

Neuropsychological factors differentiating treated children with pediatric bipolar disorder from those with attention-deficit/hyperactivity disorder

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To determine the specificity of suggested endophenotypes of pediatric bipolar disorder (PBD), the performance of 15 euthymic children with PBD was contrasted with that of 20 children with attention-deficit/hyperactivity disorder (ADHD), a population with reportedly similar executive dysfunction, and 18 children with both PBD and ADHD. Children with PBD and PBD+ADHD (ages 8 to 17) demonstrated higher intraindividual variability in reaction time, slower processing speed, and more sluggish motor preparedness than did children with ADHD. The findings support the contention that processing speed, intraindividual variability, and slower and more variable reaction time as interstimulus interval lengthens are likely specific endophenotypes of PBD.

Keywords: Pediatric bipolar disorder; Attention-deficit/hyperactivity disorder; Executive dysfunction; Endophenotypes; Neuropsychological testing; Continuous Performance Test.

INTRODUCTION

The investigation of the neurophysiologic and genetic bases for psychiatric disorders has been hampered, in part, by the heterogeneity of behavior and complaints represented by individuals carrying the same psychiatric diagnosis. There have been recent attempts to reduce this heterogeneity by determining phenotypic and endophenotypic traits of that disorder, thereby defining relatively homogeneous subpopulations of the target clinical population. A phenotype is any observable characteristic of an organism: such as its morphology, development, or biochemical or physiological properties. Phenotypes result from the expression of an organism's genes as well as the influence of environmental factors and possible interactions between the two (Johannsen, 1911). An endophenotype is a psychiatric construct and a special kind of biomarker, usually cognitive. The purpose of seeking an endophenotype is to allow one to group behavioral symptoms into more stable phenotypes

(Gottesman & Gould, 2003). To be considered a phenotype, the trait must be associated with the target clinical population, heritable, and relatively state independent.

The heterogeneity of clinical presentation is of particular significance in children with pediatric bipolar disorder (PBD). The complexities wrought by the overlap of symptoms with that of more commonly diagnosed childhood disorders and the multiplicity of differing aberrant behaviors demonstrated by the same individual over the course of the disorder (Faedda et al., 1995) have had a confounding effect on delineating a specific clinical syndrome. In an attempt to reduce the heterogeneity of symptoms within the bipolar population, a number of likely candidates have been offered as endophenotypes of PBD. It is important to note that finding cognitive differences between children with bipolar disorder and those of children without psychiatric disorder does not necessarily suggest that those cognitive differences represent an endophenotype for PBD. It is also possible that the poorer performance in children with bipolar disorder

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merely represents a general index of the presence or magnitude of psychopathology. However, finding differences in neuropsychological processes between children with pediatric bipolar disorder and a group of children with overlapping psychiatric symptomatology but different classification might offer the chance to determine specific pediatric bipolar endophenotypes rather than indices of general psychopathology. The literature indicates that there is high comorbidity in children with bipolar disorder with attention-deficit/hyperactivity disorder (ADHD; Geller et al., 1995; West, McElroy, Strakowski, Keck, & McConville, 1995; Wozniak, Biederman, Mundy, Menin, & Faraone, 1995). Therefore, determining differences in neuropsychological processes between these two clinical entities might allow one to detect those cognitive processes that might be specifically affected in pediatric bipolar disorder, rather than an index of general psychopathology, and, therefore, potentially good candidates for bipolar endophenotypes. A number of cognitive processes that may be specific to PBD have been offered to date.

Among the most commonly reported neuropsychological findings in children with PBD is a significantly higher Wechsler Intelligence Scale for Children (WISC) Verbal IQ (VIQ) than Performance IQ (PIQ). Decina et al. (1983) found a greater than 15-point discrepancy between VIQ and PIQ in children at high risk for PBD. Interestingly, this finding was greatest in the offspring of bipolar I parents than in the offspring of bipolar II parents. In this sample of high-risk children, those who were reported to exhibit expansive moods were found to be more likely to manifest this cognitive discrepancy, suggesting that this pattern might be a trait marker of a genetic predisposition to PBD. Kestenbaum (1979) and McDonough-Ryan et al. (2002) also found significant VIQ > PIQ discrepancies as well as psychomotor deficits in children at risk for PBD. This same pattern (VIQ > PIQ) is also the most commonly observed pattern in adult BPD patients (Flor-Henry, 1983; Flor-Henry, Yeudall, Koles, & Howarth, 1979; Sackheim, Decina, Epstein, Bruder, & Malitz, 1983). In contrast, the VIQ > PIQ finding is not a feature of ADHD (e.g., see Doyle et al., 2005; Jonsdottir, Bouma, Sergeant, & Scherder, 2006).

Dickstein et al. (2004) assessed 21 children and adolescents with PBD and 21 matched controls using the Cambridge Neuropsychological Test Automated Battery and found impairment on measures of attentional set-shifting and visuospatial memory. Performance on neuropsychological tests did not vary with manic symptomatology or ADHD comorbidity. Similarly, Doyle et al. (2005) assessed 57 children with PBD compared to 46 healthy controls and found that, after statistically controlling for ADHD, children with PBD demonstrated impairments on measures of sustained attention, working memory, and processing speed.

