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Impact of executive function deficits in youth with bipolar I disorder: a controlled study

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Abstract

Although psychometrically-defined executive function deficits (EFDs) and ecologically valid functional outcomes have been documented among youth with bipolar I (BP-I) disorder, little is known about their association. We hypothesized that EFDs would be associated with significant ecologically valid impairments beyond those predicted by having BP-I disorder. Youth with BP-I disorder were ascertained from psychiatric clinics and community sources. We defined EFDs as having at least two out of eight EF measures impaired from a battery of six tests. Significantly more youth with BP-I disorder had EFDs than controls (45% versus 17%). Comparisons were made between controls without EFDs (N=81), controls with EFDs (N=17), BP-I youth without EFDs (N=76), and BP-I youth with EFDs (N=62). EFDs were associated with an increased risk for placement in a special class and a decrease in academic achievement (WRAT-3 reading and arithmetic). EFDs in BP-I subjects were associated with an increased risk for speech/language disorder (as assessed in the K-SADS-E) relative to BP-I subjects without EFDs. Youth with BP-I disorder and EFDs are at high risk for significant impairments in academic functioning.

Keywords

mania; children; cognition; neuropsychology

1. Introduction

In recent years an increasing literature has begun to document important associations between pediatric bipolar disorder (BPD) and deficits in a set of higher cortical abilities referred to as executive functions (EFs). This construct has been defined as “the ability to maintain an appropriate problem set for attainment of future goals” (Welsh and Pennington,

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1989), and includes such abilities as components of attention, reasoning, planning, inhibition, set-shifting, interference control, and working memory (Pennington and Ozonoff, 1996). Executive functions are considered to be critically important for complex human behavior, and their breakdown is thought to commonly result in behavioral or psychiatric impairment (Goldberg and Seidman, 1991; Green, 1996; Chen et al., 1998; Hanks et al., 1999; Cahn-Weiner et al., 2000) supporting the critical role of EFs for sophisticated human behavior.

An emerging literature has documented that children with bipolar disorder exhibit EF deficits (EFDs) (Doyle et al., 2005; McClure et al., 2005; Bearden et al., 2007). A recent meta-analysis of pediatric BPD (Joseph et al., 2008) found neurocognitive deficits consistent with meta-analyses of adult BPD (Robinson et al., 2006; Arts et al., 2008). Effect sizes were largest in the domains of verbal memory, attention, working memory, and executive functions. Similar findings have been reported by McClure et al. (2005), Pavuluri et al. (2006), and Henin et al. (2007), and indicate that pediatric BPD is associated with EFDs and that these are not due to medication status or acute symptoms.

Pediatric BPD is frequently comorbid with ADHD (Biederman et al., 2000; Geller et al., 2000; Kim and Miklowitz, 2002) and ADHD is well known to be associated with EFDs (Pennington and Ozonoff, 1996; Seidman et al., 2001; Seidman et al., 2006). The limited literature on the subject has been equivocal as to whether the EFD findings in BPD youth are independent of the comorbidity with ADHD. Dickstein and colleagues (2004) stratified their BPD sample by comorbidity with ADHD and found no group differences, although they cautioned that their analyses may have been underpowered due to their small sample size. In contrast, Doyle et al. (2005) found that even after controlling for comorbid ADHD, BPD in youth was associated with impairments in vigilance, working memory, interference control, processing speed, abstract problem solving, and aspects of verbal learning. Pavuluri et al. (2006) also reported that children with bipolar disorder and comorbid ADHD performed worse on tasks assessing attention and executive function than children with bipolar disorder alone. Also highlighting the impact of ADHD, Rucklidge (2006) failed to find broad neurocognitive deficits in adolescents with only BPD, while participants with BPD and comorbid ADHD showed the greatest cognitive deficits. Most recently, Henin et al. (2007) found that the neuropsychological performance in children with BPD and ADHD was impaired in a manner that is very similar to that of children with ADHD alone.

Moreover, the extant literature on EFDs in pediatric BPD has exclusively reported mean differences between groups. While clearly noteworthy, such data do not lend themselves easily to have a clinical translation. In an attempt to study clinically significant EFDs, our group evaluated the clinical utility of a categorical definition of EFDs in large samples of youth and adults with ADHD. In these analyses we operationalized the presence of EFDs as having two abnormal scores out of eight measures in a battery of six neuropsychological tests assessing multiple domains of EFDs.

These studies showed that the presence of comorbid EFDs defined this way selectively increased the risk for academic dysfunction in youth with ADHD and academic and work dysfunction in adults with ADHD beyond what would have been predicted by the presence of ADHD alone. However, whether a categorical definition of EFDs will be useful to identify a subgroup of pediatric BPD patients with comorbid EFDs remains unknown. Because pediatric BPD is frequently comorbid with ADHD, a comprehensive evaluation of EFDs in pediatric BPD needs to address the comorbidity with ADHD.

The main aim of the present study was to evaluate the clinical impact of an operationalized categorical definition of EFDs in youth with bipolar I (BP-I) disorder with and without

ADHD. A control group without mood disorders will be used to define EFDs and to examine the effect of EFDs outside the context of BP-I disorder. We used a control group without mood disorders to allow an assessment of the degree to which BP-I disorder increased the risk for adverse outcomes. Based on the literature and our previous work in ADHD, we hypothesized that EFDs would be more prevalent in children with BP-I disorder relative to controls, and would be associated with higher levels of impairments than other BP-I subjects without EFDs. To the best of our knowledge this is the first assessment of this issue in youth with BP-I disorder.

