

Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome

Hower Kwon* MD;

Andrew W Ow;

Kate E Pedatella;

Linda J Lotspeich MD;

Allan L Reiss MD, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, USA.

**Correspondence to first author at Division of Child and Adolescent Psychiatry, University of Washington School of Medicine, Children's Hospital and Regional Medical Center, PO Box 5371, Mailstop M1-1, Seattle, WA 98105-0371, USA. E-mail: howerk@alum.mit.edu*

Efforts to examine the structural neuroanatomy of autism by using traditional methods of imaging analysis have led to variable findings, often based on methodological differences in image acquisition and analysis. A voxel-based computational method of whole-brain anatomy allows examination of small patterns of tissue differences between groups. High-resolution structural magnetic resonance images were acquired for nine males with high-functioning autism (HFA; mean age 14y [SD 3y 4mo]), 11 with Asperger syndrome (ASP; mean age 13y 6mo [SD 2y 5mo]), and 13 comparison (COM) participants (mean age 13y 7mo [SD 3y 1mo]). Using statistical parametric mapping, we examined contrasts of gray matter differences between the groups. Males with HFA and ASP had a pattern of decreased gray matter density in the ventromedial regions of the temporal cortex in comparison with males from an age-matched comparison group. Examining contrasts revealed that the COM group had increased gray matter density compared with the ASP or combined HFA and ASP group in the right inferior temporal gyrus, entorhinal cortex, and rostral fusiform gyrus. The ASP group had less gray matter density in the body of the cingulate gyrus in comparison with either the COM or HFA group. The findings of decreased gray matter density in ventromedial aspects of the temporal cortex in individuals with HFA and ASP lends support to theories suggesting an involvement of these areas in the pathophysiology of autism, particularly in the integration of visual stimuli and affective information.

The neurobiological underpinnings of autism and related pervasive developmental disorders (PDD) have continued to elude definitive identification. Efforts to identify specific neuropsychological differences in autism, in conjunction with clinical observations of children with the syndrome, have led to the understanding that autism is probably a condition of heterogeneous pathophysiology and etiology. Accordingly, increasing efforts have been made to enhance progress in the field through the use of new technologies, such as neuroimaging, in an effort to elucidate neurobiological correlates of this important neurodevelopmental disorder.

Imaging studies of clinical populations so far have contributed evidence which suggests the involvement of several regions of the brain in the neurobiology of autism, including the amygdala, mesial temporal cortex, fusiform gyrus (FUS), and cerebellum. As measured by functional magnetic resonance imaging (fMRI), autistic individuals have been shown to have abnormal patterns of activation in these brain regions during tasks assessing cognitive skills, e.g. theory of mind, face processing, emotion processing, and visuospatial processing (Baron-Cohen et al. 1999, Ring et al. 1999, Critchley et al. 2000, Schultz et al. 2000, Pierce et al. 2001). Several studies using positron emission tomography and single-photon emission computed tomography have also noted abnormalities in metabolism or regional blood flow in the temporal lobe and cerebellum (George et al. 1992, Mountz et al. 1995, Muller et al. 1999, Ryu et al. 1999, Zilbovicius et al. 2000, Asano et al. 2001). Unfortunately, structural neuroimaging studies have produced somewhat conflicting results so far. Aside from a convergent finding of increased brain volume in individuals with autism (Piven et al. 1995, 1996; Hardan et al. 2001b), neuroanatomic findings have been difficult to replicate for regions such as the corpus callosum (Belmonte et al. 1995, Egaas et al. 1995, Piven et al. 1997, Manes et al. 1999, Hardan et al. 2000), the amygdala and hippocampus (Piven et al. 1998, Aylward et al. 1999, Howard et al. 2000, Saitoh et al. 2001), and the cerebellar vermis (Courchesne et al. 1988, 1994; Piven et al. 1992; Hardan et al. 2001a). Possible sources of non-convergent results might include variation in diagnostic criteria used in recruitment, IQ differences in individuals, differences across studies in mean age of individuals, and differences in MRI acquisition, processing, and analysis.

