Cortical Gray and White Brain Tissue Volume in Adolescents and Adults with Autism

Heather Cody Hazlett, Michele D. Poe, Guido Gerig, Rachel Gimpel Smith, and Joseph Piven

Background: A number of studies have found brain enlargement in autism, but there is disagreement as to whether this enlargement is limited to early development or continues into adulthood. In this study, cortical gray and white tissue volumes were examined in a sample of adolescents and adults with autism who had demonstrated total brain enlargement in a previous magnetic resonance imaging (MRI) study.

Methods: An automated tissue segmentation program was applied to structural MRI scans to obtain volumes of gray, white, and cerebrospinal fluid (CSF) tissue on a sample of adolescent and adult males ages 13–29 with autism (n = 23) and controls (n = 15). Regional differences for brain lobes and brain hemispheres were also examined.

Results: Significant enlargement in gray matter volume was found for the individuals with autism, with a disproportionate increase in left-sided gray matter volume. Lobe volume enlargements were detected for frontal and temporal, but not parietal or occipital lobes, in the subjects with autism. Age and nonverbal IQ effects on tissue volume were also observed.

Conclusions: These findings give evidence for left-lateralized gray tissue enlargement in adolescents and adults with autism, and demonstrate a regional pattern of cortical lobe volumes underlying this effect.

Key Words: Autism, MRI, brain, tissue volume, neuroimaging, adolescent/adult

Autism is a neurodevelopmental syndrome defined by the presence of social deficits; communication abnormalities; stereotyped, repetitive behaviors; and a characteristic course. While the behavioral phenotype and course have been relatively well characterized, the developmental neuropathology underlying this condition has only just begun to be described. Early reports suggesting that children with autism had enlarged head size (Kanner 1943; Steg and Rapaport 1975) provided a potential clue to this underlying pathology, however, it was not until the first systematic post-mortem and MRI studies that increased brain weight (Bauman and Kemper 1985; Bailey et al 1993) and brain volume (Piven et al 1992, 1995) were described. Subsequently, increased head circumference (macrocephaly) in individuals with autism was reported (Bailey et al 1995) and it was later noted that macrocephaly, while not present at birth, appeared to emerge in a significant proportion of autistic individuals during the early post-natal years (Lainhart et al 1997; Stevenson et al 1997; Courchesne et al 2003).

While the finding of brain volume enlargement in autism now appears to be well established, little is known about the timing underlying this enlargement. For example, while recent cross-sectional studies have suggested that enlargement is present in the first few years of life (Courchesne et al 2001) or in preschoolers (Sparks et al 2002), several studies have detected increased brain volume in adolescent and adult samples (Piven et al 1992, 1995; Hardan et al 2001). Others have reported detecting enlargement in 8–12 year olds, but not in autistic individuals 13–46 years of age (Aylward et al 2002). Similarly, the pattern of enlargement across gray and white matter tissue compartments throughout the brain has also not been well characterized. Lotspeich and colleagues (Lotspeich et al 2004) recently reported enlargement of cerebral gray tissue, but not white tissue, in boys with autism ranging in age from 7.8 years to 17.9 years. Global cerebral gray tissue enlargement, but not cerebral white tissue enlargement, was found in a group of 7–15 year old high functioning children and adolescents with autism, compared to well matched controls. Others have found cerebral white tissue enlargement in children with autism that showed strong developmental (age) and regional effects (Herbert et al 2004).

Piven and colleagues (Piven et al 1996) employed a semi-automated technique to divide the brain into cortical lobe regions based on a method described by Talairach and Tournoux (1988) and found evidence that enlargement was not uniform throughout the cortical lobes in an adolescent/adult sample of autistic subjects versus IQ comparable controls. Increased volumes were noted in the temporal, parietal and occipital lobes, however, no volume differences were detected in the frontal lobes. Gray and white matter volumes were not examined in that study. Using a manually defined lobe parcellation method, Carper and colleagues (Carper et al 2002) examined a sample of autistic and healthy male controls and reported that children with autism, in a 2–4 year old age group, had significant enlargement of white matter volume in the frontal and parietal lobes, and gray matter volume in the frontal and temporal lobes. No increase in white or gray matter volume was detected for any of the lobes in an older subset of children over age 4 years.

In the present study we employ an automated method to examine gray and white matter volumes, by cortical lobe, in a sample of adolescent and adult autistic individuals previously shown to have total brain volume enlargement on MRI (Piven et al 1995, 1996).

