COGNITIVE PERFORMANCE IN PEDIATRIC BIPOLAR DISORDER

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ABSTRACT

MEGAN F. JOSEPH: Cognitive Performance in Pediatric Bipolar Disorder
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Bipolar disorder is an increasingly popular diagnosis in youth, and there has been a corresponding increase in interest in investigating neuropsychological and cognitive profiles in children and adolescents diagnosed with bipolar disorder. The extant literature reveals that youth with bipolar disorder frequently show deficits in the areas of executive functioning, short term memory, learning and long term memory, sustained attention, processing speed, intelligence testing, and academic functioning. This study examined cognitive performance and academic achievement in inpatient youth with bipolar disorder versus comparison inpatient youth with other psychiatric disorders. No differences were found on measures of cognitive ability, visual-motor integration, or academic achievement. Prior findings of cognitive deficits may be due to comparison to healthy controls, not deficits specific to bipolar disorder. When compared with other psychiatrically impaired youth, inpatient children and adolescents do not show these deficits.

TABLE OF CONTENTS

LIST OF TABLES

Table

ABBREVIATIONS

ADHD	Attention Deficit/Hyperactivity Disorder
CVLT	California Verbal Learning Test
DSM	Diagnostic and Statistical Manual of Mental Disorders
FSIQ	Full Scale Intelligence Quotient
IQ	Intelligence Quotient
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Aged Children
KTEA	Kaufman Test of Educational Achievement
MDD	Major Depressive Disorder
ODD	Oppositional Defiant Disorder
PPVT-R	Peabody Picture Vocabulary Test – Revised
ROC	Receiver Operating Characteristic
WISC	Wechsler Intelligence Scales for Children

COGNITIVE PERFORMANCE IN PEDIATRIC BIPOLAR DISORDER

Bipolar disorder is a chronic, complex mood disorder that has been increasingly diagnosed in children in recent years (Blader & Carlson, 2007; Moreno et al., 2007; Youngstrom, Findling, Youngstrom, & Calabrese, 2005). As it has risen in popularity as a diagnosis of interest, research into the nature of bipolar disorder and its many correlates has also become increasingly popular. One of the more recent areas of interest concerns the cognitive and neuropsychological performance of children with bipolar disorder (e.g., Dickstein et al., 2004; Doyle et al., 2005; McClure et al., 2005). This study will review the literature on and issues related to cognitive performance in pediatric bipolar disorder, and will then examine cognitive and academic profiles of youth with bipolar disorder in an inpatient setting in comparison to youth with Attention Deficit/Hyperactivity Disorder (ADHD) and other disorders.

Although there is a substantial body of literature exploring patterns of cognitive and neuropsychological abilities and deficits in adults with bipolar disorder (for reviews see Bearden, Hoffman, & Cannon, 2001; Murphy & Sahakian, 2001; Seidman et al., 2002), fewer research groups have conducted similar research in pediatric populations to date. Though much light has been shed on the nature of cognitive impairments experienced by children and adolescents with bipolar disorder (e.g., Dickstein et al. 2004; Glahn et al., 2005; Henin et al., 2007; McClure et al., 2005), there are many limitations to this research.

Nonetheless, this work has the potential to inform both future research studies and clinical practice.

Several areas of cognitive and neuropsychological deficits have been identified in pediatric bipolar disorder. These include impairments in executive function, memory, attention, and processing speed, as well as differences in intelligence testing results and academic functioning. Each is reviewed in more detail in the following paragraphs.

Executive Function

Executive function is defined as the ability to "engage successfully in independent, self-serving, purposive behaviors" (Lezak, 1995, p. 42). Several research groups have found that children and adolescents with bipolar disorder experience difficulty with executive functioning (Bearden et al., 2006; Meyer et al., 2004; Pavuluri et al., 2006; Shear, DelBello, Rosenberg, & Strakowski, 2004). Impairments were found in both comorbid for ADHD and non-ADHD-comorbid groups, and in both medicated and unmedicated individuals. Perhaps the strongest evidence for impairment in executive function in bipolar youth comes from a 23-year longitudinal study of children at risk for developing affective disorders (Meyer et al., 2004). Sixty-seven percent of participants who developed bipolar disorder in young adulthood had shown impairment on the executive function measure the Wisconsin Card Sorting Test (WCST) as adolescents, compared to 17% of young adults with no mood disorder diagnosis and 19% with unipolar depression.

In contrast to the above, several research groups have failed to find evidence of executive function deficits in children and adolescents with bipolar disorder (Doyle et al., 2005; Henin et al., 2007; McClellan et al., 2004; Olvera et al., 2005; Robertson, Kutcher, & Lagace, 2003; Rucklidge et al., 2006; Voelbel et al., 2006). The current evidence appears at

least equivocal if not weighted in the direction of null results for executive function deficits in pediatric bipolar disorder.

Short Term Memory

Children and adolescents with bipolar disorder have also shown impairments in working memory, or short term memory (Bearden et al., 2006; Dickstein et al., 2004; Doyle et al., 2005; Henin et al., 2007; Olvera, Semrud-Clikeman, Pliszka & O'Donnell, 2005; Pavuluri et al., 2006). However, one study found that children and adolescents with bipolar disorder failed to demonstrate differences unless they also had comorbid ADHD (Rucklidge, 2006). Additionally, in a study using a clinical comparison group, there were no differences in working memory ability (McCarthy et al., 2004). Though the evidence is not conclusive, the majority of studies exploring short term memory in youth with bipolar disorder seem to indicate that this is indeed an area of significant impairment.

Learning and Long Term Memory

Multiple research groups have found that verbal and/or visuospatial learning and long term memory is impaired in pediatric bipolar disorder. The most common neuropsychological test on which deficits in learning and long term memory are found is the California Verbal Learning Test (CVLT), which asks that subjects repeat lists of words read to them several times (Glahn et al., 2005; Henin et al., 2007; McClure et al., 2005; Pavuluri et al., 2006). Subjects affected by bipolar disorder also had a more difficult time with the delay conditions of face recognition tasks (McClure et al., 2005; Olvera et al., 2005; Pavuluri et al., 2006). Additionally, youth with bipolar disorder were impaired on pattern recognition memory and memory for spatial span, as measured by a computer-administered neuropsychological battery (Dickstein et al., 2004).

In contrast to the relatively large number of studies demonstrating impairments on the CVLT for individuals with bipolar disorder, other studies have failed to identify differences on this measure, in comparison to both healthy controls and groups with psychotic disorders (Doyle et al., 2005; McClellan, Prezbindowski, Breiger, & McCurry, 2004). Additionally, no differences were found on a visual-spatial learning and memory task when a healthy control group was used for comparison (McClure et al., 2005; Pavuluri et al., 2006; Rucklidge et al., 2006), nor when the comparison group was made up of psychiatrically diagnosed youth (McClellan et al., 2004). The literature in this area is especially unclear in that deficits have been both shown and not shown when both healthy control and clinically referred comparison groups were used.

Attention

Another area of neuropsychological function in which children and adolescents with bipolar disorder often evidence deficits is attention. A Continuous Performance Task (CPT) was typically used to measure attention, with youth with bipolar disorder sometimes achieving scores that were significantly lower than normal controls (Doyle et al., 2005; Pavuluri et al., 2006). However, other youth with bipolar disorder have not differed on a CPT when compared to healthy control youth (Henin et al., 2007; Robertson et al., 2003; Voelbel et al., 2006), nor to youth with ADHD (Henin et al., 2007), autism spectrum disorders (Voelbel et al., 2006), or MDD (Robertson et al., 2003). The literature is again equivocal; however, it is important to note that on three occasions, differences in attention failed to be identified when a psychiatrically diagnosed comparison group was used.

Processing Speed

Processing speed, or the ability to quickly and accurately process visually presented information, has also been noted as an area of deficit in pediatric bipolar disorder (Doyle et al., 2005; Henin et al., 2007). However, one study failed to show deficits in processing speed for a bipolar-only group, though a group that had both ADHD and bipolar disorder showed impaired processing speed abilities (Rucklidge, 2006). Additional studies have demonstrated that children with bipolar disorder did not show deficits in processing speed ability relative to healthy controls (Bearden et al., 2006) or to inpatient youth with other psychiatric disorders (McCarthy et al., 2004). Again, a definitive statement cannot be made with respect to processing speed deficits in pediatric bipolar disorder. The extant literature is split nearly equally for and against impairment in this area.

Intelligence Testing

There is mixed evidence for lower scores of generalized intelligence (IQ) in youth with bipolar disorder. Many research groups have failed to find differences in IQ between youth with bipolar disorder and healthy comparison youth (Dickstein, Garvey, et al., 2005; Dickstein et al., 2004; Henin et al.,2007; Lagace, Kutcher, & Robertson, 2003; McClure et al., 2005; Rucklidge, 2006). Differences were also not found when comparing children and adolescents with bipolar disorder to young individuals with other psychiatric disorders (McClellan et al., 2004).

However, some research groups have found differences in IQ between youth with bipolar disorder and youth in control conditions (Doyle et al., 2005; McCarthy et al., 2004; Meyer et al., 2004; Olvera et al., 2005; Voelbel et al., 2006). When differences were found, they were usually due to youth with bipolar disorder scoring within the average range,

though lower than the comparison subjects (Doyle et al., 2005; Meyer et al., 2004; Olvera et al., 2005; Voelbel et al., 2006). In one instance, the healthy comparison group had a mean FSIQ one standard deviation above the mean, clearly creating an artifact of lower IQ in the bipolar group (Voelbel et al., 2006). However, in another study, inpatient youth with bipolar disorder did have strikingly lower Full Scale IQ scores and Performance IQ scores when compared to inpatient youth with ADHD, ODD, or Conduct Disorder (McCarthy et al., 2004)—scores which were in the below average to borderline range.

Finding differences in IQ scores between youth with bipolar disorder and healthy controls is perhaps not surprising, given that the most widely used test of intellectual functioning (the WISC; Kamphaus, Petoskey, & Rowe, 2000) uses processing speed and working memory in calculations of overall IQ—two areas in which children and adolescents with bipolar disorder have been shown to evidence impairments (Bearden et al., 2006; Dickstein et al., 2004; Doyle et al., 2005; Henin et al., 2007; Olvera et al., 2005; Pavuluri et al., 2006). Depending on the mechanism by which these impairments occur, lower scores may represent an artifact of the way children and adolescents with bipolar disorder perform on some of the specific tasks required by the test, rather than actual lower intelligence in youth with bipolar disorder.

