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Striatal volumes in pediatric bipolar patients with and without comorbid ADHD

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ABSTRACT

The most prevalent comorbid disorder in pediatric bipolar disorder (BD) is attention-deficit/hyperactivity disorder (ADHD). As caudate volume abnormalities have been demonstrated in both BD and ADHD, this study sought to determine whether these findings could be attributed to separable effects from either diagnosis. High resolution anatomical magnetic resonance (MRI) images were obtained from youth in 4 groups: BD with comorbid ADHD ($n=17$), BD without comorbid ADHD ($n=12$), youth with ADHD alone ($n=11$), and healthy control subjects ($n=24$). Caudate, putamen, and globus pallidus volumes were manually traced for each subject using BrainImageJava software by a reliable rater blinded to diagnosis. There was a significant effect of diagnosis on striatal volumes, with ADHD associated with decreased caudate and putamen volumes, and BD associated with increased caudate, putamen, and globus pallidus volumes. Thus, the presence or absence of comorbid ADHD in patients with BD was associated with distinct alterations in caudate volumes, suggesting that these groups have different, but related, mechanisms of neuropathology.

1. Introduction

There has been a vast increase in our research knowledge of pediatric-onset bipolar disorder (BD) over the past decade. Nevertheless, many questions regarding the underlying pathophysiology of the disease remain unanswered. Finding a common biological marker of BD is complicated by the heterogeneity of the disorder, particularly as it presents frequently with comorbid disorders. The most prevalent comorbid disorder with pediatric BD is attention deficit/hyperactivity disorder (ADHD) (DelBello et al., 2004; Adler et al., 2005). These patients show impairments in attention, impulse control, and executive function in addition to the mood dysregulation that affects all patients with BD. Studying BD patient populations based on the presence or absence of ADHD may create greater homogeneity within patient groups. This may aid in distinguishing neural abnormalities unique to each disorder.

Several studies have used structural magnetic resonance imaging (sMRI) to examine regional brain volumes in both BD and ADHD. While a number of studies have demonstrated reduced caudate nucleus volumes in patients with ADHD as compared with healthy controls (Krain and Castellanos, 2006a; Schneider et al., 2006), such studies on patients with BD have been few and inconsistent. Wilke and colleagues found overall volume increases in the basal ganglia of adolescents with BD (Wilke et al., 2004), while DelBello reported increased putamen volumes compared to healthy controls (DelBello et al., 2004). In contrast, other studies in pediatric BD samples found no abnormalities in putamen (Sanches et al., 2005) or caudate volumes (Chang et al., 2005; Sanches et al., 2005). Furthermore, in the most relevant recent study that examined striatal volumes among youths with BD and/or ADHD, caudate and putamen volumes were decreased in subjects with ADHD alone, but no differences in striatal volumes were found between the subjects with BD alone or those with BD+ADHD as compared with controls (Lopez-Larson et al., 2009). Additionally, two studies of first degree relatives or offspring of bipolar parents did not show significant changes in striatal volumes as compared with controls (Singh et al., 2008; Hajek et al., 2009).

In this study, we compared the volumes of the caudate and putamen in pediatric patients with BD+ADHD, BD alone, ADHD alone, and healthy controls. We hypothesized that subjects with ADHD would have decreased striatal volumes compared to healthy controls, while subjects with BD alone would have increased striatal volumes. Thus, when both disorders co-occur (ADHD+BD), we hypothesized that individuals would present with intermediate striatal volumes that do not significantly differ from healthy controls.

2. Methods

2.1. Subjects

This study was approved by the Stanford University IRB, and all subjects gave oral and written informed consent or assent before

