Examining the Comorbidity of Bipolar Disorder and Autism Spectrum Disorders: A Large Controlled Analysis of Phenotypic and Familial Correlates in a Referred Population of Youth With Bipolar I Disorder With and Without Autism Spectrum Disorders

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ABSTRACT

Objective: Although mood dysregulation is frequently associated with autism spectrum disorders (ASD) and autistic traits are common in youth with bipolar disorder, uncertainties remain regarding the comorbid occurrence of bipolar disorder and ASD. This study examines the clinical and familial correlates of bipolar disorder when it occurs with and without ASD comorbidity in a well-characterized, research-referred population of youth with bipolar disorder. We hypothesized that in youth with bipolar disorder, the clinical and familial correlates of bipolar disorder will be comparable irrespective of the comorbidity with ASD.

Method: Clinical correlates and familial risk were assessed by secondary analysis of the data from a large family study of youth with bipolar I disorder (diagnosis based on *DSM-IV* criteria; probands n = 157, relatives n = 487; study period: November 1997–September 2002). Findings in bipolar I youth were compared with those in youth with attention-deficit/hyperactivity disorder (diagnosis based on *DSM-III-R* criteria) without bipolar I disorder (probands n = 162, relatives n = 511) and age- and sex-matched controls without bipolar I disorder or attention-deficit/hyperactivity disorder (probands n = 136, relatives n = 411). All subjects were comprehensively assessed using structured diagnostic interviews and a wide range of nonoverlapping measures assessing multiple dimensions of functioning.

Results: Thirty percent (47/155) of the bipolar I probands met criteria for ASD (diagnosis based on *DSM-III-R* criteria). The mean ± SD age at onset of bipolar I disorder was significantly earlier in the presence of ASD comorbidity (4.7 ± 2.9 vs 6.3 ± 3.7 years; $P = .01$). The phenotypic and familial correlates of bipolar disorder were similar in youth with and without ASD comorbidity.

Conclusions: A clinically significant minority of youth with bipolar I disorder suffers from comorbid ASD. Phenotypic and familial correlates of bipolar disorder were typical of the disorder in the presence of ASD comorbidity. Bipolar I disorder comorbidity with ASD represents a very severe psychopathologic state in youth.

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Both autism spectrum disorders (ASD) and pediatric bipolar disorder are severely impairing chronic conditions.[1,2] Each disorder affects at least 1% of the pediatric population.[3,4] Impairing mood symptoms of irritability and aggression are reportedly observed in one-fourth of both higher- and lower-functioning populations with ASD.[5,6] Although often diagnostically considered associated features of ASD, irritability and aggression are also the predominant mood symptoms documented in pediatric mania.[7,8] The presence of these aberrant mood symptoms in ASD populations has drawn attention to the possibility that a subset of individuals with ASD may also suffer from bipolar disorder.

A small body of literature has documented a bidirectional overlap between ASD and bipolar disorder in pediatric populations. Evidence suggestive of comorbid bipolar disorder in youth with ASD comes from case reports of aggressive behaviors and severe mood disturbances highly suggestive of mania in youth with ASD.[9,10] A previous report[11] from our program identified reciprocal comorbidity between bipolar disorder and ASD on structured diagnostic interviews in a substantial minority of psychiatrically referred youth suffering from either disorder. Notably, the clinical presentation of bipolar disorder and ASD in the comorbid state was strikingly analogous to their typical presentation, suggesting a bona fide co-occurrence of these disorders.

Much of the literature devoted to examining the extent of psychiatric comorbidity in ASD populations has not assessed for the presence of bipolar disorder.[12,13] Equally lacking is documentation of ASD comorbidity in bipolar populations. Significant ASD traits were reported in more than half of a highly selected research population of high-functioning bipolar disorder youth with no preestablished diagnosis of ASD,[14] raising the concern of underrecognition of ASD in bipolar disorder samples. Further evidence suggestive of this comorbidity comes from family genetic studies conducted in ASD populations that documented an elevated prevalence of bipolar disorder in the relatives of ASD probands.[15,16] Whether the familial risk for bipolar disorder is equally elevated in the bipolar disorder population in the context of the comorbidity with ASD remains to be examined.

Appropriate recognition of bipolar disorder in youth with ASD has important clinical implications, given that treatment interventions for these disorders differ. For instance, in individuals with ASD, if irritability and aggression associated with bipolar mania are misattributed as associated features of ASD, the opportunity to treat bipolar disorder may be missed. Conversely, if ASD features of limited abstract thinking and odd and restricted expression of emotions are misjudged for the aberrant psychopathologic

Clinical Points

- A clinically significant minority of youth with bipolar disorder suffers from autism spectrum disorders (ASD) comorbidity.
- The age at onset of bipolar I disorder is significantly earlier in the presence of ASD comorbidity.
- The phenotypic and familial correlates of bipolar I disorder are typical of the disorder in the presence of ASD comorbidity.

processes afflicting individuals with bipolar disorder, this may lead to inappropriate treatment, unnecessary exposure to psychotropics, worsening of symptoms, and misuse of mental health resources.

As clinical correlates of bipolar disorder are not well understood in the context of ASD and considering that pediatric bipolar disorder is characterized by a unique *DSM-IV* symptom profile and functional impairments,[17–19] as well as an elevated familial risk for bipolar disorder in first-degree relatives,[17,18] one approach to studying the co-occurrence of bipolar disorder with ASD is to examine the comorbidity of ASD in a well-characterized population with bipolar disorder and compare the clinical and familial correlates of bipolar disorder in subjects with and without ASD. To this end, we analyzed data from large samples of referred youth with bipolar disorder, youth with attention-deficit/hyperactivity disorder (ADHD), and healthy controls and their first-degree relatives. On the basis of the extant literature, we hypothesized that youth with bipolar disorder would have similar personal and familial correlates of bipolar disorder irrespective of the comorbidity with ASD.