Additionally, comorbidities likely play a role in lowering scores on IQ tests. Lower IQ scores are frequently found in children with ADHD (Frazier, Demaree, & Youngstrom, 2004) and a recent meta-analysis showed that ADHD and bipolar disorder are comorbid in children at a an average rate of 62% (Kowatch, Youngstrom, Danielyan, & Findling, 2005). Oppositional behavior in the testing session may also play a role (Glutting, Youngstrom, Oakland, & Watkins, 1996): Noncompliant behaviors during testing with the WISC-III were

found to result in FSIQ scores 7 to 10 points (one-half to two-thirds of a standard deviation) lower than children who displayed compliant behaviors during the testing session. Bipolar disorder and ODD are comorbid at a rate of approximately 53% in youth (Kowatch et al., 2005). Interestingly, test session behaviors have been shown to play a stronger moderating role in the measurement of intelligence than on the construct of intelligence itself (Konold, Maller, & Glutting, 1998). This suggests that lower scores could possibly indeed be attributed to processes that influence the measurement of intelligence, rather than to genuinely lower IQ scores in individuals with bipolar disorder.

Frequently, subtest scores of the WISC are used to aid in diagnosing mood or attention problems in children (e.g., Kaufman, 1994; Sattler, 2001). Though the use of the WISC as anything other than a test of cognitive ability has been widely denounced in the literature (Filippatou & Livaniou, 2005; Rispens, Swaab, & van den Oord, 1997; Robinson & Harrison, 2005; Watkins & Kush, 1994; Watkins, Kush, & Glutting, 1997), the WISC is still frequently utilized by clinicians as a diagnostic tool (Camara, Nathan, & Puente, 1998). One of the goals of this study is to add to the understanding of the utility of the WISC and other tests of cognitive ability as diagnostic tools for identifying bipolar disorder and/or ADHD.

Academic Functioning

There is some evidence that children and adolescents with bipolar disorder may experience a disproportionate amount of difficulty in the school setting. Specifically, they have been shown to experience mathematics deficits relative to individuals with Major Depressive Disorder and/or healthy comparison subjects (Doyle et al., 2005; Lagace et al., 2003) and both mathematics and reading deficits in comparison to control subjects (Henin et

al., 2007). Additionally, youth with bipolar disorder required more school services such as tutoring and placement in special classes (Doyle et al., 2005; Henin et al., 2007).

Potential Confounds

A critical look at these data reveals that ADHD comorbidity appears to be a significant confounding factor when attempting to measure neuropsychological performance in youth with bipolar disorder. Some youth with bipolar disorder exhibited cognitive and neuropsychological deficits only when they also had comorbid ADHD (Rucklidge, 2006). Other children and adolescents with bipolar disorder experienced disproportionate impairments when they had comorbid bipolar disorder and ADHD (Doyle et al., 2005; Henin et al., 2007; McClure et al., 2005; Pavuluri et al., 2006; Shear et al., 2004).

Bipolar disorder and ADHD co-occur more often in children than would be expected by chance (Singh, DelBello, Kowatch, & Strakowski, 2006). There are several theories as to why this may be; however, no clear-cut relationship has been established. A recent review of the existing literature indicated that there is empirical support for several different theories regarding the relationship (Singh et al., 2006). Arguably the best-supported theory is that some cases of ADHD may be a prodromal form or early manifestation of bipolar disorder in children (Singh et al., 2006). Evidence presented by Singh and colleagues (2006) to support this theory includes a higher rate of ADHD comorbidity in early-onset bipolar cases as compared to individuals with adolescent- or adult-onset cases; age of onset of bipolar disorder being lower in individuals with comorbid ADHD as compared to bipolar individuals without ADHD (as one would expect if ADHD were an indicator of early-onset bipolar disorder); and offspring of adults with bipolar disorder having high rates of ADHD. Singh and colleagues (2006) suggested that if ADHD is indeed a prodrome to bipolar disorder,

comorbidity of the two could represent a distinct phenotype of early-onset bipolar disorder. The literature within neuropsychology could be interpreted as supporting this theory, as it reveals that children and adolescents with comorbid bipolar disorder and ADHD experience a unique pattern of deficits that is typically more severe than that experienced by those with bipolar disorder alone or ADHD alone. However, it is unclear whether cognitive deficits may have an additive effect, in which case greater impairment would be expected for comorbid individuals.

Another possibility is that given high rates of comorbidity between ADHD and bipolar disorder (62%; Kowatch et al., 2005), neuropsychological deficits seen in bipolar disorder may actually be the result of impairments due to ADHD. To date only one study has directly examined this possibility (Henin et al., 2007). Henin and colleagues (2007), after exploring a wide range of cognitive, neuropsychological, and academic variables among youth with comorbid bipolar disorder and ADHD, ADHD alone, or no diagnosis, found that nearly all deficits observed in the bipolar plus ADHD group were also observed in the ADHD only group. These authors concluded that there were "few, if any, differences" between the comorbid and ADHD only groups (Henin et al., 2007, pp. 216), which suggests that ADHD comorbidity may play a larger role in cognitive and neuropsychological deficits in bipolar disorder than has been explored in the extant literature. Henin and colleagues (2007) do acknowledge the limitation of the lack of a bipolar disorder only group in their study.

Another factor which might seem likely to confound the results of neuropsychological testing in children and adolescents with bipolar disorder is the effect of mood symptomatology. One might hypothesize that youth experiencing acute mood

symptoms would show greater impairments than those who are not experiencing acute symptoms. Surprisingly, this is not the case. The majority of research groups that measured mood symptomatology and connected it to results of neuropsychological testing either (a) failed to find differences between those experiencing acute mania or depression symptoms and those not experiencing a high level of symptoms (Dickstein et al., 2004; Glahn et al., 2005; Shear et al., 2002) or (b) found that mania symptomatology scores were generally not associated with greater impairments (Henin et al., 2007). These findings might suggest that neuropsychological impairments experienced by individuals with pediatric bipolar disorder are a "trait" issue—that is, it is something about the neurobiology of having this disorder, and not the acute symptoms of the disorder, that causes the deficits. Some authors have supported this conclusion (Henin et al., 2007; Robinson & Ferrier, 2006; Kolur et al., 2006; Pavuluri et al., 2006). However, this area is understudied in children, and more research is needed before neuropsychological trait markers, if they exist, can be identified.

Resolving Inconsistencies

There is a wide variety of studies of cognitive and neuropsychological functioning in youth with bipolar disorder, and these studies are yielding contradictory results. Where some studies find deficits, others fail to do so. For example, some research groups found attention deficits on a CPT (Doyle et al., 2005; Pavuluri et al., 2006), while others also using a CPT failed to find these deficits (Henin et al., 2007, Robertson et al., 2003; Voelbel et al., 2006). Similarly, deficits in processing speed were found by some (Doyle et al., 2005; Henin et al., 2007) but not others (Bearden et al., 2007; McCarthy et al., 2004; Rucklidge et al., 2006).

Contradictions in the literature may stem from differences in study methodology. (See Table 1 for a summary of current literature, including study findings, notable

methodological differences, and comments on reliability and validity.) The majority of studies reviewed here compared youth with bipolar disorder to psychologically healthy youth or a mix of healthy and non-mood-disordered youth (15 out of 32 comparison groups or 47%); however, others compared them to youth with ADHD (12.5%), MDD (12.5%), or to other clinically referred children and adolescents (28%). It is possible that, in some cases, comparing youth with bipolar disorder to psychologically healthy youth yields differences which might be found for youth with any major psychiatric disorder. Although the problems identified are presented as deficits experienced by youth with bipolar disorder, they may not actually be specific to bipolar disorder.

Additionally, there is a wide variety of clinical presentations of bipolar disorder being used as entry criteria for research studies. Currently, there is no consensus statement regarding "true" diagnostic criteria for pediatric bipolar disorder, although there are several large studies underway which may lend clarity to the debate over clinical phenotypes of pediatric bipolar disorder (Birmaher, 2005; Birmaher et al., 2006; Youngstrom, Meyers, et al., 2005). Mirroring a lack of consensus in the field in general, diagnostic criteria used and phenotypes recruited are not consistent across extant reports of cognitive and neuropsychological ability in youth with bipolar disorder. For example, some studies were quite selective, and enrolled only participants with bipolar I disorder (Henin et al., 2007; Lagace et al., 2003; McClellan, et al., 2004; Pavuluri et al., 2006; Robertson et al., 2003; Shear et al., 2002), which are those individuals who have experienced a clear manic or mixed mood episode. Others (Dickstein, Garvey, et al., 2005; Dickstein et al., 2004; Glahn et al., 2005; McClure et al., 2005; Rucklidge et al., 2006) used the "narrow phenotype" criteria suggested by Geller and colleagues, which require elated mood and/or grandiosity (Geller et

al., 1998). Still others (Doyle et al., 2005; Lagace et al., 2003; Meyer et al., 2004; Olvera et al., 2005; Voelbel et al., 2006) recruited with the broader DSM-IV criteria, also allowing into their studies youth with irritability as the primary mood disturbance ("broad phenotype"; Leibenluft, Charney, & Towbin, 2003). For this reason, contradictions in the current literature may stem from what some might consider to be a comparison of "apples to oranges"—youth with the same diagnosis but very different clinical presentations, perhaps suggesting underlying differences in neurophysiology—a comparison which might be expected to yield contradictory results.

Explaining Deficits

Though there may be conflicting results, it is clear that under some circumstances youth with bipolar disorder are demonstrating cognitive and neuropsychological deficits. Whether they are specific to bipolar disorder or not, there is emerging evidence that these deficits might be explained by abnormalities in brain structure and function. The most current research suggests that cognitive dysfunction in pediatric bipolar disorder be conceptualized within a framework of recent structural and functional neuroimaging findings indicating brain abnormalities in youth with this disorder (Robinson et al., 2006).

