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No evidence for preferential involvement of medial temporal lobe structures in high-functioning autism

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ABSTRACT

Background. Autism is a neurodevelopmental disorder associated with slight increases in brain volume. There has been some suggestion that medial temporal lobe structures may be preferentially involved in this disorder, although results have not always been consistent. Here, we investigate amygdala and hippocampus volumes in medication-naive subjects with high-functioning autism.

Method. Whole-brain magnetic resonance imaging scans were acquired from 42 patients and 42 closely matched, healthy control subjects.

Results. Amygdala volume did not differ significantly between patients and controls. A significant increase in hippocampal volume was proportional to an increase in overall brain volume.

Conclusions. These results argue against preferential involvement of medial temporal lobe structures in autism, at least in high-functioning medication-naive individuals.

INTRODUCTION

Autism is a neurodevelopmental disorder defined by the presence of marked social deficits, specific language abnormalities, and stereotyped, repetitive behaviors (APA, 1994). The amygdala has been implicated in the etiology of autism (Damasio & Maurer, 1978), as it plays an important role in the mediation of social behavior (Brothers *et al*. 1990), face processing (Grelotti *et al*. 2002) and recognition of emotions (Adolphs, 2002), all processes which are deficient in autism.

Although some animal studies showed autistic-like behavior in rats and monkeys in which the amygdala was lesioned (Bachevalier, 1994; Wolterink *et al*. 2001; Daenen *et al*. 2002), this has recently been seriously questioned (Amaral *et al*. 2003). Neuropathological studies have reported abnormally small and densely packed cells in the amygdala of autistic subjects (Kemper & Bauman, 1993), although they were confounded by epilepsy (Amaral *et al*. 2003). Results from functional studies have been inconsistent, as although most studies report less or no activation in the amygdala of autistic subjects during facial recognition tasks (Baron-Cohen *et al*. 1999; Critchley *et al*. 2000; Pierce *et al*. 2001), Pierce and colleagues recently reported normal amygdala activation in response to familiar faces (Pierce *et al*. 2004). Volumetric studies have reported increases (Filipek *et al*. 1992; Abell *et al*. 1999; Howard *et al*. 2000; Sparks *et al*. 2002), decreases (Aylward *et al*. 1999; Pierce *et al*. 2001; Herbert *et al*. 2003), and no change in amygdala volume for autistic subjects compared with controls (Haznedar *et al*. 2000; Bigler *et al*. 2003) (see Table 1). More recently, Schumann and colleagues reported increased amygdala volume in high- and low-functioning children with autism, but not in adolescents (Schumann *et al*. 2004). Overall, this evidence suggests that, at least in a subgroup of autistic subjects, amygdalar

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pathology may contribute to the symptomatology of autism, although the evidence for structural abnormalities is less convincing than that for functional changes.

The hippocampus is involved in memory function in humans (Burgess *et al*. 2002), as well as in novelty processing (Strange & Dolan, 1999), and stress regulation (Hoschl & Hajek, 2001). As such, it has been suggested to integrate inputs from the senses, memory, and motivational stimuli (DeLong, 1992). On the one hand autistic subjects are known to have excellent root memory functions (Kanner, 1943; Caron *et al*. 2004). On the other hand, however, autistic subjects have difficulty dealing with complex stimuli (Burke & Cerniglia, 1990). Therefore, the hippocampus has been hypothesized to be abnormal in autism (DeLong, 1992). However, to date the literature does not confirm hippocampal involvement in autism symptomatology. Although earlier animal studies suggested hippocampal involvement in autistic-like behavior (Hirsh, 1970), more recent rat studies fail to show this effect (Wolterink *et al*. 2001; Daenen *et al*. 2002).

Neuropathological studies have reported the same pathology in the hippocampus as was found in the amygdala (Kemper & Bauman, 1993; Raymond *et al*. 1996), although not consistently (Bailey *et al*. 1998). Both decreased (Aylward *et al*. 1999; Saitoh *et al*. 2001; Herbert *et al*. 2003) and increased (Sparks *et al*. 2002; Schumann *et al*. 2004) hippocampal volumes have been reported. The majority of studies, however, failed to find significant differences in hippocampal volume between autistic and control subjects (Filipek *et al*. 1992; Saitoh *et al*. 1995; Piven *et al*. 1998; Haznedar *et al*. 2000; Howard *et al*. 2000; Bigler *et al*. 2003) (see Table 1). In sum, the evidence for hippocampal involvement in the pathology of autism is inconclusive.

