2-24-2009

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Citation: J Child Adolesc Psychopharmacol. 2009 Feb;19(1):31-9. Link to article on publisher's site

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 19, Number 1, 2009

Pp. 31–39
DOI: 10.1089/cap.2008.041

Subcortical Differences among Youths with Attention-Deficit/Hyperactivity Disorder Compared to Those with Bipolar Disorder With and Without Attention-Deficit/Hyperactivity Disorder

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Abstract

Introduction: A significant number of children with bipolar disorder (BP) have co-morbid attention-deficit/hyperactivity disorder (ADHD). It is unknown if these children have neuroimaging findings unique to their co-morbid presentation, or if their brain findings are similar to children diagnosed with BP alone.
Method: Fifty three children with *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) BP (23 with ADHD, 30 without), 29 healthy controls (HC), and 23 children with ADHD, similar in sex and age, had magnetic resonance imaging (MRI) scans on a 1.5T GE scanner. Volumetric assessments were performed for basal ganglia and limbic subcortical structures.
Results: Youths with ADHD had smaller caudate and putamen volumes compared to both BP groups and they had moderately smaller total amygdala volumes compared to the other three groups. Youths with BP + ADHD had moderately larger nucleus accumbens volumes than HC, and females in both BP groups had smaller hippocampal volumes compared to ADHD and HC. No differences were found between the BP and BP + ADHD groups.
Conclusion: These data suggest that morphometric subcortical volumes in youths with BP + ADHD are more similar to those in youths with BP. They do not share subcortical neuroanatomic correlates with the ADHD group. These findings suggest that BP + ADHD is a subtype of pediatric BP rather than severe ADHD.

Introduction

A significant proportion of children with bipolar disorder (BP) are also diagnosed with attention-deficit/hyperactivity disorder (ADHD). It is unknown if these children have neuroimaging findings unique to their co-morbid presentation, or if their brains are similar to those of children diagnosed with early-onset BP without ADHD. Magnetic resonance imaging (MRI) may offer a method for disentangling these disorders. This study sought to assess whether volumetric differences could be detected in subcortical structures in a sample of youths with ADHD, BP without ADHD, BP with ADHD (BP + ADHD), and healthy controls (HC).

Early-onset BP (onset prior to age 18 years) is among the most severe and disabling psychiatric conditions affecting children (Faedda et al. 1995; Wozniak and Biederman 1995;

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This work was supported by several research grants from the National Institutes of Health: K08 MH01573 to J.A.F., U24 RR021382 to D.N.K., and K01 MH01798 to C.M.M.; and training awards through the American Psychiatric Association's Program for Minority Research Training in Psychiatry (5T32 MH19126) and Harvard Medical School's Dupont-Warren Fellowship to M.L.L.

Ahn and Frazier 2004). Despite the well-documented morbidity and dysfunction of children diagnosed with BP, the disorder continues to be one of the most controversial topics in child psychopathology (Ahn and Frazier 2004). A leading factor that complicates the diagnosis of BP in children is the frequent co-morbidity with ADHD and the dissimilar clinical presentation as compared to adult-onset BP, i.e., insidious versus acute, chronic versus episodic, and mixed versus manic states, respectively (Faedda et al. 1995; Wozniak and Biederman 1995; Faedda et al. 2004). These factors have led investigators to raise the critical question as to whether these children have severe ADHD, BP, or both disorders. The resolution of this question has important clinical implications, considering that different and sometimes incompatible treatments are needed for children that have ADHD, BP, or both.

An emerging neuroimaging literature indicates that distinct subcortical brain structures may characterize ADHD and BP in youths. MRI studies in children with ADHD have found abnormalities in the caudate (Castellanos et al. 1994; Filipek et al. 1997; Castellanos et al. 2002), putamen (Overmeyer et al. 2001; Wellington et al. 2006; Wang et al. 2007), and globus pallidus (Aylward et al. 1996; Overmeyer et al. 2001; McAlonan et al. 2007). Reduced frontal and/or prefrontal cortical (PFC) regions have also been reported in ADHD (Hill et al. 2001; Sowell et al. 2003; Durston et al. 2004; Plessen et al. 2006; Shaw et al. 2006; McAlonan et al. 2007). These MRI findings coalesce into a relatively distinct pattern of brain abnormalities for youths with ADHD that consist of aberrations in the frontal-striatal circuits.

Overall, anatomical MRI investigations in youths with BP have not found abnormalities in the basal ganglia (Chang et al. 2005; Sanches et al. 2005; Ahn et al. 2007; Frazier et al. 2008). Nonetheless, two studies have reported enlarged striatal structures (DelBello et al. 2004; Wilke et al. 2004) in youths with BP, which is the converse of findings reported in youths with ADHD. The structural literature implicates fronto-limbic involvement in the pathophysiology of BP, which is distinctly different from the findings in youth with ADHD. Youths with BP have abnormalities in regions of the frontal/PFC (Wilke et al. 2004; Blumberg et al. 2006; Frazier et al. 2007; Najt et al. 2007), nucleus accumbens (Dickstein et al. 2005; Ahn et al. 2007; Frazier et al. 2008), hippocampus (Blumberg et al. 2003; Frazier et al. 2005b; Frazier et al. 2008; Bearden et al. 2008), and amygdala (Blumberg et al. 2003; Chen et al. 2004; DelBello et al. 2004; Blumberg et al. 2005; Chang et al. 2005; Dickstein et al. 2005). Unfortunately, a majority of these studies included youths with BP + ADHD (samples ranging from 10 to 80% co-morbid ADHD), which makes it difficult to conclude that differences in subcortical limbic structures are due to BP alone.

