

Changes in the Developmental Trajectories of Striatum in Autism

Marieke Langen, Hugo G. Schnack, Hilde Nederveen, Dienne Bos, Bertine E. Lahuis, Maretha V. de Jonge, Herman van Engeland, and Sarah Durston

Background: Repetitive and stereotyped behavior has been associated with striatum in various neuropsychiatric disorders. However, striatal involvement has not yet been shown conclusively in autism. Issues include the use of neuroleptic medication and differences in mean age between samples, where conflicting results may reflect differences in developmental stage between samples. The objective was to examine brain development in a homogeneous sample of subjects with high-functioning autism.

Methods: Magnetic resonance measures of brain structure of 188 individuals (99 subjects with high-functioning autism and 89 typically developing, matched control subjects) aged between 6 years and 25 years were compared. Measurements included the volume of brain structures, including striatum, as well as voxel-based assessment of gray matter density.

Results: Developmental trajectories of the caudate nucleus, putamen, and nucleus accumbens differed between subjects with autism and control subjects. Results were not accounted for by overall changes in brain volume or neuroleptic medication. The development of the caudate nucleus differed from typical most, as its volume increased with age in autism, while it decreased for control subjects. Voxel-based analysis showed that changes in striatum localized to the head of the caudate nucleus. Overall, caudate nucleus volume was associated with repetitive behavior in autism.

Conclusions: We report changes in striatal development in autism, while caudate volume is associated with repetitive behaviors. This emphasizes the importance of striatum in the etiology of autism, in particular in the development of repetitive behavior that characterizes the disorder.

Key Words: Autism, development, repetitive behavior, striatum, structural MRI

Autism is a severe neurodevelopmental disorder that is characterized by 1) impaired social interactions; 2) impaired communication and language development; and 3) stereotypies, repetitive or rigid behavior, and restricted interests. A formal diagnosis of autism requires the presence of problems in each of these three domains (1). While a considerable body of work has investigated brain changes associated with the first two clusters of symptoms, relatively few studies have investigated brain changes associated with repetitive behavior. This is surprising, given the prominence of repetitive behavior in the disorder: in many cases, these symptoms onset early in development and often form a significant impairment for affected individuals.

Repetitive behavior has been associated with striatum, across a range of neuropsychiatric disorders, including obsessive-compulsive disorder (OCD), schizophrenia, and Tourette syndrome. Striatum has also been implicated in autism, although results from magnetic resonance imaging (MRI) are not yet conclusive: whereas some studies have reported larger volumes in autism, particularly of the caudate nucleus (2–6), others have not (7). Furthermore, it is unclear whether the reported increase in volume is disproportional to an overall increase in brain volume

(2,8). Additionally, the subjects in these studies often used neuroleptic medication, which is associated with increases in striatal volumes (9–15). As such, findings of increased striatal volumes in autism cannot yet be considered definitive. However, some studies have implicated striatum in the development of repetitive and stereotyped behavior more directly: striatal volumes have been shown to correlate with repetitive and restricted behavior in OCD (16) and in autism (2,3,5), lending confidence to the involvement of this area in these behaviors.

In an earlier study of two smaller, independent samples of subjects with high-functioning autism, we found that the caudate nucleus was enlarged compared with typically developing individuals (17). In this study, there was a large difference in age between the two samples (mean age for the first sample was 10 years and 20 years for the second sample) and the effect was greater for the older sample (14.7% increase in volume from control subjects compared with 9.1% in the younger sample). This led us to hypothesize that autism may be associated with changes in striatal development, where differences become more pronounced with age.

In typical development, the striatum decreases in volume over time, both in childhood (18) and in adulthood (19–22). A comprehensive longitudinal study in children and adolescents showed that the developmental trajectory of the caudate nucleus follows an inverted U-shape with peak volume at age 7.5 years in girls and 10.0 years in boys (23), although a more recent study demonstrated peaks at about 10.5 years for girls and 14.0 years for boys (24). In autism, the developmental trajectory of the striatum has not been examined. As such, differences in results between studies of striatal volume in autism could, in part, reflect differences in mean age between samples (3,8,25). Other factors may include relatively small sample sizes and differences in sample composition, as some studies have included only high-functioning individuals meeting full criteria for autism, while others have chosen to also include lower-

From the Departments of Child and Adolescent Psychiatry (ML, HN, DB, BEL, MVDJ, HVE, SD) and Psychiatry (HGS), Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands.

