RESEARCH ARTICLE

Differences in Real World Executive Function between Children with Pediatric Bipolar Disorder and Children with ADHD

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Abstract

Background: Recent research evidence suggests that executive function (EF) is impaired in both pediatric bipolar disorder (PBD) and attention deficit-hyperactivity disorder (ADHD), although the underlying cognitive mechanisms are still unclear. In this study we examined EF, including cognitive and emotional control, in three pediatric groups with overlapping symptoms. Methods: Sixteen children and adolescents with PBD, 17 children and adolescents with ADHD, Type Combined, and 13 children and adolescents with PBD and comorbid ADHD (PBD+ADHD) (mean age=12.70, SD=2.21) were assessed using the Behavioral Rating Inventory of Executive Function – Parental Report (BRIEF-PR), clinical scales and neuropsychological tests of attention, working memory and executive function. Results: All groups showed impairment on the Trails A and B tests. However, there were no significant group differences. On the BRIEF-PR while all three groups were impaired in General Executive Functioning and Metacognition only the two PBD groups revealed more extensive EF dysfunction, in both cognitive and emotional control domains, relative to the ADHD group. Conversely, the ADHD group exhibited selective deficits in cognitive domains such as working memory, planning/organization, monitoring, and metacognition. The two PBD groups showed greater impairment than the ADHD group in the domains of Inhibition, Shifting, Monitoring and Emotional Control. Furthermore, results from regression analyses suggest cognitive predictors of EF impairment in ADHD and mood predictors for inhibition in PBD. Conclusions: The current results contribute new knowledge on domain-specific similarities and differences in executive dysfunction between PBD, ADHD, and the comorbid phenotype, which may inform the diagnostic process and cognitive intervention.

Key Words: pediatric bipolar disorder, ADHD, adolescent, executive function, emotion

Résumé

Contexte: Des données probantes issues de recherches récentes suggèrent que la fonction exécutive (FE) est déficiente dans le trouble bipolaire pédiatrique (TBP) et dans le trouble de déficit de l’attention avec hyperactivité (TDAH), bien que les mécanismes cognitifs sous-jacents ne soient pas encore bien définis. Dans cette étude, nous avons examiné la FE, y compris le contrôle cognitif et émotionnel, dans trois groupes pédiatriques présentant des symptômes se chevauchant. Méthodes: Seize enfants et adolescents souffrant de TBP, 17 enfants et adolescents souffrant de TDAH, de type combiné, et 13 enfants et adolescents souffrant de TBP et de TDAH comorbid (TBP+TDAH) (âge moyen = 12.70, ET = 2.21) ont été évalués à l’aide de l’inventaire de comportements liés aux fonctions exécutives – rapport des parents (BRIEF-PR), d’échelles cliniques et de tests neuropsychologiques de l’attention, de la mémoire de travail et de la fonction exécutive. Résultats: Tous les groupes ont indiqué une déficience aux Trail making tests A et B. Toutefois, il n’y avait pas de différences significatives entre les groupes. Dans le BRIEF-PR, même si les trois groupes étaient déficients dans le fonctionnement exécutif général et la métacognition, seulement les deux groupes de TBP révélaient une dysfonction importante de la FE, dans les deux domaines de contrôle cognitif et émotionnel, relativement au groupe de TDAH. À l’inverse, le groupe de TDAH a révélé des déficits sélectifs dans les domaines cognitifs comme la mémoire de travail, la planification/organisation, la surveillance et la métacognition. Les deux groupes de TBP ont montré une plus grande
Introduction

Patients with pediatric bipolar disorder (PBD) and attention deficit-hyperactivity disorder (ADHD) share common symptoms of behavioral impulsivity, poor inhibition and inattention (Galanter & Leibenluft, 2008a; Passarotti & Pavuluri, 2011a) that complicate clinical differentiation (Dickstein et al., 2005; Biederman, Russell, Soriano, Wozniak, & Faraone, 1998; Chang, 2010; Klassen, Katzman & Chokka, 2010; Wingo & Ghaemi, 2007). PBD is an episodic disorder, characterized by episodic emotional dysregulation, irritability, mania and hypomania, racing thoughts, impulsivity, decreased need for sleep, and hyper-sexuality (Geller, Warner, Williams & Zimmerman, 1998; Pavuluri & Passarotti, 2008; Galanter & Leibenluft, 2008a). ADHD is a fairly common pediatric disorder, exhibiting a profile of impulsivity, inattention, and poor executive function (Barley, 1997; Barkley, 1990; Galanter & Leibenluft, 2008a; Passarotti & Pavuluri, 2011a; Sonuga-Barke, Sergeant, Nigg & Willcutt, 2008). Both children with PBD (Dickstein et al., 2005; Pavuluri et al., 2006; Pavuluri, West, Hill, Jindal & Sweeney, 2009b; Doyle et al., 2005) and children with ADHD exhibit significant neurocognitive impairment in working memory, attention, inhibition and executive function (EF) (Rubia et al., 2001; Doyle et al., 2005; Sonuga-Barke et al., 2008; Nigg, 2001; Barkley, 2010; Sonuga-Barke, 2003).

