Available online at www.sciencedirect.com
SCIENCE DIRECT®
Psychiatry Research: Neuroimaging xx (2006) xxx–xxx
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Detection and mapping of hippocampal abnormalities in autism

Rob Nicolson[a,*], Timothy J. DeVito[b], Christine N. Vidal[c], Yihong Sui[c], Kiralee M. Hayashi[c], Dick J. Drost[b], Peter C. Williamson[a], Nagalingam Rajakumar[a], Arthur W. Toga[c], Paul M. Thompson[c]

[a]*Department of Psychiatry, The University of Western Ontario, London, Ontario, Canada*
[b]*Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada*
[c]*Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, United States*

Received 7 September 2005; received in revised form 2 February 2006; accepted 13 February 2006

Abstract

Brain imaging studies of the hippocampus in autism have yielded inconsistent results. In this study, a computational mapping strategy was used to examine the three-dimensional profile of hippocampal abnormalities in a group of males with autism. Twenty-one males with autism (age: 9.5±3.3 years) and 24 male controls (age: 10.3±2.4 years) underwent a volumetric magnetic resonance imaging scan at 3-Tesla. The hippocampus was delineated, using an anatomical protocol, and hippocampal volumes were compared between the two groups. Hippocampal traces were also converted into three-dimensional parametric surface meshes, and statistical brain maps were created to visualize morphological differences in the shape and thickness of the hippocampus between groups. Parametric surface meshes and shape analysis revealed subtle differences between patients and controls, particularly in the right posterior hippocampus. These deficits were significant even though the groups did not differ significantly for traditional measures of hippocampal volume. These results suggest that autism may be associated with subtle regional reductions in the size of the hippocampus. The increased statistical and spatial power of computational mapping methods provided the ability to detect these differences which were not found with traditional volumetric methods.

Keywords: Autism; Hippocampus; MRI

1. Introduction

Autism is a severe developmental disorder characterized by social deficits, impaired communication, and restricted and repetitive behavior patterns (American Psychiatric Association, 2000). There is strong evidence that autism is associated with abnormal brain development, but the anatomical extent of these neurobiological abnormalities is unknown (Nicolson and Szatmari, 2003).

Abnormalities of the hippocampus and related limbic structures have been hypothesized to be relevant to the pathophysiology of autism because of their role in learning, social functioning, and emotion, functions that are typically disturbed in autism (Bauman and Kemper, 1985; DeLong, 1992; Bachevalier, 1994). One postmortem study reported that patients with autism had small, densely packed neurons in the CA1 through CA4 hippocampal fields and the subiculum as well as reduced complexity and extent of dendritic arborization in the CA1 and CA4 fields

* Corresponding author. London Health Sciences Centre, 800 Commissioners Road East, E2-601, London, Ontario, Canada N6C-2V5. Tel.: +1 519 685 8427; fax: +1 519 685 8595.
E-mail address: Rnicolso@uwo.ca (R. Nicolson).

0925-4927/$ - see front matter © 2006 Published by Elsevier Ireland Ltd.
doi:10.1016/j.pscychresns.2006.02.005

(Bauman and Kemper, 1985; Raymond et al., 1996). However, other histopathological studies have failed to find similar hippocampal abnormalities (Bailey et al., 1998).

To date, anatomic studies of the hippocampus in autism using magnetic resonance imaging (MRI) have yielded inconsistent results. Five studies have found no difference in size of the hippocampus between patients and controls (Saitoh et al., 1995; Piven et al., 1998; Haznedar et al., 2000; Howard et al., 2000; Bigler et al., 2003). Others reported a reduction in the ratio of hippocampal volume to total brain volume among patients with autism (Aylward et al., 1999), while still others have reported increased hippocampal size in the disorder (Sparks et al., 2002; Rojas et al., 2004; Schumann et al., 2004).

While factors related to subject selection may have contributed to this inconsistency, the neuroanatomic definition of the hippocampus may have also played a role. Previous studies have all assessed the hippocampus in autism using traditional volumetric methods, which can be insensitive to anatomical shape variability and unlikely to identify subtle regional differences in anatomy between groups. Recently, however, computational mapping methods have been developed to examine hippocampal structure. Unlike traditional volumetric methods, the use of surface mesh models and statistical maps permits the examination of highly localized group differences in hippocampal morphology while preserving subtle variability patterns within groups (Thompson et al., 2004a,b). Although this approach is complementary to voxel-based methods that assess differences in tissue types at each voxel of stereotaxic space, the shape-modeling approach works by averaging the geometry of the anatomical models rather than comparing segmented images. These computational methods have detected regional alterations of hippocampal morphology in conditions such as schizophrenia and depression, even in the absence of significant volume reductions (Csernansky et al., 2002; Posener et al., 2003; Narr et al., 2004).

The purpose of this study was to use computational mapping methods to detect and visualize hippocampal abnormalities in autism. We hypothesized that patients with autism would have localized hippocampal abnormalities, although the direction of the abnormalities (excess or atrophy) was not predicted in advance.

2. Methods

2.1. Subjects

Twenty-one males with autism between the ages of 6 and 16 participated in this study. The diagnosis of autism was made using the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), the Autism Diagnostic Observation Schedule (ADOS-G; Lord et al., 2000), and clinical observation. On the ADOS-G, one patient was assessed with module 1, three patients with module 2, 10 patients with module 3, and 7 patients with module 4. All patients met DSM-IV-TR criteria for autism (American Psychiatric Association, 2000) as well as ADI-R and ADOS-G algorithm criteria. Patients were also assessed using the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III) or the Leiter International Performance Scale. Exclusionary criteria for patients included a non-verbal IQ below 70 or a seizure disorder or any other neurological condition. All patients had a physical examination prior to participation in this study, including height, weight, and head circumference (defined as the maximal frontal–occipital circumference). Handedness was determined through clinical observation and the report of the patients and their parents. At the time of the scan, nine patients were being treated with psychotropic medication: six were taking stimulants, five were receiving dopamine antagonists, two were taking SSRIs, and one being treated with a cholinesterase inhibitor. Among the 12 patients who were not taking medications at the time of the study, seven were medication-naïve, four had discontinued their previous medications at least four weeks prior to the scan, and one subject being treated with a stimulant had discontinued it one week before his scan.