McClure et al. (2005) administered tests of verbal and nonverbal memory to 35 outpatients with PBD and 20 healthy controls and found the PBD patients to perform more poorly than controls on measures of verbal memory and learning and delayed facial recognition memory. Memory disturbance was greater in those PBD patients with comorbid ADHD. Previously, we (Mattis & Papa-

los, 2003) conducted a prospective neuropsychological study of 21 children with PBD. This sample of children with PBD were symptomatic and demonstrated the following: a significant discrepancy between their WISC-III Verbal and Performance IQs (VIQ > PIQ); academic achievement (Wide Range Achievement Test-Third Edition, WRAT-3) that was within the average range, but poorer than expected based on Verbal IQ; language functioning that was within the average range but significantly lower than WISC-III Verbal Comprehension Index and Verbal IQ; abnormal Conners' Continuous Performance Test (CPT) performance characterized by slow and variable reaction time, a markedly conservative response bias, a slower and more variable reaction time as interstimulus interval lengthened; and significant deficits in executive processes, especially on tasks requiring motor-executive skills.

While the literature indicates that children with PBD perform more poorly than children without psychiatric or learning disorders on neuropsychological measures, there is evidence that, when treated and euthymic, children with PBD persist in demonstrating deficits in neuropsychological functions. Pavuluri et al. (2006) compared unmedicated manic pediatric PBD patients and medicated euthymic pediatric PBD cases to healthy controls and found impairments in attention, executive functioning, working memory, and verbal learning, regardless of medication and illness status. Again, deficits in attention and executive function were greater in PBD participants with comorbid ADHD. Pavuluri and colleagues suggest that the impairments they identified may be state-independent characteristics of PBD. The presence of impairments in attention, memory, and executive functions independent of mood state was also observed in adults with BPD by Martinez-Aran et al. (2004) and Joffe, MacDonald, and Kutcher (1988) who compared neuropsychological functioning in severely depressed, hypomanic or manic, and euthymic bipolar patients. Recently, Singh, DelBello, Fleck, Shear, and Strakowski (2009) using a flanker task with euthymic children with PBD, children at risk for PBD, and healthy controls highlighted intraindividual variability as a trait feature of PBD, and Brotman, Rooney, Skup, Pine, and Leibenluft (2009) using a stop signal task with children with nonmanic mood disorders, but at risk for bipolar disorder, submitted impulsivity as a probable trait marker.

In contrast to the literature indicating only limited effects of medication on improvement of neuropsychological processes in children with PBD, there is evidence that children with ADHD frequently, albeit not consistently, present with disorders in executive functions and that these impairments may improve with stimulant treatment (Hood, Baird, Rankin, & Isaacs, 2005; Kempton et al., 1999). However, no specific neuropsychological finding or cluster of findings have been consistently reported in children with ADHD (Doyle, 2006; Jonsdottir et al., 2006), and improvement in neuropsychological functioning with medication has not been consistently demonstrated (Everett, Thomas, Cote, Levesque, & Michaud, 1991; Gualtieri & Johnson, 2008; Rhodes, Coghill, & Matthews, 2006).

Because of the high comorbidity of PBD and ADHD, it is difficult to differentiate the findings that are specific to each disorder. Indeed, Faraone, Biederman, Mennin, and Russel (1998) suggested that children with both ADHD and PBD are familialy distinct from children with ADHD alone. Tillman and Geller (2006), in a prospective study of children with ADHD, found that nearly 29% of this population converted to bipolar I disorder (BDI). Factors that did not predict this switch were BDI in first-degree relatives, antidepressants, psychosocial measures, and life events. Predictors were limited to early poor general functioning, paternal recurrent major depressive disorder, and less stimulant use. Cognitive measures were not included in this study. Meyer et al. (2004), using data from a prospective study of participants at risk for BD, found that 67% of those who met criteria for BD in early adulthood had shown impairment on the Wisconsin Card Sorting Test when they were assessed in adolescence. Many of the participants at risk for BD were diagnosed as having ADHD as children. Among those participants who were diagnosed as having ADHD as children, only those who did poorly on the WCST went on to develop bipolar disorder, suggesting that the executive dysfunction observed in ADHD may, in fact, be referable to their underlying bipolar disorder and not be unique to ADHD. Rucklidge (2006) compared neurocognitive functions in adolescents with ADHD, ADHD + PBD, PBD, and healthy controls. The children with ADHD were unmedicated. In this study, the ADHD group and ADHD + PBD groups were most impaired. The children with only PBD did not differ from the healthy control group except for working memory. Rucklidge, in contrast to the conclusions of Meyer et al. (2004) and Jonsdotter et al. (2006), concluded that the adolescents with PBD did not exhibit broad neurocognitive deficits. Only those that had comorbid ADHD showed cognitive deficits, which strongly suggested that cognitive deficits in PBD are due to the presence of comorbid ADHD. Similarly, Henin et al. (2007) studied children and adolescents who were unmedicated, classified as having ADHD and PBD, ADHD without PBD, and without either ADHD or PBD. They report that the children with both ADHD and PBD did not perform differently than those with ADHD on a wide battery of neuropsychological measures, except for one measure of processing speed, and also concluded that the comorbidity of ADHD may account for many of the findings in children with PBD.

Dickstein et al. (2005) found differences between PBD and ADHD groups on a neurologic examination for soft signs. They concluded that the poor performance on repetitive motor tasks in children with ADHD reflected a core deficit of fronto-striatal neurocircuitry, whereas the poor performance on timed sequential motor movements in children with PBD reflected impaired attentional set-shifting and reversal learning—that is, frontal executive dysfunction.

Examination of the neuropsychological presentations of these three clinical groups (PBD + ADHD, PBD, and ADHD), when medicated, offers an excellent opportunity to determine the state-independent neuropsychological

profiles of each group, which may contribute to the delineation of trait markers for each disorder. Moreover, on a practical level, clinicians are often asked to examine a child who, although treated and seemingly euthymic and/or behaviorally attentive, still presents with learning and behavioral problems.

