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## Examining the Validity of Cyclothymic Disorder in a Youth Sample

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### Abstract

**Background**—Four subtypes of bipolar disorder (BP) – bipolar I, bipolar II, cyclothymia and bipolar not otherwise specified (NOS) – are defined in DSM-IV-TR. Though the diagnostic criteria for each subtype are intended for both adults and children, research investigators and clinicians often stray from the DSM when diagnosing pediatric bipolar disorder (PBD) (Youngstrom, 2009), resulting in a lack of agreement and understanding regarding the PBD subtypes.

**Methods**—The present study uses the diagnostic validation method first proposed by Robins and Guze (1970) to systematically evaluate cyclothymic disorder as a distinct diagnostic subtype of BP. Using a youth (ages 5–17) outpatient clinical sample ( $n=827$ ), participants with cyclothymic disorder ( $n=52$ ) were compared to participants with other BP spectrum disorders and to participants with non-bipolar disorders.

**Results**—Results indicate that cyclothymic disorder shares many characteristics with other bipolar subtypes, supporting its inclusion on the bipolar spectrum. Additionally, cyclothymia could be reliably differentiated from non-mood disorders based on irritability, sleep disturbance, age of symptom onset, comorbid diagnoses, and family history.

**Limitations**—There is little supporting research on cyclothymia in young people; these analyses may be considered exploratory. Gaps in this and other studies are highlighted as areas in need of additional research.

**Conclusions**—Cyclothymic disorder has serious implications for those affected. Though it is rarely diagnosed currently, it can be reliably differentiated from other disorders in young people. Failing to accurately diagnose cyclothymia, and other subthreshold forms of bipolar disorder, contributes to a significant delay in appropriate treatment and may have serious prognostic implications.

### Keywords

cyclothymic disorder; pediatric bipolar disorder; validation; Robins and Guze

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Pediatric bipolar disorder (PBD) is a relatively new concept within psychology and has been the source of diagnostic debate. Although there is generally agreement regarding the phenotypes for bipolar I and II, the definitions of bipolar disorder not otherwise specified (BP NOS) and cyclothymic disorder are still subject to controversy (Youngstrom, 2009). In fact, although there are distinct DSM criteria for each, it has been noted in the literature that many research groups do not attempt to differentiate subthreshold subtypes, relying instead on a less-precisely defined “NOS” grouping (Kessler, Avenevoli, & Merikangas, 2001; Youngstrom, Birmaher, & Findling, 2008). The differentiation of subthreshold bipolar disorder subtypes is important in order to elucidate the risk factors, developmental course, and potential for preventative measures that apply to each.

Subthreshold cases of PBD may, in fact, be in greatest need of investigation. These presentations are more common than BP I and II in young people (Lewinsohn, Klein, & Seeley, 1995; Merikangas et al., 2007; Van Meter, Moreira, & Youngstrom, 2010) and adults (Akiskal, Lancrenon, & Hantouche, 2006; Hantouche, 2009) and prove to be just as impairing as the syndromal subtypes in both clinical and community studies (Axelson et al., 2006; Birmaher et al., 2009; Birmaher et al., 2006; Findling et al., 2005; Judd & Akiskal, 2003; Kessler et al., 2001). Furthermore, subthreshold bipolar disorder likely offers the best opportunity for preventative intervention (Berk et al., 2007; Chang, 2008; Klein, Depue, & Slater, 1986; Miklowitz & Chang, 2008).

For the most part, cyclothymia is not described in research settings or diagnosed clinically (Youngstrom, Youngstrom, & Starr, 2005). The absence of cyclothymia in research studies and clinical settings suggests that cases of cyclothymic disorder are either being (1) misdiagnosed as another mood disorder, particularly BP NOS, (2) misdiagnosed as a non-affective disorder, or (3) not coming to scientific or clinical attention. Failure to recognize subthreshold cases may leave up to one-third of people with bipolar disorder untreated (Angst, Merikangas, & Preisig, 1997). This is a real concern considering that early onset bipolar disorder may represent a more pernicious type than adult onset, and early treatment could stave off some consequences associated with the disorder (Berk et al., 2007; Perlis et al., 2004).

