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Research report

Age differences in the phenomenology of pediatric bipolar disorder

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ABSTRACT

Background: The primary purpose of this study was to explore whether age differences in the phenomenology of bipolar disorders from 4 to 17 years of age exist.
Methods: Outcome measures included questionnaires pertaining to mood symptoms, psychosocial functioning, and family history of psychiatric illness. Phenomenology was examined in two diagnostic groups: syndromal bipolar disorder (bipolar I or II) and subsyndromal bipolar disorder (bipolar disorder not otherwise specified or cyclothymia) and across six age cohorts: 4–6, 7–8, 9–10, 11–13, and 14–17 years. Analyses examined linear and non-linear age effects on clinician-rated measures of mood and psychosocial functioning.
Results: Participants were 535 outpatients (339 males) ages 4–17 years. The proportion diagnosed with comorbid ADHD was significantly lower in the oldest age group. Age groups showed significant moderate decreases in motor activity, aggression, and irritability with age. Many symptoms of depression showed significant increases with age. BP I cases showed much higher manic symptoms, and BP I and BP II cases indicated slightly to moderately higher depressive symptoms, compared to subsyndromal cases. These patterns held after adjusting for comorbid ADHD, and age did not interact with syndrome status. There were also age differences in total scores for measures of mood symptoms and psychosocial functioning.
Limitations: Mood ratings were completed based on the same interview that informed the research diagnoses. Also, mood episode at time of interview was not captured.
Conclusions: These findings affirm the existence of bipolar disorder from pre-school children through adolescence, with a similar clinical presentation across a wide developmental age span.

1. Introduction

Although there has been debate about the existence of pediatric bipolar spectrum disorders (BPSD) (Biederman et al., 1998; Healy, 2006; Klein et al., 1998; Leibenluft et al., 2003; Parens et al., 2010), there has been increasing validation of the diagnosis in this population over the last decade (Geller and Luby, 1997; Nottelmann et al., 2001; Geller et al., 2004, 2008; Youngstrom et al., 2008). In fact, evidence is emerging indicating preschoolers as young as 3 years of age are presenting with classically defined and age adjusted symptom descriptions that meet criteria for bipolar disorders (Luby and Belden, 2006; Dilsaver and Akiskal, 2004). Recognition of pediatric BPSDs has corresponded with growing knowledge regarding evaluation and treatment of pediatric BPSDs in older children and adolescents.

Nevertheless, there are a number of debates regarding developmental aspects of BPSDs. The first is whether and how frequently manifestations of mania and subsyndromal mania are present in preadolescents (Leibenluft, 2011; Merikangas et al., 2010). The second is whether there are differences in clinical manifestations by age (Faraone et al., 1997a; Papolos et al., 2009; Youngstrom et al., 2008) and whether there should be modifications in numbers of symptoms for age as has been suggested for depression (Luby et al., 2003). The question of a "juvenile subtype" suggests that children manifest the condition differently from adults. One school of thought observes that the juvenile phenotype is characterized by less discrete episodes and greater irritability and volatility (Mick et al., 2003; Mick et al., 2005; Wozniak et al., 2005). There is some evidence that younger people have more mixed episodes with less complete remissions and many

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mood shifts compared to adults (Axelson et al., 2006; Findling et al., 2001; Kraepelin, 1921).

A third debate is whether there should be developmental modifications within the symptoms of mania for what constitutes a particular symptom (Geller et al., 2002). Although grandiosity or impulsive risk-taking might be features of mania across the life cycle, the specific behaviors that a child or adolescent displays may be different from behaviors an equally manic adult might show, due to differences in setting and opportunity (Youngstrom, 2009). The fourth issue is whether comorbidities vary as a function of age (Carlson et al., 1998; Carlson and Kelly, 1998; Carlson and Meyer, 2006). For example, children with mania often also meet criteria for attention-deficit/hyperactivity disorder (ADHD), leading to debate about whether the apparent comorbidity is a function of the base rate of ADHD (Galanter and Leibenluft, 2008; Youngstrom et al., 2010) versus reflecting shared symptoms (Klein et al., 1998), or perhaps a developmental subtype of bipolar disorder (Faraone et al., 1997b; Tillman and Geller, 2006). Finally, bipolar disorder not otherwise specified (BP NOS) has been defined as having the same symptoms as full syndrome mania but with shorter duration episodes (Birmaher et al., 2006; Findling et al., 2001).

A sample of children and adolescents who presented for outpatient evaluations, allows us to address the following: (a) Does the gender ratio of males to females in a sample of children with mania/bipolar disorder and subsyndromal mania change as a function of age? We hypothesize a greater ratio of boys in preadolescence and more females after puberty when rates of depression increase; (b) Do rates of externalizing disorder decrease with age?; (c) Within the confines of the symptoms ascertained by DSM criteria, is there a difference in the frequency of specific manic symptoms by age? Specifically, are rates of aggression higher in younger children and psychosis higher in adolescents?; (d) Does comorbid ADHD increase the level of severity of symptoms of mania?; (e) Is there evidence of greater depression in adolescence? Specifically, are depression ratings higher? Are mixed episodes and rapid cycling higher in teens?; (f) Is subsyndromal mania a less severe form of mania or is the symptom constellation different?

2. Methods

2.1. Subjects

Youth were recruited during two separate enrollment periods from 1/1996 to 1/2003 and 2/2003 to 5/2006 using highly similar assessment procedures. For both enrollment periods, participants were obtained as part of the screening procedures for various treatment studies being performed at a mid-western outpatient academic medical center.

Eligible youths were ages 4–17 years who met DSM-IV criteria for a BPSD. Exclusion criteria included evidence of a pervasive developmental disorder or suspected mental retardation documented by educational history, standardized cognitive ability test scores <70, or a Peabody Picture Vocabulary Test-Third Edition (Dunn and Dunn, 1997) score <70.

The University Hospitals Case Medical Center Institutional Review Board for Human Investigation approved all procedures in this study.