METHOD

Subjects

Detailed study methodology has been previously reported.[20] In brief, all subjects were recruited and assessed at the Pediatric Psychopharmacology Clinical and Research Program at Massachusetts General Hospital, Boston. The bipolar disorder study recruited 157 probands with bipolar I disorder, 6–17 years of age and of both sexes, and their 487 first-degree relatives from November 1997 to September 2002.[21] The ADHD studies recruited probands with (n = 280) and without (n = 242) ADHD, 6–17 years of age and of both sexes, and their 1,612 first-degree relatives from November 1997 to September 2011.[22,23] From 522 families participating in our case-control ADHD family studies, we randomly selected 162 nonbipolar ADHD probands and their 511 first-degree relatives, and 136 nonbipolar, non-ASD, and non-ADHD control probands and their 411 first-degree relatives so that the age and gender distribution was similar to that of the bipolar I probands. All study procedures were reviewed and approved by the human subjects institutional review board at Massachusetts General Hospital. Parents or guardians of subjects provided informed consent for their child to participate after a study clinician reviewed and explained all study procedures, risks, and potential benefits. Subjects 7–17 years of age also provided informed assent.

Ascertainment Method

Potential bipolar I probands were ascertained from our clinical service, referrals from local clinicians, and advertisements in the local media. Subjects were administered a phone screen reviewing symptoms of *DSM-IV* bipolar I disorder and, if criteria were met, were scheduled for a face-to-face structured diagnostic interview with a psychometrician. In addition to the structured diagnostic interview, a clinician with expertise in pediatric bipolar disorder performed a clinical interview with the proband and his or her parents to confirm the diagnosis of bipolar disorder. The agreement between the clinical assessment by this senior clinician and the structured diagnostic interview on the first 69 cases was 97%.[24]

As previously reported,[22] ADHD cases were ascertained from psychiatric and pediatric sources. Healthy controls were ascertained from outpatients who were referred for routine physical examinations to pediatric medical clinics at each setting and were identified as not having ADHD. Screening procedures were similar to those described for the recruitment of the bipolar probands with the exception that we queried for the presence or absence of ADHD (and not bipolar disorder) in the initial telephone screening.

Diagnostic Procedures

Psychiatric assessments of subjects younger than 18 years relied on the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (K-SADS-E), using the *DSM-III-R* version[25] for the ADHD studies and the *DSM-IV* version[26] for the bipolar studies. Assessments of adult family members were made with the Structured Clinical Interview for *DSM* (SCID), using the *DSM-III-R* version[27] for the ADHD studies and the *DSM-IV* version[28] for the bipolar studies, supplemented with modules from the K-SADS-E to include childhood disorders. Diagnoses were based on independent interviews with mothers and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either reporter resulted in a positive diagnosis. Anxiety disorders were aggregated into a binary measure that was coded positive if ≥ 2 anxiety disorders were endorsed on structured interview.[29] Psychoactive substance use disorder (PSUD) was defined as any alcohol or substance abuse or dependence. For each diagnostic module, symptoms were counted in a nonhierarchical manner and endorsed when present.

All interviews were conducted by extensively trained and highly supervised psychometricians with bachelor's degrees in psychology. All structured interview diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists or clinical psychologists. The committee members were blind to the subjects' ascertainment group and ascertainment site and to data collected from other family members. We computed κ coefficients of agreement by having experienced clinicians

diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 interviews, the median κ coefficient between raters and clinicians was 0.99. Between individual clinicians and the clinical review committee, the median κ coefficient was 0.87.

Children were diagnosed with bipolar I disorder according to *DSM-IV* criteria. As the K-SADS-E and other structured interviews lack modules for evaluating pervasive developmental disorders (PDD), we used a *DSM-III-R*–based diagnostic interview to assess this disorder. Diagnostic assessment of PDD by this interview required a lifelong severe and pervasive deficit in the development of reciprocal social interaction, impairment in communication, and the presence of restricted patterns of behavior. ASD was defined as meeting criteria for autistic disorder or PDD not otherwise specified (PDD-NOS). To be given the diagnosis of autistic disorder, the participant had to meet the *DSM-III-R* diagnostic criteria of 8 out of 16 symptoms, with at least 2 symptoms from each of the aforementioned domains of PDD. A diagnosis of PDD-NOS was received if more than 2 of the required symptoms were met with symptom(s) present from each of the 3 domains of PDD. We computed κ coefficients of agreement for PDD module–generated diagnoses by having an independent rater with expertise in the diagnosis of PDD (G.J.) diagnose subjects from audiotaped interviews made by the assessment staff. Based on 20 interviews, the median κ coefficient of agreement between raters and clinician was 0.90. The κ for reliability between independent raters and the final diagnostic decision made by a clinician-reviewer was 0.88. Additionally, excellent sensitivity for the PDD module is observed with the clinical diagnosis of ASD (94%) and with the Social Responsiveness Scale (t score ≥ 60; 96%).[30]

The *DSM* Global Assessment of Functioning Scale (GAF)[31] was used as a measure of overall functioning. Mothers completed the Social Adjustment Inventory for Children and Adolescents (SAICA),[32] which provides an evaluation of children's functioning in school, in spare time activities, and with peers, siblings, and parents. Mothers also completed the Child Behavior Checklist (CBCL),[33] which is an empirically derived dimensional measure of psychopathology. Family functioning was assessed using the Moos Family Environment Scale (FES).[34] Socioeconomic status (SES) was measured using the 5-point Hollingshead scale.[35]