2. Methods

2.1 Subjects

Subjects were derived from two family genetic studies of pediatric bipolar I (BP-I) disorder that used identical assessment methodology (N=299, 98 Controls, 201 BP-I) (Wozniak et al., 2005; Wilens et al., 2008). For this analysis, subjects between the ages of 10 and 18 years with available neuropsychological data were included (N=236, 98 Controls, 138 BP-I). Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study.

BP-I subjects (Wozniak et al., 2005; Wilens et al., 2008) met criteria for DSM-IV BP-I disorder and Controls (Wilens et al., 2008) were non-mood disordered. Psychiatric assessments relied on the Kiddie Schedule for Affective Disorders and Schizophrenia Epidemiologic Version (K-SADS-E) for DSM-IV (Orvaschel, 1994) for subjects younger than 18 years of age and the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects 18 years of age. The structured interview also included questions regarding academic tutoring, repeating grades, and placement in special academic classes. Separate assessments were conducted with both the mother about the youth and directly with youth ages 12 and older. Separate raters for the child and mother were blind to the interview data from the other interview of the child-parent pair. We combined data from direct and indirect interviews by considering a diagnostic criterion positive if it was endorsed in either interview.

All assessments were conducted by carefully selected, highly trained and closely supervised interviewers who had undergraduate degrees in psychology or a related field. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria and coding algorithms. Then, they observed interviews by experienced raters and clinicians. They subsequently conducted at least six practice (non-study) interviews and at least six study interviews while being observed by senior interviewers. Trainees were only permitted to conduct interviews independently after they executed at least three interviews that achieved perfect diagnostic agreement with an observing senior interviewer. We computed kappa coefficients of agreement between these raters and experienced board certified child and adult psychiatrists and licensed clinical psychologists. Based on 500 assessments, the median kappa coefficient was 0.98 (0.95 for mania).

We considered a disorder positive if DSM-IV diagnostic criteria were unequivocally met. A committee of board-certified child and adult psychiatrists who were blind to the subject's bipolar status, referral source, and all other ascertainment data resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only when the committee determined that diagnostic criteria were met to a clinically meaningful degree. Reviews of mother and youth interviews were conducted independently and were blind to

the interview data from the other interview of the child-parent pair. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. For these diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was 0.87 (0.78 for mania).

For a diagnosis of mania to be considered positive, the child had to meet full DSM-IV criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period of at least one week or longer of extreme and persistently elevated, expansive, or irritable mood, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance, plus criterion C, associated impairment. Interview questions asked to mothers and children were identical. The interview also included questions about impairment (mild, moderate, or severe) and treatment (counseling, pharmacotherapy, and/or hospitalization) associated with the diagnosis.

Since there are many anxiety disorders measured by our structured interviews, we aggregated them into a binary measure coded positive if two or more anxiety disorders were endorsed, and negative otherwise (Mennin et al., 2000). Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (Hollingshead, 1975).

2.2 Psychosocial assessments

In addition to diagnostic information, interviewers assessed adaptive functioning by using the DSM-IV Global Assessment of Functioning Scale (GAF) (American Psychiatric Association, 2000), which yields a composite rating of a participant's global functioning on a scale ranging from 1 (worst) to 90 (best). GAF scores were assigned to each participant on the basis of information obtained in the diagnostic interview. These scores were also reviewed by the committee. Social functioning was assessed with the Social Adjustment Inventory for Children and Adolescents (SAICA), a validated and reliable measure of children's functioning in school, in spare time activities, and with peers, siblings, and parents (John et al., 1987). The SAICA was administered as both a self-report and parent-report. The lowest functioning score reported was used for analysis.

2.3 Cognitive/neuropsychological assessments

Using the methods of Sattler (1988), we estimated Full Scale IQ from the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale—Third Edition (WISC-III) for participants ages 10-16 or the Wechsler Adult Intelligence Scales – Third Edition (WAIS-III) (Wechsler, 1991) for participants ages 17-18. Our interviewers assessed academic achievement with the arithmetic and reading Subtests of the Wide Range Achievement Test – Third Edition (WRAT-III) (Jastak and Jastak, 1993). Based on our review of the literature and our previous neuropsychological work, we chose to assess certain domains of functioning thought to be important to bipolar disorder, as well as its frequently comorbid condition ADHD, and to be indirect indices of frontal-subcortical brain systems. These include measures of sustained attention/vigilance, planning and organization, response inhibition, set shifting and categorization, selective attention and visual scanning, verbal and visual learning, and memory. The tests utilized were: 1) The copy organization and delay organization of the Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944), (scored by the Waber-Holmes method); 2) Total errors on a Continuous Performance Test (CPT) (Seidman et al., 1998); 3) Perseverative errors and loss of set of the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993); 4) The total words learned on the California Verbal Learning Test for Children (CVLT-C (Stata Corporation, 2005)) (Delis et al., 1994); 5) The color-word raw score of the Stroop test (Golden, 1978); and 6) The Freedom From Distractibility Index from the WISC-III/WAIS-III (Digit Span and Oral Arithmetic)

(Wechsler, 1991). These neuropsychological data were in part presented previously (Doyle et al., 2005; Henin et al., 2007).