2.1.1. Subject diagnoses

Schedule for affective disorder and Schizophrenia for children (*K-SADS*). For the first enrollment period, all participants and their parents/guardians were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological version (K-SADS-E) $n=79$ (15%) (Orvaschel, 1995) or the -Present and Lifetime version (K-SADS-PL) $n=308$ (58%) (Kaufman et al., 1997). The K-SADS-PL replaced the K-SADS-E to reduce subject burden. For the second enrollment period, the KSADS-PL Present and Lifetime-Plus (K-SADS-PL-Plus); $n=70$ (13%) or the -Present and Lifetime with mood symptom items from the WASH-U K-SADS (K-SADS-PL-W; $n=76$ (14%)) was used (Geller et al., 2001). The training procedures, inter-rater reliability, and K-SADS interview procedures used in this study have been described in more detail in a prior publication (Findling et al., 2001). Briefly, research assistants (ranging from B.A. degree to Ph.D/M.D.) were trained to criteria with an experienced rater and achieved an overall and item level data $\kappa > 0.85$. Unmodified DSM-IV criteria, including episode criteria, were used to assign diagnoses. It should be noted that only youth who experienced spontaneous, dysfunctional mood episodes that did not meet full criteria for any other mood disorder were given diagnosis of bipolar NOS. Thus, the operational definition emphasized change in functioning and episodic presentation.

Following the administration of the K-SADS, the interviewer completed the K-SADS Mania Rating Scale (KMRS) (Axelson et al., 2003), the Young Mania Rating Scale (YMRS) (Young et al., 1978; Youngstrom et al., 2002), the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984), the Clinician's Global Assessment Scale (CGAS) (Shaffer et al., 1983), and the Clinical Global Impressions Scale (CGI) (National Institute of Mental Health, 1985).

A general consensus has emerged that pediatric BPSDs can be divided into syndromal (bipolar I or II; Birmaher et al., 2006; Miklowitz et al., 2011) and "subsyndromal" (cyclothymia and bipolar disorder NOS) categories. Although both cyclothymic disorder and bipolar NOS are themselves DSM-IV diagnoses, they are "subsyndromal" in the sense that the patient has no lifetime history of a full manic, mixed, or major depressive episode. For analytical purposes, when looking at manic symptoms, children with mania were examined separately from children with bipolar II who were included in the subsyndromal diagnostic group by virtue of their less severe manic symptoms. However, when examining depression and global measures, youth with bipolar II were included in the syndromal group.

To further describe the phenomenology of BPSDs in children, diagnostic qualifiers including the presence of rapid mood cycling (defined as four or more distinct episodes per year) (American Psychiatric Association, 2001), mixed mood episodes (including both dysphoric mania and also highly labile mood presentations sometimes characterized as ultradian cycling) (Youngstrom et al., 2008), and psychotic symptoms (defined as the presence of hallucinations or delusions) were coded as present or absent for each participant.

2.1.2. Family history

Lifetime diagnoses were obtained in parents interviewed directly using the Schedule for Affective Disorders and Schizophrenia-Lifetime Bipolar Version (SADS-LB) (Endicott and Spitzer, 1978). If a parent could not be interviewed directly, either the Family History Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977) was administered to the parent or the diagnoses made by the psychiatrist in the adult clinic were used. Family history of BPSDs was determined only for cases in which diagnoses were available for both parents. Family history of BPSDs was considered positive if either parent met criteria for bipolar I or II, cyclothymia, or bipolar NOS.

2.1.3. Clinician-rated measures

Young mania rating scale (*YMRS*). The YMRS (Young et al., 1978; Youngstrom et al., 2002) is an 11-item clinician-rated measure of

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current mania symptoms. Clinicians rated the youth's manic symptoms over the past 1–2 weeks on five explicitly defined grades of severity, with item scores ranging from 0 to 4 (four items range from 0 to 8).

K-SADS mania rating scale (*KMRS*). The KMRS (Axelson et al., 2003) is a 13-item clinician-rated measure of mania. Items were rated based upon report from the parent and youth on a 1 to 6 scale (except item 10 rated 1 to 5). Items were summed and 13 points were subtracted from the total, yielding a total score that ranged from 0 to 64, with higher scores indicating greater psychopathology.

Children's depression rating scale-revised (*CDRS-R*). The CDRS-R (Poznanski et al., 1984) is a 17-item clinician rated measure of depressive symptoms over the past 1–2 weeks. Items were rated on a 1 to 7 scale with the exception of items 4, 5, and 16, which were rated on a 1 to 5 scale.

A previous study found very good internal consistency reliability for subjects 4 to 17 years of age in the YMRS (α=0.88–0.92), KMRS (α=0.90–0.95), and CDRS-R (α=0.90–0.94) (Frazier et al., 2007). Furthermore, the YMRS and KMRS were found to be excellent in their ability to discriminate BPSDs from other disorders (areas under the curve, AUCs=0.92–0.99) during the first two decades of life (Frazier et al., 2007).

2.1.4. Functional measures

Clinician's global assessment of functioning (*CGAS*). The clinician-rated CGAS (Shaffer et al., 1983) has scores ranging from 0 to 100, with 100 being superior functioning at home, school, and with peers.

Clinical global impressions (*CGI*). The CGI (National Institute of Mental Health, 1985) was used to assess the severity of illness. This clinician-rated instrument has scores ranging from 1 (normal) to 7 (severely ill).

2.1.5. Statistical methods

To evaluate the phenomenology of BPSDs in children and adolescents, individuals diagnosed with BPSDs were split into syndromal (BP I or BP II) and subsyndromal (BP NOS and cyclothymia) categories for most analyses. Acute mania was distinguished from hypomania/BP NOS for analysis of mania symptoms; for depressive symptoms and global functioning measures, bipolar I and II were combined as the syndromal group and compared with subsyndromal BPNOS. Analysis of variances (ANOVAs) were computed with type of bipolar disorder as the independent variables and YMRS and CDRS-R total scores as the dependent variables in separate analyses.