To date, there is only partial behavioral differentiation of the two illnesses, due to high levels of comorbidity, ranging from 60 to 90% (Singh, Delbello, Kowatch & Strakowski, 2006), and similar cognitive problems and neural dysfunction in fronto-striatal systems in PBD (Leibenluft et al., 2007; Passarotti et al., 2010c; Singh et al., 2010) and ADHD (Rubia et al., 1999; Tamm, Menon, Ringel & Reiss, 2004; Passarotti, Sweeney & Pavuluri, 2010a; Passarotti et al., 2010c). Therefore, it is important to better characterize and differentiate the phenotypes of PBD, ADHD and the comorbid illness according to meaningful functional constructs, so that we can inform early diagnosis and treatment.

The EF domain is a multi-dimensional system controlling higher order cognitive processes such as attention, working memory, cognitive flexibility, planning, goal-directed behavior and self-regulation. At the neural level these processes are implemented by an executive prefrontal control network that interacts with cortical and subcortical affective networks (Phillips, Ladouceur & Drevets, 2008; Pavuluri & Passarotti, 2008). Since adolescents and young adults with PBD and ADHD encounter numerous psychosocial and occupational challenges as they grow up and transition into adult roles in society, it is particularly important for intervention efforts to understand EF and how it relates to mood dysregulation or neurocognitive impairment.

The present study is one of the first to examine multiple dimensions of real-world EF as a promising construct of interest to better characterize and differentiate the intermediate phenotypes of cognitive and emotional dysfunction in PBD and ADHD. By including a group of children with comorbid PBD and ADHD we also afforded the unique opportunity to better understand functional similarities and differences in the separate and overlapping phenotypes. We gathered data from multiple sources, such as parental reports on the child’s executive functioning in daily activities, standardized neuropsychological tests of attention, working memory and executive functions, and mood measures. In particular, to address the multidimensional nature of the EF construct, we adopted the Behavior Rating Inventory of Executive Function –Parental Report (BRIEF-PR) scale for children (Gioia, Isquith, Guy & Kenworthy, 2000; Malone & Hoffman, 2007), a standardized scale offering the advantage of concurrently evaluating multiple domains of EF. These EF domains tap into brain circuit dysfunction as ascertained in both PBD and ADHD (Passarotti & Pavuluri, 2011a; Strakowski et al., 2012).

We hypothesized that PBD patients would show impairment in both cognitive and emotional domains on the BRIEF-PR scale, therefore exhibiting worse global functioning compared to children with ADHD. We also predicted that the ADHD group would exhibit more severe deficits in EF domains requiring sustained attention and self-monitoring while the PBD group would exhibit more severe deficits in emotional control. Moreover, based on previous findings that emotional dysregulation increases impulsivity in PBD (i.e., emotional impulsivity) (Passarotti & Pavuluri, 2011a) we hypothesized that severity of mood symptoms would predict inhibition dysfunction in PBD. Finally, we hypothesized that the PBD+ADHD group might show worse EF deficits relative to both the ADHD and the PBD groups, because of the cumulative effects of mood and attentional problems on EF.
Differences in Real World Executive Function between Children with Pediatric Bipolar Disorder and Children with ADHD

Methods

Participants

Children and adolescents with a diagnosis of PBD or ADHD were recruited from the Pediatric Mood Disorder Clinic, at the Department of Psychiatry, University of Illinois at Chicago (UIC), and from the Greater Chicago area. For all participants consent from one parent or legal guardian and assent from the child participant were obtained. The PBD patient sample (age range=9-16 years; mean age=12.70 ±2.21 years) consisted of 29 child and adolescent patients with a diagnosis of pediatric bipolar disorder, narrow phenotype, (Type I, II) (PBD group), 13 of which had a diagnosis of comorbid ADHD, Type Combined (PBD+ADHD group). Twenty-six of the 29 PBD patients (including 14 of the PBD patients and 12 of the comorbid patients) were on psychotropic medications at the time of testing. Seventeen children and adolescents with ADHD, Type Combined were also tested (ADHD group) (age range=10-17 years; mean age=12.76 ±2.28 years). Twelve of the 17 patients with ADHD were on a medication for ADHD symptoms at the time of testing. Patient groups were matched based on age, gender, and Intelligence Quotient (IQ) as estimated with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Inclusion criteria were as follows: eight to 19 years of age for all participants; for the PBD group, Axis one diagnosis of bipolar disorder, Type I or II, based on DSM-IV-TR criteria; for the ADHD group, Axis one diagnosis of ADHD type combined, based on DSM-IV-TR criteria. A diagnosis of comorbid ADHD in PBD based on the DSM-IV-TR criteria was accepted. Patients were excluded from the study if they had a history of head trauma with loss of consciousness for more than ten minutes, neurological symptoms, speech or hearing difficulties, pervasive developmental disorder, a primary diagnosis other than bipolar disorder or ADHD, and an IQ score lower than 70. The study protocol was approved by the University Institutional Review Board.

