Localized Enlargement of the Frontal Cortex in Early Autism

Ruth A. Carper and Eric Courchesne

Background: Evidence from behavioral, imaging, and postmortem studies indicates that the frontal lobe, as well as other brain regions such as the cerebellum and limbic system, develops abnormally in children with autism. It is not yet clear to what extent the frontal lobe is affected; that is, whether all regions of frontal cortex show the same signs of structural maldevelopment.

Methods: In the present study, we measured cortical volume in four subregions of the frontal cortex in 2-year-old to 9-year-old boys with autism and normal control boys.

Results: The dorsolateral region showed a reduced age effect in patients when compared with control subjects, with a predicted 10% increase in volume from 2 years of age to 9 years of age compared with a predicted 48% increase for control subjects. In a separate analysis, dorsolateral and medial frontal regions were significantly enlarged in patients aged 2 to 5 years compared with control subjects of the same age, but the precentral gyrus and orbital cortex were not.

Conclusions: These data indicate regional variation in the degree of frontocortical overgrowth with a possible bias toward later developing or association areas. Possible mechanisms for these regional differences are discussed.

Key Words: Gray matter, white matter, MRI, orbital cortex, dorsolateral, motor

The characteristic symptoms of autism—communication impairments, social deficits, and restricted or repetitive behaviors—suggest that association cortex, particularly that of the frontal lobe, may develop abnormally in this disorder. Patients with autism show deficits in joint attention (McEvoy et al 1993), set shifting (Hughes et al 1994; McEvoy et al 1993; Ozonoff et al 1991), and cognitive planning (Hughes et al 1994), functions believed to involve areas of dorsolateral prefrontal cortex. Abnormalities in motor function are also present (Müller et al 2001; Teitelbaum et al 1998) and suggest the involvement of motor regions, possibly primary motor cortex.

Neuroanatomical examinations also support the likelihood of frontal lobe and other cerebral maldevelopment. Cerebral structure has now been examined in at least 21 postmortem cases by seven different labs (Bailey et al 1998; