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A Quantitative and Qualitative Review of Neurocognitive Performance in Pediatric Bipolar Disorder

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Abstract

Bipolar disorder (BD) is an increasingly prevalent diagnosis in youth. As a result, there has been a corresponding increase in interest about neuropsychological and cognitive profiles in children and adolescents diagnosed with BD. Meta-analysis of the existing literature comparing individuals with BD to healthy controls indicated that the largest differences are observed for measures of verbal memory ($d = 0.77$). Moderate differences were found in the areas of attention ($d = 0.62$), executive functioning ($d = 0.62$), working memory ($d = 0.60$), visual memory ($d = 0.51$), visual perceptual skills ($d = 0.48$), and verbal fluency ($d = 0.45$). Small differences were found for measures of reading ($d = 0.40$), motor speed ($d = 0.33$), and full-scale intelligence quotient (IQ) ($d = 0.32$). Often, few studies have provided relevant information for a particular neurocognitive domain. Despite this, several domains displayed heterogeneity of effect sizes across studies. Methodological factors explained the variance in effect sizes to different extents depending upon the cognitive domain. The changing influence of method artifacts is likely due to variable coverage of cognitive domains across studies and the use of different measures across studies. Findings are consistent with previous meta-analyses of the adult BD neurocognitive literature, suggesting that many of the deficits observed in adults are present earlier in the course of the illness. Study reporting guidelines are offered that may help clarify the impact of illness definitions, mood state, medication status, and other methodological variables on neurocognition in pediatric BD.

Cognitive Performance in Pediatric Bipolar Disorder

Bipolar disorder (BD) is a chronic, complex mood disorder that has been increasingly diagnosed in children in recent years (Youngstrom et al. 2005; Blader and Carlson 2007; Moreno et al. 2007) and is associated with poor prognosis and outcome (Goodwin and Jamison 2007). The pediatric phenotype pediatric bipolar disorder (PBD), with illness onset before age 18, may represent an especially genetically driven form of the disorder (Lin et al. 2006; Rende et al. 2007) and is associated with increased risk of suicide and substance abuse, above and beyond levels of risk seen in BD in general (Lin et al. 2006), as well as behavioral, academic, social, and legal problems (Birmaher 2007). Poor outcomes have been demonstrated longitudinally in domains such as treatment response, recovery rates, and relapse rates; these outcomes are similar to those seen in adults with severe, treatment-resistant BD (Geller et al. 2000; Geller et al. 2001). Additionally, rates of hospitalization and psychosis in youths with BD are elevated (Birmaher and Axelson 2006), and nearly one third of youths with BD have a lifetime history of attempting suicide (Goldstein et al. 2005).

Understanding the phenomenology of PBD remains a challenge for the field. The potential cognitive and neuropsychological deficits experienced by these youths has been attracting increasing amounts of attention. Understanding cognitive abnormalities in PBD may lend insight into the neurobiological systems that are disrupted by this disorder, as well as provide a link between neurobiology and observed symptoms and behaviors. This information can also inform our understanding of the course of the illness and potentially define endophenotypes for further parsing of BD (Glahn et al. 2005; Christensen et al. 2006; Antila et al. 2007; Trivedi et al. 2008).

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The study of cognitive and neuropsychological functioning in adults with BD suggests that the disorder is associated primarily with impairments in executive function, verbal learning and memory, and attention (Bearden et al. 2001; Murphy and Sahakian 2001; Seidman et al. 2002). Two recent meta-analyses comparing those with BD to healthy controls have found large effects for executive measures such as Category Fluency, Reverse Digit Span, Trail Making Test B, and Wisconsin Card Sorting Test perseverative errors, as well as verbal learning measures such as the California Verbal Learning Test (CVLT) (Robinson et al. 2006; Arts et al. 2007). Medium effect sizes were found for deficits on sustained attention tasks. Verbal fluency has been noted as an area of difficulty and shows small-to-medium effect sizes. Measures of general cognitive ability or full-scale intelligence quotient (FSIQ), such as tests of reading or vocabulary, demonstrate the smallest effect sizes.

It is important to understand whether the impairments suggested by these meta-analyses are similar across the lifespan or whether they may differ for children and adolescents. Congruence between youth and adult neurocognitive findings would reinforce the similarity in phenotypic definition across the life cycle, providing "laboratory findings" that support the validity of the definition of PBD (Robins and Guze 1970). More nuanced analyses of pediatric neurocognitive data may also help to disentangle whether neurocognitive features represent a diathesis for PBD, versus a progressive change in brain functioning in response to episodes.

