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Caudate Nucleus Volume and Cognitive Performance: Are they related in Childhood Psychopathology?¹

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Abstract

Background—Impaired neuropsychological test performance, especially on tests of executive function and attention, is often seen in children diagnosed with autism spectrum disorders (ASD). Structures involved in fronto-striatal circuitry, such as the caudate nucleus, may support these cognitive abilities. However, few studies have examined caudate volumes specifically in children with ASD, or correlated caudate volumes to cognitive ability.

Methods—Neuropsychological test scores and caudate volumes of children with ASD were compared to those of children with bipolar disorder (BD) and of typically developing (TD) children. The relationship between test performance and caudate volumes was analyzed.

Results—The ASD group displayed larger right and left caudate volumes, and modest executive deficits, compared to TD controls. While caudate volume inversely predicted performance on the Wisconsin Card Sorting Test in all participants, it differentially predicted performance on measures of attention across the ASD, BD and TD groups.

Conclusions—Larger caudate volumes were related to impaired problem solving. On a test of attention, larger left caudate volumes predicted increased impulsivity and more omission errors in the ASD group as compared to the TD group, however smaller volume predicted poorer discriminant responding as compared to the BD group.

Keywords

executive function; attention; bipolar disorder; autism spectrum disorders; caudate volume; neuroimaging

Introduction

The diagnosis of a childhood psychopathology, while dependent on a specific profile of behavioral abnormalities, is commonly linked to impaired cognitive function. Children with autism spectrum disorders (ASD), such as autism or Asperger's syndrome, frequently show

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deficits on neuropsychological tests that measure executive function (Hughes et al 1994; Minshew et al 2002; Ozonoff et al 1991b; Prior and Hoffmann 1990; Szatmari et al 1990). In addition, children with ASD frequently evidence attentional difficulties consistent with attention deficit hyperactivity disorder (ADHD) (Ghaziuddin et al 1998; Schatz et al 2002; Yoshida and Uchiyama 2004). These findings suggest that impaired mental flexibility, problem solving and attention are common in children with ASD.

The caudate nucleus, as part of the striatum, is an integral part of the fronto-striatal circuit thought to subserve executive cognitive functions (Chow and Cummings 1999). Caudate nucleus lesions lead to impairments in planning and problem solving (Mendez et al 1989; Schmidtke et al 2002), mental flexibility (Lombardi et al 1999), learning (Poldrack et al 1999), attention (Mendez et al 1989), short-term and long-term memory (Fuh and Wang 1995), retrieval (Mendez et al 1989), and verbal fluency (Fuh and Wang 1995). Thus, the caudate may represent one underlying structural correlate of the cognitive deficits observed in ASD.

Assessment of the relationship between cognitive performance and individual brain structures in ASD populations, however, is complicated by reports of larger total brain volumes (Courchesne 2002; Sparks et al 2002) and altered brain growth trajectory (Courchesne et al 2003) in this population. Total brain volume differences between ASD and control samples are often age dependent and most evident during childhood (Aylward et al 2002; Courchesne et al 2003; Courchesne et al 2001). In fact, children with ASD demonstrate an altered brain growth trajectory with accelerated growth seen during the first year of life (Courchesne et al 2003). These findings imply that the growth of the brain, as a whole, may be dependent on psychiatric status as well as age, and point to complexities in interpreting differences in individual brain structure volumes across diagnostic groups when a measure of total brain volume is controlled.

In addition, individual brain structures appear to have developmental profiles that are distinct from general brain development (Caviness et al 1996; Herbert et al 2003; Piven et al 1996). In normal development, total brain volume is reported to peak around age 5 (Durstun et al 2001), while caudate volume peaks in late childhood (Caviness et al 1996; Thompson et al 2000), then decreases with age (Hardan et al 2003; McAlonan et al 2002; Thompson et al 2000). Analysis of caudate volume in adolescents and adults indicated no differences between individuals without psychiatric diagnoses and those diagnosed with autism when a measure of total brain was controlled (Gaffney et al 1989; Hardan et al 2003; Sears et al 1999). However, significantly larger caudate volumes were found in autistic samples when total brain volume was not included (Herbert et al 2003; Sears et al 1994). The latter study used data from children ages 7–11 years, and found that different brain structures may be disproportional in size, being excessively large or small, in young autistic boys. Thus, age and psychiatric status can differentially impact individual brain structures, beyond their effects on the size of the whole brain.

In addition to developmental variability, brain structure volume may be directly related to the symptom profile of a disorder. Among adolescents and young adults with autism (12–29 years old), an inverse correlation was found between caudate volume and ritualistic-repetitive behaviors (with and without total brain volume as a covariate), such as the presence of compulsions/rituals and difficulty changing routine (Sears et al 1994). In a somewhat older adult sample (17–55 years old) with an ASD diagnosis, a direct relationship between repetitive behaviors and right caudate volumes was noted (Hollander et al 2005). However, no relationship was observed when the autistic sample spanned childhood and adulthood (8 – 45 years old) (Hardan et al 2003). Thus, in addition to the effect of age on the size and structure of the brain, symptomatic differences may be related to caudate volume.