Voxel-based whole-brain analysis with statistical parametric mapping techniques (Friston et al. 1995) permits rapid, largely automated, whole-brain analysis of neuroanatomy. The voxel-based method of image analysis has been used extensively in fMRI and has recently been adapted for morphometric MRI analysis (Andreasen et al. 1994, Sowell et al. 1999). Potential advantages of voxel-based methods for examining structural neuroanatomy include statistical examination of the whole brain, extensive automation, reliable processing steps, and the generation of information that is, in part, complementary to that produced from volumetric methods (Brown et al. 2001). In the only previous structural MRI study examining autism with this technique, Abell et al. (1999) studied adults with Asperger syndrome (ASP) who had been diagnosed with autism as children, and found that gray matter density was decreased in the right paracingulate sulcus and left inferior frontal gyrus, and increased in the amygdala, middle and inferior temporal gyri, and cerebellum. However, the generalizability of the findings of Abell et al. (1999) to younger populations must be considered in the context of the findings of a recent

See end of paper for list of abbreviations.

study by Courchesne et al. (2001), who found age-related changes in gray and white matter occurring throughout childhood and adolescence in individuals with autism.

The purpose of this study was to investigate brain gray matter distribution in male children and adolescents with high-functioning autism (HFA) or ASP. We hypothesized that subtle differences in gray matter development would be present in HFA and ASP groups, particularly within mesial temporal, cerebellar, and prefrontal regions, and that these differences would be related to the clinical phenomenology of PDD. We conducted comparisons between the HFA and ASP groups, between each group and an age-matched comparison group, and between the comparison group and the combined HFA and ASP group. To our knowledge, no previous structural imaging study has directly compared ASP and HFA populations. In addition, specific criteria were used to address concerns about participant recruitment in previous studies, such as the presence of the condition at the time of the study and a clearly defined distinction between the diagnoses of HFA and ASP.

Methods

The study was approved by the Institutional Review Board at Stanford University and written informed consent from parents and assent from children were obtained. Thirty-seven males between the ages of 10 and 18 years were recruited. Twenty-four of these participants, with diagnoses of HFA or ASP, were recruited through the Stanford Autism Clinic and from the local community. Exclusion criteria included fragile X syndrome and neurological conditions, such as a history of seizures or head trauma. Participants were also excluded for excessive movement in the scanner or anxiety related to the MRI procedure. A total of nine males with HFA (mean age 14y [SD3.3]) and 11 with ASP (mean age 13y 6mo [SD2.4])

underwent MRI. Diagnosis of autism or ASP was based upon DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders—4th edn; American Psychiatric Association 1994), and was then confirmed using the Autism Diagnostic Interview—Revised (Lord et al. 1994) and the Autism Diagnostic Observation Schedule—Generic (Lord et al. 2000). To address the diagnostic uncertainties of some prior studies, the current study established the precedence of the diagnosis of autism, with the diagnosis of ASP being made only if there was no clinically significant language delay (such as communicative phrases used by age 3 years). Thirteen comparison participants (COM; mean age 13.6 years [SD3.1]) were recruited from the local community surrounding Stanford University. Comparison participants were screened with standardized methods developed in our laboratory to rule out the presence of developmental, educational, medical, psychological, or psychiatric abnormalities. All participants received psychometric testing consisting of the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999) and the Peabody Picture Vocabulary Test—3rd edn (Dunn and Dunn 1997).

High-resolution T_1 -weighted MR images of each participant's brain were acquired with a GE Signa 3T scanner (General Electric, Milwaukee, WI, USA) with a standard GE head coil. Coronal images were acquired with a three-dimensional volumetric radio-frequency spoiled gradient echo with the following scan parameters: TR=35ms, TE=6ms, flip angle = 45°, NEX=1, field of view=24×24cm², slice thickness=1.5 or 1.6mm, 124 slices, no gaps. Images were imported into and processed with SPM99 software (Wellcome Department of Cognitive Neurology, London, UK) with automated methods similar to those detailed elsewhere (Paus et al. 1999, Sowell et al. 1999, Brown et al. 2001). In brief, each image dataset was first normalized with a standard 12-parameter