To compare age groups and potential nonlinear effects, individuals were further split into five age ranges: 4–6, 7–8, 9–10, 11–13, and 14–17 years. The five age ranges were chosen to keep groups developmentally similar while maintaining an adequate sample size in each group. Preliminary analyses examined possible demographic, diagnostic, and family history differences between age groups. Preliminary analyses also examined comorbidity of attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (oppositional defiant disorder and conduct disorder).

To compare manic and depressive symptoms across age groups, multivariate analyses of variance (MANOVA) were computed with Age Group and Diagnostic Group (syndromal versus subsyndromal) as the independent variables and KMRS, YMRS and CDRS-R items as the dependent variables in separate analyses. If significant multivariate effects were observed, follow-up univariate ANOVAS were performed and relevant contrasts tested. To compare total levels of mania and depressive symptoms and psychosocial functioning across age groups, separate univariate ANOVAs were computed with Age Group and Diagnostic Group as the independent variables and total scores from the KMRS, YMRS, CDRS-R, CGAS, and CGI as the dependent variables. The presence of a comorbid ADHD diagnosis was included as a covariate in all MANOVAs and ANOVAs. These analyses included tests of the hypotheses that ADHD was associated with manic symptoms, as well as whether age differences persisted after controlling for ADHD. To compare diagnostic qualifiers across age groups, chi-square analyses were computed using Age Group and presence/absence of diagnostic qualifiers as independent variables.

More complex relationships between age, gender, and mood symptom ratings were evaluated using multiple regression. For these analyses, the presence of a comorbid ADHD diagnosis, age, age squared, gender, and the interaction of age and gender were entered as independent variables. Total scores on the KMRS, YMRS, CDRS-R, CGAS, and CGI served as dependent variables. Age squared was included to examine possible non-linear age-differences in symptoms. Gender and the interaction between gender and age were included to examine whether gender independently influenced symptoms or moderated the effect of age on symptoms. All analyses used the significance level (α) of 0.05.

3. Results

3.1. Participants

Across both enrollment periods, 535 youths aged 4–17 with BPSDs participated. The number of youth diagnosed with each bipolar diagnosis included BP I (n=290), BP II (n=17), BP NOS

Table 1
Demographic, diagnostic, and family history variables by age group.

Age group (Years) *N*	4–6.9 87	7–8.9 129	9–10.9 102	11–13.9 107	14–17.9 110	Total 535	F, X^2 (df; p)
Age (*SD*)	5.8 (.9)	8.1 (.6)	9.9 (.5)	12.5 (.8)	15.8 (1.1)	10.5 (3.5)	—
Males *n* (%)	52 (60%)	92 (71%)	76 (75%)	69 (65%)	50 (46%)	339 (63%)	24.72 (4; <.001)
Ethnicity *n* (%)							17.71 (12;.125)
Caucasian	64 (74%)	97 (75%)	83 (81%)	87 (81%)	88 (80%)	419 (78%)	
African-American	9 (10%)	23 (18%)	9 (9%)	14 (13%)	12 (11%)	67 (13%)	
Hispanic	1 (1%)	2 (2%)	3 (3%)	3 (3%)	3 (3%)	12 (2%)	
Other	13 (15%)	7 (5%)	7 (7%)	3 (3%)	7 (6%)	37 (7%)	
Syndromal BP (BP I or II)	50 (58%)	69 (54%)	57 (56%)	60 (56%)	71 (65%)	307 (57%)	3.28 (4;.513)
Comorbid ADHD/DBDs	41 (82%)	56 (81%)	46 (81%)	48 (80%)	44 (62%)	235 (77%)	10.99 (4;.027)
Comorbid anxiety disorder	3 (6%)	6 (9%)	6 (11%)	6 (10%)	9 (13%)	30 (10%)	1.62 (4;.806)
Subsyndromal BP (Cyc or NOS)	37 (43%)	60 (47%)	45 (44%)	47 (44%)	39 (36%)	228 (43%)	
Comorbid ADHD/DBDs	31 (84%)	45 (75%)	35 (78%)	34 (72%)	19 (49%)	164 (72%)	14.03 (4;.007)
Comorbid anxiety disorder	2 (5%)	5 (8%)	6 (13%)	5 (11%)	4 (10%)	4 (2%)	1.65 (4;.799)
Family history of bipolar illness	16 (53%)	34 (71%)	29 (83%)	29 (81%)	14 (70%)	122 (72%)	8.64 (4;.071)

*Data are presented as *n* (%) unless otherwise specified. Comorbid ADHD/DBDs=comorbid attention-deficit/hyperactivity disorder/disruptive behavior disorder, DBDs=oppositional defiant disorder and conduct disorder. Family history of bipolar illness total N=363.

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($n=155$), and cyclothymia ($n=73$). Table 1 presents demographic and family history characteristics across the five age groups. There were slightly fewer males in the youngest and substantially fewer males in the oldest age groups. There were no significant age differences in the distribution of ethnic groups or in the proportion of participants with syndromal or subsyndromal BPSDs. The proportion of participants who had comorbid ADHD was significantly lower in the oldest age group. The youngest age group had a slightly smaller proportion of cases with family history of BPSDs.

Only participants from the second wave of data collection completed the KMRS, CGAS, and CGI (KMRS $n=146$, CGAS $n=145$, CGI $n=145$). Due to incomplete data for only a few cases, the sample sizes for the YMRS ($n=534$) and CDRS-R ($n=533$) were much closer to the total sample size. No children diagnosed with BP II completed a KMRS interview.