Statistical Analysis

Comparisons were made between 4 groups and their first-degree relatives: probands with bipolar I disorder and comorbid ASD (BPD-I + ASD, n = 47; relatives, n = 137), probands with bipolar I disorder without ASD (BPD-I, n = 108; relatives, n = 336), probands with ADHD without bipolar I disorder or ASD (ADHD, n = 162; relatives, n = 511), and healthy controls without bipolar I disorder, ASD, or ADHD (controls, n = 136; relatives, n = 411). Demographic characteristics of the probands were compared between the 4 groups using the Pearson χ^2 test, analysis of variance, or Kruskal-Wallis rank test depending on the distribution of the characteristic. Demographics of the relatives were compared between the 4 groups using logistic, linear, or ordinal regression depending on the variable's distribution. To account for nonindependence within families, all analyses with relatives of probands adjusted variance estimates with Huber's[36] formula to produce P values that are robust to distributional assumptions. Proband comparisons were made with linear, logistic, or ordered logistic regression depending on the distribution of the outcome and controlled for all demographic confounds. Relatives in the 4 groups were compared on rates of bipolar I disorder using logistic regression, controlling for all demographic confounds and using Huber's correction. All statistical tests were 2-tailed, and any P values < .05 were considered statistically significant.

RESULTS

Two of 157 bipolar I probands were missing an ASD diagnosis and were excluded from analysis. Comorbid ASD was present in 30.3% (47/155) of the bipolar I probands. Of the 47 subjects with ASD, 9 (19%) had autistic disorder and 38 (81%) had PDD-NOS. All psychopathologic groups had significantly lower SES compared to the healthy control families (Table 1). There were significantly more nonwhite probands in both groups of bipolar I families (BPD-I + ASD and BPD-I) compared to the ADHD and healthy control families. Thus, all proband comparisons controlled for SES and race.

Patterns of Psychopathology in Probands

As shown in Table 1, probands with BPD-I + ASD had a significantly younger mean age at onset of bipolar disorder and significantly poorer GAF scores than BPD-I probands. As shown in Figure 1, with the exception of a higher rate of grandiosity in the BPD-I + ASD probands, the profiles for individual symptoms of mania were very similar for both bipolar I groups. As depicted in Figure 2A, bipolar I disorder, irrespective of comorbidity with ASD, was associated with significantly higher rates of psychosis, major depressive disorder, multiple (≥ 2) anxiety disorders, oppositional defiant disorder, and conduct disorder. Only BPD-I probands had a higher rate of PSUD. BPD-I + ASD probands had significantly more impaired scores on all CBCL subscales compared to BPD-I probands except for the somatic complaints scale (Figure 2B). Both bipolar I groups had significantly more impaired scores on all CBCL clinical subscales compared to ADHD and control groups.

Patterns of Dysfunction in Probands

Bipolar I probands had significantly poorer SAICA scores on measures of school behavior problems, spare time activities, spare time problems, activities with peers, problems with peers, and problems with parents, independent of comorbid ASD (Figure 3A). All 3 psychopathologic groups had significantly more probands with lower family cohesion and higher family conflict scores and higher rates of extra help and placement in a special class compared to controls (Figure 3B and 3C). However, significantly more BPD-I + ASD probands than BPD-I probands required placement in a special class. Both bipolar I groups had a significantly higher rate of

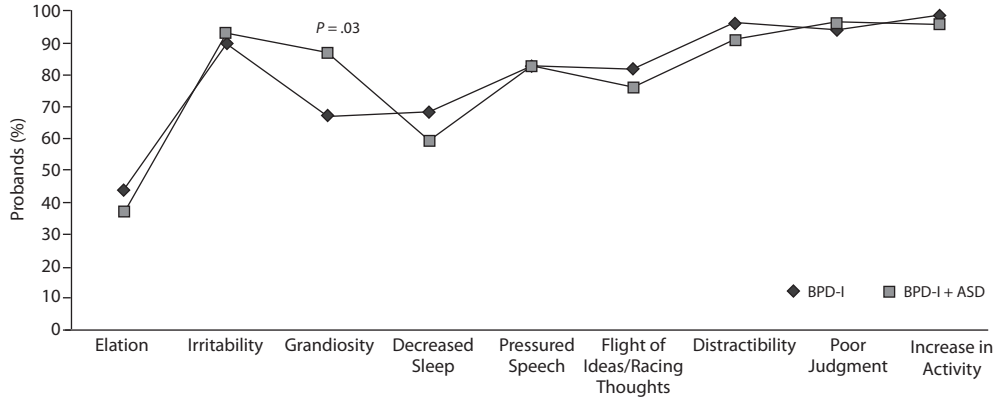
Table 1. Demographic and Clinical Characteristics