Here, we investigate amygdala and hippocampus volumes in medication-naive children and adolescents with high-functioning autism and Asperger's syndrome. Although previous studies either did not mention medication status of the autistic subjects or chose to include subjects who had been on medication but were not using medication at the time of the study, we believed it to be important to include medication-naive subjects only. Indeed, it is known from the literature that the use of (neuroleptic) medication is correlated to the size of various brain structures (Gur *et al*. 1998).

Previously, we showed increased brain volumes in these subjects (Palmen *et al*. 2004, 2005). In the current study, we investigate whether medio-temporal lobe structures are increased as well in these subjects and, if so, whether the enlargement is proportional or disproportional to the overall brain enlargement.

METHOD

Subjects

Forty-two medication-naive, high-functioning children and adolescents meeting DSM-IV criteria for autism or Asperger's syndrome (APA, 1994) were included in the present study. Clinical diagnosis was confirmed by parent interview for all participants using the ADI-R (Autism Diagnostic Interview – Revised; Lord *et al*. 1994). The control group consisted of 42 typically developing children and adolescents matched for age, gender, IQ, height, weight, handedness, and parental education (Palmen *et al*. 2004, 2005). All subjects were aged between 7 and 25 years. Written informed consent was obtained for all subjects after the procedures had been fully explained, as approved by the Institutional Review Board at the University Medical Center Utrecht. Subjects with first-degree relatives with a psychiatric disorder, a major medical or neurological illness, including epilepsy, alcohol or other drug dependence, head trauma in the past, or full IQ below 80 were excluded. All subjects participated in a magnetic resonance imaging (MRI) scanning session, and a neuropsychological assessment in order to estimate full-scale IQ (see Table 2 for demographics).

MRI acquisition and procedures

Magnetic resonance images were acquired on a Philips NT scanner operating at 1.5 T (Philips Medical Systems, Best, The Netherlands). For volumetric analysis, T1-weighted 3D fast-field echo scans were acquired with either 1·2 or 1·5 mm contiguous coronal slices of the whole head (TE 4·6 ms, TR 30 ms, flip angle 30°, FOV 256 mm, in plane voxel size 1 mm × 1 mm) as well as T2-weighted dual echo turbo-spin echo scans with 1·5 or 3·0 mm contiguous coronal

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Table 1. *Articles on volumes of amygdala and hippocampus in autism*

Author, year, journal	Structure	Subjects	Matching factors	Results	TBV correction
Schumann *et al.* (2004) *J. Neurosci.*	AMY HIP	27HFA 19LFA 25AS 27C	All male	↑ AMY only <12·5 yr; ↑ HIP at all ages	Correction for TBV did not alter the results
Bigler *et al.* (2003) *AJNR*	AMY HIP	12A, 12·8 yr, MC 26A, 14·2 yr, no MC 8C, 12·5 yr, MC 19C, 12·5 yr, no MC 17RD, 12·7 yr	Age, all male	No differences when presence of MC was taken into account	After correction for IC, effects were no longer significant
Herbert *et al.* (2003) *Brain*	AMY-HIP complex	15A, 7–11 yr 17C, 7–11 yr	All male	No differences	After correction for TBV ↓ AMY-HIP
Sparks *et al.* (2002) *Neurology*	AMY HIP	45ASD, 38 m, 4 yr 14DD, 6 m, 4 yr 26C, 18 m, 4 yr	Age	↑ AMY and HIP	After correction for TBV effects were no longer significant, except for ↑ AMY in Kanner autism
Pierce *et al.* (2001) *Brain*	AMY	7A, 29·5 yr 8C, 28·3 yr	Age, all male, handedness	↓ AMY	No
Saitoh *et al.* (2001) *Brain*	HIP 3 slices	59A, 52 m, 11·2 yr 51C, 40 m, 11·4 yr	Not mentioned	Especially in the very young ↓ AD (part of HIP)	Correction for TBV did not alter the results
Haznedar *et al.* (2000) *AJP*	AMY HIP	17A, 15 m, 27·7 yr 17C, 15 m, 28·8 yr	Not mentioned	No differences	Correction for TBV did not alter the results
Howard *et al.* (2000) *NeuroReport*	AMY HIP	10A, 16–40 yr 10 C, ? yr	Age, all male, VIQ	↑ AMY and trend towards ↓ HIP	No
Abell *et al.* (1999) *NeuroReport*	AMY	15A, 12 m, 28·8 yr 15C, 12 m, 25·3 yr	Age, gender, IQ, handedness	↑ GM density in AMY/ peri-AMY cortex	No
Aylward *et al.* (1999) *Neurology*	AMY HIP	14A, 20·5 yr 14C, 20·3 yr	Age, all male, IQ, race	↓ AMY = HIP	After correction for TBV ↓ AMY and ↓ HIP
Piven *et al.* (1998) *JADD*	HIP	35 A, 26 m, 18·0 yr 36 C, 20 m, 20·2 yr	Not mentioned	No difference	Correction for TBV (or gender or IQ) did not alter the results
Saitoh *et al.* (1995) *Neurology*	HIP Cross-sectional	33 A, 30 m, 13·8 yr 23 C, 19 m, 13·3 yr	Age	No differences	No
Filipek *et al.* (1992) *Ann. Neurol.*	AMY HIP	9 HFA, ? m, 6–10 yr 13 LFA, ? m, 6–10 yr 10 MR, ? m, 6–10 yr 24 C, ? m, 9·2 yr	Not mentioned	AMY: HFA > LFA > C HIP: no differences	No

