Neurologic Examination Abnormalities in Children with Bipolar Disorder or Attention-Deficit/Hyperactivity Disorder

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Background: *Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) are frequently comorbid and overlapping diagnoses. To move beyond diagnosis toward unique pathophysiology, we evaluated both ADHD and BPD children for neurologic examination abnormalities (NEAs) in comparison with normal control (NC) children.*

Methods: *We performed the Revised Physical and Neurological Examination for Soft Signs in three groups (ADHD, BPD, NC). Then, a rater blind to diagnosis evaluated their motor performance. Results were analyzed with a multiple analysis of covariance.*

Results: *Subjects with ADHD were impaired on repetitive task reaction time. In contrast, pediatric BPD subjects, both with and without comorbid ADHD, were impaired on sequential task reaction time.*

Conclusions: *This differential pattern of NEAs by diagnosis suggests pathophysiologic differences between ADHD and BPD in children. Repetitive motor performance requires inhibition of nonrelevant movements; ADHD subjects' impairment in this domain supports the hypothesis that ADHD involves a core deficit of fronto–striato–basal ganglia neurocircuitry. In contrast, BPD subjects' impaired sequential motor performance is consistent with behavioral data showing impaired attentional set-shifting and reversal learning in BPD subjects. Further study, going beyond symptom description to determine pathophysiologic differences, is required to refine neuronal models of these often comorbid diagnoses.*

Key Words: Bipolar disorder, attention-deficit/hyperactivity disorder, neurologic examination, child, adolescent

Considerable controversy surrounds the distinction between pediatric bipolar disorder (BPD) and attention-deficit/hyperactivity disorder (ADHD). The question is complicated because many children with BPD also meet criteria for ADHD (Biederman et al 1998; Carlson 1998; Geller et al 1998). Studies comparing BPD and ADHD subjects on the same behavioral measures might elucidate pathophysiologic differences between BPD and ADHD (Blumberg et al 2003; Casey et al 1997; Leibenluft et al 2003b; Pliszka et al 2000).

The assessment of motor control deficits might be one such behavioral measure. Perturbations of motor activity are core diagnostic features of both disorders; motor activity is increased in mania and ADHD and might be decreased in the depressive phase of BPD (American Psychiatric Association 2000). Indeed, the hyperactivity that is characteristic of both mania and ADHD has been a primary source of diagnostic confusion and controversy (Biederman et al 1996; Geller et al 1998, 2002). Despite this diagnostic overlap, there have been few standardized, systematic evaluations of motor function in these populations.

Research on neurologic "soft signs," a term often used to describe nonfocal motor deficits detected on neurologic examination, might generate insights about differences between ADHD and BPD. Many use the term "soft signs" not only to distinguish them from "hard signs," which indicate focal, localizable neuropathology, but also to connote their lack of scientific rigor; however, these neurologic abnormalities can be measured with high inter- and intrarater reliability, have longitudinal stability, and are positively correlated with poor functional outcome in adulthood (Losse et al 1991; Pine et al 1996; Rasmussen and Gillberg 2000; Rutter et al 1966, 1970; Shafer et al 1986; Stokman et al 1986). Thus, because there is little "soft" about such findings, we will refer to these abnormalities as "neurologic examination abnormalities" (NEAs) for the remainder of this article (Sanders and Keshavan 1998).

Developmental effects on NEAs have been examined in previous studies. Denckla (1973) found that motor speed and accuracy on both repetitive and sequential tasks increased with age in healthy children (n = 237). Gender influences on NEAs were found in the same study, with girls performing sequential tasks more rapidly than boys (Denckla 1973). Intelligence has also been shown to correlate inversely with numbers of NEAs (Fellick et al 2001; Shaffer et al 1985). Thus, demographic variables, including age, gender, and intelligence, all contribute to the gross and fine motor skills encompassed by NEAs.

Research has also demonstrated an association between NEAs and developmental psychopathology, although debate persists concerning the degree to which NEAs are linked to specific classes of disorders (Fisher 1993; Pan and Fisher 1994). In several studies, investigators have found positive correlations between increased NEAs and increased risk of psychiatric disorders, including anxiety, depression, and ADHD (Breslau et al 2000; Fellick et al 2001; Pine et al 1997a, 1997b; Rasmussen and Gillberg 2000; Shaffer et al 1985). With regard to diagnostic specificity, several investigators have demonstrated associations between ADHD and NEAs (Denckla and Rudel 1978; Gillberg 1998; Gillberg et al 1981, 1982), although others have not found such associations (Shaffer et al 1985). Some suggest that this possible lack of specificity might be due to referral bias inherent in studying children with psychopathology; in other words, NEAs might be a marker for psychopathology in general, rather than for a specific disorder. Also, inconsistency of NEA results might be explained by methods summing discrete findings into one

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Table 1. Sample Characteristics

