

# Impact of Irritability and Impulsive Aggressive Behavior on Impairment and Social Functioning in Youth with Cyclothymic Disorder

Anna Van Meter, PhD,<sup>1</sup> Eric Youngstrom, PhD,<sup>2</sup> Andrew Freeman, PhD,<sup>3</sup> Norah Feeny, PhD,<sup>4</sup>  
Jennifer Kogos Youngstrom, PhD,<sup>2</sup> and Robert L. Findling, MD, MBA<sup>5</sup>

## Abstract

**Objective:** Research on adults with cyclothymic disorder (CycD) suggests that irritability and impulsive aggression (IA) are highly prevalent among this population. Less is known about whether these behaviors might also distinguish youth with CycD from youth without CycD. Additionally, little is known about how irritability and IA relate to one another, and whether they are associated with different outcomes. This study aimed to compare irritability and IA across diagnostic subtypes to determine whether CycD is uniquely associated with these behaviors, and to assess how irritability and IA relate to youth social and general functioning.

**Methods:** Participants ( $n = 459$ ), 11–18 years of age, were recruited from an urban community mental health center and an academic outpatient clinic; 25 had a diagnosis of CycD. Youth and caregivers completed measures of IA and irritability. Youth and caregivers also completed an assessment of youth friendship quality. Clinical interviewers assessed youth social, family, and school functioning.

**Results:** Youth with CycD had higher scores on measures of irritability and IA than youth with nonbipolar disorders, but scores were not different from other youth with bipolar spectrum disorders. Measures of irritability and IA were correlated, but represented distinct constructs. Regression analyses indicated that irritability was related to friendship quality ( $p < 0.005$ ). Both IA and irritability were related to social impairment ( $ps < 0.05$ – $0.0005$ ) and Child Global Assessment Scale (C-GAS) scores ( $ps = 0.05$ – $0.005$ ). CycD diagnosis was associated with poorer caregiver-rated friendship quality and social functioning ( $ps < 0.05$ ).

**Conclusions:** We found that irritability and aggression were more severe among youth with CycD than among youth with nonbipolar diagnoses, but did not differ across bipolar disorder subtypes. Among youth seeking treatment for mental illness, irritability and IA are prevalent and nonspecific. Irritability and IA were uniquely related to our outcomes of social and general functioning, suggesting that it is worthwhile to assess each separately, in order to broaden our understanding of the characteristics and correlates of each.

## Introduction

CYCLOTHYMIC DISORDER (CYCD) HAS BEEN CHARACTERIZED as a prevalent, but rarely clinically diagnosed disorder among children (Youngstrom et al. 2005b; Van Meter and Youngstrom 2012). More often than not, both in research and clinical settings, youth with chronic, impairing mood dysregulation – but who never meet full criteria for (hypo)mania or depression – are diagnosed with other specified bipolar and related disorders (or bipolar disorder not otherwise specified [NOS] in *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [DSM-IV] parlance), in spite

of evidence that the cyclothymia diagnosis can be reliably made in this population (American Psychiatric Association 1994; Van Meter et al. 2011; Van Meter and Youngstrom 2012; Van Meter et al. 2013).

Validation research suggests that CycD shares much in terms of phenomenology and family history with bipolar spectrum disorders (BSDs), relative to other childhood disorders, but less is known about what the characteristics and expected outcomes are for a child with CycD, compared with a child bipolar I, II, or other specified disorder. The research on CycD among adults is deeper, and suggests important ways in which the course of CycD may

<sup>1</sup>Ferkauf Graduate School, Yeshiva University, Bronx, New York.

<sup>2</sup>Department of Psychology, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

<sup>3</sup>Department of Psychology, The University of Nevada at Las Vegas, Las Vegas, Nevada.

<sup>4</sup>Department of Psychology, Case Western Reserve University, Cleveland, Ohio.

<sup>5</sup>Johns Hopkins University/Kennedy Krieger Institute, Baltimore, Maryland.

differ from that of the other bipolar subtypes (Howland and Thase 1993; Van Meter et al. 2012). For example, CycD has been described as a prodrome to bipolar I or II (Klein et al. 1986; Shankman et al. 2009), which has important implications for youth, given that longitudinal studies suggest that approximately one third to one half of youth with subthreshold bipolar subtypes (cyclothymic or other specified bipolar disorder) tend to progress to bipolar I or II (Axelson et al. 2011), whereas two thirds stay the same or even improve (Birmaher et al. 2009; Cicero et al. 2009; Findling et al. 2013). This suggests that making a distinction between subtypes at the subthreshold level may have important prognostic implications.

Adult research also indicates that irritability may be a sensitive feature of CycD, present for large periods of time and in virtually all cases. Specifically, adults with CycD often experience extreme irritability and interpersonal problems, both of which contribute to poor functioning (Akiskal et al. 1977, 2003; Shen et al. 2008; Van Meter et al. 2012). For example, adults with CycD are described as experiencing “irritable episodes...[and] episodes of rage or intense uncontrollable anger” (Prakash and Mitra, 2008) and “irritable-explosive attacks.” These episodes of irritability and behavioral manifestations may be a key factor in the interpersonal problems also common to this population (Akiskal et al. 1979; Hantouche and Perugi 2012). Higher levels of social support, defined both as peer and family support, predict remission and better functioning among people with bipolar disorder (Cohen et al. 2004; Sullivan et al. 2012). Individuals with CycD may then be more susceptible to poor outcomes, given their irritability and difficulty maintaining relationships. This would be consistent with data indicating that youth with subthreshold bipolar disorder spend more days ill and are less responsive to treatment than those with bipolar I (Birmaher et al. 2009). Youth with bipolar disorder often have few or no friends (Geller et al. 2000) and experience significant social functioning deficits (Goldstein et al. 2006, 2009; Siegel et al. 2015). Research has shown that mood symptoms are associated with these social deficits (Siegel et al. 2015); irritability, which is related to both depressive and hypomanic symptoms for youth with CycD (Van Meter et al. 2012), may exacerbate social impairments in this population. Determining whether social deficits are prevalent among youth with CycD, specifically, would add to our limited knowledge about this disorder, and importantly, provide evidence that the interpersonal deficits characteristic of adults with CycD are also present among youth with the illness. Additionally, understanding if and how irritable mood and aggressive behavior in this population contribute to social skills deficits could motivate the development of interventions specific to irritability and aggression.