The validity of pediatric bipolar subtypes may be of particular interest now, as DSM-5 and WHO/ICD-11 committees are meeting to determine the future classification system. In order to examine the validity of cyclothymic disorder in youth, a review of the pediatric bipolar disorder literature and previous studies of cyclothymia in adults was conducted. Seven constructs, Depression and Hypomania, Irritability, Comorbidity, Age of Onset, Sleep Disturbance, and Family History, were identified to explore as potential discriminating clinical features of pediatric cyclothymia (Akiskal, Djenderedjian, Rosenthal, & Khani, 1977; Birmaher et al., 2009; Birmaher et al., 2006; Depue et al., 1981; Findling et al., 2005; Howland & Thase, 1993; Klein et al., 1986)

In order to be diagnosed with cyclothymic disorder, according to DSM nosology, youth must suffer impairing symptoms, both **depressive** and **hypomanic**, that fail to meet full criteria for either number of symptoms or duration for mania or major depression. Additionally, both depressive and hypomanic symptoms must have been present for at least 10 out of 12 months to meet criteria. In addition to chronic mood disruption, **irritability** during both hypomanic and depressive periods has been described as a marker of cyclothymic disorder (Akiskal et al., 1977). Unfortunately, irritability is also a symptom of many other childhood disorders, resulting in frequent misdiagnosis (Biederman et al., 2000; Youngstrom et al., 2008). In the case of cyclothymia, the irritability should coincide with episodes of hypomanic and depressive symptoms – not occur persistently as it might in other disorders. Concentrating on the episodic nature of the disorder is the best way to ensure that

a symptom is due to the bipolar disorder (Youngstrom et al., 2008). In the present study, we hypothesized that youth with cyclothymia would report elevated irritability corresponding with both elevated and depressed mood, reflecting significant disturbance during both mood phases.

The presence of other psychiatric disorders is common in youth with bipolar disorder, often making diagnosis difficult and complicating treatment (Lewinsohn et al., 1995; Spencer et al., 2001; Wozniak et al., 1995). Two of the most common **comorbid diagnoses** are ADHD and anxiety disorders (Kowatch, Youngstrom, Danielyan, & Findling, 2005). Given its common symptoms, particularly restlessness, irritability and impulsivity, cyclothymia is often misdiagnosed and it may be several years before a proper diagnosis is made (Faedda, Baldessarini, Glovinsky, & Austin, 2004). Some experts hypothesize that a prolonged period to diagnosis may result in greater burden of illness, including more comorbid diagnoses (McElroy, Strakowski, West, Keck, & McConville, 1997; Schraufnagel, Brumback, Harper, & Weinberg, 2001). Additionally, cyclothymia is associated with a broad range of familial psychiatric disorders, which may lead to increased comorbidity (Akiskal, Hantouche, & Allilaire, 2003; Findling et al., 2005). We hypothesized that youth with cyclothymia would be diagnosed with more comorbid diagnoses than the other youth in the study, and that they would most often report comorbid ADHD or anxiety.

The **age of symptom onset** in bipolar disorder has important implications for prognosis (Craney & Geller, 2003). Generally, the earlier symptoms begin, the more severe the disease will ultimately become (Perlis et al., 2004). Considering (1) that cyclothymia may have its foundation in temperament, (2) that cyclothymia can be the prodrome to other forms of bipolar disorder (Akiskal et al., 1985), and (3) that subsyndromal bipolar may have a younger mean age of symptom onset than BP I and II (Lewinsohn, Klein, & Seeley, 2000), we hypothesized that cyclothymia would have an earlier age of onset than other forms of bipolar disorder (Dickstein et al., 2005). Additionally, research suggests that the first mood episode is more often depressive than elevated (Strober et al., 1995); therefore we expected the index episode of cyclothymia to be characterized by depressive symptoms.

A reliable way to identify youth with bipolar disorder is by assessing **sleep disturbance** coinciding with mood episodes (Geller et al., 2002; Harvey, Mullin, & Hinshaw, 2006). People with cyclothymic disorder often experience significant sleep disturbance, during both hypomanic and depressive episodes, in part due to the restlessness and agitation associated with their disorder (Findling et al., 2005; Kowatch et al., 2005). In the present study, we expected youth with cyclothymic disorder to report disordered sleep similar to that experienced by the other youth with bipolar disorder, albeit less severe than those who reported a history of a full manic episode.