Literature in adult bipolar disorder has demonstrated that the structure and function of many areas of the brain differ in individuals with bipolar disorder relative to healthy controls. This research has only recently been extended downwards into children and adolescents (Caetano et al., 2005), and there is a small but growing body of evidence to suggest that changes in brain structure and function are present in youth as well. To date, brain abnormalities that may help to explain the cognitive and neuropsychological deficits seen in children and adolescents with bipolar disorder have been identified in the prefrontal cortex

(Chang et al., 2004; DelBello et al., 2005; Dickstein, Milham, et al., 2005; Hakala & Anglada, in press) as well as the caudate nucleus (Voelbel et al., 2006).

The prefrontal cortex, which includes multiple subregions such as the dorsolateral prefrontal cortex and the anterior cingulate cortex, is thought to subsume areas of control involved in both mood and attention, selecting movements and behaviors appropriate to task demands (Chang et al., 2004, Kolb & Whishaw, 2001). Deficits in the prefrontal cortex may, for example, lead to an inability to ignore irrelevant stimuli, trouble with appropriate social interactions due to a failure to correctly interpret environmental cues, or difficulties with planning and organizing behavior (Kolb & Whishaw, 2001). Additionally, the prefrontal cortex appears to be implicated in memory (Eysenck & Keane, 2000), particularly episodic long term memory, the type of memory that is tapped during the CVLT, which has been used extensively to test for neuropsychological deficits. Interestingly, individuals show more activity in the right prefrontal cortex when attempting to retrieve episodic memories than when trying to retrieve other kinds of memories (Wheeler, Stuss, & Tulving, 1997). It follows that abnormalities in the prefrontal cortex would be found in individuals who have difficulty accessing episodic long term memory during neuropsychological tasks.

Structurally, youth with bipolar disorder have demonstrated decreased gray matter volumes in the left dorsolateral prefrontal cortex (Dickstein, Milham, et al., 2005). Functionally, children and adolescents with bipolar disorder have also been found to demonstrate increased activation, as compared to healthy controls, in the dorsolateral prefrontal cortex and anterior cingulate cortex during a visuospatial working memory task (Chang et al., 2004). Conversely to what one might expect, the increased activation was associated with a trend toward less accurate performance on the working memory task. In

contrast, Adler, DelBello, and colleagues (2005) found that adolescents with bipolar disorder and comorbid ADHD demonstrated decreased activation in the prefrontal cortex as compared to adolescents with bipolar disorder alone during a CPT.

On the whole, these findings are similar to what has been found in the adult literature. As has been noted in pediatric subjects (Chang et al., 2004), reduced gray matter volume has been found in adults with bipolar disorder (Drevets et al., 1997). Individuals with bipolar disorder showed increased activation in the prefrontal cortex during a working memory task, which was associated with significantly poorer performance on the task (Adler, Holland, Schmithorst, Tuchfarber, & Strakowski, 2004). Additionally, increased cerebral blood flow in the anterior cingulate has been found to be associated with worse performance on the WCST in adult bipolar individuals relative to healthy subjects (Benabarre et al., 2005).

The caudate nucleus is a part of the limbic system, a network of structures that help to regulate emotion (Kolb & Whishaw, 2000). The caudate nucleus is thought to underlie executive functioning as well (Chow & Cummings, 2001; Lewis, Dove, Robbins, Barker, & Owen, 2004). Increased volume in the caudate nucleus has been shown to be related to decreased mental flexibility and poor problem solving on the WCST in youth with bipolar disorder as compared to healthy controls (Voelbel et al., 2006). Voelbel and colleagues (2006) hypothesized that either abnormal growth or impaired neuronal pruning may result in the increased volume of the caudate nucleus.

Frustratingly, and much like the literature on cognitive and neuropsychological deficits, the extant literature on the neurobiology of bipolar disorder is contradictory. It is unclear whether abnormalities of volume are that of increased or decreased volume, and whether abnormalities of activation are that of increased or decreased activation. Clearly,

more research is needed to fully understand the nature of abnormal structure and function of critical brain regions in bipolar individuals, and how these abnormalities contribute to deficits on cognitive and neuropsychological tasks.

Investigations in this area are necessarily fraught with limitations, as the brain continues to develop up to age 25 (Kyte, Carlson, & Goodyer, 2006; Pujol, Vendrell, Junque, Marti-Vilalta, & Capdevila, 1993) and therefore the possibility exists that any abnormalities observed could change or disappear over time. On the other hand, one does wonder whether these abnormalities might in fact lead to greater cognitive impairment across the lifespan than might be true of an individual who developed the disorder in adulthood, when the brain had already developed. Of course, it is as yet unclear whether these brain abnormalities intensify vulnerability to bipolar disorder, or whether the development of bipolar disorder causes the abnormalities. What also remains unclear is the effect of chronic mood disturbances and pharmacological treatments on the developing brain and, potentially, their role in the etiology of abnormalities in brain structure or function. Only rigorous, long-term, prospective studies might answer these questions.

In adults, some researchers have claimed that neuropsychological deficits appear to be trait abnormalities (Bearden, 2006; Kolur 2006), although there is also evidence that these deficits worsen over time after the onset of the illness. In euthymic adult bipolar individuals, cognitive impairments were associated with lifetime number of affective episodes (El-Badri et al., 2001). Additionally, a systematic review of the current adult literature on neuropsychological deficits revealed that greater deficits are associated with a more severe prior course of illness, specifically number of manic episodes, hospitalizations, and length of illness (Robinson & Ferrier, 2006). Increased gray matter volumes in the ventral prefrontal

cortex, as well as in areas involved in motor control, have been noted in first episode bipolar patients (Adler, Levine, et al., 2005). This might suggest that, the deficits having been observed at the onset of the disease, they are not initially a result of changes over time due to recurrent mood episodes or pharmacological treatment. However, it does seem evident that recurrent affective episodes cause further degeneration (El-Badri et al., 2001; Robinson & Ferrier, 2006).

Another potential explanation for neuropsychological deficits is that impaired cognitive processes in one domain create difficulties with other cognitive processes, causing further deficits. For example, in a study of adults referred for a neuropsychological evaluation, memory and executive function shared 50-66% of the variance in their relationship (Duff, Schoenberg, Scott, & Adams, 2005), suggesting that when something goes wrong with one, the other is affected to a substantial degree. Robinson and colleagues (2006) suggested that deficits in executive functioning may impair performance on tests of memory by impeding encoding and/or retrieval processes.

It is an extraordinary challenge to directly implicate any one event, process, or abnormality as a mechanism of cognitive impairment. We may never understand the full extent of the circumstances under which underlying processes in the brain translate into good or poor cognitive functioning, nor how abnormalities in brain structure or function are directly related to cognitive dysfunction. However, it seems likely and even intuitive that neurobiological factors are at the root of impaired cognitive and neuropsychological abilities.

Hypotheses

Given the preponderance of literature demonstrating neuropsychological and cognitive impairments for individuals with pediatric bipolar disorder (e.g., Doyle et al., 2005;

Henin et al., 2007; Lagace et al., 2003; Olvera et al., 2005; Pavuluri et al., 2006), I hypothesize that youth with bipolar disorder in this sample will show deficits relative to other psychiatrically hospitalized individuals on measures of working memory, processing speed, and academic achievement. However, if differences are found, effect sizes are projected to be small due to comparison to a psychiatric rather than healthy control sample. When looking for differences on measures of cognitive ability, ADHD diagnosis will be covaried in order to control for this potentially quite confounding factor, one which some authors have speculated may explain most if not all cognitive deficits observed in bipolar disorder (Henin et al., 2007; Rucklidge, 2006).

Given the lack of consistent evidence as well as the presence of many confounding factors, I do not hypothesize that I will find lower scores of generalized intelligence in individuals with bipolar disorder.

Finding group differences on a measure implies that the measure has the potential to be used diagnostically. This study attempted to explore whether this is possible with tests of cognitive ability, academic achievement, or visual-motor performance. Although these types of tests are often used as diagnostic tools for ADHD, bipolar disorder, or other disorders (Kaufman, 1994; Sattler, 2001b), I do not hypothesize that these data will indicate that this is a valid use of tests of cognitive ability.

Methods

Procedure

Data were collected over a period of five years (1988-1993) at a 10-bed inpatient psychiatric facility for children in New York State. The total sample n for primary analyses was 139 individuals drawn from a larger sample of 248 individuals recruited as a consecutive

case series. Length of stay was typically determined by severity of problems, rather than constraints due to health insurance coverage. Diagnoses were based on observations and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Orvaschel, Puig-Antich, Chambers, Tabrizi, & Johnson, 1982) semistructured interview of both parent and child, which was administered within the first 2 weeks of hospitalization by a clinical psychologist blind to intake information (Carlson & Youngstrom, 2003). DSM-III symptoms were assessed on a 0-3 scale. A diagnosis of bipolar disorder was established by the corroboration of the presence of mania by at least two out of three sources (parent, teacher, and hospital staff). Weekly mood and behavior ratings were tracked by hospital staff. Please see Carlson & Kelly (1998) for the original description of the sample and data collection methods.

Fourteen subjects with complete data for primary analyses had a WISC FSIQ less than 80. These subjects were subsequently excluded from analyses due to the potentially confounding effects of mental retardation. Therefore, the valid n for primary analyses was 125.

Participants

Table 2 summarizes the demographic characteristics of this sample. The sample was 88% male. Subjects were 83% Caucasian, 11% African American, 5% Hispanic, and 1% Asian. Age ranged from 5.87 to 12.91 years of age, with a mean age of 9.20 years (SD = 1.91). Length of stay ranged from 18 to 181 days, with a mean length of stay of 76.54 days (SD = 36.31). The average WISC Full Scale IQ score for children in this sample was 106 (SD = 13.42) with a range from 82 to 147. Average Verbal IQ score was 105 (SD = 14.26)

with a range from 74 to 145. Average Performance IQ score was 106 (SD = 12.80) with a range from 79 to 142.

Diagnoses included 24.2% with bipolar disorder and 74.4% with ADHD. Additionally, 51.6% of the sample had a diagnosis of conduct disorder, 73.8% oppositional defiant disorder (ODD), 28.2% major depressive disorder (MDD), 32.0% dysthymia or minor depression, 8.0% psychosis or schizophrenia, and 25.0% an anxiety disorder. Percentages add up to more than 100% due to comorbidity.