Due to the complex developmental trajectory of the caudate nucleus, as well as other age-related factors, we sought to compare male children within a narrow age range (7–13 years old) diagnosed with ASD to children diagnosed with bipolar disorder (BD) or those showing typical development (TD). Like with ASD, children diagnosed with BD often display executive and attention deficits (Castillo et al 2000; Shear et al 2002; West et al 1995; Wozniak et al 1995). However, the overall clinical and diagnostic profile of BD differs substantially from ASD. Moreover, no differences in caudate volumes are typically reported in adults with a BD diagnosis (for recent review see Beyer and Krishnan 2002), although research does suggest that caudate volume in BD may co-vary with factors such as age, gender and duration of illness (Beyer et al 2004; Brambilla et al 2001). Thus the BD group was included as a potentially informative clinical control sample. A narrow age range for participants was chosen to minimize age-related influences on brain development, age of onset, duration of illness, and medication history. We used a battery of neuropsychological measures of executive function and attention, and structural magnetic resonance image (MRI) scans of the caudate nucleus, to examine the relationship between cognitive abilities and caudate nucleus volumes in children with or without childhood psychopathologies. The ASD group was hypothesized to have larger caudate volumes than those of the BD and TD groups, based on the current theory of abnormal neurogenesis with impaired axonal pruning and cell death in ASD (Akshoomoff et al 2002). Executive functioning and attention deficits were also expected in the ASD group compared to the TD group. Based on the limited literature on executive function deficits in children with BD (Castillo et al 2000; Shear et al 2002) and on the high co-morbidity of BD with ADHD (West et al 1995; Wozniak et al 1995), we tentatively expected that similar neuropsychological deficits would be found in the BD and ASD groups, although this was not central to the current study. Finally, caudate nucleus volume was hypothesized to predict neuropsychological performance in the areas of executive function and attention.

Methods

Participants

The present sample comprised sixty-three male participants between 7 and 13 years of age. The clinical samples were recruited from outpatient, inpatient, and day programs of a university medical center, and included children with an ASD ($n = 38$) or BD ($n = 12$) diagnosis. The ASD group consisted of both high functioning autistic (HFA) children (i.e., IQs > 70 , $n = 11$) and those with Asperger's syndrome (ASP, $n = 27$). Prior research has supported the combination of children diagnosed with HFA and ASP for analysis (Leekam et al 2000; Prior et al 1998; Szatmari et al 1989). The control sample was recruited from local pediatric offices, by word of mouth, and by recruitment flyers in the community, and had no lifetime psychiatric diagnoses ($n = 13$). Table 1 presents means and standard deviations of age, socioeconomic status (Hollingshead 1975), and intelligence scales.

Children were excluded from participation if they had a history of central nervous system disease, IQ below 70, a current medical illness, maternal alcohol abuse/dependence (to prevent possible confound due to fetal alcohol effects), or if the MRI was contraindicated, refused (e.g., claustrophobia) or unusable (e.g., severe movement artifact or braces). Children who were taking psychotropic medications did not change their regimen or initiate new treatments during the study. Table 1 shows the prevalence of current psychotropic medication use. No participants in the TD group were medicated.

Clinical Diagnoses

All participants and parents were administered the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present State and Epidemiological Version (K-SADS-IVR, Ambrosini and Dixon 1996). The treating clinician's diagnosis was confirmed with the

K-SADS-IVR (BD) and a semi-structured clinical interview based on a checklist of the Diagnostic and Statistical Manual-IV criteria (American Psychiatric Association 1994) for Autism and Asperger's Syndrome (ASD). After the start of the study, the Autism Diagnostic Interview-Revised (ADI-R, Lord et al 1994) was added to the assessment battery and administered to one or both parents of participants by a certified interviewer. ADI-R data were available to confirm diagnosis in 8 children with HFA and 20 with ASP. The diagnosis of autism was confirmed in all but one child from the HFA group, who missed criteria on the communication subscale of the ADI-R (score of 5 versus 8). From the ASP group, 13 met criteria for autism and 7 narrowly missed criteria on either the social interaction or communication scales. Others have noted that the ADI-R tends to be less sensitive in detecting ASP (Gilchrist et al 2001) than autism. These data suggest that the ADI-R criteria for diagnosis of an ASD may be more stringent, but do not differ substantively from diagnosis based on the semi-structured interview employed in this study. Analyses of the full sample were replicated using only data from the ASD participants who also met ADI-R diagnostic criteria.

Measures

Intelligence—The Wechsler Intelligence Scale for Children- Third Edition (Wechsler 1991) was administered to assess fullscale, verbal, and performance IQ.