There is significant evidence that bipolar disorder is heritable: A child of a parent with bipolar disorder will be approximately 5 times more likely to develop bipolar than a child of healthy parents (Hodgins, Faucher, Zarac, & Ellenbogen, 2002; Tsuchiya, Byrne, & Mortensen, 2003). In a study of youth with manic symptoms, the youths with cyclothymic disorder were more likely to have a parent with a bipolar disorder than any other diagnostic group of youths (Findling et al., 2005). Additionally, there is evidence that the presence of a family history of mood disorder is the key factor in differentiating people with cyclothymia from others with subthreshold bipolar symptomatology (Akiskal et al., 1977; Depue, 1981). In the present study, we hypothesized that youth with cyclothymia would report a family history of bipolar disorder similar to other youth with bipolar disorders. In addition, we expected youth with cyclothymia to report family history of other psychiatric disorders at a higher rate than other diagnostic group of youths in the sample.

The primary aim of this study is to explore the validity of cyclothymic disorder as a diagnostic subtype of pediatric bipolar disorder. The Robins and Guze approach to diagnostic validation has been used widely in research (Andreasen, 1995; Feighner et al., 1972). It provides a framework of five categories (described as “phases”) of evidence collection that promote a rigorous system for the categorization of disorders without being prohibitively rigid (Widiger & Trull, 1991). In previous studies, cyclothymia in adults has been validated using modified versions of the Robins and Guze phases (Akiskal et al., 1977; Klein et al., 1986). Additionally, the Robins and Guze approaches have been used to validate pediatric bipolar disorder, demonstrating the fit of this framework to this class of disorders (Biederman et al., 2003; Findling et al., 2001; Geller & Tillman, 2005). Three of the five validity criteria – *Clinical Description*, *Delimitation from Other Disorders*, and *Family Studies* – will be addressed by data in this paper.

## Methods

### Participants

Participants were recruited from an urban community mental health center ( $N=647$ ) and from an academic outpatient medical center ( $N=180$ ). A consecutive case series of patients presenting for services at the community mental health clinic were invited to participate in the study. The only eligibility requirements were that the patient was between the ages of five and 18 years and that both the patient and their caregiver were able to speak English. The participants from the academic outpatient medical center were recruited for various treatment studies for bipolar disorder and other childhood disorders. Additionally, children of parents with bipolar disorder were recruited to the academic center. The exclusionary criteria at the academic center included the same age and language requirements as the outpatient clinic; additionally, participants were excluded if they suffered from a pervasive developmental disorder, or mental retardation.

### Measures

**Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime (K-SADS-PL) with Longitudinal Evaluation of All Available Data (LEAD) diagnosis**—(Used to measure: Diagnosis, Comorbidity, Age of Onset). Diagnoses were made taking into account the information provided during the semi-structured interview using the K-SADS-PL (Kaufman et al., 1997). All participants and their families completed a K-SADS-PL, modified with the mood disorders module of the WASH-U-K-SADS (Geller, Zimmerman, & Williams, 2001). The WASH-U-K-SADS inquires about symptoms related to depression and mania that are not well-queried in other diagnostic interviews. In order to achieve interrater reliability, research assistants were required to shadow an experienced rater for at least five K-SADS and demonstrate item-level kappa  $>.85$ . For this study, the Longitudinal Evaluation of All Available Data (LEAD) standard of diagnosis was used to designate the youth with cyclothymic disorder, in addition to all other diagnostic categories (Spitzer, 1983). The LEAD diagnoses take into account the information collected through the K-SADS interview, study questionnaires, family history, and clinical judgment. Kappa was 0.95 for bipolar diagnoses and 0.91 for all diagnoses when comparing consensus to the K-SADS diagnosis (Youngstrom, Meyers, et al., 2005). In order for a participant to receive a diagnosis of cyclothymic disorder, s/he would have to meet criteria for hypomanic symptoms and depressive symptoms, along with the duration criteria of being symptomatic (to the point of clinical impairment) for at least one year. The other diagnostic categories used in this study were bipolar I, bipolar II, bipolar NOS, depression (comprised of major depression, dysthymia, and depression NOS), ADHD, and disruptive behavior disorders (DBD; comprised of ODD, CD, and DBD NOS).

As operationalized in other research studies, age of onset refers to the age at which a participant first met diagnostic criteria for a depressive, manic, hypomanic, or mixed episode (Goldstein et al., 2005). Given the significant delay that often occurs before an accurate bipolar diagnosis is made (Marchand, Wirth, & Simon, 2006), in this study, age of symptom onset will be assessed by determining the youngest age of symptomatology, rather than diagnosis, as reported in the K-SADS interview.

