

# Caudate Nucleus Is Enlarged in High-Functioning Medication-Naive Subjects with Autism

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**Background:** Autism is defined by three symptom clusters, including repetitive and stereotyped behavior. Previous studies have implicated basal ganglia in these behaviors. Earlier studies investigating basal ganglia in autism have included subjects on neuroleptics known to affect basal ganglia volumes. Therefore, we investigated these structures in medication-naive subjects with autism.

**Methods:** Volumetric magnetic resonance measures of caudate, putamen, and nucleus accumbens were compared in two independent samples of medication-naive, high-functioning subjects with autism or Asperger syndrome: 1) 21 affected children and adolescents and 21 matched control subjects; and 2) 21 affected adolescents and young adults and 21 matched control subjects.

**Results:** Caudate nucleus was enlarged in both samples. This result remained significant after correction for total brain volume.

**Conclusions:** These results implicate caudate nucleus in autism, as an enlargement of this structure was disproportional to an increase in total brain volume in two independent samples of medication-naive subjects with autism.

**Key Words:** Autism, basal ganglia, high-functioning, magnetic resonance imaging, medication-naive, repetitive and stereotyped behavior

Autism research has often focused more on social and communicative deficits and less on the third defining cluster of symptoms, repetitive and stereotyped behaviors (RB). Broadly, repetitive behaviors are defined as recurring, nonfunctional activities or interests that occur regularly and interfere with daily functioning, including lower-order repetitive motor behavior, as well as intense circumscribed patterns of interests and higher-order rituals and compulsions (Gabriels *et al.* 2005; Lord *et al.* 1994). Repetitive behaviors are also associated with other neuropsychiatric disorders, such as obsessive-compulsive disorder (OCD) and Tourette syndrome (TS), although it has been argued that the type and nature of these behaviors may differ in these disorders (for a review, see Carcani-Rathwell *et al.* 2006; Zandt *et al.* 2006).

Animal studies have implicated the basal ganglia in RB (Arnt 1985; Bradshaw and Sheppard 2000; Fibiger *et al.* 1973; Hollander *et al.* 2005; Purcell *et al.* 1998; Ridley 1994; Ring and Serra-Mestres 2002; Rosenberg *et al.* 1997a, 1997b; Saka *et al.* 2004; Segal *et al.* 1980). Studies in humans exploring brain mechanisms behind RB have indicated involvement of the basal ganglia in OCD (Giedd *et al.* 1996; Modell *et al.* 1989; Scarone *et al.* 1992) and TS (Albin and Mink 2006; Peterson *et al.* 1993, 2003). Furthermore, frontostriatal circuitry was recently implicated in the development of autistic symptoms in individuals with 22q11 syndrome (Campbell *et al.* 2006).

To date, five papers have used magnetic resonance imaging (MRI) to investigate the neurobiology of RB in autism and other spectrum disorders. Two of these reported enlarged basal ganglia volumes proportional to an increase in total brain volume

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(TBV) (Herbert *et al.* 2003; study 1 in Sears *et al.* 1999), whereas study 2 in Sears (1999) and a third paper reported a disproportional increase in caudate nucleus volume (Hollander *et al.* 2005; replicated in an overlapping sample by Haznedar *et al.* 2006). McAlonan *et al.* (2002) found no differences in caudate volumes between groups but did report decreased gray matter density in striatal areas. Two studies implicated caudate nucleus in RB more directly (Hollander *et al.* 2005; Sears *et al.* 1999), although results were not consistent. Sears *et al.* (1999) found differential correlations between RB and caudate volume, depending on type of behavior, whereas Hollander *et al.* (2005) reported a positive correlation between caudate volumes and overall RB scores.

These findings implicate the basal ganglia, and particularly the caudate nucleus, in the pathophysiology of autism. However, it has been argued that use of neuroleptics, shown to be associated with volume changes of basal ganglia structures (Chakos *et al.* 1994; Keshavan *et al.* 1994; Lang *et al.* 2004; McCarley *et al.* 1999; Scheepers *et al.* 2001a, 2001b; Shihabuddin *et al.* 1998), may have confounded these studies. Therefore, we investigated basal ganglia volumes in never-medicated subjects with autism to further explore previously demonstrated enlargements of the basal ganglia and their involvement in RB. We hypothesized an enlargement of the basal ganglia, and particularly caudate nucleus, would be related to RB.