2.4 Defining a binary impairment indicator EFDs

Following the method proposed by Biederman et al. (2004), we defined a binary measure of executive function deficits (EFDs) based on the neuropsychological variables described above. To address age differences in test scores, the Controls were divided into subjects aged 10-13 years and subjects aged 14-18 years. These age categories were chosen to reflect maturational growth and development as well as the distribution of control participants across age in years. For each EF variable within each age group, we defined a threshold using the control data indicating poor performance if the score was 1.5 standard deviations from the mean for normally distributed variables, or within the poorest 7th percentile of performance for non-normally distributed variables. We then created binary impairment indicators for the EF variables for all subjects within each age group (ADHD and control). Thus, we could sum the number of variables for which any given subject performed poorly based on the cutoffs. We defined a subject to have EFDs if the number of tests impaired was two or more. Two issues contributed to this choice of cutoff. First, in our previous report (Doyle et al., 2000), we found that two or impaired tests showed the best discrimination between ADHD and non-ADHD subjects. Second, while one impaired test may be due to chance, two or more impaired tests would likely be interpreted as a deficit by a clinician.

2.5 Statistical analysis

The association between bipolar I (BP-I) disorder and executive function deficits (EFDs) was determined using logistic regression while controlling for the diagnosis of ADHD in order to determine the association of BP-I disorder and EFDs independent of ADHD. To address our hypothesis regarding the effect of EFDs, we modeled the outcomes as a function of group status (Controls without EFDs, Controls with EFDs, BP-I youth without EFDs, and BP-I youth with EFDs), ADHD, and any confounding variables. For any outcomes significantly associated with EFDs, we conducted a secondary analysis controlling for IQ to determine if the association was independent of IQ. Statistical models were fit with the statistical software package STATA (Stata Corporation, 2005). Logistic regression was used for binary outcomes (e.g., lifetime diagnoses) and linear regression for continuous outcomes (e.g., GAF score). Statistical tests were two-tailed and an alpha level of 0.05 was used to assert statistical significance.

3. Results

3.1 Demographics

As shown in Table 1, the BPD+EFD group was significantly younger than both the Controls and BPD groups. Youth with EFDs had significantly lower SES compared to Controls irrespective of the presence of BPD. Therefore, all subsequent analyses controlled for age and SES. Although not reaching statistical significance ($p=0.07$), we conservatively controlled for sex due to the lower rate of males in the Controls. ADHD was also controlled for due to its significant relationship to both EFDs ($\chi^2_{(1)}=18.3$, $p<0.001$) and BPD ($\chi^2_{(1)}=81.9$, $p<0.001$).

3.2 Rate of EFDs

Table 2 shows the neuropsychological scores used to create the definition of EFDs. Nearly half of the youth with BP-I disorder (62/138, 45%) met criteria for the binary definition of EFDs described above compared to only 17% (17/98) of Controls, $\chi^2_{(1)}=19.57$, $p<0.001$. The association of BP-I disorder and EFDs remained statistically significant after controlling

for ADHD, age, gender, and SES ($z=2.42$, $p=0.02$, $OR=2.6$ [1.2, 5.5]). As shown in Figure 1, the effect of ADHD and BP-I disorder on EFDs was additive, with 30% of BP-I youth without ADHD having EFDs compared to 50% of BP-I youth with ADHD, although this difference did not reach statistical significance ($z=1.91$, $p=0.06$). Based on the presence or absence of EFDs, four groups were defined: 1) Controls without EFDs (Controls, $N=81$), 2) Controls with EFDs (Controls+EFD, $N=17$), 3) BP-I youth without EFDs (BPD, $N=76$), and 4) BP-I youth with EFDs (BPD+EFD, $N=62$).

3.3 Association of EFDs with clinical outcomes

As Figure 2A shows the rate of placement in special class in the BPD group was similar to that of the Controls+EFD group and both were significantly higher than that observed in Controls. BPD+EFD subjects were at the highest risk for placement in special class (68% vs 29% and 24%, for BPD+EFD, BPD and Controls+EFD, respectively).

A similar trend was observed for the rates of tutoring. Although the rate of tutoring was significantly higher in both BPD groups than in Controls and were indistinguishable from each other statistically, the BPD+EFD subjects had a 13% higher rate of tutoring than BPD subjects. The same trend was observed among controls where those with EFDs who had an 18% higher rate of tutoring than controls without EFDs (Figure 2A).

Lower IQ and WRAT reading scores were significantly associated with EFDs irrespective of the presence of BPD. However, BPD+EFD subjects had significantly more impaired scores on the WRAT arithmetic than other BPD subjects. (Figure 2B).

BPD was significantly associated with more psychosocial impairment as measured by the GAF and SAICA scores and higher rates of psychiatric comorbidities irrespective of the presence or absence of EFD (Table 3). The only exception was that BPD+EFD was associated with a significantly higher rate of speech and language disorders (as assessed using K-SADS-E) compared with BPD group.

EFDs were not significantly associated with the age of BPD onset ($BPD=8.6\pm4.3$ years, $BPD+EFD=6.9\pm3.8$; $t_{(133)}=-1.41$, $p=0.16$) or the number of BPD symptoms ($BPD=5.9\pm1.3$ years, $BPD+EFD=5.8\pm1.3$; $t_{(133)}=-0.43$, $p=0.66$). There were also no meaningful differences between the BPD and BPD+EFD groups on rates of individual BPD symptoms (all p 's >0.05). The BPD and BPD+EFD groups did not significantly differ on treatment received for BPD (Table 3).