Based upon the observed sample sizes, the power to detect all main effects and interactions was estimated to be quite good for all measures based upon a medium effect size of partial eta-squared=0.06 (based on benchmarks from Cohen, 1988) (lowest power=0.97, $\alpha=0.05$, two-tailed test) (Faul et al., 2009). Power was more variable when examined for a small effect size of partial eta-squared=0.01 (power range=.23–.74, $\alpha=.05$, two-tailed test) with better power observed for the YMRS and CDRS-R due to the larger number of cases for these measures. For characterizing effect sizes, we used Cohen's benchmarks of 0.01=small, 0.06=medium, and 0.14=large for partial eta-squared rather than Cohen's *d* because we wanted to use multiple degrees of freedom to test for nonlinear effects of age group on symptom presentation.

3.2. Manic Symptoms

Mean YMRS scores differed significantly between children diagnosed with BP I (25.96, $SD=8.11$) compared to the youth diagnosed with the other BPSDs including: BP NOS (18.80, $SD=5.98$), BP II (18.76, $SD=6.38$), and cyclothymia (17.57, $SD=7.06$; $F=46.73$, $df=3$, $p<.001$). Table 2 presents manic symptoms on the YMRS by age and diagnostic groups—BP I versus the rest of the spectrum. Both Age Group ($F(44, 2064)=1.87$, $p<0.001$) and Diagnostic Group ($F(11, 513)=14.61$, $p<0.001$) had significant multivariate effects. The Age Group by Diagnostic Group multivariate effect was not significant ($F(44, 2064)=1.06$, $p=0.362$). Univariate analyses indicated significant linear age differences for 4 of the 11 YMRS items. Motor Activity (Item 2, $p<0.0005$), Irritability (Item 5, $p=0.011$), and Aggression (Item 9, $p<0.0005$) all decreased linearly with age. No quadratic or higher order polynomials were significant, with the exception of a quadratic effect on Aggression due to the 9–10 year old group having the highest average score ($p=0.018$). In contrast, Thought Content (Item 8, $p=0.042$) showed a small but significant tendency to increase with age. Follow-up analyses examining differences between BP I versus the rest of the BPSDs were significant for all items except bizarre appearance. The effect sizes for age differences ranged from almost medium (eta-squared of 0.05 for the decreased level of motor activity as age increased) to the miniscule and non-significant.

As expected, syndromal cases showed higher symptom levels for all items, with the effect sizes ranging from medium (0.09 for hypersexuality) to very large (e.g., 0.38 for irritability or 0.35 for motor activity). The one exception was a lack of significant results for bizarre appearance, attributable to low endorsement rate and lack of variability (see Table 2). Effect sizes for the Age by Diagnostic Group interaction failed to reach even "small" levels.

Table 3 presents mania symptoms on the KMRS by age and diagnostic groups. Results indicated a significant Diagnostic Group multivariate effect ($F(13, 120)=4.27$, $p<0.001$), but no significant Age Group ($F(52, 492)=1.51$, $p=.151$) or Age Group by Diagnostic Group ($F(52, 492)=0.78$, $p=0.861$) multivariate effects. Follow-up univariate analyses indicated that individuals diagnosed with BP I showed significantly higher symptom levels for all but three items (poor judgment, hallucinations, and mood liability). These three items still showed moderate effect sizes favoring the BP I group.

The effect size of Diagnostic Group again was large or very large for most symptoms. On the KMRS, the univariate effects for Age Group and the Age Group by Diagnostic Group interactions all were small or negligible (see Table 3). Adding a quadratic term or higher order polynomial to test for nonlinear changes never improved model fit.

Table 2
Clinician-rated mania symptoms on the YMRS by age, syndromal versus subsyndromal bipolar diagnostic status, and ADHD comorbidity, Sorted in descending order by size of age effect.

YMRS item	Diagnostic group *M* (*SD*)		Unique effect (Partial eta-squared)			
	Bipolar I ($n=290$)	All other BP disorders ($n=245$)	Age (4 *df*)	Dx (1 *df*)	Age × Dx. (4 *df*)	ADHD (1 *df*)
Motor activity (#2)	2.8 (1.0)	2.1 (1.0)	.04***	.35***	.01	.00
Aggression (#9)	4.1 (2.0)	2.7 (1.7)	.04***	.34***	.01	.04*
Irritability (#5)	4.7 (1.7)	3.3 (1.6)	.02*	.38***	.01	.01
Thought content (#8)	1.7 (1.8)	1.1 (1.5)	.02*	.12***	.01	.00
Elevated mood (#1)	2.5 (1.0)	2.0 (.9)	.01	.24***	.00	.02
Sleep (#4)	2.1 (1.3)	1.4 (1.2)	.01	.29***	.01	.00
Appearance (#10)	.1 (.4)	.1 (.4)	.01	.01	.01	.00
Sexual interest (#3)	.8 (1.1)	.4 (.9)	.00	.09**	.00	.00
Speech (#6)	4.2 (1.9)	3.1 (1.5)	.00	.26***	.02	.00
Thought disorder (#7)	2.1 (1.0)	1.7 (1.0)	.00	.11***	.01	.04*
Insight (#11)	.8 (1.2)	.4 (.9)	.00	.11**	.02	.01

Ratings for the irritability, speech and aggression items were made on a 0–8 scale; all other items were 0–4, consistent with original conventions for the instrument (Young et al., 1978). Higher scores indicate greater severity.

* $p<.05$.
** $p<.005$.
*** $p<.0005$, two-tailed.

The effect sizes for Diagnostic Group again were large or very large for most symptoms. On the KMRS, the univariate effects for Age Group and the Age Group by Diagnostic Group interactions all were small or negligible (see Table 3). Adding a quadratic term or higher order polynomial to test for nonlinear changes never improved model fit.