## Methods and Materials

### Participants

**Sample 1.** Twenty-one medication-naive, high-functioning children and adolescents meeting DSM-IV criteria for autism or Asperger syndrome (American Psychiatric Association 1994) and 21 typically developing control subjects were included. Subjects with autism and control subjects were matched for gender, age, intelligence quotient (IQ), height, weight, handedness, and socioeconomic status (SES) (Table 1). The present sample was described in two earlier studies (Palmen *et al.* 2005, 2006).

**Sample 2.** Twenty-one medication-naive, high-functioning adolescents and young adults meeting DSM-IV criteria for autism or Asperger syndrome (American Psychiatric Association 1994) and 21 healthy comparison subjects were included. Subjects with autism and healthy control subjects were matched for gender, age, IQ, height, weight, handedness, and SES (Table 1). The present sample was described in two earlier studies (Palmen *et al.* 2004, 2006).

**Table 1.** Demographic Data and Characteristics of the Samples

Variable	Subjects with Autism ( <i>n</i> = 21)	Normal Control Subjects ( <i>n</i> = 21)
<b>Sample 1</b>		
Gender (Male/Female)	21/0	21/0
Age, Mean ± SD (Range), years	11.12 ± 2.18 (6.9–14.6)	10.37 ± 1.84 (7.3–14.4)
Total IQ, Mean ± SD (Range)	106.52 ± 13.68 (80–138)	102.52 ± 14.58 (80–151)
Verbal IQ, Mean ± SD (Range)	108.33 ± 17.54 (70–131)	100.86 ± 15.81 (76–144)
Performance IQ, Mean ± SD (Range)	103.43 ± 16.81 (73–141)	103.62 ± 14.54 (73–138)
Height, Mean ± SD, cm <sup>a</sup>	149.19 ± 16.17	145.83 ± 15.88
Weight, Mean ± SD, kg <sup>a</sup>	38.81 ± 11.79	38.61 ± 10.11
Handedness (Right/Left), <i>n</i>	20/1	19/2
Parental Education, Mean ± SD, years <sup>b</sup>	14.10 ± 2.45	12.84 ± 2.63
ADI-R: Social Deficits	16.38 ± 4.61	
ADI-R: Abnormalities in Communication	13.00 ± 4.59	
ADI-R: Ritualistic-Repetitive Behavior	3.76 ± 2.625	
Higher-Order	2.29 ± 1.65	
Lower-Order	1.48 ± 1.29	
<b>Sample 2</b>		
Gender (Male/Female)	19/2	20/1
Age, Mean ± SD (Range), years	20.08 ± 3.10 (15.5–24.7)	20.28 ± 2.22 (17.3–24.8)
Total IQ, Mean ± SD (Range)	114.90 ± 19.18 (81–126)	112.62 ± 10.20 (96–130)
Verbal IQ, Mean ± SD (Range)	112.90 ± 19.64 (77–132)	107.62 ± 9.89 (88–122)
Performance IQ, Mean ± SD (Range)	114.00 ± 16.22 (84–129)	116.95 ± 11.53 (94–134)
Height, Mean ± SD, cm	180.62 ± 10.40	179.95 ± 7.37
Weight, Mean ± SD, kg	70.14 ± 12.94	74.24 ± 9.10
Handedness (Right/Left), <i>n</i>	19/2	17/4
Parental Education, Mean ± SD, years	14.76 ± 2.00	13.52 ± 2.71
ADI-R: Social Deficits	19.62 ± 5.88	
ADI-R: Abnormalities in Communication	15.90 ± 3.74	
ADI-R: Ritualistic-Repetitive Behavior <sup>c</sup>	3.95 ± 3.15	
Higher-Order <sup>d</sup>	2.32 ± 1.82	
Lower-Order <sup>d</sup>	1.32 ± 1.42	

IQ, intelligence quotient; ADI-R, Autism Diagnostic Interview-Revised.

