Passarotti et al., Bipolar Disord 2015, 1:1
DOI: 10.4172/2472-1077.1000101

Bipolar Disorder: Open Access

Research Article Open Access

Executive Function in Adolescent Bipolar Disorder With and Without ADHD Comorbidity

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Abstract

Background: In adolescents with bipolar disorder (ABD) a profile of mood dysregulation, impulsivity and poor cognitive control has been associated with poor executive function. However the underlying mechanisms of real-life executive dysfunction in ABD are scarcely understood.

Method: This study examined domains of Executive Function (EF) in twenty-nine adolescents with adolescent bipolar disorder (ABD), with and without ADHD comorbidity (mean age=12.66; SD=2.21), using the Behavioral Rating Inventory of Executive Function-Parent Report (BRIEF-PR), the Revised Conners' Parental Rating Scale (CPRS-R), and standardized neuropsychological tests of attention, working memory and executive function. Moreover, we explored whether ADHD comorbidity in ABD may worsen EF.

Results: Our findings indicate that relative to population norms both patient groups exhibited significant impairment on the BRIEF sub-domains. Moreover, the comorbid group was significantly more impaired than the ABD group in the BRIEF-PR Monitoring domain.

Conclusion: The current findings document pervasive deficits in everyday life executive function and related cognitive and affective domains in ABD, while also contributing initial knowledge about the effects of ADHD comorbidity in ABD on executive function.

Keywords: Bipolar; Adolescent; ADHD; Comorbidity; Executive function; Emotion; Attention; Working memory

Introduction

Pediatric bipolar disorder is a debilitating developmental illness characterized by chronic emotional dysregulation, mania and hypomania, elation, grandiosity, irritability, racing thoughts, decreased need for sleep, and hyper-sexuality [1-3]. According to a recent meta-analysis of international epidemiological studies the estimated prevalence of the pediatric bipolar spectrum is 1.8% [4]. There is now growing evidence that in addition to chronic mood dysregulation adolescents with bipolar disorder (ABD) exhibit also significant neurocognitive deficits in executive functions, attention and verbal working memory, which affect all aspects of daily life functioning [5-8]. These deficits are somewhat independent of comorbid attention-deficit hyperactivity disorder (ADHD) [6,8], persist in euthymic state [6] and worsen with development if not treated [7]. Pharmacological and psychosocial interventions in ABD focus primarily on the affective symptoms, and mood medications are not usually effective in fully treating the neurocognitive deficits [9-12]. This leads to poor academic and psychosocial functioning [13], with lifelong negative outcome [14,15].

These findings suggest trait-related cognitive deficits that may represent core features and potential markers of neuropathology and disease vulnerability in ABD youths. However, we still do not know the underlying mechanisms of dysfunction, and a deeper understanding needs to be reached in order to inform diagnosis and cognitive treatment in ABD. Since executive functions play a key role in self-regulation and adaptive behavior it is of paramount importance to understand executive function deficits and how they may be remediated in this patient population early in development, when brain and cognitive systems are more malleable.

Executive functions (EF) are a multi-dimensional system that supervises and monitors multiple processes such as attention, working memory, cognitive flexibility, monitoring, goal-directed behavior and decision-making. Maturation of the neural substrates of EF throughout adolescence is associated with marked improvements not only in cognitive control but also in emotional regulation [16-20]. Notably, cognitive and emotional regulation are chronically impaired in ABD [3,11]. However, we do not have a comprehensive explanatory model of these functional regulatory deficits.

The first study goal was to examine multiple dimensions of EF as they relate to *cognitive* and *emotional control* in youth with bipolar disorder. One significant challenge to this goal is that it is often difficult to clearly grasp the extent of everyday EF dysfunction in mentally-ill patients by solely using laboratory tasks that provide an artificial structure and simplified task demands compared to real life situations. Moreover, most of the published studies on EF do not directly measure emotion regulation as part of EF while in fact these two aspects are quite intertwined during development, and especially so in ABD pathophysiology [15,21,22]. Therefore, it is important to use neuropsychological scales that are sensitive enough to differentiate multiple behavioral domains of EF, including those related to emotional

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Received September 15, 2015; **Accepted** December 28, 2015; **Published** January 05, 2016

Citation: Passarotti AM, Trivedi N, Patel M (2016) Executive Function in Adolescent Bipolar Disorder With and Without ADHD Comorbidity. Bipolar Disord 1: 101. doi:10.4172/2472-1077.1000101

regulation. These multiple domains can then be measured in more depth through neurocognitive tasks that identify specific operations and that parametrically vary difficulty levels for each cognitive domain.

In order to examine the complex construct of EF all participants were administered the Behavior Rating Inventory of Executive Function –Parental Report (BRIEF-PR) scale for children [23,24], a developmentally appropriate standardized scale that concurrently measures multiple domains of EF (e.g., working memory, inhibition, shift, planning, monitoring, emotional control). These specific domains map onto recent findings of brain circuit dysfunction in lateral prefrontal and limbic regions in bipolar disorder [15,25]. While there is not currently any published data on EF in ABD, a study on adults with BD Type I [26] found significant deficits on every domain of executive function in real life setting using the adult version of the BRIEF scale (BRIEF-A) [27], which correlated with severity of mood symptoms. However, we still do not know whether the same results may occur in youth with bipolar disorder who are still developing.

The second study goal was to examine whether patients with ABD and ADHD comorbidity may exhibit worse executive dysfunction relative to patients with ABD only, which has implications for tailored interventions. A better differentiation of the ABD and ADHD phenotypes is a very important and still unresolved clinical issue. In fact, high comorbidity rates and symptom overlap [28] between pediatric bipolar disorder and ADHD complicate the diagnostic process and may delay appropriate treatment [3,29,30].