The primary aim of the present study was to determine whether or not neuropsychological findings in treated children with PBD who are euthymic are relatively specific to PBD when compared to treated children with ADHD who are attentive. Based on the literature concerning cognitive function in unmedicated and medicated children with PBD and those with ADHD, it was hypothesized that, in general, on measures of neuropsychological functioning, children with comorbid PBD and ADHD would perform more poorly than children with only PBD or ADHD and that children with PBD would perform more poorly than children with ADHD. Specifically, review of the neuropsychological findings in PBD suggests that such children, when euthymic, are likely to persist in demonstrating a WISC VIQ > PIQ, relative impairments in sustained attention (particularly in the relationship of reaction time to length of interstimulus interval), higher variability in reaction time, poorer verbal and nonverbal memory, slower motor speed, and more extensive executive dysfunction (especially set flexibility, fluency, and motor executive processes).

METHOD

Ascertainment

Participants with PBD were ascertained for study participation through the Juvenile Bipolar Research Foundation (JBRF) web-based data acquisition program. The JBRF has archived data on 5,120 children aged 5–17 years old whose parents and primary caregivers have entered clinical and demographic data to a secure domain on the JBRF website. Of these, 3,430 (66.9%) have been assigned a *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV*; American Psychiatric Association, 1994) diagnosis of PBD by a clinician in their community.

Participants with ADHD only were ascertained via referrals from the Child Attention-Deficit/Hyperactivity Disorder (CHADD) website and from local neurology practices.

Initial screening and diagnostic confirmation

The instrument used in initial screening of all participants was the Child Bipolar Questionnaire (CBQ; Papolos, Hennen, Cockerham, Thode, & Youngstrom, 2006), a parent-report questionnaire composed of 65 items drawn from *DSM-IV* symptom criteria for mania, major depression, and common comorbid conditions, rated on a Likert scale: “1” (“never”), “2” (“sometimes”), “3” (“often”), or “4” (“very often or almost constantly”). Devised as a rapid screener to aid in identifying homogeneous subgroups for research studies, the CBQ is a lifetime measure with a core index subscale of symptom dimensions fre-

quently reported in pediatric PBD and scoring algorithms for *DSM-IV* PBD, with and without ADHD. The CBQ total score is a count of all items rated “3” (“often”) or “4” (“very often or almost constantly”). Participants are considered initially eligible for participation in JBRF-sponsored studies of pediatric PBD if they scored ≥ 40 out of 65 items on the CBQ. The mean CBQ score for the PBD study group was 56.2. The mean score for the ADHD study group was 37.5. Final eligibility for each study group was determined by diagnostic classification of PBD or ADHD using the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Version (K-SADS P/L; Kaufman et al., 1997), administered by graduate-level interviewers. Children were excluded who demonstrated neurologic impairment or medical disorders affecting cognition or mood, and those that had IQ scores less than 80.

Diagnostic confirmation

The K-SADS P/L was administered independently to both parents and children. For each participant, information was gathered regarding ages of onset and offset, number of episodes, and treatment history. One child who met initial eligibility for the ADHD group was diagnosed, upon interview, with depressive disorder not otherwise specified (NOS) and was deemed ineligible. A total of 9 of the children who screened positive for PBD were diagnosed with bipolar I disorder and the remainder with bipolar disorder not otherwise specified (BP-NOS). All of the children diagnosed with BP-NOS met full *DSM-IV* symptom criteria for a manic episode, but due to rapidly alternating moods, failed to satisfy the minimum episode duration criterion. A total of 14 of the 33 participants in the PBD group were diagnosed with comorbid ADHD (42.4%), a rate consistent with the findings of prior systematic studies (Geller et al., 1995; West et al., 1995; Wozniak et al., 1995).

Medication and psychiatric status at time of neuropsychological testing

All children were in treatment and were assessed while in a euthymic state. All children were initially referred to the collaborating physicians as outpatients in a clinically acute state that required immediate treatment, and the treatment was effective. The decision to assess all children while medicated was informed by two factors. Ethical consideration precluded the decision to discontinue medications that successfully controlled psychotic and suicidal behavior and thoughts. The decision to assess the children in a euthymic state was further bolstered by the literature that the neuropsychological findings in adults and children with bipolar disorder are not appreciably changed with effective treatment.

No assessment of the affective state of the child was made at the time of testing. It should be noted, however, that each child was referred for testing by their physician when their physician judged them to be medically stable

and euthymic. The neuropsychological procedures (see below) required the child to be engaged for five consecutive hours, not counting transportation to and from the office, on two separate days. During the examination all of the children were judged to be euthymic and attentive by the examiner and supervising neuropsychologist—that is, no mood or behavioral disturbance or mood alteration was observed. One of the PBD participants was undergoing a medication change, and the decision was made to delay testing until this child stabilized on the new medication. All of the children with PBD and all but 2 of the children in the ADHD group were treated with medication at the time of neuropsychological testing. Medication type and dosage level were not controlled. A combination of mood stabilizers and antipsychotics were the predominant psychopharmacological treatment for children diagnosed with PBD, including those in the PBD+ADHD group. The mood stabilizers included lithium salts, carbamazepine, oxcarbamazepine, and sodium valproate. The antipsychotics included risperidone, quetiapine, and aripiprazole. A total of 3 of the children with PBD+ADHD were also being treated with methylphenidate for ADHD. The children with ADHD were treated with the stimulants methylphenidate and atomoxetine.