Measures Administered

Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS). The K-SADS is a semi-structured interview designed to capture symptoms of many core DSM-IV disorders experienced by children and adolescents (Ambrosini, 2000). The interview is designed to be administered to the child and his/her parent, yielding a "summary score" which takes into account both reports (Ambrosini, 2000). In this sample, the K-SADS-Epidemiologic Version (Lifetime Version; K-SADS-E; Orvaschel, 1995), modified to make diagnoses of ODD and Conduct Disorder, was administered within two weeks of admission by a clinical psychologist blind to intake data, capturing lifetime DSM-III diagnoses (Carlson & Kelly, 1998). The KSADS-E has been shown to have adequate interrater reliability for mood disorders (r = .73; Ambrosini, 2000). Concurrent validity for K-SADS assessment of depression has been established; the K-SADS correlates at r = .90 with the Beck Depression Inventory, r = .82 with the Hamilton Rating Scale for Depression, and r = .89 with the Children's Depression Inventory (Ambrosini, 2000).

Wechsler Intelligence Scales for Children (WISC). The WISC is the most commonly used measure of general intelligence for children and adolescents (Kamphaus et al., 2000). It

is a measure of broad and specific intellectual functioning that reflects general cognitive ability, verbal and visuospatial reasoning ability, and the effects of prior learning experiences. The version of the WISC initially used in this study was the WISC-R, which is comprised of ten core and two supplemental subtests (Wechsler, 1974). In addition to the Full Scale IQ score, the WISC-R yields a Verbal IQ score, measuring verbal and abstract reasoning and acquired factual knowledge, and a Performance IQ score, measuring visuospatial reasoning and problem-solving skills. The WISC-R has excellent reliability: split half reliability is .96 and test-retest reliability is .95 (Wechsler, 1974). The WISC-R correlates at r = .82 with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), r = .95 with the Wechsler Adult Intelligence Scale (WAIS), and r = .74 with the Stanford-Binet Intelligence Scales. The WISC-III (Wechsler, 1991) was published in 1991, and consistent with ethical guidelines for practice, subsequent admissions (47%) were tested with the WISC-III. The subtests of the WISC-R were retained in the WISC-III, and a large number of studies indicate a high degree of correspondence between standard scores derived for the old and new versions (e.g., Dixon & Anderson, 1995; Gunter, Sapp, & Green, 1995; Lyon, 1995; Slate & Saarnio, 1995).

Peabody Picture Vocabulary Test—Revised (PPVT-R). The PPVT-R (Dunn & Dunn, 1981) is an individually administered test of verbal intelligence. A word is read to the examinee, who then chooses one of four pictures in order to indicate the meaning of the presented word. The PPVT-R has excellent internal consistency reliability (median = .94) and test-retest reliability (median rtt = .89; Sattler, 2001b). Content and construct validity have been established, and it has satisfactory concurrent validity (Sattler, 2001b).

Kaufman Test of Educational Achievement (KTEA). The KTEA (Kaufman & Kaufman, 1998) is an individually administered test of academic achievement in the areas of reading, mathematics, and spelling (Sattler, 2001b). The KTEA yields a Composite score as well as subtest scores in the areas of Reading Decoding, Reading Comprehension, Mathematics Applications, Mathematics Computation, and Spelling (Sattler, 2001b). Scores are in the form of both age and grade equivalents. Though the manual does not report reliabilities for the 1997 norms, the 1985 norms yield excellent reliability coefficients: for the Composite score, median internal consistency reliability is .97 and median test-retest reliability is .96 (Sattler, 2001b). Concurrent and construct validity have been established. Concurrent validity is satisfactory; the KTEA correlates at r = .82 with the Wide Range Achievement Test (Sattler, 2001b).

Bender Visual Motor Gestalt Test (Bender-Gestalt). The Bender-Gestalt is an individually or group-administered test of visual-motor integration (Sattler, 2001a). The examinee is shown nine cards with one figure on each and is asked to copy each figure. The scoring system used in the present study is the Koppitz Developmental Bender Test Scoring System (Koppitz, 1964). There are 30 developmental scoring items, each of which receives a rating of 0 or 1 depending on the absence or presence of an error. Therefore, high Koppitz scores represent more errors. The Koppitz system shows excellent inter-rater reliability (median r = .91) and adequate test-retest reliability (median r = .70). Sattler (2001a) notes that the wide range of demonstrated test-retest reliabilities (.50 to .90) might indicate that the Koppitz system is not adequate for making diagnostic decisions, but that it may be used to formulate hypotheses about visual-motor ability.

During all analyses involving the Bender-Gestalt, age was used as a covariate because the scores were only available in raw form rather than as age-normed scores.

Results

Power Analysis

Based on prior findings from a meta-analysis of cognitive performance in pediatric bipolar disorder (Doyle et al., 2005), power was calculated for the suggested effect sizes of d = .74 for WISC-III Digit Span, d = .66 for WISC-III Oral Arithmetic, d = 1.06 for Digit Symbol/Coding, and d = .67 for Symbol Search, where a d of .2 corresponds to a small effect, .5 to a medium effect, and .8 or above to a large effect (Cohen, 1988). A meta-analysis of adult bipolar individuals (Robinson et al., 2006) further suggests an effect size for IQ of d = .19.

With one exception, there was more than adequate power to detect effects for all primary analyses, including a potentially small effect for IQ (= .88 to 1.0). For a ROC analysis of WISC FSIQ, power was only .15, suggesting that had there been a true effect for IQ, a ROC analysis conducted in this dataset might not have found it.

In general, secondary analyses were somewhat underpowered. For the PPVT as a measure of IQ, power ranged from .08 to .10 depending on the type of analysis used. As there was no precedent for effect size for academic achievement, power was calculated for the KTEA for small (= .09), medium (= .28 to .56), and large effects (= .66 to .89).

Descriptives and Missing Data

Analyses began with descriptive statistics. Means and standard deviations were acquired, and skewness and kurtosis were used to determine that distributions did not depart

substantially from an approximately normal distribution. Minimum and maximum values of each variable were obtained in order to confirm that these values were theoretically possible.

There were substantial amounts of missing data throughout the overall sample of 248. Twenty-three percent of the sample was missing at least one of the primary outcome variables (WISC or Bender-Gestalt scores). Sixty-one percent of the sample was missing data on variables intended for secondary analyses (KTEA and PPVT scores). For primary analyses, missing data were excluded listwise, which provides less bias than pairwise deletion and is a recommended approach if the actual amount of data missing is small (Allison, 2002).

Dummy codes were created to indicate the presence or absence of data, and correlations between variables and missing data indicators were analyzed for patterns or associations with demographics, diagnosis, or other key outcome variables. Pearson's product-moment correlations revealed statistically significant relationships between demographic variables or outcome variables and missing data, suggesting that the group that completed testing was different from the group that did not complete testing (i.e., the data were not missing at random). Notably, younger children were more likely to be missing WISC scores, while older children were more likely to be missing Bender-Gestalt scores. Those with a shorter length of stay were more likely to be missing data on the Bender-Gestalt, PPVT, and KTEA, though not the WISC, perhaps suggesting that the WISC was usually the first test administered and therefore more likely to be complete for a child with a short stay. Females were more likely to be missing KTEA scores. Those missing the WISC were more likely to be missing on the PPVT or KTEA, though not the Bender.

Patterns in the missing data were examined using principal components analysis (PCA) (Cohen, Cohen, West, & Aiken, 2003), which showed two underlying components explaining the patterns of missingness. The components revealed that the tests were usually omitted in pairs, with the WISC and Bender-Gestalt frequently missing together, and the PPVT and KTEA missing together. This, along with percentages of missing data, suggests that the psychological tests typically were administered in pairs, with the WISC and Bender being given first and the PPVT and KTEA being given second (and often not being given if the length of stay was short).

Analysis of Variance (ANOVA)

Ideally, due to the need for elucidating the role of the potential confounding or moderating factor presented by comorbid ADHD, comorbidities between bipolar disorder and ADHD would be considered during ANOVA by comparing four groups: bipolar, no ADHD; bipolar, with ADHD; ADHD, no bipolar; and a comparison group. However, due to a small number of participants in the bipolar, no ADHD cell (only two individuals), the two bipolar groups were collapsed in order to preserve statistical power to detect effects. Therefore, the groups used were (a) bipolar disorder (presence of mania corroborated by at least 2 out of 3 informants), with or without comorbid ADHD; (b) ADHD, with no comorbid bipolar disorder; and (c) a comparison group of all other inpatient youth for whom there was sufficient data to conduct primary analyses. This includes youth with Major Depressive Disorder, dysthymia, psychotic disorders, Conduct Disorder, ODD, and anxiety disorders. Youth in the bipolar and ADHD groups may frequently have had additional comorbid diagnoses.

ANOVA procedures were performed in order to look for differences in means on generalized intelligence and visual-motor ability as measured by the WISC and Bender-Gestalt. Means between the bipolar group (n = 30), ADHD only group (n = 65), and comparison group consisting of children with other diagnoses (n = 30) were compared. All primary outcome variables failed to show significant differences in means between the bipolar group versus either the ADHD only group or the group of all other comparison youth. Effect sizes were small to medium, ranging from d = .05 to d = .47 (see Table 3 for all effect sizes).

Linear Regression

Linear regressions predicting performance on the cognitive and visual motor variables using dummy codes for diagnostic categories (e.g., ADHD status, bipolar status, etc.) revealed that all models using bipolar diagnosis as a predictor while controlling for ADHD diagnosis were nonsignificant. For all analyses, including age or gender in the model failed to change the significance of bipolar diagnosis as a predictor of cognitive or visual-motor performance. See Tables 4 & 5 for R2 values, raw regression weights, and associated tests of significance.

Receiver Operating Characteristic (ROC)

ROC curves were used in order to evaluate the diagnostic efficiency of each test, as well as each individual subtest of the WISC. ROC looks at the tradeoff between the test's sensitivity (the proportion of individuals correctly identified by the test as having the disorder in question) and specificity (the proportion of individuals correctly identified as not having the disorder). A ROC yields an Area Under the Curve (AUC) value, which measures sensitivity versus (1 – specificity) and may be thought of as a numerical representation of

true positives against false positives. ROC is an especially useful technique for determining the clinical significance of using a particular test diagnostically, since it gives the proportion of individuals correctly identified as having a disorder at a better-than-chance level of accuracy.