Based on the existing literature our overarching hypothesis was that ABD patients would be impaired in both cognitive and emotional domains of the BRIEF-PR scale. We predicted that mood symptoms would affect EF domains involved in inhibition and self-control. Furthermore, we hypothesized that relative to patients with ABD only, patients with ADHD comorbidity may exhibit worse attention-related processes because of the generalized inattention and dis-inhibition typical of ADHD symptoms [31,32].

Method

Participants

ABD patient participants were recruited from the Pediatric Mood Disorder Clinic, at the Department of Psychiatry, University of Illinois at Chicago, and from the community, through clinician referrals, fliers, and postings**.** The present study was approved by the University Institutional Review Board. Consent from one parent or legal guardian and assent from minors were obtained. The sample (age range=9-16 years; mean age=12.66 ± 2.21 years) consisted of 29 pediatric patients with a diagnosis of pediatric bipolar disorder, narrow phenotype (Type I, Type II), 13 of which had a diagnosis of comorbid ADHD, Type Combined. Twenty-six of our patients were on a regimen of psychotropic medications at the time of testing. Groups were matched based on age, gender, and Intelligence Quotient (IQ) as estimated with the Wechsler Abbreviated Scale of Intelligence (WASI) [33]. The clinical diagnoses were based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [34]. Additionally, the Young Mania Rating Scale (YMRS) [35] and the Child Depression Rating Scale-Revised (CDRS-R) [36] were administered to all participants. The Behavioral Rating Inventory of Executive Function, Parental Report (BRIEF-PR) [23] and the Revised Conners' Parent Rating Scale [37] (CPRS-R) were administered to assess executive and attentional functions. Inclusion criteria were as follows: 8 to 19 years of age for all subjects; for the ABD group axis one diagnosis of bipolar disorder Type I or II, based on DSM-IV-TR. ABD patients with a diagnosis of comorbid ADHD based on the DSM-IV criteria were accepted in the study. Patients were excluded from the study if they had a history of head trauma with loss of consciousness for more than 10 minutes, neurological symptoms, speech or hearing difficulties, a primary diagnosis other than bipolar disorder and an IQ score lower than 70.

Standardized neuropsychological scales

The *behavior* rating inventory of executive function -parental report (brief-pr) scale: The BRIEF-PR scale [23] is an 86-item scale for parental report on child's behaviors (age: 5 to 18 years). It consists of 8 clinical scales measuring different aspects of executive functioning: Inhibition, Shift, Emotional Control, Initiation, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The eight scales compose a Behavioral Regulation index and a Metacognition index. The *Behavior Regulation Index* (BRI) comprises components of behavior regulation, such as Inhibition, Shift, and Emotional Control, and measures the child's ability to control his/her behavior as it relates to impulsiveness, cognitive flexibility, and emotions. The *Metacognition Index* (MI) comprises components of metacognition, such as Initiation, Working Memory, Plan/Organize, Monitor and Organization of Materials. It measures metacognition skills related to beginning new activities, paying attention, remembering and focusing while completing activities, goal-setting and organization, monitoring performance, taking care of own belongings and cleaning up. The BRI and MI comprise a *Global Executive Composite* (GEC) which measures global functioning. The scale to index configuration is based on the theoretical assumption that there are separable regulatory functions in a clinically meaningful way, but also that they are related to an overarching executive system [38]. Each item in the questionnaire is rated as "never", "sometimes", or "often". Higher scores indicate greater functional impairment. Raw scores for each sub-scale are converted into standardized T scores based on four developmental groups and gender.

The revised conners' parent rating scale (cprs-r): The CPRS-R [37] obtains parental report of child behavior problems such as ADHD and related symptoms (age: 3-17 years). It comprises the following sub-scales: Oppositional (i.e., conduct disorder), Cognitive Problems/ Inattention (i.e., inattention), Hyperactivity (i.e., impulsivity and hyperactivity), and ADHD Index. Parents rate each of the 27 items using a 4-point Likert scale ranging from 0 (not at all) to 3 (very much true). Raw scores for each sub-scale are converted into standardized T scores based on five age groups and on gender.

Standardized neuropsychological tests

Participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI) [33] to assess global intellectual functioning and derive the Full Scale IQ (FSIQ). Moreover, the neurocognitive domains of interest and the tests used to assess them were as follows: *Attention (*including attention and processing speed*)*: Trail Making Test (TMT) A [39]; *Executive Functions* (including working memory, cognitive flexibility and processing speed): TMT B [39]; *Verbal Working Memory*: Digit Span Test (forward, backward) (WISC III) [40]; *Academic skills*: Reading Fluency (assessing reading comprehension skills) and Math Fluency (assessing math and calculation skills) from the Woodcock-Johnson Tests of Achievements [41].

Note that both the forward and backward Digit Span tests require working memory (i.e., the ability to hold and maintain information in mind for a few seconds). However, relative to the forward digit span

test the backward digit span test additionally requires to manipulate the numerical information present in working memory, in order to repeat the numbers backwards.

Demographic, clinical and behavioral data analyses

Statistical data analyses: To examine whether the two patient groups may differ on demographic and clinical measures separate ANOVAs were carried out on a given measure (e.g., Age, Estimated IQ, YMRS, CDRS) as the within-subject factor, and group (ABD, ABD+ADHD) as the between-subjects factor. Pearson Chi Squared tests were carried out for categorical variables (gender, race) (Table 1).

With regard to the BRIEF-PR and the CPRS-R the raw scores for each sub-scale were transformed into T scores (with mean=50 and SD=10). Moreover, for the BRIEF-PR the BRI, MI, and GEC indexes were also obtained. T-tests were used to compare the patients' mean T scores to population norms to assess whether patients' scores were at clinically significant levels of impairment. Typically, a T>60 is considered as indicating a clinically significant deficit (i.e., greater than 1 SD from the population mean). Effect size (ES) was measured for each of these neuropsychological variables using Cohen's d, where a d=1 indicates that the patients' scores differed significantly from the normative scores by 1 standard deviation (SD) (Table 2). ANOVAs examined group differences for each of the BRIEF sub-scales and indexes and for the CPRS-R sub-scales.