Clinical and Demographical Assessment

The clinical diagnoses of PBD, narrow phenotype (Type I and II) and ADHD, Type Combined, were based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000). Moreover, mania symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler & Meyer, 1978) and depression symptoms were assessed with the Child Depression Rating Scale-Revised (CDRS-R) (Poznanski, Cook & Carroll, 1979). The Conners’ Parent Rating Scale (CPRS-R) (Conners, Sitarenios, Parker & Epstein, 1998) was administered to assess ADHD-related symptoms.

Functional Assessment of EF

In order to assess EF in daily life the Behavioral Rating Inventory of Executive Function, Parental Report (BRIEF-PR) (Gioia et al., 2000) was administered. The BRIEF-PR is a 86-item scale for parental report on child’s behaviors (age: five to 18 years), consisting of eight clinical scales measuring different aspects of EF: Inhibition, Shift, Emotional Control, Initiation, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The eight scales compose the Behavioral Regulation index (BRI) and the Metacognition index (MI). The BRI assesses processes involved in behavior regulation, such as Inhibition, Shift, and Emotional Control. The MI measures processes related to the Metacognition domain: Working Memory, Plan/Organize, Monitor and Organization of Materials. Finally, the BRI and MI comprise the Global Executive Composite (GEC), which measures global functioning. Raw scores for each sub-scale are converted into standardized T scores based on four developmental groups and gender. Higher T scores on this scale indicate greater functional deficit.

Neuropsychological Assessment

All participants were assessed using the following neuropsychological battery: a) Estimated IQ. The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was used to estimate global intellectual functioning and derive the Full Scale IQ (FSIQ); b) Attention and Working Memory (including attention, working memory and processing speed): Trail Making Test (TMT) A (Reitan, 1958), Digit Span Test - Forward, (WISC III) (Wechsler, 1991); Spatial Span Test - Forward (Corsi Block Task, Corsi, 1972) (Berch, Krikorian & Huha, 1998); c) Executive Function (including working memory, cognitive flexibility and processing speed): TMT B (Reitan, 1958); Digit Span Test - Backward (WISC III) (Wechsler, 1991), Spatial Span Test - Backward (Berch et al., 1998).

 Statistical Data Analyses

All analyses were conducted using Statistical Package for the Social Sciences (SPSS) 22.0. Separate ANOVAs were performed on each demographic and clinical measure as the within-subject factor, and patient group (PBD, PBD+ADHD) as the between-subjects factor. Pearson Chi Squared tests were carried out for categorical variables (i.e., gender, race).

The raw scores for each sub-scale of the BRIEF-PR and CPRS-R were transformed into T scores (mean=50 and SD=10). A T>60 typically indicates a clinically significant deficit (i.e., greater than 1 SD from the population mean). 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; number of errors were calculated as well. For the Spatial Span test
we calculated percentage of correct answers. In order to examine group differences, separate ANOVAs were performed for the BRIEF-PR, CPRS-R and each of the tasks considered.

Furthermore, hierarchical Multiple Regression was carried out in SPSS to examine the contributions of mood or attention-related symptoms to EF patterns in PBD and ADHD. For each group, we carried out a series of regression models separately for each BRIEF sub-scale by including YMRS as predictor in the first step of the model (Model 1), YMRS and CDRS-R as predictors for Model 2, and YMRS, CDRS-R and ADHD Index as predictors for Model 3.

**Results**

**Demographic and Clinical Data**

There were no group differences on demographic measures, IQ estimate, or CDRS-R scores. PBD and PBD+ADHD exhibited higher YMRS scores and higher Oppositional and Hyperactivity scores on the CPRS-R than ADHD, but did not differ from each other. The two PBD groups had mean YMRS scores above 12 (a score < 12 indicates euthymia) (Young et al., 1978). Note that ten of the 16 PBD patients (63%) and four of the 13 PBD+ADHD patients (31%) had YMRS scores above 12, indicating hypomania or mania at the time of testing. With regard to depression scores, both the PBD and the PBD+ADHD group had mean CDRS-R scores above 28 (a score < 28 indicates remission, with minimal or no symptoms) (Mayes, Bernstein, Haley, Kennard & Emslie, 2010). Six of the 16 PBD patients (38%) and seven of the 13 comorbid patients (54%) had CDRS-R scores above 28, indicating borderline or active depression at the time of testing (Table 1).

**Neuropsychological Assessment Results**

**BRIEF-PR Scale Results.** As illustrated in Table 2, relative to healthy population norms the PBD and PBD+ADHD groups exhibited clinically significant deficits (i.e., T>60) in all BRIEF-PR sub-domains, as well as the BRI, MI
and GEC composites. The ADHD group exhibited clinically significant deficits only in the domains of Working Memory, Planning/organization, Monitoring, and the MI and GEC composites. ANOVAs results show a significant group effect for Inhibition \[F(1, 13)=15.59, p=.001\], Shifting \[F(1, 13)=16.00, p=.001\], Emotional Control \[F(1, 13)=16.00, p=.001\], Initiation \[F(1, 13)=5.98, p=.005\], Monitoring \[F(1, 13)=12.54, p=.001\], BRI \[F(1, 13)=7.24, p=.001\], MI \[F(1, 13)=6.23, p=.004\] and GEC \[F(1, 13)=7.16, p=.002\]. There were no group differences for Working Memory, Planning/organization, and Organization of Materials (all \(p>.05\)). Table 2 reports results from Tukey HSD post-hoc comparisons (95% confidence interval) for the domains with a significant main effect of group.