In the context of this study, the ROC curves helped to elucidate whether performance on the WISC or its subtests or the Bender-Gestalt accurately predicts into which diagnostic group a child will fall, and therefore whether any of these tests can be used as diagnostic classification tools for identifying youth with bipolar disorder. This is especially clinically relevant given that in many settings, psychology professionals frequently use tests of cognitive ability to make decisions about a child's or adolescent's diagnosis (Kaufman, 1994; Sattler, 2001; see introduction).

ROC analyses did not indicate that WISC FSIQ or subtest scores or the Bender-Gestalt had a significant ability to discriminate individuals with bipolar disorder from those without bipolar disorder.

Secondary Analyses

Because this study represents a secondary analysis of an established dataset, it was not possible to obtain full data for all variables of interest (i.e., there is a substantial amount of missing data for some measures). Nevertheless, there are areas of functioning such as academic achievement that are important to explore despite missing data. Secondary analyses within this study examined academic achievement with the KTEA as well as additionally considering the PPVT-R as another measure of generalized intelligence. Missing data were excluded pairwise in these analyses to preserve statistical power to detect effects. ANOVAs, linear regressions, and ROC procedures were run exactly as stated for the

primary analyses, except with the KTEA and PPVT-R as dependent variables. Total n for secondary analyses was 61.

Nonsignificant results were found for the relationship between bipolar diagnosis and outcome variables on ANOVAs, linear regressions, and ROC curves examining the PPVT-R and KTEA. Effect sizes for secondary analyses were small, ranging from d = .01 to d = .20.

Discussion

Bipolar disorder in children and adolescents is an increasingly popular line of research (Blader & Carlson, 2007; Moreno et al., 2007; Youngstrom, Findling, et al., 2005), and research questions related to the cognitive and neuropsychological abilities of these individuals have begun to emerge (Kyte et al., 2006). The present study attempted to describe the nature of cognitive deficits, if any, present in a sample of inpatient youth with bipolar disorder. Unlike many previous studies (Bearden et al., 2007; Dickstein et al., 2004; Glahn et al., 2005; McClure et al., 2005; Pavuluri et al., 2006; Shear et al., 2002), the comparison group was made up of youth with other psychiatric disorders, rather than a healthy control group.

Current Literature

The extant literature is contradictory regarding the presence and nature of cognitive and neuropsychological deficits in youth with bipolar disorder. Current research seems to suggest that if deficits do exist, they may be in the areas of executive functioning (Bearden et al., 2006; Meyer et al., 2004; Pavuluri et al., 2006; Shear et al., 2004), short term memory (Dickstein et al., 2004; Doyle et al., 2005; Henin et al., 2007; Olvera et al., 2005; Pavuluri et al., 2006), learning and long term memory (Bearden et al., 2006; Dickstein et al., 2004; Glahn et al., 2005; Henin et al., 2007; McClellan et al., 2004; McClure et al., 2005; Olvera et

al., 2005; Pavuluri et al., 2006), attention (Doyle et al., 2005; Pavuluri et al., 2006), processing speed (Doyle et al., 2005; Henin et al., 2007), and general intelligence (McCarthy et al., 2004). There is some evidence that youth with bipolar disorder may also have a disproportionate degree of difficulty in the school setting, both academically and with respect to requiring special services (Doyle et al., 2005; Henin et al., 2007; Lagace et al., 2003). Differences in cognitive and neuropsychological performance between youth with bipolar disorder and healthy youth could be due to underlying changes in brain structure or function in areas involved in cognitive processes such as executive function and memory. Abnormalities that have been documented in the nascent field of neuroimaging in pediatric bipolar disorder include decreased volume and increased activity in the prefrontal cortex (Adler, DelBello, et al., 2005; Chang et al., 2004; Dickstein, Milham et al., 2005) and increased volume in the caudate nucleus (Voelbel et al., 2006).

Despite findings indicating deficits in bipolar disorder, however, several studies have failed to find differences for youth with bipolar disorder when attempting to replicate findings of impaired cognitive or neuropsychological functioning in areas such as executive functioning, (Doyle et al., 2005; Henin et al., 2007; McClellan et al., 2004; Olvera et al., 2005; Robertson, Kutcher, & Lagace, 2003; Rucklidge et al., 2006; Voelbel et al., 2006), short term memory (McCarthy et al., 2004; Rucklidge, 2006), learning and long term memory (Doyle et al., 2005; McClellan et al., 2004; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge et al., 2006), attention (Henin et al., 2007; Robertson et al., 2003; Voelbel et al., 2006), processing speed (Bearden et al., 2006; McCarthy et al., 2004; Rucklidge, 2006), and general intelligence (Dickstein, Garvey et al., 2005; Dickstein et al., 2004; Doyle et al., 2005; Henin et al., 2007; Lagace et al., 2003; McClure et al., 2005; Meyer et al., 2004;

Olvera et al., 2006; Rucklidge, 2006; Voelbel et al., 2006). One explanation for the contradictory nature of the findings in the current literature may be that by comparing youth with bipolar disorder to psychologically healthy youth—the most common approach (47% of comparison groups)—these investigations revealed a difference that may exist merely between youth with serious mental illnesses and youth without. In other words, the deficits found may not be specific to bipolar disorder. In fact, the adult neuropsychological literature also fails to find differences between individuals with bipolar disorder and those with other serious psychiatric disorders (Bearden et al., 2006; Depp et al., 2007), or in some cases even finds that individuals with bipolar disorder perform better (Krabbendam, Arts, van Os, & Aleman, 2005; Schretlen et al., 2007).

An alternative explanation is that these contradictions may be a result of an "apples to oranges" comparison at the diagnostic construct level. Extant studies were not consistent with regard to diagnostic inclusion criteria, which might be viewed as a result of the existing uncertainty about phenomenology and "true" diagnostic criteria in the broader field of pediatric bipolar disorder. The nature and presentation of bipolar disorder in children is still unclear. What is clear is that irritability as the only mood disturbance, combined with other symptoms of mania/hypomania, is an extremely common presentation in children (Leibenluft et al., 2003). However, many believe that a "classically" bipolar presentation—one that is characterized by the "hallmark" symptoms of elated mood and grandiosity—is the only true phenotype of bipolar disorder (Geller et al., 1998).

This dichotomy in presentation of predominantly irritable vs. elated mood invites several questions: Are these the same disorder? Should a bipolar diagnosis be given when the mood disturbance is irritability, with no elation present? Are irritable and

elated/grandiose presentations, in fact, separate constructs? If the latter is indeed the case, putting studies with different diagnostic inclusion criteria side-by-side truly is a comparison of apples to oranges. In this case, one might even predict inconsistent findings.

Study Findings

Participants in this study were drawn from a consecutive case series of 248 youth admitted to a psychiatric hospital in New York State between 1988 and 1992. Primary analyses examined the cognitive abilities of 125 youth with bipolar disorder using the Wechsler Intelligence Scale for Children (WISC) and the Bender-Gestalt Test of Visual Motor Integration (Bender-Gestalt), including working memory and processing speed ability, as well as overall intelligence and visual-motor integration ability. Secondary analyses investigated scores on the Peabody Picture Vocabulary Test-Revised (PPVT-R) and the Kaufman Test of Educational Achievement (KTEA) in 61 youth. Results indicated that there were no statistically significant or clinically meaningful cognitive ability or academic achievement deficits in the bipolar group relative to a group with ADHD (no bipolar), nor to a group with other psychiatric disorders. The utility of these instruments as diagnostic tools was also examined. None of the psychological assessments, nor any subtests of the WISC, were able to discriminate youth with bipolar disorder from all others. Power analyses suggested that the null results found for differences between inpatient youth with bipolar disorder and youth with other disorders were due to lack of effects, and not insufficient power.

The results for this comparison of youth with bipolar disorder to other psychiatrically disordered youth do not conform to the existing literature, the large majority of which asserts that cognitive deficits exist for children and adolescents with bipolar disorder. These results

do fit with another study using a psychiatric comparison group that found that youth with bipolar disorder were indistinguishable from youth with other disorders on the basis of their neuropsychological profile (McClellan et al., 2004). When compared to youth with other psychiatric disorders in an inpatient setting, children and adolescents with bipolar disorder do not demonstrate poorer performance on intelligence tests, including on subtests measuring processing speed and working memory, nor do they demonstrate poorer performance on achievement tests. These data as well as the data presented by McClellan and colleagues (2004) and others reviewed in this paper (Henin et al., 2007; Lagace et al., 2003; McCarthy et al., 2004; Meyer et al., 2004; Robertson et al., 2003; Smith et al., 2006; Voelbel et al., 2006) further support an hypothesis that the cognitive and neuropsychological deficits currently implicated in bipolar disorder are not, in fact, specific to bipolar disorder.

A survey of the literature on ADHD quickly reveals that, indeed, similar cognitive deficits and neurobiological abnormalities are found for youth with ADHD. Youth with ADHD have shown impairment relative to healthy controls in executive function (e.g., Mahone & Hoffman, 2007), memory (e.g., Jakobson & Kikas, 2007; Martinussen & Tannock, 2006), and processing speed (e.g., Shanahan et al., 2006). As in bipolar disorder, neurobiological abnormalities are found for youth with ADHD in fronto-striatal structures, specifically the prefrontal cortex, cingulate cortex, and caudate (for a review see Bush, Valera, & Seidman, 2005; for a meta-analysis see Dickstein, Bannon, Castellanos, & Milham, 2006). Fronto-cortical dysfunction is also common in other psychiatric disorders, such as schizophrenia, autism, and Huntington's disease (Singh et al., 2006).