3.4 Controlling for IQ

The association of BP-I disorder and EFDs remained statistically significant after controlling for IQ ($z=2.07$, $p=0.04$, $OR=2.5$ [1.05, 5.9]). The BPD+EFD group had significantly higher rates of placement in a special class ($\chi^2_{(1)}=8.80$, $p=0.003$) and speech and language disorders ($\chi^2_{(1)}=4.82$, $p=0.03$) compared to the BPD group after controlling for IQ. The higher rate of placement in a special class in the Controls+EFD group compared to the Control group lost significance when IQ was controlled for ($\chi^2_{(1)}=3.35$, $p=0.07$). The association between EFDs and lower WRAT arithmetic remained statistically significant after controlling for IQ in both subjects with BP-I disorder ($F_{(1,217)}=5.70$, $p=0.02$) and Controls ($F_{(217)}=4.94$, $p=0.03$). For WRAT reading, the BPD+EFD group had a statistically significant lower score compared to the BPD group after controlling for IQ ($F_{(1,225)}=6.33$, $p=0.01$), but the effect of EFDs lost significance in the Controls ($F_{(1,225)}=3.21$, $p=0.07$).

4. Discussion

Using neuropsychological data from a large sample of children and adolescents of both sexes with and without BP-I disorder, we found that BP-I disorder was associated with a significant overrepresentation of our binary definition of EFDs compared to Controls. The association of BP-I disorder and EFDs remained statistically significant after controlling for ADHD, age, gender, and SES.

The presence of EFDs in youth with BP-I disorder significantly increased the risk for placement in a special class and lower academic achievement, even after stringent statistical controls for covariates. These effects could not be accounted for by differences in the clinical features of BP-I disorder or medication status. These findings suggest that the presence of EFDs in youth with BP-I disorder increases the risk for impaired educational outcomes beyond those predicted by BP-I disorder. The mechanism by which elements of executive function may impair academic functioning is an empirical question not directly addressed by the current study. Nonetheless, higher-order neurocognitive functions such as executive functions are defined by The International Society of Neuropsychology as the necessary for the types of complex processing and adaptation to external demands that are required by youth as they navigate school. Understanding the specific aspects of school functioning that are impacted may be a worthwhile endeavor in terms of designing interventions with external validity. These findings also provide further support for the clinical and heuristic utility of an empirically derived binary definition of EFDs. Although it may be argued that examination of quantitative scores is clinically useful, clinicians frequently need to make binary decisions (e.g., should a child be referred for further testing or for psychoeducational services). Clinicians often struggle to interpret neuropsychological assessments that include numerous tests of different domains of executive and related functioning. Although knowing these detailed scores is useful for describing a patient's full profile of neuropsychological strengths and weaknesses, we have shown that a dichotomous definition of neurocognitive impairment has external validity (i.e., is associated with functional impairment). Further work is needed to determine whether other domains of neurocognitive function, dichotomized in a similar manner would be helpful when a binary clinical or research decision is called for.

Strengths of this study include the large sample of youth with and without BP-I disorder, the comprehensive assessment battery, the reliance on well-established psychometric tests of executive functions, and the use of an a priori operationalized binary definition of EFDs. The rate of EFDs in our Controls with and without ADHD is consistent with our previous work on the subjects using a similar binary definition of EFDs.

The finding that nearly half of our BP-I subjects had EFDs is consistent with a mounting literature documenting large group differences in measures of executive functioning between youth with BPD and controls (Joseph et al., 2008). Our findings that BP-I subjects with and without EFDs had similar rates of treatment and symptoms are consistent with literature documenting that neuropsychological deficits of BPD youth are not due to medication status or acute symptoms (McClure et al., 2005; Pavuluri et al., 2006; Henin et al., 2007).

The finding that the BP-I subjects with EFDs were significantly younger than the BP-I subjects without EFDs indicates that the younger age group (10-13 years) had a higher rate of EFDs compared to the older age group (14-18 years). In fact, Table 2 shows that the mean differences between the BP-I and Control subjects are larger in the younger group compared to the older group for all neuropsychological scores. Longitudinal studies should seek to

determine if there is some normalization of neurocognitive functioning as children with BP-I disorder reach adolescent years.

Also additive was the relationship between EFDs and BP on educational outcomes. The rate of placement in special class for BP-I youth without comorbid EFDs was similar to that for Controls with EFDs (29% and 24%, respectively) and both were significantly higher than the rates observed for Controls without EFDs. In contrast, the risk for placement in special class was 68% in BPD+EFD subjects. A similar trend was also observed for the rates of tutoring. Although the rate of tutoring was significantly higher in both BPD groups than in Controls and were indistinguishable from each other statistically, BPD+EFD subjects had a 13% higher rate of tutoring than other BPD subjects. BP-I subjects with EFDs had significantly more impaired scores on the WRAT arithmetic than other BP-I subjects and this association also followed an additive model.

