Changes in the Development of Striatum Are Involved in Repetitive Behavior in Autism

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Background: Repetitive behavior is a core feature of autism and has been linked to differences in striatum. In addition, the brain changes associated with autism appear to vary with age. However, most studies investigating striatal differences in autism are cross-sectional, limiting inferences on development. In this study, we set out to 1) investigate striatal development in autism, using a longitudinal design; and 2) examine the relationship between striatal development and repetitive behavior.

Methods: We acquired longitudinal structural magnetic resonance imaging scans from 86 individuals (49 children with autism, 37 matched control subjects). Each individual was scanned twice, with a mean scan interval time of 2.4 years. Mean age was 9.9 years at time 1 and 12.3 years at time 2. Striatal structures were traced manually with high reliability. Multivariate analyses of variance were used to investigate differences in brain development between diagnostic groups. To examine the relationship with behavior, correlations between changes in brain volumes and clinical measures were calculated.

Results: Our results showed an increase in the growth rate of striatal structures for individuals with autism compared with control subjects. The effect was specific to caudate nucleus, where growth rate was doubled. Second, faster striatal growth was correlated with more severe repetitive behavior (insistence on sameness) at the preschool age.

Conclusions: This longitudinal study of brain development in autism confirms the involvement of striatum in repetitive behavior. Furthermore, it underscores the significance of brain development in autism, as the severity of repetitive behavior was related to striatal growth, rather than volume per se.

Key Words: Autism, brain development, corticostriatal circuitry, insistence on sameness, repetitive behavior, striatum

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder, characterized by restricted, repetitive, and stereotyped patterns of behavior and interests and impairments in social interaction and communication. Autism spectrum disorder is defined behaviorally, and despite strict diagnostic criteria, ASD is a heterogeneous disorder with clinical profiles differing significantly across affected individuals.

It is thought that this clinical heterogeneity may reflect similar heterogeneity in the underlying neurobiology: recent studies have shown that separable neurobiological and genetic pathways are involved in distinct clinical domains and phenotypes (1,2). As such, heterogeneity in the phenotypic presentation of autism spectrum disorders has been cited as one explanation for the difficulty in pinpointing specific neurobiological mechanisms involved in the disorder (3).

Identifying neuroanatomical changes in ASD is further challenged by studies demonstrating that brain differences in autism are not stable but rather appear to change with age (4). This observation has made brain development an increasingly important theme in neuroanatomical studies of ASD. There are now several convincing reports of changed growth trajectories for overall brain volume in ASD. It seems that brain development in ASD may include a period of early overgrowth (before age 2 to 4), probably followed by normal or even decreased growth (4–6), so that by adulthood brain volume is within normal range or even decreased (4,7,8). Both gray and white matter have been implicated in early overgrowth. The deviant growth pattern in early childhood is believed to follow a regional gradient, where the frontal, temporal, and cingulate cortices are most affected (9). These findings highlight the dynamic nature of developmental changes in ASD and may partially explain the discrepancies between brain imaging studies at different ages (10,11).

Reports of changes in brain development seem to concur with the clinical observation of variability in the timing of onset and development of behaviors associated with ASD (12), although direct links between brain growth patterns and clinical symptoms are needed to fully warrant this claim. Up to now, only one study has linked developmental differences to clinical measures in ASD (6). This study showed relationships between cortical thinning and socioemotional reciprocity (frontal lobe) and cortical thinning and rigid, repetitive, and stereotyped behaviors (temporal lobe) in a modest sample of 34 participants ($n = 18$ ASD, $n = 16$ control subjects).

To date, the longitudinal literature of brain development in ASD has mainly reported findings on total brain volume, the volume of the various lobes (4–6,9) or cortical thickness (5,6). Given the known regional specificity of brain development in both typically developing control subjects (13–15) and ASD (9,16) and accompanying changes in clinical and cognitive/behavioral profiles (17–19), this calls for a closer look at the developmental trajectories of regions known to be involved in ASD and related clinical measures. Therefore, in this longitudinal study, we set out to investigate striatal development in a large and homogeneous sample of high-functioning children with ASD and control subjects. Following from earlier cross-sectional work where we reported changes in striatal development in autism, as well as an association of caudate volume with repetitive behavior (16), we hypothesized that there would be 1) changes in the growth

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trajectories of striatum and 2) a relationship between striatal growth and repetitive behavior.

Methods and Materials

Participants

In this study, we report on a subsample of our ongoing longitudinal ASD neuroimaging project. From a dataset of approximately 500 scans, we included data from individuals under 18 years of age and for whom we had available 1) two neuroimaging datasets and 2) a complete set of phenotypic and clinical data. This resulted in the current sample of 172 magnetic resonance imaging (MRI) scans from 86 individuals (49 individuals meeting DSM-IV criteria for autism or Asperger syndrome and 37 typically developing control subjects). Each individual was scanned twice, with a mean scan interval time of 2.4 years. Mean age was 9.9 years at time 1 and 12.3 years at time 2.