Limitations

The primary limitation of this study was the degree to which there were missing data. Although power was more than adequate to detect effects for the WISC and Bender-Gestalt, this study was potentially underpowered for examinations of the KTEA and PPVT-R due to large amounts of missing data for these measures. Had the data been more complete, the question of whether youth with bipolar disorder experienced academic deficits or demonstrated lower scores on a test of verbal intelligence might have been answered more definitively. Additionally, data were missing in a nonrandom fashion, suggesting that there were extraneous variables that influenced who received psychological testing, as well as who received particular psychological tests. Certain groups being under- or over-represented in the data creates the potential for bias to have been introduced into the results of data analyses. Age and gender were significantly correlated with dummy codes for the presence of missing data, and were subsequently tested as covariates and found not to have an effect on outcomes. However, statistically covarying a variable is not equivalent to sampling in a truly random fashion.

An additional limitation is that not all youth were given the same version of the Wechsler Intelligence Scales for Children. An updated version of the WISC was published mid-study, and under the American Psychological Association's ethical guidelines (American Psychological Association, 2002), the version of the WISC used in the study was updated as well. About 53% of the sample were administered the WISC-R, while 47% were administered the WISC-III. Despite studies demonstrating continuity between the two versions (Dixon & Anderson, 1995; Gunter et al., 1995; Lyon, 1995; Slate & Saarnio, 1995), it does limit the conclusions that can be drawn somewhat. There is a possibility that power

was reduced by introducing additional variance due to slight differences in the measures used, or as a reflection of the Flynn effect (Flynn, 1999). Youth tested with the WISC-III might have been assigned lower scores due to norms having been adjusted for upward drift in intelligence scores across time. The WISC-III norms may not have been in concert with the WISC-R norms, yet these data were aggregated for the purposes of this study. However, this effect is likely to be small (~3 point difference), and in fact there was no significant difference between the sample averages for the WISC-R versus WISC-III. Finally, a new version of the WISC, the WISC-IV, is now the version used clinically, limiting the generalizability of these results somewhat.

A final limitation concerns the definition of bipolar disorder used in this study. The criterion used to determine a positive state for bipolar disorder was the corroboration of the presence of mania by at least two out of three sources (parent, teacher, and hospital staff). Though requiring corroboration served its purpose by decreasing the likelihood that a cluster of nonspecific symptoms (e.g., irritability, talkativeness, hyperactivity or psychomotor agitation) might be identified as mania, it is not equivalent to a rigorous application of DSM-IV criteria. The intensity and duration of mania symptoms is unclear, and these are frequently the deciding factors when assigning a diagnosis of bipolar I (at least one week of moderate to severe symptoms) or II (at least four days of mild symptoms) versus another bipolar spectrum disorder. Similarly, "mania" is used as a broad construct in this study to identify individuals on the bipolar spectrum, but it does not allow for analyses involving subtypes of bipolar disorder. As has become apparent, phenotypic heterogeneity may be the culprit in the equivocal nature of the current literature in the area of cognitive and neuropsychological deficits in pediatric bipolar disorder.

Despite the limitations of this study, the importance of its findings should not be dismissed. Bipolar disorder is a serious and impairing psychiatric disorder. However, it may represent no greater detriment to cognitive functioning than many other psychiatric disorders.

Future Directions

Clearly, more research is needed in this area before any specific or definitive statements can be made about the cognitive and neuropsychological profiles of youth with pediatric bipolar disorder. There are many important issues and potential confounds that future research should target or at least consider, including the role of ADHD; "comparing apples to apples," or using clinically relevant comparison groups; and explicating the effect of recurrent mood episodes and long-term psychotropic medication treatments on cognitive functioning. Furthermore, researchers should consider incorporating the valuable technique of neuroimaging in order to connect brain abnormalities with cognitive and neuropsychological impairments.

It has been well demonstrated that ADHD has the potential to greatly influence the nature and severity of cognitive deficits in children and adolescents with bipolar disorder (Doyle et al., 2005; Henin et al., 2007; McClure et al., 2005; Pavuluri et al., 2006; Rucklidge, 2006; Shear et al., 2004). Understanding the specific ways in which each disorder contributes to those impairments, and to what extent, is extremely challenging. A study that explores all possible combinations of ADHD and bipolar disorder is necessary for further elucidating the complex relationship between these two disorders and the resulting effects on neuropsychological functioning in children and adolescents.

The inability to make definitive statements about the presence vs. absence of specific cognitive and neuropsychological deficits is a direct consequence of wide variations in study

methodology, including diagnostic inclusion criteria. It is possible that there are distinct subtypes of bipolar disorder that are not currently differentiated by the DSM-IV and which may reflect underlying differences in pathophysiology. If this is indeed the case, comparing these subtypes to one another might create contradictory study outcomes that make definitive statements that much more difficult.

Many research designs call for comparisons to a healthy control group. This is an artificial contrast, as it is not the contrast made in order to make a decision in a clinical setting, nor does it allow one to draw conclusions about whether deficits or impairments are due specifically to bipolar disorder. There is some evidence that cognitive deficits reported in the literature on pediatric bipolar disorder are also experienced by youth with other disorders (Jakobson & Kikas, 2007; Mahone & Hoffman, 2007; Martinussen & Tannock, 2006; Shanahan et al., 2006). Future research studies in this area should include comparison groups made up of clinically referred children. The most powerful design would include comparison groups made up of youth with disorders that are challenging in the differential diagnosis of bipolar disorder, such as ADHD, MDD, and ODD.

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. Though this is the most time-consuming and costly research to undertake, it is also the most powerful way to control for confounding factors, and therefore the most powerful way in which we can hope to understand the nature of cognitive and neuropsychological deficits.

Finally, future research should utilize structural and functional neuroimaging and neurobiological assessments such as magnetic resonance spectroscopy (MRS) in pursuit of a firmer understanding of the neurophysiological and neurobiological deficits associated with pediatric bipolar disorder. In particular, neuroimaging conducted concurrently with neuropsychological tasks may further elucidate the means by which brain abnormalities translate into functional impairments.

Table 1

Study Characteristics, Outcomes, Reliability, and Validity Of Existing Literature

Author (Year)	**n BP Group**	**n Comparison Group(s)**	**Nature of Bipolar Group***	**Mood Status of Bipolar Group**	**Nature of Comparison Group(s)**	**Neuropsycho-logical Measures Administered**	**Nature and Direction of Findings for Bipolar Group****	**Reliability & Validity of Study**
Bearden et al. (2007)	33	44	DSM-IV criteria for Bipolar I disorder via KSADS-PL (elevated or expansive mood only; irritability excluded)	14 euthymic (YMRS $\leq$ 6 and HAM-D $\leq$ 8) or mild mood symptoms (YMRS < 12 and HAM-D < 17); 2 depressed (HAM-D $\geq$ 17); 17 manic/mixed (YMRS $\geq$ 12)	No history of Axis I Disorder on KSADS-PL and no history of affective disorder in first-degree relatives	TONI; Digit Symbol Substitution Test (computerized version of WAIS-III Digit Symbol subtest); D-KEFS Trail Making Test, Verbal Fluency, Design Fluency; AIM; WISC-III Digit Span; SCAP	Abstract reasoning^{-} Spatial working memory^{-} Verbal fluency^{-} Visual scanning and sequencing^{-} Processing speed$^{<>}$ Short-term auditory memory$^{<>}$ Design Fluency$^{<>}$	Reliability: High Validity: Low-Moderate Narrow diagnostic criteria a threat to external validity Comparison to normal controls limits external validity
Dickstein, Garvey et al. (2005)	27 (14 BPD+ ADHD; 13 BPD-ADHD)	37 (17 ADHD; 20 normal controls)	DSM-IV criteria (elevated or expansive mood only; irritability excluded) via KSADS-PL; further broken down into BPD+ADHD and BPD-ADHD	Not reported	ADHD: DSM-IV combined type Normal controls: negative psychiatric history in	PANESS	FSIQ $^{<>}$ Time to complete task^{--} (in comparison to both ADHD & NC groups) Motor overflow on left repetitive tasks^{-}	Reliability: Moderate Validity: Moderate Narrow diagnostic criteria a threat to external validity Reliability of measure and

					subject and first-degree relatives		(in comparison to NC group)	interrater reliability of assessors unclear Comparison to normal controls limits external validity (although comparison to ADHD strengthens ecological and external validity)
Dickstein et al. (2004)	21	21	DSM-IV criteria (elevated or expansive mood only; irritability excluded) via KSADS-PL	Euthymic (n=11); or YMRS and CDRS scores indicating hypomania without depression (n=8)	Age- and gender-matched with negative psychiatric history in subject and first-degree relatives	Seven CANTAB subtests	FSIQ<>[] Attentional set-shifting-- Visuospatial memory (spatial span)-- Pattern recognition memory latency—(though same on # correct)	Reliability: High Validity: Low-Moderate Narrow diagnostic criteria a threat to external validity Comparison to normal controls limits external validity
Doyle et al. (2005)	57	46	Lifetime DSM-IV diagnosis of Bipolar I (89%) or Bipolar II (11%) via KSADS-E	Not reported	Absence of bipolar disorder or other mood disorder	WISC-III or WAIS-III Vocabulary and Block Design (used to estimate IQ), Oral Arithmetic, Digit Span, Digit Symbol/Coding, and Symbol Search subtests; Stroop; WCST; ROCF; Auditory Working Memory	Wechsler FSIQ-- <u>After controlling for ADHD:</u> Sustained attention-- Working memory-- Processing speed-- Interference control<>	Reliability: High Validity: Moderate Exclusion of BP-NOS a threat to external validity (NOS diagnoses represent a large proportion of youth presenting with bipolar disorder) Good interrater reliability

						CPT; CVLT; WRAT-III Reading & Arithmetic subtests	Abstract problem solving/set shifting<>; Visuospatial organization<>; Verbal learning<>; Arithmetic--; School functioning--	demonstrated by KSADS κ = .89 with expert
Glahn et al. (2005)	41 (21 BPI; 10 BPII; 10 BPNOS)	17	DSM-IV criteria (grandiosity or elevated mood required) via KSADS-PL	Manic and depressive symptomat-ology present	No history of Axis I disorder via KSADS-PL and no history of affective disorder in first-degree relatives	CVLT	TONI IQ<>; Recall— (BPI group vs. all other groups); Semantic clustering<>; Reliance upon serial recall<>; Perseverative errors/intrusions— (BPNOS vs. healthy); Delayed recognition-- (BPI vs. healthy)	Reliability: High Validity: Low Grandiosity and elevated mood not confirmed as cardinal symptoms; limits external validity Comparison to normal controls limits external validity Did not covary ADHD status (68% of bipolar group) which may have a large effect on neuropsychological functioning
Henin et al. (2007)	73	222 (102 ADHD; 120 control)	DSM-IV diagnosis of Bipolar I Disorder via KSADS-E plus	"Symptom-atic"; details not reported	ADHD: DSM-IV diagnosis via KSADS-E	WISC-III or WAIS-III Vocabulary and Block Design	(All comparisons of BPD+ADHD vs. ADHD only were ns, except for one	Reliability: High Validity: Moderate Narrow diagnostic