The effects of medication

To assess the effects of medication on our findings, a metric was developed to quantify the impact of medication on performance. In general, the medications were offered in sequential order, starting with a mood stabilizer, then antipsychotic, stimulant, and anxiolytic. In the ADHD population, those with mood disorders were excluded, and medication was limited to long-acting and/or short-acting stimulants. The dosages (mg/kg) within each class of drugs did not differ substantially across children. Following the procedure described by Strakowski et al. (2009), we used the total number of different psychotropic medications the participant was taking at the time of testing as our medication metric. This metric ranged from 1 to 5.

Sample

The study groups consisted of 20 children and adolescents who met *DSM-IV* criteria for attention-deficit/hyperactivity disorder—combined type (ADHD), but who did not meet criteria for PBD, and 33 children who met *DSM-IV* criteria for bipolar disorder, inclusive of bipolar I disorder (BPI) and bipolar disorder not otherwise specified (BP-NOS). As is common in samples of children with pediatric PBD, 17 children (approximately 52% of the PBD group) presented with comorbid attention-deficit/hyperactivity disorder—combined type (ADHD). We thus had three groups—that is, 15 children with bipolar disorder, 20 children with ADHD, and 18 children who met criteria for both PBD and ADHD. All children were between the ages of 7 and 15 and had WISC-IV Full Scale IQ scores equal to or greater than 80.

Neuropsychological testing procedure

Each child was tested on two separate days, a week apart, for five hours each day, paced by breaks for lunch and when deemed clinically necessary.

The following tests, frequently used in the study of children with mood and attentional disorders, were administered:

General intellectual ability: WISC-IV (Wechsler, 1991).

Academic achievement: Wide Range Achievement Test-Third Edition (WRAT-3; Wilkinson, 1993); Test of Written Language-Third Edition (TOWL-3; Hammill & Larsen, 1996); Passage Comprehension (Woodcock-Johnson III Achievement Tests; Woodcock, McGrew, & Mather, 2001).

Attention: Conners' Continuous Performance Test II (Conners & MHS Staff, 2000).

Memory: California Verbal Learning Test for Children (CVLT-C; Delis, Kramer, Kaplan, Ober, & Fridlund, 1994); Benton Test of Visual Retention, Administration A (Benton, 1972).

Language: Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983); Spreen-Benton Token Test (Spreen & Strauss, 1998); Spreen-Benton Sentence Repetition Test (Spreen & Strauss, 1998); assessment of buccal-lingual praxis (Blakely, 1980); sound blending (Illinois Test of Psycholinguistic Abilities, ITPA; Kirk, McCarthy, & Kirk, 1968).

Executive skills: Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, and Tower subtests of the Delis-Kaplan Executive Functions (D-KEFS; Delis et al., 1994); Wisconsin Card

Sorting Test (WCST; Heaton & PAR Staff, 1999); Luria Assessment of Praxis (Luria, 1966).

Motor skills: Graphomotor Examination (Jantzen & Mattis, 1986); Purdue Pegboard (Spreen & Strauss, 1998); Halstead-Reitan Finger Tapping Test (Spreen & Strauss, 1998).

Data analysis

Comparisons of each of the neuropsychological tests among PBD, PBD + ADHD, and ADHD groups were performed using three-way analysis of variance (ANOVA), with adjustments to the degrees of freedom for nonhomogeneity of variance, when appropriate, and Bonferroni adjustment for multiple comparisons. After Bonferroni correction, significant factors are considered those that have a p -value $< .01$. Tukey b was used for post hoc comparisons.

RESULTS

Table 1 summarizes the psychoeducational data characterizing the three groups. The data are expressed as z scores.

General intellectual abilities

The WISC-IV does not generate a Verbal or Performance IQ. The early studies using the WISC-III demonstrated a consistent Verbal/Performance IQ discrepancy. Presently, using the WISC-IV, no differences were found among the groups on their Verbal Comprehension

TABLE 1
Psychoeducational measures

Measure		Bipolar + ADHD ($n = 18$)	Bipolar ($n = 15$)	ADHD ($n = 20$)	Significance ^a
Age (years)		10.2 (2.3)	10.8 (2.7)	10.5 (2.5)	<i>ns</i>
Gender (% male)		61.1	60.0	65.0	<i>ns</i>
WISC-IV	Verbal Comprehension	0.3 (0.6)	0.7 (0.9)	0.8 (1.2)	<i>ns</i>
	Perceptive Reasoning	0.1 (0.8)	0.2 (0.9)	0.4 (1.0)	<i>ns</i>
	Working Memory	0.3 (0.8)	-0.2 (0.7)	0.4 (0.7)	.025
	Processing Speed	-0.9 (1.0)	-0.5 (1.1)	0.2 (0.7)	.002
	Full Scale IQ	-0.1 (0.7)	0.3 (0.9)	0.6 (1.0)	.032
WRAT-3	Reading	0.1 (0.9)	0.8 (0.6)	0.6 (0.7)	.009
	Spelling	0.4 (1.0)	0.2 (0.9)	0.5 (0.8)	<i>ns</i>
	Arithmetic	0.0 (0.8)	-0.3 (0.9)	0.3 (1.0)	<i>ns</i>
Woodcock-Johnson III	Passage Comprehension	-0.3 (0.7)	0.4 (0.8)	0.3 (1.0)	.017
	TOWL-3				
	Writing Conventions	-0.3 (1.2)	0.6 (0.8)	-0.3 (0.9)	<i>ns</i>
	Language	-0.3 (1.2)	0.4 (1.2)	0.3 (0.9)	<i>ns</i>
	Story Construction	0.0 (0.7)	0.5 (0.9)	0.5 (0.9)	<i>ns</i>

Note. ADHD = attention-deficit/hyperactivity disorder. WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition. WRAT-3 = Wide Range Achievement Test-Third Edition. TOWL-3 = Test of Written Language-Third Edition. Standard deviations in parentheses.