Characteristic	BPD-I	BPD-I + ASD	ADHD	Controls	Test Statistic	P Value
Demographic characteristics						
Probands	n = 108	n = 47	n = 162	n = 136		
Age, mean ± SD, y	10.8 ± 3.3	9.8 ± 2.9	10.6 ± 3.0	10.7 ± 3.0	$F_{3,449} = 1.32$	.27
Sex, male, n (%)	82 (76)	41 (87)	121 (75)	99 (73)	$\chi^2_3 = 4.12$	.25
Race, white, n (%)	99 (92)[a]	43 (91)[a]	160 (99)	132 (97)	$\chi^2_3 = 10.85$	.01
IQ, mean ± SD	102.9 ± 14.9[a,b]	103.2 ± 15.4[b]	107.7 ± 13.9[b]	115.7 ± 11.5	$F_{3,377} = 17.52$	< .001
First-degree relatives	n = 336	n = 137	n = 511	n = 411		
Age, mean ± SD, y	30.7 ± 16.3	30.1 ± 15.9	31.2 ± 14.7	31.6 ± 14.7	$F_{3,450} = 0.84$	.47
Sex, male, n (%)	164 (48)	73 (52)	264 (52)	207 (50)	$\chi^2_3 = 2.67$	.45
Race, white, n (%)	313 (92)[a,b]	131 (94)[a]	507 (99)	404 (98)	$\chi^2_3 = 12.80$	.005
Family SES, mean ± SD	1.8 ± 0.9[b]	1.9 ± 0.9[b]	1.8 ± 1.0[b]	1.5 ± 0.7	$\chi^2_3 = 8.67$	.03
Family size, mean ± SD	4.2 ± 1.2	4.0 ± 1.1	4.2 ± 1.0	4.0 ± 0.9	$\chi^2_3 = 0.57$	.90
Family intactness, n (%)[c]	54 (73)	25 (74)	120 (74)	115 (85)	$\chi^2_3 = 6.12$	.11
Clinical characteristics of bipolar disorder in probands						
Onset, mean ± SD, y	6.3 ± 3.7	4.7 ± 2.9	NA	NA	$t_{151} = -2.61$	.01
Duration, mean ± SD, y	3.3 ± 3.0	4.0 ± 3.3	NA	NA	$t_{149} = 1.32$	.19
No. of episodes, mean ± SD	21.3 ± 64.5	26.1 ± 57.5	NA	NA	$z = 0.73$	.47
No. of symptoms, mean ± SD	5.8 ± 1.1	6.0 ± 1.1	NA	NA	$z = 0.65$	.52
Sequence of mood onset					$\chi^2_2 = 0.28$	.87
Depression precedes mania	25 (25)	10 (23)	NA	NA		
Mania precedes depression	39 (40)	19 (44)	NA	NA		
Simultaneous onset	35 (35)	14 (33)	NA	NA		
Mixed state	98 (99)	42 (98)	NA	NA	$\chi^2_2 = 0.37$	.54
Chronic course of bipolar disorder (≥ 1 y)	82 (77)	35 (74)	NA	NA	$\chi^2_1 = 0.15$	.70
Severe impairment, n %	66 (61)	31 (66)	NA	NA	$z = 0.56$	.58
GAF score, mean ± SD	41.1 ± 6.0	39.5 ± 5.9	NA	NA	$t_{151} = -2.04$	.04

[a]$P < .05$ vs ADHD. [b]$P < .05$ vs control. [c]Values are based on the numbers of subjects for whom data were available (for BPD-I, n = 74; for BPD-I + ASD, n = 34).

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorders, BPD-I = bipolar I disorder without autism spectrum disorder, BPD-I + ASD = bipolar I disorder and comorbid autism spectrum disorder, GAF = Global Assessment of Functioning, NA = not applicable, SES = socioeconomic status (5-point Hollingshead scale).

Figure 1. Mania Symptom Profile



Abbreviations: BPD-I= bipolar I disorder without autism spectrum disorder, BPD-I + ASD = bipolar I disorder and comorbid autism spectrum disorder.

psychiatric hospitalization compared to ADHD and control groups (Figure 3D).

Familial Risk Analysis

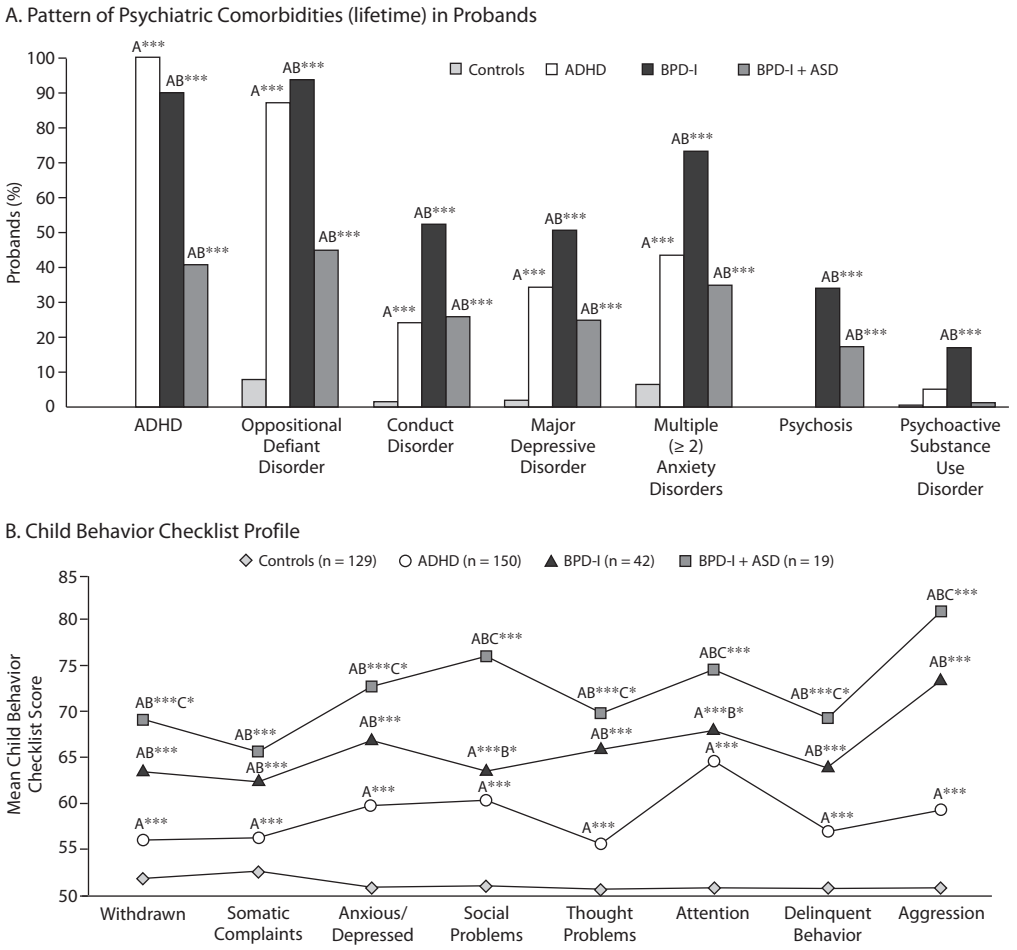
As shown in Figure 4A, familial risk analysis revealed similar familial risk for bipolar I disorder in first-degree relatives of bipolar I probands, irrespective of the comorbidity with ASD. These risks were significantly higher than those observed in relatives of ADHD and control probands.