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participation. Forty patients were recruited from the Stanford University child and adolescent psychiatry clinic. Participants included 17 with BD and ADHD (BD+ADHD group), 12 with BD only (BD−ADHD group), and 11 with ADHD only (ADHD group). Twenty-four healthy volunteers were recruited from the community (Healthy Control group). Participants were included if they were 9–18 years old, had IQ>70, had no contraindications to undergoing an MRI scan, and did not have any major neurological disorders, medical conditions, or developmental disorders (such as a pervasive developmental disorder) which may affect brain functioning. Diagnoses were made by a trained clinician using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 1996) and the Schedule for Affective Disorders and Schizophrenia for School-age Children, Present and Lifetime (Kaufman et al., 1997). All diagnoses were confirmed by a board-certified child psychiatrist (KC). Subjects with BD met DSM-IV criteria for bipolar I disorder. ADHD participants met DSM-IV criteria for attention-deficit hyperactivity disorder (inattentive, hyperactive, or combined) with no additional diagnoses of any other psychiatric disorders. Healthy volunteers did not have any current or lifetime DSM-IV diagnoses. Parental diagnoses were also obtained using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995).

2.2. Image acquisition

Subjects discontinued use of psychostimulants for 24 h prior to magnetic resonance imaging (MRI) due to a concurrent functional MRI study. Participants were allowed to continue taking other medications such as mood stabilizers and antidepressants to prevent mood destabilization.

All imaging procedures were conducted at the Lucas Center for Magnetic Resonance Spectroscopy and Imaging at Stanford University, Palo Alto, CA. Magnetic resonance images of each subject's brain were acquired with a Signa 3.0-T scanner (GE Medical Systems, Milwaukee, WI). Images were acquired in the coronal plane, using a 3-D volumetric radiofrequency spoiled gradient echo pulse sequence with the following scan parameters: TR = 35 ms, TE = 6ms, flip angle = 45°, number of excitations = 1, image matrix = 256 × 192 field of view = 24 cm, slice thickness = 1.5 mm, 124 slices, acquired resolution = 1.5 × 0.9 × 1.2 mm^3. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9 mm^3 spatial resolution.

Seven of the BD−ADHD subjects were scanned with the same pulse sequence parameters, but using a different headcoil due to their concurrent participation in another study. Before combining these data, we systematically investigated the effects of each headcoil type on measures of caudate volume. Four subjects (2 male, 2 female) with no family history of psychiatric illness were scanned using both headcoils and using the same pulse sequences and volumetric measures as used in this study. Reliability analysis performed by a single measure intraclass correlation calculated in SPSS 17.0 found excellent intraclass correlations (ICC) for all measures: Volume of gray matter ICC = 0.99, white matter ICC = 0.99, and cerebrospinal fluid ICC = 0.98. Measures of total caudate volume were also highly comparable between headcoils. Right caudate total volume had an ICC of 0.99, and left caudate total volume had an ICC of 0.99. Thus, headcoil type did not contribute significant variance to the measure of striatal volumes for this study, and we therefore included these seven subjects in our analyses.

2.3. Volumetric analysis

Images were imported to the program BrainImageJava, version 5.3.7 (BIJ; Center for Interdisciplinary Brain Sciences Research; http://spnl.stanford.edu). Non-brain tissue was removed using a semi-automated process, and the images were corrected for field bias artifact before importing into BIJ. Images were positionally normalized (rigid body transformation) based on positions of the anterior and posterior commissures (Talairach and Tournoux, 1988). Total brain volume (TBV) was calculated as the sum of the total tissue and total CSF of the cerebrum, cerebellum, ventricles, and brainstem.

All regions of interest (ROIs) were outlined by a single trained rater blinded to diagnosis and to the subjects' identity (IL). High intraclass reliability (ICC>0.9) was first established with a set of gold standard ROIs traced on a separate set of control images. A brief description of each ROI follows, and an example of a coronal slice with outlined ROIs is seen in Fig. 1. These tracings are in accordance with previously published descriptions (Murphy et al., 1992; Chang et al., 2005).

2.3.1. Caudate

Tracing the caudate began at the most anterior slice where the gray matter of the head of the caudate was visible and proceeded posteriorly until gray matter of the caudate tail was no longer visible. The medial border was the lateral ventricle, and the lateral border was the internal capsule. When a small gray matter connection was seen between the putamen and the caudate, the inferior border of the caudate was moved to a straight line between this gray matter and the most inferior point of the lateral ventricle. This served to exclude the nucleus accumbens from the ROI.