3.3. Depression symptoms

Mean CDRS-R scores differed significantly between children diagnosed with BP II (mean=33.29, $SD=11.52$) compared to the youth diagnosed with the other BPSDs including: BP I (mean=16.37, $SD=13.99$), cyclothymia (mean=16.23, $SD=9.84$), and BP NOS (mean=13.18, $SD=11.97$; $F=12.83$, $df=3$, $p<0.001$). Table 4 presents depression symptoms on the CDRS-R by age and diagnostic groups. Results indicated a significant multivariate effect for Age Group ($F(68, 2036)=2.86$, $p<0.001$), but no significant multivariate effects for Diagnostic Group ($F(17, 506)=1.40$, $p=0.130$) or the Age Group by Diagnostic Group interaction ($F(68, 2036)=0.78$, $p=0.904$). Follow-up univariate analyses indicated significant age effects for all but two items (Physical Complaints and Guilt). For the latter two items, results were marginally significant (p values=0.071 and 0.080), but the effect sizes were small. In general, symptoms increased gradually with increasing age (smallest linear contrast $p<0.020$), with the exception of weeping, where symptoms

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Table 3
Clinician-rated mania symptoms on the KMRS by age, syndromal versus subsyndromal bipolar diagnostic status, and ADHD comorbidity, sorted in descending order by size of age effect.

KMRS item	Diagnostic group *M* (*SD*)		Unique effect (Partial eta-squared)			
	Syndromal bipolar (*n*=58)	Subsyndromal (*n*=85)	Age (4 *df*)	Dx (1 *df*)	Age × Dx. (4 *df*)	ADHD (1 *df*)
Rapid thinking (#8)	4.0 (1.2)	3.3 (.9)	.08*	.25**	.03	.02
Grandiosity (#6)	2.6 (1.3)	2.1 (1.1)	.05	.15*	.01	.00
Unusually energetic (#4)	3.9 (1.2)	3.3 (1.2)	.05	.21**	.03	.18*
Pressured speech (#7)	3.8 (1.2)	3.3 (.9)	.04	.20**	.05	.00
Poor judgment (#9)	3.4 (1.3)	2.9 (1.4)	.04	.07	.02	.02
Hallucinations (#11)	1.2 (.5)	1.1 (.4)	.04	.08	.01	.03
Elation/expansive Mood (#1)	3.4 (1.0)	3.0 (.9)	.03	.25**	.04	.25**
Distractibility (#10)	3.1 (1.2)	2.2 (1.2)	.03	.33***	.01	.01
Irritable mood (#2)	4.2 (.8)	3.7 (.8)	.03	.31***	.03	.11*
Delusions (#12)	1.1 (.4)	1.0 (.2)	.03	.17*	.02	.09
Decreased need for sleep (#3)	3.5 (1.7)	2.4 (1.4)	.02	.29***	.04	.04
Increased activity (#5)	3.9 (1.2)	2.9 (1.3)	.01	.35***	.01	.09
Mood lability (#13)	3.6 (.9)	3.5 (.8)	.00	.05	.01	.08

KMRS ratings for the Distractibility item were made on a 1–5 scale, all other items were 1–6. Items are keyed so that higher scores indicate greater severity.

* $p < .05$.
** $p < .005$.
*** $p < .0005$, two-tailed.

Table 4
Clinician-rated depression symptoms on the CDRS-R by age, syndromal versus subsyndromal bipolar diagnostic status, and ADHD comorbidity, Sorted in descending order by size of age effect.

CDRS-R item	Diagnostic group *M* (*SD*)		Unique effect (Partial eta-squared)			
	Syndromal bipolar (*n*=306)	Subsyndromal (*n*=227)	Age (4 *df*)	Dx (1 *df*)	Age × Dx. (4 *df*)	ADHD (1 *df*)
Excessive fatigue (♯6)	2.4 (1.6)	2.2 (1.3)	.08***	.03	.01	.09***
Self-esteem (♯10)	2.9 (1.7)	2.5 (1.5)	.06***	.07***	.01	.05*
Schoolwork (Item ♯1)	2.2 (1.5)	1.8 (1.1)	.06***	.06**	.00	.02
Depressed feelings (♯11)	2.8 (1.5)	2.6 (1.2)	.05***	.06***	.00	.09***
Anhedonia (♯2)	2.5 (1.6)	2.2 (1.4)	.05***	.05*	.01	.08**
Suicidal ideation (♯13)	1.6 (1.1)	1.5 (1.0)	.05***	.01	.00	.01
Sleep (♯4)	1.9 (1.3)	1.6 (1.0)	.04***	.04*	.01	.04*
Depressed affect (♯15)	1.6 (1.1)	1.5 (1.0)	.04***	.02	.00	.05*
Irritability (♯8)	3.1 (1.6)	2.8 (1.4)	.04*	.03	.01	.07**
Tempo of speech (♯16)	1.2 (.6)	1.1 (.4)	.03**	.03*	.00	.00
Hypoactivity (♯17)	1.3 (.9)	1.3 (.7)	.03**	.01	.01	.02
Decreased appetite (♯5)	1.8 (1.1)	1.6 (1.0)	.03*	.04*	.00	.08**
Social withdrawal (♯3)	2.4 (1.5)	2.1 (1.3)	.03*	.03*	.00	.08**
Weeping (♯14)	1.8 (1.3)	1.9 (1.2)	.03*[a]	.00	.00	.04*
Morbid ideation (♯12)	1.4 (.9)	1.4 (.9)	.02*	.01	.01	.04*
Physical complaints (♯7)	1.7 (1.2)	1.7 (1.1)	.01	.00	.00	.03*
Guilt (♯9)	1.7 (1.2)	1.6 (1.0)	.01	.00	.00	.04*

Ratings for the sleep, decreased appetite, and tempo of speech were made on a 1–5 scale; all other items were 1–7; higher scores indicate greater severity.

* $p < .05$.
** $p < .005$.
*** $p < .0005$, two-tailed.
[a] Weeping was the only item to show significant *decreases* with age.

decreased with age (linear contrast $p=0.017$). The cumulative effect size attached to age was typically in the small to medium range, whereas the Age Group by Diagnostic Group effect sizes were always small (e.g., partial eta squared values ranging between 0.00 and 0.01).