Table I: Regions of significant differences in gray matter density

| <i>Anatomical regions</i> | <i>p (corrected)</i> | <i>Voxels (n)</i> | <i>Z score (maximum)</i> | <i>Peak location Talairach coordinates (x, y, z)</i> |
|---|--------------------------|-----------------------|------------------------------|--|
| Comparison–Asperger | | | | |
| Cingulate | <0.001 | 831 | 3.50 | 6 10 36 |
| Right inferior temporal gyrus, entorhinal cortex, and rostral tip of fusiform gyrus | 0.020 | 480 | 4.21 | 28 –4 –48 |
| Left inferior temporal gyrus and middle temporal gyrus | 0.024 | 463 | 3.48 | –58 –14 –30 |
| Comparison–HFA | | | | |
| No significant region | – | – | – | – |
| Comparison–PDD | | | | |
| Right inferior temporal gyrus, entorhinal cortex, and rostral tip of fusiform gyrus | 0.035 | 461 | 4.12 | 28 –4 –46 |
| Asperger–comparison | | | | |
| No significant region | – | – | – | – |
| HFA–comparison | | | | |
| No significant region | – | – | – | – |
| PDD–comparison | | | | |
| No significant region | – | – | – | – |
| HFA–Asperger | | | | |
| Cingulate gyrus | 0.011 | 543 | 3.92 | 8 –4 38 |
| Asperger–HFA | | | | |
| No significant region | – | – | – | – |

HFA, high-functioning autism group; PDD, pervasive developmental disorder group (i.e. combined HFA and Asperger groups).

affine transformation that mapped the images to the SPM template brain image and corrected for inhomogeneity artifacts. All images were then segmented into gray matter, white matter, and cerebrospinal fluid based on signal intensity; non-brain tissue was simultaneously removed by means of the segmentation algorithm native to SPM. Probability distribution maps for gray matter were produced from the segmentation algorithm. To minimize the potential effects of noise and anatomic variance, the gray tissue was then smoothed with an 8mm isotropic full-width half-maximum kernel. Average gray matter maps of all participants were generated to permit visualization of the correlation Z-maps on the structural datasets. Voxel-by-voxel unpaired *t*-tests were used to compare signal intensities between groups. To identify significant voxel clusters and to minimize Type II error, height ($p < 0.01$) and extent ($p < 0.05$) thresholds were employed to account for spatial correlations in the data.

Results

The three groups did not differ significantly in age ($df = 2, 30$; $F = 0.07$; $p = 0.93$) or in performance IQ ($df = 2, 30$; $F = 1.08$, $p = 0.35$).

In the first set of anatomical analyses we examined contrasts that would identify regions in which gray matter density was greater in the HFA and/or ASP groups than in the COM group. The ASP–COM, HFA–COM, and PDD–COM (in which PDD is the combined group of ASP and HFA) contrasts yielded no significant area (Table I).

In the next set of analyses we examined contrasts yielding regions in which gray matter density was greater in the COM group than in the HFA and/or ASP groups. In comparison with the HFA group, the COM group showed no regions with greater gray matter density. However, in comparison with the ASP group, the COM group showed significantly greater gray matter density in the right inferior temporal gyrus (ITG), entorhinal cortex, rostral tip of the FUS, left ITG, middle temporal gyrus, and body of the cingulate gyrus (Fig. 1a). When compared with the entire PDD group, the COM group showed significantly greater gray matter density in the right ITG,

entorhinal cortex, and rostral tip of the FUS (Fig. 1b). The locations in Talairach space of the neuroanatomical differences seen in the right temporal cortex in both contrasts were practically identical. It is noteworthy that we observed no gray matter density difference in the amygdala or cerebellar vermal lobules.

The findings in the temporal cortex seem to be consistent when contrasts are examined for differences between PDD and COM groups. The ASP and combined ASP and HFA groups showed significantly decreased gray matter density in the ventromedial temporal cortex. Although the COM–HFA contrast failed to yield any significant structural differences, the presence of differences in the COM–PDD contrast suggested sub-threshold differences in the HFA group as well. In support of this hypothesis, when the height threshold was relaxed to $p < 0.1$ for the COM–HFA contrast, differences in the same region of the temporal cortex were observed (data not shown).