Executive Function Measures—The Wisconsin Card Sorting Test (WCST, Heaton et al 1993), a test of set shifting and hypothesis testing, was administered in the standard format. The number of perseveration errors (WCST-P) and completed categories (WCST-C) were used in the analyses. Mental flexibility was assessed with the Phonetic and Semantic Word Fluency Tests of the Controlled Oral Word Association Test (Benton 1973). Measures were the number of words produced within 1 minute that began with the letters F, A, and S (phonetic fluency) or that fell in the categories of animals, food, and jobs (semantic fluency). The number correct from the CW page of the Stroop Color Word Test (Golden 1978) measured the participant's ability to suppress automatic responding to the lexical feature of a word and instead attend to the printed color, which is incongruent with the meaning of the word. The Children's version of Trail Making Test Part B (TMT-B, Reitan and Wolfson 1985) measures cognitive flexibility and complex tracking skills, and was administered to participants from ages 9 to 13 years. Participants younger than 9 were administered the Progressive Figures Test (PFT, Reitan and Wolfson 1990), which is similar to the TMT-B in that it requires the participant to alternate responding sequentially while tracing a line (Reitan and Wolfson 2004). Total time to complete the task was used in the analyses of TMT-B and PFT performance. Two age-dependent versions of the Category Test (Reitan and Wolfson 1993), which measure concept development and hypothesis testing, were administered for participants ≤ 8 years and > 8 years of age, with total number of errors as the dependent measure. All performance scores were converted to age corrected T-scores for analyses. Higher T scores indicate better performance.

Attention Measures—The Continuous Performance Test (CPT, Conners 1995), a test of sustained attention, was administered in its standard format. Four measures were used for analyses: CPT-Index, (the overall performance index score, higher T-scores indicate poorer performance), CPT-Omit (number of omission errors, higher T-scores indicate fewer errors); CPT-Risk (risk taking-beta, lower T-scores indicate a more risky response style (frequent responding) and higher T-scores indicate a more cautious response style (infrequent responding); and CPT-d' (a measure of discriminant responding, higher T-scores reflect better ability to discriminate between target and nontarget stimuli).

MRI Acquisition

Magnetic Resonance Images (MRI) scans were acquired with a head coil on a high field strength (1.5 Tesla) General Electric Clinical Scanner. A coronal series of 124 contiguous

1.5mm thick, 0-gap, T-1 weighted SPGR (spoiled grass) images (VBw, EDR, FAST, Irp, TR 25ms TE 5ms, TI/Flip 40, Bandwidth 16.0, FOV 24, 256*192 matrix), were obtained.³ One of the investigators or a parent stayed with each child during imaging to provide reassurance and promote cooperation and image quality. No sedation was administered prior to the MRI scan. Each coronal series MRI scan took 10 min 18sec.

Volumetric Analysis

Post-processing conversion and volumetric analysis were performed using AnalyzePC software (Robb 2001). Image files were converted from a dicom format to an AVW format with 0.5 mm³ voxels (using cubic spline interpolation) and aligned on the anterior and posterior commissure axis. Unbiased volume estimates of the intracranial volumes (ICV) were obtained using the Cavalieri method of point counting (Roberts et al 2000). A 14 × 14 pixel grid with a 10-slice increment and random starting positions was used to produce more than 200 counted points and a coefficient of error of less than 2%. ICV included all gray and white matter and cerebral spinal fluid in the lateral and third ventricles and excluded the cerebellum and brainstem. An inter-rater reliability correlation of .98 (between two raters), and intra-rater reliability correlation (intra-class correlation coefficient) of greater than .97 for each rater was established on 10 image files.

The caudate head was manually segmented bilaterally on all coronal slices on which it was visible. The posterior section of the caudate tail was segmented until the posterior commissure was visible. The lateral boundary of the caudate was the internal capsule. The mesial boundary was the lateral ventricle. See Figure 1a and 1b for segmentation of the caudate nucleus head and tail. The nucleus accumbens was excluded. This segmentation protocol is similar to the method used by Brambilla (2001). All tracing was performed by the same rater (GTV) and the reliability of segmentation of the caudate was established by segmenting 15 image files twice, yielding a high intra-rater reliability (interclass correlation = .98) for both the left caudate volume (LCV) and right caudate volume (RCV). Raters of the ICV and caudate nucleus volumes were blinded to group classification.

Procedure

Following a telephone screening interview, interested parents and their children were scheduled for an in-person interview. The family was given a thorough explanation of the research project, written informed consent was obtained from parents, and verbal assent was obtained from the children. During the parent interview, the neuropsychological battery was administered to the child. The neuropsychological battery was fixed and administered in the same order to all participants. The neuropsychological assessment took approximately 6 hours (with breaks). If the child showed signs of fatigue, the assessment was completed over two sessions scheduled on separate days within the same week. After cognitive and neuropsychological testing was completed, the child was scheduled for the brain MRI, usually within 2 weeks. Children received a video showing the sequence of procedures that would occur from arrival at the imaging center through completion of MRI acquisition with a similarly aged child to familiarize them with the imaging process prior to entering the scanner. Parents of children in the clinical groups received a written diagnostic and neuropsychological report in return for participation. Control group participants were reimbursed \$100.00 in lieu of the report. This study was approved by the Institutional Review Boards of Rutgers University and UMDNJ Robert Wood Johnson Medical School.

³Slight changes in imaging acquisition occurred due to software upgrades of the scanner over the 4 years that the data were collected. The majority of participants received the image acquisition listed. Analyses revealed no significant effect of acquisition on total brain volume.