<sup>a</sup>Information was unavailable for three control subjects.

<sup>b</sup>Information was unavailable for two control subjects.

<sup>c</sup>Information was unavailable for one subject.

<sup>d</sup>Information was unavailable for two subjects.

All procedures were approved by the Institutional Review Board at the University Medical Center and informed consent was obtained from all subjects, as well as parental consent for subjects aged under 18 years.

### MRI Acquisition and Processing

**Acquisition.** Magnetic resonance images were acquired on a Gyroscan (Philips Medical Systems, Best, The Netherlands) operating at 1.5 T. For volumetric measurements, T1-weighted three-dimensional (3-D) fast field echo scans and T2-weighted dual echo turbo spin echo scans were acquired. Acquisition details have been previously described (Palmen *et al.* 2004, 2005, 2006).

**Processing.** Magnetic resonance processing was performed at the Department of Child and Adolescent Psychiatry. All images were coded and half were randomly flipped over the y axis to ensure rater blindness to subject identity, diagnosis, and laterality. Volumetric measures of intracranial volume (ICV) and total brain volume were obtained semiautomatically (Palmen *et al.* 2004, 2005). Basal ganglia structures were traced manually by a single experienced rater (M.L.). Caudate nucleus, putamen, and nucleus accumbens were outlined in contiguous coronal slices in an anterior-posterior direction (Figure 1 and Figure 2). Detailed tracing guidelines are available in Supplement 1. Ten scans were duplicated and randomly intermixed with the data set to allow

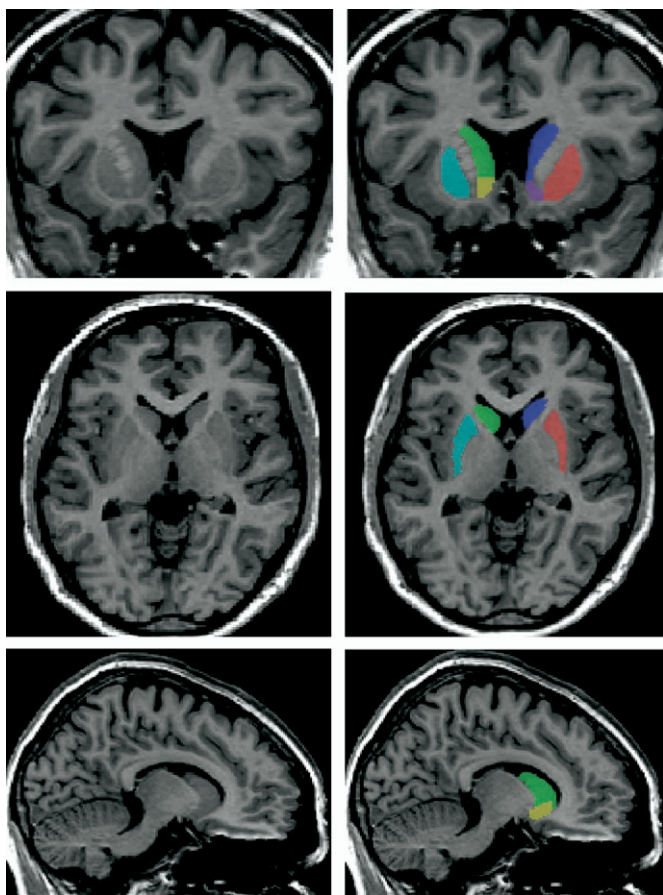
for an estimation of intrarater reliability using intraclass correlation coefficients (ICCs). Intraclass correlation coefficient scores were .99 for caudate nucleus, .96 for putamen, and .97 for nucleus accumbens.

### Statistical Analysis

SPSS 12.0 statistical package (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. Data from both samples were first analyzed independently. All clinical data and brain volume measurements were normally distributed. Independent sample *t* tests were performed to investigate differences in basal ganglia volumes between groups. To correct for multiple comparisons, a Bonferroni corrected critical *p* value of .017 was employed. For significant results, follow-up analyses were performed to control for age, IQ, TBV, and ICV. To investigate relationships between basal ganglia volumes and repetitive behavior scores on the Autism Diagnostic Interview-Revised (ADI-R), Spearman correlations were calculated for the group as a whole (for 42 subjects with autism).