To our knowledge, this is the first study to assess whether volumetric differences could be detected in subcortical structures comparatively based on BP status in youths with ADHD, BP alone, BP + ADHD, and HC. On the basis of the extant literature, we hypothesized that: (1) youths with ADHD would have smaller basal ganglia structures, including the caudate and putamen; (2) youths with BP would have reduced limbic structures, including hippocampal and amygdala volumes, and enlarged right nucleus accumbens volumes; (3) youths with co-morbid BP and ADHD would have limbic abnormalities similar to youths with BP alone and would have smaller basal ganglia structures similar to youths with ADHD.

Methods

This paper reports on a volumetric analysis that includes a library of MRI scans that has been used in prior studies (Frazier et al. 2005a; Frazier et al. 2005b; Frazier et al. 2008). The full details of the diagnostic and scanning methods have been reported elsewhere (Frazier et al. 2005a; Frazier et al. 2005b) and will be briefly described herein.

Subjects

The Institutional Review Boards at McLean Hospital and Cambridge Health Alliance approved this study. Subjects were recruited through McLean Hospital and the Cambridge Health Alliance from the outpatient, partial, inpatient programs, and from advocacy groups. HC were recruited through local advertisements and by word of mouth. Inclusion criteria for all subjects in this analysis were: age 6–19 years old, right-handedness. Inclusion criteria for patients included: either a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) diagnosis of ADHD or a diagnosis of BP I (mixed or manic lifetime) with or without a concurrent diagnosis of ADHD. Healthy controls had no DSM-IV Axis I diagnosis based on structured and clinical interviews. Healthy controls had no first-degree family history of BP, ADHD, psychosis, or any other psychiatric family history. Youths with ADHD did not have a history of any other DSM-IV Axis I disorder. Family history was obtained by clinical interview with one or both parents.

Exclusion criteria for all subjects and HC were: major sensorimotor handicaps (e.g., deafness, blindness, paralysis); full scale intelligence quotient (IQ) < 70 or learning disabilities; history of claustrophobia, autism, schizophrenia, anorexia nervosa or bulimia, drug or alcohol dependence/abuse (during 2 months prior to scan or total past history $\geq$12 months); active medical or neurological disease; history of electroconvulsive therapy (ECT); metal fragments or implants; and current pregnancy or lactation. History of learning disabilities was obtained via parental interview, and these youths were excluded due to the potential for confounding of neuroanatomical findings. Other co-morbid conditions were acceptable for all diagnostic groups.

All subjects provided written assent, and their parents (or legal guardians) provided written informed consent for their child's participation. All children, including HC, underwent clinical interview and a diagnostic semistructured Kiddie Schedule for Affective and Schizophrenic Disorders–Epidemiologic Version (K-SADS-E) (Orvaschel and Puig-Antich 1987) by board-certified child psychiatrists. Parents also were administered a K-SADS-E regarding their children (see Frazier et al. 2005a and Frazier et al. 2005b for further details). All raters achieved a high degree of interrater reliability; the mean kappa value was 0.9 and all disorders achieved kappa coefficients of > 0.82. Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield 1971). Measures of current psychopathology were obtained using the Mania Rating Scale (MRS), including the psychosis items (Young et al. 1978), and Global Assessment of Functioning scale (GAF) (American Psychiatric Association 1994). All of the bipolar subjects and HC have been included in prior publications (Frazier et al. 2005a; Frazier et al. 2005b; Ahn et al. 2007; Frazier et al. 2008). None of the data on the youths with ADHD has been published before.

MRI protocol

Structural imaging was performed at the McLean Hospital Brain Imaging Center on a 1.5 Tesla Scanner (Signa; GE Medical Systems, Milwaukee, WI) and details have been fully described previously (Frazier et al. 2005a; Frazier et al. 2005b). The acquisitions included a 3-D inversion recovery-prepped, spoiled gradient recalled echo coronal series, which was used for structural analysis (124 slices, prep = 300 msec, echo time [TE] = 1 minute, flip angle = 25°, field of view [FOV] = 24 cm^2, slice thickness 1.5 mm, acquisition matrix 256×192, number of excitations = 2). All scans were clinically reviewed by a neuroradiologist to rule out gross pathology.

Image analysis for subcortical segmentation

The regions of interest (ROIs) in this study consisted of all subcortical structures (Fig. 1). Each dataset was segmented according to the anatomic boundaries described in detail in Filipek et al. (1994) and Frazier et al. (2005a, 2005b). In brief, structural scans were positionally normalized to overcome variations in head position and then segmented into gray, white, and cerebrospinal fluid (CSF) tissue classes. The segmentation method uses a semiautomated intensity contour algorithm for external border definition and signal intensity histogram distributions for delineation of gray-white borders. As reported previously, this method provides excellent intra- and interrater reliability (Frazer et al. 2005a; Frazer et al. 2005b; Ahn et al. 2007). Total cerebral volume (TCV) was defined as all tissue in the cerebrum, including CSF, and excluded cerebellum and brain stem.