Methods and Materials

Sample
Subjects for this study were a subset of a previously described sample of autistic and control subjects where brain enlargement on MRI was observed in the autistic individuals (Piven et al 1996). This sample provided an ideal opportunity to explore regional patterns of gray and white matter tissue volumes in a sample of...
autistic individuals with increased average total brain volume. The study was reviewed and approved by the University of Iowa Institutional Review Board. Written informed consent was obtained from both the parent/legal guardian of each subject and, following an explanation of the study, from each subject. No subjects were sedated for the MRI scan.

For the current study, a subset of 23 subjects with autism and 15 controls were selected (blind to diagnosis) from the original sample (from Piven et al 1996, briefly described below) on the basis of their having MRI scans of sufficient quality to run the tissue segmentation methods used in this study (described below). The mean age of the 23 subjects with autism was 19.1 years and average performance IQ was 89.9. The average age for the control subjects was 21.6 years and mean performance IQ was 102.3. Mean (SD) scores on the ADI were as follows: Social 29.78 (6.1), Communication (Nonverbal) 17.6 (5.1), Repetitive 6.5 (2.1), and Abnormal Development 3.6 (1.6). All subjects were males as there were too few females for a meaningful analysis of females only. Sample descriptives are provided in Table 1 and a description of the original sample follows.

The original sample was comprised of 35 subjects (26 males, 9 females) who were diagnosed with autism at the Child Psychiatry Clinics at the University of Iowa Hospitals and Clinics, as previously described in Piven and colleagues (Piven et al 1996). Briefly, the criteria for inclusion into the study included meeting Autism Diagnostic Interview (ADI) (LeCouteur et al 1989) and DSM-III-R (American Psychiatric Association 1987) criteria for autistic disorder. Individuals with a history of significant medical or neurological disorders or with Fragile X disorder were excluded from the sample. The mean age for the subjects with autism was 18.0 years (range 12–29 years). The mean estimate for performance (nonverbal) IQ was 91.0 (range 52–136) from either the WAIS-R (Wechsler Adult Intelligence Scale-Revised, Wechsler 1981), WISC-III (Wechsler Intelligence Scale for Children-3rd Edition, Wechsler 1991), or Leiter International Performance Scales (Arthur 1952), depending on subject age and language capability.

The original sample of comparison subjects consisted of 36 healthy volunteers (20 males and 16 females) recruited from the community as described in Piven and colleagues (Piven et al 1996). The mean age for the comparison group was 20.2 years (range 13–28). Control subjects were selected to resemble the autism cases in age, sex, and IQ. Subjects were screened for psychiatric disorder using a modified version of the Comprehensive Assessment of Symptoms and History (Andreasen et al 1992). Control subjects were excluded for a history of treatment for a psychiatric disorder (including drug or alcohol abuse), history of a learning disability, or a significant medical or neurological disorder. The mean nonverbal IQ for the control group, as assessed on the WAIS-R or WISC-III, was 102.1 (range 72–135).

MRI Acquisition

MRI scans were obtained with a T1-weighted three-dimensional spoiled gradient (SPGR) sequence on a 1.5 Tesla GE scanner (GE Medical Systems, Milwaukee, Wisconsin) in the coronal plane with the following parameters: T1-weighted three-dimensional SPGR sequence with 1.5 mm slices, no gap, flip angle 40 degrees, with 24 msec repetition time (TR), 5 msec echo time (TE), two excitations, 26 cm field of view (FOV), and a 256 × 192 matrix. Using these parameters, 124 contiguous slices through the brain were obtained.

Table 1. Subject Descriptives

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age Mean (SD)</th>
<th>Age Range in Years</th>
<th>PIQ Mean (SD)</th>
<th>PIQ Range in Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>23</td>
<td>19.1 (4.6)</td>
<td>13–29</td>
<td>89.9 (21.6)</td>
<td>52–136</td>
</tr>
<tr>
<td>Controls</td>
<td>15</td>
<td>21.6 (3.98)</td>
<td>14–29</td>
<td>102.3 (10.9)</td>
<td>80–122</td>
</tr>
</tbody>
</table>

PIQ, Performance IQ standard score.