Fewer studies have examined neurocognitive deficits in pediatric cases than adults with BD. These studies have yielded findings of impairment in executive function, memory, attention, and processing speed, as well as differences in intelligence testing results and academic functioning for youth with PBD (e.g., Dickstein et al. 2004; Doyle et al. 2005; McClure et al. 2005a; Bearden et al. 2007). In a qualitative review of PBD neuropsychological functioning, Kyte et al. (2006) suggest that impairments in attention, decision-making, and response inhibition are particularly common. These authors also suggest that there are greater similarities than differences in neuropsychological performance between child, adolescent, and adult BD.

Though there has been progress in understanding neurocognitive functioning in BPD, there are many unanswered questions about the nature of potential deficits. Namely, the exact magnitude of deficits for respective cognitive domains remains unclear, as well as whether the existing data suggest global or more specific cognitive deficits. The present paper offers a quantitative and qualitative review of the current literature related to cognitive performance in PBD. The quantitative review focuses on determining the magnitude of PBD/control differences in neurocognitive domains, including FSIQ and academic measures of reading. The qualitative review component focuses on other areas of interest, including differences between individuals with PBD and other conditions, identifying gaps in the literature, and developing recommendations for methodological reporting in future studies of PBD.

Methods

We searched PsycInfo and PubMed using the terms "bipolar" and "children or adolescents or youth" along with the terms "cognitive" and "neuropsy*." Additional studies were garnered by reviewing the references of each article found.

Inclusion/exclusion criteria

There were no sample size-based inclusion or exclusion criteria. Small studies can contribute to estimation of accurate pooled effect sizes, even if they themselves are underpowered. Studies were included in the quantitative analysis only if they provided data for a healthy control group; comparisons using psychiatric control groups have been described in the qualitatitive analyses.

Studies were excluded if the average age of the sample was greater than 18 ($n = 2$); primary outcome variables were neurological soft signs, but not neuropsychological instruments ($n = 1$); the measure of neurocognitive functioning was a behavioral checklist or questionnaire instead of a performance task ($n = 1$); and/or the study lacked an adequate control group ($n = 1$). One study was excluded because it only examined mathematics performance; as no other studies specifically reported on this domain, meta-analysis was not possible. Effect sizes for IQ were excluded if the study reported intentionally matching subjects on IQ. For one study (Olvera et al. 2005), IQ and neurocognitive differences between PBD and controls were very large due to a very high functioning control group (i.e., average FSIQ was 114 in the control group, whereas 100 would be average performance for the general population). This study was a clear outlier and was excluded from subsequent analyses because of the problem of having an exceptionally high-functioning control group (the "super-controls" problem; Faraone et al. 1999). In the event that a research group had published multiple manuscripts, only the study with the most complete data and/or the largest sample size was included ($n = 2$). When language functioning was an outcome variable, only fluency was included: The measures used to assess other language functioning differed from those used for fluency and were idiosyncratic across studies.

A total of 10 studies were identified that satisfied the inclusion and exclusion criteria. Table 1 presents the methodological characteristics of each study included in the meta-analysis. Three studies contributed two bipolar versus control comparisons: One study included separate unmedicated and medicated bipolar samples (Pavuluri et al. 2006), another included bipolar only and bipolar plus attention-deficit/hyperactivity disorder (ADHD) comparisons (Rucklidge 2006), and a final study included euthymic and manic bipolar samples (DelBello et al. 2004). These additional comparisons were included to increase generalizability of the analyses and to facilitate *post hoc* comparisons examining the influence of study characteristics on effect sizes. Although nested effect sizes are best evaluated using hierarchical linear modeling, the small number of nested effect sizes and the small overall sample suggested that little information would be gained from this approach (Raudenbush and Bryk 2002).

Study coding

Exploratory *post hoc* analyses examined the influence of study characteristics on effect sizes. The reviewer (T.F.) recorded sample size as well as demographic characteristics of both the bipolar and control groups such as age, gender,