The negative educational outcomes observed in our Controls with EFDs were clearly smaller than those observed in BPD groups. These results suggest that EFDs compound the already compromised educational functioning of a BP-I child. Taken together these results also stress that children with BP-I disorder with comorbid EFDs are at very high risk for impaired educational outcomes and that these risks are particularly compromising in subjects with BP-I disorder and ADHD.

On the other hand, there were no differences in BP-I features between BP-I subjects with and without EFDs, such as age of onset and number and type of BP-I Symptoms. This suggests that EFDs among BP-I youth is not simply an expression of a subset of these clinical features.

With the exception of higher rate of speech and language disorder in the BP-I youth with EFDs, EFDs were not associated with any other psychiatric comorbidity or unique deficits in psychosocial functioning. The reasons for the increased prevalence of speech and language disorder in youth with BP-I disorder and EFDs are unclear and require further investigation,

The finding that EFDs confers a selective risk for more impaired educational outcomes is consistent with our previous finding observed in the context of ADHD. Considering that the EF system evolved as a means of successfully negotiating an increasingly competitive social environment (Barkley, 2001), it seems plausible that the deficits associated with EFDs may become more pervasive and impairing as a person enters adulthood. Since our subjects have not passed through the age of risk for the full detrimental impact of EFDs in non-academic domains, it is possible that such deficits are not manifested until adulthood. Such a possibility is consistent with our recent work documenting that EFDs significantly increases the risk for work deficits in the context of ADHD (Biederman et al., 2006).

The finding that children with EFDs come from families with a lower SES than those without is intriguing. There are several possible explanations for this finding. First, if EFDs are at least partially genetically determined, it could be that the parents of the children with EFDs also have EFDs, and this impairment has led to lower educational and occupational achievement. Alternatively, it is also plausible that exposure to low SES environments may have impeded the neuropsychological development of children with EFDs. Unfortunately, our study design cannot tease apart the direction of the effect.

Our cut-off for EFDs, two or more tests 1.5 standard deviations from the mean of the controls, has face validity as a clinically relevant standard of EFDs. However, we recognize that our method of dichotomizing the number of tests impaired to create a binary EFD

measure may result in a loss of some information. We considered this loss of information to be a reasonable trade-off for the applicability and clinical relevance of our method.

Our results should be considered in the light of methodological limitations. The sample of BP-I participants was clinically referred, so we do not know to what degree our findings will generalize to non-referred children with BP-I disorder in the community. Thus, our results should be confirmed in community samples. Also, since the vast majority of our subjects were Caucasians, our results may not generalize to other ethnic groups. Another methodological shortcoming pertains to our assessments of psychopathology in children younger than 12 years. Although youth older than 12 years were directly interviewed, the lack of direct psychiatric interviews with children younger than twelve may have decreased the sensitivity of some diagnoses, particularly “internalizing” disorders. However, since children younger than 12 have limited expressive and receptive language abilities, there is a question about whether their lifetime history of psychopathology and behavior can be reliably assessed through self-report (Loeber et al., 1991). Although limited, studies of interview techniques for children under the age of 12 suggest that their responses are unreliable (Achenbach et al., 1987).

Although, it was not practical to conduct more than two hours worth of neuropsychological testing with study subjects, there are other interesting neuropsychological domains that were not assessed, such as measures of facial or emotional processing. Future studies should evaluate the extent to which such measures show a relationship to functional impairment. For example, it is possible that impaired facial processing would show a greater association with impaired social functioning than was found in the current study.

In addition, we relied on our own data to generate the cut-offs for defining poor performance for each executive measure within specific age groups. Although there are published norms for some of the tests in our battery, the quality of these norms varies widely in terms of the numbers of subjects in the normative group and its representativeness of the general population. The use of norms could introduce errors because the size, age range, and gender distribution of the samples used to generate the norms varies from test to test. Children may be more likely to be categorized as impaired on some executive measures than others due to differences in their normative samples. Using our own sample provides a valid case-control comparison and a meaningful estimate of the prevalence of EFDs in our BP-I sample. Because that estimate cannot be generalized to the population, improved norms or studies of population samples are needed to clarify this issue.

In a similar vein, the use of our own controls to define the cutoffs for impairment may have led to an unusual cut point since outlying observations could have a disproportionately large influence on the result. However, our control sample was large enough to minimize the effect of extreme observations. Another limitation is that, because of continuous neuropsychological development throughout childhood, we cannot say for certain that performance deficits on our battery exhibited by children at one age are due to the same mechanism as that by children of an older age. In either case, the deficit may or may not be due to EFDs. Moreover, because our control+EFD sample was small, comparisons with that group had low statistical power. Although this does not diminish the differences found with that group, negative findings should be viewed cautiously.

Despite these considerations, our results show that the presence of EFDs in youth with BP-I disorder increases significantly the already compromised educational functioning of these children, and that this effect was independent of ADHD and social class. These results suggest that children with BP-I disorder and EFDs may be at particularly high risk for a compromised educational environment. Future studies of adults with and without BP-I

disorder assessed with adequate neuropsychological measurements are needed to help clarify the full impact of EFDs beyond the educational domain.