AMY, Amygdala; HIP, hippocampus; AD, area dentata of the hippocampus; HFA, high-functioning autism; LFA, low-functioning autism; AS, Asperger syndrome; C, controls; ↑, larger in autism compared with controls; TBV, total brain volume; MC, macrocephaly; RD, reading disorder; IC, intracranium; ↓, smaller in autism compared with controls; ASD, autism spectrum disorder; DD, developmental delay; m, male; ?, unknown; =, no difference between autistic subjects and controls; VIQ, verbal IQ; GM, grey matter; MR, mental retardation.

AJNR, *American Journal of Neuroradiology*; AJP, *American Journal of Psychiatry*; JADD, *Journal of Autism and Developmental Disorders*.

Table 2. *Demographic data*

	Autistic subjects	Healthy controls
Participants (male/females), *n*	40/2	41/1
Age, mean ± S.D. (range), years	15·60 ± 5·25 (6·9–24·7)	15·33 ± 5·40 (7·3–24·8)
Total IQ, mean ± S.D.	114·90 ± 19·18	112·62 ± 10·20
Verbal IQ, mean ± S.D.	112·90 ± 19·64	107·62 ± 9·89
Performance IQ, mean ± S.D.	114·00 ± 16·22	116·95 ± 11·53
Height, mean ± S.D., cm	164·90 ± 20·81	164·21 ± 20·93
Weight, mean ± S.D., kg	54·48 ± 20·02	57·79 ± 20·32
Handedness (right/left), *n*	39/3	36/6
ADI: social deficits	18·00 ± 5·47	
ADI: abnormalities in communication	14·45 ± 4·39	
ADI: ritualistic-repetitive behavior	4·12 ± 2·46	

ADI, Autism Diagnostic Interview.
None of the demographic variables differed significantly between the autistic subjects and the healthy controls.

slices (TE1 14 ms, TE2 80 ms, TR 6350 ms, flip angle 90°, FOV 256 mm, in plane voxel size 1 mm × 1 mm). Processing was carried out on the neuroimaging computer network of the Department of Psychiatry. As previously reported, semi-automated, histogram-based algorithms were used to estimate intracranial, total brain, ventricle, cerebellar, and gray and white matter volume (Palmen *et al*. 2004, 2005). Ten subjects were scanned using both scanning protocols. The reliability for volume estimates between scanners was determined using intraclass correlation coefficients (ICCs), and was 0·90 or higher. The amygdala and the hippocampus were manually traced by a single experienced rater (H.N.) in contiguous coronal slices from anterior to posterior. The sagittal and axial planes were used for reference. Amygdala segmentation commenced in the first slice where the structure was discernible after the anterior commissure no longer appeared as a continuous tract. The lateral border was defined by the surrounding white matter and the inferior horn of the lateral ventricle. Posteriorly, the amygdala was bordered by the hippocampus. The medial border was formed by the cerebrospinal fluid, excluding the entorhinal cortex. The superior border was formed by a straight line from the supero-lateral aspect of the optic tract to the most infero-medial point of the inferior portion of the circular sulcus. Hippocampus segmentation commenced in the slice in which the mammillary bodies first exhibit their characteristic round shape. The posterior border was the slice before the slice in which the fornix forms a continuous tract for the first time. Superiorly, the hippocampus was bordered by the inferior horn of the lateral ventricle. The inferior border was the white matter (Baaré *et al*. 2001). ICCs were 0·83 for left amygdala, 0·84 for right amygdala, 0·86 for left hippocampus and 0·91 for right hippocampus.