An assessment of the percent of individuals in each group with \(T>60\) for each BRIEF sub-scale revealed that 83% of the PBD patients, 88% of the PBD+ADHD patients and 43% of the ADHD patients had a \(T\) score greater than 60 on the BRIEF sub-scales. Supplemental Figure 1 illustrates percentages for each BRIEF-PR sub-scale. It is noteworthy that for PBD the Emotional Control domain yielded the highest percent of clinically elevated \(T\) scores (100%), while for the comorbid group this percent was 69% and for the ADHD group it was 18%. Based on these percentages the groups differed significantly from each other for this domain (Chi Square, two-tailed, \(p<.05\)). Moreover, for ADHD the highest percent was for Working Memory (76%) and for PBD+ADHD the highest percent was for Working Memory and Monitoring (both 100%).

**Neuropsychological Test Results.** Supplemental Table 1 illustrates results from the neuropsychological tests, which yielded no significant group differences. Regarding the attention/working memory domain the PBD and ADHD groups exhibited elevated completion times on the TMT A. Digit Span Forward performance was within the average range (i.e., scores were within one SD from mean) for all groups. Regarding the EF domain, all groups, and especially the PBD group, exhibited severe deficits on the TMT B, while their Digit Span Test - Backward performance was within the average range.

**Regression Analyses Results**

Table 3 presents the variance explained by each model, including test of significance and effect sizes, separately by group. We focused on medium to large effects (i.e., \(R^2\) greater or equal to .09) (Cohen, 1988).

For the ADHD group, Model 3 (i.e., YMRS, CDRS, ADHD index) was the only significant model. It was significant for Initiation \(F(3, 13)=18.72, p=.001\); Adj. \(R^2=.77\), Working Memory \(F(3, 13)=6.38, p=.007\); Adj. \(R^2=.50\), Planning \(F(3, 13)=7.10, p=.005\); Adj. \(R^2=.53\), Monitoring \(F(3, 13)=12.13, p=.001\); Adj. \(R^2=.68\), and MI \(F(3, 13)=11.23, p<.001\); Adj. \(R^2=.66\). Results indicate that YMRS (beta= 0.51, \(t=2.76, p=.002\)), CDRS-R (beta= -0.50, \(t=2.72, p=.002\)) and ADHD index (beta= 0.78, \(t=6.38, p<.001\)) were all significant predictors for Initiation. Note that negative beta values for CDRS-R indicate inverse relation between dependent and independent variable. ADHD index was the only significant predictor for Working Memory (beta= 0.76, \(t=4.23, p<.001\)), Planning (beta= 0.77, \(t=4.46, p<.001\)), Monitoring (beta= 0.78, \(t=5.40, p<.001\)) and MI (beta= 0.83, \(t=5.56, p<.001\)).

For the PBD group, Model 1 (i.e., YMRS) was significant for Inhibition only \(F(1, 13)=5.6, p=.034\); Adj. \(R^2=.25\). Manic symptom severity (i.e., YMRS scores) was a significant predictor for Inhibition (beta=-0.54, \(t=2.37, p=.034\)). Model 2 was not significant (\(p>.05\)). Model 3 (i.e., YMRS, CDRS-R, ADHD index) was the strongest model for PBD, based on \(R^2\). It was significant for Initiation \(F(3, 11)=7.53, p=.005\); Adj. \(R^2=.58\), Planning \(F(3, 11)=7.05, p=.007\); Adj. \(R^2=.57\), and GEC \(F(3, 11)=9.89, p=.002\); Adj. \(R^2=.66\). In particular, both depression symptom severity as measured by the CDRS-R (beta= 0.47, \(t=2.61, p=.024\)) and ADHD index (beta= 0.61, \(t=3.43, p=.006\)) were significant predictors for Initiation. Also, CDRS (beta= 0.46, \(t=2.79, p=.017\)) and ADHD index (beta= 0.64, \(t=3.93, p=.002\)) predicted GEC. ADHD index alone was a significant predictor for Planning (beta= 0.72, \(t=3.96, p=.002\)).

For the PBD+ADHD group, only Model 3 (i.e., YMRS, CDRS-R, ADHD index) was significant, and it was significant for Shift \(F(3, 9)=5.72, p=.02\); Adj. \(R^2=.54\) and Initiation \(F(3, 9)=4.69, p=.031\); Adj. \(R^2=.48\). YMRS (beta= -0.76, \(t=3.52, p=.014\)) and CDRS-R (beta= 0.81, \(t=3.42, p=.008\)) scores were significant predictors for Shift, while YMRS (beta= -0.93, \(t=3.49, p=.007\)) and ADHD index (beta= 0.54, \(t=2.39, p=.041\)) were significant predictors for Initiation. Note that negative beta values for YMRS indicate inverse relation between dependent and independent variable.