TABLE 1. DEMOGRAPHICS AND SELECTED STUDY CHARACTERISTICS

Study	*PBD diagnosis*[a]	*Control* (n)	*PBD* (n)	*Control: % male*	*PBD: % male*	*Control age M (SD)*	*PBD age M (SD)*	*PBD % medicated*	*PBD manic*[b]	*PBD depressed*[b]	*PBD % co-morbid ADHD*	*PBD % co-morbid ODD/CD*
Bearden et al. (2007)	1	44	33	50	61	12.90 (2.80)	12.10 (3)	73	1	1	79	39
DelBello et al. (2004)	1	10	10	50	50	15 (2)	16 (1)	60	0	0	40	—
	1	10	10	50	40	15 (2)	16 (2)	60	1	1	20	—
Dickstein et al. (2004)	2	21	21	71	71	12.68 (2.36)	12.74 (2.37)	100	0.5	0	57	—
Doyle et al. (2005)	2	46	57	67	77	13.60 (2.20)	13.30 (2.40)	86	—	—	74	93
Glahn et al. (2005)	1	17	21	47	71	12.82 (2.40)	11.57 (2.50)	76	1	1	76	67
Henin et al. (2007)	1	120	73	51	67	11.9 (2.70)	9.7 (2.50)	0	1	1	100	100
McClure et al. (2005)	2	20	35	65	54	13.50 (2.20)	12.90 (2.60)	85.7	0.5	0.5	57	34
Pavuluri et al. (2006)	1	28	28	46	54	11.19 (2.57)	12.12 (3.38)	0	1	1	50	—
	1	28	28	46	54	11.19 (2.57)	11.90 (3.02)	100	0	0	50	—
Rucklidge et al. (2006)	2	41	12	46	17	15.52 (1.03)	16.02 (1.46)	—	—	—	0	17
	2	41	12	46	58	15.52 (1.03)	15.54 (1.64)	—	—	—	100	67
Voelbel et al. (2006)	2	13	12	100	100	10.77 (1.48)	10.08 (1.31)	73	—	—	75	—

[a]1 = bipolar I disorder; 2 = all bipolar spectrum disorders.
[b]1 = the sample was primarily manic or depressed; 0.5 = some of the sample was manic or depressed; 0 = the sample was euthymic.
PBD, pediatric bipolar disorder; ODD, obsessive compulsive disorder; CD, compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation.

and medication status. Percentages of the bipolar sample that were co-morbid with ADHD and oppositional defiant disorder (ODD) were recorded. Differences in age between the bipolar and control groups were calculated.

The nature of the bipolar sample varied across studies. The type of BD diagnosis was assigned a value of 1 (bipolar I only) or 2 (any bipolar spectrum). Mood criteria used to generate a bipolar diagnosis was also coded (1 = elevated/euphoric mood for all participants, 2 = irritable mood only permitted) to address the distinction that has been made between "narrow" and "broad" phenotypes of PBD (Leibenluft et al. 2003). Additionally, the current mood of the sample was recorded when possible. If the study reported that no or very few participants in the sample were experiencing mania, a value of 0 was assigned. If the study reported that a proportion of the sample was manic or gave a score range for the Young Mania Rating Scale (YMRS) that overlapped with the clinical range, a score of 0.5 was assigned. If the study reported that the sample was primarily or completely experiencing mania or the YMRS range fell well into the clinical range, a score of 1 was assigned. An identical approach was used for depression; the samples in three categories were sorted on the basis of severity of depression.

Studies meeting inclusion/exclusion criteria were examined to determine the relative coverage of cognitive domains across studies. Few studies included information regarding affect recognition or social cognition; therefore, this domain was excluded. The specific measures analyzed for each domain were based upon what was reported in identified studies. Studies varied in the number of measures reported, with several studies reporting either aggregate or multiple measures within a particular cognitive domain. The domains with best coverage across studies were: (1) FSIQ, (2) reading achievement, (3) attention, (4) working memory, (5) executive functioning, (6) verbal memory, (7) visual memory, (8) verbal fluency, (9) visual perceptual skills, and (10) motor speed. For studies reporting multiple measures within a domain (for example, multiple CVLT scores evaluating verbal memory), effect sizes were averaged across the relevant scores evaluating that particular domain to create a single effect size per sample (Lipsey and Wilson 2001). Table 2 displays the measures used to compute aggregate effect sizes.

Calculation of effect sizes

For each domain, we computed the standardized mean difference in effect size using pooled standard deviations, the Cohen *d*, with formulas provided in Lipsey and Wilson (2001). The magnitude of effect sizes was defined by Cohen's (1988) criteria as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$). For each domain, we calculated the unweighted mean, median, and weighted mean effect sizes along with the 95% confidence interval (CI) for the weighted mean effect size. Homogeneity analyses were also computed for each domain. The latter test evaluates whether the observed effect sizes likely result from sampling one population of effect sizes. For measures with heterogeneous distributions of effect sizes, correlations between methodological factors and effect sizes were performed to determine whether methodological characteristics were related to the magnitude of differences between PBD and control groups (see Table 3). Correlational analyses cannot establish causation and due to the sparseness of the literature, we could not use regression to try to parse how much variance was uniquely attributable to a given factor. Given the exploratory nature of *post hoc* analyses examining the influence of study and sample characteristics, only large effects (*r* values > 0.50) are interpreted.