Data analyses

SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL) was used for statistical analysis. All statistical tests were two-tailed with $\alpha = 0.05$ unless otherwise specified. Comparability of groups across demographic and clinical variables was evaluated by analyses of variance for continuous variables and chi-squared tests for categorical variables.

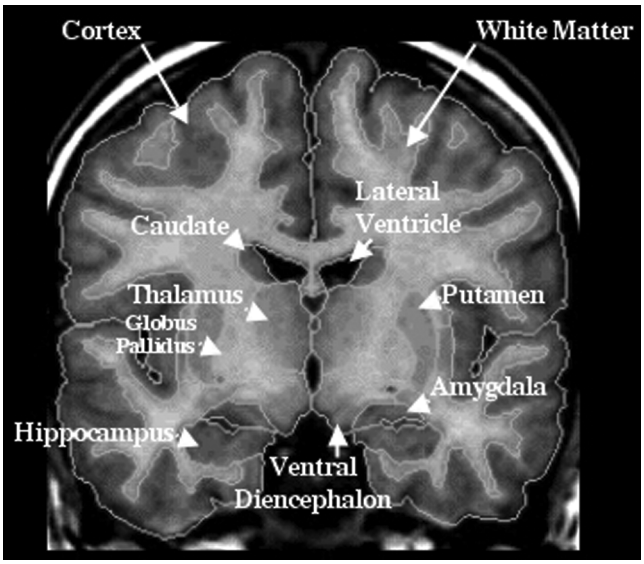

FIG. 1. T_1-weighted magnetic resonance imaging coronal slice showing subcortical regions of interest.

Subcortical structures were analyzed in sets according to system: the limbic system comprised the hippocampus, amygdala, and nucleus accumbens; the basal ganglia system comprised the caudate, putamen, and globus pallidus; and the thalamus was analyzed separately. We analyzed total volume (the sum of right and left regions) and the symmetry coefficient: [(left − right) / (left + right)] * 200. For each set of regions, a general linear mixed model with an unstructured covariance matrix was run to estimate overall diagnosis effects while controlling the multicolinearity among the regions of interest. Given a significant region-by-diagnosis effect, a series of univariate analyses of covariance (ANCOVA) were performed with diagnosis (HC, ADHD, BP + ADHD, BP) and sex (female, male), plus their interaction, as factors, and with age and TCV as covariates. TCV was excluded as a covariate in the analysis of symmetry coefficients (age was the only covariate). *Post hoc* mean comparisons were made for significant main effects and interactions using Tukey's Honestly Significant Difference, with $\alpha = 0.05$ to control for pairwise comparisons, and by the Student *t*-test to indicate modest (uncorrected) effects. For modest effects, effect sizes (the Cohen *d*) were estimated as the difference between least squares means divided by their pooled standard deviation.

Pearson and Spearman (rank) correlations were performed on clinical variables (bipolar onset and duration, ADHD onset and duration, current GAF, and MRS mania and psychosis scores), the number of psychoactive medications (atypicals, stimulants, mood stabilizers, lithium, antidepressants, chlorpromazine equivalents), and age for only those structures that differed significantly between diagnostic groups and HC. Given the large number of comparisons, correlations were reported if both the Pearson and the Spearman correlations were significant at $p \leq 0.05$.

Results

Data from 105 subjects, including 53 children with DSM-IV BP (23 with ADHD, 30 without), 29 HC, and 23 children with ADHD are included in this report (see Table 1). The youths with BP + ADHD and those without ADHD had a mean MRS score of 19.0 ± 8.6 and 22.5 ± 10.2, respectively. Of the 30 youths with BP alone, 6 were manic, 13 mixed, 4 depressed, and 7 were euthymic at the time of assessment. Of the 23 youths in the BP + ADHD group, 4 were manic, 10 mixed, 3 depressed, and 6 were euthymic at the time of assessment. Thirteen youths with BP (25%) had histories of psychosis (7 in the BP group and 6 in the BP + ADHD group). Clinical and treatment characteristics of the diagnostic groups are shown in Table 2. At the time of assessment, 22 (73.3%) of the youths with BP were on atypical antipsychotics, 5 (16.7%) were taking stimulants, 11 (36.7%) were on mood stabilizers, 6 (20.0%) were on antidepressants, 9 (30.0%) were on other medications including α- and β-adrenergic agents, and 2 (6.7%) were taking clonazepam. Of the youths with BP + ADHD, 17 (73.9%) were on atypical antipsychotics, 6 (26.1%) were taking stimulants, 11 (47.8%) were on mood stabilizers, 9 (39.1%) were on antidepressants, and 1 (4.3%) was taking other medications including α- and β-adrenergic agents. Twelve (52.2%) of the youths with ADHD were taking stimulants, 3 (13.0%) were on antidepressants, 2 (8.7%) were taking other medications including α- and β-adrenergic agents, and 2 (8.7%) were taking clonazepam. The volumetric observations are provided in Table 3.