**Discussion**

The current results contribute novel knowledge on domain-specific similarities and differences in real-world executive dysfunction in three pediatric clinical phenotypes, i.e., PBD, ADHD and the comorbid phenotype, that often exhibit overlapping cognitive symptoms. The present findings from standardized neuropsychological tests indicate that all groups exhibited significant deficits on TMT A and B, two tests measuring attention/working memory and EF, respectively. However, there were no significant group differences. The BRIEF-PR scale was a more sensitive measure than neuropsychological testing in terms of identifying group differences in EF domains.

Real-World Executive Functioning: Greater Cognitive and Emotional Control Impairment in PBD and PBD+ADHD relative to ADHD.
### Table 2. Mean T scores and standard deviation (SD) on each of the BRIEF-PR sub-scales for the ADHD group, the PBD group and the PBD+ADHD group. Scores are standardized relative to population norms (i.e., $T=50$, $SD=10$)

<table>
<thead>
<tr>
<th>BRIEF-PR Scales</th>
<th>Group</th>
<th>Mean (SD)</th>
<th>F</th>
<th>P</th>
<th>Group comparisons (Tukey HSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition*</td>
<td>ADHD</td>
<td>56.53 (11.85)</td>
<td></td>
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<tr>
<td></td>
<td>PBD</td>
<td>70.13 (11.35)</td>
<td>13.59</td>
<td>P=0.001</td>
<td>ADHD vs PBD, $p=0.003$; ADHD vs PBD+ADHD, $p=0.001$; PBD vs PBD+ADHD, $p=0.2$</td>
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<tr>
<td></td>
<td>PBD+ADHD</td>
<td>77.46 (10.26)</td>
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<tr>
<td>Shifting*</td>
<td>ADHD</td>
<td>52.06 (9.351)</td>
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</tr>
<tr>
<td></td>
<td>PBD</td>
<td>70.25 (10.31)</td>
<td>16.00</td>
<td>P=0.001</td>
<td>ADHD vs PBD, $p=0.001$; ADHD vs PBD+ADHD, $p=0.001$; PBD vs PBD+ADHD, $p=0.994$</td>
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<tr>
<td></td>
<td>PBD+ADHD</td>
<td>69.85 (11.82)</td>
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<tr>
<td>Emotional Control*</td>
<td>ADHD</td>
<td>48.12 (11.34)</td>
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<tr>
<td></td>
<td>PBD</td>
<td>74.13 (7.10)</td>
<td>24.37</td>
<td>P=0.001</td>
<td>ADHD vs PBD, $p=0.001$; ADHD vs PBD+ADHD, $p=0.001$; PBD vs PBD+ADHD, $p=0.428$</td>
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<tr>
<td></td>
<td>PBD+ADHD</td>
<td>68.85 (14.86)</td>
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<tr>
<td>Initiation*</td>
<td>ADHD</td>
<td>57.47 (12.31)</td>
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<td></td>
<td>PBD</td>
<td>65.94 (11.64)</td>
<td>5.98</td>
<td>P=0.005</td>
<td>ADHD vs PBD, $p=0.079$; ADHD vs PBD+ADHD, $p=0.004$; PBD vs PBD+ADHD, $p=0.427$</td>
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<tr>
<td></td>
<td>PBD+ADHD</td>
<td>71.08 (7.61)</td>
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<tr>
<td>Working Memory</td>
<td>ADHD</td>
<td>68.24 (10.35)</td>
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<tr>
<td></td>
<td>PBD</td>
<td>70.69 (11.00)</td>
<td>2.49</td>
<td>p=0.10</td>
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<tr>
<td></td>
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<td>76.08 (6.24)</td>
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<tr>
<td>Planning/Organization</td>
<td>ADHD</td>
<td>62.76 (14.07)</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>ADHD</td>
<td>58.82 (8.20)</td>
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<tr>
<td>Organization of Material</td>
<td>ADHD</td>
<td>61.69 (10.45)</td>
<td>2.22</td>
<td>p=0.12</td>
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<td></td>
<td>PBD</td>
<td>65.46 (5.99)</td>
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<tr>
<td></td>
<td>PBD+ADHD</td>
<td>61.18 (12.76)</td>
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<tr>
<td>Monitoring*</td>
<td>ADHD</td>
<td>71.06 (6.72)</td>
<td>12.54</td>
<td>p=0.001</td>
<td>ADHD vs PBD, $p=0.04$; ADHD vs PBD+ADHD, $p=0.001$; PBD vs PBD+ADHD, $p=0.045$</td>
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<td></td>
<td>PBD</td>
<td>78.31 (6.66)</td>
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<td></td>
<td>PBD+ADHD</td>
<td>52.18 (8.06)</td>
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<tr>
<td>Behavior Regulation Index (BRI)*</td>
<td>ADHD</td>
<td>61.18 (12.76)</td>
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<tr>
<td></td>
<td>PBD</td>
<td>75.56 (8.25)</td>
<td>37.24</td>
<td>p=0.001</td>
<td>ADHD vs PBD, $p=0.001$; ADHD vs PBD+ADHD, $p=0.001$; PBD vs PBD+ADHD, $p=0.99$</td>
</tr>
<tr>
<td></td>
<td>PBD+ADHD</td>
<td>75.38 (10.41)</td>
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<tr>
<td>Metacognition Index (MI)*</td>
<td>ADHD</td>
<td>64.12 (12.11)</td>
<td></td>
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<tr>
<td></td>
<td>PBD</td>
<td>72 (10.56)</td>
<td>6.23</td>
<td>p=0.004</td>
<td>ADHD vs PBD, $p=0.10$; ADHD vs PBD+ADHD, $p=0.003$; PBD vs PBD+ADHD, $p=0.31$</td>
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<td>PBD+ADHD</td>
<td>77.92 (8.92)</td>
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</tr>
<tr>
<td>Global Executive Composite (GEC)*</td>
<td>ADHD</td>
<td>63.59 (13.37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBD</td>
<td>73.44 (9.56)</td>
<td>7.16</td>
<td>P=0.002</td>
<td>ADHD vs PBD, $p=0.03$; ADHD vs PBD+ADHD, $p=0.001$; PBD vs PBD+ADHD, $p=0.52$</td>
</tr>
<tr>
<td></td>
<td>PBD+ADHD</td>
<td>77.85 (7.56)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The symbol * indicates significant group differences. Note that higher T scores on the BRIEF-PR indicate greater impairment.
A key finding of the present study is that the two PBD groups exhibited dual dysfunction in both cognitive domains (i.e., Inhibition, Shifting and Monitoring) and the Emotional Control domain of the BRIEF-PR, while the ADHD group exhibited a more circumscribed deficit in cognitive domains. These results are suggestive of a pervasive breakdown of EF in PBD that is likely contributing to the behavior regulation problems often seen in this patient population (Passarotti & Pavuluri, 2011a; Pavuluri & Passarotti, 2008; Dickstein & Leibenluft, 2006; Galanter & Leibenluft, 2008a). The current results are also in line with findings of fronto-cingulate impairment in EF circuits in PBD during tasks involving inhibition (Passarotti et al., 2010c; Leibenluft et al., 2007; Singh et al., 2010), working memory (Passarotti, Sweeney & Pavuluri, 2010b), cognitive flexibility (Adleman et al., 2011; Gorrindo et al., 2005), as well as the interface of cognitive and affective processing (Adleman et al., 2011; Pavuluri, Passarotti, Harral &