Finally, the ASP and HFA groups were compared with each other. The HFA group had greater gray matter density in the body of the cingulate gyrus (Fig. 1c). The ASP–HFA contrast yielded no regions of significantly different gray matter density.

Discussion

The present study found that males who were high-functioning with PDD between the ages of 10 and 18 years had a pattern of decreased gray matter density involving the ventromedial regions of the temporal cortex in comparison with males from an age-matched comparison group. Examining contrasts revealed differences in the right ITG, entorhinal cortex, and rostral FUS in which the COM group had increased gray matter density compared with ASP or the combined PDD group. The ASP group had less gray matter density in the body of the cingulate gyrus in comparison with either COM or HFA.

Our finding of decreased gray matter density in temporal regions lends support to theories implicating these regions in the pathophysiology of autism. The importance of the limbic system and, more specifically, the amygdala in the assignment of emotional valence to stimuli has been well established. In monkeys, the ventral and medial aspects of the ITG are parts

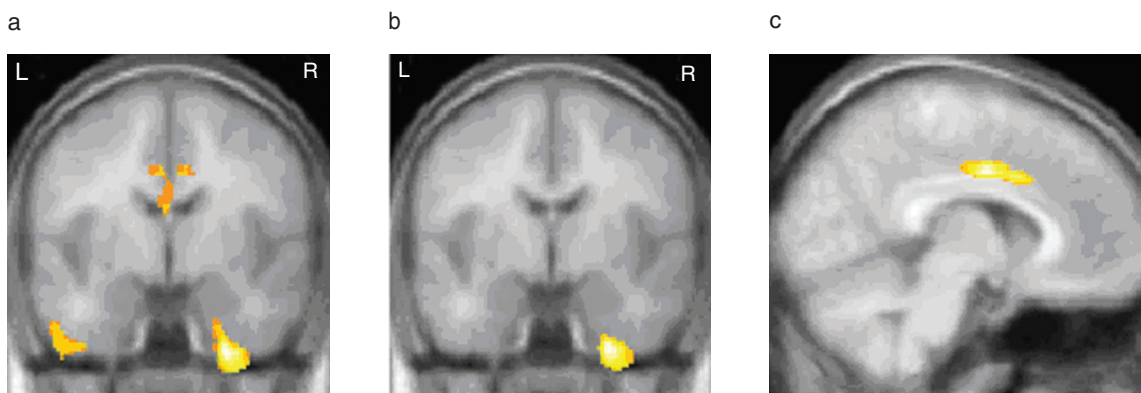


Figure 1: Differences in gray matter density between individuals with pervasive developmental disorders and comparison participants. Gray matter density differences were found in contrasts comparing the following groups: (a) comparison–Asperger (Talairach coordinate $y = -4$); (b) comparison–combined pervasive developmental disorders group ($y = -4$); and (c) high-functioning autism–Asperger ($x = 8$). For all contrasts, activation height threshold was set at $p < 0.01$ and extent threshold at $p < 0.05$. Regions of structural differences were overlaid on a structural image averaged from all participants.

of the pathway connecting visual cortex and visual association areas with the amygdala (Amaral and Price 1984). Connections between the ITG and amygdala are highly reciprocal, allowing emotional states mediated by the amygdala to exert an influence upon the processing of sensory stimuli (Pitkanen 2000). These connections have been proposed to be involved in the attribution of fear to visual stimuli, so that the circuitry is thought to contribute to integration of processed visual information and attribution of emotions (Bachevalier 2000). Information relevant to subsequent higher-order processing of emotional and sensory input is then passed on through projections to brain regions such as the prefrontal and orbitofrontal cortices, regions that are known to be involved in the regulation of social behavior.