Bipolar I disorder was significantly associated with familial psychosis, irrespective of comorbidity with ASD (Figure 4B). BPD-I + ASD was not significantly associated with any other familial disorders beyond the risk already conferred by bipolar I disorder.

DISCUSSION

This study conducted a systematic assessment of phenotypic and familial correlates of bipolar I disorder in youth with and without ASD to investigate whether presentation of mania in youth with comorbid ASD truly represents bipolar disorder. Findings revealed that the phenotypic features of bipolar I disorder were largely similar in youth with bipolar I disorder irrespective of comorbidity with ASD. Familial risk analysis revealed that the risk of bipolar I disorder in

Figure 2. Patterns of Psychopathology in Probands[a]



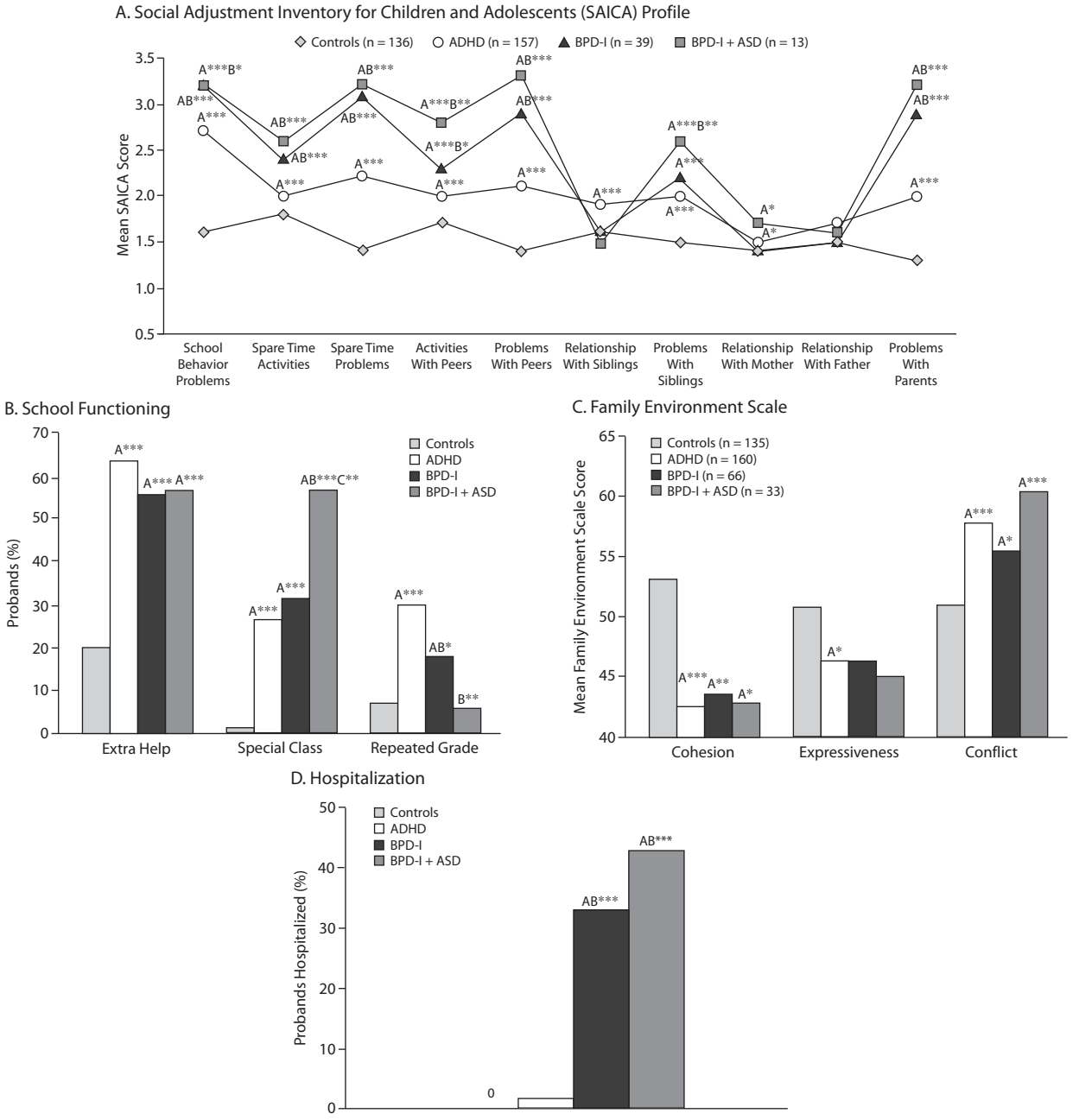
[a]A = vs controls, B = vs ADHD, C = vs BPD-I.
*$P < .05$, **$P < .01$, ***$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BPD-I = bipolar I disorder without autism spectrum disorder, BPD-I + ASD = bipolar I disorder and comorbid autism spectrum disorder.

first-degree relatives was equally high in relatives of bipolar I probands regardless of comorbidity with ASD. These results provide support for the hypothesis that the presentation of bipolar I disorder in youth with ASD is consistent with the typical presentation of bipolar disorder in pediatric populations. These results also indicate that youth with ASD who meet the symptomatic threshold for the diagnosis of bipolar disorder also present with familial and other clinical correlates typical of pediatric bipolar disorder and thus may benefit from established therapeutic approaches for this disorder.