Address correspondence to Marieke Langen, M.Sc., Neuroimaging (NICHE) Laboratory, Department of Child and Adolescent Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, HP A01.468-438, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands; E-mail: m.langen@umcutrecht.nl.

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functioning individuals and individuals with other disorders in the autism spectrum.

Therefore, we set out to investigate structural brain development in a large and homogeneous sample of high-functioning individuals with autism and control subjects ($n = 188$). We hypothesized that the caudate nucleus would be enlarged in autism and that its developmental trajectory would differ from that of control subjects.

Methods and Materials

Participants

Ninety-nine, high-functioning individuals meeting DSM-IV criteria for autism were recruited through the Department of Child and Adolescent Psychiatry at the University Medical Center in Utrecht, the National Autism Society in the Netherlands, an outpatient clinic for individuals with pervasive developmental disorders, and through advertising. Diagnosis was clinically established by a child and adolescent psychiatrist from our department and was confirmed by trained and qualified clinicians using the Autism Diagnostic Interview-Revised (ADI-R) (26). All subjects with autism had IQ greater than 75. Twelve subjects with autism were using neuroleptic medication and four additional subjects had previously received neuroleptic medication. Eighty-nine typically developing control subjects were recruited through schools and educational centers in the area. For control subjects under 18 years of age, a parent participated in a semi-structured interview session with a trained rater to confirm absence of any psychiatric diagnosis (Diagnostic Interview Schedule for Children-Parent Version [DISC-P]) (27). For older subjects, the absence of psychopathological abnormalities was established using questionnaires and a short version of the Comprehensive Assessment of Symptoms and History (CASH) (28). For both groups, subjects with a psychiatric diagnosis (current or prior), major physical or neurological illness, history of head trauma, alcohol or other drug dependence, or full IQ below 75 were excluded. Control subjects with a family history of psychiatric illness were also excluded. Groups were matched for gender, age, IQ, height, weight, hand preference, pubertal development (assessed using Tanner scales), and for parental educational level (Table 1).

Written informed consent was obtained for all subjects. For

subjects under 18 years of age, a parent signed for consent, while assent was obtained from the subject. All subjects participated in an MRI scanning session and a neuropsychological assessment (Wechsler Adult Intelligence Scale/Wechsler Adult Intelligence Scale-Third Edition [WAIS/WAIS-III] [29,30]; Wechsler Intelligence Scale for Children-Revised/Wechsler Intelligence Scale for Children-Third Edition [WISC-R/WISC-III] [31,32]). Children less than 13 years of age were acclimated to the scanning procedure in a dummy scan session prior to the actual magnetic resonance (MR) scan (33). For all subjects, MRI scans were evaluated by independent clinical neuroradiologists. No gross abnormalities were reported for any of the subjects.

The procedure was approved by the Institutional Review Board of the University Medical Center Utrecht, the Netherlands.