Consequently, brain structures, such as the temporal lobe, amygdala, and other limbic structures, have received considerable attention in the efforts to identify the neuroanatomical substrates underlying the pathophysiology of autism. In an animal model of PDD, rhesus monkeys exhibited social and emotional deficits analogous to those observed in autism after neonatal temporal lobe lesions (Bachevalier et al. 2001). Functional MRI studies in individuals with PDD have yielded results implicating the ITG, FUS, and amygdala. For example, in an experiment examining emotion processing, Critchley et al. (2000) found that individuals with PDD showed activation differences in the left amygdala, left cerebellum, and FUS.

In another experiment examining face processing in individuals with PDD, Schultz et al. (2000) found that during a face discrimination task, individuals with PDD showed increased right ITG activation and decreased right FUS activation, a pattern that was akin to that seen during object discrimination in comparison groups. Schultz et al. (2000) proposed that individuals with PDD use an alternative pathway for visual face processing: a ventrolateral pathway that is more consistent with a feature-based strategy seen in object processing in typical individuals. Results from the present study suggest that these differences in patterns of activation might also be a result of the relative reduction of neural tissue in regions critical to those tasks, specifically in ventromedial portions of the temporal cortex involved in the visual stream from the FUS to the anterior portions of the ITG. The differences found in gray matter in the ITG, entorhinal cortex, and FUS, but not in the amygdala, suggest 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. Moreover, neuroanatomical involvement of the inferior temporal lobe suggests that deficits in social cognition in individuals with autism might occur at the neurofunctional point of synthesis of sensory and emotional information.

The hypothesis of alternative pathways being used for visual processing in autism is consistent with our finding of altered structural neuroanatomy in the ventromedial portion of the temporal lobe connecting the FUS with entorhinal cortex and parahippocampal gyrus. One hypothesis explaining the neuroanatomical and neurofunctional differences in PDD is that the presence of an underlying structural abnormality in the ventromedial temporal lobe that forces the development of alternative strategies in face processing. An alternative theory is that an inherent difference in individuals with PDD in cognitive strategies during face processing results in a lack of use of the ventromedial pathway and a relative loss of tissue volume.

Specific neuroanatomical studies examining the development of the inferior temporal lobe in PDD will be required to help resolve these questions.

Abell et al. (1999) used a similar whole-brain voxel-based analysis in adults diagnosed with autism as children, and found that gray matter density was decreased in the right paracingulate and left inferior frontal gyri and was increased in the amygdala, middle temporal gyrus, ITG, and cerebellum. Although we also detected differences in the temporal lobe of our PDD groups, the lack of frontal, cerebellar, and amygdala findings in our study might be associated with dissimilar methods for participant inclusion. Specifically, the criteria used in the present study required the direct examination and diagnosis of child participants, whereas Abell et al. used retrospective diagnoses of autism in an adult sample. The developmental nature of neuroanatomic differences in autism was highlighted in a recent study that showed that individuals with autism might have distinct trajectories of brain development during childhood and adolescence, resulting in variable morphometric differences depending on the age of the cohorts studied (Courchesne et al. 2001). Volumetric studies performed on younger children with PDD examining the specific regions identified in this study might answer the question of whether these regions have decreased gray matter tissue from a very early age or whether these regions demonstrate a non-linear trajectory of gray matter development.

The present study provides evidence for the presence of specific structural neuroanatomical abnormalities in the ventromedial aspect of the temporal lobe in individuals with HFA and ASP. In future, in order to define the aberrant neural circuitry and anatomy in PDD better, it will be important to pursue these leads with a combination of neuroimaging approaches, including techniques that permit the evaluation of size, shape, connectivity, and function of the brain. Studies might also examine the genetic influences of neuroanatomical differences in PDD. Such studies will also need to include individuals representing the wider spectrum of PDD. Longitudinal studies examining the development of sensory and emotional processing might lead to the development of specific treatments addressing deficits in these cognitive functions in children with PDD.

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List of abbreviations

| | |
|-----|-----------------------------------|
| ASP | Asperger syndrome |
| COM | Comparison group |
| FUS | Fusiform gyrus |
| HFA | High-functioning autism |
| ITG | Inferior temporal gyrus |
| PDD | Pervasive developmental disorders |