**Parent General Behavior Inventory**—(Used to measure: Irritability, Sleep Disturbance). Irritability was assessed during periods of both depressive and elevated mood using select items from the *Parent-General Behavior Inventory (P-GBI)* (Youngstrom, Findling, Danielson, & Calabrese, 2001). The P-GBI is a modified version of the General Behavior Inventory (GBI) (Depue, 1981), completed by parents about their child. The questions comprise two scales, the depressive and the hypomanic/biphasic, both scales with high construct validity and very high internal consistency (alphas of 0.97 for depression and 0.94 for hypomanic/biphasic) (Youngstrom et al., 2001). This scale was originally developed in order to be sensitive to subthreshold manifestations of mood disorder and has proven to do a good job discriminating cases from the full spectrum of bipolar disorders (Depue, 1981; Youngstrom et al., 2004; Youngstrom, Meyers, et al., 2005).

Items representing depressive or hypomanic irritability were selected by three independent raters. Reliability was high; for depressive irritability, items 3, 14, 34, 39, 44, 50, and 53 (Cronbach's  $\alpha$  .87) and for elevated irritability, items 22, 27, 51, and 54 (Cronbach's  $\alpha$  .71). Sleep disturbance was assessed using the seven-item sleep subscale from the P-GBI, (Cronbach's  $\alpha$  0.83) (Meyers & Youngstrom, 2008).

**Family Index of Risk for Mood**—(Used to measure: Family History). Family psychiatric health history was assessed using *Family Index of Risk for Mood (FIRM)* (Algorta et al., under review). The FIRM provides a simple method by which information about study participants' family history of mental health issues can be gathered. It consists of an array of questions about mental health history for close relatives (parents, grandparents, aunts/uncles, siblings and children), resulting in a total of 25 checkboxes that respondents can endorse; higher scores indicate greater psychopathology among family members. The FIRM was validated in a pediatric bipolar study of 162 families. The family history information showed a clinically meaningful association with youth diagnoses of PBD and the number of family risk factors discriminated cases with diagnoses of PBD from all other cases. Because this measure was developed towards the end of the protocol, scores are only available on a subset of cases.

**Child's Global Assessment Scale**—(Used to measure: Level of Functioning). The C-GAS (Shaffer et al., 1983) was used to gauge youth's current level of overall functioning. Participants' C-GAS scores were used to control for degree of impairment, which may account for greater variability in symptom severity than diagnosis.

## Procedure

All caregivers signed written consent, and youth participants provided written assent. The youth and parent each completed the K-SADS interview separately (administered by the same interviewer). While the parent was being interviewed, youth 11 years and older completed a series of questionnaires. While the child was being interviewed, the caregiver completed the P-GBI, FIRM, and other questionnaires. The scores on all questionnaires were recused from the consensus diagnosis meeting, which followed the Longitudinal Evaluation of All Available Data (LEAD) procedure (Spitzer, 1983).

**Analytic Plan**—Age, gender, substance use and C-GAS score were covariates in subsequent analyses as covariates. Historically, bipolar disorder has been considered an adult diagnosis, though it is now accepted that bipolar occurs in children, risk is thought to increase through adolescence into early adulthood (Shankman et al., 2009). Although previous research has not found sex differences in the prevalence of bipolar disorder (Merikangas et al., 2007), it may be that there are differences in youth clinical diagnosis, with boys more likely to receive a diagnosis of bipolar than girls (Moreno et al., 2007). Substance use is often associated with other psychiatric disorders, including pediatric bipolar disorder (Brook, Cohen, & Brook, 1998; Kandel et al., 1997; Wilens et al., 1999).

Chi-squared analyses compared rates and categorical variables across diagnostic groups. Scores from the P-GBI and family risk factors were converted into a percent of the maximum possible score (POMP). Converting summed scores into percents provides a framework by which to interpret differences (Cohen, Cohen, Aiken, & West, 1999). ANOVA was used to compare means on rating scales and family history. Linear regression models were used to compare mean differences, while controlling for gender, age, and C-GAS. Repeated-measures ANOVA was used to investigate the pattern of irritability across elevated and depressive periods. Post-hoc comparisons used Tukey's HSD procedure, which allows for between-group comparisons following an ANOVA, correcting for the increased likelihood of Type I error due to multiple comparisons.