Results

Table 4 presents meta-analytic results for all domains. All domains showed a significant difference between PBD and healthy controls (smallest $z = 2.22$, $p = 0.014$). However, there were substantial differences in the magnitude of effects across domains.

FSIQ and academic functioning

The magnitude of the mean, weighted mean, and median effect sizes for FSIQ fell in the small to medium range. Effect sizes varied significantly across studies. Larger *n* studies produced smaller IQ differences ($r = -0.57$). Qualitative review of these data suggests that when differences were found, they were usually due to youth with BD scoring within the average range, though lower than the control subjects (DelBello et al. 2004; Meyer et al. 2004; Doyle et al. 2005; Voelbel et al. 2006). Extending beyond this quantitative review, differences have not been found when comparing children and adolescents with BD to young individuals with other psychiatric disorders (McClellan et al. 2004). Additionally, co-morbidities such as ADHD and ODD likely play a role in lowering scores on IQ tests by affecting performance on the test and/or test session behavior (Glutting et al. 1996; Frazier et al. 2004).

Similar to findings for FSIQ, the magnitude of mean, weighted mean, and median effect sizes for reading achievement fell in the small to medium range. Effect sizes did not vary significantly across studies. Although not examined in the quantitative review due to failing inclusion criteria, one study found that youth with PBD experienced mathematics deficits relative to individuals with major depressive disorder (MDD) and healthy comparison subjects (Lagace et al. 2003). Additionally, although school services were not examined quantitatively, qualitative review indicated that PBD youth also required more school services such as tutoring and placement in special classes than healthy comparison youth (Doyle et al. 2005), and youth with PBD and co-morbid ADHD required more school services than youth with ADHD alone (Henin et al. 2007).

Attention, motor speed, and executive function

The magnitude of mean, weighted mean, and median effect sizes for attention fell in the medium range. Effect sizes varied substantially across studies (*d* ranging from 0.31 to 1.15). Analysis of this variability did not reveal any major contributors, although inclusion of the bipolar spectrum rather than just bipolar I disorder was associated with larger effects for deficits in attention. This was unexpected, given that bipolar spectrum disorders might be considered less impaired with respect to mood than bipolar I; yet inclusion of these cases yielded stronger effects for impairments in attention. Studies in which all or nearly all of the bipolar group had ADHD tended to contribute the largest effect sizes (Doyle et al. 2005; Rucklidge 2006; Henin et al. 2007), but this

TABLE 2. MEASURES USED TO CALCULATE AGGREGATED EFFECT SIZES

Study	*PBD (n)*	*Aggregated measures*
		Attention
DelBello et al. (2004)	10 10	CPT 0% degradation: discrimination, % correct, false positives
Doyle et al. (2005)	57	Digit Symbol, Symbol Search, CPT vigilance
Henin et al. (2007)	73	Digit Symbol, Symbol Search, CPT vigilance
Pavuluri et al. (2006)	28 28	TMT Part A: Time and Penn CPT true positives and false positives
Rucklidge et al. (2006)	12 12	CPT omissions, RAN variables, and PSI
		Working Memory
Bearden et al. (2007)	33	Digits Forward and Digits Backward
Dickstein et al. (2004)	21	Spatial Span total errors, span length, total usage errors and Spatial Working Memory strategy and total errors
Doyle et al. (2005)	57	Digit Span and Arithmetic
Henin et al. (2007)	73	Digit Span and Arithmetic
Pavuluri et al. (2006)	28 28	WMS-III Digit Span raw score and Spatial Span raw score
Rucklidge et al. (2006)	12 12	Digit Span and Arithmetic
		Executive Function
Dickstein et al. (2004)	21	Intra-Extradimentional Shift variables and Stockings of Cambridge variables
Doyle et al. (2005)	57	WCST categories, perseverative errors, non-perseverative errors, and failure to maintain set and Stroop color-word and interference
Henin et al. (2007)	73	WCST categories, perseverative errors, non-perseverative errors, and failure to maintain set and Stroop color-word and interference
McClure et al. (2005)	35	CPT A-X response bias, discriminability, CPT flanker reaction time cost, Identical pairs CPT response bias, Stop Signal Test reaction time and change reaction time
Pavuluri et al. (2006)	28 28	Set Shifting total errors, Penn Conditional Exclusion Test total errors, Trail Making Test Part B: time, Controlled Oral Word Association Test: raw score
Rucklidge et al. (2006)	12 12	Stroop color-word and interference; Color Trails variables; WCST categories, perseverative errors and conceptual level responses; CPT commissions, task response variability and confidence index
Voelbel et al. (2006)	12	Category Test, TMT-Part B/PFT, Stroop Color Word correct, WCST-Categories, WCST-Perseverative errors
		Verbal Fluency
Bearden et al. (2007)	33	FAS, animals and boys' names, and switching
Voelbel et al. (2006)	12	Phonemic and semantic fluency measures Verbal Memory
Glahn et al. (2005)	21	CVLT all learning trials averaged
McClure et al. (2005)	35	CVLT and TOMAL
Pavuluri et al. (2006)	28 28	CVLT-C trials 1–5, short delay, long delay
Rucklidge et al. (2006)	12 12	WRAML story memory and verbal learning