Table 1. Characteristics of Youths with Bipolar Disorder, Bipolar Disorder and Attention-Deficit/Hyperacitivity Disorder, Attention-Deficit/Hyperactivity Disorder, and Healthy Controls

Characteristic	*HC* (n = *28*)	*ADHD* (n = *24*)	*BP* (n = *31*)	*BP + ADHD* (n = *23*)	*Omnibus F statistic*
Age	10.5 ± 2.9	11.4 ± 3.5	11.1 ± 2.9	10.3 ± 3.0	N.S.
<12 Age Group (%)	20 (69)	16 (69.6)	19 (63.3)	18 (78.3)	N.S.
Edinburgh Handedness Laterality Quotient	75.9 ± 25.4	64.4 ± 40.5	60.2 ± 60.5	71.9 ± 37.9	N.S.
Number of females (%)	12 (41.4)	7 (30.4)	17 (56.7)	7 (30.4)	N.S.
Number of Caucasian (%)	24 (82.8)	17 (73.9)	30 (100.0)	22 (95.7)	$\chi^2 = 18.4$, $p < 0.01$
Height (cm)	141 ± 17.0	144.3 ± 20.3	147.3 ± 17.5	138.9 ± 13.0	N.S.
Weight (kg)	40.9 ± 17.3	40.0 ± 18.6	48.4 ± 16.5	46.2 ± 17.3	N.S.
Head circumference (cm)	52.3 ± 8.9	51.5 ± 9.7	54.0 ± 1.8	54.2 ± 1.4	N.S.
Number of prepubertal (%)	13 (44.5)	9 (39.1)	12 (40.0)	9 (39.1)	N.S.
Hollingshead Low (III-V) Socioeconomic Status (%)	10 (34.5)	1 (4.3)	11 (36.7)	5 (21.7)	N.S.

Abbreviations: HC = Healthy controls; ADHD = attention-deficit/hyperactivity disorder; BP = bipolar disorder; N.S. = not significant.

There were significant diagnosis (F[3, 96] = 4.9, $p = 0.003$) and sex (F[1, 96] = 44.0, $p < 0.0001$) differences in total cerebrum volume. The BP and BP + ADHD groups had significantly smaller volumes (mean difference = 64.4 mL and 91.5 mL, respectively) than the HC group (Q[4, 96] = 4.0 and 5.1, respectively, $p = 0.03$ and 0.003). In addition, females were significantly smaller than males (mean difference = 121.5 mL, statistic cited above). Investigation of the modest interaction effect (F[3, 96] = 2.3, $p = 0.09$) indicated no group effects in the males (least-squares mean volumes range 1190–1248 mL); while females with BP + ADHD were significantly smaller than HC females (mean difference = 149.1 mL, Q[8, 96] = 5.1, $p = 0.01$).

Limbic structures

The linear mixed model for total volumes of structures in the limbic system indicated significant diagnosis by region effects (F[9, 105] = 3.5, $p = 0.001$) as well as significant covariate effects of age (F[3, 105] = 4.3, $p = 0.007$) and TCV (F[3, 105] = 16.2, $p < 0.001$).

There was a significant main effect of diagnosis for total volumes of the hippocampus (F[3, 95] = 3.6, $p = 0.017$). Youths with BP + ADHD had smaller volumes than those with ADHD (mean difference 0.7 mL, Q[4, 95] = 4.1, $p = 0.02$) or HC (mean difference 0.6 mL, Q[4, 95] = 4.0, $p = 0.03$), while not significantly different from BP (0.4 mL smaller). A moderate interaction effect (F[3, 95] = 2.6, $p = 0.06$) indicated that females with BP or BP + ADHD were significantly smaller than female HC (mean differences 0.7 and 1 mL, respectively, t[95] = 2.5 and 2.9, both $p < 0.05$ uncorrrected, $d = 0.9$ and 1.4) or females with ADHD (mean differences 0.7 and 1 mL, respectively, t[95] = 2.1 and 2.7, both $p < 0.05$ uncorrrected, $d = 0.9$ and 1.4) (see Fig. 2).

There was also a significant main effect of diagnosis for total volumes of the amygdala (F[3, 95] = 2.9, $p = 0.04$). Youths with ADHD had smaller amygdala volumes than BP + ADHD (mean difference 0.48 mL, t[95] = 2.5, $p < 0.05$ uncorrected,

Table 2. Clinical and Treatment Characteristics of Youths with Attention-Deficit/Hyperactivity Disorder, Bipolar Disorder, and Bipolar Disorder + Attention-Deficit/Hyperactivity Disorder

Characteristic[a]	*Healthy controls*	*ADHD*	*BP*	*BP + ADHD*	*Statistical significance of group difference*
Global Assessment of Functioning	68.3 ± 2.7	59.7 ± 4.0	51.6 ± 6.3	51.5 ± 6.0	F = 71.4[b] $p < 0.001^{1\text{-}5}$
Mania Rating Score (MRS)	1.7 ± 3.4	2.6 ± 3.4	22.5 ± 10.2	19.0 ± 8.6	F = 39.5[b] $p < 0.001^{2,3}$
MRS Psychosis Score	0.5 ± 1.6	0.1 ± 0.2	4.0 ± 2.9	1.4 ± 1.5	F = 16.2[b] $p < 0.001^{2,4,6}$
Age at onset of BP (years)			7.0 ± 3.9	5.5 ± 3.8	N.S.
Age at onset of ADHD (years)		4.9 ± 2.4		4.4 ± 1.7	N.S.
Duration of illness (years)		5.6 ± 3.4	2.2 ± 2.6	4.7 ± 3.3	N.S.
History of hospitalizations (n, %)		1 (4.7)	9 (31.0)	5 (21.7)	N.S.
Chlorpromazine equivalents at entry in study			106.1 ± 113.2	114.4 ± 92.5	N.S.
Number of psychoactive medications at entry in study[c]		1.4 ± 0.7	1.9 ± 2.2	2.2 ± 1.2	N.S.