For the Digits Span Test raw data were transformed into scaled scores (ss: mean=10, SD=3), and a composite working memory scaled score was obtained after summing the forward and backward digit span scores. For Trails A and B raw scores were transformed into Z scores. For Reading and Math Fluency scores, we transformed the raw scores into age (AE) and grade (GE) estimates. Separate ANOVAs were performed for each of the tasks considered.

Finally, exploratory Pearson's correlation analyses examined correlations between executive functions as measured with the BRIEF scale and the other study measures.

Results

Demographic and clinical data

Demographic and clinical data for all participants are presented in Table 1. The ABD and ABD+ADHD groups did not differ on demographic measures and IQ scores, as estimated with the WASI, which were in the average range. Moreover, there were no significant group differences on clinical measures of manic (YMRS) and depressive (CDRS-R) symptoms.

Neuropsychological assessment results

BRIEF-PR scale results: Table 2 illustrates mean T score and standard deviation for each subscale of the BRIEF-PR in each group. Relative to healthy population norms the two patient groups exhibited significant ($p<0.05$) performance deficits in all BRIEF sub-domains, as well as in the BRI, MI and GEC. Post-hoc comparisons indicate that the ABD+ADHD group had significantly higher scores than the ABD group in the Monitoring sub-domain [$F(1,27)=8.403$; $p<0.007$]. There was also a non-significant trend such that the ABD+ADHD group had higher scores than the ADB group on the Inhibition sub-scale ($p=0.08$) (Figure 1).

CPRS-R results: As shown in Table 1, the Conners' ADHD Index scores were elevated to clinically significant levels in both groups (ABD T=72, in ABD+ADHD T=77); however there were no significant group differences. There was only a non-significant trend ($p=0.09$) such that ABD+ADHD yielded more elevated scores than ABD on the Inattentive subscale.

Neurocognitive results: As Table 3 illustrates, both patient groups showed clinically significant impaired scores on the neuropsychological tests, with the exception of the Digit Span Test were scores were within the average range. Relative to the comorbid group the ABD group yielded significantly worse completion times on TMT A [$F(1,27)=4.24$, $p=0.049$] and a non-significant trend for worse completion times on the TMT B [$F(1,27)=3.97$, $p=0.06$]. However, the comorbid group had an

	ABD (n=16)	ABD with ADHD (n=13)	Total (n=29)	
	Mean (SD/%)	**Mean (SD/%)**	**Mean (SD/%)**	***(F), p* value**
Variables				
Age (years)	12.62 (2.217)	12.69 (2.29)	12.66 (2.21)	(0.01), p=0.94
WASI-FSIQ	96.69 (15.42)	99.92 (14.44)	98.24 (14.74)	(0.29), p=0.60
YMRS	16.07 (8.89)	13.15 (8.68)	14.71 (8.76)	(0.76), p=0.39
CDRS-R	29.47 (7.30)	30.54 (9.76)	29.96 (8.38)	(0.11), p=0.74
Connors Oppositional Scale	70.00 (11.97)	69.85 (12.27)	69.93 (11.88)	(0.001), p=0.97
Connors Inattention Scale	68.31 (14.89)	76.46 (8.04)	71.97 (12.79)	(3.14), p=0.09
Connors Hyperactivity Scale	74.94 (11.42)	74.77 (14.35)	74.86 (12.57)	(0.001), p=-0.97
Connors ADHD Index	71.88 (11.09)	77.15 (8.22)	74.24 (10.10)	(2.03), p=0.17
Variables	**N (%)**	**N (%)**	**N (%)**	**Pearson Chi Squared**
Gender				**(two-tailed)**
Male	8 (50%)	8 (61.5%)	16 (55%)	p=0.54
Female	8 (50%)	5 (38.5%)	13 (45%)	
Race				
Caucasian	11 (69%)	9 (69.2%)	20 (69%)	p=0.89
Asian	2 (12.5%)	1 (7.7%)	3 (10%)	
African-American	3 (18.8%)	3 (23.1%)	6 (21%)	

Note. FSIQ was estimated with Wechsler Abbreviated Scale of Intelligence (WASI; Matrix Reasoning and Vocabulary Subtests); YMRS=Young Mania Rating Scale; CDRS-R=Child Depression Rating Scale-Revised.

Table 1: Demographic and clinical characteristics for the adolescent bipolar disorder group (ABD), the adolescent bipolar disorder group with ADHD comorbidity (ABD+ADHD), and the combined sample.