It is likely that irritability and aggression play a key role in the social deficits observed among youth with CycD, similar to what research in adult samples has shown. However, youth with CycD are certainly not the only youth who exhibit significant irritability and aggression. Irritability is an emotional state that has been referred to as a “fever” symptom, meaning it can indicate a mental health concern, but is far from specific, just as a fever might be indicative of a flu, strep throat, or other infection (Geller et al. 2002). Research suggests that irritability and aggression are associated with genetic (van Beijsterveldt et al. 2003; Ligthart et al. 2005), biological (Blair 2001), and environmental factors (Kupersmidt et al. 1995; Lyons-Ruth 1996), but our knowledge about how risk factors may vary by diagnosis is limited. Irritability in youth is associated with psychiatric illness in adulthood (Stringaris et al. 2009), as well as other negative outcomes, including suicide (Leibenluft 2011; Leibenluft and Stoddard 2013). Aggressive

youth, independent of diagnosis, are more likely to do poorly in school (Loveland et al. 2007), which limits opportunities for future academic and professional success. Explosive behaviors also increase parenting stress, negatively impact family relations (Podolski and Nigg 2001), and may increase familial expressed emotion, which is associated with more frequent and severe mood episodes (Miklowitz et al. 2004, 2009; Sullivan et al. 2012). Finally, irritable mood and aggressive behavior put youth at higher risk for violent behavior in adulthood, and for incarceration (Farrington 1991; Thomas et al. 2008; Kokko et al. 2009). If youth with CycD are similarly explosive as their adult counterparts, it is likely to have consequences in other aspects of their quality of life and development; however, whether they are likely to be more affected by the consequences of irritability and impulsive aggression (IA) than other youth is unknown.

Although the constructs of irritability and IA can be related, and the terms may be used somewhat interchangeably to indicate interpersonal hostility, differentiating between the two constructs could have important clinical implications. Irritability has an affective component, and may be more related to emotion regulatory systems, whereas IA is behavior and may often reflect a failure of behavioral inhibitory mechanisms (Quay 1993, 1997). For example, distinguishing reactive and proactive aggression is meaningful because proactive aggression often leads to antisocial behaviors in adulthood, whereas youth exhibiting only reactive aggression usually grow out of it (Dodge 1991; Blair 2001; Buchmann et al. 2014). However, assessment of IA and irritability is often conducted with one scale, with items related to each type of behavior. For example, the IA scale derived from the General Behavior Inventory (GBI) (Depue et al. 1989; Jensen et al. 2007) includes items related to both depressed and hypomanic/biphasic mood states, but does not distinguish items assessing irritability (e.g., *Have you become sad, depressed, or irritable for several days or more without really understanding why?*) and those assessing aggression (e.g., *Have there been times when you were feeling low and depressed, and you also had to struggle very hard to control inner feelings of rage or an urge to smash or destroy things?*). On the other hand, the IA scale from the Child Behavior Checklist (CBCL) (Achenbach and Rescorla 2001) includes items from multiple syndrome scales, but focuses on behaviors related just to aggression (Jensen et al. 2007). More precise measurement of these constructs could have prognostic and treatment implications.

The objectives of the current study were to 1) adapt the IA rating scale from the GBI to assess for irritability and IA separately and evaluate how they relate to one another, 2) describe the severity of irritability and IA among youth with CycD, relative to other youth with mental health problems, and 3) determine the contribution of irritability and IA to youth social and overall functioning. We expected IA and irritability scales to be moderately correlated, suggesting related, but not equivalent constructs. We expected youth with CycD to score high on both scales, consistent with the high levels of irritability and aggression described in the literature about adults with CycD. Additionally, we anticipated that youth with CycD would score significantly higher on irritability and IA than youth with nonbipolar diagnoses. We hypothesized that irritability, more so than IA, would be associated with poorer youth social and overall functioning, because irritability is more likely to be persistent, and, consequently, affect all relationships, whereas IA is more likely to be limited to a set of discrete incidents rather than characterizing a relationship. Finally, as an exploratory analysis, we investigated whether the relation among irritability, IA, and social outcomes is moderated by CycD diagnosis.

## Methods

### Participants

Participants ( $n=459$ ), 11–18 years of age, were recruited from an urban community mental health center ( $n=336$ ) and an academic outpatient clinic ( $n=123$ ) as part of a larger study on child and adolescent mental health. Although the larger study includes children as young as 5 years of age, the present study focuses on both youth and parent reports of irritability and IA; consequently, only youth old enough to complete self-report measures are included here. In addition to age requirements, all participants and their parents were required to be English speaking. Youth from the academic outpatient clinic were also excluded if they met criteria for intellectual disability or pervasive developmental disability.

### Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL). Both youth and their caregivers were interviewed using the K-SADS-PL with the mood disorders module from the Washington University in St. Louis K-SADS (WASH-U-K-SADS) (Kaufman et al. 1997; Geller et al. 2001). Additionally, the Longitudinal Evaluation of All Available Data (LEAD) standard of diagnosis was used in order to determine all diagnoses (Spitzer 1983). This method is particularly helpful for episodic illnesses, such as BSDs, because it takes into account information from the interview, family history, and clinical observations. Kappa for diagnoses was high; 0.95 for BSDs and 0.91 for other diagnoses (as compared with K-SADS diagnosis, Youngstrom et al. 2005a). Youth with CycD were compared with youth with diagnoses of bipolar I, bipolar II, bipolar NOS, depression (composed of major depression, dysthymia, and depression NOS), depression with comorbid attention-deficit/hyperactivity disorder (ADHD), ADHD, and disruptive behavior disorders (DBD) (composed of oppositional defiant disorder [ODD], conduct disorder [CD], and DBD NOS). The category to which a youth belonged was based on the consensus diagnosis team's determination of the youth's primary (most impairing) diagnosis (e.g., if a youth met criteria for any BSD diagnosis, the youth would be in that category, regardless of comorbidity). The only exception was depression; youth with depression were split into two groups to differentiate those who had comorbid ADHD from those who did not, because depression with comorbid ADHD has a clinical presentation more similar to BSD. All diagnoses were reviewed by a licensed clinical psychologist.

Additionally, the social impairment scales from the depression, mania, ODD, and ADHD sections of the K-SADS assessed social impairment related to mood symptoms (e.g., Lewinsohn et al. 2003). For the purposes of this study, we combined the items from these four sections using the "OR rule;" therefore, social impairment was rated "yes" if it was reported for any section.