## Results

### Preliminary analyses

The sample was comprised of 496 (60%) male participants and 331 (40%) female participants. The sample had an average age of 10.92 years ( $SD=3.44$ ). Sixty-nine percent ( $N=573$ ) of subjects reported their race as Black, 22% ( $N=185$ ) White, 2% ( $N=20$ ) Hispanic, .2% ( $N=2$ ) Asian, and 5% ( $N=45$ ) reported race as Other. Two people declined to report race information.

There was no gender difference in the rate of bipolar disorders ( $X^2(1)=2.2, p=.13$ ); nor was there any difference in the average age of youths with versus without bipolar disorders ( $F(1)=1.0, p=.31$ ). Sixteen percent of the sample met criteria for any substance use, with no difference between those participants on the bipolar spectrum and the rest of the sample ( $X^2(1)=2.6, p=.12$ ). There was a significant difference in mean C-GAS score between participants with bipolar spectrum disorders (49.1) and those with non-affective disorders (53.1), ( $F(1)=52.6, p<.0001$ ).

### Irritability

The mean elevated irritability score for youth with cyclothymia was 33 ( $SD=21$ ), significantly higher than the mean score of 23 ( $SD=22$ ) for the rest of the sample (all youth without a diagnosis of cyclothymia) ( $t(808)=-3.21, p<.001$ ). There were also significant differences in total irritability scores across diagnostic groups, ( $p<.0001$ ). The mean depressive irritability score for youth with cyclothymia was 43 ( $SD=19$ ), also significantly higher than the mean score of 29 ( $SD=24$ ) for the rest of the sample ( $t(808)=-4.11, p>.0001$ ). See Table 1.

Repeated-measures ANOVA, investigating the pattern of irritability across elevated and depressive periods, was significant ( $F(3)=4.63, p<.01$ ), such that the difference in level of irritability across elevated and depressed episodes depended on the bipolar subtype. Further consideration of the mean difference between elevated and depressive irritability across

bipolar subtypes indicated that participants with BP II have a larger difference between levels of irritability than each of the other BP subtypes ( $p < .05$ ). See Figure 1.

The hypothesis that youth with cyclothymia will have similar levels of irritability in both elevated and depressive episodes, was not supported; there was significantly greater irritability experienced during depressive periods ( $t(51) = -3.59, p < .001$ ).

### Comorbidity

Of the 52 youth with cyclothymia in the sample, 51 (98%) met criteria for a comorbid diagnosis. Nineteen (37%) had a comorbid anxiety disorder. This is not significantly different from the rest of the sample ( $X^2(1) = 3.37, p = .07$ ). Forty-three of the youth with cyclothymia (83%) had comorbid ADHD; significantly more than the rest of the sample ( $X^2(1) = 9.13, p < .005$ ).

As a group, the bipolar subtypes do not differ in the number of total comorbid diagnoses ( $F(3) = 2.3, p = .08$ ). See Table 2. However, youth with cyclothymia were the most likely to meet ADHD criteria. Youth with cyclothymia did have a higher number of comorbid diagnoses than those youth without bipolar spectrum disorders ( $F(4) = 23.8, p < .0001$ ).

### Age of onset

Thirty-eight of the youth with cyclothymia (73%) had symptom onset prior to the age of 10. This is significantly different from the rest of the sample, 32% of whom had onset before 10, ( $X^2(1) = 14.76, p < .0001$ ). However, youth with cyclothymia were not more likely to have mood onset prior to age 10 than the other bipolar spectrum disorders, ( $X^2(3) = 6.04, p = .11$ ). Cox regression examined whether or not youth with cyclothymia exhibit mood symptomatology at younger ages than children with other bipolar subtypes. Cyclothymia had a younger age of onset than bipolar II, ( $Wald = 5.6, p < .05$ ). See Figure 2.

Forty-three of the youth with cyclothymia (83%) experienced depressive symptoms before experiencing hypomanic symptoms. However, there was no difference in the polarity of the index episode between bipolar subtypes ( $p = .91$ ); all bipolar subtypes were more likely to report depressive, rather than hypomanic, symptoms first.

### Sleep disturbance

Youth with cyclothymia had a mean score of 31 ( $SD = 21$ ) on the P-GBI sleep subscale, significantly higher than the rest of the study sample (mean = 22,  $SD = 22$ ) ( $t(808) = -2.77, p < .01$ ).