			Young Mania Rating Scale score > 15		(comorbid depression, anxiety, or disruptive behavior disorders OK) Control: Similar age and sex as bipolar group (depression, anxiety, or disruptive behavior disorders OK)	(used to estimate IQ), Digit Span, Oral Arithmetic, Digit Symbol/Coding, and Symbol Search subtests; Stroop; CVLT; WCST; ROCF; Seidman CPT; WRAT-III Reading & Arithmetic subtests	measure of processing speed where BPD+ADHD performed worse) Wechsler FSIQ, Verbal IQ, & Performance IQ<>>br> Interference control-- Processing speed-- Verbal learning and memory-- Arithmetic & reading achievement-- Special school services-- Sustained attention<> Set shifting<>	criteria a threat to external validity Comorbid status of both MDD and normal control comparison groups maximizes ecological and external validity Large *n*'s strengthen statistical validity Lack of a bipolar-only comparison group threatens internal validity
Lagace et al. (2003)	44	75 (30 MDD; 45 control)	DSM-III-R diagnosis of Bipolar I Disorder (in remission) via KSADS-P and/or Mini Structured Clinical Interview for DSM-III-R, computerized	Euthymic	MDD: DSM-III-R diagnosis of MDD (in remission) via KSADS-P and/or Mini Structured	WRAT-II spelling, mathematics, and reading subtests; PIAT; BAFPE; TONI-II	TONI IQ<> WRAT-II reading & spelling achievement<> WRAT-II mathematics achievement-- (vs.	Reliability: High Validity: Moderate Narrow diagnostic criteria a threat to external validity Comparison to normal controls

			version		Clinical Interview for DSM-III-R, computerized version Healthy control: No psychiatric history		control group) PIAT reading achievement^{<>} PIAT mathematics achievement⁻⁻ (vs. control group) BAFPE, time to complete mathematics task⁻⁻ (vs. MDD and control groups)	limits external validity (although comparison to MDD strengthens ecological and external validity)
McCarthy et al. (2004)	22	90 (grouped by primary diagnosis: 15 schizophrenia spectrum; 24 psychosis NOS; 31 ADHD; 20 Conduct Disorder or Oppositional Defiant Disorder [disruptive behavior disorders])	DSM-IV diagnostic criteria applied by treating psychiatrist	Not reported (retrospective chart review)	Inpatient youth with other psychiatric disorders diagnosed by treating psychiatrist	Retrospective chart review of WISC-III FSIQ, Verbal IQ, and Performance IQ scores, and Digit Span and Coding subtest scores	WISC-III FSIQ^{<>} WISC-III Verbal IQ^{<>} WISC-III Performance IQ⁻⁻ (vs. those with ADHD and disruptive behavior disorders) Digit Span^{<>} Coding^{<>}	Reliability: Moderate Validity: High Clinical diagnoses of pediatric bipolar disorder are typically highly unreliable Comparison to youth with all other psychiatric disorders demonstrates optimal ecological and external validity
McClellan et al. (2004)	22	47 (27 schizophrenia; 20 psychosis NOS)	DSM-IV criteria for Bipolar I disorder via SCID	Not reported	Schizophrenia via SCID Psychosis NOS via SCID	WISC-III or WAIS-R; WCST; CVLT; COWAT; WRAML visual learning subtest; VMI	Global cognitive ability^{<>} Executive functioning^{<>}	Reliability: High Validity: Moderate Narrow diagnostic criteria a threat to external validity

							Memory$^{<>}$ Attention$^{<>}$ Visual motor skills$^{<>}$ Information processing$^{<>}$	Comparison to youth with psychosis demonstrates ecological and external validity
McClure et al. (2005)	35	20	DSM-IV diagnostic criteria for "narrow phenotype" (at least one episode of hypomania/mania that included expansive, elevated mood; irritability only excluded) via KSADS-PL	Euthymic (n=21); Symptomatic (mania and depression; n=14)	Age-, gender-, ethnicity-, and handedness-matched; psychologically and physically healthy via KSADS-PL and physical examination; no history of any DSM-IV disorder in first-degree relatives	WASI; CVLT; TOMAL memory for stories and facial memory subtests; ROCF	WASI FSIQ$^{<>}$ Verbal learning and memory^{-} (worse if comorbid ADHD) Visuospatial memory$^{<>}$	Reliability: High Validity: Low-Moderate Grandiosity and elevated mood not confirmed as cardinal symptoms; limits external validity Comparison to normal controls limits external validity
Meyer et al. (2004) [23-year prospective study of at-risk individuals of offspring of mothers with	9	86 (22 unipolar depression; 64 no mood disorder)	At Time 5 (mean age 22 $\pm$ 2.3 to 3.5): DSM-IV criteria via SCID	Not reported	Unipolar depression via SCID No mood disorder via SCID	At Time 3 (mean age 11 $\pm$ 2.3): WISC-R At Time 4 (mean age 14 $\pm$ 2.6): WCST; Trail Making Test, Parts A and B	WISC FSIQ^{-} (vs. unipolar group; however, mean FSIQ for bipolar group was 110) Verbal IQ$^{<>}$ Performance IQ^{-} (vs. no mood	Reliability: High Validity: High Highly rigorous longitudinal design and methodology indicates good reliability External validity

unipolar depression, bipolar disorder, or no psychiatric history]							disorder group) WCST¯ (vs. unipolar and no mood disorder groups) Trail-Making Test A<>] Trail-Making Test B<>	maximized by comparison to youth with depression and youth with no mood disorder but other Axis I disorders
Olvera et al. (2005)	36	16	DSM-IV criteria via KSADS-PL; all subjects were incarcerated juvenile offenders with comorbid Conduct Disorder	Assessed, but not reported	Age-, sex-, ethnicity-, and SES-matched controls from the community, not meeting KSADS-PL criteria for bipolar disorder or Conduct Disorder (ADHD and MDD OK)	Differential Abilities Scale; Stroop; WCST; Tower of London; d2 Test of Attention; TOMAL; CELF-3; Judgment of Line Orientation; VMI	DAS General Cognitive Ability¯ (vs. control group) DAS Verbal, Non-verbal, and Spatial ability¯ (vs. control group) Executive function (WCST perseverative responses)¯ (vs. control group) Executive function (Stroop, Tower of London, d2 Test of Attention) <> Verbal memory/language functioning¯ Visuospatial skills¯	Reliability: Moderate Validity: Low Use of only juvenile offenders limits external validity External validity maximized by comparison to youth with other Axis I disorders Subjects recruited if they had "histories of severe mood lability as judged by their counselor" – potentially biased, limits reliability and internal validity

Pavuluri et al. (2006)	56 (28 un-medicated symptom-atic; 28 medicated euthymic)	28	DSM-IV Bipolar I Disorder via WASH-U-KSADS (elated mood or grandiosity required); further broken down into unmedicated symptomatic and medicated euthymic	Euthymic (n=28); Symptomatic (mania and depression; n=28)	Age-, sex-, race-, SES-, intelligence- and word reading ability-matched; no DSM-IV psychiatric disorder via WASH-U-KSADS	WASI; Trail Making Test, A & B; WMS-III Spatial Span & Digit Span subtests; CVLT; University of Pennsylvania computerized battery, selected subtests (Conditional Exclusion Test, CPT, Face Memory, Judgment of Line Orientation); Cogtest computerized battery (Set Shifting Test, COWAT, finger tapping speed)	WASI FSIQ^{--} Attention^{--} (all BP subjects; worse if comorbid ADHD) Executive function^{--} (all BP subjects; worse if comorbid ADHD) Working memory^{--} (all BP subjects) Verbal memory^{--} (all BP subjects) Visual-spatial perception$^{<>}$ Visual memory$^{<>}$ Motor skills$^{<>}$	Reliability: High Validity: Low Grandiosity and elevated mood not confirmed as cardinal symptoms; limits internal and external validity Narrow diagnostic criteria limits external validity Comparison to normal controls limits external validity
Robertson et al. (2003)	44	75 (30 unipolar depression; 45 normal controls)	DSM-III-R Bipolar I Disorder (not meeting criteria for current episode) via KSADS or Mini-SCID computerized version; all diagnoses reviewed to ensure adherence to DSM-IV after it was published	Euthymic	Unipolar depression: DSM-III-R Major Depressive Disorder (not meeting criteria for current episode) via KSADS or Mini-SCID computerized version	WISC-III Freedom from Distractibility Index; Conners' CPT; WCST; Problem-solving and Concentration subscale of the Sickness Impact Profile	Attentional focus$^{<>}$ Arithmetic^{--} (vs. unipolar and control groups) Sustained attention$^{<>}$ Attentional shift$^{<>}$ Subjective reports of cognitive/attentional	Reliability: High Validity: Moderate Narrow diagnostic criteria a threat to external validity Comparison to normal controls limits external validity (although comparison to MDD strengthens ecological and

