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A Preliminary Longitudinal Volumetric MRI Study of Amygdala and Hippocampal Volumes in Autism

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Abstract

Background: Previous studies suggest that amygdala volume, when compared with healthy controls, is increased in young children with autism, is unchanged in cohorts of older youth, and is smaller in adults. Hippocampal volume, however, does not appear to have age-related changes, and it is unclear whether individuals with autism have volumetric differences in this structure. The goal of this pilot investigation is to characterize the developmental trajectories of the amygdala and hippocampus in children with autism between the ages of 8 and 14 years and to examine clinical correlates of volume change.

Methods: Twenty-three children with autism and 23 controls between the ages of 8 and 12 underwent a magnetic resonance imaging procedure of the brain (T1-weighted) at two time points. Nine children with autism and 14 controls had good quality scans from both time points; however, all usable scans from all subjects (15 children with autism and 22 controls) were included in a mixed effect analysis. Regression models were used to estimate group differences in amygdala and hippocampus volumes. Changes in amygdala and hippocampal volumes (Time 2 – Time 1) were correlated with clinical severity measures.

Results: Amygdala volume changes with time were similar between the two groups. Within the autism group, right amygdala volume change was correlated with the ability to establish appropriate eye contact. Right hippocampal volume was significantly increased in the autism

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group when compared with controls. Differences in right hippocampal volume change with time between the two groups approached significance.

Conclusion: This study provides preliminary evidence of normalization of amygdala volumes in late childhood and adolescence. It also suggests that hippocampal volumetric differences may exist in autism in late childhood and adolescence.

Keywords

Amygdala; hippocampus; autism

1. Introduction:

The amygdala and hippocampus have been implicated in deficits associated with Autism Spectrum Disorders (ASD), including social cognition, perception of eye-gaze direction, and emotion(Kawashima et al. 1999; Greicius et al. 2003; Fanselow and Dong 2010; Conty and Grezes 2011). To date, all MRI investigations examining amygdala and hippocampal volumes were cross-sectional with the exception of two recent studies that reported on the size of the amygdala in young children with autism (Mosconi et al. 2009; Nordahl et al. 2012). Cross-sectional studies confound within- and between-subject source of variations and cannot capture changes in the trajectories (Stanfield et al. 2008; Thompson et al. 2011). However, there is mounting evidence from these cross-sectional studies, suggesting that, compared with controls, amygdala volume is increased in young children with autism (Sparks et al. 2002; Munson et al. 2006; Mosconi, Cody-Hazlett et al. 2009; Schumann et al. 2009; Kim et al. 2010; Nordahl, Scholz et al. 2012), is unchanged in cohorts of older youth (Haznedar et al. 2000; Bigler et al. 2003; Palmen et al. 2006) and smaller in adults (Aylward et al. 1999; Pierce and Courchesne 2001; Rojas et al. 2004; Nacewicz et al. 2006). In contrast, findings from cross-sectional studies of hippocampal volume in autism have not been consistent and no clear age-related changes have emerged. This observation could be related to the heterogeneity of the samples included in those investigations or to the actual absence of a developmental effect.

The goal of this investigation is to characterize the developmental trajectories of the amygdala and hippocampus in a small group of children with autism between the ages of 8 and 14 years and to examine any possible clinical correlates of volume change.

2. Methods:

2.1 Participants (Table 1)

The original sample included 46 male participants. Good quality scans were available on 37,subjects, 15 with autism and 22 healthy controls (age range at baseline: Autism: 8.1-12.9 years; controls: 7.9-13; age range at follow-up: autism 10.9-14.3 years, controls: 10.1-14.1, p(time 1)=0.675, p(time 2)=0.561).

Autism participants met the following inclusion criteria: 1) diagnosis of autistic disorder through expert clinical evaluation confirmed with the Autism Diagnostic Interview-Revised (ADI-R) (Rutter et al. 2003) and the Autism Diagnostic Observation Schedule (ADOS)

(Lord et al. 2002) and 2) absence of any medical, neurological, or genetic disorders. Control participants were typically developing children and adolescents with full-scale IQ scores ≥ 70 and negative personal and family histories for neurological or psychiatric disorders. After procedures were fully explained, parents of all participants or their legal guardians provided written informed consent. Verbal assent was obtained from all participants. The Institutional Review Board approved the study. Additional demographic and clinical information on this sample have previously been published (Frazier et al. 2012).