[a]All measures given as mean ± standard deviation unless otherwise noted.
[b]Bonferroni-corrected pairwise comparisons shows that significant differences ($p \leq 0.05$) between (1) HC and ADHD, (2) HC and BP, (3) HC and BP + ADHD, (4) ADHD and BP, (5) ADHD and BP + ADHD, (6) BP and BP + ADHD.
[c]Includes atypical antipsychotics, antidepressants, sedatives, mood stabilizers, and stimulants.
BP = bipolar disorder; ADHD = attention-deficit/hyperactivity disorder.

Table 3. Mean Volumes (mL) and Symmetry Coefficients (%) for Limbic, Basal Ganglia, and Thalamic Regions of Interest

Region	*HC* *Mean ± SE*	*ADHD* *Mean ± SE*	*BP + ADHD* *Mean ± SE*	*BP* *Mean ± SE*
Total cerebrum volume (*)	1210.2 ± 16.3	1170.4 ± 19.8	1118.6 ± 19.6	1145.8 ± 15.9
Limbic structure volume				
Hippocampus	7.8 ± 0.1	7.8 ± 0.2	7.1 ± 0.2	7.5 ± 0.1
Amygdala	3.2 ± 0.1	2.8 ± 0.1	3.3 ± 0.1	3.2 ± 0.1
Nucleus Accumbens	1.2 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.4 ± 0.0
Basal ganglia structure volume				
Caudate	8.1 ± 0.2	7.4 ± 0.2	8.3 ± 0.2	8.3 ± 0.2
Putamen	10.4 ± 0.2	9.7 ± 0.3	10.9 ± 0.3	10.6 ± 0.2
Pallidum	3.4 ± 0.1	3.2 ± 0.1	3.5 ± 0.1	3.4 ± 0.1
Thalamus volume	15.7 ± 0.2	15.2 ± 0.2	15.8 ± 0.2	15.7 ± 0.2
Limbic structure symmetry				
Hippocampus	−2.9 ± 1.3	−2.0 ± 1.5	−1.3 ± 1.6	−2.8 ± 1.2
Amygdala	−2.6 ± 2.4	−6.4 ± 2.9	−1.0 ± 3.0	−0.8 ± 2.4
Nucleus Accumbens	10.9 ± 2.8	4.7 ± 3.4	2.9 ± 3.5	3.4 ± 2.8
Basal ganglia structure symmetry				
Caudate	−3.6 ± 1.1	−3.4 ± 1.3	−4.9 ± 1.4	−2.7 ± 1.1
Putamen	−0.9 ± 0.8	−0.9 ± 1.0	−1.2 ± 1.0	−1.4 ± 0.8
Pallidum	3.9 ± 1.3	5.9 ± 1.5	5.4 ± 1.6	5.1 ± 1.2
Thalamus symmetry	−1.4 ± 0.6	1.9 ± 0.7	−0.6 ± 0.7	−0.8 ± 0.6

Note: Values are the least-squares means and standard errors for the diagnosis effect from the analysis of covariance. Other terms in the model are sex, a diagnosis by sex interaction, age, and total cerebrum volume (except where noted *).

Abbreviations: BP = Bipolar disorder; HC = healthy control; ADHD = attention-deficit/hyperactivity disorder; SE = standard error.

$d = 0.7$), as well as BP (mean difference 0.45 mL, t[95] = 2.6, $p < 0.05$ uncorrected, $d = 0.7$) and HC (mean difference 0.41 mL, t[95] = 2.3, $p < 0.05$ uncorrected, $d = 0.6$) . There was no significant main effect of sex (F[1, 95] = 1.0, $p = 0.3$) or an interaction between diagnosis and sex (F[3, 95] = 1.1, $p = 0.3$).

There were no significant effects for the total volumes of the nucleus accumbens. Youths with BP + ADHD had moderately larger volumes than HC (mean difference 0.17 mL, t[95] = 2.1, $p < 0.05$ uncorrected, $d = 0.6$) and there was a trend for BP to have larger nucleus accumbens volumes than HC (mean difference = 0.14 mL, T[95] = 1.9, P = 0.06, $D = 0.5$) (see Fig. 3).

The linear mixed model for symmetry of structures in the limbic system showed no significant diagnosis by region effects (F[9, 103] = 1.3, $p = 0.2$), but a significant covariate effect for the symmetries to become more leftward with age (F[3, 103] = 4.7, $p = 0.004$). There was a moderate interaction effect in the nucleus accumbens whereby males with ADHD were rightward asymmetric (−3.6%), whereas HC males and females with ADHD were leftward asymmetric (12.7% and 13%, respectively, t(95) = 3.2 and 2.5, both $p < 0.05$, uncorrected, $d = 1.1$ and 1.1).

Basal ganglia structures

The linear mixed model for total volumes of structures in the basal ganglia system indicated significant diagnosis by region effects (F[9, 105] = 2.5, $p = 0.01$) as well as significant covariate effects of age (F[3, 105] = 3.0, $p = 0.035$) and TCV (F[3, 105] = 9.7, $p < 0.001$).