Analyses

General Linear Models and regression analyses were performed with SAS 9.1 (SAS Institute Inc., Cary, NC). Diagnostic groups were dummy coded using the ASD group as the reference group. To control for Type I error related to multiple comparisons, a Bonferroni correction was used for the 11 neuropsychological tests ($\alpha = .0045$) in the main effects models. In view of this conservative approach and limitations on power related to sample size, effect size differences between diagnostic groups were also considered to minimize Type II error. Models were examined with and without a number of covariates that may influence the observation of differences between diagnostic groups. Age was positively correlated with many of the neuropsychological test scores, and ICV was positively correlated with caudate volume. Thus, these variables were included as covariates in the appropriate models to enhance statistical power. Zero-order and ICV partialled correlation coefficients between medication use (Table 1) and caudate volumes were very low (average absolute $r = .06$), indicating that inclusion of medications as covariates was unnecessary. Due to the potential for stimulant medication to influence performance on measures of attention, however, analyses were conducted with and without the use of stimulant medication as a covariate. Finally, although full-scale IQ was significantly different between diagnostic groups, it was unrelated to caudate volumes. When added to the caudate models, it did not change the pattern of results, and thus to conserve power, it was not included in subsequent analyses.

Results and Discussion

There were no diagnostic group differences in age or SES. Compared to the TD group, however, the ASD and BD groups had a significantly lower mean full-scale IQ and verbal IQ, and the ASD group had a significantly lower performance IQ (Table 1). In addition, ICV did not differ significantly between the diagnostic groups ($p > .05$), suggesting that heterogeneity of intracranial brain volumes within diagnostic groups exceeded between group differences.

Caudate Volume

The present study focused on the fronto-striatal circuits in boys between the ages of 7 and 13 who received a diagnosis of ASD, compared to those diagnosed with BD or no psychiatric history. Without ICV as a covariate, diagnostic group differences in LCV and RCV failed to meet statistical significance. With ICV as a covariate, significant group differences in LCV and RCV were observed. Similarities in the p levels and the proportions of unique variance explained by diagnostic group in the models with and without ICV as a covariate supports the idea that inclusion of ICV in the model led to a statistically significant difference in caudate volume by boosting power of the analysis, rather than suggesting that caudate volume differences were disproportional to overall cerebral volume (Table 2). The same pattern of differences in caudate volumes was observed when stimulant use was added as a covariate, and when only those ASD participants whose diagnosis was confirmed as autism by the ADI-R were included in the model.

A comparison of least squares means of caudate volumes, from models including stimulant use and ICV, showed significant differences between the ASD and TD groups in the LCV and RCV (Figure 2, Table 2). These findings are similar to those reported by Herbert et al. (2003), who also observed larger caudate volumes in a similarly aged (7–11) autistic sample, as compared to controls. However, in their study, differences were only significant when total brain volume was not included. This discrepancy may be related to their autistic sample's trend for larger total brain volumes, or their inclusion of cerebellum and brain stem in their measure of total brain volume.

Executive Function and Attention Measures

The ASD group performed, in general, more poorly on tests of executive function than the BD and TD groups. However, these differences did not achieve statistical significance when the more stringent $p < .0045$ level was used to correct for multiple comparisons. Table 3 shows the means and standard deviations of each executive function measure.⁴ A consideration of effect sizes revealed that 6.8% of the variance in performance on the semantic fluency and 13.2% of the variance in the Trail Making Test were explained by the diagnosis of ASD versus TD. Parallel results were observed when only those ASD participants with an ADI-R confirmation of diagnosis were analyzed. The present results are thus generally consistent with previous findings of reduced verbal fluency and mental flexibility in individuals with ASD (e.g., Minshew et al 2002; Ozonoff et al 1991a; Prior and Hoffmann 1990; Szatmari et al 1990). The diagnostic groups did not differ on any of the four measures of attention, with or without stimulant medication included as a covariate.

Caudate Volumes and Cognitive Performance

Regression analyses were used to examine the relationship of the LCV and RCV to executive function and attention measures, using age, stimulant use and diagnostic group as covariates. Larger LCV and RCV significantly predicted an increase in perseverative errors (lower T-score) and decrease in completed categories (lower T-score) on the WCST (all $p < .0003$, Table 4). Thus, larger caudate volumes, regardless of the presence of a diagnosis, were associated with decreased mental flexibility and poorer problem solving on this test. The relationship between caudate volume and perseveration is generally consistent with the finding that larger right caudate volumes were associated with an increase in ritualistic/repetitive behaviors in an older-aged ASD sample (Hollander et al 2005).

In adults without primary psychiatric conditions, a positive relationship between executive function and caudate activity (Lombardi et al 1999; Volkow et al 1998) and volume (Fuh and Wang 1995; Mendez et al 1989) has been found. The present sample, however, included children prior to the age at which caudate volumes peak (Caviness et al 1996; Hardan et al 2003; McAlonan et al 2002; Thompson et al 2000). The finding that ASD was associated with larger caudate volumes in this sample suggests that while larger caudate volumes may correlate to enhanced executive performance in adults, increased volume in children may be more indicative of abnormal growth or impaired neuronal pruning such that decreases in executive function are correlated with increases in caudate volume beyond those expected based on the basis of age. To further test this idea, interaction terms were created to examine the relationship of caudate volume to neuropsychological test performance in the ASD group relative to its relationship in the BD and TD groups.