Image Processing

Images were processed on a Silicon Graphics Personal Iris 4-D workstation (Silicon Graphics Inc., Mountain View, California). The technician was blind to the identity of the subjects, including group membership, sex, and age. The initial image processing, as previously discussed (Piven et al 1996), used the BRAINS software program developed at the University of Iowa (Andreasen et al 1992, 1993, 1996; Arndt et al 1994; Cohen et al 1992). The program produced thresholded images used to generate volumes of tissue and CSF. Simple thresholding based on signal intensity was performed to obtain a tissue classified image (e.g., brain tissue, CSF, background) based on tissue probabilities. At the time of the original data analyses (Piven et al 1996) this was the extent of image processing available. Reliable segmentation of gray and white tissue was not possible.

In the current study, a new version of the software, BRAINS2, was used. The program was revised to allow for more reliable tissue classification as well as to make minor improvements in the Talairach parameters used to separate the brain into cortical lobes. The BRAINS2 program (Magnotta et al 2002) employs a voxel-based tissue classification method to obtain gray, white, and CSF volumes from either discrete (“sharp” image) or continuously (“fuzzy” image) classified output images. Although this tool ideally uses multi-channel information (e.g., T1, PD, T2), tissue segmentation is possible with only T1 images when parameters are optimized for single-channel segmentation. Using this automatic tissue segmentation procedure, some of the MRI scans in the original sample (12 subjects with autism, 21 controls) were unable to be processed due to inadequate image quality for this advanced tissue segmentation. These cases were excluded from further processing and analysis.

All scans were first registered along an AC-PC (anterior-posterior commissure) axis and corrected for within image inhomogeneities. A semi-automated tissue segmentation was then performed which produced both discretely and continuously classified images. For the purposes of this study, the discretely classified image was used to obtain voxel segmentations into gray, white, and CSF as the discretely classified image is reported to have the most robust validity and reliability (Harris et al 1999). A Talairach grid was then applied to the segmentations to obtain the individual lobe volumes. Brainstem was excluded from the analysis. For this study, total cerebral volume represents all cortical brain tissue (gray/white) and CSF volumes but excluded cerebellum and the subcortical area (Talairach subcortical box) due to the difficulty segmenting these areas reliably into tissue types.

Statistical Analyses

To re-establish that the subset examined in this study was similar to the original sample in showing brain volume enlargement in autistic versus control subjects, a regression model was fit to compare total brain volumes between the groups. In this model total cerebral volume was the dependent variable, and autism versus control status was the predictor of interest, with age and performance IQ included as covariates.
Secondly, a repeated measures mixed model was employed to examine hemisphere (right/left), tissue (gray/white), and cortical lobe volumes in autistic individuals and controls. Performance IQ (PIQ) and age were included in all analyses to take into account these possible confounding factors (Piven et al 1997). A single repeated-measures analysis was conducted to control for type I error-rates and to increase precision (Jennrich et al 1986) by including all dimensions simultaneously (i.e., hemisphere, lobe, and tissue) and requiring multiple degree-of-freedom tests for each dimension before conducting individual comparisons. This provides more power as error terms are computed after considering all three dimensions simultaneously. Results are less biased in that the differences in volume associated with hemisphere, region, and tissue type are not the same across the other two dimensions because the model allows for interactions among the dimensions. An empirical estimator was used to adjust for heteroscedasticity across the tissues and lobes (White 1980). As the empirical estimates of the standard errors are too small in small samples, the standard errors were further adjusted as described by Hinkley (1977).

The analysis model was fit to assess the 16 observations for each individual (hemisphere × tissue × lobe volume). Volume was the outcome, and hemisphere (left/right), lobe (frontal, temporal, parietal, and occipital) and tissue type (gray/white) were the within-subject predictors of interest. Autism status was the between-subjects predictor of interest. All two-, three, and four-way interactions among the four predictors of interest were included as well as interactions between age × tissue and performance IQ × tissue. To help control for type I error rates, the analysis strategy involved testing blocks of predictors that included region (lobe), and then examining individual predictors of regional differences within blocks only if that block was statistically significant. Laterality effects were compared between groups. Laterality indices for gray and white tissue volumes were calculated using the following formula: \([L − R]/(L+R) \times 100\] where left hemisphere laterality is indicated by positive (+) values and right hemisphere laterality is indicated by negative (−) values.

### Results

Consistent with results reported in the original sample (Piven et al 1996), total cerebral volume was significantly increased in the subset of autistic individuals versus controls included in this analysis (\(F_{1.34} = 5.16, p = .03\)). Mean total cerebral volume (SD) for the subjects with autism was 1222.8 cm\(^3\) (25.6) versus 1123.7 cm\(^3\) (32.5) for controls.