Twenty-four males between the ages of 6 and 16, drawn from the local community through advertisement and word of mouth, participated as control subjects. They were assessed with the Schedule for Affective Disorders and Schizophrenia-Childhood Version (Kaufman et al., 1997) to ensure that none had an axis I psychiatric disorder. Additionally, none had a personal history of neurological disorders or a family history of autism or mental retardation. Control subjects were also assessed with the WISC-III or the Wechsler Abbreviated Scale of Intelligence, and a full-scale IQ of less than 70 was exclusionary. Head circumference and handedness were determined in control subjects using the same method as in the patients.

This study was approved by the local Research Ethics Board. The parents or legal guardians of all subjects provided written consent for participation in this study, while the subjects provided written assent.

2.2. Magnetic resonance imaging

All subjects were scanned on a 3.0-Tesla head-only scanner (IMRIS, Winnipeg, Canada) with a quadrature head coil. All patient scans and the majority of control

subject scans were acquired during the evening. To facilitate completion of their scans, 14 patients with autism received sedation with oral midazolam.

Standard T1-weighted localizer images were acquired initially. Images used for volumetric analysis were then acquired using a T1-weighted 3-D MP-RAGE (Magnetization Prepared Rapid Gradient Echo) sequence (TI = 200 ms, TR = 11 ms, TE = 5 ms, flip-angle = 12°, Field of View = 24 cm, total scan time: 8 min) with 1.2-mm isotropic voxels.

2.3. Image processing and analysis

Each brain volume was corrected for radio frequency field inhomogeneities (Sled et al., 1998) and resliced into a standard orientation. Twenty standard anatomical landmarks were identified by a trained operator (C.V.) in all three planes and matched with a set of corresponding point locations defined on the ICBM53 stereotaxic brain template (Mazziotta et al., 2001). As in previous studies (e.g., Thompson et al., 2004a), these landmarks were used to compute a three-translation and three-rotation rigid-body linear transformation for each brain volume to align it to the standardized coordinate system of the ICBM53 average brain. Each brain volume was reoriented to correct for head alignment and resampled to 1.0 mm isotropic voxels using trilinear interpolation and a 6-parameter Procrustes fit. In addition, a second set of analyses were performed to adjust the data for overall differences in brain scale. To do this, each brain was uniformly scaled into the ICBM53 stereotaxic space using a 9-parameter linear transformation, allowing the brain to be scaled to match the standardized average brain template.

2.4. Hippocampal modeling

The hippocampi were digitized bilaterally by a single individual blind to subject data and hemisphere (data were randomly flipped in the midsagittal plane to avoid any possible bias). Anatomical segmentation was performed according to criteria adapted from the detailed protocol of Pantel et al. (2000), using a standard neuroanatomical atlas of the hippocampus (Duvernoy and Bourgouin, 1998). One rater (Y.S.) blind to group status traced the gray/white or gray/CSF interfaces separating the hippocampi from surrounding anatomy using interactive segmentation software (Woods, 2003). Boundaries were traced on the rigidly re-aligned gray scale brain volumes. The hippocampi were traced in coronal brain slices from anterior to posterior and the digitized surface contours were displayed simultaneously in all three viewing planes to facilitate the accurate identification of neuroanatomic boundaries, particularly that between the hippocampus and amygdala (see Fig. 1a). Contours were drawn on images magnified four-fold to allow subvoxel precision and faithful tracking of small-scale features. Hippocampal tracing in each hemisphere began at the indentation of the hippocampal sulcus, or when not visible, at the most medial point of the hippocampus in the coronal plane. The alveus was used as the superior boundary and the white matter of the parahippocampal gyrus as the inferior boundary. The inferior temporal horn of the lateral ventricle was used as the lateral boundary and the ambient cistern as the medial boundary. The subiculum was included in hippocampal tracings. As suggested by Pantel et al. (2000), the use of all three planes was critical to separating the hippocampus from the amygdala. The alveus, as viewed in three dimensions, was used as the border between the hippocampus and the amygdala anteriorly. The alveus itself was excluded from the measurement. In mid-anterior hippocampal regions, the invagination of the hippocampal sulcus was followed. Hippocampal outlines were continued posteriorly until hippocampal gray matter formed an oval mass medial to the atrium of the lateral ventricles, but excluded the subsplenial gyrus. Volumes were obtained from the hippocampal surface tracings for use as dependent measures in statistical analyses. This method has previously shown high inter- and intra-rater reliability for hippocampal measurements (Thompson et al., 2004a).

2.5. Anatomical surface averaging

Anatomical mesh modeling methods were used to match equivalent hippocampal surface points, obtained from manual tracings, across subjects and groups. To match the digitized points representing the hippocampal surface traces in each brain volume, the manually derived contours were made spatially uniform by modeling them as a three-dimensional parametric surface mesh (see Fig. 1). These three-dimensional parametric surface models are indexed using two-dimensional parameter space. The anatomical mesh modeling procedures allow the averaging of hippocampal surface morphology across all individuals belonging to a group and the recording of the amount of three-dimensional variation among homologous surface points relative to the group averages.