^aFor informational purposes, *ns* is reported for all variables with $p > .05$. After Bonferroni correction, significant factors are considered those that have a $p < .01$.

(VCI) and Perceptual Reasoning (PRI) composite indices, and no group demonstrated a significant difference between their VCI and PRI scores. The only significant difference between groups was found in Processing Speed. Children with ADHD were significantly faster than children with PBD or PBD+ADHD who did not differ from each other.

Academic achievement

Among the academic measures, single-word reading was significantly poorer in children with PBD + ADHD than in children with PBD or ADHD who did not differ from each other.

In brief, children with PBD and those with PBD + ADHD performed most poorly on the WISC-IV measure of processing speed, especially when a graphomotor component was a prominent requirement of the task. In this population, WRAT-3 single-word reading differentiated children with PBD + ADHD from those with PBD and ADHD.

Table 2 presents the neuropsychological performance of each group.

A total of 10 parameters demonstrated differences among the three groups using $p = .01$ to determine significance. A total of 6 of the measures were derived from the Conners' CPT—that is, Errors of Omission, Hit Reaction Time (RT) Standard Error, Variability, Hit RT Interstimulus Interval (ISI) Change, and Hit RT ISI Change Standard Error. The remaining 4 were derived from the D-KEFS—that is, Verbal Fluency: Letter and Category Fluency; Color Word Interference: Color Naming and Word Reading.

Post hoc comparisons indicate that children with ADHD performed better on the Continuous Performance Test measures than did children with PBD and PBD + ADHD who did not differ from each other. In contrast, on the D-KEFS measures, the PBD + ADHD group performed more poorly than the ADHD and PBD groups who did not differ from each other.

The effect of medication

Covarying by the medication metric did not alter the significance of any group or post hoc comparisons.

DISCUSSION

While the literature supports the contention that there are significant comorbid symptomologic features in clinically diagnosed children with PBD and ADHD, the present study suggests that, when treated, each clinical entity demonstrates relative differences in their pattern of neuropsychological strengths and weaknesses. Children with PBD and PBD + ADHD performed significantly worse on the WISC-IV Processing Speed Composite, CPT measures of Errors of Omission, Hit RT Standard Error, Variability, Hit RT ISI Change, and Hit Reaction Time ISI Change Standard Error than did

children with ADHD. Our findings of slow WISC-IV Processing Speed Index strongly suggest that slow processing speed may be a trait feature of pediatric bipolar disorder. Adult euthymic patients with bipolar I and bipolar II have slower processing speed than healthy controls but do not differ from each other (Dittmann et al., 2008). It should be noted that the Processing Speed Index contains two of the six subtests comprising the older WISC-III and Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Performance IQ. It is possible that the Verbal IQ > Performance IQ findings previously reported in PBD and adult BD may reflect the contribution of the Processing Speed subtests. In children with PBD, slowed visual-motor functioning has been associated with structural abnormalities in lower orbital frontal white matter (Kafantaris et al., 2009).

Our finding of greater intraindividual variability in children with PBD corroborates the findings of Singh et al. (2009). The fact that the findings are similar using a different continuous performance test, together with the observation that the intraindividual variability was greater than that found in children with ADHD supports the contention that intraindividual variability is a core feature of PBD. However, intraindividual variability may not be a general feature of PBD. Buzy, Medoff, and Schweitzer (2009) recently reported high intraindividual variability in working memory to be a feature of children with ADHD. It is likely that motor variability rather than general variability is the key feature of PBD.

In addition, reaction time and variability in reaction time as a function of interstimulus interval are not distinguishing features of the ADHD profile. To our knowledge, this is the first report indicating that reaction time is differentially longer and more variable as interstimulus interval lengthens in treated children with PBD compared to treated children with ADHD. The relationship between reaction time and variability of reaction time with interstimulus interval reflects a differential level of preparedness to respond in children with PBD (Francis, 1996; Silverstein, Weinstein, & Turnbull, 2004). When stimuli are presented at a relatively rapid rate, individuals become alerted and prepared for immediate response. As the interval between stimuli lengthens, there tends to be a general relaxation or reduction in tonic arousal, which reduces preparatory alertness and reduces the overall reaction time (Okazaki et al., 2004; Parsons & Bruhn, 1973). The children with PBD have an excessive reduction in arousal level or preparedness level as a function of lengthening interstimulus interval, as indicated by their increased reaction time as the interval between stimuli lengthens. It should be noted that the findings in this study were very similar to those observed in our pilot study with symptomatic children with PBD. The replication of our original findings increases our confidence in the inference that abnormally slow and variable reaction time as a function of longer interstimulus intervals is differentially present in children with PBD and may be a trait feature of pediatric bipolar disorder.

Deiber, Ibanez, Sadato, and Hallet (1996) in a positron emission tomography and regional cerebral blood flow study of healthy adults found that motor prepara-