BRIEF Subscales	Group	Mean T (SD)	t	p	Cohen's d	Effect Size
Inhibition	*ABD*	70.13 (11.35)	7.09	p<0.0001	1.88	0.69
	ABD+ADHD	77.46 (10.26)	9.65	p<0.0001	2.71	0.80
Shifting	*ABD*	70.25 (10.31)	7.86	p<0.0001	1.99	0.71
	ABD+ADHD	69.85 (11.82)	6.051	p<0.0001	1.81	0.67
Emotional control	*ABD*	74.13 (7.10)	13.60	p<0.0001	2.78	0.81
	ABD+ADHD	68.85 (14.86)	4.57	p<0.001	1.49	0.60
Initiation	*ABD*	65.94 (11.64)	5.485	p<0.0001	1.75	0.66
	ABD+ADHD	71.08 (7.61)	9.99	p<0.0001	2.37	0.76
Working memory	*ABD*	70.69 (11.00)	7.53	p<0.0001	1.97	0.70
	ABD+ADHD	76.08 (6.24)	15.07	p<0.0001	3.13	0.84
Planning/Organization	*ABD*	68.88 (10.58)	7.13	p<0.0001	1.83	0.68
	ABD+ADHD	71.62 (10.28)	7.58	p<0.0001	2.13	0.73
Organization of Material	*ABD*	61.69 (10.45)	4.47	p<0.0001	1.14	0.50
	ABD+ADHD	65.46 (5.99)	9.30	p<0.0001	1.88	0.68
Monitoring	*ABD*	71.06 (6.72)	12.54	p<0.0001	2.47	0.78
	ABD+ADHD	78.31 (6.66)	15.32	p<0.0001	3.33	0.86
Behavior Regulation Index (BRI)	*ABD*	75.56 (8.25)	12.40	p<0.0001	2.79	0.81
	ABD+ADHD	75.38 (10.41)	8.79	p<0.0001	2.49	0.78
Metacognition Index (MI)	*ABD*	72 (10.56)	8.33	p<0.0001	2.14	0.73
	ABD+ADHD	77.92 (8.92)	11.29	p<0.0001	2.95	0.83
Global Executive Composite (GEC)	*ABD*	73.44 (9.56)	9.81	p<0.0001	2.40	0.77
	ABD+ADHD	77.85 (7.56)	13.28	p<0.0001	3.14	0.84
Connors Oppositional Score	*ABD*	70 (11.97)	6.685263	p<0.0001	1.81	0.67
	ABD+ADHD	69.85 (12.27)	5.833333	p<0.0001	1.77	0.66
Connors Inattention Score	*ABD*	68.31 (14.89)	4.919589	p<0.0001	1.44	0.58
	ABD+ADHD	76.46 (8.04)	11.87031	p<0.0001	2.91	0.82
Connors Hyperactivity Score	*ABD*	74.94 (11.42)	8.737599	p<0.0001	2.32	0.76
	ABD+ADHD	74.77 (14.35)	6.224426	p<0.0001	2.00	0.71
Connors ADHD Index T score	*ABD*	71.88 (11.09)	7.892283	p<0.0001	2.07	0.72
	ABD+ADHD	77.15(8.22)	11.90414	p<0.0001	2.97	0.83

Table 2: Mean T scores and standard deviation (SD) for each of the BRIEF sub-scales for the Adolescent Bipolar Disorder (ABD) group and the Adolescent Bipolar Disorder group with ADHD comorbidity (ABD+ADHD). Cohen's d and effect size for patient group scores relative to population norms (i.e., T=50) are reported.

	ABD (n=16)	ABD+ADHD (n=13)	Statistical Analyses (F), p
TMT A (sec) **Z score** ***Errors (n)***	43 sec; Z=4.57 0.37	35 sec; Z=2.41 0.46	(4.24), p=0.05
TMT B (sec.) **Z score** ***Errors (n)***	123 sec; Z=7.13 1.19	94 sec; Z=3.89 0.62	(3.97), p=0.06
Digit Span Task, ss (SD)	ss=9 (2.16)	ss=10 (3.47)	(0.099), p=0.76
Math Fluency Raw (SD)	59 (26.42)	68 (29.28)	(0.699), p=0.41
Math Fluency (AE; GE)	10-0; 4.6	10-9; 5.4	-
Reading Fluency Raw (SD)	53 (22.26)	59 (18.50)	(0.741), p=0.40
Reading Fluency (AE; GE)	12-3; 6.9	13-8; 8.4	-

Table 3: Mean standardized scores on the TMT A&B, the Digit Span Task, and Math and Reading Fluency Tests from the Woodcock-Johnson Tests of Achievement in ABD, ABD+ADHD, and the combined sample; ss=scaled score; AE=Age Estimate; GE=Grade Estimate.

elevated number of errors on both TMT tests compared to ABD. The two groups did not differ significantly on the Digit Span test [F (1, 27) =0.10, p=0.76], on the Math Fluency test [F (1, 27) =0.70, p=0.41] or the Reading Fluency test [(F (1, 27) =0.74, p=0.40].

Correlation analyses results

Correlation results are reported in Table 4. Correlation results did not survive Bonferroni corrections for multiple comparisons. For exploratory purposes, we briefly present here significant correlation results across all patients' data, with an uncorrected p value.

Correlations between BRIEF-PR scores and academic performance: There was a negative correlation between Math Fluency scores and the BRIEF GEC (r=-0.40, p<0.05) and MI (r=-0.53, p<0.01) scores. Math Fluency scores also correlated negatively with the BRIEF scores for Shifting (r=-0.38, p<0.05) and Planning/Organization (r=-0.43, p<0.05).

Correlation between BRIEF-PR scores and neurocognitive tasks: The Digit Span test scores correlated negatively with the BRIEF Inhibition scores (r=-0.38, p<0.05). No other results were significant.

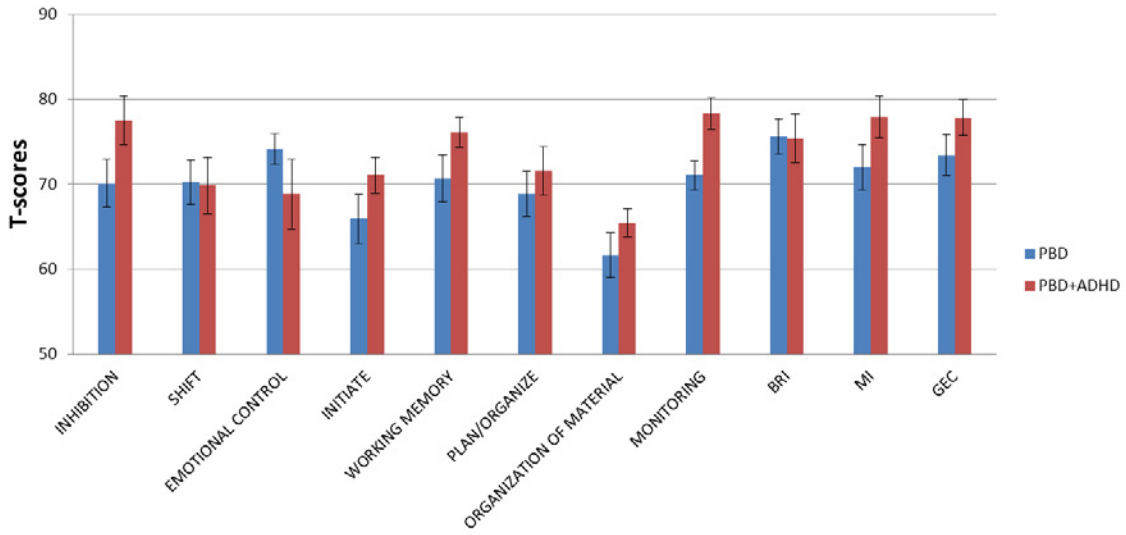

Figure 1: T scores on the BRIEF sub-scales for the ABD and ABD+ADHD groups. *=significant group difference, p<0.01. Error bars represent standard error of the mean (SEM).