2.3.2. Lenticular nucleus

The lenticular nucleus includes the putamen and the globus pallidus. Tracing began at the most anterior slice where the putamen became visible lateral to the caudate. The lateral border was the external capsule and the medial border was the internal capsule. The inferior border was the medial border until the anterior commissure became visible, at which point it became the anterior commissure. The superior border was the corona radiata and the internal capsule.

2.3.3. Globus pallidus and putamen

From the lenticular nucleus ROI, the globus pallidus ROI was isolated by tracing between the globus pallidus and the putamen and deleting the putamen from the ROI. The globus pallidus was not originally part of the hypothesis, but due to this method of isolating the putamen ROI, we did exploratory measurements of GP volumes. Putamen measurements were taken indirectly by subtracting the globus pallidus volumes from the lenticular nucleus volumes.

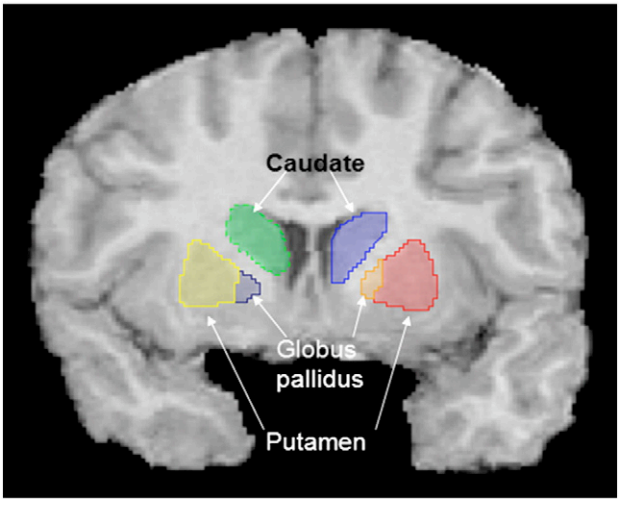

Fig. 1. Coronal view of all regions of interest.

2.4. Statistical analysis

One-way analyses of variance (ANOVAs) were performed to compare the four subject groups on demographic and clinical variables. All volumetric analyses of individual structures used linear regression models in SPSS software. Binary variables were centered as +0.5/−0.5. These included bipolar diagnosis (yes or no) and ADHD diagnosis (yes or no). The linear variable used as a covariate, total cerebral tissue, was centered by subtracting the global mean value from each value. A corrected threshold of $p = 0.05/3$ models $= 0.0167$ was used to determine significance. In order to use these parametric statistics, the data were first examined for normality. The data were also examined for outliers, and one outlier datapoint was found and verified to be accurate. Follow-up hemispheric analyses were conducted as exploratory and thus no correction for multiple comparisons was performed. Medication exposure was included as a factor to investigate whether effects of diagnosis were due to medications.

3. Results

3.1. Demographic variables and total brain volume

Neither age ($F = 1.59$, d.f. $= 3$, $p = 0.20$), total brain volume (TBV) ($F = 1.17$, d.f. $= 3$, $p = 0.33$), nor IQ ($F = 1.76$, d.f. $= 3$, $p = 0.17$) exhibited significant differences between groups (Tables 1 and 2). However, we covaried for TBV in our analyses of striatal volumes as we found high correlations between TBV and striatal volumes. The BD+ADHD and BD−ADHD groups did not differ in scores on the Young Mania Rating Scale ($F = 0.06$, d.f. $= 1$, $p = 0.80$), Children's Depression Index ($F = 0.14$, d.f. $= 1$, $p = 0.71$), age of BD onset ($F = 0.07$, d.f. $= 1$, $p = 0.79$), or ratings on the Children's Global Assessment Scale ($F = 1.01$, d.f. $= 1$, $p = 0.33$) (Table 1). The groups differed in current medication usage (see Table 1). All subjects with ADHD (with or without BD) had combined type. Twenty-five of the 29 subjects (86%) with BD had at least one parent with BD. ADHD subjects had parents with no DSM-IV diagnoses other than ADHD, and healthy controls had parents with no DSM-IV diagnoses. ADHD participants and healthy controls also had no first degree relatives with BD. Five of the 12 subjects (42%) with BD only had a parent with ADHD, while 14 of the 17 subjects with BD+ADHD (82%) had a parent with ADHD. Information on whether bipolar subjects were manic, depressed, or euthymic at the time of the scan was not collected outside of the YMRS and CDI scales given. No subjects had symptoms of psychosis.