General Behavior Inventory (GBI). Irritability and IA were measured using the Parent-General Behavior Inventory (P-GBI) (Depue 1981; Youngstrom et al. 2001), and the Adolescent-General Behavior Inventory – both derived from the original GBI, which has shown strong diagnostic efficiency for identifying subthreshold presentations of mood disorders (Depue et al. 1989; Youngstrom et al. 2004; Reichart et al. 2005). The P-GBI is completed by caregivers about their child, and the A-GBI is an adolescent self-report. Previous research on IA led to the selection of specific items to measure this construct by mixing irritability and aggression items (e.g., Jensen et al. 2007). Likewise, other studies have used

select items from the P-GBI and A-GBI to measure irritability (Van Meter et al. 2011, 2013). A.V.M., E.Y., and A. F. reviewed these items to arrive at the two mutually exclusive scales for IA and irritability used in this study.

Seven items that assess for irritability were selected from both the P-GBI and the A-GBI for the irritability scale (items #3, #14, #22, #34, #50, #53, and #54); reliability was good, Cronbach's  $\alpha=0.85$  for the A-GBI and 0.88 for the P-GBI. Five items comprised the IA scale (items #27, #39, #42, #44, and #51); reliability was also adequate for the IA scales,  $\alpha=0.77$  for the A-GBI and 0.74 (for the P-GBI).

Achenbach System of Empirically Based Assessment (ASEBA). The parent-rated Child Behavior Checklist (CBCL) and youth-rated Youth Self Report (YSR) are both part of the Achenbach System, and are widely used in clinical and research settings (Achenbach 1991a,b; Achenbach and Rescorla 2001; Pauschardt et al. 2010). Ten items (16, 20, 21, 37, 41, 57, 87, 95, 97, and 104) were selected to assess for IA based on previous research (Jensen et al. 2007). Reliability for the CBCL scale in our sample was good (Cronbach's  $\alpha=0.85$ ), and was similar for the YSR scale (Cronbach's  $\alpha=0.81$ ). The items of the ASEBA scales do not lend themselves to an independent irritability scale.

Additionally, the T scores from the social problems scales for both the CBCL and YSR were used to assess the level of social impairment experienced by the youth.

Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents–Revised (KINDL-R). The KINDL-R measures a youth's quality of life across six dimensions (physical, emotional, self-esteem, family, friends, and school) as reported by both the youth and the youth's caregiver (Ravens-Sieberer and Bullinger, 2000; Wee et al. 2005; Bullinger et al. 2008). The KINDL-R has been validated in a broad range of populations, including those with mental illness (Freeman et al. 2009). For the purposes of this study, we included the friend scale from both parent- and youth-report to assess how well the youth got along with peers. The reliability in this sample was good for the parent-report version (Cronbach's  $\alpha=0.73$ ), and was acceptable for the youth version (Cronbach's  $\alpha=0.62$ ).

Sheehan Disability Scales (SDS). The SDS were developed to assess impairment across three domains: Work/school, social life, family life/home responsibilities (Sheehan et al. 1996). The SDS have demonstrated good reliability and validity in both adult patients with bipolar disorder (Arbuckle et al. 2009) and adolescents in the community (Pallanti et al. 2006). In our study, clinical interviewers rated youth on their impairment on the SDS social life scale using a scale from 0 (not at all) to 10 (extremely). SDS were available for only 261 youth in the current study, because of the SDS being added at a later date to the protocol.

Child Global Assessment Scale (C-GAS). C-GAS scores were determined during the consensus diagnosis meeting and were meant as a measure of the youth's current level of functioning across all domains (Schaffer et al. 2006). In the present study, C-GAS scores were used to assess for the influence of irritability and IA on youths' global functioning.

### Procedure

Caregivers and youth participants provided consent/assent. Caregivers and youth were then interviewed using the K-SADS;

interviews were conducted with the parent and youth separately, by the same interviewer. During the other person's interview, the youth and caregiver both filled out a series of questionnaires including the P-GBI/A-GBI, CBCL/YSR, and KINDL-R. The Case Western Reserve University institutional review board (IRB) approved all procedures.

**Analytic plan.** A series of item-level, confirmatory factor analyses were fit to the data to examine whether the proposed factor structures displayed appropriate fit across informants. Confirmatory factor analysis (CFA) models were fit using weighted least squares means and variance adjusted (WLSMV) in MPlus 7.31 (Muthen and Muthen 1998–2011). Models were considered to demonstrate excellent fit if root mean square error of approximation (RMSEA)  $\leq 0.06$  and comparative fit index (CFI)  $\geq 0.90$  (Hu and Bentler 1999). A series of generalized multivariate analyses of variance (MANOVAs) compared youth with CycD with youth with bipolar I, bipolar II, bipolar NOS, unipolar depression with ADHD, unipolar depression, ADHD, DBDs, and other diagnoses. Post-hoc ANOVAs with Games–Howell post-hoc comparisons assessed differences between groups on the irritability, IA, and social functioning scales. Correlational analyses tested for associations between irritability and IA scores, and the outcome measures of current C-GAS score, KINDL friendship quality, SDS social life, CBCL and YSR social problems, and the K-SADS social impairment scale. Variance decomposition quantified the degree of overlap in the predictor variables. A multivariate linear regression model tested the relation between the independent variables of interest (irritability, IA, CycD diagnosis) and the social functioning variables as dependent variables (KINDL-R friend scale scores, C-GAS, SDS social life, CBCL and YSR social problems, and K-SADS social impairment), while controlling for age, gender, and social phobia diagnosis. Post-hoc linear regressions were fit to the outcomes that the multivariate regressions indicated as significant, with age, gender, and social phobia diagnosis as control variables.

## Results

### Preliminary analyses

Table 1 reports the demographic and clinical characteristics of the sample. Twenty-five youth met criteria for cyclothymic disorder. Youth with CycD were significantly younger than youth with

TABLE 1. SAMPLE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS ( $N=410$ )

	n (%)
Female	198 (46)
White	108 (25)
African American	277 (68)
K-SADS social impairment	267 (65)
Comorbid anxiety	119 (29)
Comorbid ADHD	225 (55)
Comorbid ODD	144 (35)
Comorbid conduct disorder	74 (18)
	<i>Mean (SD)</i>
Age	13.5 (1.9)
Number of comorbid diagnoses	2.73 (1.4)

K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder.