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**Table 3. Hierarchical regression each BRIEF-PR domain in PBD, ADHD and PBD+ADHD groups (tot. N=46).**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj. R²</td>
<td>Adj. R²</td>
<td>Adj. R²</td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>0.41</td>
<td>0.21</td>
<td>0.48</td>
</tr>
<tr>
<td>Shifting</td>
<td>0.89</td>
<td>-0.07</td>
<td>0.14</td>
</tr>
<tr>
<td>Emotional</td>
<td>2.82</td>
<td>0.07</td>
<td>0.37</td>
</tr>
<tr>
<td>Control</td>
<td>5.65</td>
<td>0.21</td>
<td>0.67</td>
</tr>
<tr>
<td>Initiation</td>
<td>4.44</td>
<td>0.15</td>
<td>0.53</td>
</tr>
<tr>
<td>Plan</td>
<td>1.83</td>
<td>0.03</td>
<td>0.66</td>
</tr>
<tr>
<td>Organization</td>
<td>3.43</td>
<td>0.10</td>
<td>0.35</td>
</tr>
<tr>
<td>Monitor</td>
<td>0.04</td>
<td>-0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>MI</td>
<td>1.23</td>
<td>0.12</td>
<td>0.46</td>
</tr>
<tr>
<td>BRI</td>
<td>0.23</td>
<td>0.02</td>
<td>0.27</td>
</tr>
<tr>
<td>GEC</td>
<td>0.50</td>
<td>0.04</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>PBD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>0.00</td>
<td>-0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>Shifting</td>
<td>11.20</td>
<td>0.52</td>
<td>0.66</td>
</tr>
<tr>
<td>Emotional</td>
<td>4.21</td>
<td>0.22</td>
<td>0.39</td>
</tr>
<tr>
<td>Control</td>
<td>3.16</td>
<td>0.22</td>
<td>0.36</td>
</tr>
<tr>
<td>Initiation</td>
<td>2.20</td>
<td>0.24</td>
<td>0.61</td>
</tr>
<tr>
<td>Plan</td>
<td>3.54</td>
<td>0.24</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Note: Model 1: YMRS; Model 2: YMRS, CDRS; Model 3: YMRS, CDRS, ADHD Index. *p<.05; **p<.01.
Sweeney, 2009a; Passarotti et al., 2010a; Wegbreit et al., 2012; Brotman et al., 2007; Rich et al., 2008; Rich et al., 2005).