With few exceptions, a striking similarity in the clinical features of mania was observed in youth with bipolar I disorder irrespective of the comorbidity with ASD. Among both bipolar proband groups, the symptomatic picture of mania was characterized by predominantly irritable mood, long duration, and a highly episodic course, with mixed symptoms and severe impairment. The few exceptions noted were that in the presence of ASD, youth with bipolar I disorder experienced mania at an earlier age and more often with grandiosity. In a previous study on this subject, a clinically referred population of youth with bipolar disorder had an earlier age at onset of mania in the context of comorbidity with ASD (4.9 ± 3.8 vs 6.4 ± 4.6 years [not statistically significant]) similar to the age at onset reported in the present study (4.7 ± 2.9 vs 6.3 ± 3.7 years).[11] In the present study, grandiosity was the only feature that occurred at a higher rate in the comorbid cases versus those cases of bipolar disorder without ASD. This observation raises questions about the unique quality of grandiosity in individuals with ASD as well as the utility of grandiosity as a cardinal symptom of mania (ie, might it occur in autistic individuals without bipolar disorder in some form?). An area of future research could address the quality and quantity of grandiosity in individuals with ASD, with bipolar disorder and ASD, and with bipolar disorder without ASD.

From a clinical perspective, sometimes bipolar symptoms are more notable and disruptive, and the intensity of the presentation of mood dysregulation masks the PDD-NOS. For example, consider the case of an 8-year-old boy who was psychiatrically hospitalized 6 times since age 5 for aggressive outbursts toward his parents and younger sibling. These

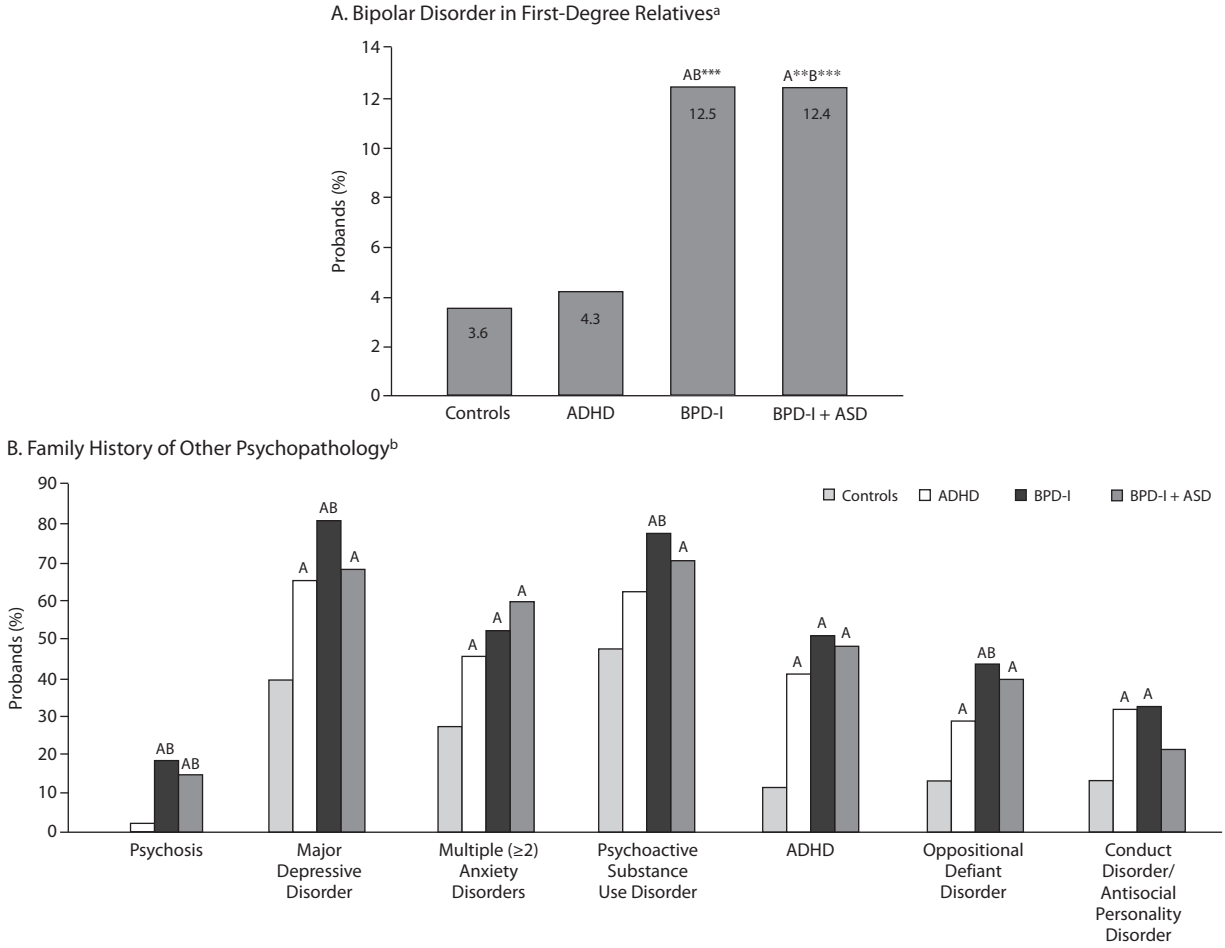
Figure 3. Patterns of Associated Dysfunction[a]