BSDs ( $p=0.01$ ) and youth with unipolar depression without ADHD ( $p=0.03$ ). Youth with depression with and without ADHD were also significantly older than youth with ADHD ( $p<0.005$ ,  $p<0.04$ , respectively). There were no differences in racial background among the youth with BSDs or among youth with non-BSDs (all  $ps > 0.05$ ). There were no gender differences among youth with BSDs ( $\chi^2 = 1.94$ ,  $p=0.58$ ). Among the youth with non-BSDs, those with an ADHD diagnosis were more likely to be male than youth with DBDs ( $p=0.035$ ) or unipolar depression ( $p<0.001$ ). Youth with depression and comorbid ADHD were more likely to be male than youth with depression only ( $p=0.001$ ).

The rates of comorbid diagnoses were high; among youth with BSDs, the average number of diagnoses was 3.28 (SD=1.56). Among the nonbipolar diagnosis comparison group, the average rate of comorbid diagnoses was 2.59 (SD=1.36). ANOVA indicated significant differences in comorbid diagnoses among the diagnostic groups ( $F[6, 403]=27.88$ ,  $p<0.005$ ). Youth with CycD were not significantly different from youth with bipolar spectrum diagnoses ( $p=0.36$ ); however, youth with CycD had significantly more diagnoses than youth with unipolar depression without ADHD, ADHD, and DBDs, ( $ps<0.05$ ). Youth with depression with ADHD had significantly more comorbidity than youth with unipolar depression without ADHD, ADHD, and DBDs ( $p<0.05$ ).

### Factor analysis of irritability and IA scales

Table 2 displays the CFA results by measure and informant. CFA analyses indicate that the 10 items of the ASEBA displayed acceptable fit as a unidimensional measure of IA. The YSR IA scale demonstrated excellent fit (RMSEA = 0.05, CFI = 0.98). The CBCL IA scale demonstrated acceptable fit to the unidimensional model, (RMSEA = 0.07, CFI = 0.99). For each informant, two items measuring destruction of property (items #20 and #21) displayed local dependence. To account for the local dependence, the error terms of the two items were allowed to covary to account for the covariation of the items that was not accounted for by the IA factor. The 10 item IA scale had acceptable internal consistency across all informants (Cronbach's  $\alpha s \geq 0.81$ ).

The CFAs of the GBI scales displayed adequate to poor fit when treated as unidimensional scales. The youth-GBI displayed good fit (RMSEA = 0.07, CFI = 0.97), whereas the caregiver-GBI displayed marginal fit (RMSEA = 0.11, CFI = 0.95). Separating the GBI into two scales significantly improved model fit ( $ps < 0.05$ ). The overall fit of the caregiver and adolescent models changed mildly so that both scales displayed adequate or better fit (RMSEAs = 0.10, 0.07 and CFIs = 0.96, 0.98).

### Assessing Clinical Characteristics of CycD

**Irritability.** The average score for youth with CycD was 9.20 (SD=4.33) on the P-GBI irritability scale and 6.40 (SD=5.39) on the A-GBI irritability scale. MANOVA indicated significant differences among diagnostic groups in irritability as reported by caregivers ( $F[8, 401]=19.70$ ,  $p<0.005$ ) and youth ( $F[8, 401]=2.81$ ,  $p=0.005$ ), and overall ( $F[16, 802]=8.85$ ,  $p<0.005$ ). Youth with CycD scored significantly higher on the P-GBI irritability scale than youth with ADHD, DBDs, and other diagnoses (all  $ps < 0.01$ ). Additionally, youth with mood disorders (bipolar I, bipolar II, CycD, bipolar NOS, and unipolar depression with and without ADHD) were significantly more irritable than youth without mood disorders (ADHD, DBD, and other diagnoses) (all  $ps < 0.01$ ), but not significantly different from each other (all  $ps > 0.10$ ). Although the overall MANOVA was significant, post-hoc

TABLE 2. PSYCHOMETRIC PROPERTIES FOR IRRITABILITY AND IMPULSIVE AGGRESSION

<i>Impulsive aggression derived from</i>	<i>Free parameters</i>	<i>RMSEA (90% CI)</i>	<i>CFI</i>	<i>TLI</i>	<i>Cronbach's <math>\alpha</math></i>
CBCL	31	0.07 (0.05–0.08)	0.99	0.98	0.87
YSR	31	0.05 (0.03–0.07)	0.98	0.97	0.81
Parent GBI					
One factor	48	0.11 (0.10–0.12)	0.95	0.93	0.83
Two factor*	49	0.10 (0.09–0.11)	0.96	0.95	Irritability ( $\kappa=7$ )=0.87 Impulsive aggression ( $\kappa=5$ )=0.73
Adolescent GBI					
One factor	48	0.07 (0.06–0.08)	0.97	0.97	0.84
Two factor*	49	0.07 (0.05–0.08)	0.98	0.97	Irritability ( $\kappa=7$ )=0.82 Impulsive aggression ( $\kappa=5$ )=0.75

Child Behavior Checklist (CBCL) items measuring destruction of personal belongings (#20) and others' belongings (#21) displayed local dependence, and results are reported allowing the two items to correlate.

\* $p < 0.01$  for DIFFTEST of nested models indicates the better fitting model.

RMSEA, root mean square error of approximation; CFI, comparative fit index; TLI, Tucker–Lewis Index; YSR, Youth Self-Report; GBI, General Behavior Inventory.

tests did not indicate significant differences in self-reported irritability among diagnoses (see Table 3).

**IA.** MANOVA indicated significant differences in IA on the P-GBI ( $F[8, 401]=8.07, p < 0.005$ ), CBCL ( $F[8, 401]=9.24, p < 0.005$ ), and YSR ( $F[8, 401]=2.85, p = 0.004$ ), but not the A-GBI ( $F[8, 401]=1.29, p = 0.25$ ). Overall  $F(32, 1604)=4.22, p < 0.005$ . Youth with CycD and bipolar I had significantly higher IA scores according to both the CBCL and P-GBI than did youth without mood disorders (all  $ps < 0.05$ ). Youth with bipolar I self-reported more IA than youth with unipolar depression and without mood disorders (all  $ps < 0.05$ , see Table 3).