2.2 MRI acquisition:

MRI scans were acquired using a 1.5-T GE Signa MR Scanner (General Electric Medical Systems, Milwaukee, WI, USA) at both time points. A T1-weighted sequence was acquired using the following parameters: slice thickness = 1.5 mm, slice number = 124, echo time (TE) = 5 ms, repetition time (TR) = 24 ms, flip angle = 40°, number of excitations (Amaral et al.) = 2, field of view (Smith et al.) = 26 cm, matrix = 256 X 192.

2.2.1 Amygdala and hippocampus measurements:

The amygdala and hippocampus were manually delineated in the coronal plane for each participant according to previously described protocols (Karchemskiy et al. 2011). Briefly, volumetric analysis was performed using BrainImageJava software v.0.13.4 (http://cibsr.stanford.edu) for semi-automated image processing and quantification. Raters who conducted morphometric analyses were blind to the diagnosis of each subject.

Regions were drawn on positionally registered brain image stacks in the coronal orientation. Hippocampi were traced starting at the slice where a clear distinction between amygdala and hippocampus was first visible and outlined proceeding posteriorly until the structure disappeared. The superior white matter tract extending from the temporal lobe was used as an inferior border of the hippocampus, medial border was defined by CSF and by the pons, where present, and the lateral border was marked by CSF or white matter tracts on the lateral edge of the hippocampus.

Amygdalae were traced starting on the slice demonstrating the thickest extent of the anterior commissure and following the structure towards the posterior end of the brain. The most superior white matter tract extending from the temporal lobe marked the inferior border, CSF marked the medial border, entorhinal sulcus marked the superior border, and a thick, central white matter tract of the temporal lobe was used as the lateral border of amygdala. The reliability of the hippocampus and amygdala regions of interest was established by achieving an intraclass correlation coefficient > 0.9, between two raters.

2.3 Statistical analysis:

Mixed effects regression models were used to estimate group differences in amygdala and hippocampus volumes. Diagnostic group was used as a fixed-effects factor, while baseline socioeconomic status (SES), full-scale IQ (FSIQ), and total brain volume (TBV) were used as time-invariant predictors and age was used as a time-varying covariate in each model. Measurements at baseline and 2-year follow-up were included as repeated measures dependent variables. Mixed effects regression models are advantageous to repeated measures

ANOVA in that they accommodate missing time points, explicitly evaluate the effects of age rather than the time of the measurement (baseline and follow-up), directly model the relationship between age and brain volumes, and utilize all available data. Model fit was considered by iteratively examining alternative covariance structures. Final models were estimated using restricted maximum likelihood estimation and were based on fixed effects and scaled identity covariance structures. All analyses were performed using SPSS (IBM SPSS Statistics v19).

A significant Age effect specifies amygdala or hippocampal growth with age, regardless of diagnostic group. A significant Diagnostic Group effect indicates differences in amygdala or hippocampal volume between individuals with autism and healthy controls, irrespective of age. A significant two-way interaction between Age and Diagnostic Group identifies a unique pattern of amygdala or hippocampal growth in autism. This interaction is a *longitudinal* comparison based on all available data. Changes in amygdala and hippocampal volumes (Time 2 – Time 1) were correlated with baseline ADI-R social interaction domains scores, ADOS social domain scores, and SRS total t-scores in autism participants. In addition, given the importance of amygdala function with respect to eye gaze, we explored relationships between amygdala volume changes and the SRS item evaluating appropriate eye contact.

3. Results

Of the 15 participants with autism with good quality scans, 14 had data at time 1 and 10 had data at Time 2. Of the 22 controls with good quality scans, 19 had data at Time 1 and 17 at time 2. Complete data at both time points was available for 9 youth with autism and 14 controls.

There were no significant differences between the baseline SES of the two groups ($t=0.06$, $p=0.949$). There was a significant difference between baseline FSIQ scores (mean FSIQ for autism = 98.1 ± 20.1; mean FSIQ for controls = 117.2 ± 12.3; $t = -3.61$, $p<0.001$).

3.1. Amygdala and hippocampus volumes (Figure 1, Table 2).

Irrespective of diagnostic group, there were small increases in amygdala volume across the entire age range ($F(1,50)=2.10$, $p=0.153$) (Figure 1A). There were no significant differences between youth with autism and healthy controls for left, right, or total amygdala volumes (largest $F(1,50)=0.80$, $p=0.377$), and the volume changes over time were comparable (largest $F(1,49)=0.71$, $p=0.404$).