### Results

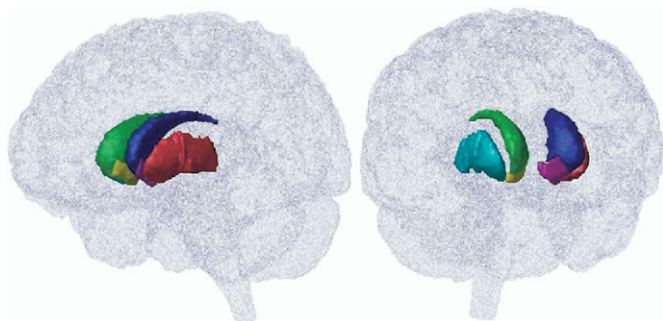
Table 2 lists mean volumes for both independent samples. Total caudate nucleus volume was significantly enlarged for subjects with autism compared with control subjects in both



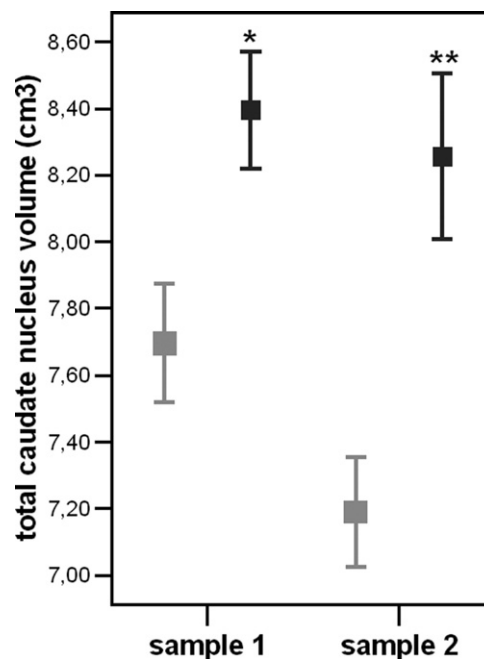
**Figure 1.** Segmentation of the basal ganglia in (from top to bottom) coronal, axial, and sagittal view. Caudate nucleus (L/R) is displayed in green and blue, putamen in turquoise and red, and nucleus accumbens in yellow and purple. L, left; R, right.

samples ( $|t| = 2.79$ ;  $p = .008$ ). (Figure 3). In addition, bilateral putamen was significantly enlarged for subjects with autism compared with control subjects in sample 1 ( $|t| = 2.27$ ;  $p = .03$ ). The increase in caudate volume remained significant when covarying for TBV and ICV ( $|t| > 2.67$ ;  $p < .01$ ) in sample 2 and at least at trend level in sample 1 ( $|t| = 1.78$ ;  $p = .08$ ). All results remained significant when covarying for age and IQ.

No significant correlations with ADI-R scores for higher-order or lower-order RB (Carcani-Rathwell *et al.* 2006; Szatmari *et al.* 2006) and any basal ganglia structures were found.



**Figure 2.** 3-D visualizations of the basal ganglia in the brain. Caudate nucleus is displayed in green and blue, putamen in turquoise and red, and nucleus accumbens in yellow and purple. 3-D, three-dimensional.



**Figure 3.** Total caudate nucleus volumes by group in samples 1 and 2 (mean  $\pm$  1 SE). Black = autistic group; light gray = control group; \*significant at  $p < .05$ ; \*\*significant at  $p < .001$ .

## Discussion

This study implicates basal ganglia, and particularly caudate nucleus, in the etiology of autism, as a significant increase in caudate volume was found in two independent samples of medication-naïve subjects with autism.

We report an increase in caudate nucleus volume disproportional to total brain volume in both children and adolescents with autism. As this result is found in both age groups, it suggests that caudate nucleus continues to be involved in autism over development. These findings contrast with other childhood neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), where an initial reduction in caudate volume has been shown to normalize in adolescence (Castellanos *et al.* 2002), possibly suggesting a developmental decline in its involvement in the disorder.