**Social functioning.** Table 3 displays the means and SDs for social functioning. MANOVA indicated a significant overall difference in social functioning on the CBCL social problems ( $F[8, 389]=4.61, p < 0.005$ ), parent reported KINDL-R friendship scale ( $F[8, 389]=6.13, p < 0.005$ ), YSR social problems ( $F[8, 389]=2.11, p = 0.03$ ) and clinician-rated K-SADS social impairment ( $F[8, 389]=1.54, p < 0.005$ ), and C-GAS scores ( $F[8, 389]=8.91, p < 0.005$ ), but not the youth self-report KINDL-R friendship scale ( $F[8, 389]=1.81, p = 0.07$ ). Overall  $F(8, 2334)=3.20, p < 0.005$ . Post-hoc tests indicated that youth with CycD had significantly worse functioning than youth without mood disorders according to both the parent-report KINDL-R and the CBCL social problems scale, as well as the clinician-rated K-SADS social impairment and C-GAS scores (all  $ps < 0.05$ ). Exploratory analyses with a subset of participants who were rated by clinicians on the social impairment scale of the Sheehan Disability Scales indicated that youth with CycD and unipolar depression with comorbid ADHD were rated as having significantly lower social functioning than youth without mood disorders ( $F[8, 252]=5.14, p < 0.005$ ). Most notably, 96% of youth with CycD were rated as socially impaired on the K-SADS.

### Scale correlations

Table 4 displays the correlation matrix. The two measures of irritability were weakly correlated with each other across parent and youth self-report ( $r = 0.22, p < 0.05$ ). The measures of IA were moderately correlated with each other within informant ( $rs > 0.42$ ) and weakly correlated across informants ( $rs > 0.13$ ). The measures of social functioning were moderately correlated with each other

within informant ( $rs > 0.32$ ), except for the two self-report measures (YSR and youth KINDL-R), and were weakly correlated across informants ( $rs > 0.18$ ).

We used variance decomposition to examine the overlap between predictor scales. With the exception of scales that came from the same measure (e.g., P-GBI irritability and P-GBI IA), the scales showed good specificity (i.e., measures of IA and irritability were assessing unique constructs) with an average  $R^2$  of 0.17 across constructs.

### Regression analyses

**Social problems.** Multivariate regression with the social impairment variables as the dependent variable and CycD, irritability, and IA as the independent variables indicated multivariate effects for CycD ( $F[6, 385]=3.67, p < 0.005$ , incremental  $r^2_s = 0.02–0.03$ ); both youth ( $F[6, 385]=4.91, p < 0.005$ ) and parent-reported irritability ( $F[6, 385]=6.12, p < 0.005$ ); and both youth ( $F[6, 385]=9.76, p < 0.005$ ) and parent-reported IA on the CBCL ( $F[6, 385]=27.15, p < 0.005$ ). The independent variables of CycD diagnosis, irritability, and IA measured by the CBCL and YSR accounted for between 2% and 34% of the variance in social functioning. The youth ( $F[6, 385]=1.33, p = 0.24$ ) and parent-reported ( $F[6, 385]=0.55, p = 0.77$ ) GBI IA scales were not significant predictors of social functioning after controlling for CycD, irritability, and the YSR/CBCL IA scales; these were not included as predictors in the post-hoc linear regressions. Most of the social functioning scales were predicted by CycD, irritability, and IA (all  $ps < 0.005$ ). However, the youth-report KINDL-R friendship subscale was not significantly predicted by any of the predictors ( $F[7, 390]=1.12, p = 0.35$ ). Consequently, this scale was not included as a dependent variable in the post-hoc linear regressions.

Table 5 displays the results from the individual linear regressions used to evaluate the influence of the independent variables that were significant in the multivariate regression on the social functioning outcomes that were significant. Final models predicted 38% of the variance in YSR social problems, 38% in CBCL social problems, 17% of the variance in C-GAS score, 17% of the variance in K-SADS social impairment, 15% of the variance in parent-reported KINDL-R friendship scale, and 14% of the variance in the SDS social scale. In general, the more irritability that was reported, the worse social functioning was across domains ( $ps < 0.05$ ). YSR

TABLE 3. DIFFERENCES IN SCALE SCORES ACROSS DIAGNOSTIC GROUPS

	Cyclothymic Disorder		Bipolar (BP) I		Bipolar (BP) II		BP NOS		Depression with ADHD		Depression		ADHD		DBD		Other	
	n	25	18	13	27	72	84	104	37	30								
		<i>Mean (SD)</i>																
Irritability	A-GBI	6.40 (5.4)	9.17 (5.6)	8.38 (5.9)	7.59 (5.2)	7.60 (5.7)	7.12 (4.6)	5.32 (4.6)	5.05 (4.5)	5.67 (5.4)								
	P-GBI	9.20 (4.3) <sup>ghi</sup>	9.89 (5.7) <sup>ghi</sup>	12.96 (3.4) <sup>ghi</sup>	9.37 (5.0) <sup>ghi</sup>	8.97 (4.3) <sup>ghi</sup>	7.54 (4.6) <sup>bghi</sup>	4.01 (3.9) <sup>abcdef</sup>	3.12 (3.5) <sup>abcdef</sup>	4.07 (4.1) <sup>abcdef</sup>								
Impulsive-Aggression	A-GBI	9.22 (3.4)	10.50 (4.0)	9.85 (3.4)	10.04 (3.5)	9.83 (3.8)	9.11 (3.2)	8.94 (3.6)	8.61 (3.5)	8.30 (3.3)								
	P-GBI	5.52 (2.5) <sup>ghi</sup>	6.89 (3.6) <sup>ghi</sup>	6.15 (2.9) <sup>ghi</sup>	5.54 (3.4) <sup>ghi</sup>	5.04 (3.4) <sup>ghi</sup>	3.71 (3.2) <sup>a</sup>	3.15 (2.7) <sup>abcde</sup>	3.11 (3.1) <sup>abce</sup>	2.47 (2.1) <sup>abcde</sup>								
	YSR	6.40 (3.6)	9.89 (4.8)	6.15 (3.3)	6.67 (3.8)	6.69 (4.3)	5.58 (3.5)	6.14 (4.3)	6.05 (4.7)	4.67 (3.57)								
	CBCL	11.84 (4.6) <sup>fi</sup>	11.11 (4.9) <sup>ei</sup>	10.23 (3.6) <sup>i</sup>	10.19 (4.8) <sup>fi</sup>	10.17 (4.9) <sup>fi</sup>	6.65 (4.9) <sup>acdeg</sup>	10.13 (4.6) <sup>fi</sup>	8.11 (5.4)	4.63 (3.1) <sup>abcdeg</sup>								
Social Impairment	YSR	61.84 (10.1)	62.06 (9.4) <sup>ghi</sup>	58.25 (9.3)	58.69 (7.9)	60.54 (9.0)	57.46 (7.1) <sup>a</sup>	59.20 (9.3) <sup>a</sup>	56.31 (5.9) <sup>a</sup>	56.28 (8.0) <sup>a</sup>								
	CBCL	70.80 (8.9) <sup>ghi</sup>	67.28 (10.7)	64.92 (7.6)	64.00 (10.3)	66.90 (10.9) <sup>ghi</sup>	61.89 (8.9) <sup>de</sup>	64.60 (9.3)	60.81 (8.3) <sup>de</sup>	59.48 (8.4) <sup>de</sup>								
	Youth KINDL	65.50 (18.1)	54.17 (22.1)	62.50 (15.8)	63.70 (21.3)	54.91 (23.2) <sup>g</sup>	59.80 (19.4)	64.73 (19.0) <sup>e</sup>	59.72 (18.1)	62.72 (20.0)								
	Parent KINDL	47.25 (19.9) <sup>ghi</sup>	56.02 (20.1)	58.85 (18.9)	56.17 (18.5)	52.86 (16.7) <sup>ghi</sup>	63.16 (19.5) <sup>de</sup>	64.36 (18.8) <sup>de</sup>	68.75 (19.9) <sup>de</sup>	71.12 (16.9) <sup>de</sup>								
	C-GAS	50.98 (4.0) <sup>i</sup>	48.92 (3.3) <sup>ghi</sup>	48.65 (5.5) <sup>i</sup>	50.98 (4.0) <sup>hi</sup>	52.15 (5.6) <sup>hi</sup>	50.42 (4.3) <sup>i</sup>	54.49 (5.2) <sup>i</sup>	58.50 (11.0) <sup>ace</sup>	51.67 (6.3) <sup>abcdefg</sup>								
	SDS Social Impairment	6.25 (1.77) <sup>ghi</sup>	6.11 (2.20)	5.50 (2.39)	5.55 (2.44)	5.85 (2.06) <sup>ghi</sup>	4.81 (2.19)	4.12 (1.87) <sup>de</sup>	4.00 (2.06) <sup>de</sup>	3.67 (2.66) <sup>de</sup>								
		n = 16	n = 9	n = 20	n = 20	n = 47	n = 52	n = 65	n = 26	n = 18								
	K-SADS Impairment	96	83	77	78	76	70	66	36	24								