3.4. Differences in clinician-rated total scores for mood

Fig. 1 presents clinician-rated total scores on the KMRS, YMRS, and CDRS-R. In order to interpret differences across the age groups more easily, the scores from the total scores of the KMRS, YMRS, and CDRS-R were converted into a percent of the maximum possible score (POMP). The converted scores are then presented on a standard scale that allows readers to inspect differences uniformly regardless of the scale's scoring range (Cohen et al., 1999). Results indicated significant Diagnostic Group effects for the KMRS ($F(1, 136)=35.28$, $p < 0.001$) and YMRS ($F(1, 524)=118.96$, $p < 0.001$) total scores. Not surprisingly, individuals with syndromal bipolar illness were rated as having greater mania symptoms than individuals with subsyndromal illness. There were no significant Age Group effects for the KMRS total score (largest $F(4, 524)=1.27$, $p=.286$). However, the Age Group by Diagnostic Group ($F(4, 524)=2.19$, $p=.069$) effects were marginally significant for the YMRS total score. The marginally significant Age Group effect indicated that symptoms were higher in the childhood age groups than adolescent age groups. The marginally significant Age Group by Diagnostic Group interaction indicated that mania symptom levels were most discrepant between syndromal and subsyndromal cases in the middle age

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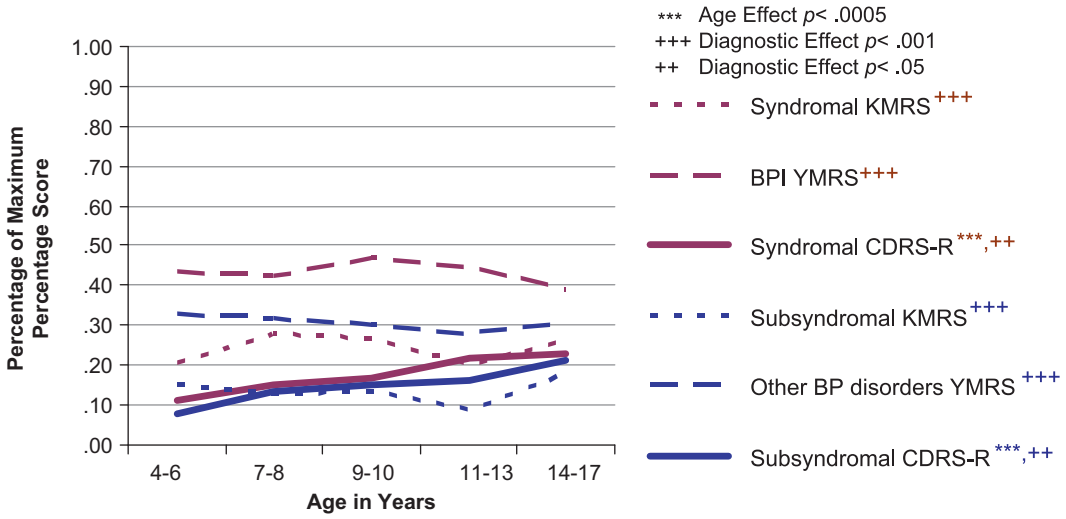

Fig. 1. KMRS, YMRS and CDRS-R total scores across age and diagnostic groups. KMRS=K-SADS mania rating scale, YMRS=young mania rating sclae, CDRS-R=children's depression rating sclae-revised; KMRStotal $N=146$; YMRS total $N=534$, CDRS-R total $N=533$.

group (ages 9-10) and least discrepant in the youngest and oldest age groups (ages 4–6 and 14–17).

Results for the CDRS-R indicated significant Age Group ($F(4, 525)=9.14$, $p<0.001$) and Diagnostic Group ($F(1, 525)=9.37$, $p=0.002$) effects for the CDRS-R total score. Depression symptoms increased with age and syndromal cases had greater symptom counts than subsyndromal cases. The Age Group by Diagnostic Group interaction was not significant ($F(4, 525)=0.40$, $p=0.809$).

Results indicated no significant overall prediction of mania symptoms total scores on either the KMRS ($F(5, 140)=1.57$, $p=0.171$) or YMRS ($F(5, 528)=2.14$, $p=0.059$) using the presence of a comorbid ADHD diagnosis, age, age squared, gender, and the interaction of age and gender. Overall, prediction of depression symptoms total score on the CDRS-R was highly significant ($F(5, 529)=14.99$, $p<0.001$). However, the only significant predictors were comorbid ADHD diagnosis ($t(529)=-3.67$, $p=<0.001$ and the youth's age ($t(529)=2.98$, $p=0.003$). Youth's age squared, gender, and the interaction of age and gender did not contribute significantly to the prediction (largest $t(529)=1.93$, $p=0.054$). Overall prediction of psychosocial functioning was not significant on the CGAS or CGI, nor did the effect of diagnosis on functioning change with age (all p values >0.05).

3.5. Differences in clinician-rated total scores for global functioning

Results indicated significant Diagnostic Group effects for both the CGAS ($F(1, 134)=21.62$, $p<0.001$) and CGI ($F(1, 134)=14.46$, $p<0.001$) scores. Syndromal bipolar cases showed significantly worse functioning than subsyndromal cases. However, the Age Group and Age Group by Diagnostic Group effects were not significant for the CGAS (largest $F(1, 134)=0.52$, $p=0.724$) or CGI (largest $F(1, 134)=0.82$, $p=0.517$). There were no significant differences in the presence of rapid cycling across age groups, $X^2(4)=8.33$, $p=0.080$; or in the presence of mixed episodes or psychosis (largest $X^2(4)=4.00$, $p=0.407$).