Figure 1B presents left and right hippocampal volumes across ages 7-16 for both autism and healthy control groups. Children with autism had a significantly larger right hippocampii ($F(1,48)=4.40$, $p=0.041$; Cohen's $d=0.61$). Overtime, individuals with autism had large reductions in right hippocampal volume, whereas healthy controls had stable or slightly increasing hippocampal volumes, with the autism pattern trending toward normalization with age ($F(1,46)=3.27$, $p=0.077$; Cohen's $d=.53$). There were no significant differences between youth with autism and healthy controls for total or left hippocampal volumes

(largest F(1,46)=2.59, p=0.115) and volume changes across age were comparable (largest F(1,44)=1.08, p=0.186).

3.2 Clinical correlates and volume changes (Table 3).

More appropriate eye contact at baseline was significantly associated with larger increases over time in amygdala volume (Time 2-Time1) in individuals with autism (r=−0.86, p=0.006). This finding survives Benjamini-Hochberg multiple comparison correction (Benjamini Y 1995; Benjamini Y 2000). No associations were found between change in amygdala and hippocampal volumes and ADI-R social interaction domains scores, ADOS social domain scores, or SRS total scores.

4. Discussion:

In this study we examined the developmental trajectory of amygdala and hippocampal volumes in children and adolescents with Autism compared to age- and gender –matched typically developing controls. Specifically, in our sample, amygdala volumes as well as volume increases with age were similar in individuals with autism and controls. In addition, within the autism group, volume change of the right amygdala was correlated with the capability to establish appropriate eye contact, which is an impaired ability in autism that is related to amygdala function (Tazumi et al. 2010; Adams et al. 2011; Boll et al. 2011). Further, right hippocampal volume was significantly increased in the autism group when compared with controls. Finally, a trend towards significance was observed in the change of right hippocampal volume over time between the two groups.

Deficits in amygdala structure and function have been proposed as the basis of some of the abnormalities observed in autism, including impairments in social cognition (Baron-Cohen et al. 2000). Increased amygdala volume was found to be associated with joint attention in young children with autism(Mosconi, Cody-Hazlett et al. 2009). In addition, studies have also reported a relationship between amygdala volume, social functioning, gaze avoidance, and eye fixation in individuals with autism (Nacewicz, Dalton et al. 2006; Kim et al. 2010). Interestingly, no correlations between amygdala volumes and social abilities, as measured by the ADOS and ADI social domains, were observed in the present study. However, there was a significant correlation between change in amygdala volume during childhood and adolescence and the eye contact item score on the SRS, suggesting that changes in amygdala volume over time may be related to social behavior associated with amygdala function (e.g., eye contact). This observation should be interpreted in light of the previous findings of increased amygdala size in young children with autism (Sparks, Friedman et al. 2002; Munson, Dawson et al. 2006; Mosconi, Cody-Hazlett et al. 2009; Schumann, Barnes et al. 2009; Kim, Mo et al. 2010; Nordahl, Scholz et al. 2012) which could be related to compensatory mechanisms (e.g. increased amygdala neuropil) mitigating functional and/or anatomical deficits in other brain regions and possibly preceding the decrease in amygdala volume observed in adolescents and young adults in previous studies (Aylward, Minshew et al. 1999; Pierce and Courchesne 2001; Rojas, Smith et al. 2004; Nacewicz, Dalton et al. 2006).

Most studies investigating hippocampal volume in autism did not report differences compared with controls. However, differences in hippocampal volumes in children at a similar age range to our current study were reported by Schumann et al (2004), which showed an increase in the size of this strucutre in a large sample of children with autism (N=98) between the ages of 7.5 and 18 years when compared to controls (31). This finding is concordant with our result and suggests that hippocampal changes are still ongoing in late childhood and adolescence. Consistent with this hypothesis, our study showed a trend towards an age by diagnosis interaction for the right hippocampus, a finding requiring further investigation with larger samples.

Findings from the present study are promising but should be interpreted in the context of development as suggested by previous MRI studies in other disorders (Shaw et al. 2007) (Shaw and Rabin 2009) (Shaw et al. 2006) (Hoeft et al. 2010). For example, cortical development lagged in children with ADHD by almost three years and was most prominent in regions important for control of attention(Shaw, Eckstrand et al. 2007) suggesting the existence of, delayed cortical maturation in at least some cases. Further, longitudinal studies indicated that different clinical outcomes may be associated with different developmental trajectories in adolescence and adulthood (Shaw and Rabin 2009). In fact, children with ADHD who exhibit a normalization of their cerebral or caudal volumes with development have a better outcome than those who had more persistent volumetric alterations (Shaw, Lerch et al. 2006). This evidence form the ADHD literature and from other disorders such as Fragile X highlight the importance of longitudinal studies that appears to be more informative than cross-sectional studies not only for the developmental trajectories but also for prognostic inferences. Another example for the contribution of longitudinal studies comes from research in fragile X syndrome, the most common cause for inherited intellectual disability (Hoeft, Carter et al. 2010). Specifically, a recent voxel-based morphometry (VBM) study reported a longitudinal investigation of boys with fragile X syndrome between the ages of 1 and 3 years. This study suggested an early alteration in neurodevelopment in fragile X syndrome, which could not be detected in a cross sectional study.