2.6. Surface distance mapping

The three-dimensional parametric mesh models of each individual's hippocampi were analyzed to estimate the regional specificity of hippocampal volume changes in autism. A "medial curve" was defined along the

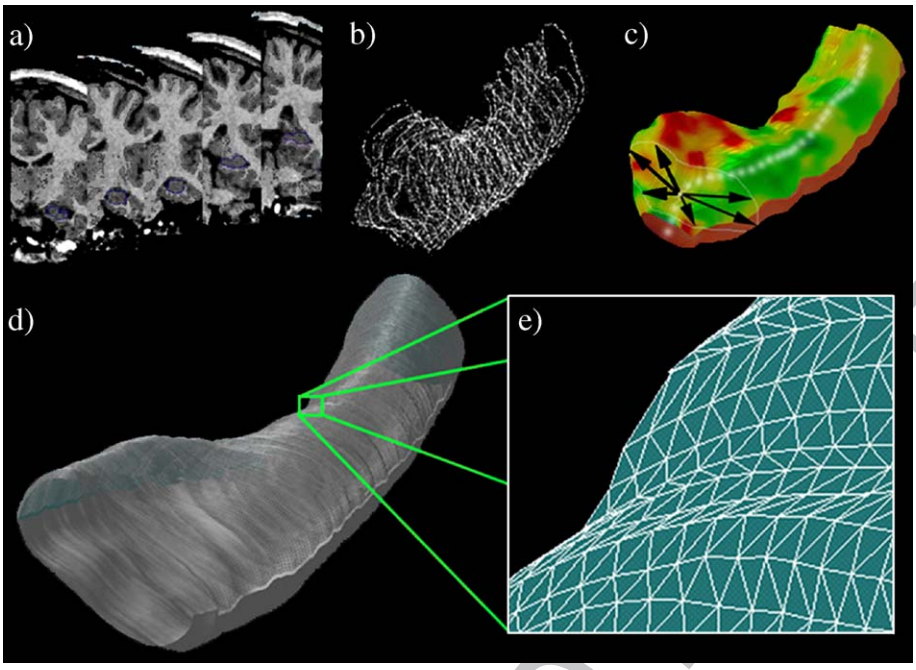

Fig. 1. Hippocampal surface modeling. Each individual's hippocampus is traced in coronal MRI sections (a) and converted to a mesh surface representation (b and c) in which the radial size of the hippocampus is measured from a centerline and plotted in color on the surface to index radial atrophy. Arrows in (c) represent vectors from the centerline to various points on the hippocampal surface. These meshes are averaged across subjects (d), and atrophy or expansion relative to the control mean is computed at each surface point (e).

anterior–posterior axis of the hippocampus in stereotaxic coordinate space and the radial size of each hippocampus at each boundary point was assessed by measuring the radial distances from homologous hippocampal surface points to the central core of the individual's hippocampal surface model (Fig. 1c) (Narr et al., 2004; Thompson et al., 2004a). Since radial distances from the medial core to the surface boundary are measured at thousands of points along the surface, the resulting radial distance maps detect nonuniform volumetric changes on a very local scale and may be compared statistically between groups at equivalent hippocampal surface points.

2.7. Statistical analysis

Age, race, handedness, height, head circumference, the scaling factor needed to transform each brain volume into stereotaxic space, and intelligence quotient (verbal, non-verbal, and full-scale) were compared using *t*-tests or chi-square analyses.

Thickness measures improve the localization of deficits but may be less sensitive to differences in the length of the hippocampus. Traditional volumetric measures may thus be more sensitive than thickness maps for detecting group differences in some instances, while thickness maps may be more sensitive in others. Therefore, we used both traditional volumetric methods and statistical maps in order to compare the ability of both methods to detect hippocampal abnormalities among patients with autism.

Right and left hippocampal volumes measured using traditional volumetric methods were compared between groups using Analysis of Variance, with group as the between subjects factor. This analysis was applied to both the raw and scaled hippocampal volumes (i.e., both before and after controlling for group differences in brain size through scaling; see section on brain size correction below).

To evaluate regional differences in hippocampal volume as indexed by measures of hippocampal radial distance, Student's *t*-tests were performed at equivalent locations on the hippocampal surface maps. Uncorrected *t* values and their corresponding two-tailed probability values were mapped onto the averaged hippocampal surface models of the entire group and displayed in three dimensions in scaled and raw space.

For tests of overall volume differences and for statistical mapping of surface-based measures, a two-tailed alpha level of $P<0.05$ was used as the significance threshold. However, for statistical mapping, comparisons were made at thousands of hippocampal surface points. Permutation

testing was therefore used to confirm the overall significance of the statistical mapping results, adjusting for multiple comparisons. This accounts for the spatial autocorrelation of the residuals of the statistical model while adjusting for the multiple comparisons implicit in conducting multiple statistical tests at each point on a surface (Nichols and Holmes, 2002). Using a threshold of $P<0.05$, uncorrected, the number of significant results between patients with autism and the control subjects in the actual data was compared to the number of significant results produced during the permutation testing to produce a corrected overall significance value for each map (Thompson et al., 2004c).

2.8. Brain size correction

For statistical mapping of hippocampal surface parameters, image volumes and the hippocampal contours were mapped into stereotaxic space, adjusting for differences in brain size. However, uncertainty exists as to whether or not brain size corrections increase or decrease error variance for region of interest comparisons (Arndt et al., 1991; Mathalon et al., 1993). To allow for either possibility, we built the same anatomical maps and performed the same comparisons using raw ("descaled") hippocampal volumes, which were derived by dividing each hippocampal volume by the scaling factor used to transform it to the ICBM53 average brain. To descale the three-dimensional maps created previously, the inverse of the global scaling transformation matrix was applied to the hippocampal surface points. A least squares rigid transform with 6 parameters (without scaling) was then applied to the resulting hippocampal traces to align them rigidly with the ICBM53 average brain dataset. Maps of group differences were created both before and after adjusting for any individual and group differences in brain size.