	TMT A	TMT B	Digit Span Test	Math Fluency	Reading Fluency	YMRS	CDRS-R	CPRS-R ADHD Index
Inhibition	-0.16	-0.007	**-0.38***	-0.16	-0.20	**0.38***	0.23	0.27
Shifting	0.22	0.27	-0.13	**-0.45***	-0.31	-0.13	0.31	0.00
Emotional Control	0.11	0.07	-0.11	-0.32	-0.36	-0.08	0.29	0.11
Initiation	-0.12	-0.02	0.06	-0.23	0.005	-0.20	0.31	**0.55****
Working memory	-0.12	-0.12	0.03	-0.14	0.02	-0.04	0.35	**0.57****
Planning/Organization	0.02	0.13	0.09	**-0.43***	-0.18	-0.13	0.22	**0.51****
Organization of Material	0.14	0.21	0.06	-0.26	-0.15	-0.01	0.28	**0.43***
Monitoring	-0.08	-0.02	-0.29	**-0**.12	-0.02	0.004	0.03	0.25
Behavior Regulation Index (BRI)	-0.03	0.04	-0.22	-0.17	-0.12	-0.03	**0.39***	0.15
Metacognition Index (MI)	0.09	0.13	-0.19	**-0.53****	**-0.37***	0.17	**0.38***	**0.52****
Global Executive Composite (GEC)	0.003	0.11	-0.13	**-0.40***	-0.22	-0.08	**0.42***	**0.52****

Table 4: Significant and non-significant results for Pearson correlations (r, p value) between BRIEF sub-scales and neuropsychological tasks, mood scales (YMRS, CDRS) or ADHD Index score from the Conners' ADHD Rating scale across all ABD patients. * p<0.05 **; p<0.01.

Correlations between BRIEF-PR scores and mood scores or cprs-r ADHD index: There was a significant positive correlation between the BRIEF Inhibition scores and YMRS scores (r=0.38, p<0.05). There were also significant positive correlations between CDRS-R scores and the GEC (r=0.42, p<0.05), BRI (r=0.39. p<0.05), and MI (r=0.38, p<0.05). The CPRS-R ADHD Index scores correlated positively with the BRIEF GEC (r=0.52, p<0.01) and MI (r=0.52, p<0.01) as well as with Initiation (r=0.55, p<0.01), Working Memory (r=0.57, p<0.01), Planning/Organization (r=0.51, p<0.01), and Organization of Material (r=0.43, p<0.05).

Discussion

The present findings are among the first to demonstrate dysfunction in multiple real-life dimensions of EF related to cognitive and emotional control in ABD youth, with and without ADHD comorbidity. Moreover, our results shed some preliminary light on how EF may relate to mood, cognitive domains and academic skills in ABD.

In line with our hypotheses we found that ABD patients exhibited clinically significant deficits in all sub-scales of the BRIEF-PR as well as the behavior regulation, metacognition and global functioning composites. Greater impairment was found in the domains of inhibition, working memory, planning and monitoring, and emotional control. The present results agree with findings of neurocognitive deficits in inhibition, attention, working memory, and cognitive flexibility in ABD youth [2,11,42]. Relatedly, brain imaging findings in ABD have shown altered functioning in EF circuits during fMRI tasks measuring working memory [21], inhibition [43-45] and the cognitive-affective interface [46-52].

With regard to the question of whether BRIEF domain scores may be mediated by neurocognitive performance, our correlation results did not survive Bonferroni corrections and therefore do not provide any clear-cut results. Future studies with larger samples may further examine the possible relation between Inhibition scores on the BRIEF-PR and working memory tasks such as the Digit Span Test. Similarly, it may be important to further examine the potential relation between BRIEF-PR Monitoring or Global Functioning scores and academic skills such as math calculations. Previous studies showed a close relationship between EF and math skills in healthy children, and more specifically in bipolar youths [7,53], since math calculations require not only efficient attention and working memory processes, but also intense executive control and continuous monitoring of multiple cognitive operations until a solution is reached.

Furthermore, we wished to study the relation between EF and emotional regulation in ABD [15,21,22]. The present findings suggest that both patient groups showed clinically significant impairment on the BRIEF Emotional Control domain, which is in line with the clinical manifestations of BD. While preliminary, our correlation results suggest a possible relation between severity of mania and deficits on the BRIEF-PR Inhibition domain, that is, impulsivity. Impulsivity has been suggested as a prominent phenotype in bipolar disorder [54]. Interestingly, our preliminary results are in line with the only published study on BRIEF measures in adult BD patients, which also found that manic symptoms predicted impairment in the Inhibition domain on the BRIEF-A scale [26]. This similarity between child and adult BD results is suggestive of persistency of the underlying mechanisms of impulsivity through the lifespan.

Understanding the interaction between affect and EF is particularly important in bipolar pathophysiology, where affect and cognition deficits are highly and uniquely interconnected [15,21]. For instance, recent studies found that cognitive functioning worsened in ABD in the presence of negative emotions, suggesting a direct link between an over-reactivity to negative emotions in and poor cognitive performance in these patients [7,21,43,48]. While the current results are preliminary, they confirm the importance of studying emotional influences on impulsivity (i.e., emotional impulsivity) in youth with BD with or without ADHD comorbidity, to help better understand and differentiate the clinical phenotype of ABD from other developmental illnesses suffering from impulsivity [15].