3.2. ROI volumetric regression analyses

The brain region volumetric measurements in cm^3 are given in Table 2 and Fig. 2. The results of the three regression models are given in Table 3. For the model of total caudate volume, the main effect of bipolar diagnosis and the main effect of ADHD diagnosis were both significant (see Table 3), and in opposite directions (e.g. bipolar diagnosis was associated with a larger caudate, while ADHD diagnosis was associated with a smaller caudate). The interaction was not significant.

A similar pattern was seen for total putamen volume. The main effect of bipolar diagnosis, the main effect of ADHD diagnosis, and the interaction of bipolar × ADHD were significant. Again, those with a bipolar diagnosis had a larger putamen, while those with an ADHD diagnosis had a smaller putamen volume.

The main effect of bipolar diagnosis was significant for total globus pallidus volume, such that bipolar diagnosis was associated with a larger volume. No other factors were significant for globus pallidus volume.

After the initial three models were examined and found to be significant, we performed exploratory analyses on left and right hemispheric volumes for the different structures. For left caudate, the main effect of bipolar was significant ($p = 0.0001$, positive effect), the main effect of ADHD was significant ($p = 0.0001$, negative effect), while the interaction was not significant ($p = 0.045$). For the right caudate, the main effect of bipolar was significant ($p = 0.0001$, positive effect), the main effect of ADHD was significant ($p = 0.0001$, negative effect), while the interaction was not significant ($p = 0.155$). For the left putamen, the effects were as follows: bipolar: $p = 0.0001$ positive; ADHD: $p = 0.0001$ negative; interaction $p = 0.002$. For the right putamen, the effects were as follows: bipolar: $p = 0.0001$ positive; ADHD: $p = 0.0001$ negative: interaction $p = 0.057$. For the left GP, the effects were as follows: bipolar $p = 0.0001$ positive; ADHD; $p = 0.274$, interaction $p = 0.046$. For the right GP, the effects were as follows: bipolar $p = 0.138$; ADHD $p = 0.253$; interaction $p = 0.760$. We also performed exploratory analyses investigating whether the caudate head or body/tail were differently affected. Both the head and the body/tail showed similar effects as the total caudate (caudate head: main effect of bipolar diagnosis: $p = 0.0001$, main effect of ADHD diagnosis: $p = 0.0001$, the interaction of bipolar × ADHD was not significant NS;

Table 1
Descriptive and clinical measures by group[a].

	Bipolar+ADHD	Bipolar–ADHD	ADHD	Controls	p [b]
N	17	12	11	24	
Age mean (SD)	14.4 (2.6)	15.8 (2.5)	13.4 (3.3)	14.2 (2.7)	0.20
Gender (%male)	76%	42%	82%	71%	0.14
IQ[c]	109 (11.7)	109 (9.0)	114 (14.2)	116 (8.3)	0.17
Age of BD onset (S.D.)	12.6 (2.4)	12.9 (3.0)	–	–	0.79
YMRS mean (SD)[d]	14.1 (8.4)	15.1 (10.5)	–	–	0.80
C-GAS mean (S.D.)[e]	54.6 (8.2)	50.8 (8.5)	–	–	0.33
CDI mean (S.D.)[f]	14.3 (8.2)	16.3 (9.5)	–	–	0.71
% exposed to any psychotropic	94%	25%	73%	0%	
% exposed to antidepressants	94%	17%	18%	0%	
% exposed to mood stabilizers[g]	71%	25%	0%	0%	
% exposed to antipsychotics [h]	29%	17%	9%	0%	
% exposed to stimulants	73%	17%	73%	0%	

[a] Attention-deficit/hyperactivity disorder only (ADHD), bipolar disorder with comorbid ADHD (BD+ADHD), bipolar disorder without comorbid ADHD (BD−ADHD), and healthy controls (Control).
[b] p values obtained from 4-group analyses of variance: main effect of group
[c] As measured by Wechsler Abbreviated Scale of Intelligence
[d] Young Mania Rating Scale
[e] Children's Global Assessment Scale
[f] Children's Depression Inventory
[g] Mood stabilizers include lithium, valproate, lamotrigine, and carbamazepine.
[h] Includes both typical and atypical antipsychotics.