Statistical analyses

SPSS 9.0 statistical package for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All clinical data and brain volume measures were normally distributed.

To examine whether absolute amygdala and hippocampal volumes differed between the autistic subjects and the healthy controls, independent sample *t* tests were performed with amygdala and hippocampal volumes as dependent variables. Analyses were repeated with intracranial and total brain volume separately as covariates to investigate whether volumetric differences in amygdala and hippocampal volume were proportional to increases in those volumes. In the patient group, there was one outlier in the volume of the amygdala. Therefore, data were analyzed both with and without this subject to determine if this volume contributed disproportionately to the results.

To investigate whether developmental trajectories differed between subjects with autism and controls, linear regressions were performed with amygdala and hippocampal volumes as dependent variables and age and diagnosis as independent factors.

Finally, to investigate whether medial temporal lobe volumes were significantly correlated to social behavior, Pearson's correlations with the social impairment subscale of the ADI were

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Table 3. *Volumes (ml) of intracranium, cerebrum, and limbic structures of 42 autistic subjects and 42 healthy comparison subjects*

	Autistic subjects ($n=42$) Mean ± S.D.	Healthy controls ($n=42$) Mean ± S.D.	t (df = 1,82)	p
Intracranium	1553·10 ± 109·49	1484·96 ± 78·80	3·27	0·002*
Total brain	1408·36 ± 99·32	1345·59 ± 78·77	3·21	0·002*
Total amygdala	2·82 ± 0·56	2·82 ± 0·50	−0·14	0·99
Left amygdala	1·32 ± 0·38	1·29 ± 0·30	0·34	0·74
Right amygdala	1·51 ± 0·27	1·53 ± 0·29	−0·43	0·67
Total hippocampus	6·87 ± 0·93	6·46 ± 0·75	2·21	0·03*
Left hippocampus	3·49 ± 0·49	3·29 ± 0·42	2·04	0·04*
Right hippocampus	3·38 ± 0·48	3·17 ± 0·42	2·08	0·04*

* p significant difference between autistic subjects and healthy controls ($p \leqslant 0{\cdot}05$).

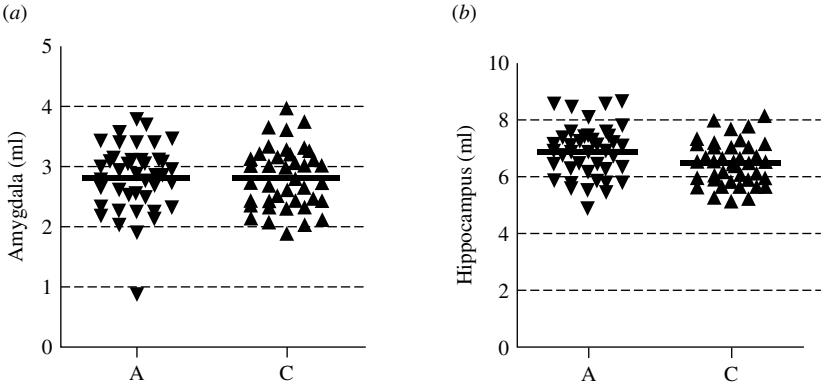


FIG. 1. Scatterplots of volumes of the (*a*) amygdala and (*b*) hippocampus in 42 autistic subjects (A) and 42 healthy controls (C).

calculated for both amygdala and hippocampal volume.

RESULTS

Mean (±S.D.) amygdala volume was 2·82 (±0·56) for the autistic subjects and 2·82 (±0·50) for the controls. Mean hippocampal volume was 6·87 (±0·93) for the autistic subjects and 6·46 (±0·75) for the control subjects (see also Table 3 and Fig. 1). Significant lateralization effects were not found for amygdala or hippocampus volume.