Group Differences in the Relation of Caudate Volumes and Cognitive Performance

Interaction terms between the dummy coded diagnostic groups and caudate volumes were created and added as a second step to main effect regression models. To avoid nonessential collinearity in the interaction terms, caudate volumes were mean-centered (Cohen et al 2003). A statistically significant increment in the model R^2 as the result of adding the interaction terms indicated that the relationship between neuropsychological test performance and caudate volume differed in the ASD group compared to the BD or TD groups. As in the main effect models, age and stimulant use were included as covariates.

The addition of the interaction terms identified several significant differences between the ASD and the other diagnostic groups in the relation of caudate volume to measures of attention

⁴These means were virtually identical to the least square means corrected for age and stimulant medication use.

(Table 5). A larger LCV and RCV in the ASD group predicted a more frequent and risky response style, whereas the opposite relationship was true in the BD and TD groups (Figure 3). In model, only the ASD versus TD group comparison reached statistical significance. In addition, a larger LCV and RCV in the ASD and BD groups predicted more omission errors on the CPT, while the inverse was true of the TD control sample (Figure 4). Finally, while larger LCV and RCV were related to similar discrimination ability (CPT-d') between target and non-target stimuli in all three groups, smaller volumes were significantly related to decreased CPT-d' in the ASD group compared to the BD group.

While these interactions need to be replicated in independent samples prior to drawing any firm conclusions, the findings suggest subtle, yet potentially important differences in brain-behavior relationships in the ASD, BD and TD groups. Larger caudate volumes may have differential impact on children dependent on the presence and type of psychopathology. Children with ASD, for example, may experience attention deficits primarily as difficulties in shifting (Courchesne et al 1994; Hughes et al 1994) or disengaging attention (Landry and Bryson 2004), as opposed to sustaining attention. Thus, the relationship of different components of attentional performance, such as an impulsive response pattern, omission errors, and perceptual sensitivity, to caudate structure may represent a different underlying neurodevelopmental course of ASD versus BD.

General Discussion

While many neuropsychological and volumetric studies have been published on adults with ASD, few studies have focused specifically on children with this disorder. As a result, much remains to be learned about the relationship of caudate volume and/or neuropsychological test performance in ASD populations to the developmental delays and behavioral deficits reported during childhood. In addition, the relationship between brain structures and cognitive abilities in children from the general population, or with specific psychiatric diagnoses, is largely uncharted. The present study compared caudate volumes, neuropsychological test performance, and this structure-function relationship in young boys diagnosed with ASD to those with BD or without psychiatric disorder. The results indicated that ASD in children is related to larger caudate nuclei, as compared to the TD control sample and that caudate volume is inversely related to some aspects of executive function in children regardless of diagnosis. Small to medium effect size decrements on two measures of executive functioning were also noted in the ASD group, although these failed to reach strict levels of statistical significance when Bonferroni corrections were made to alpha levels. This was no doubt due to the limited sample sizes of the comparison groups and heterogeneity within the diagnostic samples.

While no relationship between caudate volumes and measures of attention were found in the sample as a whole, caudate volumes were differentially correlated with performance on measures of attention in children diagnosed with ASD as compared to the BD and TD groups. The significance of this is unclear, but raises the possibility that subtle differences exist in the attentional features of ASD and BD, and that the mechanisms by which the caudate regulates attention may be diverse. Speculating more globally, if assumes that the range of caudate volumes observed in the TD group fall within a “normal” category, then the structure-function relationship in the TD groups should reflect the “normal” relationship (i.e., larger caudate volumes—as long as they are not abnormally large—predict a more cautious performance pattern and fewer errors of omission). As caudate volumes increase further, they may fall within an “overgrowth” range, potentially suggesting abnormal neuronal pruning, and performance deficits on the CPT increase. Both the BD and ASD groups displayed an opposite relationship between caudate volumes and omission errors versus the TD group, and both groups have larger average volumes (although they not significantly different between the BD and TD groups). This may indicate that increased omission errors may be particularly sensitive to

moderate levels of caudate “overgrowth.” As caudate volumes become increasingly “abnormally” large, the overall pattern of responding on the CPT test may become more impulsive. On this measure of the CPT, the ASD group showed a structure-function relationship that was opposite to that seen in the BD and TD groups. Finally, the ASD and BD groups showed an opposite structure-function relationship on the CPT-d' measure with poorer discrimination related to smaller caudate in the ASD group, but larger caudate in the BD group. These suggestions are highly speculative and require replication in larger, independent samples.