3.6. Effects of ADHD comorbidity on mood symptoms

Comorbid ADHD was a significant covariate for both manic and depressive symptoms. ADHD was associated with significantly higher scores on the thought disorder (item #7, $p=0.01$) and disruptive/aggressive behavior (item #9, $p<0.001$) YMRS items. ADHD significantly covaried negatively with the elation/expansive mood ($p<0.001$), irritable mood ($p=0.04$) and unusually energetic ($p=0.01$) items on the KMRS, suggesting that these were scored in a way that attempted to isolate mania from symptoms of ADHD. ADHD status was also associated with most depression items. The only CDRS-R items that comorbid ADHD was not found to be a significant covariate included: schoolwork, suicidal ideation, tempo speech, and hypoactivity (all p values >0.05). Comorbid ADHD was associated with significantly lower scores on items such as excessive fatigue, low energy irritability, and appetite disturbance. It is unclear whether these associations might be due to stimulant medication instead of the ADHD itself. All of the effects were in the small or medium range. For the mania items, the differences between syndromal versus subsyndromal were always larger than the effects for ADHD. However, ADHD's effects on depressive symptoms were similar in magnitude to the effects of syndromal versus subsyndromal status.

4. Discussion

One of the key points in the debate about pediatric BPSD has been the extent to which it presents similarly to BPSD as seen in adults (Carlson and Glovinsky, 2009). Because DSM-IV (American Psychiatric Association, 2001) and the proposed DSM-5 criteria (http://www.dsm5.org/meetus/pages/mooddisorders.aspx) both diagnose based on symptom presentation, rather than matching prototypes or focusing on – as yet poorly understood – pathophysiology, the question of whether symptom patterns change is crucial to whether diagnosis "works" consistently. DSM, ICD, and the diagnostic recommendations recently made by the International Society for Bipolar Disorders (Ghaemi et al., 2008; Youngstrom et al., 2008) all recommend using the same core symptoms and definitions of mood states for diagnosing mood disorders in children and adolescents as well as adults. Currently, it is accepted that the presentation in adolescents is similar to the picture in adults (Birmaher and Axelson, 2006; Carlson and Glovinsky, 2009; Goodwin and Jamison, 2007; Leibenluft, 2011; Nottelmann et al., 2001; Youngstrom, 2009). Less prior work has addressed using mania definitions and ratings in prepubertal youths, and next to none in preschool age ranges. Extant work has focused on the validity of global definitions and diagnoses, for example, comparing youths with diagnoses of BP I to youths with ADHD or no diagnosis (Geller and Luby, 1997; Pavuluri et al., 2006), or else examining the psychometric validity of global scores on rating

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scales (Fristad et al., 1992; Fristad et al., 1995). Although the accumulating evidence for the diagnosis (Biederman et al., 2005; Birmaher and Axelson, 2006; Findling et al., 2001; Geller and Luby, 1997; Youngstrom et al., 2008) or summary scores (Axelson et al., 2003; Frazier et al., 2007; Fristad et al., 1992; Fristad et al., 1995; Youngstrom et al., 2002) has been quite promising, there also have been indications that specific items or symptoms might be less valid in youths. Behavior that might indicate hypomania or mania in an adolescent could be developmentally appropriate for a preschooler, for example (Carlson, 1990). Similarly, higher rates of ADHD presenting to a clinic within younger age groups might artificially inflate scores on mania scales (Galanter and Leibenluft, 2008).

Overall, the results indicate that age effects on manic symptoms are almost entirely small, whether measured via the widely used YMRS or with the newer, more developmentally anchored KMRS. The few patterns that achieved statistical significance involved slight decreases in motor activity and aggressive behavior with age. These patterns remained significant after adjusting for comorbid ADHD. However, age effects were small enough that they "washed out" and had no statistically discernible impact at the level of the summary total score for either instrument. Hallucinations (KMRS Item #11), delusions (KMRS #12) and bizarre thought content (YMRS #8) were equally rare at all ages, and did not show an increase with adolescence. "Bizarre Appearance" (YMRS #10) and "Poor Insight" (YMRS #11) had previously been identified as showing poor factor loadings or item-total correlations in prior work, leading to questions about their developmental appropriateness. In the present analyses, consistently low levels of endorsement across all ages were found, and poor insight showed no association with syndromal versus subsyndromal status. These results suggest that they are poor indicators of mania in general: across all ages, rather than just being inappropriate for younger cases.

Findings consistently showed negligible interactions between age and syndrome status, indicating that age did not have any more impact on the symptom presentation for BP II, BP NOS and cyclothymia versus BP I cases. An important implication is that the symptoms of mania, or depression, show consistent associations with the subsyndromal presentations. Thus, relying on the core symptoms as a basis for identifying diagnoses or quantifying the severity of mood symptoms produces consistent results at younger ages as well as in adolescence. This pattern of findings is consistent with the ISBD recommendations and the DSM-5 proposal to use the same symptoms to identify mania and hypomania in childhood and adolescence as well as in adulthood.

Depression showed more and moderate age effects, with average item scores consistently increasing with age (with the exception of "crying a lot," which decreased significantly with age). This finding coincides with the well-established increase in depressive symptoms and major depressive episodes with the onset of puberty (Costello et al., 2006; Cyranowski et al., 2000). Furthermore, this result supports a previous examination that also found that depressive symptoms worsened in 12–17 year olds compared to 3–11 year olds with bipolar disorder (Staton et al., 2008). Differences between BP I or II versus cyclothymic disorder or NOS were smaller on the depression items, but because both the age and the syndrome status effects always aligned in the same way, the aggregate effect at the summary score level was a medium sized increase in CDRS-R total with age (eta squared = 0.06), and a medium increase in severity of depression comparing syndromal to subsyndromal presentations (eta squared = 0.07). Again, there was no interaction between syndromal status and age for the depression items or total score, indicating that this set of symptoms showed consistent performance between the syndromal status groups across the full range of ages.