MRI Acquisition and Processing

Acquisition. Magnetic resonance imaging scans were acquired on a 1.5-T scanner (Philips, Best, The Netherlands). Data were acquired over 8 years. For the definition of all brain measures, a T1-weighted three-dimensional (3-D) fast field echo scan with 130 to 150 1.5-mm contiguous coronal slices (earlier scans; 63 autism spectrum disorder [ASD], 55 control subjects) or 160 to 180 1.2-mm contiguous coronal slices (later scans; 36 ASD, 34 control subjects) of the whole head (echo time [TE] 4.6 msec; repetition time [TR] 30 msec; flip angle 30°; field of view [FOV] 256 mm; in-plane voxel size 1 mm × 1 mm) were acquired. For 118 subjects (63 ASD, 55 control subjects), T2-weighted dual echo turbo spin echo scans with 65 to 75 3.0-mm contiguous coronal slices or 120 1.6-mm contiguous coronal slices of the whole head (echo time 1 [TE1] 14 msec; echo time 2 [TE2] 80 msec; TR 6350 msec; flip angle 90°; FOV 256 mm; in-plane voxel size 1 mm × 1 mm) were acquired for the definition of the intracranial volume. For the remaining 70 subjects (36 ASD, 34 control subjects), a single-shot echo-planar imaging (EPI) scan, (sensitivity-encoding [SENSE] factor 2.5; flip angle 90°; 60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; FOV 240 mm; TE 78 msec) and a magnetization transfer (MT) scan (60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; FOV 240 mm; flip angle 8°; TE 4.5 msec; TR 37.5 msec) were combined to define the intracranial volume.

Processing. All images were coded to ensure rater blindness to subject identity and diagnosis. The T1-weighted images were

Table 1. Demographic Data and Characteristics of the Sample

Variable	Subjects with Autism ($n = 99$)	Normal Control Subjects ($n = 89$)
Gender (Male/Female)	91/8	82/7
Age, Mean ± SD (Range), Years	12.89 ± 4.45 (7.0424.67)	12.36 ± 4.79 (6.2824.75)
Total IQ, Mean ± SD (Range)	107.59 ± 13.56 (81138)	109.99 ± 12.81 (80138)
Height, Mean ± SD, cm ^a	156 ± 19	152 ± 20
Weight, Mean ± SD, kg ^b	47 ± 17	45 ± 19
Handedness (Right/Left/Ambidexterity), n	85/9/5	76/12/1
Parental Education, Mean ± SD, Years ^c	14.38 ± 2.2	13.74 ± 2.3
Tanner A ^d	1.22 ± 1.24	1.13 ± 0.87
ADI-R: Social Deficits ^e	19.12 ± 5.36	
ADI-R: Abnormalities in Communication ^e	15.32 ± 4.15	
ADI-R: Ritualistic-Repetitive Behavior ^e	5.18 ± 2.75	

ADI-R, Autism Diagnostic Interview-Revised; ASD, autism spectrum disorder; IQ, intelligence quotient.

^aInformation was unavailable for five control subjects and two ASD subjects.

^bInformation was unavailable for five control subjects and four ASD subjects.

^cInformation was unavailable for two control subjects and two ASD subjects.

^dInformation was unavailable for 26 control subjects and 25 ASD subjects.

^eInformation was unavailable for two ASD subjects.

automatically placed in Talairach orientation (34) without scaling, by registering them to a model brain in Talairach orientation. The translation and rotation parameters of this registration were then applied to the images (35). After linear registration to the T1-weighted image, the intracranial segment served as a mask for all further segmentation steps. The T1-weighted images were corrected for field inhomogeneities using the N3 algorithm (36). An automatic image processing pipeline was used to define the volume of total brain, gray matter (GM) and white matter (WM) of the cerebrum, cerebellum, and lateral ventricles. The software included updated versions of previously described histogram analysis, mathematical morphology operations, and anatomical knowledge based rules to connect all voxels of interest (37,38). The segments for intracranial volume, total brain, lateral ventricles, and cerebellum were all visually checked and edited to ensure an accurate segmentation.

Manual Tracing. Striatal structures were traced manually by two experienced raters (D.B. and M.L.). To ensure rater blindness to laterality, half of the images were randomly flipped over the y axis. Caudate nucleus, putamen, and nucleus accumbens were outlined in contiguous coronal slices in an anterior-posterior direction. The sagittal and axial planes were used for reference. Segmentation procedures are described in detail in Langen *et al.* (17). Intrarater reliabilities (estimated using intraclass correlation coefficients [ICCs]) were above .95 for all structures. Interrater reliabilities were .93 for caudate nucleus, .86 for nucleus accumbens, and .71 for putamen.