No significant differences in amygdala volumes were found between autistic and control subjects ($t=-0{\cdot}01$, $p=0{\cdot}99$). Exclusion of the outlier did not alter the results significantly ($t=0{\cdot}43$, $p=0{\cdot}67$). Absolute hippocampus volumes were significantly enlarged in the autistic subjects compared with the controls ($t=2{\cdot}21$, $p=0{\cdot}03$ for total hippocampal volume; $t=2{\cdot}04$, $p=0{\cdot}04$ for left hippocampus; $t=2{\cdot}08$, $p=0{\cdot}04$ for right hippocampus), although these findings were no longer significant after covarying for either intracranial or total brain volume.

No significant correlations were found in the autism sample between scores on the social impairment subscale of the ADI and either amygdala ($r=0{\cdot}13$, $p=0{\cdot}40$) or hippocampal ($r=0{\cdot}01$, $p=0{\cdot}94$) volume.

Finally, as our patient sample consisted of both subjects with high-functioning autism ($n=21$) and subjects with Asperger's syndrome ($n=21$), a t test was performed with diagnosis (high-functioning autism *versus* Asperger's syndrome) as independent variable and intracranium, total brain, amygdala and hippocampus volume as dependent variables in order to investigate whether these diagnoses contributed differentially to the results. None of the volumes differed significantly between high-functioning autism and Asperger's syndrome

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(intracranium: $t=0{\cdot}52$, $p=0{\cdot}61$, total brain: $t=0{\cdot}84$, $p=0{\cdot}41$, amygdala: $t=0{\cdot}39$, $p=0{\cdot}70$ and hippocampus: $t=1{\cdot}04$, $p=0{\cdot}30$).

DISCUSSION

This cross-sectional study compared the volumes of medio-temporal lobe structures in 42 medication-naive, high-functioning children and adolescents with autism and 42 matched control subjects. Volume of the amygdala did not differ significantly between patients and controls. Although there was an absolute increase in hippocampus volume, this increase was no longer present once brain size was controlled for. Age did not have a differential impact on the developmental trajectories of the investigated structures.

The present study demonstrates that volumes of the medial-temporal lobe structures in autistic subjects are generally proportional to intracranial and total brain volume.

Several factors may have contributed to the equivocal findings in the literature. First, in some studies, brain size was not controlled for (Howard *et al.* 2000; Pierce *et al.* 2001), or differences were no longer present once brain size was controlled for (Sparks *et al.* 2002) (see Table 1). Secondly, small samples may have been composed of mixed populations (high-functioning and/or low-functioning subjects; with and/or without seizures) and finally, the procedures for segmenting the amygdala (Brierley *et al.* 2002) and the hippocampus (Geuze *et al.* 2005) varied between studies.

Although both hippocampus and amygdala were not enlarged relative to total brain volume in this study, an absolute increase in volume did reach significance for the hippocampus but not for the amygdala. This is most likely related to a relatively larger variance in amygdala than hippocampus volume. However, we cannot preclude that this difference might reflect differential processes between the two structures. As such, amygdala pathology might not be a characteristic of autism proper, but might contribute to co-morbid anxiety in autism, as was recently suggested (Amaral *et al.* 2003). Furthermore, the absence of differences in bulk volume of medial temporal lobe structures does not exclude the possibility of abnormalities at a cellular level. Indeed, increased cell packing density and smaller neurons have been reported in the limbic system of autistic subjects (Kemper & Bauman, 1993). Similarly, these data do not exclude the possibility of functional impairments in autism. Indeed, recently it was suggested that involvement of the amygdala in the symptomatology of autism might be due to abnormalities in its interconnections with surrounding cortical tissue rather than to any morphological abnormality in the amygdala proper (Kwon *et al.* 2004).

Limitations

The limitations of this study should be taken into consideration when interpreting its findings. First, this study was restricted to high-functioning subjects with autism. Thus, results may not be representative of mentally retarded subjects, about 75% of all autistic individuals. Furthermore, this study is cross-sectional. The interindividual variation in brain morphometry is huge, probably many times larger than developmental changes within an individual (Caviness *et al.* 1996). Therefore, findings relating to changes over time need to be interpreted with caution, until they can be replicated in longitudinal samples.

CONCLUSION

Once head size was controlled for, autistic subjects and controls showed no significant differences in amygdala and hippocampus volume. Thus, volumetric changes in medial-temporal lobe structures in high-functioning autistic subjects are proportional to changes in intracranial and total brain volumes.

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DECLARATION OF INTEREST

None.

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