3. Results

3.1. Subjects

The groups did not differ significantly in terms of age, race, height, head circumference, or the scaling factor used to transform each image volume into stereotaxic space (see Table 1). While there was no significant difference in non-verbal IQ between the two groups, patients did have a significantly lower verbal IQ ($P=0.0003$) and full-scale IQ ($P=0.007$). Consistent with previous studies (Escalante-Mead et al., 2003), there was a significantly greater proportion of left-handed subjects in the patient group ($P=0.007$). Mean ADI-R algorithm scores for subjects in the autism group are presented in Table 2.

3.2. Hippocampal volume

Using traditional volumetric methods, patients with autism did not differ significantly from controls in the volume of the individual hippocampi or the combined hippocampal volume (see Table 3). The pattern of results was similar when either the descaled (native space) images were used or when differences in brain size were controlled for through the use of the scaled images.

3.3. Hippocampal distance maps

Permutation tests on the descaled (native space) maps of the hippocampi did not reveal any regions with

Table 1
Demographic characteristics of patients with autistic disorder and control subjects

Measures	Patients ($n=21$)	Control subjects ($n=24$)	Test statistic	*df*	*P*
Age (years)	9.5±3.3	10.3±2.4	$t=1.0$	43	0.9
Race (# Caucasian)	20	24	$\chi^2=1.2$	1	0.3
Handedness (R:L)	15:6	24:0	$\chi^2=7.9$	1	0.007
Height (cm)	145.1±19.7	145.1±13.3	$t=0.01$	38	0.9
Head circumference (cm)	55.3±2.6	54.8±1.8	$t=0.6$	43	0.5
Image scaling factor[a]	1.3±0.1	1.4±0.1	$t=0.6$	43	0.5
Verbal IQ	90.9±11.3	106.3±11.3	$t=4.0$	35	0.0003
Non-verbal IQ	98.3±14.2	104.4±14.6	$t=1.4$	41	0.2
Full-scale IQ	93.8±11.9	105.4±12.1	$t=2.8$	35	0.007

All continuous data presented as mean±standard deviation. Note that degrees of freedom vary across tests due to missing data for some subjects, including the lack of a verbal or full-scale IQ for subjects tested using the Leiter International Performance Scale.

[a] The Image Scaling Factor refers to the scaling factor used to transform each image volume into stereotaxic space.

t2.1 Table 2
t2.2 Autism Diagnostic Interview-Revised (ADI-R) algorithm scores for subjects with autism (n=21)

t2.3 Domain	Score
t2.4 Social interactions	22.5±5.4
t2.5 Communication	
t2.6 Verbal subjects (n=20)	15.8±3.7
t2.7 Non-verbal subjects (n=1)	14.0
t2.8 Restricted and repetitive behavior	4.2±1.0

t2.9 All continuous data presented as mean±standard deviation.

significant group differences (see Fig. 2). Small regions of volume excess in autism (red colors, Fig. 2(a) and (c)) were visible in the anterior hippocampus, but these changes were not significant when permutation testing was performed.

However, when total brain size was controlled for through the use of the scaled maps, significance maps (Fig. 3) revealed several localized group differences. Patients with autism had a significant reduction in hippocampal volume in the right medial posterior hippocampus (Fig. 3b, red color and white color) and a regional increase in thickness in the right medial anterior hippocampus (Fig. 3c, red color). Permutation tests on these specific regions of interest to control for multiple testing confirmed the significant reduction in the right medial posterior hippocampus of patients with autism (P=0.02), but the increase in the right medial anterior hippocampus among patients did not reach significance. There were no significant group differences in the left hippocampus.

4. Discussion

To our knowledge, this is the first study to use computational mapping methods to investigate hippocampal abnormalities in autism. While traditional methods did not reveal any significant group differences in total hippocampal volume, computational methods revealed a localized reduction in volume of the right medial posterior hippocampus in patients with autism after controlling for total brain size. This volume reduction could be due to specific abnormalities of the dentate gyrus, the hippocampal CA1 region, the CA3 region, or the CA4 region, or a combination of these regions. Although the methodology employed here is not able to determine which of these regions contributes to the volumetric deficit seen among patients, the three previous studies of the posterior hippocampus have not detected significant differences between patients and controls in the total cross-sectional area of the subiculum and CA1 through CA3 regions in patients with autism. (Saitoh et al., 1995, 2001; Bigler et al., 2003). Saitoh et al. (2001), however, did report a reduction in cross-sectional area in the combined CA4 and dentate gyrus (the area dentata). While the other two studies of the posterior hippocampus did not find significant reductions in the size of the area dentata in autism, they both had smaller sample sizes and also subdivided their patient groups by the presence or absence of macrocephaly (Bigler et al., 2003) or the presence or absence of mental retardation or seizures (Saitoh et al., 1995), thereby further reducing the number of subjects used in each comparison.

As noted previously, studies of the hippocampus in patients with autism have yielded contradictory results. This inconsistency may be due, at least in part, to factors such as sample size, subject age and gender, specific diagnosis (i.e., autism, Asperger's syndrome, or pervasive developmental disorder not otherwise specified), and the presence or absence of mental retardation and seizures. The neuroanatomic definition of the hippocampus may have also contributed to the inconsistency seen in earlier studies. In contrast to the computational mapping methods used here, previous studies of the hippocampus in autism examined the total volume of the hippocampus using traditional methods of analysis. However, given the anatomical and functional differences of hippocampal subregions (Duvernoy and

t3.1 Table 3
t3.2 Hippocampal volume, with and without correction for brain size, in patients with autism and comparison subjects

t3.3 Measure[a]	Patients (n=21)	Comparison subjects (n=24)	F	df	P
t3.4 Native space					
t3.5 Left hippocampus	2654.2±348.7	2536.6±248.4	1.7	1,43	0.2
t3.6 Right hippocampus	2730.1±333.8	2680.6±289.5	0.3	1,43	0.6
t3.7 Total hippocampus	5384.3±657.3	5217.2±487.8	0.9	1,43	0.3
t3.8 Scaled					
t3.9 Left hippocampus	3533.2±411.0	3440.7±283.0	0.8	1,43	0.4
t3.10 Right hippocampus	3635.0±394.1	3640.0±383.6	0.1	1,43	0.9
t3.11 Total hippocampus	7168.2±773.5	7080.7±596.3	0.2	1,43	0.7

t3.12 [a] Hippocampal volumes given in mm^3. All continuous data presented as mean±standard deviation.