A second study goal was to investigate the effects of ADHD comorbidity on EF in ABD youth. The present results indicate that the ABD+ADHD group exhibited overall more impairment on the BRIEF-PR scale relative to the ABD group. More specifically, ABD+ADHD exhibited significantly greater impairment than ABD in the Monitoring domain, and a non-significant trend for greater impairment than ABD in the Inhibition domain, and the Metacognition Index (MI). The two groups, however, did not differ on the Behavior Regulation Index (BRI), or on the global Executive Composite (GEC), suggesting that the comorbid group differs from ABD in terms of specific sub-domains rather than broader categories of EF.

Monitoring functions heavily rely on sustained attention, selective attention and working memory. Interestingly, our current results are in line with findings of greater intra-subject variability in attention and monitoring in individuals with ADHD [55,56] as well as in children at familial risk for BD who have an existing diagnosis of ADHD [57]. Deficits in inhibition are also well documented in ADHD [58,59]. However, it is not always the case that children with ADHD have worse inhibition deficits compared to those with ABD [43].

Our current neurocognitive findings on effects of ADHD comorbidity in BD are not definite. The two groups did not differ in verbal working memory performance, as assessed with the Digit Span Test. Moreover, against our expectations it was the ABD group who had longer completion times than ABD+ADHD on the TMT A, a test of visual attention and processing speed, and just missed significantly worse completion times than ABD on the more complex TMT B, involving task shifting, working memory, and inhibition. However, the comorbid group, while faster, had more elevated errors on these tests, suggesting a speed-accuracy trade-off that is possibly related to poor attention and monitoring.

Past research evidence has been ambiguous in terms of whether the comorbid group may present with worse attentional performance on cognitive tests or not. In a neurocognitive study by Pavuluri et al. [6] ADHD comorbidity was found to exacerbate deficits in attention, working memory and executive functions in youth with bipolar disorder. A recent study [60] did not find differences due to ADHD comorbidity in bipolar youth while performing an affective synonym matching task, with the exception of reduced accuracy in the comorbid group when neutral words were embedded with negative words, which may suggest poorer selective attention. Moreover, while a fMRI study by Adler et al. [61] found worse neural deficits in posterior temporo-parietal regions during a simple attention task in a comorbid group relative to ABD only, recent fMRI studies did not find more severe dysfunction in the comorbid group relative to BD youth during tasks involving attention and response inhibition [44,45]. The discrepancy in behavioral and fMRI results points to the need for a better definition of a neurobiological model of ADHD comorbidity in ABD, and the development of specific, more sensitive, neurocognitive measures to assess the comorbid phenotype.

The current findings, while preliminary, may provide some insights for the development of cognitive remediation programs that are tailored to ABD patients, with their unique challenges stemming from altered interactions between cognitive and affective systems [21,43,48]. Cognitive remediation studies in children have found general improvement in working memory functions closely related to the trained exercises [62,63] or improvement in math skills after training in children with poor working memory [64]. However, to date there are no published studies on cognitive remediation in bipolar youth, and no clear models explaining how the pairing of EF and emotion deficits in bipolar youth may influence the outcome of cognitive interventions.

Notably, recent developmental studies confirm the importance of EF in affect regulation. A study by Lantrip et al. [65] examined the relationship between emotion regulation and EF in the everyday life using the BRIEF-Self-Report scale with 12-18 years old typically developing adolescents. Results indicated that adolescents with better executive functions had also greater ability to use reappraisal as an emotion regulation strategy in their life was associated with better executive functions, while reliance on suppression was associated with poorer executive functions. Hence, the potential of cognitive remediation in ABD might be significant, given that by strengthening the cognitive executive systems in the dorsolateral prefrontal cortex we may target the mechanisms of cognitive recovery and resilience, which may in turn lead to more efficient learning of emotion regulation skills.

A strength of the current study is that it gathered data from multiple sources, such as parental reports on the child's executive functions in daily functioning, clinical scales measuring mood, and standardized neuropsychological tests of attention, working memory and executive functions. However, there are also a few limitations that limit generalizability of the current findings and suggest caution with data interpretation. Our samples were relatively small, and larger samples may be needed to better characterize differences in specific EF domains in ABD+ADHD relative to ABD. At the time of study assessment the ABD patients were not fully remitted and exhibited mania and depression symptoms which may have potentially affected ADHD symptoms. Therefore, based on the present data it is difficult to disentangle the specific contribution of mood or ADHD symptoms, or their addition, to executive dysfunction in ABD. Moreover, it is important to note that our correlation results did not survive Bonferroni corrections. Therefore they should be considered just as a preliminary examination and should be interpreted with caution. Furthermore, since this study is cross-sectional we cannot elucidate

the developmental trajectory of executive dysfunction, especially as it relates to emotional regulation, in ABD. Longitudinal studies will need to investigate how the neuro-developmental progression of bipolar illness hinders normal development of executive functioning. Finally, there is some evidence that ADHD ratings may be more susceptible to parental rater biases, because the capturing of ADHD symptoms is based on more subjective criteria relative to other more socially disruptive behaviors [66]. Therefore it is possible that the parental evaluation of ADHD-like symptoms in the ABD group without ADHD and in the comorbid group may be somewhat inflated or deflated, based on individual differences in parental expectations. However, our study measured ADHD symptoms with the Conners' Parent Rating Scale, which has been found to be particularly robust against rater biases [67].

In conclusion, findings from the present study document pervasive deficits in everyday life executive function and related cognitive domains in ABD. The present results inform future studies aimed at developing illness-specific interventions based on explanatory models of how executive dysfunction in ABD may modulate cognition and affect.