Several caveats that potentially limit the generalizability of this study's findings should be considered. The sample size was reduced and potential bias was added because the child's assent for the MRI was required and MRI scans with movement artifacts were excluded. Moreover, the MRI analyses used overall tissue volumes, and did not distinguish between gray and white matter. There is evidence that the relationship of ASD to gray versus white matter within certain brain regions may be distinct (Herbert et al 2003; McAlonan et al 2002). Children in this study were not matched for IQ, thus creating a potential confound (although the IQ of all participants was above 70, and within a similar range), however the relationship between caudate volume, diagnosis and neuropsychological test performance was not altered when full-scale IQ was included as a covariate. Due to the populations studied, many children were taking one or more medications at the time of testing. Psychotropic medications were not discontinued for a wash out period before the assessment due to ethical treatment concerns, but this potentially increased variance in or otherwise biased neuropsychological performance and/or volumetric analysis, even though these effects were not evident statistically.⁵ The inclusion of stimulant use in the analyses, however, did not substantively alter our results. Finally, high rates of ADHD were reported in the clinical samples, as is frequently the case, and thus an independent effect of ADHD symptoms on the basal ganglia cannot be ruled out (Hendren et al 2000). Overall, the statistical control of covariates is not ideal, but rather a compromise in trying to further understanding of the multiple sources of neurocognitive heterogeneity in real-world clinical samples.

The present study also examined the brain-behavior relationship in a combined sample of children diagnosed with either HFA or ASP. Currently, there is debate within the field whether these conditions lie on a continuum, and thus represent a single disorder, or whether they are more accurately classified as different disorders. There is mounting evidence on both sides of the argument. Due to restricted sample sizes and the diagnostic tools used, this paper cannot contribute substantively to that dialogue. Nonetheless, the same pattern of diagnostic group differences related to caudate volumes and neuropsychological test performance was observed when analyses were confined to the subset of ASD participants whose diagnosis was confirmed by the ADI-R.

Multilevel examinations of neuropsychological and neuroanatomical data from children with ASD can help to elucidate the etiology, course, and potentially the treatment of these complex childhood psychopathologies. The clinical implications of these findings are in line with others (McAlonan et al 2002) that the fronto-striatal pathway may play a unique role in ASD, even in young children, and may correspond to differences in cognitive processing that could ultimately be a treatment target or useful outcome measure. To more completely understand the role of the fronto-striatal pathway in childhood psychopathologies, volumetric studies of

⁵Caudate volumes of children diagnosed with ASD who were medicated at the time of study were compared to unmedicated participants within this group. Individual drug types as well as a composite variable (for those using multiple drug types) were analyzed separately. No differences in LCV or RCV were observed between medicated and unmedicated ASD children. When children being treated with any one or combination of medications were excluded from the analyses, the LCV and RCV remained significantly different between the ASD and TD groups. These data support the likelihood that the differences in caudate volumes noted between the diagnostic groups are primarily attributable to the disorder, and not medication use or history.

the prefrontal and anterior cingulate gyri, and their relationship to cognitive and behavioral disruptions is warranted.

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Figure 1. Segmentation and boundaries of the caudate nucleus head (**A**) and tail (**B**) using the lateral ventricles, internal capsule and lamina affixa as markers. CN, caudate nucleus; LV, lateral ventricle; IC, internal capsule; LA, lamina affixa.

Figure 2.

The least squares mean $\pm$ standard error of caudate nucleus volume (cm³) in the autism spectrum disorder (ASD), bipolar disorder (BD) and typically developing control (TD) samples. * denotes $p < .05$, as compared to the TD group.

Figure 3.

The interaction between diagnostic group and caudate volume in predicting CPT response style (CPT-risk). A larger left (upper panel) and right (lower panel) caudate volume (in cm^3) in the autism spectrum disorder (ASD) group predicted a more frequent and risky response style (lower T-score). The opposite relationship was observed in the bipolar disorder (BD) and typically developing control (TD) groups compared to the ASD group. Only the ASD versus TD group comparison reached statistical significance.

Figure 4.

The interaction between diagnostic group and caudate volume in predicting CPT omission errors. A larger left (upper panel) and right (lower panel) caudate volume (in cm^3) in the autism spectrum disorder (ASD) and bipolar disorder (BD) groups predicted more omission errors (lower CPT omission T-score). The opposite relationship was seen were in the typically developing control (TD) group. Only the ASD versus TD group comparison reached statistical significance.

Table 1Means $\pm$ standard deviations of background variables, and percentages of current medication use.

	ASD	BD	TD
n	38	12	13
Age	10.16 $\pm$ 1.92	10.08 $\pm$ 1.31	10.77 $\pm$ 1.48
SES	53.72 $\pm$ 10.39	50.92 $\pm$ 11.83	53.58 $\pm$ 9.15
ICV (cm³)	1294.99 $\pm$ 103.08	1267.37 $\pm$ 77.16	1274.10 $\pm$ 114.48
FSIQ	99.37 $\pm$ 16.08 ^d (73-127) ^a	102.17 $\pm$ 12.16 ^e (86-126)	115.15 $\pm$ 9.41 (93-133)
VIQ	104.55 $\pm$ 18.04 ^d	101.17 $\pm$ 12.48 ^d	118.77 $\pm$ 12.34
PIQ	94.42 $\pm$ 16.85 ^d	103.41 $\pm$ 14.43	108.54 $\pm$ 9.54
ADHD^a	47%	75%	-
Medications			
Total Medicated ^c	20 (54%)	8 (73%)	
Stimulant	11 (30%)	2 (18%)	-
Neuroleptic	5 (14%)	6 (55%)	-
SSRI	10 (27%)	3 (27%)	-
Mood Stabilizer	3 (8%)	6 (55%)	-

SES = socioeconomic status, ICV = intracranial volume, FSIQ = full scale IQ, VIQ = verbal IQ, PIQ = performance IQ, ADHD = Attention Deficit Hyperactivity Disorder, SSRI = selective serotonin reuptake inhibitor.