[a]A = vs controls, B = vs ADHD, C = vs BPD-I.
*$P < .05$, **$P < .01$, ***$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BPD-I = bipolar I disorder without autism spectrum disorder, BPD-I + ASD = bipolar I disorder and comorbid autism spectrum disorder.

outbursts of anger were more frequent and intense during periods associated with marked irritability, excessive energy, increased talkativeness, laughing fits, inappropriate sexual touching (of self and others), and demanding and disruptive behavior. While sometimes he was able to weather transitions and disappointments, other times small precipitants would result in loud complaining, threats, and hitting, kicking, and biting. During these times of increased irritability, he also developed a bouncing behavior, where he was unable to sit still and laughed loudly as he bounced in his chair. Parents also noted disinhibited people-seeking with giddy immature behavior and baby talk, which would often deteriorate into anger and crying. The boy would also cry and self-berate after an outburst, saying, "Why am I alive?" The frequency and intensity of these anger outbursts and mood swings worsened with age. During times of mood stability, the boy was socially awkward and isolated. He obsessed about collecting Pokémon cards and would watch the same cartoon recurrently, repeating favorite phrases. By the time he was 10 years old, medications led to longer periods of mood stability, and

Figure 4. Familial Risk Analysis in First-Degree Relatives



[a]A = vs controls, B = vs ADHD. *$P < .05$, **$P < .01$, ***$P < .001$.
[b]A = $P < .05$ vs controls, B = $P < .05$ vs ADHD.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BPD-I = bipolar I disorder without autism spectrum disorder, BPD-I + ASD = bipolar I disorder and comorbid autism spectrum disorder.

teachers and parents noted the boy's rigidity of thinking; his poor reading of social cues; his isolation from his peers, who found him odd; and the persistence of his immature interests as his peers became socially more sophisticated. He was diagnosed with PDD-NOS at age 11.

At other times, the patient is ascertained with a clear diagnosis of ASD and bipolar disorder develops or becomes apparent. Consider the case of a 12-year-old girl with above-average intellectual ability and a history of significant deficits in social interaction (poor nonverbal communication, poor social and emotional reciprocity, inability to share activities) and social communication (pedantic speech, scripting passages from Shakespeare's plays, tendency to engage in monologues on topic of interest—dinosaurs) who displayed restricted repetitive behaviors (restricted interest in dinosaurs, routine bound, transitional difficulties, occasional flapping and rocking). These symptoms were noted as autism in her earliest years of life. As she got older, she developed periods of mood dysregulation marked by irritability and anger outbursts, often triggered by transitional and social difficulties. Her parents had increasing difficulty managing her outbursts as they became more frequent, lasting over an hour, and as they involved more self-injurious and aggressive behaviors, such as hitting, kicking, and biting herself and others. During these periods of increased irritability and anger outbursts—lasting from weeks to a month—she slept for fewer hours each day, was restless, and paced, with increased flapping and scripting in pressured speech. Additionally, she began to disrobe in public and wander, making inappropriate sexual comments. During these phases, she had increased preoccupation with dinosaurs and playing piano; interrupting either activity would result in an extreme outburst of anger. In school, her intellectual and social performance worsened. She would disrupt the class by repeatedly asking questions and challenging and arguing with teachers, and she would be bossy and controlling with peers, leading to aggressive outbursts and suspensions. Along with these "increased energy–irritable" periods, she experienced lasting phases of increased sleep, lack of mood reactivity, amotivation in pursuing her preferred activities, increased appetite, and marked social withdrawal.

The pattern of psychiatric comorbidity noted in bipolar I youth with ASD was highly consistent with patterns of comorbidity observed in youth with bipolar I disorder across many sites.[7,37,38] These include high rates of comorbidity with major depressive disorder, ADHD, oppositional defiant disorder, conduct disorder, and anxiety disorders. Although not statistically significant, the risk for PSUD was lower in the presence of comorbid ASD in youth with bipolar I disorder. This result is consistent with our previous report[39] documenting significantly lower rates of PSUD in youth with ASD than in other psychiatrically referred populations.

Consistent with the psychiatric comorbidity are the findings on the CBCL. Parents reported significantly worse behavioral problems across all CBCL clinical subscales in youth with bipolar I disorder with and without comorbid ASD than in youth with ADHD and in controls. Furthermore, parents endorsed on the CBCL significantly worse behavioral difficulties in bipolar I youth in the presence of ASD, suggesting that ASD complicates the already compromised course of youth with bipolar I disorder. These findings are consistent with those from a previous study[11] that reported a similar pattern of emotional problems on the CBCL in a psychiatrically referred population of youth with comorbid bipolar disorder and ASD.

Also consistent with the extant literature[40] on pediatric bipolar disorder are the findings documenting high levels of impairment in interpersonal functioning as assessed through parent report on the SAICA in youth with bipolar I disorder independent of comorbidity with ASD. These results document that youth with bipolar I disorder with and without comorbid ASD had significantly more impaired interpersonal relationships with peers, siblings, and parents at home and in school than youth with ADHD and controls. Other indices of psychosocial functioning also suggested a similar pattern of poor functioning among youth with bipolar I disorder with and without comorbid ASD. Significantly more youth with bipolar I disorder, irrespective of comorbidity with ASD, required psychiatric hospitalization than youth with ADHD or healthy controls. These findings are consistent with previous reports of very impaired interpersonal functioning and high rates of psychiatric hospitalization in youth with bipolar disorder.[40]

Although without distinguishing between the groups, the presence of bipolar I disorder as well as ASD exerted a severe toll on educational and family functions as assessed through the measures of repeated grades, placement in special classes, and need for tutoring and the more dysfunctional scores on the FES. It is noteworthy that, consistent with the severity of the comorbid picture, significantly more bipolar I youth with versus without ASD required placement in special classes.