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References

- Achenbach TM, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: Implications of cross-informant correlations for situational specificity. *Psychological Bulletin* 1987;101:213–232. [PubMed: 3562706]
- American Psychiatric Association. Text Revision (DSM-IV-TR). Fourth. American Psychiatric Association; Washington, DC: 2000. Diagnostic and Statistical Manual of Mental Disorders.
- Arts B, Jabben N, Krabbendam L, van Os J. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine* 2008;38:771–785. [PubMed: 17922938]
- Barkley RA. The executive functions and self-regulation: an evolutionary neuropsychological perspective. *Neuropsychology Review* 2001;11:1–29. [PubMed: 11392560]
- Bearden CE, Glahn DC, Caetano S, Olvera RL, Fonseca M, Najt P, Hunter K, Pliszka SR, Soares JC. Evidence for disruption in prefrontal cortical functions in juvenile bipolar disorder. *Bipolar Disorders* 2007;9:145–159. [PubMed: 17543033]
- Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Pediatric Mania: A developmental subtype of bipolar disorder? *Biological Psychiatry* 2000;48:458–466. [PubMed: 11018219]
- Biederman J, Monuteaux M, Seidman L, Doyle AE, Mick E, Wilens T, Ferrero F, Morgan C, Faraone SV. Impact of Executive Function Deficits and ADHD on Academic Outcomes in Children. *Journal of Consulting and Clinical Psychology* 2004;72:757–766. [PubMed: 15482034]
- Biederman J, Petty C, Fried R, Fontanella J, Doyle AE, Seidman LJ, Faraone SV. Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry* 2006;163:1730–1738. [PubMed: 17012683]
- Cahn-Weiner DA, Malloy PF, Boyle PA, Marran M, Salloway S. Prediction of functional status from neuropsychological tests in community-dwelling elderly individuals. *The Clinical Neuropsychologist* 2000;14:187–195. [PubMed: 10916193]
- Chen ST, Sultzer DL, Hinkin CH, Mahler ME, Cummings JL. Executive dysfunction in Alzheimer's disease: association with neuropsychiatric symptoms and functional impairment. *Journal of Neuropsychiatry and Clinical Neurosciences* 1998;10:426–432. [PubMed: 9813788]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test for Children. The Psychological Corp; San Antonio, TX: 1994.
- Dickstein DP, Treland JE, Snow J, McClure EB, Mehta MS, Towbin KE, Pine DS, Leibenluft E. Neuropsychological performance in pediatric bipolar disorder. *Biological Psychiatry* 2004;55:32–39. [PubMed: 14706422]
- Doyle AE, Biederman J, Seidman LJ, Weber W, Faraone SV. Diagnostic efficiency of neuropsychological test scores for discriminating boys with and without attention deficit-hyperactivity disorder. *Journal of Consulting and Clinical Psychology* 2000;68:477–488. [PubMed: 10883564]
- Doyle AE, Wilens T, Kwon A, Seidman LJ, Faraone SV, Fried R, Swezey A, Snyder L, Biederman J. Neuropsychological functioning in youth with bipolar disorder. *Biological Psychiatry* 2005;58:540–548. [PubMed: 16199011]
- First, M.; Spitzer, RL.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders. American Psychiatric Press; Washington, DC: 1997.

- Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, Soutullo CA. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2000;10:157–164. [PubMed: 11052405]
- Goldberg, E.; Seidman, LJ. Higher cortical functions in normals and in schizophrenia: a selective review. In: Nasrallah, HA., editor. *Handbook of Schizophrenia*. Elsevier; Amsterdam: 1991. p. 553–597.
- Golden, CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Use*. Stoelting Company; Chicago: 1978.
- Green M. What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry* 1996;153:321–330. [PubMed: 8610818]
- Hanks RA, Rapport LJ, Millis SR, Deshpande SA. Measures of executive functioning as predictors of functional ability and social integration in a rehabilitation sample. *Archives of Physical Medicine and Rehabilitation* 1999;80:1030–1037. [PubMed: 10489004]
- Heaton, RK.; Chelune, GJ.; Talley, JL.; Kay, GG.; Curtiss, G. *Wisconsin Card Sort Test Manual: Revised and Expanded*. Psychological Assessment Resources, Inc.; Odessa: 1993.
- Henin A, Mick E, Biederman J, Fried R, Wozniak J, Faraone SV, Harrington K, Davis S, Doyle AE. Can Bipolar Disorder-Specific Neuropsychological Impairments in Children be Identified? *Journal of Consulting and Clinical Psychology* 2007;75:210–220. [PubMed: 17469879]
- Hollingshead, AB. *Four Factor Index of Social Status*. Yale Press; New Haven: 1975.
- Jastak, J.; Jastak, S. *Wide Range Achievement Test*. Third. Jastak Associates; Wilmington: 1993.
- John K, Gammon GD, Prusoff BA, Warner V. The Social Adjustment Inventory for Children and Adolescents (SAICA): Testing of a new semistructured interview. *Journal of the American Academy of Child and Adolescent Psychiatry* 1987;26:898–911. [PubMed: 3429410]
- Joseph MF, Frazier TW, Youngstrom EA, Soares JC. A quantitative and qualitative review of neurocognitive performance in pediatric bipolar disorder. *Journal of Child and Adolescent Psychopharmacology* 2008;18:595–605. [PubMed: 19108664]
- Kim EY, Miklowitz DJ. Childhood mania, attention deficit hyperactivity disorder and conduct disorder: a critical review of diagnostic dilemmas. *Bipolar Disorders* 2002;4:215–225. [PubMed: 12190710]
- Loeber R, Green SM, Lahey BB, Stouthamer-Loeber M. Differences and similarities between children, mothers, and teachers as informants on disruptive child behavior. *Journal of Abnormal Child Psychology* 1991;19:75–95. [PubMed: 2030249]
- McClure EB, Treland JE, Snow J, Dickstein DP, Towbin KE, Charney DS, Pine DS, Leibenluft E. Memory and learning in pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44:461–469. [PubMed: 15843768]
- Mennin D, Biederman J, Mick E, Faraone SV. Towards defining a meaningful anxiety phenotype for research in ADHD children. *Journal of Attention Disorders* 2000;3:192–199.
- Orvaschel, H. *Nova Southeastern University. Center for Psychological Studies; Fort Lauderdale: 1994. Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version*.
- Osterrieth PA. Le test de copie d'une figure complexe. *Archives de Psychologie* 1944;30:206–256.
- Pavuluri MN, Schenkel LS, Aryal S, Harral EM, Hill SK, Herbener ES, Sweeney JA. Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. *American Journal of Psychiatry* 2006;163:286–293. [PubMed: 16449483]
- Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry* 1996;37:51–87. [PubMed: 8655658]
- Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Les Archives de Psychologie* 1941;28:286–340.
- Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders* 2006;93:105–115. [PubMed: 16677713]
- Rucklidge JJ. Impact of ADHD on the neurocognitive functioning of adolescents with bipolar disorder. *Biological Psychiatry* 2006;60:921–928. [PubMed: 16839520]