Voxel-Based Morphometry. Voxel-based morphometry (VBM) was used to investigate where differences in striatum between diagnostic groups were localized. Voxel-based morphometry included the following steps. First, a model brain was created, similar to the method used in Hulshoff Pol *et al.* (39). Second, the binary gray matter and white matter masks were blurred using a 3-D Gaussian kernel (full-width at half maximum [FWHM] of 8 mm). The voxel values of these blurred segments (between 0 and 1) reflect the local presence or concentration of GM and WM, respectively, and are referred to as density maps. Third, to compare brain tissue at the same anatomical location in all subjects, the GM segments were transformed into a standardized coordinate system (i.e., the model brain). These transformations were calculated in two steps. The T1-weighted images were linearly transformed to the model brain. In this linear step, a joint entropy mutual information metric was optimized (35). Nonlinear (elastic) transformations were calculated to register the linearly transformed images to the model brain up to a scale of 4 mm (FWHM), thus removing global shape differences between the brains but retaining local differences. For this step, the Automatic Nonlinear Image Matching and Anatomical Labelling (ANIMAL) algorithm was used (40). Fourth, the density maps were transformed to the model space by applying the concatenated linear and nonlinear transformations. Finally, the maps were resampled to voxels sized 2 mm × 2 mm × 2.4 mm. To allow a region of interest analysis of striatum, a mask was created by segmenting the striatum on the model brain and dilating it by 2 mm.

Statistical Analysis

SPSS 16.0.2 statistical package for Apple Mac (SPSS Inc., Chicago, Illinois) was used for statistical analysis of the clinical and volumetric data. All clinical data, matching variables, and brain volume measurements were normally distributed, except for the volume of the lateral ventricles. A natural logarithm transformation was applied to this measure before including it in

further analyses. Matching data were compared between groups using independent sample *t* tests.

Group Differences in Brain Development. A multivariate analysis of variance procedure was used to investigate differences in brain development between diagnostic groups. In the primary analysis, volumetric measurements were included as dependent variables, diagnosis was included as a fixed factor, and age was included as a covariate. To control for effects of total brain volume, acquisition protocol (1.2 mm vs. 1.5 mm slice thickness), and present or past use of neuroleptic medication, additional analyses were performed including these measures as covariates or fixed factors. For brain structures showing main effects of age or age by diagnosis interactions, the shape of the developmental curves was investigated by examining whether a quadratic or linear model best fit the data. Linear regression analyses were performed with age and quadratic age as predictors and brain structure volumes as dependent variables. Models were calculated for the group as a whole for structures showing main effects of age and for diagnostic groups separately for structures showing interactions between age and diagnosis.

Voxel-Based Morphometry. In the voxel-wise analysis, linear regressions were performed through all brains for each voxel separately in the GM and WM density maps. Group (autism or control subject), age, gender, handedness, medication use, and scan protocol were included in the analysis as regressor variables. Correction for multiple comparisons was carried out using false discovery rate (41) ($\alpha < .05$, two-tailed), allowing for an overall 5% chance of false positives.

Correlations with Behavior. To investigate relationships with behavior, correlations were calculated between the three striatal volumes and three symptom clusters of repetitive behaviors using Spearman rank-order correlations. Autism Diagnostic Interview-Revised repetitive behavior items were clustered into repetitive motor behavior (RBM), insistence on sameness (IS), and circumscribed interests (CI), based on the clusters reported in a recent factor analysis on ADI-R scores in 316 subjects (42). Repetitive motor behaviors included the items Repetitive Use of Objects, Hand and Finger Mannerisms, and Other Complex Mannerisms/Stereotyped Body Movements. Insistence on sameness included Difficulties with Minor Changes in Personal Routine and Environment, Resistance to Trivial Changes in the Environment, and Compulsions and Rituals. Circumscribed interests included Circumscribed Interests, Unusual Preoccupations, and Unusual Attachment to Objects.

Results

Group Differences in Brain Development

The primary multivariate analysis showed interactions between diagnosis and age for caudate nucleus volume ($F = 12.8$, $p < .001$) and lateral ventricle volume ($F = 4.2$, $p = .042$); there was a main effect of diagnosis on caudate nucleus volume ($F = 7.5$, $p = .007$) and a main effect of age on cerebellum, gray matter, white matter, nucleus accumbens, lateral ventricle, and total brain volume.