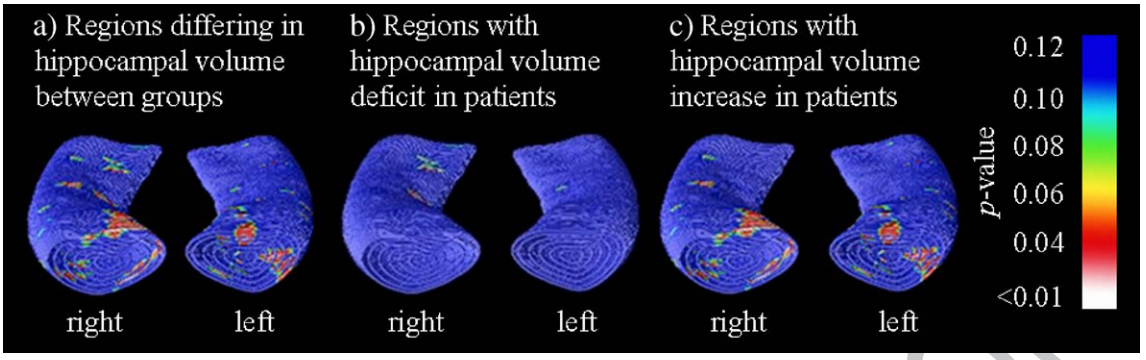

Fig. 2. Raw (descaled) hippocampal surface probability maps of patients with autism and controls, showing regions of overall differences between the groups (a), regions where patients had reductions in hippocampal volume relative to comparison subjects (b), and regions where patients had local increases in hippocampal volume relative to comparison subjects (c). While small regions of volume excess in autism were visible in the anterior hippocampus (red colors, (a) and (c)), these changes were not significant when permutation testing was performed to correct for multiple comparisons. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Bourgouin, 1998) as well as the limited diagnostic specificity afforded by traditional methods, such an approach may be less suitable than computational mapping methods. Computational maps, in conjunction with permutation testing, have more power than traditional volumetric measurements to detect group differences that are spatially heterogeneous and that do not affect the entire volume of a structure uniformly (Thompson et al., 2004b, 2005; Lin et al., 2005). As a result, subtle regional abnormalities may be detected with computational methods, even in the absence of global volumetric differences, as is the case in this study. The lower power of traditional volumetric measures may explain why studies using them have had inconsistent results, with many finding no significant group differences, as was noted here.

The spatial localization of volumetric abnormalities of the hippocampus provided by computational mapping methods permits a greater insight into the hippocampal regions potentially involved in the pathophysiology of autism. Functional brain imaging studies have indicated the importance of the hippocampus in facial encoding and recall (Haxby et al., 1996; Critchley et al., 2000; Kircher et al., 2001; Gur et al., 2002;). In particular, the right posterior hippocampus, the region differing between patients and controls in the present study, has been noted to be activated during the encoding and processing of facial emotions in adults without developmental disorders (Haxby et al., 1996; Critchley et al., 2000). The right hippocampus is also involved in self-recognition, a process that may be an index of self-awareness (Kircher et al., 2001). Similarly,

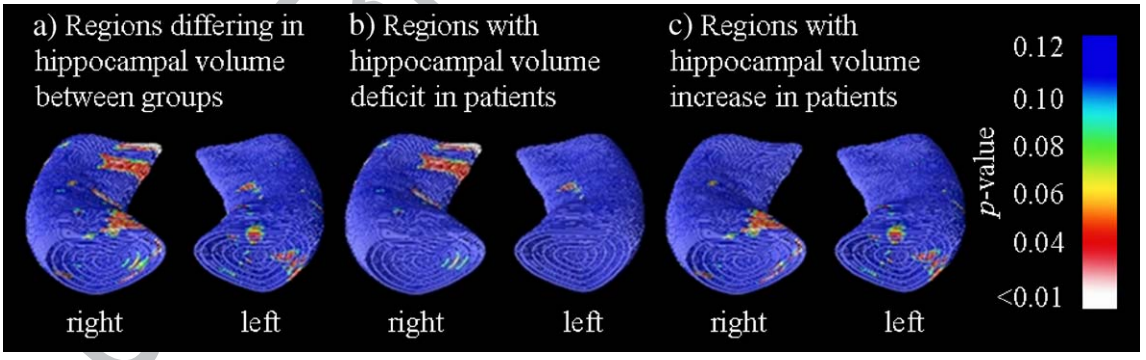

Fig. 3. Scaled hippocampal surface probability maps of patients with autism and controls, showing regions of overall differences between the groups (a), regions where patients showed reductions in hippocampal volume relative to comparison subjects (b), and regions where patients exhibited regional increases in hippocampal volume relative to healthy comparison subjects (c). Patients with autism showed a reduction in regional volume in the right medial posterior hippocampus (b) and an increase in regional volume in the right medial anterior hippocampus (c). When permutation testing was performed to correct for multiple comparisons, the only significant group difference was the reduction in regional volume in the right medial posterior hippocampus (red areas and white areas in (b)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

studies of single neuron activity have demonstrated activity of the hippocampus during facial recognition (Fried et al., 1997, 2002). The deficits of facial and emotional processing and recall associated with autism (Dawson et al., 2002) could thus reflect abnormalities of the hippocampus.