Table 2
Brain region volumetric measurements (in cm^3) by group[a].

Brain region mean volume, cm^3 (SD)	ADHD $n=11$	BD+ADHD $n=17$	BD–ADHD $n=12$	Control $n=24$
TBV[b]	1502.1 (150.7)	1427.3 (115.0)	1457.7 (100.5)	1497.7 (118.3)
Total caudate	7.45 (0.80)	9.27 (0.94)	9.63 (1.17)	9.22 (1.17)
Left caudate	3.68 (0.37)	4.57 (0.50)	4.74 (0.59)	4.63 (0.58)
Right caudate	3.77 (0.49)	4.70 (0.46)	4.90 (0.56)	4.59 (0.60)
Total putamen	10.12 (1.00)	10.95 (1.03)	10.81 (1.07)	10.73 (0.88)
Left putamen	5.23 (0.46)	5.49 (0.48)	5.49 (0.55)	5.46 (0.50)
Right putamen	4.89 (0.60)	5.46 (0.62)	5.32 (0.54)	5.27 (0.45)
Total globus pallidus	3.50 (0.52)	3.71 (0.45)	3.42 (0.60)	3.50 (0.41)
Left globus pallidus	1.73 (0.19)	1.85 (0.26)	1.76 (0.34)	1.66 (0.24)
Right globus pallidus	1.77 (0.27)	1.87 (0.22)	1.66 (0.27)	1.84 (0.33)

[a] Attention-deficit hyperactivity disorder only (ADHD), bipolar disorder with comorbid ADHD (BD+ADHD), bipolar disorder without comorbid ADHD (BD–ADHD), and healthy controls (Control).
[b] TBV = Total Brain Volume.

caudate tail and body: main effect of bipolar diagnosis $p=0.009$, main effect of ADHD diagnosis: $p=0.007$, the interaction of bipolar × ADHD diagnoses NS. All effects were in the same direction as in the total caudate volume.

Medication exposure analyses revealed no effect on striatal volumes (caudate, putamen, globus pallidus) from exposure status to stimulants ($p=0.13$, $p=0.95$, $p=0.52$), antipsychotics ($p=0.50$, $p=0.89$, $p=0.80$), mood stabilizers ($p=0.22$, $p=0.33$, $p=0.98$), or SSRIs ($p=0.95$, $p=0.89$, $p=0.94$), respectively.