Conversely, the ADHD group exhibited clinically significant deficits only in selected cognitive domains, such as Working Memory, Planning/organization, and Monitoring, a pattern in line with findings of neurocognitive deficits in attention and working memory in ADHD, (Rubia et al., 2001; Doyle et al., 2005; Sonuga-Barke et al., 2008; Nigg, 2001) that have also been found to be associated with impaired fronto-striatal circuits (Barkley, 1990; Durston, Mulder, Casey, Ziemans & Engeland, 2006; Rubia et al., 1999; Passarotti et al., 2010c).

Importantly, only the two PBD groups, but not the ADHD group, exhibited clinically significant impairment on the BRIEF Emotional Control domain. The PBD and PBD+ADHD group differed significantly from the ADHD group, but did not differ from each other, for this domain. Note that scores on the Emotional Control sub-scale are contributed by items such as “over-reacts to small problems”, “has explosive angry outbursts”, “mood changes frequently”, “small events trigger big reactions”, and “becomes upset too easily”, which more closely match the exaggerated emotional reactions and over-sensitivity to negative emotions seen in PBD (Passarotti et al., 2010a; Passarotti et al., 2010b; Passarotti et al., 2010c; Passarotti, Fitzgerald, Sweeney & Pavuluri, 2013; Langenecker, Jacobs & Passarotti, 2014) than the instances of anger and irritability usually seen in patients with ADHD. Moreover, the PBD group exhibited a significantly higher percent of clinically elevated T scores for the Emotional Control domain compared to the comorbid group. At present we do not have a clear explanation for this percent difference between the two bipolar groups. This result may be due to a random effect of patient group sampling, or to the fact that the PBD+ADHD group may be more heterogeneous than the PBD group, including individuals with less severe emotion dysregulation but more pronounced ADHD symptoms, as potentially suggested by the YMRS and ADHD index scores.

The present results do not indicate significant impairment in Emotional Control in the ADHD sample. Of note, the presence of emotional problems is now more acknowledged in ADHD (Skirrow & Asherson, 2013; Barkley, 2010), and there is growing evidence that at least a portion of children with ADHD diagnosis may exhibit difficulties in emotional regulation and emotion processing. However, these difficulties seem to be primarily due to a deficient cognitive control system that also fails during emotional challenge in social settings or when emotional information interferes with cognitive processes (Friedman et al., 2003; Skirrow, McLaughlin, Kuntsi & Asherson, 2009; Skirrow & Asherson, 2013; Passarotti & Pavuluri, 2011a; Barkley & Fischer, 2010; Van Cauwenberge, Sonuga-Barke, Hoppenbrouwers, van Leeuwen & Wiersema, 2015; Barkley, 2010), rather than to primary emotional dysregulation as seen in PBD. The PBD+ADHD group exhibited greater impairment than PBD only in the Monitoring domain. Most of the significant differences for this group were in relation to the ADHD group, encompassing both cognitive control and emotional control, with consequently worse GEC, BRI and MI. To date there is no clear-cut evidence on neurocognitive differences between PBD and PBD+ADHD. While a small number of studies have shown that patients with comorbid PBD and ADHD exhibit worse clinical symptoms than patients with PBD only (Galanter & Leibenluft, 2008a) other studies did not show greater cognitive impairment in this group (Pavuluri et al., 2006; Passarotti et al., 2013; Adler et al., 2005). The inconclusive results may be due to sample heterogeneity or perhaps to diagnostic confusion. At present, it is still unclear whether ADHD comorbidity in BD leads to a more severe profile of cognitive dysfunction or not, and whether the comorbid phenotype is just a more severe form of PBD or altogether a distinct clinical phenotype.

Finally, it is noteworthy that the current results from the PBD group on the BRIEF-PR are in agreement with those from a study with adult BD patients (Peters et al., 2014), who exhibited significant deficits in each domain of the BRIEF scale (BRIEF-A) (Roth, Isquith & Gioia, 2005), that were associated with mood symptoms, illness chronicity and psychiatric comorbidity. The similarity in EF deficits between adolescents and adults with BD suggests life-long persistency of the underlying mechanisms of dysfunction. However, we still do not understand whether the mechanisms by which BD psychopathology affects development of prefrontal cortex and EF are “neurodevelopmental” or “neurodegenerative” in nature (Lee et al., 2014).

**Differential Predictors of Executive Dysfunction in PBD, ADHD and PBD+ADHD.**

The present regression analysis findings providing some initial insights into distinct predictors of EF deficits in PBD and ADHD.

For the ADHD group ADHD symptoms were the only significant predictor for higher order cognitive domains such as Working Memory, Planning, Monitoring, Initiation and Metacognition. This result confirms our interpretation of a more cognitively-based EF impairment in ADHD. To a lesser degree, another predictor was depressive symptom severity, which was inversely related to Initiation of activities.