^a range of FSIQ scores

^b ADHD diagnosis was determined based on parental reports from the K-SADS-IVR, and included all subtypes (inattentive, hyperactive and combination).

^c The number and percent of individuals in each group being medicated with any drug during the study

^d No significant differences were noted between the ASD and BD groups. Compared to the TD group, however, several significant differences were observed: $p < .05$ &

^e $p < .01$.

Table 2

Statistics from models of diagnostic group predicting left and right caudate volumes, with and without ICV and stimulant medication as covariates, and with the ASD group confined to cases with ADI-R confirmed diagnoses.

Covariates	Left Caudate Volume			Right Caudate Volume		
	Overall Model	ASD v. BD	ASD v. TD	Overall Model	ASD v. BD	ASD v. TD
None	F(2, 60) = 2.05 <i>p</i> = .1375	<i>t</i> = -1.13, <i>p</i> = .2649 UV = 2.0%	<i>t</i> = -1.91, <i>p</i> = .0609 UV = 5.7%	F(2, 60) = 3.08 <i>p</i> = .0531	<i>t</i> = -1.69, <i>p</i> = .0953 UV = 4.3%	<i>t</i> = -2.18, <i>p</i> = .0333 UV = 7.2%
ICV	F(3, 59) = 20.07 <i>p</i> < .0001	<i>t</i> = -0.88, <i>p</i> = .3832 UV = 0.6%	<i>t</i> = -2.12, <i>p</i> = .0383 UV = 3.8%	F(3, 59) = 22.13 <i>p</i> < .0001	<i>t</i> = -1.66, <i>p</i> = .1021 UV = 2.2%	<i>t</i> = -2.50, <i>p</i> = .0151 UV = 5.0%
Stimulant use + ICV	F(4, 55) = 13.76 <i>p</i> < .0001	<i>t</i> = -0.72, <i>p</i> = .4739 UV = 0.5%	<i>t</i> = -2.33, <i>p</i> = .0232 UV = 5.0%	F(4, 55) = 15.54 <i>p</i> < .0001	<i>t</i> = -1.71, <i>p</i> = .0925 UV = 2.5%	<i>t</i> = -2.85, <i>p</i> = .0061 UV = 6.9%
ADI-R confirmation of diagnosis ^a	F(4, 37) = 8.12 <i>p</i> < .0001	<i>t</i> = -0.64, <i>p</i> = .5240 UV = 0.6%	<i>t</i> = -1.99, <i>p</i> = .0541 UV = 5.7%	F(4, 37) = 9.34 <i>p</i> < .0001	<i>t</i> = -1.49, <i>p</i> = .1445 UV = 3.0%	<i>t</i> = -2.48, <i>p</i> = .0177 UV = 8.3%

ASD: autism spectrum disorder; BD: bipolar disorder; TD: typically developing controls. ICV: Intracranial Volume, ADI-R: Autism Diagnostic Interview – Revised; UV: Percent of unique variance explained.
^aStimulant use and ICV were included as covariates in this model.

Table 3
Neuropsychological test performance in the ASD, BD, and TD groups on measures of executive function.

Category Test	Mean (Standard Deviation)		
	ASD	BD	TD
Category Test	53.47 (11.53)	55.08 (8.99)	59.76 (8.38)
Semantic Fluency ^a	47.44 (11.07)	51.38 (13.07)	53.30 (12.75)
Phonetic Fluency	46.43 (10.72)	44.27 (10.96)	47.10 (5.84)
TMT-B/PFT ^{b,c}	42.72 (13.13)	48.11 (11.13)	54.37 (6.89)
Stroop	43.51 (8.72)	45.00 (8.81)	51.63 (11.09)
WCST-P	52.81 (11.40)	54.11 (4.65)	57.54 (7.25)
WCST-C	4.89 (1.65)	5.89 (0.33)	5.85 (0.55)

ASD: autism spectrum disorder; BD: bipolar disorder; TD: typically developing controls; TMT-B: Children's version of Trail Making Test, Part B; PFT: Progressive Figures Test, Stroop: Stroop Color Word Test; WCST-P: Wisconsin Card Sorting Test, Perseveration errors; WCST-C: Wisconsin Card Sorting Test, Completed Categories. Higher T scores indicate better performance.

^aThe overall model: $F(4, 55) = 2.84, p < .04$; ASD versus TD: $t=2.12, p < .04$ with a unique variance = 6.8%.

^bThe overall model: $F(4, 54) = 2.64, p < .05$; ASD versus TD: $t=2.92, p < .006$ with a unique variance = 13.2%.

^cChildren < 9 yrs old were given the PFT in lieu of the TMT-B;

Table 4

Unstandardized (B) and standardized (β) regression weights and unique variances (UV) from the regressions predicting executive function and attention measures from caudate volumes, using age, stimulant medication and diagnostic group as covariates.