Individuals with ASD were recruited through the Department of 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. The presence of autism spectrum disorder was confirmed by trained and qualified clinicians using the Autism Diagnostic Interview Revised (ADI-R) (20). Eight participants with ASD were using or had previously used neuroleptic medication, risperidone for most cases.

Typically developing control subjects were recruited through schools in the area. For all control subjects, a parent participated in a semistructured interview session with a trained rater to confirm absence of any psychiatric diagnosis (Diagnostic Interview Schedule for Children-Parent version) (21). Only control subjects with no psychiatric diagnosis (current or prior) were included in the study.

For both groups, individuals with major physical or neurological illness, history of head trauma, or alcohol or other drug dependence were excluded. Control subjects with a family history of psychiatric illness were also excluded. Groups were matched for gender, IQ, height, weight, hand preference, pubertal development (assessed using Tanner scales), and for parental educational level (Table 1).

For all participants, a parent signed for consent, while assent was obtained from the participant. All individuals participated in two MRI scanning sessions and a neuropsychological assessment [Wechsler Adult Intelligence Scale/Wechsler Adult Intelligence Scale-Third Edition (22,23), Wechsler Intelligence Scale for Children-Revised/Wechsler Intelligence Scale for Children-Third Edition (24,25)]. Children under 13 years of age were acclimated to the scanning procedure in a dummy scan session before the actual magnetic resonance scan (26). An independent clinical neuroradiologist evaluated all MRI scans. 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

Magnetic resonance imaging scans were acquired on a 1.5T scanner (Philips, Best, The Netherlands). Data were acquired over 8 years. For the definition of all brain measures, a T1-weighted three-dimensional fast field echo scan with 130 to 150 1.5-mm contiguous coronal slices (scan 1: 18 ASD, 16 control subjects; scan 2: 12 ASD, 0 control subjects) or 160 to 180 contiguous coronal 1.2-mm slices (scan 1: 31 ASD, 21 control subjects; scan 2: 37 ASD, 37 control subjects) of the whole head (echo time 4.6 msec, repetition time 30 msec, flip angle 30°, field of view 256 mm, in-plane voxel size 1 mm × 1 mm) were acquired. For the great majority of participants ($n = 64$), scan acquisition protocols were identical for both measurements. For the other 22 participants (6 ASD, 16 control subjects), protocols at time 1 and time 2 differed only with respect to slice thickness (1.5 mm vs. 1.2 mm).

MRI Processing

All images were coded to ensure rater blindness to subject identity and diagnosis. An automated image processing pipeline was used to determine volumes of total brain, gray and white matter, cerebellum, and lateral ventricles [see (16) for a detailed description of this pipeline].

Manual Tracing. Striatal structures were traced manually by three experienced raters (D.B., S.D.S.N., 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 the Supplement 1. Intrarater reliabilities (estimated using intraclass correlation coefficients) were above .93 for all structures. Interrater reliabilities were .96 for caudate nucleus, .77 for putamen. and .72 for nucleus accumbens.

Statistical Analysis

SPSS 20 statistical package for Apple Mac (SPSS Inc., Chicago, Illinois) was used for statistical analysis of the data. All clinical data, matching variables, and brain volume measurements were normally distributed. Matching data were compared between groups using independent sample *t* tests.

Table 1. Demographic Data and Characteristics of the Sample

Variable	Autism Group ($n = 49$)	Control Group ($n = 37$)	
Gender, Male/Female	44/5	31/6	ns
Mean Age T1 + T2, Mean ± SD, Years (Range)	12.08 ± 2.28 (7.75–17.62)	10.81 ± 1.77 (7.08–13.54)	.006
Total IQ, Mean ± SD (Range)	107.47 ± 18.58 (61–137)	111.92 ± 15.02 (81–143)	ns
Handedness (Right/Left/Unknown), *n*	37/4/7	30/4/3	ns
Parental Education, Mean ± SD, Years	13.02 ± 2.2	13.37 ± 1.7	ns
Scan Interval, Mean ± SD, Years (Range)	2.28 ± 1.36 (1.5–6.5)	2.45 ± 1.61 (1.58–7.08)	ns
Neuroleptic Use, *n* Participants	8	0	NA
ADI-R: Social Deficits (Range)	18.34 ± 5.25 (8–28)	NA	
ADI-R: Abnormalities in Communication (Range)	14.55 ± 4.78 (3–25)	NA	
ADI-R: Ritualistic-Repetitive Behavior (Range)	4.83 ± 2.58 (1–10)	NA	

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