<sup>a</sup>Different from BD I,  $p < 0.05$ .

<sup>b</sup>Different from BD II,  $p < 0.05$ .

<sup>c</sup>Different from BD NOS,  $p < 0.05$ .

<sup>d</sup>Different from cyclothymic disorder (CycD),  $p < 0.05$ .

<sup>e</sup>Different from major depressive disorder (MDD) with ADHD,  $p < 0.05$ .

<sup>f</sup>Different from MDD,  $p < 0.05$ .

<sup>g</sup>Different from ADHD,  $p < 0.05$ .

<sup>h</sup>Different from DBD,  $p < 0.05$ .

<sup>i</sup>Different from Other,  $p < .05$

NOS, not otherwise specified; ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behavior disorder; A-GBI, Adolescent-Report General Behavior Inventory; P-GBI, Parent-Report General Behavior Inventory; YSR, Youth Self-Report; CBCL, Child Behavior Checklist; C-GAS, Child Global Assessment Scale; SDS, Social Impairment Scale (added to the protocol at a later date, and is only available on a subset of youth); K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children.

TABLE 4. CORRELATIONS AMONG CYCLOTHYMIC DIAGNOSIS, IRRITABILITY, IMPULSIVE AGGRESSION, AND OUTCOME MEASURES

Cyclothymic disorder	Irritability		Impulsive aggression				Social functioning					
	A-GBI	P-GBI	A-GBI	P-GBI	YSR	CBCL	YSR	CBCL	Youth KINDL	Parent KINDL	C-GAS	K-SADS Impairment
Irritability												
A-GBI	-											
P-GBI	0.22***	-										
Impulsive aggression												
A-GBI	0.74***	0.17**	-									
P-GBI	0.14**	0.65***	0.13*	-								
YSR	0.49***	0.11*	0.50***	0.20***	-							
CBCL	0.01	0.29***	0.08	0.42***	0.31***	-						
Social functioning												
YSR	0.09	0.48***	0.07	0.39*	0.09	0.53***	0.14**	-				
CBCL	0.17***	0.07	0.26***	0.05	0.28***	0.22***	0.57***	0.31***	-			
Youth KINDL	0.06	0.01	-0.02	0.06	-0.00	-0.02	0.07	-0.08	-0.03	-		
Parent KINDL	-0.18***	-0.10*	-0.31***	-0.04	-0.20***	-0.13**	-0.19***	-0.24***	-0.45***	0.18***	-	
C-GAS	-0.03	-0.19***	-0.25***	-0.16**	-0.22***	-0.27***	-0.31***	-0.26***	-0.27***	0.25***	-	
K-SADS	0.16**	0.12*	0.20***	0.16**	0.22***	0.20***	0.23***	0.22***	0.24***	-0.28***	-0.32***	-
Impairment												
SDS Social	0.16*	0.23***	0.26***	0.16*	0.17*	0.15*	0.20**	0.21**	0.36***	-0.16*	-0.36***	-0.46***
Impairment <sup>a</sup>												0.29***

<sup>a</sup>SDS was added at a later date to the protocol and is only available on a subset of youth.

\* $p < 0.05$ , \*\* $p < 0.005$ , \*\*\* $p < 0.0005$  two tailed.

A-GBI, Adolescent-Report General Behavior Inventory; P-GBI, Parent-Report General Behavior Inventory; YSR, Youth Self-Report; CBCL, Child Behavior Checklist; C-GAS, Child Global Assessment Scale; SDS, Social Impairment Scale (added to the protocol at a later date, and is only available on a subset of youth); K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children.