References

1. Geller B, Warner K, Williams M, Zimerman B (1998) Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. J Affect Disord 51: 93-100.
2. Pavuluri MN, Passarotti A (2008) Neural bases of emotional processing in pediatric bipolar disorder. Expert Rev Neurother 8: 1381-1387.
3. Galanter CA, Leibenluft E (2008) Frontiers between attention deficit hyperactivity disorder and bipolar disorder. Child Adolesc Psychiatr Clin N Am 17: 325-346.
4. Van Meter AR, Moreira AL, Youngstrom EA (2011) Meta-analysis of epidemiologic studies of pediatric bipolar disorder. J Clin Psychiatry 72: 1250-1256.
5. Dickstein DP, Garvey M, Pradella AG, Greenstein DK, Sharp WS, et al. (2005) Neurologic examination abnormalities in children with bipolar disorder or attention-deficit/hyperactivity disorder. Biol Psychiatry 58: 517-524.
6. Pavuluri MN, Schenkel LS, Aryal S, Harral EM, Hill SK, et al. (2006) Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. Am J Psychiatry 163: 286-293.
7. Pavuluri MN, West A, Hill S, Jindal K, Sweeney JA, et al. (2009) Neurocognitive functions in pediatric bipolar disorder: 3-year follow-ups show cognitive development lagging behind health youth. J Am Acad Child Adolesc Psychiatry 48: 299-307.
8. Doyle AE, Willcutt EG, Seidman LJ, Biederman J, Chouinard VA, et al. (2005) Attention-Deficit/Hyperactivity Disorder Endophenotypes. Biological Psychiatry 57: 1324-1335.
9. Pavuluri MN, Schenkel LS, Aryal S, Harral EM, Hill SK, et al. (2006) Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. Am J Psychiatry 163: 286-293.
10. Pavuluri MN, Passarotti AM, Parnes SA, Fitzgerald JM, Sweeney JA, et al. (2010) A Pharmacological fMRI study probing the interface of cognitive and emotional brain systems in pediatric bipolar disorder. Journal of Child and Adolescent Psychopharmacology 20: 395-406.
11. Passarotti AM, Sweeney JA, Pavuluri MN (2011) Fronto-limbic Dysfunction in Mania Pre-Treatment and Persistent Amygdala Over-activity Post-Treatment in Pediatric Bipolar Disorder. Psychopharmacology 216: 485-499.
12. West AE, Pavuluri MN (2009) Psychosocial treatments for childhood and adolescent bipolar disorder. Child Adolesc Psychiatr Clin N Am 18: 471-482, x-xi.
13. Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, et al. (2004) Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 6: 224-232.
14. Pavuluri MN, Shenkel LS, Aryal S, Harral E, Hill K, et al. (2006) Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. American Journal of Psychiatry 163: 286-293.
15. Passarotti AM, Pavuluri MN (2011) Brain functional domains inform therapeutic interventions in attention-deficit/hyperactivity disorder and pediatric bipolar disorder. Expert Review of Neurotherapeutics 11: 897-914.
16. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, et al. (1999) Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 2: 861-863.
17. Luna B, Thulborn KR, Munoz DP, Merriam EP, Garver KE, et al. (2001) Maturation of widely distributed brain function subserves cognitive development. Neuroimage 13: 786-793.
18. Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA (2004) Maturation of cognitive processes from late childhood to adulthood. Child Dev 75: 1357-1372.
19. Posne MI, Rothbart MK (2000) Developing mechanisms of self-regulation. Dev Psychopathol 12: 427-441.
20. Blakemore SJ, Choudhury S (2006) Development of the adolescent brain: implications for executive function and social cognition. J Child Psychol Psychiatry 47: 296-312.
21. Passarotti AM, Sweeney JA, Pavuluri MN (2010) Emotion Processing Influences Working Memory Circuits in Pediatric Bipolar Disorder and Attention Deficit Hyperactivity Disorder. Journal of the American Academy of Child and Adolescent Psychiatry 49: 1064-1080.
22. Campos J1, Frankel CB, Camras L (2004) On the nature of emotion regulation. Child Dev 75: 377-394.
23. Gioia GA, Isquith PK, Guy SC, Kenworthy L (2000) Behavior rating inventory of executive function. Child Neuropsychology 6: 235-238.
24. Mahone EM, Hoffman J (2007) Behavior ratings of executive function among preschoolers with ADHD. Clin Neuropsychol 21: 569-586.
25. Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, et al. (2012) The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord 14: 313-325.
26. Peters AT, Peckham AD, Stange JP, Sylvia LG, Hansen NS, et al. (2014) Correlates of real world executive dysfunction in bipolar I disorder. J Psychiatr Res 53: 87-93.
27. Roth RM, Isquith PK, Gioia GA (2005) BRIEF-A: Behavior Rating Inventory of Executive Function - Adult Version. Psychological Assessment Resources, Luts, FL.
28. Singh MK, DelBello MP, Kowatch RA, Strakowski SM (2006) Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. Bipolar Disord 8: 710-720.
29. Youngstrom EA, Arnold LE, Frazier TW (2010) Bipolar and ADHD Comorbidity: Both Artifact and Outgrowth of Shared Mechanisms. Clin Psychol (New York) 17: 350-359.
30. Biederman J, Faraone S, Mick E, Wozniak J, Chen L, et al.(1996) Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? J Am Acad Child Adolesc Psychiatry 35: 997-1008.
31. Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychological Bulletin 121: 65-94.
32. Barkley RA (1999) Response inhibition in attention-deficity hyperactivity disorder. Mental Retardation and Developmental Disabilities Research Reviews 5: 177-184.
33. Wechsler D (1999) Wechsler Abbreviated Scale of Intelligence (WASI). Psychological Corporation, San Antonio, TX.
34. Powers AD, Gleason ME, Oltmanns TF (2013) Symptoms of borderline personality disorder predict interpersonal (but not independent) stressful life events in a community sample of older adults. J Abnorm Psychol 122: 469-474.
35. Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133: 429-435.
36. Poznanski EO, Cook SC, Carroll BJ (1979) A depression rating scale for children. Pediatrics 64: 442-450.
37. Conners CK, Sitarenios G, Parker JD, Epstein JN (1998) The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 26: 257-268.