After including total brain volume as a covariate in the model, the interaction between age and diagnosis remained significant for the caudate nucleus ($F = 8.1$, $p = .005$) but not for lateral ventricle volume ($F = 2.8$, $p = .096$); an interaction between age and diagnosis was also significant for nucleus accumbens volume ($F = 4.0$, $p = .046$). The main effect of diagnosis on caudate nucleus volume remained significant ($F = 4.8$, $p = .031$) and main effects of diagnosis for putamen and nucleus accumbens

Table 2. Brain Volumes

Variable	Subjects with Autism	Normal Control Subjects
	Mean \pm SD (cm ³)	Mean \pm SD (cm ³)
Intracranium	1540.56 \pm 114.32	1520.45 \pm 116.39
Total Brain	1414.83 \pm 105.28	1396.61 \pm 114.08
Cerebellum	159.18 \pm 12.36	157.64 \pm 17.40
Gray Matter	776.31 \pm 68.55	762.48 \pm 75.78
White Matter	477.23 \pm 99.01	463.50 \pm 49.52
Lateral Ventricles ^a	12.65 \pm 6.97	9.69 \pm 5.37
Nucleus Accumbens ^{b,c}	2.26 \pm .36	2.23 \pm .37
Caudate Nucleus ^{b,d}	7.83 \pm 1.03	7.61 \pm .89
Putamen ^{b,c}	9.81 \pm 1.09	9.51 \pm 1.01

Multivariate analysis, age and total brain volume were included as covariates and use of neuroleptic medication as a fixed factor.

^aA natural logarithm transformation to obtain normal distribution was applied to this measure before including it in further analyses.

^bMain effect of diagnosis, $p < .05$.

^cInteraction of diagnosis and age, $p < .05$.

^dInteraction of diagnosis and age, $p < .01$.

volume also became significant ($F = 5.0$, $p = .026$ and $F = 4.1$, $p = .045$, respectively). Main effects of age were significant for gray matter, white matter, and lateral ventricle volume.

When present or past neuroleptic use was included in the model as a fixed factor, the interaction between age and diagnosis remained significant for all three striatal structures (caudate nucleus: $F = 8.5$, $p = .004$; putamen: $F = 4.1$, $p = .043$; nucleus accumbens: $F = 4.0$, $p = .046$), as did the main effect of diagnosis (caudate: $F = 5.2$, $p = .024$; putamen: $F = 6.6$, $p = .011$; accumbens: $F = 4.0$, $p = .046$) (Table 2). When subjects on neuroleptic medication were excluded from the primary analysis, results were similar for both the interaction between age and diagnosis (caudate nucleus: $F = 7.9$, $p = .005$; putamen: $F = 4.3$, $p = .040$; nucleus accumbens: $F = 4.5$, $p = .036$) and the main effect of diagnosis (caudate nucleus: $F = 4.8$, $p = .030$; putamen: $F = 6.7$, $p = .011$; nucleus accumbens: $F = 4.5$, $p = .036$). Including acquisition protocol as covariate did not change the results.

Developmental Trajectories

For structures showing main effects of age (gray and white matter and lateral ventricles), the shape of the developmental curve was investigated by comparing linear and quadratic fits for the group as a whole. A linear model best explained the variance for lateral ventricle volume ($t = 4.81$, $p < .001$) and total gray matter volume ($t = -5.62$, $p < .001$). For white matter, no fits were significant.

For structures showing an interaction between age and diagnosis (caudate nucleus, putamen, and nucleus accumbens), linear and quadratic models were fit for diagnostic groups separately. For the caudate nucleus, a linear model best explained the variance in both the control group ($t = -3.13$, $p = .002$) and the autism group ($t = 2.06$, $p = .042$). For the nucleus accumbens, a quadratic fit best explained the variance in the autism group ($t = -3.03$, $p = .003$), while no fits were significant for the autism group. For putamen, no fits were significant (Figure 1).