TABLE 5. RESULTS OF THE REGRESSION MODELS PREDICTING FUNCTIONAL OUTCOMES FROM CYCLOTHYMIC DIAGNOSIS, IRRITABILITY, AND IMPULSIVE AGGRESSION SCALES

Predictors	Parent KINDL-R	YSR Social Problems	CBCL Social Problems	C-GAS	SDS Social Impairment <sup>a</sup>	K-SADS Social Impairment	Nagelkerke R <sup>2</sup>
	Friends	Problems	Problems		Impairment <sup>a</sup>	Impairment	
	β (95% CI)						Odds ratio (95% CI)
Block 1: Gender, age, social phobia (3 df)	0.14** (0.04, 0.23)	-0.14* (-0.22, -0.06)	-0.09* (-0.17, -0.01)	0.00 (-0.09, 0.10)	0.04 (-0.08, 0.17)	0.90 (0.79, 10.01)	0.01
Block 2: GBI irritability (2 df)	0.02 (-0.08, 0.11)	0.01 (-0.08, 0.09)	0.06 (-0.03, 0.14)	0.04 (-0.05, -0.14)	0.04 (-0.08, -0.16)	0.96 (0.60, 1.53)	0.09*
Block 3: Achenbach IA (2 df)	-0.06 (-0.15, 0.03)	0.03 (-0.05, 0.11)	0.07 (-0.01, 0.15)	0.03 (-0.06, 0.12)	0.09 (-0.03, 0.20)	1.04 (0.27, 3.94)	0.14*
Block 4: Cyclothymic disorder (1 df)	-0.04 (-0.15, 0.08)	0.34*** (0.25, 0.44)	0.05 (-0.05, 0.14)	-0.10 (-0.21, 0.01)	0.19* (0.04, 0.34)	1.03 (0.98, 1.09)	0.17*
Full model coefficients	-0.28*** (-0.38, -0.19*)	-0.05 (-0.13, 0.04)	0.09* (0.01, 0.18)	-0.16** (-0.25, 0.06)	0.16* (0.03, 0.29)	1.07* (1.01, 1.12)	
Age	-0.07 (-0.18, 0.04)	0.37*** (0.27, 0.46)	0.02 (-0.08, 0.12)	-0.14* (-0.25, -0.03)	-0.04 (-0.19, 0.11)	1.07* (1.00, 1.15)	
Gender	-0.06 (-0.16, 0.05)	0.01 (-0.08, 0.10)	0.53*** (0.44, 0.62)	-0.22*** (-0.32, -0.12)	0.18* (0.04, 0.31)	1.06* (1.01, 1.12)	
Social Phobia	-0.12* (-0.21, -0.03)	0.08* (0.00, 0.16)	0.07 (-0.01, 0.15)	0.02 (-0.07, 0.11)	0.09 (-0.03, 0.21)	8.86* (1.16, 67.49)	
A-GBI Irritability							
P-GBI Irritability							
YSR IA							
CBCL IA							
Cyclothymic disorder							

95% confidence intervals are included in parentheses after the standardized regression coefficient/odds ratio.

<sup>a</sup>SDS was added at a later date to the protocol and is only available on a subset of youth.

\**p* < 0.05, \*\**p* < 0.005, \*\*\**p* < 0.0005, two-tailed.

A-GBI, Adolescent-Report General Behavior Inventory; P-GBI, Parent-Report General Behavior Inventory; YSR, Youth Self-Report; CBCL, Child Behavior Checklist; C-GAS, Child Global Assessment Scale; SDS, Social Impairment Scale; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children.

social problem score significantly associated with age ( $\beta = -0.14, p = 0.001$ ), A-GBI irritability ( $\beta = 0.34, p < 0.0001$ ), YSR IA ( $\beta = 0.37, p < 0.0001$ ), and CycD diagnosis ( $\beta = 0.08, p = 0.052$ ). CBCL social problem score was significantly associated with age ( $\beta = -0.09, p = 0.033$ ), P-GBI irritability ( $\beta = 0.09, p = 0.038$ ), and CBCL ( $\beta = 0.53, p < 0.0001$ ). C-GAS scores were predicted by P-GBI irritability ( $\beta = -0.16, p = 0.002$ ), YSR IA ( $\beta = -0.14, p = 0.012$ ), and CBCL IA ( $\beta = -0.22, p < 0.0001$ ). K-SADS social impairment was associated with P-GBI irritability (OR = 1.07,  $p = 0.013$ ), YSR IA (OR = 1.07,  $p = 0.05$ ), CBCL IA (OR = 1.06,  $p = 0.026$ ), and CycD diagnosis (OR = 8.86,  $p = 0.035$ ). Parent-reported KINDL-R friendship scale was associated with age ( $\beta = 0.14, p = 0.004$ ), P-GBI irritability ( $\beta = -0.28, p < 0.0001$ ), and CycD diagnosis ( $\beta = -0.12, p = 0.013$ ). Finally, SDS social scale was associated with A-GBI irritability ( $\beta = 0.19, p = 0.012$ ), P-GBI irritability ( $\beta = 0.16, p = 0.014$ ), and CBCL IA ( $\beta = 0.18, p = 0.013$ ).

The interaction terms for CycD and irritability or IA were not significant in predicting any of the social functioning outcomes ( $ps > 0.05$ ).

### Discussion

The present study aimed to determine whether youth with CycD experienced irritability and IA, as has been described in adults with CycD (Akiskal et al. 1977, 1979, 2003; Prakash and Mitra 2008; Shen et al. 2008; Hantouche and Perugi 2012; Van Meter et al. 2012). Youth with CycD experienced more intense irritability (as measured by the P-GBI) and IA (as measured by the P-GBI and CBCL) than youth with non-mood diagnoses. The average scores were consistent with other youth on the bipolar spectrum. This suggests that, although irritability and IA are associated with CycD, these symptoms are not unique to this diagnosis. As others have described, among youth with mental health problems, irritability – and perhaps aggression – is common and, although it indicates a problem, is not specific to any one diagnosis (Carlson and Klein 2014). Similar to adults with CycD, youth with CycD displayed intense irritability; however, irritability was not specific to CycD. Distinguishing whether chronic irritability is associated with CycD versus another disorder is important, because as children grow, their self-control and socialization mature, resulting in decreases in irritability and IA (Rothbart et al. 2006), but a substantial portion of youth with CycD will develop more severe mood disorders (Klein et al. 1986; Shankman et al. 2009). This would help explain why, although irritability and aggression are not diagnostically specific among youth, among adults these symptoms suggest a cyclothymic presentation. The persistence of irritable and aggressive traits could suggest a strong genetic influence (van Beijsterveldt et al. 2003), which is consistent with research on the heritability of CycD (Klein et al. 1985; Evans et al. 2005).

Social impairment, like irritability and IA, was common among the youth in this sample. Parents rated youth with CycD as more impaired than youth with DBD, ADHD, or depression, but youth-rated scales did not discriminate between diagnostic categories. Youth with BSDs (Geller et al. 2000; Goldstein et al. 2006, 2009), as well as other mental health problems (Hecht et al. 1990; Greene et al. 2002; Solanto et al. 2009), struggle to make and maintain relationships. However, a consequence of their social functioning impairment may be that these youth have limited insight into how they function with peers, relative to other youth. This is consistent with the fact that irritability and IA scores that differentiated between diagnostic groups in our study were most often parent, rather than youth, rated. Youth may not have insight into how their



irritable behavior is perceived, or they may downplay the effects of their aggression on others (Freeman et al. 2011).