TABLE 2
Comparison of neuropsychological tests between groups

Variable		Bipolar + ADHD (n = 18)	Bipolar (n = 15)	ADHD (n = 20)	p	
CPT-II	Omissions	1.1 (1.7)	0.5 (1.7)	-0.4 (0.6)	.005	
	Commissions	-0.2 (1.3)	-0.2 (1.1)	-0.3 (1.0)	ns	
	Hit RT	0.7 (1.4)	0.4 (1.3)	-0.4 (1.2)	.025	
	Hit RT SE	0.9 (1.2)	0.4(1.3)	-0.5 (0.9)	.001	
	Variability	0.6 (1.1)	0.2 (1.1)	-0.6 (0.9)	.004	
	Detectability (<i>d'</i>)	-0.1 (1.1)	0.0 (1.1)	0.0 (0.9)	ns	
	Response Style (B)	0.6 (1.5)	0.4 (1.0)	-0.2 (1.2)	.075	
	Perseverations	0.6 (1.7)	-0.1 (0.7)	-0.3 (0.3)	.031	
	RT Block Change	0.0 (0.8)	0.1(0.9)	0.0 (0.9)	ns	
	RT Block Change SE	-0.1 (0.8)	0.1 (1.0)	-0.1 (0.9)	ns	
	RT ISI Change	1.0 (1.4)	0.5 (1.1)	-0.4 (0.6)	<.001	
RT ISI Change SE	0.5 (1.0)	0.3 (0.8)	-0.4 (0.7)	.006		
California Verbal Learning Test	Total Trials	-0.6 (1.1)	-0.2 (1.8)	0.1 (1.0)	ns	
	Trial 1 Free Recall	-0.1 (1.1)	-0.1 (1.2)	-0.1 (0.8)	ns	
	Trial 5 Free Recall	-0.7 (1.1)	-0.2 (1.5)	0.1 (1.0)	ns	
	Short Delay Free Recall	-0.7 (1.0)	-0.5 (1.3)	0.3 (0.8)	.021	
	Short Delay Cued Recall	-0.7 (0.8)	-0.5 (1.4)	0.3 (1.1)	.023	
	Long Delay Free Recall	-0.7 (1.1)	-0.7 (1.2)	0.3 (1.0)	.013	
	Long Delay Cued Recall	-0.7 (0.9)	-0.4 (1.3)	0.1 (0.8)	.086	
	List B Free Recall	-0.1 (1.2)	-0.3 (0.6)	0.2 (1.1)	ns	
	Delayed Recognition Hits	-.03 (0.9)	0.0 (1.3)	0.5 (0.5)	.028	
	Discriminability	0.1 (0.8)	0.0 (1.4)	0.5 (0.8)	ns	
	Delayed False Positives	-0.6 (0.5)	-0.2 (1.2)	-0.4 (0.8)	ns	
	Response Bias	-0.8 (1.0)	-0.1 (1.1)	0.1 (0.9)	.023	
	Wisconsin Card Sorting Test	All parameters	ns			
Delis-Kaplan Executive Functions System	Trail Making	Visual Scanning	-0.4 (0.8)	0.0 (1.0)	0.1 (1.0)	ns
		Number Sequencing	-0.5 (1.4)	0.1 (0.8)	0.1 (1.1)	ns
		Letter Sequencing	-0.5 (1.1)	-0.2(0.7)	0.0 (1.2)	ns
		Number-Letter Switching	-0.6 (1.2)	-0.5(1.3)	-0.2 (1.3)	ns
		Motor Speed	0.1 (0.9)	0.1 (1.1)	0.2 (0.9)	ns
	Verbal Fluency	Letter Fluency	-06 (0.7)	0.3 (1.1)	0.7 (0.9)	<.001
		Category Fluency	-0.6 (0.8)	0.5 (1.2)	0.5 (1.2)	.004
		Switching No. Correct	-0.5 (0.9)	0.1 (1.3)	0.1 (1.1)	ns
	Design Fluency	Switching Accuracy	-0.1 (0.8)	0.4 (1.3)	0.5 (1.0)	ns
		Filled Dots	0.0 (0.9)	0.3 (1.1)	-0.3 (0.7)	ns
Color-Word Interference	Empty Dots	0.1 (1.1)	0.2 (1.1)	-0.1 (0.9)	ns	
	Switching	-0.1 (0.8)	0.1 (1.1)	-0.1 (1.0)	ns	
	Total Correct	0.2 (1.1)	0.4(1.1)	0.0 (0.8)	ns	
	Color Naming	-1.4 (1.3)	0.0 (1.1)	0.2 (1.0)	<.001	
	Word Reading	-1.0 (1.3)	0.2 (0.8)	0.3 (0.8)	<.001	
Tower	Color-Word Inhibition	-1.1 (1.3)	-0.3 (1.5)	-0.1 (1.1)	.06	
	Inhibition/Switching	-1.3 (1.4)	-0.6 (1.3)	-0.2 (1.1)	.04	
	Achievement	-0.4 (0.7)	-0.2 (0.8)	0.1 (0.9)	ns	
BVRT ^a	No. Correct	-0.2 (1.1)	0.1 (1.1)	0.1 (0.8)	ns	
	No. Errors	0.3 (1.3)	-0.2 (0.8)	-0.2 (0.8)	ns	

Note. ADHD = attention-deficit/hyperactivity disorder. CPT = Continuous Performance Test. BVRT = Benton Visual Retention Test. RT = reaction time. ISI = interstimulus interval. SE = standard error.

^aBVRT measures shown as *z* scores from the full sample mean: No. correct mean = 5.0 (2.6); No. errors mean = 7.3 (5.3).

tion was associated with increased regional blood flow in a common set of cerebral regions: the contralateral frontal cortex (sensorimotor, premotor, cingulate, and supplementary motor cortex), parietal association cortex, basal ganglia, thalamus, and ipsilateral cerebellum. The investigators noted that the same areas were activated in motor preparation independent of the movement

information conditions, strongly suggesting a single anatomic substrate for motor preparation. There is evidence using event-related potential paradigms that links preparatory processes with both developmental and pathological changes in dorsolateral prefrontal cortex (Jonkman, 2006; Okazaki et al., 2004; Rosahl & Knight, 1995). Impairment in these preparatory processes elicited

by manipulating the interstimulus interval may implicate abnormal functioning of dorsolateral prefrontal cortex in the etiology of pediatric PBD and/or the manifest symptoms of the disorder.

