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Two years changes in the development of caudate nucleus are involved in restricted repetitive behaviors in 2–5-year-old children with autism spectrum disorder

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ABSTRACT

Caudate nucleus volume is enlarged in autism spectrum disorder (ASD) and is associated with restricted and repetitive behaviors (RRBs). However, the trajectory of caudate nucleus volume in RRBs of young children remains unclear. Caudate nucleus volume was measured in 36 children with ASD and 18 matched 2–3-year-old subjects with developmentally delayed (DD) at baseline (Time 1) and at 2-year follow-up (Time 2). The differential growth rate in caudate nucleus volume was calculated. Further, the relationships between the development of caudate nucleus volume and RRBs were analyzed. Our results showed that caudate nucleus volume was significantly larger in the ASD group at both time points and the magnitude of enlargement was greater at Time 2. The rate of caudate nucleus growth during this 2-year interval was faster in children with ASD than DD. Right caudate nucleus volume growth was negatively correlated with RRBs. Findings from this study suggest developmental abnormalities of caudate nucleus volume in ASD. Longitudinal MRI studies are needed to explore the correlation between atypical growth patterns of caudate nucleus and phenotype of RRBs.

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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by qualitative impairments in social interaction as well as restricted, repetitive behaviors (RRBs). RRBs are the core symptoms of ASD, and are diagnostic of autism, according to the Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (American Psychiatric Association, 2000). Based on the Diagnostic and Statistical Manual of Mental Disorder-5 (American Psychiatric Association, 2013), RRBs remain the key diagnostic criteria. The category of RRBs is very broad, and includes such behaviors as motor stereotypies (e.g., turns in circles), repetitive use of parts of objects (e.g., buttons on clothes), adherence to nonfunctional routines (e.g., insists on taking certain routes/paths), and compulsive behavior (e.g., need for things to be even or symmetrical).

Increasing evidence suggests that RRBs first emerge in toddlers and preschoolers, even as early as 8 months of age in children later diagnosed with ASD (Watson et al., 2007; Kim and Lord, 2010). The wide variety of repetitive behaviors also occur in *typically developing* (TD) young children, including intellectual disability, obsessive compulsive disorder (OCD), Parkinson's disease, and Tourette syndrome (TS) (Evans et al., 1997; Boyer and Liénard, 2006). However, difficulties in classification and quantification complicate systematic research of repetitive behavior in distinct neuropsychiatric disorders (Langen et al., 2011). Several studies have found increased RRBs in both adults and young children even as young as 18–24 months of age with ASD compared with *developmentally delayed* (DD) controls (Richler et al., 2007; Morgan et al., 2008).

Previous structural magnetic resonance imaging (MRI) of individuals with clinical disorders investigating neuroanatomical correlates of repetitive behavior has suggested changes in basal ganglia, particularly *caudate and putamen*. For example, results of imaging studies with medication-naive TS patients, have indicated reductions in *caudate and putamen* volumes (Bloch et al., 2005) although increases (Fredericksen et al., 2002) and similar volumes (Zimmerman et al., 2000) have also been reported. In addition,

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smaller caudate nucleus volume in children predicted increased severity of TS symptoms in adulthood (Bloch et al., 2005; Hyde et al., 1995). In terms of OCD, Radua and Mataix-Cols (2009) conducted a voxel-wise meta-analysis using 12 MRI studies, which showed increased gray matter volume in basal ganglia, including putamen and caudate nucleus. This analysis also indicated a correlation between OCD severity and increased magnitude of basal ganglia volume.