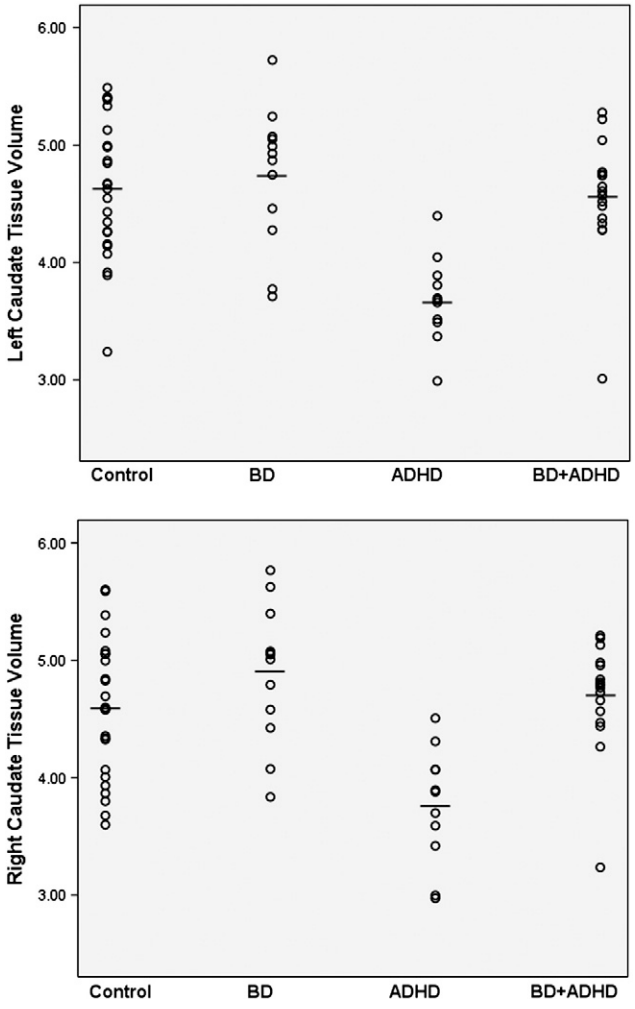

Fig. 2. Left and right caudate volumes in healthy controls (Control, $n=24$), subjects with bipolar disorder without comorbid ADHD (BD–ADHD, $n=12$), subjects with only attention-deficit hyperactivity disorder (ADHD, $n=11$), and subjects with bipolar disorder with comorbid ADHD (BD+ADHD, $n=17$). There was a significant effect of diagnosis on striatal volumes, with ADHD associated with decreased caudate volumes and BD associated with increased caudate volumes.

Exploratory correlations were performed to examine possible relationships between caudate volume and bipolar disorder duration and manic symptom severity at time of scan. Bipolar illness duration ($r=-0.37$, $p=0.08$) and YMRS ($r=0.16$, $p=0.55$) did not correlate significantly with total caudate volume.

One outlier was found in the BD+ADHD group with caudate volumes significantly below others within the group. This subject was kept in the dataset as ROI drawings for the subject were reexamined and confirmed to be in accordance with the ROI protocol. Additionally, an investigational analysis found that excluding the outlier did not affect the results of the study.

3.3. Effect sizes

We calculated effect sizes for comparisons of caudate volumes between the four groups. Cohen's d and effect size r were as follows: ADHD only vs. controls: $d=-1.77$, $r=-0.66$; BD+ADHD vs. controls: $d=0.05$, $r=0.02$; BD–ADHD vs. controls: $d=0.35$, $r=0.17$; BD+ADHD vs. BD–ADHD: $d=0.34$, $r=0.17$.

4. Discussion

We found that having a diagnosis of BD or ADHD independently affected caudate volumes in our cohort of youth with ADHD, BD alone, BD+ADHD, and healthy controls. Specifically, presence of ADHD was associated with a reduced caudate volume, whereas presence of BD was associated with an increased caudate volume. These effects were seen in both the left and right caudate, as well as both the head and body/tail of

Table 3
Results of regression analyses of brain regional volumes.

Factor	Regression coefficient	Std error	t	p
Total caudate tissue				
Bipolar	1.38	0.122	5.49	0.0001
ADHD	−1.29	0.251	−5.17	0.0001
Bipolar × ADHD	0.895	0.501	1.79	0.0790
Total putamen tissue				
Bipolar	1903.385	321.008	5.929	0.0001
ADHD	−1596.8	318.021	−5.021	0.0001
Bipolar × ADHD	−1765.5	640.235	−2.758	0.0080
Total globus pallidus tissue				
Bipolar	476.097	157.620	3.021	0.004
ADHD	−208.229	156.153	−1.333	0.187
Bipolar × ADHD	−416.367	314.365	−1.324	0.190

the caudate, and psychotropic medication exposure did not affect these findings. Effect size calculations revealed a large effect size for the difference in caudate volume between ADHD subjects and healthy controls, and medium effect sizes for BD−ADHD subjects compared with controls, and BD only subjects compared with BD+ADHD subjects.

We could grossly restate these findings by stating that patients with ADHD have decreased caudate volumes, patients with BD have increased caudate volumes, and those with both ADHD and BD have normal caudate volumes. However, it would likely be an oversimplification to conclude that those with both disorders have an intermediate volume because the effects on the caudate of the disorders "canceled" each other. Previous studies regarding the role of the caudate in both executive functioning and mood regulation suggest more informed interpretations.