	BPD (n = 27)	ADHD (n = 17)	NC (n = 20)
Age (y), Mean ± SD	12.5 ± 2.5	10.6 ± 1.8	13.1 ± 2.5
Male/Female (n)	16/11	12/5	11/9
Primary Screening Instrument	K-SADS-PL	DICA	K-SADS-PL
Current Comorbid Axis I Diagnoses (n)			
ADHD	15/27		
Anxiety	16/27	0	
ODD	7/27	0	
Enuresis/encopresis	6/27	0	
Tic disorders	0/27	1	
Psychotropic Medication Status	Medicated	Unmedicated	Unmedicated
Full-Scale IQ,[a] mean ± SD	110 ± 13.6	102.5 ± 11.8	112.7 ± 10.2
Conners' Parent Rating Scale-Revised Long Version,[b] mean ± SD			
ADHD index	69.90 ± 7.46	77.83 ± 12.14	43.00 ± 2.37
Global index: restless/impulsive	71.52 ± 10.03	77.17 ± 12.58	42.33 ± 0.82
Global index: emotional lability	66.24 ± 11.79	60.17 ± 10.61	42.33 ± 0.82

BPD, bipolar disorder; ADHD, attention-deficit/hyperactivity disorder; NC, normal control subjects; K-SADS-PL, Kiddie-Schedule for Affective Disorders, Present and Lifetime Version; DICA, Diagnostic Interview for Children and Adolescents; ODD, oppositional defiant disorder; IQ, intelligence quotient.

Scores are age/gender normed T-scores. Conners' Subscales presented: ADHD Index, Global Index: Restless/Impulsive, and Global Index: Emotional Lability.

[a]Full-Scale IQ: IQ data are available on 12 of 17 ADHD subjects, 24 of 27 BPD subjects, and 15 of 20 NC subjects. No significant between-group Full-Scale IQ difference [$F(2,48) = 2.43$, $p = .1$].

[b]Conners' Parent Rating Scale-Revised Long Version: completed by parents for all subjects.

overall NEA measure, thus obscuring potential specific associations between psychiatric disorders and specific NEAs.

We sought to use NEAs to address the dearth of knowledge about pathophysiologic differences between BPD and ADHD. To the best of our knowledge, this is one of the few studies in which ADHD, BPD, and normal control (NC) children are compared on the same behavioral measure. In particular, we investigated the diagnostic specificity of NEAs during repetitive and sequential motor tasks. Repetitive tasks, such as finger tapping, require the subject to perform the same motor task again and again, using cognitive control to alternately inhibit and excite motor activity to maintain a regular cadence (Fallgatter et al 2004). In contrast, sequential tasks, such as the opposition of one's thumb to each of the other four fingers in sequence, require cognitive control to inhibit touching the same finger twice and to instead move on to the next finger. Consistent with a number of prior studies, we hypothesized that ADHD subjects would demonstrate increased NEAs on repetitive motor tasks (Ben Pazi et al 2003; Gillberg and Kadesjo 2003; Leth-Steensen et al 2000; Mostofsky et al 2003). In contrast, we hypothesized that BPD subjects would show greater deficits than both NC subjects and those with ADHD on sequential motor tasks. The latter hypothesis was based on our work showing that BPD children have deficits in attentional set-shifting and reversal learning, behavioral paradigms that require motor flexibility in the context of a complex task (Dickstein et al 2004; Gorrindo et al, in press; McClure et al, in press). Similar to those tasks, the sequential motor tasks in the Revised Physical and Neurological Examination for Soft Signs (PANESS) require subjects to exercise cognitive control as they flexibly adjust their motor performance in a complex, multistep paradigm.

Methods and Materials

Subjects

We present data on three child subject groups (BPD, ADHD, NC) participating in two ongoing studies conducted at and approved by the institutional review board of the National Institute of Mental Health (NIMH). Although ADHD subjects were recruited and studied by the NIMH Child Psychiatry Branch, and BPD and NC subjects were recruited and studied by the NIMH Pediatrics and Developmental Neuropsychiatry Branch, the same physician (DPD) scored all NEA evaluations, blind to subjects' diagnosis and recruitment source. Also, both groups were administered the PANESS in the same, standardized manner. All minor subjects and their parents signed informed assent and consent forms, respectively, before study participation (Table 1). Groups were not assessed for socioeconomic status.

Pediatric BPD Subjects

Pediatric BPD (n = 27) subjects were enrolled in an ongoing longitudinal neurocognitive and neuroimaging study of the phenomenology of childhood-onset BPD. Subjects were recruited nationwide through material placed on support groups' websites, distributed at professional conferences, and sent to child and adolescent psychiatrists.

Pediatric BPD subject inclusion criteria consisted of meeting DSM-IV criteria for BPD (American Psychiatric Association 2000), including a history of at least one hypomanic or manic episode meeting full duration criteria (i.e., lasting >4 days for hypomania and >7 days for mania), during which the child exhibited abnormally elevated or expansive mood and a total of at least three other DSM-IV criterion "B" mania symptoms (Geller et al 2002; Leibenluft et al 2003); involvement with ongoing mental health treatment; and presence of a primary caretaker to grant informed consent and to participate in the research process. Children with irritability only, without elevated or expansive mood, were excluded because irritability is a nonspecific symptom in childhood psychiatric disorders (American Psychiatric Association 2000; Geller et al 1998, 2002; Leibenluft et al 2003a, 2003c). Thus, the study sample represents the narrow phenotype of pediatric BPD (Leibenluft et al 2003c).

Exclusion criteria were intelligence quotient (IQ) < 70; autistic disorder or severe pervasive developmental disorder;