For the PBD group, depression and ADHD symptoms predicted GEC and Initiation, while ADHD symptoms alone predicted Planning. Importantly, severity of mania symptoms was the only significant predictor for Inhibition in that higher mania was associated with worse inhibition functions. This finding is in line with those from previous studies (Strakowski et al., 2010), confirming an association between mania and impulsivity. Impulsivity is a vulnerability
marker for bipolar disorder in high risk population (Wessa, Kollmann, Linke, Schonfelder & Kanske, 2015), and a prominent phenotype in bipolar patients (Bora, Yucel & Pantelis, 2009). The present findings confirm our hypothesis of a strong contribution of mood to cognitive control in PBD (i.e., “emotional impulsivity”) and also suggest additional effects of ADHD symptoms on higher order aspects of global executive functioning (i.e., initiation, planning).

For the PBD+ADHD group, higher mania or lower ADHD symptoms were associated with better Initiation of activities. Higher mania or lower depression was associated with better cognitive flexibility. For the comorbid group these results are suggestive of a combined contribution of mood and ADHD symptoms to Initiation and Shifting (i.e., cognitive flexibility). However, at present we do not have a clear-cut interpretation for the directionality of these results.

Lastly, the present findings on domain specific EF deficits in PBD and ADHD yield important implications for cognitive intervention in these youths. There are currently no published cognitive remediation studies in PBD. Cognitive remediation studies in children with ADHD have found significant improvement in the trained tasks, while it is still an open question whether the trained skills may significantly transfer to other cognitive domains (van der Donk, Hiemstra-Beernik, Tjenc-Kalf, van der Leijt & Lindauer, 2015). The current research findings point to the importance of tailoring cognitive intervention programs to illness-specific symptoms. For instance, in ADHD providing initial cognitive structure and organization to the child behavior in interaction with the cognitive training (e.g., externally reducing the working memory and attention burden) is of paramount importance for the success of the cognitive intervention (Antshel & Olszewski, 2014; Evans, Owens & Bunford, 2014; Boyer, Geurts, Prins & van der Oord, 2015). Conversely, for PBD patients it is important to stabilize mood first, and then address the unique cognitive and emotional control challenges stemming from altered interactions between cognitive and affective systems in BD. This will require supplementing the cognitive intervention with psychosocial intervention aimed at improving self-regulation, mood monitoring, cognitive restructuring of negative affect, as well as motivational support (Passariotti & Pavuluri, 2011a). The potential benefit of cognitive remediation in PBD and ADHD is significant, given that by strengthening the cognitive e systems in the fronto-temporo-parietal networks that are affected in these illnesses we may tap into mechanisms that improve cognitive recovery and resilience, leading to better self-regulation.

There are a few noteworthy study limitations that may limit generalizability of results. The patient with PBD were recruited from university clinics, which may have involved patients with greater severity of symptoms, while the patients with ADHD were recruited both from university clinics and from the community, which may have resulted in a less severely impaired ADHD group. At the time of testing a number of the PBD patients were not fully remitted and exhibited mania, hypomania and depression. Therefore the active mood symptoms may have worsened EF in these PBD patients. Moreover, because of the study chronology we followed DSM IV-TR criteria to diagnose the narrow phenotype of PBD (Type I and II). Therefore we did not screen for or did not include in our sample individuals with disruptive mood dysregulation disorder (DMDD), a new diagnostic category added to the DSM V (American Psychiatric Association, 2013), characterized by “chronic” irritability and anger (i.e., persistent mood symptoms as baseline) as compared to the “episodic” irritability and mood swings seen in PBD (i.e., periodicity of symptoms) (Noller, 2016, Wiggins et al., 2016). However, given the current clinical differentiation of the two pediatric illnesses in the DSM V it will be important that future studies investigate whether there are EF and cognitive differences between PBD and DMDD to inform treatment. Additionally, the study samples, while appropriate for the current analyses, are relatively small. Hence, larger samples from different recruitment sources may help better characterize differences in specific EF domains in PBD relative to ADHD. The neuropsychological tests result did not reveal group differences in performance. However, this may be due to the fact that the present neuropsychological battery was limited, and a broader battery including several standardized tests for each domain of interest may be better suited to uncover group differences in neuropsychological performance. Finally, our BRIEF-PR and CPRS-R data were based on parental report only. Obtaining self-report and teacher’s data from these scales may provide a more solid profile of EF dysfunction and more strictly cognition-related ADHD symptoms.

In conclusion, findings from the present study inform neuropsychological models of PBD and ADHD dysfunction by revealing domain-specific deficits in EF in PBD relative to ADHD. The current findings also potentially inform future studies on cognitive intervention to remediate EF dysfunction in these youths.

Supporting information
Additional supporting information may be found in the online version of this article:
Supplemental Table 1: Performance scores for the TMT A&B (Z scores), the Digit Span Task (standardized scores) and the Spatial Span Task (percent correct) in each group.
Supplemental Figure 1: Graphical representation of percent of individuals in each group with T>60 for each BRIEF-PR sub-scale.

Acknowledgements / Conflicts of Interest
The authors have no financial relationships to disclose.
References


bipolar disorder and attention deficit hyperactivity disorder. Journal of the International Neuropsychological Society, 16, 106-117.


Differences in Real World Executive Function between Children with Pediatric Bipolar Disorder and Children with ADHD.