Table 2 presents the overall results of the repeated measures mixed model analyses showing significant tissue by hemisphere effects in cases versus controls. A detailed comparison of mean volumes by tissue and hemisphere appears in Table 3. Mean volumes were significantly increased in autistic subjects versus controls for left gray tissue volumes, but were not significantly increased for right gray or white volumes. Effect sizes (\(X_{\text{autism}} − X_{\text{controls}} / \text{average SD}\)) ranged from moderate (left white, right gray and right white) to high (left gray), with average percent volume increases of 2.9% (right gray); 7.9% (left white); 7.6% (right white), and 7.0% (left gray). A significant effect for lobe × tissue × hemisphere was detected (\(F = 2.8, p = .053\)), therefore, case-control contrasts of gray tissue volumes by individual lobe were conducted. Subjects with autism were found to have significant enlargements in left gray tissue for frontal lobe (\(t = 2.8, p = .01\)) and temporal lobe (\(t = 2.3, p = .03\)), but not significant for parietal lobe (\(t = 1.9, p = .07\)) and occipital lobe (\(t = 1, p = .91\)). These mean lobe volumes by group are reported in Table 4 and the percent difference seen in these volumes are displayed in Figure 1.

Consistent with the observation of a disproportionate increase in left gray matter volume (above), a significant laterality effect (left-sided) was observed for gray volume in autistic subjects (mean laterality ratio for autism = (+1.10) versus (−)1.1 for controls, \(p = .05\)), whereas no significant laterality effect was seen in white tissue volume (mean laterality ratio for autism = (−)1.28 versus (−)4.7 for controls, \(p = .91\)).

### Table 2. Effect of Diagnosis, Hemisphere, Tissue and Lobe Volumes

<table>
<thead>
<tr>
<th>Effects</th>
<th>df (Num, den)</th>
<th>t Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1,13</td>
<td>2.9</td>
<td>.097</td>
</tr>
<tr>
<td>Lobe × Group (autism vs. control)</td>
<td>3,33</td>
<td>.4</td>
<td>.760</td>
</tr>
<tr>
<td>Hemisphere × Group</td>
<td>1,13</td>
<td>1.1</td>
<td>.782</td>
</tr>
<tr>
<td>Hemispheric × Lobe × Group</td>
<td>3,33</td>
<td>3.3</td>
<td>.791</td>
</tr>
<tr>
<td>Tissue × Group</td>
<td>1,13</td>
<td>0.8</td>
<td>.383</td>
</tr>
<tr>
<td>Tissue × Lobe × Group</td>
<td>3,33</td>
<td>0.6</td>
<td>.631</td>
</tr>
<tr>
<td>Tissue × Hemisphere × Group</td>
<td>1,13</td>
<td>5.8</td>
<td>.022</td>
</tr>
<tr>
<td>Tissue × Hemispheric × Lobe × Group</td>
<td>3,33</td>
<td>2.9</td>
<td>.048</td>
</tr>
<tr>
<td>Age</td>
<td>1,13</td>
<td>4.5</td>
<td>.042</td>
</tr>
<tr>
<td>Age²</td>
<td>1,13</td>
<td>1.0</td>
<td>.327</td>
</tr>
<tr>
<td>Age × Gray</td>
<td>1,13</td>
<td>6.4</td>
<td>.016</td>
</tr>
<tr>
<td>Age × Gray</td>
<td>1,13</td>
<td>53.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PIQ</td>
<td>1,13</td>
<td>11.7</td>
<td>.002</td>
</tr>
<tr>
<td>Gray × PIQ</td>
<td>1,13</td>
<td>37.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Age = linear age effect; Age² = quadratic age effect.

### Table 3. Tissue Volumes by Hemisphere

<table>
<thead>
<tr>
<th>Tissue Volumes by Hemisphere</th>
<th>Autism (M cm³ (SE))</th>
<th>Controls (M cm³ (SE))</th>
<th>Diff (t(33))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Gray</td>
<td>325.4 (7.4)</td>
<td>301.6 (4.1)</td>
<td>23.8</td>
<td>2.57</td>
</tr>
<tr>
<td>Left White</td>
<td>213.3 (6.0)</td>
<td>197.6 (4.7)</td>
<td>15.7</td>
<td>2.63</td>
</tr>
<tr>
<td>Right Gray</td>
<td>317.8 (6.1)</td>
<td>308.9 (6.2)</td>
<td>8.9</td>
<td>.90</td>
</tr>
<tr>
<td>Right White</td>
<td>235.0 (7.5)</td>
<td>218.4 (5.6)</td>
<td>16.6</td>
<td>1.71</td>
</tr>
</tbody>
</table>

*Adjusted for age and PIQ.