Youth with cyclothymia scored significantly higher on the P-GBI sleep scale than youth with non-bipolar spectrum disorders ( $p < .0001$ ) with the exception of those youth with depression (mean = 26,  $SD = 22$ ) ( $p = 0.4$ ). When compared to other youth with bipolar spectrum disorders, youth with cyclothymia differed only from those with BP II ( $p < .01$ ), the mean score for youth with cyclothymia (31) was lower than those with BP II (53).

### Family history

All of the youth with cyclothymia in the sample for whom family history was reported had family history of psychiatric disorder. See Table 3. Youth with cyclothymia had significantly greater family history of psychiatric disorder than the rest of the sample ( $p < .05$ ). Additionally, youth with cyclothymia had greater family history of bipolar disorder than the rest of the sample ( $p < .01$ ).

Youth with cyclothymia had more family risk for psychiatric disorder than those with disruptive behavior disorders ( $p<.001$ ), ADHD ( $p<.0001$ ), and depression ( $p<.05$ ). Additionally, youth with cyclothymia had more family history of mood than disruptive behavior disorders ( $p<.0001$ ), ADHD ( $p<.0001$ ), and depression ( $p<.05$ ). Youth with cyclothymia also had more family risk for bipolar disorder than disruptive behavior disorders ( $p<.01$ ) and ADHD ( $p<.001$ ).

There was no difference in the level of familial bipolar risk between the bipolar subtypes. Similarly, there was not a significant difference between bipolar subtypes in the level of general psychiatric illness risk, though the scores vary (Cyclothymia mean=51, BP I mean=13, BP II mean=32, BP NOS mean=32). Unfortunately, these analyses are underpowered, due to small sample size with family history information available.

## Discussion

The primary aim of this study was to examine the validity of cyclothymic disorder in a youth population using the diagnostic validation system proposed by Robins and Guze (1970). In this study of 827 youth seen for outpatient services, we were able to address three of the five major categories of validation: The data related to Clinical Description, Delimitation from Other Disorders, and Family Studies makes a compelling argument for the inclusion of cyclothymia on the bipolar spectrum, and offers clues for future areas of research.

### Irritability

Youth with cyclothymia in the sample exhibited high levels of irritability associated with both depressive and elevated mood; a diagnosis of cyclothymia was a significant predictor of high total irritability (elevated or depressed) – more so than any of the other, non-BP disorders. Whereas we hypothesized that, on average, cyclothymia would be associated with similar levels of irritability across moods, depressive irritability was more severe. This is clinically important, given the fact that people with cyclothymia are more likely to be seen for treatment during depressive episodes (Akiskal et al., 1977). It may be that the heightened irritability signals increased internal agitation, which is more unpleasant both for the individual with cyclothymia and for those close to him/her. Interestingly, youth with unipolar depression had similar levels of average irritability to youth with cyclothymia. This suggests that the overall irritability score may be driven by the depressive irritability score. Whereas irritability is most often discussed with regard to periods of elevated mood in bipolar disorder (Biederman et al., 2000; Kowatch et al., 2005; Wozniak et al., 1995), it appears that irritability during depressive episodes may, in fact, be more severe.

### Comorbidity

Cyclothymic disorder was almost always comorbid with at least one other condition. The rate of comorbid ADHD among the youth with cyclothymia (83%) was, if anything, higher than anticipated. Previous studies have found rates closer to 60% among both youth with cyclothymia and the other bipolar subtypes (Birmaher et al., 2006; Findling et al., 2005), though rates as high as 97% have been reported for BP I (Biederman et al., 2005). More interesting is the fact that the youth with cyclothymia had higher rates of ADHD than the other bipolar subtypes. This may provide some support to the theory that cyclothymia is associated with more varied family history of psychiatric disorder, beyond just mood disorder, and that those with cyclothymia are more likely to also suffer from other disorders.