In conjunction with other medial temporal lobe structures, the regions of the posterior hippocampus found to be smaller in patients with autism in this study (the dentate gyrus and the CA1, CA3, and CA4 fields of the hippocampus) are part of a neural circuit that is essential to long-term memory formation and consolidation (Squire et al., 2004). Abnormalities of the hippocampal components of this system, including the regions differing between patients and controls in this study, could disrupt the normal functioning of these circuits and result in significant memory deficits (Squire et al., 2004). While recent studies suggest aberrant spatial working memory and episodic memory in patients with autism (Salmond et al., 2005; Williams et al., in press), some uncertainty remains about the precise nature of memory abnormalities in autism (Tsatsanis, 2005). However, based upon the role of the hippocampus in the integration, abstraction, and organization of information constituting memories (Eichenbaum, 2000), it has been proposed that the hippocampus is also critical to relational memory processing. This process involves the binding together of inputs to permit the establishment of associations between items and events in a memory and, thus, form a cohesive memory (Cohen et al., 1999). Abnormalities of the hippocampus and its connections with the prefrontal cortex could lead to impairments in this process of "feature binding", which might be of relevance in understanding the aberrant cognition seen in autism (Dawson et al., 2002). Frith (1989) has suggested that autism is characterized by "weak central coherence", a reduction in the ability to integrate information into a coherent and meaningful whole. Aberrant hippocampal structure in autism, such as that seen in this study, could lead to deficits in relational memory processing and the ability to bind features of various memories together and, ultimately, to impairments in the ability to integrate information appropriately.

In addition to identifying regional abnormalities of the hippocampus potentially related to the pathophysiology of autism, the spatial localization of volumetric differences by computational mapping methods also provides important information about the diagnostic specificity of these hippocampal abnormalities. Studies using traditional volumetric methods may also have limited diagnostic specificity, in part, perhaps, because of the inability of traditional methods to detect localized abnormalities. For example, traditional morphometric methods have been used to detect reductions in the total volume of the hippocampus in many psychiatric illnesses, including schizophrenia, depression, bipolar disorder, and post-traumatic stress disorder (Geuze et al., 2005). However, the significantly enhanced spatial resolution of computational mapping methods may provide further information about the diagnostic specificity of hippocampal abnormalities. Previous studies using this methodology have reported localized volume reductions in the head of the hippocampus bilaterally and the left anterolateral hippocampus in schizophrenia (Csernansky et al., 2002; Narr et al., 2004), the subiculum in patients with depression (Posener et al., 2003), the left lateral head of the hippocampus in Alzheimer's disease (Thompson et al., 2004a), and in the left anterolateral hippocampus among methamphetamine abusers (Thompson et al., 2004b). Additionally, a study of patients with Tourette syndrome using methods similar to those employed here reported an increase in the volume of the dentate gyrus (Choi and Peterson, 2004). The reduction in the right medial posterior hippocampus detected with computational mapping methods in the present study differs from the regions noted to be abnormal in these studies of other neuropsychiatric disorders, suggesting that it may be specific to autism.

The results of this study should be interpreted cautiously due to several limitations including the small sample size and the lack of female subjects. However, given the known gender differences in prevalence and severity of autism (Yeargin-Allsop et al., 2003), and in the developmental trajectory of the hippocampus (Giedd et al., 1996), the inclusion of males only in this study may have highlighted group differences by removing gender variables affecting the size of the hippocampus. A number of patients in the present study were taking psychotropic medication, which could potentially have influenced the results. However, studies of children and adolescents with schizophrenia (Matsumoto et al., 2001) or bipolar disorder (Frazier et al., 2005) have not detected significant differences in hippocampal volume when patients who were or were not receiving medication were compared. At the same time, longitudinal studies of patients with childhood-onset schizophrenia who were being treated with antipsychotic medications have noted progressive reductions in hippocampal volume relative to controls (Giedd et al., 1999), although it is difficult to determine whether these ongoing changes are due to medication or are effects of the illness itself. Future studies with larger samples will be required to delineate the effects of psychotropic medications on the hippocampus in patients with autism.

In this study, a computational mapping strategy was used to detect and visualize patterns of hippocampal thinning in children with autism, the greatest abnormalities being noted in the right medial posterior hippocampus. Shape and computational mapping may reveal the spatial pattern of hippocampal deficits with greater visual and statistical power than traditional volumetric methods and may thus provide important insights into the timing of neurodevelopmental abnormalities in autism as well as abnormal neural connectivity in the disorder. Future studies are required to confirm these differences in larger samples, and longitudinal studies will be needed to assess whether ongoing developmental changes in the hippocampus among patients with autism differ from those seen in typically developing children and adolescents.

Acknowledgement

Presented at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Miami Beach, 2003. This work was supported by the Child and Parent Resource Institute and by grants from the London Health Sciences Research, Inc., the Ontario Mental Health Foundation, the Hospital for Sick Children Foundation (to R.N.), the National Institute for Biomedical Imaging and Bioengineering, the National Center for Research Resources, and the National Institute on Aging (to P.T.: R21 EB01651, R21 RR019771, P50 AG016570). Additional support was provided by grants PO1 EB001955, U54 RR021813, MO1 RR000865, and P41 RR13642 (to A.W.T.).

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. American Psychiatric Association, Washington, D.C. Text Revision.

Arndt, S., Cohen, G., Alliger, R.J., Swayze, V.W., 1991. Problems with ratio and proportion measures of imaged cerebral structures. Psychiatry Research. Neuroimaging 40, 79–89.