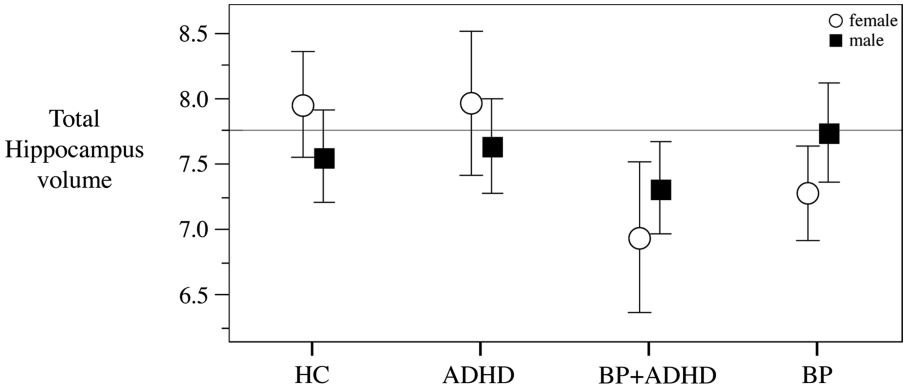

FIG. 2. Least-squares means and 95% confidence intervals for the total hippocampus volume (in mL) for each diagnostic group and sex. The horizontal line represents the mean of the HC group. HC = Healthy control; ADHD = attention-deficit/hyperactivity disorder; BP + ADHD = bipolar disorder and attention-deficit/hyperactivity disorder; BP = bipolar disorder.

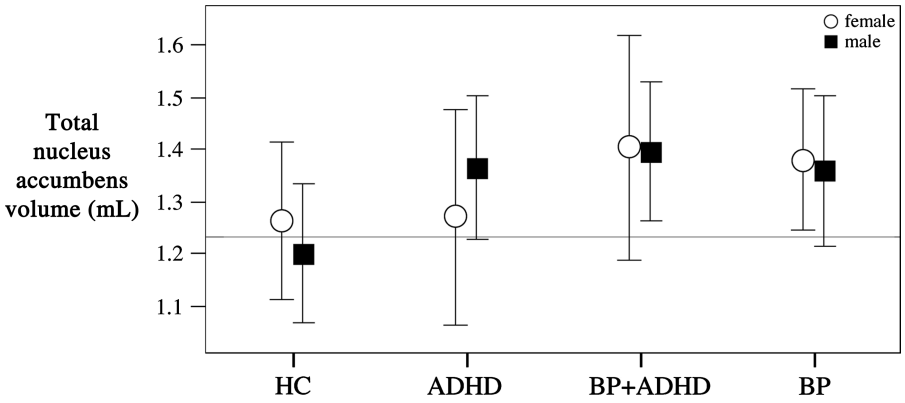

FIG. 3. Least-squares means and 95% confidence intervals for the total nucleus accumbens volume (in mL) for each diagnostic group and sex. The horizontal line represents the mean of the HC group. HC = Healthy control; ADHD = attention-deficit/hyperactivity disorder; BP + ADHD = bipolar disorder and attention-deficit/hyperactivity disorder; BP = bipolar disorder.

There was also a significant main effect of diagnosis for total volumes of the caudate ($F[3, 95] = 4.8$, $p = 0.004$). Youths with ADHD had smaller caudate volumes than BP + ADHD (mean difference 0.95 mL, $Q[4, 95] = 4.4$, $p = 0.013$), as well as BP (mean difference 0.97 mL, $Q[4, 95] = 5.0$, $p = 0.004$), and HC (mean difference 0.71 mL, $t[95] = 2.5$, $p < 0.05$, uncorrected, $d = 0.7$). There was no significant main effect of sex ($F[1, 95] = 0.1$, $p = 0.8$) or an interaction between diagnosis and sex ($F[3, 95] = 1.0$, $p = 0.4$).

There were significant main effects of diagnosis ($F[3, 95] = 3.9$, $p = 0.01$) and sex ($F[1, 95] = 4.9$, $p = 0.03$) in total volumes of the putamen. Youths with ADHD had smaller volumes than those with BP + ADHD (mean difference 1.21 mL, $Q[4, 95] = 4.6$, $p = 0.008$). Similarly, youths with ADHD had moderately smaller volumes than those with BP alone (mean difference 0.84 mL, $t[95] = 2.6$, $p < 0.05$ uncorrected, $d = 0.7$) and HC (mean difference 0.72 mL, $t[95] = 2.1$, $p < 0.05$ uncorrected, $d = 0.6$). In addition females had significantly smaller volumes than males (mean difference 0.64 mL, statistic cited above). There was no significant interaction between diagnosis and sex ($F[3, 95] = 0.7$, $p = 0.5$).

There were no significant effects of diagnosis ($F[3, 95] = 2.3$, $p = 0.08$) or sex ($F[1, 95] = 2.4$, $p = 0.13$) for the total volumes of the pallidum. Youths with ADHD had moderately smaller volumes than those with BP + ADHD (mean difference 0.35 mL, $t[95] = 2.6$, $p < 0.05$ uncorrected, $d = 0.8$). There was no significant interaction between diagnosis and sex ($F[3, 95] = 0.4$, $p = 0.7$).

The linear mixed model for symmetry of structures in the basal ganglia system showed no significant diagnosis by region effects ($F[9, 105] = 0.3$, $p = 0.9$), nor a significant covariate effect of age ($F[3, 105] = 0.8$, $p = 0.5$). No trend effects were noted.