### Table 4. Mean Volumes for Left Gray Tissue by Lobe

<table>
<thead>
<tr>
<th>Lobe Volumes</th>
<th>Autism Mean (SE)</th>
<th>Controls Mean (SE)</th>
<th>Diff Mean (SE)</th>
<th>t(33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>124.4 (4.0)</td>
<td>112.8 (2.1)</td>
<td>11.6</td>
<td>4.2</td>
<td>.28</td>
</tr>
<tr>
<td>Temporal</td>
<td>82.2 (2.2)</td>
<td>76.2 (2.1)</td>
<td>6.0</td>
<td>2.6</td>
<td>.23</td>
</tr>
<tr>
<td>Parietal</td>
<td>74.8 (2.3)</td>
<td>68.9 (2.3)</td>
<td>5.9</td>
<td>3.2</td>
<td>.19</td>
</tr>
<tr>
<td>Occipital</td>
<td>44.1 (2.5)</td>
<td>43.8 (2.1)</td>
<td>0.3</td>
<td>2.6</td>
<td>.19</td>
</tr>
</tbody>
</table>

*Adjusted for age and PIQ.

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Figure 1. Percent difference (autism – controls) in left gray volumes by lobe.

Discussion

In this study we examined gray and white tissue volumes by hemisphere and cortical lobe, in a group of autistic individuals known to have brain enlargement on MRI. Results revealed an increase in left-sided, cortical, gray tissue volume with no significant increase in white tissue volume. Subjects with autism had significant enlargement of gray tissue in the frontal and temporal, but not parietal or occipital lobes.

Our finding of increased gray tissue volume suggests the presence of an aberrant neurodevelopmental mechanism that results in increased neuronal tissue. Examples of such disruptions in early neuronal development might include an overproduction in cells (e.g., neurons, glia, astrocytes), or decreased neuronal elimination. Given evidence inferred from head circumference studies (Lainhart et al 1997; Stevenson et al 1997; Courchesne et al 2003; Hazlett et al, in press), that increased rate of brain growth may occur in early post-natal life, a decrease in the normal occurrence of dendritic pruning resulting in increased dendritic arborization may provide the most plausible mechanism.

We report a disproportionate increase in left gray tissue volume in subjects with autism. While normal individuals have been reported to show left > right brain volumes, the effects in our sample of autistic individuals are even more exaggerated. Increased brain volume (approximately 10%), primarily due to increased cortical gray tissue, has been found in typically developing males compared to females (Reiss et al 1996). Our observation that autistic males have greater left-sided tissue volumes than normal male controls is consistent with the “extreme male brain theory” put forward by Simon Baron-Cohen (Baron-Cohen 2002; Baron-Cohen and Hammer 1997). This finding is also consistent with reports of atypical lateralization seen in individuals with high functioning autism (Escalante-Mead et al 2003).

Our cross-sectional design limits our ability to examine the developmental effect of brain volume enlargement. Similar to a post-adolescence decrease in gray tissue and increase in white tissue reported by Giedd et al 1999, we do find gray tissue volumes decreased and white tissue volumes increased across the age range we examined, but no case-control difference was noted for this age effect. Longitudinal studies of autistic individuals will be necessary to clarify the developmental trajectory of gray and white tissue volumes from early childhood into adulthood, as they have been shown to do in normal individuals (Giedd et al 1999). We report elsewhere (Hazlett et al, in press) significant generalized gray and white cortical tissue enlargement in a young sample of two year olds with autism. The current adolescent and adult study described here would suggest that effects in older samples may not be as generalized. (Courchesne et al 2003) has suggested that brain enlargement in autism is limited to the early years of life, while Aylward et al (2002) has described brain volume increases occurring only in children less than 12 years of age. The results from this study show increased gray matter volumes in an adolescent and adult sample, consistent with previous independent findings of brain enlargement from our group (e.g., Piven et al 1992) and others (Lotspeich et al 2004; Palmen et al 2005). Clearly it is premature to conclude, from cross-sectional studies, that these effects are limited to early ages in autistic individuals. The absence of significant effects in other reports may well be the result of limited power given the well known heterogeneity in autism or the failure to take IQ into account (Courchesne et al 2001). Alternatively, it is also possible that the effect of brain volume enlargement in older samples is less robust. Clarification of the timing of brain enlargement in autism will undoubtedly require studies involving large samples of autistic individuals followed longitudinally from very early ages.