(*continued*)

Table 2. Measures Used to Calculate Aggregated Effect Sizes (Cont'd)

Study	*PBD (n)*	*Aggregated measures*
		Visual Memory
Dickstein et al. (2004)	21	Spatial and Pattern Recognition Memory mean correct latency and percent correct
McClure et al. (2005)	35	Rey-Osterreith delayed memory, TOMAL, and face memory
Pavuluri et al. (2006)	28 28	Penn face memory task, facial recognition task, immediate and delayed facial recognition total scores
Rucklidge et al. (2006)	12 12	WRAML Visual Memory Index
		Motor Speed
Pavuluri et al. (2006)	28 28	Finger tapping right and left hand total taps
		Visual-Perceptual Skills
Doyle et al. (2005)	57	Rey-Osterreith copy and delay organization
Henin et al. (2007)	73	Rey-Osterreith copy and delay organization

CPT = Continuous Performance Task; CVLT = California Verbal Learning Test; PFT = Progressive Figures Test; PSI = Processing Speed Index (Wechsler Intelligence Scales for Children); RAN = Rapid Automatized Naming; TMT-B = Trail Making Test B; TOMAL = Test of Memory and Learning; WCST = Wisconsin Card Sorting Test; WRAML = Wide Range Assessment of Memory and Learning.

was not universally the case (Pavuluri et al. 2006). It is also important to note that qualitative review showed that in four different studies, differences in attention failed to be identified when a psychiatrically diagnosed comparison group was used. (e.g., ADHD, autism spectrum disorders, MDD, psychosis not otherwise specified [NOS], and schizophrenia) (Robertson et al. 2003; McClellan et al. 2004; Voelbel et al. 2006; Henin et al. 2007).

Motor speed differences between PBD and controls were small in magnitude. Effect sizes did not vary significantly across studies. Qualitative review highlights that in one case a group that had both ADHD and PBD showed impaired motor speed abilities, whereas those with PBD alone did not (Rucklidge 2006). Additionally, when PBD was compared to other clinical disorders such as psychotic disorders, ADHD, conduct disorder, and ODD, no differences were found (McCarthy et al. 2004).

Effect sizes for executive function were based upon measures of planning, organization, response inhibition, and set shifting. Executive function differences between PBD and controls were moderate in magnitude and did not vary significantly across studies. Qualitative review highlights that executive function impairments were found in both ADHD–co-morbid and non-ADHD–co-morbid groups (Shear et al. 2002; Meyer et al. 2004; Bearden et al. 2006; Pavuluri et al. 2006) , and in both medicated and unmedicated individuals (Pavuluri et al. 2006). In contrast to results found when youth with BD were compared to healthy controls, executive function deficits were not found on the Wisconsin Card Sorting Test (WCST) when an MDD comparison group was used (Meyer et al. 2004), nor when comparison groups of schizophrenia or psychosis NOS were used (McClellan et al. 2004). The heterogeneity in executive functioning measures used within and across studies made interpretations complicated. Inspection of the individual study findings indicates that some measures show larger effects whereas others show no significant effect or small effects. Unfortunately, no reliable pattern of specific executive function deficits could be discerned.

Working memory

The magnitude of mean, weighted mean, and median effect sizes for working memory fell in the medium to large

Table 3. Relationship between Method Variables and Effect Size for Heterogeneous Domains

Domain	*Study (n)*	*% ADHD*	*% Medicated*	*Manic*	*Depressed*	*BP diagnosis type*[a]
FSIQ	−0.57	−0.33	0.23	−0.29	−0.25	0.28
Attention	−0.17	0.34	0.31	−0.39	−0.39	0.43
Working memory	−0.62	−0.39	0.15	−0.08	0.02	0.45
Verbal memory	−0.49	−0.01	0.03	−0.35	−0.35	−0.39

[a]Bipolar spectrum versus BP I only.
ADHD = attention-deficit/hyperactivity disorder; BP = bipolar disease; FSIQ = full-scale intelligence quotient.