Thalamus

There were no significant main effects of diagnosis ($F[3, 95] = 1.6$, $p = 0.2$) or sex ($F[1, 95] = 3.2$, $p = 0.07$) in the total volumes of the thalamus. Males with ADHD have moderately smaller volumes than males with BP or BP + ADHD (mean differences 0.9 and 1.0 mL, respectively, $t[95] = 2.4$ and 2.9, both $p < 0.05$ uncorrected, $d = 0.9$ and 1.0). There is a significant main effect of diagnosis in the symmetry of the thalamus ($F[3, 96] = 5.3$, $p = 0.002$), but not a significant effect of sex ($F[1, 96] = 0.1$, $p = 0.8$). Youths with ADHD have leftward symmetry, while all other groups have rightward symmetry (BP + ADHD, − 0.8%; BPD, − 0.9; HC, − 1.4%; all $Q[8, 96] > 4.0$, all $p < 0.03$).

Clinical correlations

Significant clinical correlations are as follows with the Pearson and then the Spearman (rank) correlations reported, respectively. In youths with BP, the amygdala was negatively correlated with MRS score ($r = -0.44$, $p = 0.03$; rho = − 0.41, $p = 0.05$). For youths with BP + ADHD, the nucleus accumbens negatively correlated with number of medications ($r = -0.62$, $p \leq 0.01$; rho = − 0.64, $p \leq 0.01$). Finally for HC, the putamen ($r = 0.49$, $p \leq 0.01$; rho = 0.50, $p \leq 0.01$) and the thalamus ($r = 0.37$, $p = 0.05$; rho = 0.42, $p = 0.02$) positively correlated with age.

Discussion

Youths with BP + ADHD had distinct differences in subcortical structures compared to youths with ADHD. For example, youths with ADHD differed significantly from youths with BP + ADHD and youths with BP in the basal ganglia (caudate and putamen) and in the amygdala. There were no differences in subcortical structures between the youths with BP alone and those with BP + ADHD. These data indicate that morphometric subcortical volumes in youths with BP + ADHD are more similar to those with BP and do not share neuroanatomic correlates with the ADHD group.

Compared to HC, youths with BP + ADHD had smaller TCV and a moderately larger nucleus accumbens volume. In addition, youths with BP were also noted to have a trend toward larger accumbens volumes compared to HC. These findings have been reported by this group previously (Ahn et al. 2007; Frazier et al. 2008). It is of interest that the study by Ahn and colleagues noted a trend toward a larger right nucleus accumbens in a combined sample of youths with BP ($n = 46$, 76% with co-morbid ADHD). In another study, our group compared subcortical (limbic and basal ganglia) structures between four groups of youths—those with BP with and without psychosis, those with schizophrenia (SCZ) and HC. We found that both BP groups (with and without

psychosis) had enlarged nucleus accumbens, and that youths with BP + psychosis did not share any neuroanatomic findings with the SCZ group (Frazier 2008). Overall, our findings suggest that abnormally large nucleus accumbens is specific to BP and may be associated with increased illness severity (symptoms of ADHD and psychosis).

Inconsistent with the literature, this study did not find differences in regions of the basal ganglia in ADHD as compared to HC after correction for multiple comparisons (Castellanos et al. 1994; Aylward et al. 1996; Filipek et al. 1997; Overmeyer et al. 2001; Castellanos et al. 2002; Wellington et al. 2006; McAlonan et al. 2007; Wang et al. 2007). However, the volumetric raw means and the large effect sizes for regions of the basal ganglia including the caudate ($d = 0.7$) and putamen ($d = 0.7$) indicate that these regions are smaller in youths with ADHD compared to HC. Our lack of finding is likely due to the small sample size of the groups. We did find that the caudate was significantly smaller in the ADHD group compared to both BP groups. For the amygdala and putamen, the ADHD group had significantly smaller volumes as compared to both BP groups and the BP + ADHD group, respectively. Youths with BP and BP + ADHD were not found to have any differences in striatal regions in comparison to HC. In summary, our findings suggest regions of the basal ganglia are more likely to be involved in the pathophysiology of ADHD rather than BP.

Our study indicates that there is not an overlap in subcortical abnormalities in youths with BP + ADHD as compared to ADHD youths, which suggests that youths with BP +ADHD may not have a "true" ADHD co-morbidity. However, there is emerging evidence that adults with BP + ADHD may share similar neuroanatomical correlates with those with ADHD in cortical structures. In fact, in a similar study in adults with BP + ADHD, BP alone and ADHD, distinct differences between BP + ADHD and BP were found in cortical but not subcortical structures (Biederman et al. 2007). Furthermore, adults with BP + ADHD had neuroanatomic similarities to adults with both ADHD and BP alone (Biederman et al. 2007). In addition, two functional (f)MRI studies comparing youths with BP and BP + ADHD have also found distinct differences in activation between the groups in cortical but not subcortical (including limbic) structures (Adler et al. 2005; Leibenluft et al. 2007). Therefore, it is possible that youths with BP + ADHD have shared cortical neuroanatomic correlates of both BP and ADHD. Unfortunately, the fMRI studies did not include an ADHD group, so it is difficult to determine if the differences in cortical activation are due to ADHD co-morbidity or to a BP subtype difference.