Familial risk analyses revealed that, irrespective of the comorbidity with ASD, the presence of bipolar I disorder in the proband significantly increased the risk for bipolar I disorder in first-degree relatives compared with the risks in relatives of ADHD and control probands. Furthermore, the familial risk for bipolar disorder in first-degree relatives was almost identical in bipolar I probands with and without comorbidity with ASD. Additionally, bipolar I youth with and without comorbid ASD shared a substantially similar pattern of familial risk for other psychopathologies. Considering the well-documented familiality of pediatric bipolar disorder,[17,18] these findings provide compelling support for the hypothesis that bipolar disorder in the comorbid state with ASD represents a valid "nosologically true" disorder with a pattern of familial risk that is characteristically typical of the disorder.

Our findings should be considered in the context of some methodological limitations. Subjects in this study were ascertained for bipolar I disorder, and the diagnosis of ASD was an outcome from structured diagnostic interview information. Thus, this study did not employ full clinical evaluation of ASD or standardized assessments of ASD symptomatology. Also, all diagnoses of ASD in this study occurred in the context of bipolar disorder. Future studies would benefit from the inclusion of ASD-ascertained subjects, employing standardized diagnostic assessments, with and without bipolar disorder. Finally, because this sample was referred and primarily white, these results may not generalize to nonreferred children or to families of other ethnicities.

Despite these considerations, the similarities in phenotypic, functional, and familial correlates of bipolar disorder in youth satisfying *DSM-IV* diagnostic criteria for bipolar I disorder with and without comorbidity with ASD indicate that such youth are afflicted with phenotypically valid bipolar disorder. Although our findings require confirmation, they draw attention to the importance of clinicians' taking into consideration the possibility of comorbid bipolar disorder in ASD youth with mood dysregulation who meet diagnostic threshold for bipolar disorder and, upon recognition of this diagnosis, providing appropriate interventions specific to the disorder.

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Author contributions: **Dr Joshi:** data analysis/interpretation, drafting article, critical revision, and data collection. **Dr Biederman:** concept/design, critical revision, and approval of article. **Mr Petty:** statistics, drafting article, and critical revision. **Ms Goldin:** critical revision. **Ms Furtak:** critical revision. **Dr Wozniak:** concept/design, data analysis/interpretation, and critical revision.

Potential conflicts of interest: **Dr Joshi** currently receives research support from Forest and Duke University and is a coinvestigator for clinical trials sponsored by Schering-Plough, Shire, ElMindA, and US Department of Defense. In 2011, Dr Joshi received research support from Shire, Johnson & Johnson, Eli Lilly, Forest, Schering-Plough, ElMindA, and National Institute of Mental Health (NIMH). In previous years, Dr Joshi received research support from the following sources: Ethel DuPont Warren Fellowship Award (2005–2006), Pilot Research Award from the American Academy of Child and Adolescent Psychiatry (2005), NIMH (reviewer and member of the NIMH Editorial Board), McNeil Pediatrics (CME sponsored by SynerMed Communications), Bristol-Myers Squibb (site principal investigator [PI] for multicenter trial); and GlaxoSmithKline (site PI for multicenter trial); Shire (member of national advisory board) and was a subinvestigator for clinical trials sponsored by Shire, Johnson & Johnson, Pfizer, Merck, Cephalon, McNeil, Eli Lilly, Abbott, Novartis, Bristol-Myers Squibb, Organon, Otsuka, Takeda, and New River. **Dr Biederman** currently receives research support from ElMindA, Janssen, McNeil, Next Wave, and Shire. In 2011, Dr Biederman gave a single unpaid talk for Juste Pharmaceutical Spain and received honoraria from MGH Psychiatry Academy for a tuition-funded CME course. He also received an honorarium from Cambridge University Press for a chapter publication. In 2010, Dr Biederman received a speaker's fee from Fundación Dr. Manuel Camelo AC, provided single consultations for Shionogi

and Cipher, and received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course. In 2009, Dr Biederman received speaker's fees from Fundacion Areces, Medice, and the Spanish Child Psychiatry Association. In previous years, Dr Biederman received research support, consultation fees, or speaker's fees from Abbott, Alza, AstraZeneca, Bristol-Myers Squibb, Celltech, Cephalon, Eli Lilly, Esai, Forest, Glaxo, Gliatech, Janssen, McNeil, Merck, National Alliance for Research on Schizophrenia and Depression, National Institute on Drug Abuse, New River, National Institute of Child Health and Human Development, NIMH, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Prechter Foundation, Shire, Stanley Foundation, UCB, and Wyeth. In 2011–2012, **Dr Wozniak** received research support from Merck/Schering-Plough, McNeil, and Shire. In the past, she has received research support, consultation fees, or speaker's fees from Eli Lilly, Janssen, Johnson & Johnson, McNeil, Pfizer, and Shire. She is the author of the book *Is Your Child Bipolar?* published May 2008, Bantam Books. In 2011–2012, her spouse, John Winkelman, MD, PhD, received consultation fees from Pfizer, UCB, Zeo, and Sunovion for his role as consultant. He received research support from GlaxoSmithKline for his role as research study staff. In the past, he has received research support, consultation fees, or speaker's fees from Axon, Boehringer-Ingelheim, Covance, Cephalon, Eli Lilly, GlaxoSmithKline, Impax, Jazz, King, Luitpold, Novartis, Neurogen, Novadel, Pfizer, Sanofi-Aventis, Sepracor, Sunovion, Takeda, UCB (Schwarz), Wyeth, and Zeo.
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