Voxel-Based Morphometry

Voxel-based morphometry was used to explore where differences in striatum were localized. There was a main effect of diagnosis in the head of the caudate nucleus (max $t = 4.11$ in right caudate nucleus; $p = .002$). There were no white

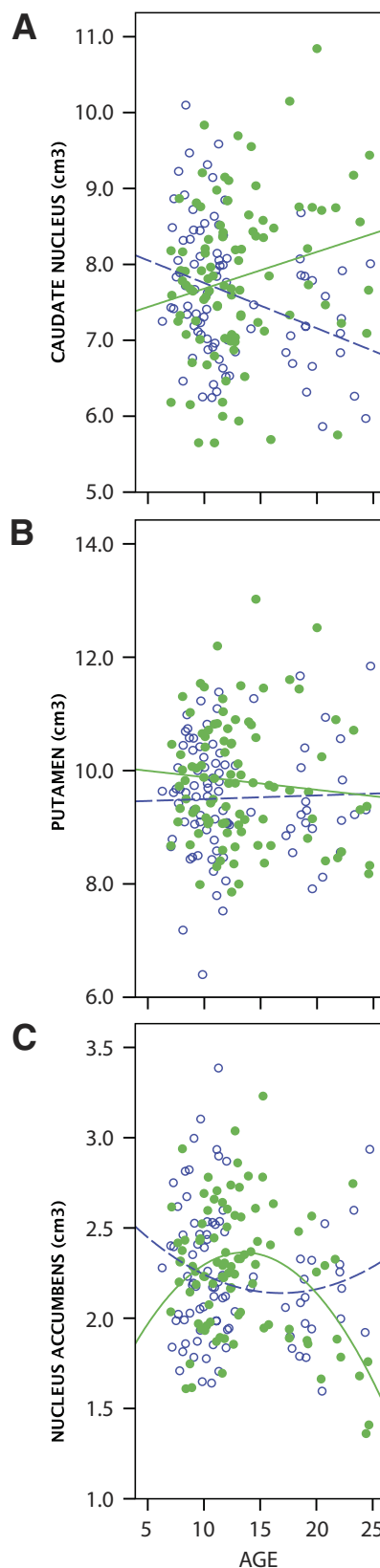


Figure 1. Scatterplots of striatal volume with age in autism and control subject. (A) caudate nucleus; (B) putamen; (C) accumbens nucleus. Green solid circles and solid fit line: autism group; blue open circles and dashed fit line: control group.

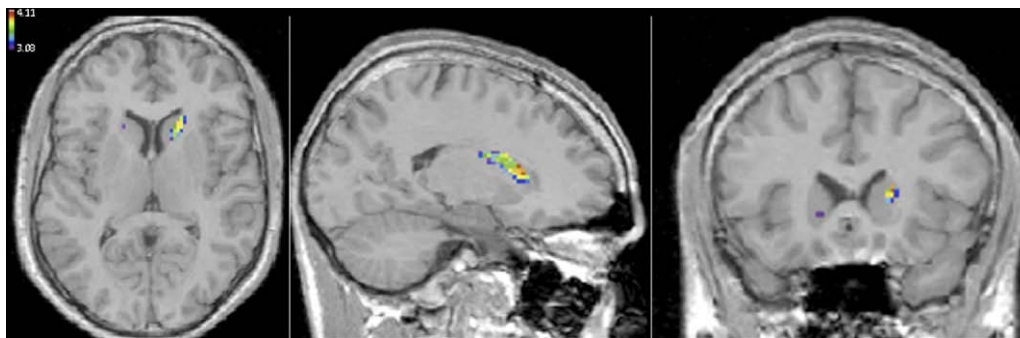


Figure 2. Focal increases in gray matter density in autism. The map is thresholded at the critical t ($t > 3.08$) and superimposed on axial, sagittal, and coronal sections through the magnetic resonance image of the model brain.

matter density changes in adjacent areas, such as the internal capsule (Figure 2).