This study has several methodological limitations, including small sample size, the lack of multiple time point and the absence of information on pubertal status of participants, which may affect the developmental trajectory of the amygdala and hippocampus(Bramen et al. 2011).

Conclusion:

This study provides preliminary evidence of the possible normalization of amygdala volumes in late childhood and adolescence. It also suggests that hippocampal volumetric differences may exist in autism in late childhood and adolescence. Additional investigations are warranted to examine longitudinal samples across a wide age range, at multiple time points, to estimate developmental trajectories of the amygdala and hippocampus and their relationships to clinical features.

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Highlights

1. This is a pilot investigation of hippocampal and amygdala development in autism.
2. Participants with autism and controls were 8-14 years of age.
3. Amygdala volume changes with time were similar between the two groups.
4. Amygdala volume change correlated with the ability to establish eye contact.
5. Hippocampal volume change with time between the groups approached significance.

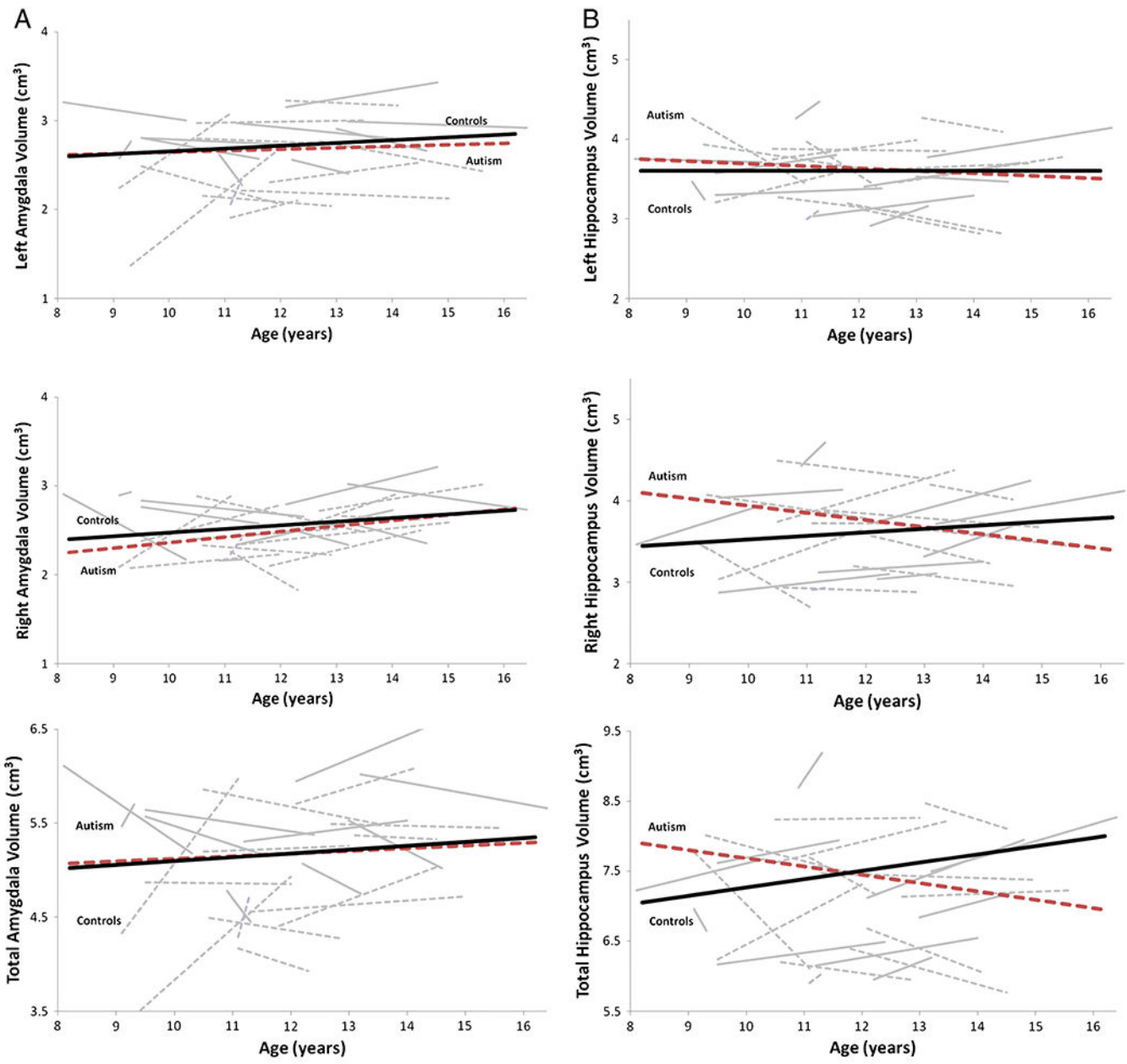

Figure 1.

A: Left, right, and total amygdala volumes across ages 8-16 for both autism and healthy control groups, individual volume change between the two time points as well as the general trajectories are shown (solid lines – controls, dashed lines – autism).

B: Left, right, and total hippocampal volumes across ages 8-16 for both autism and healthy control groups, individual volume change between the two time points as well as the general trajectories are shown (solid lines – controls, dashed lines – autism).

Table 1:

Demographic and clinical characteristics of participants with autism and healthy controls.

	Autism	Healthy Controls	
	M (SD)	M (SD)	t (p)
N	15	22	
Age at Time 1 (Antenor-Dorsey et al.)	10.6 (8-12)	10.6 (7-13)	0.05 (.959)