Table 4. Mean and Weighted Mean Effect Sizes for Comparison of Cases with Bipolar versus Healthy Controls, the 95% Confidence Intervals (CIs), and Tests of Homogeneity (*Q*)

Domain	n *studies*	k *effect sizes*	*M*	*Weighted M*	*Md*	*95% CI*	*z*	*Q*
FSIQ	10	14	0.52	0.32	0.41	0.17–0.47	4.29	27.66[a]
Reading achievement	3	4	0.40	0.40	0.39	0.20–0.60	3.95	0.10
Attention	6	9	0.70	0.62	0.51	0.45–0.78	7.27	15.86[a]
Motor speed	4	7	0.37	0.33	0.34	0.09–0.58	2.71	8.21
Executive function	8	10	0.62	0.55	0.56	0.39–0.70	6.93	8.52[b]
Working memory	6	8	0.75	0.60	0.80	0.44–0.77	7.13	12.72[b]
Verbal fluency	2	2	0.38	0.45	—	0.05–0.85	2.22	—
Visual-perceptual skills	3	4	0.51	0.48	0.52	0.19–0.77	2.91	1.45
Visual memory	5	7	0.51	0.51	0.52	0.30–0.72	4.69	2.39
Verbal memory	6	8	0.88	0.77	0.78	0.59–0.94	8.70	11.33[b]

[a] $p < .05$
[b] $p = .08$

range. Effect sizes varied minimally across studies (homogeneity $p = 0.08$), but larger n studies tended to produce smaller effects ($r = -0.62$). Qualitative review showed that in one study children and adolescents with BD failed to demonstrate differences unless they also had co-morbid ADHD (Rucklidge 2006). In a study using a clinical comparison group made up of youths with psychotic disorders, ADHD, conduct disorder, and ODD, there were no differences in working memory ability (McCarthy et al. 2004).

Verbal fluency and visual perceptual skills

Only two effect sizes were identified for verbal fluency ($d = 0.24$ and 0.52), making conclusions regarding this domain especially tentative. Preliminarily, verbal fluency appears to show small to medium differences between PBD and controls. Similarly, only four studies yielded effect sizes for visual perceptual skills (see Table 2). A medium effect was observed for the difference between PBD and controls.

Visual and verbal long-term memory

Visual memory effect sizes fell in the medium range, whereas verbal memory effect sizes were large in magnitude. Effect sizes for verbal memory showed a trend toward heterogeneity ($p = 0.08$), and this was most strongly associated with larger n studies producing smaller effect sizes ($r = -0.49$). Inspection of studies examining verbal memory indicated that the percentage of participants with ADHD or on medicine did not moderate this effect (r values < 0.05). This may imply that verbal memory deficits are more specific to BD.

Discussion

The goal of this paper was to review the literature about neurocognitive functioning in PBD, using a combination of quantitative methods where possible, supplemented by a qualititative analysis. The literature search yielded 10 studies that contributed to the quantitative analyses. Findings were broadly consistent with conclusions of two recent meta-analyses of neurocognitive functioning in adult BD (Robinson et al. 2006; Arts et al. 2007), and generally indicated that PBD is associated with deficits in functioning compared to healthy controls. This consistency is reassuring corroborative evidence for the validity of research diagnoses of PBD. It was difficult to identify neurocognitive deficits that might be specific to PBD based on the extant literature.

Verbal memory measures showed the largest difference between PBD and controls. This is consistent with the adult literature examining neurocognitive deficits in BD (Robinson et al. 2006; Arts et al. 2007). The weighted mean effect size for verbal memory is quite consistent with those reported in the adult literature: $d = 0.77$ here versus $d = 0.85$ (Arts et al. 2007) and $d = 0.71$–0.90 (depending on the measure) (Robinson et al. 2006). These data are also consistent with fronto-limbic abnormalities identified in adolescents and adults with BD (Caetano et al. 2005; Frazier et al. 2005; Monkul et al. 2005; Kyte et al. 2006; Frey et al. 2007). This pattern of results indicates that verbal memory deficits are not likely to be solely a consequence of chronic course or long-term treatment of BD. However, these data do not speak to whether verbal memory deficits precede the onset of the illness. Future studies are needed to examine this more carefully.

Several other measures showed moderate effects, including attention, working memory, executive function, visual memory, and visual-perceptual skills. Although these moderate differences emerged when comparing youth with BD to healthy controls, qualitative review suggested that differences were not found when psychiatric comparison groups were used, particularly for attention. Attention deficits may not be specific to PBD, but may represent findings for general psychopathology (Arts et al. 2007).