Correlations Between Striatal Volumes and Symptom Clusters

For subjects with autism, correlations were calculated between striatal volumes and three clusters of repetitive behavior symptoms (repetitive motor behavior, insistence on sameness, and circumscribed interests). Caudate volume correlated negatively with the insistence on sameness cluster ($r = -.239, p = .023$). There were no significant correlations for the clusters of repetitive motor behavior or circumscribed interests or for the other striatal structures (putamen and nucleus accumbens). To assess whether this relationship changed with development, we controlled for the effect of age in a partial correlation analysis. Secondly, we investigated this relationship in the older and younger age group separately using a median split for age. When controlling for age using partial correlations, the correlation no longer reached significance, although the direction of the correlation stayed the same ($r = -.149, p = .160$). In the median split analysis, the correlation was at trend level for the younger group ($r = -.266, p = .068$) and not significant for the older group ($r = -.149, p = .340$). As such, it appears that our brain-behavior relationship may be mediated by age-related changes in insistence on sameness, where the correlation is more apparent at younger ages.

Discussion

In this study, we report changes in the trajectory of striatal development in autism. Differences in caudate development were particularly striking, as the volume of this structure increased with development in autism, while it decreased in control subjects. Changes were not attributable to changes in overall brain volume or the use of neuroleptic medication and were localized to the head of the caudate nucleus. Furthermore, caudate volume was associated with severity of repetitive behavior (insistence on sameness) in subjects with autism.

We report similar developmental trajectories for total brain, gray and white matter, and lateral ventricles for control subjects and subjects with autism. For both groups, total gray matter volume decreased, while ventricular volume increased, with age. This pattern is in accordance with earlier reports of typical development (18,23). However, the developmental trajectories of striatum, caudate nucleus in particular, differed between subjects with autism and control subjects. In the typically developing children, caudate nucleus volume decreased with age, similar to findings in one earlier cross-sectional study of typical development (18). However, in autism, caudate nucleus continued to increase in volume with age. This is concordant with one earlier report suggesting differential developmental trajectories for subjects with Asperger syndrome and control subjects (25),

Table 3. Brain-Repetitive Behavior Correlations

ADI-R Items	Langen <i>et al.</i> (Present Study) <i>n</i> = 88	Sears <i>et al.</i> (1999) <i>n</i> = 35	Hollander <i>et al.</i> (2005) <i>n</i> = 12	Rojas <i>et al.</i> (2006) <i>n</i> = 24
Repetitive Use of Objects		ns		
Hand and Finger Mannerisms	Repetitive Motor Behavior (ns)	ns	Low order (ns)	
Other Complex Mannerisms/Stereotyped Body Movements		Low order + ^a		
Resistance to Trivial Changes in the Environment		ns	NA	Repetitive and stereotyped behavior domain + ^a
Difficulties with Minor Changes in Routine	Insistence on Sameness – ^a	High order – ^b	NA	
Compulsions and Rituals		High order – ^b	High order + ^a	
Circumscribed Interests		ns		
Unusual Preoccupations	Circumscribed Interests (ns)	ns		
Unusual Attachment to Objects		ns	NA	

ADI-R repetitive behavior items used in the Sears *et al.* (2), Hollander *et al.* (3), Rojas *et al.* (6), and the present study. Cells are merged to indicate when items were clustered in the analyses. Minus sign (–) or plus sign (+) signifies direction of correlation.

ADI-R, Autism Diagnostic Interview-Revised; NA, not applicable; ns, nonsignificant.

^aSignificant correlation with caudate volume ($p < .05$).

^bSignificant correlation with caudate volume ($p < .01$).

although this finding was not specific to caudate nucleus; in this study, brain and caudate nucleus volumes were reported to remain stable over development in Asperger syndrome, while they decreased in control subjects.