38. Gioia GA, Isquith PK, Retzlaff PD, Espy KA (2002) Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. Child Neuropsychol 8: 249-257.

39. Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills 8: 271-276.

40. Wechsler D (1991) Manual for the Wechsler Intelligence Scale for Children—Third Edition. The Psychological Corporation, New York.

41. Woodcock RW, Mcgrew KS, Mather N (2001) Woodcock-Johnson III Tests of Achievement. Riverside Publishing, Itasca.

42. Dickstein DP, Treland JE, Snow J, McClure EB, Mehta MS, et al. (2004) Neuropsychological performance in pediatric bipolar disorder. Biol Psychiatry 55: 32-39.

43. Passarotti AM, Sweeney JA, Pavuluri MN (2010) Neural Correlates of Response Inhibition Deficits in Pediatric Bipolar Disorder and Attention Deficit Hyperactivity Disorder. Psychiatry Research 181: 36-43.

44. Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, et al.(2007) Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. Am J Psychiatry 164: 52-60.

45. Singh MK, Chang KD, Mazaika P, Garrett A, Adleman N, et al. (2010) Neural correlates of response inhibition in pediatric bipolar disorder. Journal of Child and Adolescent Psychopharmacology 20: 15-24.

46. Adleman NE, Kayser R, Dickstein D, Blair RJ, Pine D, et al. (2011) Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 50: 1173-1185.

47. Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA (2009) An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry 48: 308-319.

48. Passarotti AM, Sweeney JA, Pavuluri MN (2010) Differential Engagement of Cognitive and Affective Neural Systems in Pediatric Bipolar Disorder and Attention Deficit Hyperactivity Disorder. Journal of the International Neuropsychological Society 16: 106-117.

49. Wegbreit E, Passarotti AM, Ellis JA, Wu M, Witowski N, et al. (2012) Where, when, how high, and how long? The hemodynamics of emotional response in psychotropic-naïve patients with adolescent bipolar disorder. Journal of Affective Disorders 147: 304-311.

50. Brotman MA, Rich BA, Schmajuk M, Reising M, Monk CS, et al. (2007) Attention bias to threat faces in children with bipolar disorder and comorbid lifetime anxiety disorders. Biol Psychiatry 61: 819-821.

51. Rich BA, Fromm SJ, Berghorst LH, Dickstein DP, Brotman MA, et al (2008) Neural connectivity in children with bipolar disorder: impairment in the face emotion processing circuit. Journal of Child Psychology and Psychiatry 49: 88-96.

52. Rich BA, Bhangoo RK, Vinton DT, Berghorst LH, Dickstein DP, et al. (2005) Using affect-modulated startle to study phenotypes of pediatric bipolar disorder. Bipolar Disord 7: 536-545.

53. Perna R, Loughan AR, Le J, Hertza J, Cohen MJ, et al.(2014) Spectrum of Mathematical Weaknesses: Related Neuropsychological Correlates. Appl Neuropsychol Child 4: 1-9.

54. Bora E, Yucel M, Pantelis (2009) Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 113: 1-20.

55. Klein C, Wendling K, Huettner P, Ruder H, Peper M (2006) Intra-subject variability in attention-deficit hyperactivity disorder. Biol Psychiatry 60: 1088-1097.

56. Saville CW, Feige B, Kluckert C, Bender S, Biscaldi M, et al.(2015) Increased reaction time variability in attention-deficit hyperactivity disorder as a response-related phenomenon: evidence from single-trial event-related potentials. J Child Psychol Psychiatry 56: 801-813.

57. Patino LR, Adler CM, Mills NP, Strakowski SM, Fleck DE, et al. (2013) Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder. Bipolar Disord 15: 264-271.

58. Rubia K, Taylor E, Smith AB, Oksanen H, Overmeyer S, et al. (2001) Neuropsychological analyses of impulsiveness in childhood hyperactivity. Br J Psychiatry 179: 138-143.

59. Tamm L, Menon V, Ringel J, Reiss AL (2004) Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 43: 1430-1440.

60. Passarotti AM, Fitzgerald JM, Sweeney JA, Pavuluri MN (2013) Negative Emotion Interference During a Synonym Matching Task in Pediatric Bipolar Disorder With and Without Attention Deficit Hyperactivity Disorder. Journal of the International Neuropsychological Soc 19: 601-612.

61. Adler CM, Delbello MP, Mills NP, Schmithorst V, Holland S, et al. (2005) Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. Bipolar Disord 7: 577-588.

62. Thorell LB, Lindqvist S, Bergman Nutley S, Bohlin G, Klingberg T (2009) Training and transfer effects of executive functions in preschool children. Dev Sci 12: 106-113.

63. Klingberg T, Fernell E, Olesen PJ, Johnson M, Gustafsson P, et al.(2005) Computerized training of working memory in children with ADHD – a randomized controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry 44: 177-186.

64. Holmes J, Gathercole SE, Dunning DL (2009) Adaptive training leads to sustained enhancement of poor working memory in children. Dev Sci 12: F9-15.

65. Lantrip C, Isquith PK, Koven NS, Welsh K, Roth RM (2015) Executive Function and Emotion Regulation Strategy Use in Adolescents. Appl Neuropsychol Child.

66. Saudino KJ, Ronald A, Plomin R (2005) The etiology of behavior problems in 7-year-old twins: substantial genetic influence and negligible shared environmental influence for parent ratings and ratings by same and different teachers. J Abnorm Child Psychol 33: 113-130.

67. Pinto R, Rijsdijk F, Frazier-Wood AC, Asherson P, Kuntsi J, et al. (2012) Bigger families fare better: a novel method to estimate rater contrast effects in parental ratings on ADHD symptoms. Behav Genet 42: 875-885.