- Sattler, J. Psychological Assessment. McGraw-Hill; New York: 1988.
- Seidman LJ, Biederman J, Monuteaux MC, Doyle AE, Faraone SV. Learning disabilities and executive dysfunction in boys with attention-deficit/hyperactivity disorder. *Neuropsychology* 2001;15:544–556. [PubMed: 11761044]
- Seidman LJ, Biederman J, Valera EM, Monuteaux MC, Doyle AE, Faraone SV. Neuropsychological functioning in girls with attention-deficit/hyperactivity disorder with and without learning disabilities. *Neuropsychology* 2006;20:166–177. [PubMed: 16594777]
- Seidman LJ, Breiter HC, Goodman JM, Goldstein JM, Woodruff PW, O'Craven K, Savoy R, Tsuang MT, Rosen BR. A functional magnetic resonance imaging study of auditory vigilance with low and high information processing demands. *Neuropsychology* 1998;12:505–518. [PubMed: 9805320]
- Stata Corporation. Stata User's Guide: Release 9. Stata Corp LP; College Station: 2005.
- Wechsler, D. Manual for the Wechsler Intelligence Scale for Children. Third. The Psychological Corporation, Harcourt Brace Jovanovich, Inc.; San Antonio: 1991.
- Welsh MC, Pennington BF. Assessing frontal lobe functioning in children: Views from developmental psychology. *Developmental Neuropsychology* 1989;4:199–230.
- Wilens TE, Biederman J, Adamson JJ, Henin A, Sgambati S, Gignac M, Sawtelle R, Santry A, Monuteaux MC. Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: A controlled study. *Drug and Alcohol Dependence* 2008;95:188–198. [PubMed: 18343050]
- Wozniak J, Biederman J, Kwon A, Mick E, Faraone S, Orlovsky K, Schnare L, Cargol C, van Grondelle A. How cardinal are cardinal symptoms in pediatric bipolar disorder? An examination of clinical correlates. *Biological Psychiatry* 2005;58:583–588. [PubMed: 16197929]

Figure 1.
Percent of EFDs in youth with and without BP-I and ADHD

Figure 2.
Academic functioning in youth with and without BP-I and EFDs

Table 1
Demographic features in bipolar (BPD) children and controls with and without executive function deficits (EFDs).

Demographic Features	Controls (N=81)	Controls+EFD (N=17)	BPD (N=76)	BPD+EFD (N=62)	Test statistic	P-value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD		
Age (years)	13.6±2.1	13.9±2.3	13.7±2.1	12.8±2.4 ^{a,c*}	F _(3,232) =2.78	0.04
Socioeconomic status	1.8±0.9	2.5±1.0 ^{a,**}	2.0±1.0	2.5±1.2 ^{a***,c*}	Chi ² ₍₃₎ =17.88	<0.001
	N (%)	N (%)	N (%)	N (%)		
Gender (male)	47 (58)	12 (71)	52 (68)	49 (79)	Chi ² ₍₃₎ =7.20	0.07

^a =vs. Control-EFD

^b =vs. Control+EFD

^c =vs. BPD-EFD

* p≤0.05

** p≤0.01

*** p≤0.001

Table 2

Neuropsychological scores used to estimate executive function deficits (EFDs).