Our hypothesis that irritability would be a stronger predictor of social functioning than IA was partially supported. The P-GBI irritability subscale had stronger effect sizes than the IA scales on the parent-rated KINDL-R friendship scale. However, CBCL IA had a stronger effect on the CBCL social problems scale than either irritability measure. Although IA is associated with multiple negative outcomes over time (Farrington 1991; Loveland et al. 2007; Thomas et al. 2008; Kokko et al. 2009), it tends to be provoked and is not likely to be present chronically, the way irritability might. Irritability – directed broadly – could interfere with the initiation and maintenance of friendships more significantly than IA because irritability increases the risk for more hostile interactions that might not rise to the level of an aggressive behavior. Targeted treatments may be able to directly impact the specific manifestation of anger/irritability that a child exhibits, leading to more significant improvements (Sukhodolsky et al. 2005).

Although the irritability and IA scales were correlated in our sample (with the exception of the A-GBI scales and the CBCL; see Table 3), the correlations were mostly small to moderate (the GBI irritability and IA scales within reporter were highly correlated [A-GBI  $r=0.74$ , P-GBI  $r=0.65$ ]), suggesting related, but distinct constructs. Similarly, the CFAs of the P-GBI and A-GBI scales indicated that a two factor model fit the data better than a unidimensional model (and unidimensional models fit the CBCL and YSR IA scales well). These results, along with the fact that the scales had different relations with the outcome variables, indicate that it is worthwhile to measure each behavior separately, rather than using combined irritability/impulsive aggression scales. Irritability may be conceptualized as a characteristic of affect dysregulation, whereas IA is related more to a failure to inhibit one's impulses (Quay 1993). Connecting these two behavioral phenotypes to endophenotypes may lead to a better understanding of the transdiagnostic presentation of these behaviors (Insel et al. 2010; Sanislow et al. 2010).

Contrary to our hypothesis, CycD was not associated with greater social impairment, above and beyond irritability and IA, on most outcome measures. The exceptions were the parent-rated KINDL-R and the K-SADS social impairment scale. The KINDL-R focuses on being liked and spending time with other youth, rather than on specific social skills, which may better capture the specific deficits that youth with CycD have. Similarly, the K-SADS scale specifically accounts for mood-related social impairment, which we would expect to affect youth on the bipolar spectrum more than other youth. Despite this, irritability and IA do not account for the entirety of social impairment experienced by youth with CycD. The regressions indicate the same: Irritability and IA, on average, accounted for 2–20% of the variance in the social functioning variables. This suggests that other factors, such as emotional lability (Keenan-Miller and Miklowitz 2011; Siegel et al. 2015), social cognition deficits (Schenkel et al. 2014), and poor social skills (Goldstein et al. 2009) are likely also strong predictors of whether or not youth – particularly those with BSDs – get along well with peers.

### Limitations

This study has three important limitations. First, the predictor variables of irritability and IA were rated by the same reporters (youth, caregiver) as the KINDL-R friendship quality measure. This may increase the association between predictor and outcome variables rated by the same person. Future studies could help to

better describe the relation between youth irritability/IA and social functioning by including performance measures of these constructs, such as behavior on a frustration tolerance task (irritability) or peer ratings of youth popularity (social functioning; Prinstein and Cillessen 2003). We mitigated this concern some by also examining clinician-rated outcomes (SDS, C-GAS, K-SADS social impairment), and cross-informant predictions, using parent predictors for youth outcomes, and vice versa.

The second limitation is related to the first; relying solely on questionnaires is not the most ecologically valid method of assessing how youth behavior affects social functioning. Behavioral observations could be a more helpful way to better explain these relations. However, questionnaires are useful in a variety of clinical contexts, enhancing the generalizability of results.

Finally, our measurements all occurred at one time point, limiting our ability to comment on the predictive value of irritability and IA. If it had been possible to evaluate irritability and IA prior to assessing youth social functioning using a longitudinal design, we would be in a better position to comment on the temporal relation between youth acting out behaviors and their social functioning.

### Conclusions

CycD is rarely diagnosed among youth, but is associated with a high level of impairment, consistent with other BSDs. Although among adults, CycD is often characterized by extreme presentations of irritability and IA, in our youth sample, we found that irritability and IA, although more severe than among youth with nonbipolar diagnoses, did not set youth with CycD apart from youth with other BSDs. This is likely because, among young people with mental illness, these hostile behaviors are prevalent and nonspecific.

Our hypothesis that irritability would be more strongly associated with poor social functioning than IA was partly supported. Although irritability was related to more of the outcomes measures, IA is also an important determinant. The fact that each type of behavior related to outcomes differently suggests that it is worthwhile to assess each separately, so that we can learn more about the specific consequences associated with each.

### Clinical Significance

The results of this study are consistent with previous reports that irritability and IA are common among youth with psychological disorders and are not specific to any one disorder. These behaviors are associated with a number of negative outcomes, including poor social functioning. A diminished capacity to make and maintain relationships may limit youths' ability to benefit from psychosocial treatments; therefore, targeting these behaviors specifically is important to a more positive prognosis. Finally, although youth with cyclothymic disorder experience irritability and IA at a level of intensity similar to other youth with BSDs, the adult literature suggests that they may be less likely to “outgrow” these behaviors, resulting in more significant social impairment and worse outcomes over time.

### Disclosures

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Coronado Biosciences, Dana Foundation, Elsevier, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson and Johnson, Jubilant Clinsys, KemPharm, Lilly, Lundbeck, Merck, NIH, Neurim, Novartis, Noven, Otsuka, Oxford University Press, Pfizer, Physicians Postgraduate Press, Purdue, Rhodes Pharmaceuticals, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and WebMD. Eric Youngstrom has consulted with Lundbeck and Otsuka. Norah Feeny, Andrew Freeman, Anna Van Meter, and Jennifer Kogos Youngstrom have no conflicts of interest to disclose.

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Address correspondence to:  
*Anna Van Meter, PhD*  
*Yeshiva University*  
*1165 Morris Park Avenue*  
*Bronx, NY 10461*

*E-mail:* anna.vanmeter@einstein.yu.edu