### Age of onset

The mean age of mood symptom onset for youth with cyclothymic disorder was six years, five months. This supports a growing body of evidence that bipolar disorder very often does begin in childhood (Lewinsohn et al., 2000; Perlis et al., 2004). And, while the differences in age of onset between bipolar subtypes failed to reach significance, the average age of onset for youth with cyclothymia was a full year younger than that for BP I and NOS and two and a half years younger than onset for BP II. An earlier age of onset associated with cyclothymia could support the theory that cyclothymia has a more trait-like, temperamental foundation and chronic course (Akiskal, 1996; Akiskal & Akiskal, 1992; Geller, Tillman, Bolhofner, & Zimmerman, 2008; McElroy et al., 1997; Perlis et al., 2004). Given the relatively small number of participants from which to make these comparisons, additional, prospective research is indicated to further explore this potential difference.

The hypothesis that youth with cyclothymia would tend to have a depressive episode before exhibiting hypomanic symptoms was supported, although they were not any more likely than the other bipolar subtypes to exhibit this pattern. Previous research has repeatedly found that depressive episodes tend to precede [hypo]manic episodes in bipolar youth (Birmaher et al., 2009; Strober et al., 1995). Unfortunately, these data tend to be retrospective, as is the case with the current study; therefore, the report of symptom onset may be confounded with the increased likelihood that people with cyclothymia will seek treatment during depressive episodes (Akiskal et al., 1977; Youngstrom, 2009).

### Sleep disturbance

As expected, youth with cyclothymia reported disrupted sleep. Though the mean score on the P-GBI sleep subscale was lower than the mean score found previously for bipolar youth (Meyers & Youngstrom, 2008), it was significantly higher than the sleep disturbance reported by those youth without bipolar disorder in this sample. There is evidence to support the theory that bipolar disorders are caused, in part, by abnormalities of an individual's circadian rhythms that can "trigger" affective episodes (Grandin, Alloy, & Abramson, 2006; Harvey et al., 2006). The fact that the youth with cyclothymia in this study shared symptoms of sleep disruption with the other bipolar subtypes – but not with those unaffected by bipolar disorders – is important: Based on the circadian rhythm theory, it suggests a shared biology among the bipolar disorders.

### Family history

Youth with cyclothymia had greater family history of psychiatric disorder than the non-bipolar youth. Additionally, they had greater family history of mood disorder than those youth with disruptive behavior disorders, ADHD, and depression. Interestingly, the youth with depression and youth with cyclothymia had similar rates of familial bipolar disorder. This supports the theory that heritability of mental illness is not always specific; but it also suggests that these are all on a spectrum of mood disorder (DelBello & Geller, 2001).

Youth with cyclothymia did not differ from other bipolar subtypes in their reported family history of psychiatric disorder (mood or other). These results offer further evidence that cyclothymia is on the mood disorder spectrum, and is associated with heritable risk.

### Conclusion

The present study explored both similarities and differences across the bipolar spectrum, the results indicate that cyclothymia is, in fact, on the bipolar spectrum (and would not be better cast as a temperament or personality disorder), but retains characteristics that distinguish it from the other subtypes. Distinguishing cyclothymia from BP NOS is, as hypothesized, challenging and perhaps not possible based solely on levels of irritability, comorbid

diagnoses, or family history, alone. That is not to say that cyclothymia is distinguishable *only* by DSM criteria, which are admittedly imperfect; many of the results seem to hint at differences that may have failed to reach significance simply because the sample was not large enough. Based on the findings in this study, further investigation of comorbid ADHD, family history and age of onset, in particular, is indicated.

**Limitations and future directions**—The current study was proposed and executed as an exploration of the diagnosis of cyclothymic disorder in young people. Given the lack of previous research on this population, this study contributed important information about the phenomenology, etiology and comorbid conditions associated with this disorder. Still, there are limitations worth noting. Because it is theorized that cyclothymia may result from a varied genetic foundation, resulting in more pervasive, undifferentiated impairment, the results of genetic and biologic studies are of particular interest, but were not addressed in this study. Greater understanding of the systems implicated in the origin and maintenance of cyclothymia could provide valuable clues into the origin and course of this chronic, debilitating disorder.