While increased brain volume in autism is now recognized as a well replicated and real phenomenon, studies of the patterns of enlargement in tissues and structures throughout the brain, the timing of this enlargement, and associated clinical features are only now emerging. A few reports exist suggesting a relationship between head circumference in autism and verbal-performance IQ discrepancies (Deutsch and Joseph 2003), as well as brain...
enlargement and severity of certain autistic symptoms as measured on the ADI (Carper et al 2002). In the present study of a relatively high functioning (on nonverbal IQ) sample of adolescents and adults with autism, we explored whether a relationship between brain volumes and several clinical characteristics existed. In our data we found no significant relationship between ADI domain scores on social, ritualistic/repetitive behaviors, and abnormal development and gray tissue volumes; however, there was a trend suggesting increased scores on the communication domain of the ADI (indicative of more severe deficits) were associated with increasing left gray matter volume. The significance of this observation is not clear. While language is linked to the dominant (typically left) hemisphere, communication as measured on the ADI is a more complex construct involving social use of language that almost certainly involves multiple structures and regions of the brain. Communication level, however, is known to be a strong predictor of outcome in autism and likely to index heterogeneous subgroups (Collaborative Linkage Study of Autism Group 2001). If communication abnormality in autism is linked to an abnormal increase in left gray matter volume, it lends validity to the idea that autistic individuals with increased gray matter volume may be a meaningful subtype. Clearly this observation requires replication before further claims for its validity or meaning can be made.

We observed a significant IQ effect in our model, suggesting that cognitive ability is an important variable to consider when looking for brain differences in autism, a syndrome where the majority of affected individuals also have mental retardation. Recent findings by Lotspeich and colleagues (Lotspeich et al 2004) suggest that IQ effects may exist for gray and white tissue, but may not be the same for different tissue types. We have previously suggested in our analysis of cerebellar size in autism that IQ is a potential confounder to consider in studies of brain size in autism (Piven et al 1992). The current study supports this approach with adolescent and adult populations in brain volume studies.

We also detected an overall significance of lobe by autism diagnosis in our model, and were able to further explore specific case-control contrasts by lobe volume. In our previous study (Piven et al 1996) the pattern showed increased total tissue volume in temporal, parietal, and occipital lobes. This study differed from our previous findings in that the pattern of differences using the segmented brain tissue volumes showed increased frontal and temporal, but not parietal or occipital, gray tissue in the autism group. A number of factors may contribute to this difference. These include the limitation to males in the current study, the smaller sample size, and the use of a newer tissue segmentation methodology that allowed us to look specifically at gray and white tissue volumes (while the previous study examined total lobe volumes only). While not consistent with our previous report, this finding is consistent with Carper et al (2002) who found frontal and temporal gray tissue volumes increased in their less than four year old sample. These data suggest that regional differences, as opposed to generalized cortical gray matter enlargement, exist in adolescents and adults with autism.

There are a number of limitations to the current study. First, given the heterogeneity in autism the sample in this study was relatively small. This study was also limited by having only T1 scans available for the tissue segmentations. Tissue segmentation with multi-channel input from both SPGR and FSE scans would have allowed us to process more scans from the original sample. Although not optimal, T1 only studies are commonly reported and have the advantage of high spatial resolution. Our lab did a comparison study of brain segmentation methods using single (T1) or multiple channels (Stynner et al 2002) and found comparable results. Additionally, while automated procedures like the Talairach lobe parcellation method (Talairach and Tournoux 1988; Andreasen et al 1996) offer the advantage of reliability and efficiency, the validity of this approach has been questioned. More refined anatomical brain parcellations may provide better estimates for lobe volumes with difficult boundaries, such as posterior temporal-parietal or parietal-occipital borders. The clinical data available were not originally intended to test specific hypotheses about brain-behavior correlations but were evaluated to explore possible relationships. Finally, the cross-sectional nature of the study prevented us from exploring whether brain volume differences changed across adolescence into adulthood. Longitudinal studies of brain development would help clarify the trajectory of gray and white tissue growth in autism.

We express our appreciation for the assistance we received from the following: Drs. Stephen Arndt, Franck Polleux, Anthony-Samuel Lammantia, and Vincent Magowitz.

This research was supported by National Institute of Mental Health grant MH61696 to JP and National Institute of Health Mental Retardation and Development Disabilities Research Center Grant 5 P30 HD03110 to JP.