A number of animal studies of lesions of the caudate nucleus have been performed in many species, and a comprehensive review of these data concluded that while early studies on motor function suggested that the caudate serves to inhibit behaviors initiated in the cortex, its function is actually much more complex and nuanced (White, 2009). Based on studies in monkeys, cats, and rats, the authors conclude that caudate lesions affect memory function, and specifically reinforced stimulus-response learning. Observational studies of basal ganglia lesions in humans indicate that the caudate is involved in cognitive functions, including planning and sequencing, memory, and sustained attention (Benke et al., 2003; Grahn et al., 2008; White, 2009). Functional MRI studies in healthy control populations have found caudate activation during executive function tasks, particularly response inhibition (Aron et al., 2003; Luna and Sweeney, 2004; Ali et al., 2010), but also goal achievement (Tricomi and Fiez, 2008), learning (Nomura and Reber, 2008), reward prediction (Haruno and Kawato, 2006), reward-related learning (Haruno et al., 2004), and planning and set-shifting (Monchi et al., 2006).

With these functions, it is not surprising that the caudate has been consistently associated with ADHD, which is characterized by inattention and/or impulsivity/hyperactivity (Sonuga-Barke, 2005). Reductions in caudate volume have been widely reported in participants with ADHD (Krain and Castellanos, 2006; Schneider et al., 2006). However, Castellanos et al. have suggested that caudate volumes in ADHD may "normalize" over the trajectory of development from childhood to adulthood (Castellanos et al., 2002). A recent DTI study also suggests normalization of the caudate during late adolescence (Silk et al., 2009). This is consistent with findings of increased caudate volume in older adolescents (ages 15 to 19) with ADHD (Mataro et al., 1997; Garrett et al., 2008). Thus, our findings of smaller caudate volumes in children with ADHD are consistent with previous reports in early/mid adolescence, as our subjects had a mean age of 13.4 ± 3 years.

The finding of increased caudate volumes in subjects with BD suggests that abnormalities in the caudate are also associated with BD separately, which may have several explanations. First, regarding brain anatomy, bigger is not always better (Foster et al., 1999; Roth et al., 2010), so increased caudate volume may indicate an abnormality, albeit with a different etiology. This different abnormality may result in a different set of impairments than those seen in ADHD, as cognitive impairments have indeed been reported in BD. A longitudinal study over 30 months found that adults with BD had cognitive deficits during all mood states, including depressive, manic, and euthymic (Malhi et al., 2007). However, while not all patients with BD have been found to have these cognitive deficits (Jamrozinski, 2010), most of these studies did not separate out the effects of comorbid ADHD. The only study that examined the effects of comorbid ADHD on neuropsychological functioning in pediatric BD found significant cognitive impairment in the ADHD group *and* the BD+ADHD group, but not in the BD only group (Rucklidge, 2006).

While increased caudate volume may not mediate cognitive impairment in BD, it may be directly related to mood regulation difficulties. The caudate is a component in limbic circuits that also include the amygdala and prefrontal cortex (Ring and Serra-Mestres, 2002). Mood dysfunction often develops in neurodegenerative disorders that affect the caudate, including Parkinson's (Gotham et al., 1986) and Huntington's Disease (Peyser and Folstein, 1990). Additionally, recent studies have implicated the caudate in other mood disorders such as major depressive disorder (Lee et al., 2008), and subjects with major depression have been reported to show decreased activation in the caudate in response to rewards (Pizzagalli et al., 2009). In healthy control subjects, a recent study reported robust caudate activation to negative but not positive emotion-related picture content, and suggested that the caudate plays a role in emotional withdrawal (Carretie et al., 2009). Thus, abnormal control of emotion-related processes could be related to abnormal caudate volume in BD subjects. Still, it is unclear why caudate volume would be increased in the context of mood regulation, but decreased in the context of behavioral response inhibition.