The present study is unable to comment on characteristics of the course of cyclothymia, including episode pattern / duration and prognosis. Given that its chronic nature is one of the primary features of the disorder, this is a significant limitation. Unfortunately, cyclothymia has not been differentiated in any of the pediatric longitudinal studies reported to-date – even though the outcome for cyclothymic youth should be of great interest. Specifically, given that cyclothymia may be the most prevalent form of bipolar in adults – and that BP NOS is (by clinical diagnosis) more prevalent in children than adults, following the course of these two subthreshold forms of bipolar disorder may help to elucidate differences. Most importantly, what is the course of chronic, early-onset bipolar spectrum disorder? Who among the subthreshold cases goes on to develop BP I or II, whose symptoms remit? Data from a large, longitudinal study suggests that subsyndromal cases of pediatric bipolar disorder are likely to convert to BP I or II (Birmaher et al., 2009; Birmaher et al., 2006). However, this study does not distinguish between BP NOS and cyclothymic disorder, so it is impossible to draw conclusions about why 38% of cases progressed over the four-year follow-up and the rest did not. Additionally, there is evidence to suggest that some forms of pediatric bipolar disorder may resolve in young adulthood, without future episodes (Cicero, Epler, & Sher, 2009). Without prospective tracking of the specific characteristics of subthreshold bipolar subtypes, along with risk and protective factors, the gains possible from the field of bipolar research are limited. Subthreshold subtypes likely represent the greatest opportunity for preventative measures (Miklowitz & Chang, 2008).

In conclusion, the results of this study suggest that cyclothymia is firmly situated on the mood disorder spectrum. It shares characteristics with both other bipolar disorders and depression. The discussion regarding whether or not depression and bipolar disorder are on the same spectrum is ongoing (Angst et al., 2010; Goodwin & Jamison, 2007), but it seems that further investigation of cyclothymia may offer some answers, not only about the mood spectrum, but about its interactions with temperament, circadian rhythms and other disorders.

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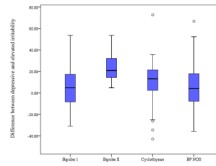
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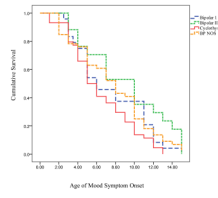
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**Figure 1.**  
Difference in irritability between depressive and elevated periods



**Figure 2.**  
Survival analysis of age of mood symptom onset by bipolar subtype



**Table 1**

Mean POMP irritability scores from the P-GBI by diagnosis

	N	Depressive Irritability	Elevated Irritability	Total Irritability	Difference btwn Dep & Elevated
DBD <sup>§</sup>	138	20.5 (20.0)*	20.6 (20.2)*	21.2 (19.0)*	-0.1 (16.7)*
ADHD	194	18.4 (19.6)*	19.1 (20.5)*	19.2 (18.7)*	-0.7 (17.4)*
Depression	222	38.2 (22.6)	24.4 (23.0)	34.2 (21.5)	13.8 (18.7)
Cyclothymia	52	42.8(19.1)	33.0(20.9)	40.5(17.9)	9.8(19.6)
BP NOS	52	41.9(21.7)	35.7(24.9)	40.9(21.2)	6.2(20.8)
BP II	18	60.7(16.6)*	37.0(20.1)	53.7(17.9)*	23.7(14.2)
BP I	31	52.6(26.0)	47.9(25.7)*	52.5(24.9)	4.8(19.6)

\* Significantly different ( $p < .05$ ) from cyclothymia based on Tukey's HSD posthoc test

<sup>§</sup> DBD refers to disruptive behavior disorders

**Table 2**

## Comorbid diagnoses

	<i>N</i>	Mean number comorbid Dx	% with comorbid anxiety	% with comorbid ADHD
DBD	139	3.2(1.4)*	9 <sup>§</sup>	58 <sup>§</sup>
ADHD	197	3.3(1.2)*	12 <sup>§</sup>	-
Depression	222	4.1(1.8)*	33	48 <sup>§</sup>
Cyclothymia	52	4.9(1.6)	37	83
BP NOS	52	4.2(1.6)	28	57
BP II	18	4.2(2.2)	50	50
BP I	31	4.0(1.6)	35	61

\* Significantly different ( $p < .05$ ) from cyclothymia based on Tukey's HSD posthoc test

<sup>§</sup> Significantly different ( $p < .05$ ) from cyclothymia based on Kruskal-Wallis nonparametric test

**Table 3**

Percent with family risk factors for psychiatric disorder by diagnosis

	<i>N</i>	Family history of psychiatric disorder %	Family history of mood disorder %	Family history of Bipolar %
DBD	42	71	52	31
ADHD	69	70	48	23
Depression	86	80	71	46
Cyclothymia	15	100	93	60
BP NOS	19	84	79	42
BP I & II	9	83	50	33