Neuropsychological score	Ages 10-13 Years	
	Controls (N=43)	BPD (N=77)
	Mean $\pm$ SD	Mean $\pm$ SD
Continuous Performance Test errors	7.3 $\pm$ 4.5	12.9 $\pm$ 7.1
Freedom from Distractibility Index	24.0 $\pm$ 5.8	18.0 $\pm$ 5.4
Stroop color-word	32.2 $\pm$ 9.8	21.9 $\pm$ 7.8
Wisconsin Card Sorting Test perseverative errors	12.9 $\pm$ 11.0	18.3 $\pm$ 12.2
Wisconsin Card Sorting Test loss of set	1.1 $\pm$ 1.5	1.4 $\pm$ 1.5
Rey-Osterrieth Complex Figure copy organization	9.0 $\pm$ 3.2	7.1 $\pm$ 2.7
Rey-Osterrieth Complex Figure delay organization	6.5 $\pm$ 3.7	5.6 $\pm$ 3.4
California Verbal Learning Test total words learned	53.7 $\pm$ 7.2	44.9 $\pm$ 11.4
	Ages 14-18 Years	
	Controls (N=55)	BPD (N=61)
	Mean $\pm$ SD	Mean $\pm$ SD
Continuous Performance Test errors	6.1 $\pm$ 4.2	7.4 $\pm$ 5.0
Freedom from Distractibility Index	21.4 $\pm$ 5.8	19.8 $\pm$ 6.4
Stroop color-word	39.6 $\pm$ 9.5	35.3 $\pm$ 8.2
Wisconsin Card Sorting Test perseverative errors	9.1 $\pm$ 5.4	14.0 $\pm$ 9.2
Wisconsin Card Sorting Test loss of set	0.8 $\pm$ 1.3	0.9 $\pm$ 1.3
Rey-Osterrieth Complex Figure copy organization	9.7 $\pm$ 3.3	9.3 $\pm$ 3.5
Rey-Osterrieth Complex Figure delay organization	8.1 $\pm$ 3.9	7.3 $\pm$ 3.7
California Verbal Learning Test total words learned	53.3 $\pm$ 7.6	47.7 $\pm$ 11.3

Table 3

Social and psychiatric outcomes and treatment in bipolar (BPD) children and controls with and without executive function deficits (EFDs).

	Controls (N=81)		Controls+EFD (N=17)		BPD (N=76)		BPD+EFD (N=62)		Test statistic	P-value
Psychosocial functioning	Mean ± SD	N (%)	Mean ± SD	N (%)	Mean ± SD	N (%)	Mean ± SD	N (%)		
GAF score	61.8 ± 7.0	NA	59.5 ± 9.1	NA	38.9 ± 5.5 <i>ab***</i>	53 (70)	38.4 ± 5.5 <i>ab***</i>	41 (66)	$F_{(3, 228)}=103.24$	<0.001
SAICA average score	2.0 ± 0.4	NA	1.9 ± 0.6	5 (29)	2.5 ± 0.6 <i>a***b**</i>	60 (79) <i>ab***</i>	2.7 ± 0.5 <i>ab***</i>	56 (90) <i>ab***</i>	$F_{(3, 121)}=9.72$	<0.001
Psychiatric comorbidity										
Major depressive disorder (with severe impairment)									$z=-0.08$	0.93
Multiple (≥2) anxiety disorders	28 (35)	NA	5 (29)	5 (29)	60 (79) <i>ab***</i>	60 (79) <i>ab***</i>	56 (90) <i>ab***</i>	56 (90) <i>ab***</i>	$\chi^2_{(3)}=36.69$	<0.001
Speech/language disorder	9 (11)	9 (11)	2 (12)	2 (12)	11 (14)	11 (14)	24 (39) <i>ac**</i>	24 (39) <i>ac**</i>	$\chi^2_{(3)}=12.81$	0.005
Oppositional defiant disorder	15 (19)	15 (19)	4 (24)	4 (24)	70 (92) <i>ab***</i>	70 (92) <i>ab***</i>	58 (94) <i>ab***</i>	58 (94) <i>ab***</i>	$\chi^2_{(3)}=58.47$	<0.001
Conduct disorder	9 (11)	9 (11)	3 (18)	3 (18)	52 (68) <i>ab***</i>	52 (68) <i>ab***</i>	41 (66) <i>a***b**</i>	41 (66) <i>a***b**</i>	$\chi^2_{(3)}=37.74$	<0.001
Tics/Tourettes disorder	10 (12)	10 (12)	1 (6)	1 (6)	18 (24)	18 (24)	18 (29)	18 (29)	$\chi^2_{(3)}=1.98$	0.58
Psychoactive substance use disorder	4 (5)	4 (5)	1 (6)	1 (6)	29 (38) <i>a***b**</i>	29 (38) <i>a***b**</i>	11 (18) <i>a***</i>	11 (18) <i>a***</i>	$\chi^2_{(3)}=25.49$	<0.001
Smoking	4 (5)	4 (5)	1 (6)	1 (6)	23 (30) <i>a***b*</i>	23 (30) <i>a***b*</i>	11 (18) <i>a*</i>	11 (18) <i>a*</i>	$\chi^2_{(3)}=16.82$	<0.001
Treatment for bipolar disorder										
None	--	--	--	--	4 (5)	4 (5)	3 (5)	3 (5)		
Counseling only	--	--	--	--	3 (4)	3 (4)	2 (3)	2 (3)		
Pharmacotherapy only	--	--	--	--	5 (7)	5 (7)	1 (2)	1 (2)	$\chi^2_{(4)}=2.47$	0.65
Counseling+Pharmacotherapy	--	--	--	--	30 (39)	30 (39)	30 (48)	30 (48)		
Hospitalization	--	--	--	--	34 (45)	34 (45)	26 (42)	26 (42)		

^a =vs. Control-EFD

^b =vs. Control+EFD

^c =vs. BPD-EFD

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

NA=Not applicable due to exclusion criteria