Voxel-based morphometry showed that striatal differences in our study localized to the head of the right caudate nucleus. This nucleus is part of an intricate system integrating multimodal information and regulating complex behavior. It encompasses distinct corticostriatal feedback loops that feed into each other in a ventral to dorsal pattern with outputs targeting premotor, prefrontal, and motor cortical areas (43,44). As such, these results are consistent with other studies showing atypical functional connectivity between caudate nucleus and cortical areas in autism (45–47). The caudate nucleus is in the more dorsal part of the circuit and is linked to dorsolateral prefrontal, lateral orbitofrontal, and oculomotor loops. Given these associations, it is implicated in higher-order functions, such as planning, set shifting, and cognitive control (46). This suggests that the changes in caudate nucleus development in the current study could be associated with problems in corticostriatal feedback and may therefore be related to behavioral problems.

The laterality of our voxel-based results is in line with a previous study that also found changes predominantly in the right hemisphere (3). As discussed in that study, atypical symmetry between the two caudate heads for subjects with autism may be related to functional abnormalities (3).

Our finding of a relationship between volume of the caudate nucleus and the insistence on sameness cluster is concordant with other studies that have implicated striatum in repetitive behavior across neuropsychiatric disorders (2,3,5,16,48,49). A clear hypothesis on the direction of the relationship between repetitive behavior and caudate volume in autism is not immediately obvious from the literature. Whereas Sears *et al.* (2) reported a positive correlation for low-order repetitive behavior and caudate volume and a negative correlation for high-order repetitive behavior and caudate volume, Hollander *et al.* (3) reported a positive correlation for high-order repetitive behavior and caudate volume. Last, Rojas *et al.* (5) demonstrated a positive correlation between repetitive behavior (including both high- and low-order items) and caudate nucleus volume. Our own finding is of a negative correlation between caudate volume and a form of high-order repetitive behavior. However, when considering which ADI-R items were clustered in the different studies, it becomes apparent that these results are not as contradictory as they initially appear: there is clear overlap between the items included in the clusters that show a negative correlation with caudate volume in three of four studies (Table 3).

Furthermore, the factor analysis of repetitive behavior by Lam *et al.* (42) suggests that the clusters of repetitive behaviors as used in our analyses are associated with distinct profiles of symptoms. As such, the factors could be associated with distinct neural circuits that may not necessarily all involve the basal ganglia. This could form part of the explanation why we only find correlations with one of the three factors identified by Lam *et al.* (42). In addition, this could contribute to the seemingly contrary results in the literature of both positive and negative correlations between symptoms of repetitive behavior and striatal structures: if different neural circuits support different aspects of this symptom cluster, the relationships between structure and function could feasibly take different forms.

This said, it does seem counterintuitive that in the autism group larger caudate nucleus volumes are associated with less

severe repetitive behavior. As was suggested by Sears *et al.* (2), the negative correlation between specific high-order repetitive behavior and caudate nucleus volume may reflect abnormal functional relationships with other brain areas, resulting in behavioral inflexibility. Alternatively, larger caudate volumes in autism could reflect compensatory sparing of function in this structure, where those individuals with larger volumes are best able to compensate for rigid or stereotyped behaviors. A similar finding has been reported in Tourette disorder. Plessen *et al.* (50) demonstrated an association of larger prefrontal cortical volumes and lower tic severity in children with Tourette syndrome and suggested that increased prefrontal volumes could represent a compensatory mechanism, facilitating control of tics.

There are some limitations to our study. First, the use of a cross-sectional design limits the developmental conclusions that can be drawn from our findings (see [51] for a full discussion). A longitudinal approach would be more sensitive to detecting developmental changes and would permit a more accurate assessment of the shape of developmental curves. Specifically, although our findings for typical caudate nucleus development are consistent with other cross-sectional studies (18), longitudinal studies have reported that typical development of caudate nucleus follows an inverted U-shape trajectory (23,24).

Second, we included only high-functioning individuals who met full criteria for autism in our sample. As such, this limits the inferences that can be made in terms of other individuals in the autism spectrum.

Conclusion

In conclusion, we report changes in striatal development in autism, as well as an association of caudate volume with repetitive behaviors. This emphasizes the importance of striatum in the etiology of autism, in particular in the development of repetitive behavior that characterizes the disorder.

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