Youths with ADHD were found to have a reversal of the normal symmetry of the thalamus as compared to HC as well as both BP groups. Thalamic volume abnormalities have not previously been reported in ADHD. However, thalamic injury in youths with closed head trauma increases the risk of secondary ADHD (Gerring et al. 2000). The pathophysiologic underpinnings of ADHD are thought to involve fronto-striatial circuits. The role of the thalamus as an interconnecting relay station between frontal and subcortical structures makes it an interesting target for future investigation.

Our findings in this study are consistent with our hypothesis of a reduction in hippocampal volumes and an increase in nucleus accumbens volumes in youths with BP. However, unlike other studies (Blumberg et al. 2003; DelBello et al. 2004; Chang et al. 2005; Chen et al. 2004; Blumberg et al. 2005; Dickstein et al. 2005), we did not find reduced amygdala volumes in either BP group. However, we did find an inverse relationship between amygdala volume and MRS scores, suggesting that children with BP who have more significant symptoms have smaller amygdala volumes, thus implicating this structure in the BP presentation. The lack of amygdala abnormalities in BP has been reported by this group elsewhere (Frazier et al. 2005b), and our group speculated that this could be due to methodological differences in amygdala measurement, the younger age of our sample (mean age range of prior studies was 13.4–16.3 as compared to our study with mean 10.7), and the variable inclusion rates of co-morbid ADHD (ranged from 10 to 80%) in studies. Interestingly, we did find reduced volumes for the amygdala in youths with ADHD. Therefore, abnormal amygdala findings in the BP literature could be due to the inclusion of youths with co-morbid ADHD. In support of this hypothesis, youths with ADHD have been found to have a smaller basolateral complex of the amygdala compared to HC (Plessen et al. 2006).

This study included both male and female subjects, and sex–structure interactions were assessed. Sex was noted to be an important factor for TCV and putamen and a moderate sex-by-diagnosis interaction was found for the hippocampus, which has been reported by this group elsewhere (Frazier et al. 2005b; Frazier et al. 2008). The impact of sex on subcortical structures has been reported by others (for review, see Durston et al. 2001). Normatively, hippocampal and caudate volumes are larger in females and cerebral volumes and amygdala volumes are larger in males (Durston et al. 2001; Goldstein et al. 2001). There have been very few neuroimaging studies that have investigated sex differences in cortical and subcortical structures in neuropsychiatric illness (Frazier et al. 2008); therefore, further research is warranted in this area of investigation.

Nucleus accumbens volume in the BP + ADHD group was the only region found to correlate negatively with number of medications. The effects of psychotropic medications, such as antidepressants, mood stabilizers, and antipsychotics, on brain structures, particularly subcortical brain structures, remain unknown. However, there have been several recent studies, which have attempted to explore the impact of medications on gray matter (GM) and white matter (WM) and on specific regions of the brain. For instance, Castellanos and colleagues found greater WM deficits in unmedicated ADHD youths than medicated youths (Castellanos et al. 2002). Furthermore, an increase in GM volumes has been reported in individuals taking lithium (Sassi et al. 2002; Monkul et al. 2007). An exploratory analysis of youths with BP found that individuals with past lithium or valproate exposure tended to have greater amygdala GM volumes than subjects with BP without exposure (Chang et al. 2005). Basal ganglia enlargement has been noted with typical but not atypical antipsychotics (Chakos et al. 1995; Frazier et al. 1996; Corson et al. 1999). Overall, the impact of at least some medications on brain structures may be significant and, in part, account for the discrepant findings of neuroanatomic structures in the neuropsychiatric literature. Further investigations of the impact of medications on GM and WM and on specific brain regions in neuropsychiatric disorders are needed.

The findings in this study should be interpreted with caution given its limitations, which include the cross-sectional nature, the use of multiple diagnostic comparisons, and the relatively small sample sizes. Furthermore, many subjects

were taking psychotropic medication at the time of the study. Last, we included youths in different mood states at the time of scan, which may be a potential confound.

Conclusion

This is one of the first studies to compare subcortical structures in a sample of youths with BP alone, BP + ADHD, ADHD, and HC. The morphometric subcortical findings indicate that youths with BP + ADHD have disparate subcortical findings as compared to youths with ADHD, particularly in the basal ganglia. However, further investigation of cortical structures in a similar sample of youths is needed to evaluate whether or not shared cortical abnormalities exist in youths with ADHD and BP + ADHD. Youths with BP + ADHD had larger nucleus accumbens and a smaller hippocampus compared to HC, whereas the BP group only showed a trend for a larger nucleus accumbens. These results suggest BP + ADHD is a subtype or perhaps a more severe form of early-onset BP. Abnormal structure does not necessarily imply abnormal function. Therefore, longitudinal multimodal structural and functional investigations are needed to evaluate the similarities and distinctions in the underlying neurodevelopmental circuits and their trajectories in youths with BP alone, ADHD, and BP + ADHD.

Disclosures

Dr. Frazier has received grant support or served as a consultant for Bristol-Myers Squibb Company, Eli Lilly and Company, Glaxo Smith Kine, Johnson and Johnson, Neuropharm, Otsuka America Pharmaceutical, and Pfizer Inc. Drs. Lopez-Larson, Kennedy, Moore, Makris, and Caviness and Ms. Michael, Ms. Terry, Ms. Breeze, Mr. Hodge, and Ms. Tang have no conflicts of interest or financial ties to disclose.

Acknowledgments

We would like to thank the children and their families for their participation in this study. Without their enthusiastic involvement, the study could not have been completed.

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