It should be noted that measures directly assessing impulsivity did not differ among the three groups. For example, the groups did not differ on CPT Errors of Commission, Inhibition, or Inhibition/Switching subtests of the Color-Word Interference Test. However, there have been findings that children at risk for bipolar disorder (Singh et al., 2009) and adults with BD (Gruber, Rathgeber, Braunig, & Gauggel, 2007; Strakowski et al., 2009) have longer stop signal reaction times than healthy controls and that this longer stop signal reaction time is considered to be a measure of impulsivity. Singh et al. (2009) contrasted the performance of adolescents with nonmanic mood disorder but with a family history that placed them at high risk for developing mania with the performance of adolescents without significant psychiatric disorder and with a negative family history of psychiatric illness. Both groups were given a Stop Signal Task, the Conners' Continuous Performance Test, and the Delis-Kaplan Color-Word Interference Test (CWIT). In the Stop Signal Task, the participant is asked to respond when a signal is presented but is to stop the response when a subsequent signal is introduced. The interval between the onset of the go signal and the onset of the stop signal is varied until the probability of responding after the stop signal is 50%. The measure of interest is the stop signal reaction time, which is defined as the mean go reaction time minus the time interval between the go signal onset and the final stop signal onset. The authors submit that stop signal reaction time lengthens with impulsivity and represents a failure to inhibit a motor response in the presence of a stop signal. In the Singh et al. study, the clinical group, compared to the control group, showed longer stop signal reaction time reflecting greater motor disinhibition. On the CWIT, the clinical group showed slower color naming than the control group but did not demonstrate differences in word reading, inhibition, or inhibition/switching scores. Based primarily on results of the Stop Signal Task, the authors conclude that psychomotor disinhibition may be a trait-related deficit in bipolar disorder.

While stop signal performance may be a trait feature of bipolar disorder, it would appear to measure a different aspect of impulsivity than that assessed by the CPT or CWIT inhibition and inhibition/switching subtests. Strakowski et al. (2009) noted that in symptomatic manic adults, stop signal performance reaction time correlated only modestly ($r = -.34, p = .02$) with their CPT measure of vigilance (A'); however, they do not note the correlation between stop signal reaction time and errors of commission. A measure of ability to delay gratification had little correlation with either the stop signal or CPT parameters. It is reasonable to assume that in the euthymic child with PBD differing measures of impulsivity may have differing sensitivities. However, it is also possible that stop signal reaction time measures another aspect of motor preparedness. That is, it is possible that as one varies the stop signal latency to obtain a duration that results in a 50% probability of failure to stop a response, one is also

lengthening the interval between the go signal and stop signal and bringing to bear the longer reaction time that children with PBD evidence as the interval between stimuli lengthens. In those studies, in which both a stop signal and CPT paradigms are used, it would be interesting to note the relationship between interstimulus interval parameters and those of stop signal latency.

The D-KEFS measures that significantly differentiated the PBD + ADHD group from the ADHD and PBD groups are all rapid naming measures. On these measures, the PBD + ADHD group performed significantly more poorly than either the ADHD or PBD groups. The latter two groups were indistinguishable from each other. The timed verbal tasks, especially the Color Naming and Word Reading subtests of the D-KEFS Color-Word Interference Test, are very similar to the tasks devised by Denckla and Rudel (1976), which they termed "rapid automatized naming" (RAN). In their study, RAN deficiencies were strongly associated with reading difficulties, directly affecting initial decoding. In our study, the PBD + ADHD group demonstrated significantly more difficulty on verbal fluency and rapid naming than did either of the other two groups. The PBD + ADHD group also demonstrated the poorest reading score. Performance on rapid naming tasks is associated with the relative integrity of orbital frontal and anterior cingulate cortex (Broome et al., 2009; Whitney, Weis, Krings, Huber, & Kircher, 2008). Biederman et al. (2008) note that patients with bipolar disorder demonstrate a smaller orbital frontal cortex and larger right thalamus. Patients with ADHD have smaller frontal volume, a smaller right anterior cingulate gyrus, and less cerebellar grey matter. Patients with both ADHD and BD show both morphological features. It seems reasonable to assume that the rapid naming deficiency observed in children with PBD + ADHD reflects this population's atypical morphology in both orbital frontal cortex and anterior cingulate gyrus.

In this study, there was a clear distinction between the performance levels of the PBD + ADHD, PBD, and the ADHD groups. The ADHD group performed best, the PBD + ADHD group performed worst, and the PBD group was in the middle, sometimes aligned with the children with PBD + ADHD and sometimes with those with ADHD. The findings corroborate previous studies indicating that children with comorbid PBD and ADHD tend to perform more poorly than children with ADHD or PBD alone (e.g., Biederman et al., 2008; McClure et al., 2005). The primary inference is that the poorer performance of the PBD + ADHD children reflects the greater cortical and subcortical impairment of this group. However, an arguable contention is that the poorer performance of the PBD + ADHD children may be due to the fact that the children in the PBD + ADHD group were not given specific medication to treat ADHD symptomatology. Therefore the possibility arises that the unmedicated ADHD symptomatology rather than greater neuropathology may be the factor contributing to their poorer performance. This argument rests on the assumption that the children with PBD + ADHD were not treated for their ADHD symptoms and complaints. In general children with PBD + ADHD are given mood stabilizers, then atyp-

ical antipsychotics. Only when the first two classes are insufficient to modulate the mood and ADHD symptomatology do most clinicians add a stimulant (McClellan, Kowatch, Findling, & Work Group on Quality Issues, 2007; Nandagopal, DelBello, & Kowatch, 2009). Potter et al. (2009) report that in children with comorbid PBD and ADHD, atypical psychotics alone treat the ADHD symptoms in 56% of the patients studied. In addition, 3 of the 18 PBD + ADHD children had received stimulants. In sum, it is reasonable to assume that most, if not all, of the PBD + ADHD children received treatment for their ADHD symptomatology. However, the lack of a full description of the mood and behavioral status of the children at the time of testing is a weakness in this study and leaves open the question as to mechanism underlying the relatively poor performance of the PBD + ADHD group.