Lopez-Larson and colleagues performed a similar analysis across the same four groups in youth with BD only, ADHD only, and both BD and ADHD and healthy controls (Lopez-Larson et al., 2009). Consistent with our results, they found decreased caudate volumes in subjects with ADHD only as compared to each of the other three groups. However, unlike our study, they did not find volumetric differences in striatal structures in subjects with BD alone as compared to either healthy controls or those with BD+ADHD. This difference in findings may be due to a difference in our study populations. The subjects in their study were significantly younger (mean age of 10.8 vs. 14.4 years in our study) with a higher proportion of prepubertal patients. It is very possible these structural differences do not appear until later in development, when disease duration, medication exposure, and development all play a role in affecting brain structures. Our study also included a predominance of BD subjects who had a family history of the disorder, which may be a more genetically and neurobiologically homogeneous group than the group in the Lopez-Larson study. Finally, our statistical approach differed from that of Lopez-Larson et al.

We also found that ADHD and BD diagnoses had significant effects on putamen and globus pallidus volumes. Putamen volumes followed the same patterns as for caudate, whereas GP volume was affected only by BD diagnosis (increased). Putamen volume has previously been found increased in some (DelBello et al., 2004) but not all studies of youth with BD (Ahn et al., 2007) or in offspring of bipolar patients (Hajek et al., 2009). However, putamen activation has been found to be elevated in fMRI studies of bipolar youth (Blumberg et al., 2003; Chang et al., 2004; Rich et al., 2006). Globus pallidus volume has not been reported to be abnormal in youth with BD (DelBello et al., 2004; Ahn et al., 2007). In youth with ADHD, both putamen and globus pallidus volumes have been reported to be decreased compared with controls (Ellison-Wright et al., 2008; Qiu et al., 2009). Thus, our findings in general are in accord directionally with these previous findings: increased striatal volume in BD, decreased striatal volume in ADHD.

It should be noted that psychotropic medications have been associated with changes in regional cortical volumes, including striatum. For example, two studies reported increases in basal ganglial volumes with chronic exposure to typical antipsychotics (Corson et al., 1999; Lang et al., 2001), while one reported decreased basal ganglia volumes with chronic exposure to atypical antipsychotics (Corson et al., 1999). A recent systematic review of 33 articles found that typical antipsychotic exposure, even for a short duration (<12 weeks), was associated with increased basal ganglial volumes (Navari and Dazzan, 2009). Exposure to atypicals did not have a consistent association with basal ganglial volumes, with one study finding increased volumes (Massana et al., 2005), while several other studies finding unchanged or decreased volumes (Heitmiller et al., 2004; Navari and Dazzan, 2009).

Our groups differed significantly by medication exposure. Unfortunately, we could not compare medication-exposed to medication-naive subjects within each group statistically, as the groups were unbalanced in this regard, and the number of subjects would have

been too small in each group to perform valid statistical comparisons. Specifically, the ratios of medication-exposed to medication-naive subjects for each group were as follows: BD—ADHD: 3/9, ADHD 8/3, and BD+ADHD 16/1. We attempted to address this question using a regression analysis that showed exposure to each type of medication did not have a significant effect on striatal volumes. However, this post-hoc medication analysis was underpowered and thus we cannot conclude that medication had no effect. Additionally, as discussed above, psychotropic medications have been shown to affect brain volumes, so our findings should be interpreted in this context and taken as preliminary.

It should be noted that only 25% (3/12) of the BD—ADHD group had been exposed to psychotropic medications. It is possible that this group is slightly healthier than the other groups in the study; however, clinical characteristics, including similar duration of illness and CGAS scores, suggest that this group did not differ significantly from the other groups in severity of illness.

There were several limitations to our study, including the relatively small sample sizes, particularly within the BD—ADHD group. While the study was adequately powered to find significant differences between groups, other less robust differences may have been missed. Effect sizes for comparisons between the four groups on caudate volumes were provided for future hypothesis testing. Also, while we addressed the headcoil difference in the methods section, this difference could have confounded our analysis in unknown ways. Lastly, as is the case with all regional structural studies of the brain, a structural difference does not necessarily correspond to a functional difference. Recent fMRI studies have suggested functional abnormalities in the caudate nuclei of bipolar patients (Wessa et al., 2007). However, more studies are needed to elucidate the function of the caudate in BD with and without comorbid ADHD.

Nonetheless, our findings suggest that different caudate abnormalities may be associated with ADHD and BD. Future studies should take this difference into account, particularly when studying youth with BD and comorbid ADHD, as differential functional deficits may lead to relatively normal volumetric findings.

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