					Normal controls: No personal history of psychiatric or neurolog-ic problems, or learning disability		problems¯ (vs. unipolar and control groups)	external validity)
Rucklidge et al. (2006)	24 (12 BP only; 12 BP + ADHD)	71 (30 ADHD; 41 normal controls)	DSM-IV diagnosis of Bipolar I, Bipolar II, or BP-NOS via WASH-U-KSADS mood disorders supplement (elated mood or grandiosity required); further broken down into bipolar only and bipolar + ADHD groups	Not reported	ADHD: DSM-IV-TR diagnosis via KSADS-PL plus positive behavior rating scales by collateral informant(s) Normal controls: No history of problems with attention, hyperactivity or impulsivity, or significant mood disturbances	Rapid Automatized Naming subtests (Letters, Numbers, Colors, Objects, Colors/Numbers/ Letters); WISC-III or WAIS-III Processing Speed and Working Memory Indexes; WRAML short form (Picture Memory, Design Memory, Verbal Learning, Story Memory, Finger Windows); Stroop; WCST computerized version; Color Trails Test; Conners' CPT	Naming and processing speed<> (BP only group) Memory<> (BP only group) Response inhibition+ (BP only group vs. ADHD only and BP+ADHD groups) Planning/set-shifting<> Visual scanning/cognitive flexibility<> Inhibitory control<>	Reliability: High Validity: Moderate Grandiosity and elevated mood not confirmed as cardinal symptoms; limits internal and external validity Comparison to normal controls limits external validity (although comparison to ADHD strengthens ecological and external validity)
Shear et al. (2002)	31 (20 with ADHD; 9 without	14	DSM-IV Bipolar I criteria via WASH-U-KSADS; further broken down into	Not reported	Did not meet criteria for any Axis I disorder	BRIEF (parent report)	Behavioral Regulation Index¯ (worse if comorbid ADHD)	Reliability: Moderate Validity: Low-Moderate

	ADHD; 2 comorbid-ity status unknown)		BP with and without ADHD		other than phobia and no history of severe mental illness in any first degree relative		Metacognition Index¯ (worse if comorbid ADHD)	Good interrater reliability; KSADS κ = .94 Extent to which parent report reliably measures executive functioning unclear Narrow diagnostic criteria a threat to external validity Comparison to normal controls limits external validity
Smith et al. (2006)	21	75 (42 MDD; 33 healthy controls)	DSM-IV criteria via SCID, plus Ghaemi diagnostic criteria for Bipolar Spectrum Disorder	Euthymic	MDD: diagnosis via SCID and not fulfilling Ghaemi criteria Healthy controls: no personal history of depression	NART; WAIS-R Block Design; CVLT; Brixton Spatial Anticipation Test; Trail Making Test A & B; Stroop	Verbal learning¯ (vs. MDD group and healthy controls) Attention¯ (vs. healthy controls) Executive function¯ (vs. healthy controls, and vs. MDD group on Trail Making Test B only)	Reliability: Low Validity: Moderate Diagnostic criteria very narrow, not in concert with any other study in this area, and possibly lacking an evidence base Comparison to normal controls limits external validity (although comparison to MDD strengthens ecological and external validity)

Voelbel et al. (2006)	12 (male only)	(38 autism spectrum [ASD; male only]; 13 controls [male only])	DSM-IV criteria via KSADS-IVR	Not reported	ASD: autism spectrum diagnosis via KSADS-IVR, semi-structured interview based on DSM-IV criteria for autism and Asperger's disorder, and ADI-R Controls: No lifetime psychiatric diagnoses via KSADS-IVR	WCST; COWAT; Stroop; Trail Making Test B; Conners CPT	WISC FSIQ^{--} (vs. controls) WISC Verbal IQ^{--} (vs. controls) WISC Performance IQ$^{<>}$ Executive Function$^{<>}$ Attention$^{<>}$	Reliability: High Validity: Moderate Broad diagnostic criteria used, expanding external validity Included only male gender; limits external validity Comparison to normal controls limits external validity Comparison to ASD strengthens ecological and external validity, but rate of comorbidity and difficulty of differential diagnoses between BP and ASD unclear

*Outpatient unless otherwise indicated.
**Superscript + indicates that the bipolar group had more favorable scores on outcome variables than the comparison group(s);
-- indicates that the bipolar group had less favorable scores;
<> indicates that there was no difference between bipolar and comparison groups.
ADI-R = Autism Diagnostic Interview – Revised; AIM = Abstraction and Working Memory Test; BAFPE = Bay Area Functional Performance Evaluation Task-Oriented Assessment; BRIEF = Behavior Rating Inventory of Executive Function; CELF-3 = Clinical Evaluation of Language Fundamentals - Third Edition; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Task; CVLT = California Verbal Learning Test; FSIQ = Full Scale Intelligence Quotient; KSADS-E = Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic Version; KSADS-IVR = Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present State and Epidemiological Version; KSADS-P = Schedule for

Affective Disorders and Schizophrenia for School-Aged Children, Present Episode Version; KSADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present & Lifetime Version; MDD = Major Depressive Disorder; PANESS = Revised Physical and Neurological Examination for Soft Signs; PIAT = Peabody Individual Achievement Test; ROCF = Rey-Osterreith Complex Figure; SCAP = Spatial Working Memory Capacity Task; SCID = Structured Clinical Interview for DSM-IV; SES = socioeconomic status; Stroop = Stroop Color-Word Test; TOMAL = Test of Memory and Learning; TONI-II = Test of Nonverbal Intelligence - Second Edition; VMI = Test of Visual Motor Integration; WAIS-III = Wechsler Adult Intelligence Scale - Third Edition; WASH-U KSADS = Washington University, St. Louis, Mo., Schedule for Affective Disorders and Schizophrenia for School-Aged Children; WASI = Wechsler Abbreviated Scale of Intelligence; WCST = Wisconsin Card Sort Test; WISC-III = Wechsler Intelligence Scales for Children - Third Edition; WMS-III = Wechsler Memory Scale - Third Edition; WRAML = Wide Range of Memory and Learning Test; WRAT-III = Wide Range Achievement Test - Third Edition. Note: Adapted and expanded from Bearden et al. (2007).

Table 2

Demographic Characteristics

	M	***SD***	**Minimum**	**Maximum**
Age	9.20	1.91	5.87	12.91
Length of Stay	76.54	36.31	18	181
WISC Full Scale IQ	106	13.42	82	147
WISC Verbal IQ	105	14.26	74	145
WISC Performance IQ	106	12.80	79	142

Gender	***n* (%)**
Male	110 (88)
Female	15 (12)
Ethnicity	
Caucasian	88 (83)
African American	12 (11)
Hispanic	5 (5)
Asian	1 (1)
Diagnosis*	
ADHD	74.4
Anxiety Disorder	25.0
Bipolar Disorder	24.2
Conduct Disorder	51.6
Dysthymia or Minor Depression	32.0

Major Depressive Disorder	28.2
Psychosis or Schizophrenia	8.0

*Percentages add up to more than 100% due to comorbidity.

Table 3

Effect Sizes

Outcome Variable	**Effect Size (*d*)**
Wechsler Intelligence Scales for Children (WISC)	
Full Scale IQ	.45
Verbal IQ	.34
Performance IQ	.41
Information	.47
Similarities	.24
Oral Arithmetic	.13
Vocabulary	.38
Comprehension	.20
Digit Span	.17
Picture Completion	.33
Picture Arrangement	.29
Block Design	.16
Object Assembly	.34
Digit Symbol/Coding	.16
Bender-Gestalt	.05
Peabody Picture Vocabulary Test - Revised	.10
Kaufman Test of Educational Achievement (KTEA)	
Comprehension	.05

Mathematics	.01
Reading	.11
Spelling	.20

Table 4

R^2 and Significance for Linear Regression Models Using Bipolar Diagnosis as a Predictor of Cognitive, Achievement, and Visual-Motor Performance

Outcome Variable	R^2	*p*
Wechsler Intelligence Scales for Children (WISC)		
Full Scale IQ	.02	.32
Verbal IQ	.02	.25
Performance IQ	.02	.39
Information	.03	.19
Similarities	.02	.34
Oral Arithmetic	.01	.63
Vocabulary	.02	.33
Comprehension	.04	.07
Digit Span	.02	.28
Picture Completion	.03	.21
Picture Arrangement	.02	.40
Block Design	.03	.16
Object Assembly	.01	.60
Digit Symbol/Coding	.01	.53
Bender-Gestalt*	.40	<.01
Peabody Picture Vocabulary Test - Revised	.01	.82
Kaufman Test of Educational Achievement (KTEA)		
Comprehension	.001	.98

Mathematics	.002	.94
Reading	.001	.97
Spelling	.002	.94

*This model was significant overall due to covarying age to correct for raw scores; bipolar diagnosis was not a significant predictor.

Table 5

Regression Weights, Standard Error, and Significance for Linear Regression Models Using All Covariates

Predictor*	***B***	***SE***	***p***
WISC Full Scale IQ			
Age	-.77	0.64	.23
Gender	-6.41	3.71	.09
ADHD diagnosis	1.75	2.92	.55
Bipolar diagnosis	1.57	2.85	.59
WISC Verbal IQ			
Age	-1.45	0.67	.03
Gender	-8.70	3.85	.03
ADHD diagnosis	2.6	3.02	.39
Bipolar diagnosis	-.73	3.04	.81
WISC Performance IQ			
Age	.35	0.63	.58
Gender	-1.94	3.59	.59
ADHD diagnosis	.07	2.33	.98
Bipolar diagnosis	3.68	2.79	.19
Bender-Gestalt			
Age	-.85	0.11	<.01
Gender	.69	0.62	.27
ADHD diagnosis	1.13	0.48	.02

Bipolar diagnosis	.23	0.47	.63
PPVT			
Age	-.05	1.00	.96
Gender	1.12	5.89	.85
ADHD diagnosis	2.40	4.07	.56
Bipolar diagnosis	-1.44	3.79	.71
KTEA Comprehension			
Age	.44	1.33	.74
Gender	2.87	8.97	.75
ADHD diagnosis	8.90	5.67	.12
Bipolar diagnosis	-3.83	5.32	.48
KTEA Mathematics			
Age	-.13	1.63	.94
Gender	-9.78	10.87	.37
ADHD diagnosis	9.2	6.81	.18
Bipolar diagnosis	-3.68	6.46	.57
KTEA Reading			
Age	1.05	1.48	.48
Gender	2.81	10.04	.78
ADHD diagnosis	12.35	6.37	.06
Bipolar diagnosis	-4.31	5.99	.48
KTEA Spelling			
Age	-.31	1.55	.84

Gender	-1.10	11.00	.92
ADHD diagnosis	11.33	6.66	.09
Bipolar diagnosis	-6.69	6.31	.29

*Regression weights for WISC subtest scores available upon request.

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