Roughly 75% of the syndromal cases and 64% of the subsyndromal cases also met criteria for ADHD based on the research diagnostic interview. This rate of comorbidity is fairly typical of research samples ascertained for mood disorders (Carlson, 1998; Galanter and Leibenluft, 2008; Youngstrom et al., 2010). ADHD status showed significant associations with most depression items and with a few mania items. Cases with ADHD had significantly lower scores for depressive symptoms such as fatigue, social withdrawal, appetite disturbance—all of which might be reduced by the chronically increased activity level associated with ADHD, or which might have been mitigated by stimulant medication (which unfortunately was not available as a variable to include in the statistical analyses). Cases with ADHD still frequently showed moderate or severe elevations on the CDRS-R total score, consistent with the literature on the association between ADHD and depressive disorders (Costello et al., 2006; Kessler et al., 2006). In comparison, the effects of ADHD on mania symptoms were relatively few and typically small. ADHD was associated with slight increases in aggressive behavior and thought problems, and with lower scores on elated mood. This last finding was initially surprising, but further examination indicated that the cases with ADHD often were less likely to show the "narrow phenotype" presentation with only elated mood or grandiosity and lower aggression; instead they were more likely to have high aggression, albeit still on average having moderate elated mood during their hypomania or mania. This finding may help to reconcile findings in the literature: bipolar samples ascertained from settings heavily enriched for ADHD might find more cases with high levels of irritable mood and aggressive behavior, and only more moderate amounts of elated mood or grandiosity (Wozniak et al., 1995); and other settings with somewhat lower rates of ADHD might find more elated mood (Findling et al., 2001; Hunt et al., 2009). In addition, lower rates of ADHD were found in the older participants compared to the younger participants. These findings warrant further investigation. It also is important to consider that present analyses were limited to mood symptoms: there are likely to be more and larger age differences in other clinically significant aspects of presentation.

4.1. Clinical implications

Results indicate that it is possible to distinguish between symptoms of mania or hypomania versus ADHD, even if confronting cases that may meet full criteria for both disorders. These interviews focused on identifying spontaneous changes in mood and energy and episodic presentations as heuristics for distinguishing between mood versus non-mood disorder diagnosis. When viewed through this lens, the effects of bipolar status are much larger than the effects of ADHD on the mania symptom ratings. These analyses suggest that the YMRS might be stronger if it omitted the "bizarre appearance" item, which has previously been criticized on psychometric grounds (Youngstrom et al., 2002), and also when based on parent-report as well as interview ratings (Gracious et al., 2002). The poor performance of this item is not a developmental issue; instead, it appears to be a weak indicator of mania at all ages (cf. Double, 1991).

4.2. Limitations

It is important to note that the sample reported here does not represent the typical clinical or epidemiological samples. This sample was recruited for possible inclusion into research studies, and analyses were limited to the subset of cases that met DSM-IV criteria for a BPSD. There are two aspects to the question of whether mania presents differently in children versus adults. One issue is whether the core set of symptoms of mania or depression perform similarly in children versus adults. The data and analyses here directly address this issue using a large enough dataset to detect even small age effects and interactions, and the evidence is that any age effects on the core symptoms are small. The other issue is whether there are additional symptoms or associated features of pediatric BPSD that differ from adult presentations

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(Papolos and Papolos, 2002). These analyses do not speak to that important set of questions.

Another limitation is that the mood ratings were completed based on the same interview that informed the research diagnoses. Because of the way interviews were conducted, decisions were made about whether to "credit" the level of energy or aggression to a mood disorder (based on the symptom having a more spontaneous, episodic presentation) versus a more chronic, non-episodic condition (e.g., ADHD or a disruptive behavior disorder). Clinicians make a similar calibration when deciding what is age appropriate behavior, but it would be difficult to use the present data to address the question of how these behaviors compare to "typical" norms for children or adolescents given that all of the youths met criteria for DSM-IV BPSDs. In addition, although there were few participants in this sample that met DSM-IV criteria for an anxiety disorder outside of the context of mood episodes, a more detailed examination of anxiety symptoms endorsed in the KSADS interview or collected by specific anxiety measures may provide much needed information about comorbidity between bipolar disorder, ADHD and anxiety symptoms.

Moreover, another limitation that should be acknowledged is that this sample included few children and adolescents with BP II ($n=17$). The small number of participants who met DSM-IV criteria for BP II may be an indication that the KSADS may lack the sensitivity to diagnosis this disorder in young children. Another explanation may be based on Dilsaver and Akiskal's (2009) findings that children who should be diagnosed with BP II are mistakenly diagnosed with unipolar depression due to diurnal variations in symptom presentations and the time of assessment. Finally, another limitation that should be noted is that mood episode at time of interview was not captured. For this reason, the ability to note which specific mood episodes were present at the time of the interview are not available. This shortcoming is one that might be readily addressed in future studies.

Conflict of interest

Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Rhodes Pharmaceuticals, Sanofi-Aventis, Schering-Plough, Seaside Therapeutics, Sepracore,Shire, Solvay, Sunovion, Supernus Pharmaceuticals, Validus, and Wyeth. Dr. Youngstrom has received travel support from Bristol-Myers Squibb. Dr. Frazier has received federal funding or research support from, acted as a consultant to, or received travel support from Shire Development, Inc., Bristol-Myers Squibb, National Institute of Health, and NARSAD. Dr. Calabrese has received federal funding or research support from, acted as a consultant to/served on advisory boards for, or provided CME lectures to the Department of Defense, Health Resources Services Administration, National Institute of Mental Health, Abbott, Adamed, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Dainippon Sumitomo, Eli Lilly, EPI-Q, Inc., Eisai, Elan, Forest, France Foundation, Genaissance, GlaxoSmithKline, Janssen, Johnson and Johnson, Jazz Pharmaceuticals, JDS Pharmaceuticals, Lundbeck, Merck, Memory Pharmaceuticals, NARSAD, Neurosearch, Novartis, Organon, OrthoMcNeil, Otsuka, Pfizer, Repligen, Sanofi Aventis, Schering-Plough, Servier, Solvay, Stanley Medical Research Institute, Supernus, Synosia, Takeda, Tikvah, and Wyeth. Drs. Carlson and McNamara, and Mss. Demeter, Rowles, Lingler, and DiFrancesco have no financial ties to disclose.

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