	Left Caudate Volume				Right Caudate Volume			
	B	β	UV	Overall Model Statistics	B	β	UV	Overall Model Statistics
Category Test	-.001	-.064	0.0	$F(5, 50) = 1.73, ns$	-.000	-.002	0.0	$F(5, 50) = 1.69, ns$
Semantic Fluency	-.004	-.208	3.7	$F(5, 54) = 2.84, p < .05$	-.002	-.105	0.9	$F(5, 54) = 2.37, ns$
Phonetic Fluency	-.001	-.078	0.5	$F(5, 54) = 0.64, ns$	-.001	-.043	0.2	$F(5, 54) = 0.59, ns$
TMT-B	.001	.038	0.1	$F(5, 53) = 2.09, ns$	.002	.088	0.6	$F(5, 53) = 2.17, ns$
Stroop	-.000	-.016	0.0	$F(5, 49) = 1.10, ns$	-.000	-.058	0.3	$F(5, 49) = 1.14, ns$
WCST-P	-.005	-.272	6.2 ^a	$F(5, 49) = 6.22, p < .0002$	-.005	-.289	6.7 ^a	$F(5, 49) = 6.36, p < .0001$
WCST-C	-.001	-.306	7.9 ^a	$F(5, 49) = 5.84, p < .0003$	-.001	-.323	8.4 ^a	$F(5, 49) = 5.98, p < .0002$
CPT-Index	-.001	-.104	0.9	$F(5, 52) = 0.73, ns$	-.002	-.127	1.3	$F(5, 52) = 0.78, ns$
CPT-d'	.001	.073	0.5	$F(5, 52) = 2.13, ns$	.000	.045	0.2	$F(5, 52) = 2.09, ns$
CPT-Risk	-.002	-.060	0.3	$F(5, 52) = 0.93, ns$	-.001	-.032	0.0	$F(5, 52) = 0.90, ns$
CPT-Omit	-.004	-.234	4.6	$F(5, 52) = 1.29, ns$	-.004	-.231	4.3	$F(4, 56) = 1.26, ns$

TMT-B: Children's version of Trail Making Test, Part B; PFT: Progressive Figures Test, Stroop: Stroop Color Word Page; WCST-P: Wisconsin Card Sorting Test, number of Perseveration errors; WCST-C: Wisconsin Card Sorting Test, Completed Categories; CPT: Continuous Performance Test, including overall performance index score (Index), the number of omission errors (Omit), discriminant responding (d'), and risk taking (Risk).

^a $p < .05$.

Change in R^2 with the inclusion of diagnostic group $\times$ caudate volume interactions in regressions predicting executive function and attention measures

Table 5

	Left Caudate Volume				Right Caudate Volume			
	R^2	ΔR^2	%UV (ASD - BD)	%UV (ASD - TD)	R^2	ΔR^2	%UV (ASD - BD)	%UV (ASD - TD)
Category Test	.15	.03	1.0	2.2	.14	.03	1.4	2.2
Semantic Fluency	.21	.05	4.3	0.0	.18	.04	3.9	0.0
Phonetic Fluency	.06	.03	1.1	2.6	.05	.02	0.4	1.7
TMT-B	.16	.03	1.6	0.1	.17	.01	0.2	0.6
Stroop	.10	.02	1.7	0.2	.10	.03	2.2	0.0
WCST-P	.39	.00	0.2	0.1	.39	.00	0.0	0.1
WCST-C	.37	.00	0.0	0.4	.38	.00	0.0	0.2
CPT-Index	.07	.07	6.4	0.9	.07	.05	5.3	0.2
CPT-d ^a	.17	.09	6.0 ^d	4.6	.17	.08	6.2 ^d	3.3
CPT-Risk ^b	.08	.14	5.5	11.2 ^e	.08	.11	5.0	7.4 ^d
CPT-Omit ^c	.11	.16	0.1	15.8 ^f	.11	.11	0.6	11.4 ^e

R^2 : associated with the main effects model (Table 4); ΔR^2 : the increment in R^2 with the addition of the interaction term, UV: % unique variance explained by diagnostic group differences, TMT-B: Children's version of Trail Making Test, Part B; PFT: Progressive Figures Test, Stroop: Stroop Color Word Page; WCST-P: Wisconsin Card Sorting Test, Perseveration errors; WCST-C: Wisconsin Card Sorting Test, Completed Categories; CPT: Continuous Performance Test, overall performance index score (Index), discriminant responding (d'), number of omission errors (Omit), and risk taking (Risk).

^aLCV $\times$ CPT-d' (F (7, 50) = 3.05, $p < .01$), RCV $\times$ CPT-d' (F (7, 50) = 2.69, $p < .05$).

^bLCV $\times$ CPT-risk (F (7, 50) = 4.64, $p < .01$), RCV $\times$ CPT-risk (F (7, 50) = 3.23, $p < .01$).

^cLCV $\times$ CPT-omit (F (7, 50) = 5.45, $p < .01$), RCV $\times$ CPT-omit (F (7, 50) = 3.66, $p < .01$).

^d $p < .05$.

^e $p < .01$.

^f $p < .005$.