In this study, ADHD children without mood disorders performed at higher levels than the other two groups and did not present an atypical distribution of WISC-III composite scores, academic achievement difficulties, attention abnormalities, memory difficulties, executive function disorders, or abnormal fine motor dexterity. It is possible that comparison to a control group without either a mood or attention disorder would have revealed the attentional and executive disorders frequently observed in the ADHD population. However, it is also possible, as suggested by the findings of Meyer et al. (2004), Jonsdottir et al. (2006), and Doyle (2006) that the untreated comorbid affective disorders often present in the ADHD population account for the differing and inconsistent findings of executive deficits found in multiple studies of children with ADHD.

Covarying number of medications that a child was taking did not alter the significance of our results. The lack of relationship between medication and measures of impulsivity was also found by Strakowski et al. (2009) in their study of symptomatic adult manic patients. The authors reported that the total number of medications taken was related only to the vigilance measure of their CPT (A'). No other measure of impulsivity was correlated with total number of medications taken. In our study, the vigilance measure (d') did not differ among the groups. Brotman et al. (2009) were able to divide their total population into smaller groups of children taking a given medication and compared their performance with those who were not. Brotman et al. also found that medication did not affect the significance of the high variability in reaction time found in euthymic children with PBD and children at risk for bipolar disorder as compared to healthy controls. Our small number of children in each group did not allow us to make such comparisons with any reasonable degree of power.

Recently, Henin et al. (2009) reported that children with bipolar disorder taking mood stabilizers performed more poorly on measures of processing speed and working memory than did unmedicated children with bipolar disorder. Treatment with other medications, including atypical antipsychotics, did not affect performance on other neuropsychological measures. The specific measures affected in the Henin et al. study were the Symbol Search subtest of the WISC-III, but not the Coding subtest, and the Color Naming and Word Reading sub-

tests of the D-KEFS Color-Word Interference Test (CWIT). In our study, the Processing Speed Index of the WISC-IV was performed more poorly by children with PBD and PBD + ADHD than by children with ADHD. A post hoc analysis indicated that the WISC-IV Symbol Search subtest was performed more poorly by both PBD groups than by the ADHD group, supporting an inference that mood stabilizers may have contributed to their poorer performance. However, in our study, the Color Naming and Word Reading subtests of the CWIT were performed more poorly by the children with PBD + ADHD than by children with only PBD or ADHD. The children with PBD or ADHD did not differ from each other. Mood stabilizers were taken by both groups of children with PBD. Thus, mood stabilizers did not appear to be a significant factor contributing to the performance on the CWIT measures. Therefore, while it is possible that mood stabilizers affect processing speed and verbal fluency, it is also possible that in Henin et al.'s study the medicated children with PBD had a higher proportion of comorbid ADHD than did the unmedicated children with PBD, and it was the greater anatomic abnormality of the medicated PBD group rather than the presence of mood stabilizers that accounted for the differences between medicated and unmedicated children. Nonetheless, the present study does not directly address the contribution of medication effects on neuropsychological processes in children with PBD, and the question bears further study.

A number of weaknesses in the study have been noted that constrain the interpretation of the findings. The three major considerations are (a) the small number of children within each group, which precluded a more systematic study of the effects of medication on performance and decreased the power available to detect group differences, (b) the absence of a contrast group of children without psychiatric disturbance, which limited the interpretation of the seemingly adequate performance of the children with ADHD, and (c) the lack of an assessment of mood and behavior of the children at the time of testing to support the contention of a euthymic and attentive state.

In this study, our hypotheses concerning the relative performance of the three clinical groups was largely supported. Children with ADHD performed well on all neuropsychological measures compared to children with PBD. Children with both PBD and ADHD performed more poorly than children with PBD or ADHD and were statistically poorer on measures of fluency, rapid automatized naming, and single-word reading. Children with PBD, when euthymic, compared to treated children with ADHD, performed more poorly on the WISC-IV measure of processing speed, measures of response preparedness, and intraindividual variability on a reaction time task. It is submitted that slowed processing speed, response preparedness—that is, slower and more variable reaction time as the interval between stimuli lengthens—and intraindividual variability are good candidates for trait features of pediatric bipolar disorder.

The practical implications of these findings are somewhat different for appropriately treated children with PBD, including those with concomitant ADHD, than for

those with ADHD but without mood disorder. Treated children with PBD demonstrate a significant diminution of mood-related behavioral disorders; however, they persist in their cognitive disorder—that is, relatively poor processing speed and poor preparedness to respond—which results in atypical behavior both in school and at home, which requires additional psychotherapeutic and special educational treatment. Those children with both PBD and ADHD, even when treated, appear to show additional difficulty with verbal fluency when compared to children with PBD, which results in the development of effortful and inefficient decoding. Thus, it would seem prudent to evaluate children with PBD+ADHD for the presence of disorders in the acquisition of reading and other academic difficulties and to assess the necessity of school-based programs to enhance phonic awareness and decoding, even when the children are behaviorally relatively quiescent. Children with ADHD who are treated, yet persist in demonstrating cognitive deficiencies, should be considered for further evaluation of mood disorder.

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