Aylward, E.H., Minshew, N.J., Goldstein, G., Honeycutt, N.A., Augustine, A.M., Yates, K.O., Barta, P.E., Pearlson, G.D., 1999. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology 53, 2145–2150.

Bachevalier, J., 1994. Medial temporal lobe structures in autism: a review of experimental and clinical findings. Neuropsychologia 32, 627–638.

Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M., Rutter, M., Lantos, P., 1998. A clinicopathological study of autism. Brain 121, 889–905.

Bauman, M.L., Kemper, T.L., 1985. Histoanatomic observations of the brain in early infantile autism. Neurology 35, 866–874.

Bigler, E.D., Tate, D.F., Neeley, E.S., Wolfson, L.J., Miller, M.J., Rice, S.A., Cleavinger, H., Anderson, C., Coon, H., Ozonoff, S., Johnson, M., Dinh, E., Lu, J., Mc Mahon, W., Lainhart, J.E., 2003. Temporal lobe, autism, and macrocephaly. American Journal of Neuroradiology 24, 2066–2076.

Choi, H.A., Peterson, B., 2004. Morphology of the amygdala and hippocampus in Tourette's Syndrome. Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Washington.

Cohen, N.J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., Nash, C., 1999. Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. Hippocampus 9, 83–98.

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S., Van Amelsvoort, T., Robertson, D., David, A., Murphy, D., 2000. Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. Human Brain Mapping 9, 93–105.

Csernansky, J.G., Wang, L., Jones, D., Rastogi-Cruz, D., Posener, J.A., Heydebrand, G., Miller, J.P., Miller, M.I., 2002. Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. American Journal of Psychiatry 159, 2000–2006.

Dawson, G., Webb, S., Schellenberg, G.D., Dager, S., Friedman, S., Aylward, E., Richards, T., 2002. Defining the broader phenotype of autism: genetic, brain, and behavioral perspectives. Development and Psychopathology 14, 581–611.

DeLong, G.R., 1992. Autism, amnesia, hippocampus, and learning. Neuroscience and Biobehavioral Reviews 16, 63–70.

Duvernoy, H.M., Bourgouin, P., 1998. The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI, 2nd edition. Springer, New York.

Eichenbaum, H., 2000. A cortical-hippocampal system for declarative memory. Nature Reviews. Neuroscience 1, 41–50.

Escalante-Mead, P.R., Minshew, N.J., Sweeney, J.A., 2003. Abnormal brain lateralization in high-functioning autism. Journal of Autism and Developmental Disorders 33, 539–543.

Frazier, J.A., Chiu, S., Breeze, J.L., Makris, N., Lange, N., Kennedy, D.N., Herbert, M.R., Bent, E.K., Koneru, V.K., Dieterich, M.E., Hodge, S.M., Rauch, S.L., Grant, P.E., Cohen, B.M., Seidman, L.J., Caviness, V.S., Biederman, J., 2005. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. American Journal of Psychiatry 162, 1256–1265.

Fried, I., MacDonald, K.A., Wilson, C.L., 1997. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron 18, 753–765.

Fried, I., Cameron, K.A., Yashar, S., Fong, R., Morrow, J.W., 2002. Inhibitory and excitatory responses of single neurons in the human medial temporal lobe during recognition of faces and objects. Cerebral Cortex 12, 575–584.

Frith, U., 1989. Autism: Explaining the Enigma. Blackwell, Oxford.

Geuze, E., Vermetten, E., Bremner, J.D., 2005. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Molecular Psychiatry 10, 160–184.

Giedd, J.N., Vaituzis, A.C., Hamburger, S.D., Lange, N., Rajapakse, J.C., Kaysen, D., Vauss, Y.C., Rapoport, J.L., 1996. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. Journal of Comparative Neurology 366, 223–230.

Giedd, J.N., Jeffries, N.O., Blumenthal, J., Castellanos, F.X., Vaituzis, A.C., Fernandez, T., Hamburger, S.D., Liu, H., Nelson, J., Bedwell, J., Tran L., Lelane, M., Nicolson, R., Rapoport, J.L., 1999. Childhood-onset schizophrenia: progressive brain changes during adolescence. Biological Psychiatry 46, 892–898.

Gur, R.C., Schroeder, L., Turner, T., McGrath, C., Chan, R.M., Turetsky, B.I., Alsop, D., Maldjian, J., Gur, R.E., 2002. Brain activation during facial emotion processing. NeuroImage 16, 651–662.

Haxby, J.V., Ungerleider, L.G., Horwitz, B., Maisog, J.M., Rapoport, J.I., Grady, C.L., 1996. Face encoding and recognition in the human brain. Proceedings of the National Academy of Sciences of the United States of America 93, 922–927.

Haznedar, M.M., Buchsbaum, M.S., Wei, T.C., Hof, P.R., Cartwright, C., Bienstock, C.A., Hollander, E., 2000. Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. American Journal of Psychiatry 157, 1994–2001.

Howard, M.A., Cowell, P.E., Boucher, J., Broks, P., Mayes, A., Farrant, A., Roberts, N., 2000. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport 11, 2931–2935.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry 36, 980–988.

Kircher, T.J., Senior, C., Phillips, M.L., Rabe-Hesketh, S., Benson, P.J., Bullmore, E.T., Brammer, M., Simmons, A., Bartels, M., David, A.S., 2001. Recognizing one's own face. Cognition 78, B1–B15.

Lin, J.J., Salamon, N., Lee, A.D., Dutton, R.A., Geaga, J.A., Hayashi, K.M., Luders, E., Toga, A.W., Engel, J., Thompson, P.M., 2005. Mapping reduced cortical thickness and complexity in mesial temporal lobe epilepsy with hippocampal sclerosis. Annual Meeting of the Organization for Human Brain Mapping, Toronto, Canada.

