Changes in the Developmental Trajectories of Striatum in Autism

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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-

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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.
[a]Information was unavailable for five control subjects and two ASD subjects.
[b]Information was unavailable for five control subjects and four ASD subjects.
[c]Information was unavailable for two control subjects and two ASD subjects.
[d]Information was unavailable for 26 control subjects and 25 ASD subjects.
[e]Information was unavailable for two ASD subjects.