Small effects were found for FSIQ, reading achievement, and motor speed. The data for FSIQ in pediatric subjects reported here are consistent with those reported in adults: Both suggest little difference in the overall ability of individuals with BP and controls. Meta-analyses of adult data have found $d = 0.16$–$0\ .19$ (Robinson et al. 2006; Arts et al. 2007).

Confounds in the literature

Though this meta-analysis found neurocognitive deficits in PBD, there remain several concerns about possible confounds in the literature. The potential impact of these confounds is great enough that we recommend interpreting the

results of this meta-analysis with caution. First, as mentioned above, the use of healthy control comparison groups sets up an artificial contrast that may speak only to deficits associated with general psychopathology, not deficits specific to BD (Youngstrom et al. 2006). This is a limitation in the adult literature as well, where deficits are also not found when psychiatric comparison groups are used (Krabbendam et al. 2005; Bearden et al. 2006; Depp et al. 2007; Schretlen et al. 2007). There is some evidence that cognitive deficits reported in the literature on PBD are also experienced by youths with other disorders (Martinussen and Tannock 2006; Shanahan et al. 2006; Jakobson and Kikas 2007; Mahone and Hoffman 2007). Future research studies in this area should include comparison groups made up of clinically referred children. The most useful design for identifying features specific to PBD would include comparison groups made up of youths with disorders that are challenging in the differential diagnosis of BD, such as ADHD, MDD, ODD, and schizophrenia.

Second, aggregating extant studies may cause an "apples to oranges" problem at the diagnostic construct level. Currently, there is no consensus statement regarding "true" diagnostic criteria for PBD (Youngstrom et al. 2008), and we do not yet know whether BD with irritability as the only mood symptom is a qualitatively different entity from BD with euphoria (Leibenluft et al. 2003). Mirroring a lack of consensus in the field in general, research groups are not consistent with regard to diagnostic inclusion criteria, and accordingly there are a wide variety of clinical presentations of BD across research studies. If there are indeed different subtypes of PBD with important phenomenological differences, then it is quite possible that there are distinct neurocognitive profiles associated with the subtypes, and the different definitions used by researchers could lead directly to the differences observed in findings. At present, there are no studies we found that look at neurocognitive differences between bipolar I, II, or NOS in pediatric samples, nor that directly compare neurocognition in the broad versus narrow phenotypes. The comparisons between BD and "severe mood dysregulation" (which originally was conceptualized as part of the "broad phenotype" but now appears to be a more specific entity that involves non-bipolar mood dysregulation) suggest both that many neurocognitive deficits will be nonspecific, and also that it may be possible to identify more discrete processes affected by BD (such as more focal emotion processes) (Rich et al. 2005a; Rich et al. 2005b; Dickstein and Leibenluft 2006; Brotman et al. 2007; Brotman et al. 2008). Although it is ambiguous whether the "severe mood dysregulation" construct is on the bipolar spectrum, it would be highly productive to adopt similar methods to investigate whether there are differences between putative subtypes within the bipolar spectrum.

Third, ADHD co-morbidity appears to be a significant confounding factor when attempting to measure neuropsychological performance in youths with BD. Given high rates of co-morbidity (averaging 62% in a meta-analysis of seven studies) (Kowatch et al. 2005), neuropsychological deficits reported in PBD may actually be the result of impairments due to ADHD. To date only one study has directly examined this possibility, concluding that there were "few, if any, differences" between the co-morbid and ADHD-only groups (p. 216 in Henin et al. 2007), which suggests that ADHD co-morbidity may play a larger role in cognitive and neuropsychological deficits in BD than has been explored yet in the literature. A study that explores all possible combinations of ADHD and BD is necessary for further elucidating the complex relationship between these two disorders and the resulting effects on neuropsychological functioning in children and adolescents. The present data suggest that verbal memory deficits are likely the most specific finding to BD, as individuals with ADHD show minimal deficits in this domain (Seidman et al. 1997). Research has yet to address adequately whether the overlapping symptomatology and neurocognitive impairments, among other similarities, seen in ADHD and BD may actually be a result of a common underlying disruption in neural circuitry. Future studies addressing this question with neuroimaging techniques are greatly needed.

Finally, the literature does not yet speak to the effects of medication or mood state on neurocognitive performance, let alone long-term development, in youths with PBD.

Limitations

The present quantitative review did not examine measures of emotional processes. Some data suggest that individuals with PBD have difficulty with social cognition, including problems labeling facial emotions (McClure et al. 2003; McClure et al. 2005b) and social skills performance deficits (Goldstein et al. 2006). Additional research is needed examining specific social cognition skills to determine which deficits are specific to BD.

