked with various biological constructs (30). The present study lacked sufficient power to see an effect of a comorbid anxiety disorder, and future studies should consider a history of comorbid anxiety disorders, as there is conflicting evidence of its effect on BIS-11 scores in individuals with and without bipolar I disorder (31, 32).

Our findings suggest that the BIS-11, particularly the motor and non-planning subscales, may be a potentially valuable candidate endophenotype for bipolar I disorder. However, additional information, namely demonstrating that BIS-11 scores are heritable and genetically correlated with bipolar disorder, is needed before this index can be fully established as an endophenotype for the illness (33). The use of quantitative endophenotypes should improve our ability to identify genes that influence risk for bipolar disorder (34), which in turn could provide new treatment targets for this debilitating illness.

## Acknowledgments

Financial support for this study was provided by RO1 MH080912 (DCG).

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**Table 1**

Demographic characteristics and Barratt Impulsiveness Scale, version 11 (BIS-11) scores of the sample

	Bipolar disorder (n = 54)	Sibling (n = 57)	Controls (n = 49)
<b>Demographics</b>			
Female, n (%)	36 (66.7)	36 (63.2)	28 (57.1)
Age (years), mean (SD) [range]	31.9 (11.0) [18–59]	31.4 (13.0) [18–60]	30.4 (10.7) [18–55]
Education (years), mean (SD) [range]	14.2 (1.8) [10–18]	14.3 (2.0) [9–18]	15.2 (2.1) [12–20]
Race, n (%)			
Non-Hispanic White	43 (79.6)	47 (82.5)	38 (77.6)
African American	2 (3.7)	3 (5.3)	7 (14.3)
Hispanic/Latino	5 (9.3)	4 (7.0)	1 (2.0)
Other	4 (7.4)	3 (5.3)	3 (6.1)
<b>Comorbid alcohol/drug history, n (%)</b>			
Past alcohol abuse/dependence	27 (50.0)	7 (12.3)	3 (6.1)
Past drug abuse/dependence	26 (48.1)	6 (10.5)	3 (6.1)
<b>Medications, n (%)</b>			
Mood stabilizer(s)	27 (50.0)		
Antidepressant(s)	23 (42.6)	5 (8.8)	
Atypical antipsychotic(s)	23 (42.6)		
Anxiolytic/benzodiazepine(s)	22 (40.7)	2 (3.5)	
Lithium	13 (24.1)		
Unmedicated	6 (11.1)		
Typical antipsychotic(s)	1 (1.9)		
<b>HAMD score</b> , mean [range]	2.9 [0–9]	1.0 [0–6]	0.2 [0–3]
<b>YMRS score</b> , mean [range]	1.8 [0–8]	0.5 [0–6]	0.1 [0–1]
<b>Criminal history<sup>a</sup>, n (%)</b>			
Arrested	21 (51.2)	9 (18.8)	4 (10.0)
Convicted	12 (29.3)	2 (4.2)	2 (5.0)
<b>GAF score</b> , mean (SD) [range]	81.4 (8.9) [55–93]	90.7 (4.3) [75–98]	93.1 (3.8) [80–99]
<b>BIS-11 scores</b> , mean (SD)			
Total	72.9 (12.1) <sup>b,c</sup>	58.9 (11.5) <sup>b</sup>	52.4 (8.9)
Attentional	18.7 (4.2) <sup>b,c</sup>	13.9 (4.6)	12.3 (3.4)
Motor	26.1 (4.9) <sup>b,c</sup>	22.3 (4.2) <sup>b</sup>	19.8 (3.1)
Non-planning	28.0 (5.5) <sup>b,c</sup>	22.6 (4.7) <sup>b</sup>	20.3 (4.4)

GAF = Global Assessment of Functioning Scale; HAMD = Hamilton Depression Scale; YMRS = Young Mania Rating Scale.

<sup>a</sup>Data only available on 41 bipolar disorder subjects, 48 siblings, and 40 controls.<sup>b</sup>Significantly different from the healthy control group ( $p < 0.05$ ).<sup>c</sup>Significantly different from the sibling group ( $p < 0.0001$ ).