Age at Time 2 (Antenor-Dorsey, Hershey et al.)	13.1 (11-15)	12.5 (9-16)	1.05 (.304)
Δ in age: (years)	2.2 (0.7)	1.9 (1.0)	0.70 (.437)
SES	4.5 (0.6)	4.5 (0.5)	0.06 (.949)
FSIQ	98.1 (20.1)	117.3 (12.3)	−3.61 (<.001)
SRS – Total T-score	84.1 (8.4)	41.6 (3.4)	17.19 (<.001)
ADI-R Total	52.0 (7.1)		
ADOS Total	15.4 (2.9)		

Note. SES=Socioeconomic status, FSIQ=full scale intelligence quotient, SRS-Total T-score=Social Responsiveness Scale Total age-adjusted T-score. Δ in age: Change in age between follow-up and baseline in years. DF=35, except Δ Time 2-Time 1 DF=29, Age at Time 2 DF=29, and SRS Total T-score DF=28.

Table 2:

Amygdala and Hippocampus volumes (cm^3) at baseline and 2-year follow-up.

	Baseline				2-Year Follow-Up						
	Autism		Controls		Autism		Controls		*Age*	*Diagnosis*	*Age X Diagnosis*
	M	SD	M	SD	M	SD	M	SD	Cohen's d	Cohen's d	
Total Amygdala	5.07	.32	5.11	.28	5.19	.31	5.19	.33	.41	.21	.18
Left Amygdala	2.65	.23	2.66	.20	2.70	.23	2.72	.23	.35	.25	.24
Right Amygdala	2.43	.12	2.44	.10	2.49	.10	2.47	.11	.29	.07	.03
Total Hippocampus	7.33	.43	6.99	.33	7.17	.49	7.05	.37	.01	.49	.40
Left Hippocampus	3.58	.16	3.47	.12	3.51	.18	3.47	.12	.10	.26	.20
Right Hippocampus	3.76	.28	3.66	.32	3.52	.22	3.58	.25	.10	.61*	.53^

^ p<.10,

* p<.05.

Positive effect sizes (d) indicate increasing volume with age (Age), lower volume in the autism group (Diagnosis), and larger increases in volume with age in the autism group relative to the controls (Age X Diagnosis). Means and SDs are estimated from mixed effects regression models and therefore totals are not a simple sum of left and right values.

Table 3:

Correlations between clinical measures of social behavior and changes in amygdala and hippocampal volumes.

	Amygdala		Hippocampus	
	Left	**Right**	**Left**	**Right**
ADI-R Total Social Interaction Raw Score	.39	.15	−.34	.05
ADOS Total Social Raw Score	.12	−.20	.27	.65
SRS Total T-Score	−.54	−.51	.05	.53
SRS Item 16 – eye contact	−.07	−.86*	−.02	.62

*p<.01