Additionally, this meta-analysis aggregated measures in several cases; although this was done within domains, combining different measures may have diluted some effects by reducing specificity of the aggregated effect sizes. However, given the limited number of studies available, aggregation was necessary to increase reliability of the findings. As this literature further develops, future meta-analyses can examine individual neuropsychological measures rather than broad cognitive domains, as has been done in ADHD (Frazier et al. 2004). This work will hopefully be able to include more specific social cognition, attention, and executive functioning measures to determine what aspects of these domains may be most impaired in PBD. Finally, the review was limited in its ability to address questions pertaining to psychosis, due to the limited information reported in the literature.

Recommendations for future study reporting

One of the most significant limitations of this meta-analysis was the lack of consistency in reporting of results by studies found within the neurocognitive literature for PBD. Specifically, sample and methodological characteristics varied widely and demonstrated significant correlations with effect sizes, suggesting that these differences in study characteristics may contribute to the inconsistencies in published findings. To reduce variability and increase generalizability, future studies of neurocognitive performance in PBD should provide a detailed report of: (1) diagnostic criteria used for inclusion; (2) medication status of participants; (3) current mood state of participants (both manic and depressed moods); and (4) psychiatric co-morbidities, especially ADHD. The diagnostic debate within PBD is not likely to be resolved quickly; therefore, while different sets of diagnos-

tic criteria continue to be used, detailed reporting is crucial to facilitate comparing studies. Ideally, given the potential effects of pharmacological treatment on neuropsychological performance as well as uncertainty about the long-term brain effects of medication treatment for BD, future neuropsychological studies in PBD ideally should include both medicated and unmedicated subjects separated out by medication status. It is also important to understand whether observed deficits are "state" or "trait" impairments.

Beginning with Emil Kraepelin, data suggest that neurocognitive performance may fluctuate along with affective symptoms over the course of bipolar illness. To make the distinction between lifetime diagnosis versus mood state effects, mood status should remain consistent within groups and ideally be compared between groups within the same study. Similarly, psychiatric co-morbidities, particularly ADHD, may significantly "muddy the waters" when measuring neurocognitive impairments. ADHD status should likewise be documented consistently and ideally be compared between groups within each study. Spurious findings may be avoided by rigorously controlling for these potentially powerful methodological confounds, and these factors are much better disentangled by changes in design rather than post hoc statistical adjustments. There have been general reporting guidelines offered for clinical trials (e.g., CONSORT) and diagnostic studies (STARD) (Bossuyt et al. 2003). What we are suggesting is a brief, adjunctive set of key design features that could be routinely reported to accelerate progress in integrating findings around neurocognition and PBD.

Future directions

Future studies of neurocognition in PBD should target several important research questions. First, determining which deficits or markers precede symptom onset remains a crucial point of understanding for both adult and PBD. A related question is whether changes in neurocognitive functioning are the result of normal developmental processes, the progression of the disease, pharmacological treatment, or some combination of the above. Long-term, prospective studies of at-risk populations are essential for getting a clear understanding of whether cognitive and neuropsychological deficits are "state" or "trait" phenomena. Additionally, such studies would allow for analyses of the neurobiological effects of recurrent mood episodes and pharmacological treatments.

Additionally, future work should examine whether neurocognitive deficits exist in healthy siblings, similar to findings in the adult literature (Arts et al. 2007). Finding deficits in first-degree relatives may lend credibility to neurocognitive abnormalities as an endophenotype for BD (Glahn et al. 2005; Christensen et al. 2006; Antila et al. 2007; Trivedi et al. 2008). Failing to find deficits might support the hypothesis that identified neurocognitive abnormalities are simply a marker of generally disrupted functioning in psychopathology.

Finally, although studies have shown abnormal structure and function in youth with PBD (Chang et al. 2004; DelBello et al. 2004; Caetano et al. 2005; Dickstein et al. 2005), it is important to link neurocognitive processes with these neurobiological abnormalities by demonstrating correlations between neurocognitive deficits and structural magnetic resonance imaging (MRI) findings as well as studies examining neural correlates of cognitive functions in vivo using functional (f)MRI. These connections will elucidate the pathophysiology of PBD, and hopefully will inform more effective treatments as well as assessment strategies.

Disclosures

Ms. Joseph and Drs. Frazier and Youngstrom have no conflicts of interest or financial ties to report. Dr. Soares is on the speaker's bureau at Eli Lilly and AstraZeneca, is a consultant for Organon and Shire, and receives grant funding from Pfizer and GlaxoSmithKline.

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