Although our findings are in line with previous studies showing increases in basal ganglia volumes in autism (Herbert *et al.* 2003; Hollander *et al.* 2005; Sears *et al.* 1999), we were not able to replicate previously reported correlations between RB and caudate volume (Hollander *et al.* 2005; Sears *et al.* 1999). However, ADI-R scores on stereotyped and repetitive behavior scales were low in both samples and variability was therefore limited. An instrument more sensitive to detecting complex RB may have been more suitable to assess the relationship between RB and brain measures.

A number of limitations to our findings should be acknowledged. First, we included only high-functioning individuals in our two samples, limiting inferences regarding low-functioning subjects with autism. A second limitation is the use of the ADI-R for measuring RB. A more sensitive instrument may have provided more scope to detect relationships between basal ganglia volumes and behavioral variables, including differentiating between subclasses of RB. Finally, the use of a cross-sectional design limits the developmental conclusions that can be drawn from these findings. A longitudinal approach would be more

**Table 2.** Basal Ganglia Volumes for Both Samples

Brain Structure	Subjects with Autism, Mean $\pm$ SD, cm <sup>3</sup>	Normal Control Subjects, Mean $\pm$ SD, cm <sup>3</sup>	[t] ( <i>df</i> = 40)	<i>p</i> Value
Sample 1				
Intracranium	1542.10 $\pm$ 103.02	1475.17 $\pm$ 69.44	2.47	.02
Total Brain	1422.79 $\pm$ 92.62	1357.85 $\pm$ 70.02	2.56	.01
Total Caudate Nucleus	8.40 $\pm$ .81	7.70 $\pm$ .81	2.79	.008
Left	4.13 $\pm$ .40	3.76 $\pm$ .40	3.04	.004
Right	4.27 $\pm$ .47	3.94 $\pm$ .49	2.24	.03
Total Putamen <sup>a</sup>	10.64 $\pm$ .98	10.03 $\pm$ .72	2.27	.03
Left <sup>a</sup>	5.39 $\pm$ .48	5.10 $\pm$ .35	2.24	.03
Right <sup>a</sup>	5.25 $\pm$ .54	4.93 $\pm$ .42	2.11	.04
Total Nucleus Accumbens	2.32 $\pm$ .32	2.24 $\pm$ .39	.72	.47
Left	1.19 $\pm$ .21	1.12 $\pm$ .21	1.08	.29
Right	1.13 $\pm$ .16	1.12 $\pm$ .20	.17	.87
Sample 2				
Intracranium	1564.11 $\pm$ 117.08	1494.74 $\pm$ 87.77	2.17	.04
Total Brain	1393.92 $\pm$ 105.87	1333.33 $\pm$ 86.61	2.03	.05
Total Caudate Nucleus	8.26 $\pm$ 1.14	7.20 $\pm$ .75	3.59	.001
Left	4.12 $\pm$ .67	3.55 $\pm$ .36	3.45	.001
Right	4.13 $\pm$ .51	3.64 $\pm$ .44	3.39	.002
Total Putamen	9.74 $\pm$ 1.23	9.52 $\pm$ 1.06	.61	.55
Left	4.91 $\pm$ .73	4.84 $\pm$ .56	.31	.76
Right	4.83 $\pm$ .57	4.68 $\pm$ .52	.96	.36
Total Nucleus Accumbens	2.07 $\pm$ .46	2.13 $\pm$ .31	.42	.67
Left	1.04 $\pm$ .24	1.07 $\pm$ .15	.45	.65
Right	1.04 $\pm$ .24	1.06 $\pm$ .18	.35	.73

<sup>a</sup>Putamen volume could not be estimated for one control subject (*df* = 39).

sensitive to detecting developmental changes in basal ganglia structures and their involvement in autism.

In conclusion, we report an increase in caudate nucleus volume, disproportional to an increase in total brain volume, in two independent samples of medication-naïve subjects with autism. These results are consistent with evidence from other neuropsychiatric disorders implicating frontostriatal circuitry in repetitive and stereotyped behaviors, one of the defining symptom clusters of autism.

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