However, previous cross-sectional structural MRI studies exploring the neurobiology of RRBs are limited in ASD. Sears et al. (1999) found a significant negative association between caudate nucleus volume and three *Autism Diagnostic Interview* (ADI) repetitive behavior items: difficulties with minor changes in routine, compulsions/rituals, and complex mannerisms. Hollander et al. (2005) reported increased right caudate nucleus volume in ASD, which were positively correlated with higher order RRBs of *ADI*. The same pattern was observed when putamen volumes were correlated with repetitive behavior scores. Using adult and adolescent samples, Rojas et al. (2006) largely replicated these results in a later study. In two studies using a wider age range (7–25 years), Langen et al. (2007, 2009) also reported larger caudate nucleus volume in highly functional ASD individuals compared with typically developing controls. These investigators reported either no significant correlations with Autism Diagnostic Interview-Revised (ADI-R) repetitive behavior scores (Langen et al., 2007) or a negative correlation with insistence on sameness cluster (Langen et al., 2009). Estes et al. (2011), however, examined basal ganglial morphometry in 3–4-year-old children with ASD compared with DD and TD controls. After controlling for cerebral volume no differences in caudate nucleus volume was found between ASD and TD children but the difference between ASD and DD participants persisted. Further, no systematic relationship between caudate nucleus volume and RRBs was observed for any of the three measures of RRBs. This observation was at odds with the recent results of Wolff et al. (2013) who reported that the compulsive and ritual subscales of Repetitive Behavior Scale-Revised were significantly positively associated with caudate nucleus volume in 3–6-year-old ASD children. To date, in the longitudinal study of caudate nucleus development in autism, Langen et al. (2014) reported that an increase in the growth rate of striatal structures, especially caudate nucleus in individuals with autism mean age was 9.9, compared with typically developing controls. Faster striatal growth was correlated with more severe RRBs (insistence on sameness). Abnormally high caudate volumes in early childhood, typically between 10 and 15 years of age, and then abnormal decline in adulthood were found in 100 male participants with ASD compared with 56 typically developing controls scanned over an 8-year period (Lange et al., 2015).

In general, most cross-sectional and longitudinal studies have focused on adults or school-age children with ASD and the early trajectory of caudate nucleus from infancy through middle childhood remains unclear. It is necessary to determine whether young children with ASD have greater volumes and atypical growth patterns of caudate nucleus than other children, and whether volumes of caudate nucleus correlate with RRBs. Therefore, in the present longitudinal study, we evaluated caudate nucleus development during a 2-year interval in 2–3-year-old children with ASD and DD subjects. The following hypotheses were tested:

1. Caudate nucleus is enlarged in ASD children compared with DD children.
2. The ASD sample exhibits changes in early developmental growth trajectory of caudate nucleus; and
3. Caudate nucleus morphological growth is correlated with RRBs.

2. Methods

2.1. Participants

We included data from the original sample of approximately 116 scans in our ongoing 2-year longitudinal neuroimaging imaging project. Data included: (1) two neuroimaging datasets; (2) a consistent diagnosis at both times and (3) good quality scans. Eight scans were excluded. MRI scans were acquired in 54 individuals at both time points individually: 36 with ASD and 18 with DD matched for gender, age, developmental quotient (DQ) and intelligence quotient (IQ) (see Table 1). Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Board of Nanjing Brain Hospital of Nanjing Medical

Table 1
Participants: clinical demographics.

	ASD (M ± SD)	DD (M ± SD)	t/x^2	p
N	36	18		
Gender (male:female)	30:6	13:5	0.913	0.339
Δ in age: (years)	2.0 ± 0.4	2.1 ± 0.4	−1.098	0.277
Time 1				
Age (years)	2.5 ± 0.3	2.4 ± 0.4	1.195	0.238
DQ	66.22 ± 9.6	66.18 ± 15.4	0.008	0.993
ADI-R: Social Deficits	21.8 ± 5.8	15.1 ± 6.5	3.785	<0.001***
ADI-R: Abnormalities in Communication	12.6. ± 4.6	8.1 ± 4.8	3.247	0.002**
ADI-R: Ritualistic-Repetitive Behavior	3.8 ± 1.5	1.9 ± 1.5	4.268	<0.001***
Higher order RRBs	1.4 ± 1.2	0.7 ± 0.7	2.230	0.030*
Lower order RRBs	2.4 ± 1.2	1.4 ± 1.7	3.065	0.004**
Time 2				
Age (years)	4.5 ± 0.4	4.5 ± 0.2	<0.001	1.000
IQ	89.2 ± 27.87	80.3 ± 32.3	0.886	0.382
ADI-R: Social Deficits	19.7 ± 5.5	15.1 ± 7.6	2.212	0.033*
ADI-R: Abnormalities in Communication	13.1 ± 4.9	8.2 ± 5.1	2.904	0.006**
ADI-R: Ritualistic-Repetitive Behavior	3.6 ± 1.9	1.5 ± 0.9	3.790	<0.001***
Higher order RRBs	1.7 ± 1.4	0.5 ± 0.6	2.674	0.010*
Lower order RRBs	2.0 ± 1.3	1.0 ± 0.9	2.532	0.015*

ASD, autism spectrum disorder; DD, developmentally delayed; DQ, developmental quotient; IQ, intelligence quotient; ADI-R, Autism Diagnostic Interview-Revised; Δ in age, the interval between two scans.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

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