Lord, C., Rutter, M., Le Couteur, A., 1994. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders 24, 659–685.

Lord, C., Risi, S., Lambrecht, L., Cook Jr., E.H., Leventhal, B.L., DiLavore, P.C., Pickles, A., Rutter, M., 2000. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders 30, 205–223.

Mathalon, D.H., Sullivan, E.V., Rawles, J.M., Pfefferbaum, A., 1993. Correction for head size in brain-imaging measurements. Psychiatry Research. Neuroimaging 50, 121–139.

Matsumoto, H., Simmons, A., Williams, S., Pipe, R., Murray, R., Frangou, S., 2001. Structural magnetic imaging of the hippocampus in early onset schizophrenia. Biological Psychiatry 49, 824–831.

Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., Holmes, C., Collins, L., Thompson, P., MacDonald, D., Iacoboni, M., Schormann, T., Amunts, K., Palomero-Gallagher, N., Geyer, S., Parsons, L., Narr, K., Kabani, N., Le Goualher, G., Boomsma, D., Cannon, T., Kawashima, R., Mazoyer, B., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philosophical Transactions of the Royal Society of London. Series B, Biolocial Sciences 356, 1293–1322.

Narr, K.L., Thompson, P.M., Szeszko, P., Robinson, D., Jang, S., Woods, R.P., Kim, S., Hayashi, K.M., Asunction, D., Toga, A.W., Bilder, R.M., 2004. Regional specificity of hippocampal volume reductions in first-episode schizophrenia. NeuroImage 21, 1563–1575.

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human Brain Mapping 15, 1–25.

Nicolson, R., Szatmari, P., 2003. Genetic and neurodevelopmental influences in autistic disorder. Canadian Journal of Psychiatry 48, 526–537.

Pantel, J., O'Leary, D.S., Cretsinger, K., Bockholt, H.J., Keefe, H., Magnotta, V.A., Andreasen, N.C., 2000. A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy. Hippocampus 10, 752–758.

Piven, J., Bailey, J., Ranson, B.J., Arndt, S., 1998. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. Journal of Autism and Developmental Disorders 28, 105–110.

Posener, J.A., Wang, L., Price, J.L., Gado, M.H., Province, M.A., Miller, M.I., Babb, C.M., Csernansky, J.G., 2003. High-dimensional mapping of the hippocampus in depression. American Journal of Psychiatry 160, 83–89.

Raymond, G.V., Bauman, M.L., Kemper, T.L., 1996. Hippocampus in autism: a Golgi analysis. Acta Neuropathologica 91, 117–119.

Rojas, D.C., Smith, J.A., Benkers, T.L., Camou, S.L., Reite, M.L., Rogers, S.J., 2004. Hippocampus and amygdala volumes in parents of children with autistic disorder. American Journal of Psychiatry 161, 2038–2044.

Saitoh, O., Courchesne, E., Egaas, B., Lincoln, A.J., Schreibman, L., 1995. Cross-sectional area of the hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. Neurology 45, 317–324.

Saitoh, O., Karns, C., Courchesne, E., 2001. Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area. Brain 124, 1317–1324.

Salmond, C.H., Ashburner, J., Connelly, A., Friston, K.J., Gadian, D.G., Vargha-Khadem, F., 2005. The role of the medial temporal lobe in autistic spectrum disorders. European Journal of Neuroscience 22, 764–772.

Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., Lotspeich, L.J., Kwon, H., Buonocore, M.H., Lammers, C.R., Reiss, A.L., Amaral, D.G., 2004. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. Journal of Neuroscience 24, 6392–6401.

Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A non-parametric method for automatic correction of intensity non-uniformity in MRI data. IEEE Transactions on Medical Imaging 17, 87–97.

Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G., Dager, S.R., 2002. Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59, 184–192.

Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annual Review of Neuroscience 27, 279–306.

Thompson, P.M., Hayashi, K.M., De Zubicaray, G.I., Janke, A.L., Rose, S.E., Semple, J., Hong, M.S., Herman, D.H., Gravano, D., Doddrell, D.M., Toga, A.W., 2004a. Mapping hippocampal and ventricular change in Alzheimer disease. NeuroImage 22, 1754–1766.

Thompson, P.M., Hayashi, K.M., Simon, S.L., Geaga, J.A., Hong, M.S., Sui, Y., Lee, J.Y., Toga, A.W., Ling, W., London, E.D., 2004b. Structural abnormalities in the brains of human subjects who use methamphetamine. Journal of Neuroscience 24, 6028–6036.

Thompson, P.M., Lee, A.D., Dutton, R.A., Geaga, J.A., Hayashi, K.M., Eckert, M.A., Bellugi, U., Galaburda, A.M., Korenberg, J.R., Mills, D.L., Toga, A.W., Reiss, A.L., 2005. Abnormal cortical complexity and thickness profiles mapped in Williams Syndrome. Journal of Neuroscience 25, 4146–4158.

Tsatsanis, K.D., 2005. Neuropsychological characteristics in autism and related conditions. In: Volkmar, F.R., Paul, R., Klin, A., Cohen, D. (Eds.), Handbook of Autism and Pervasive Developmental Disorders, Third edition. John Wiley and Sons, Inc., Hoboken, pp. 365–381.

Williams, D.L., Goldstein, G., Carpenter, P.A., Minshew, N.J., in press. Verbal and spatial working memory in autism. Journal of Autism and Developmental Disorders.

Woods, R.P., 2003. Multitracer: a java-based tool for anatomic delineation of grayscale volumetric images. NeuroImage 19, 1829–1834.

Yeargin-Allsop, M., Rice, C., Karapurkar, T., Doernber, N., Boyle, C., Murphy, C., 2003. Prevalence of autism in a US metropolitan area. Journal of the American Medical Association 289, 48–55.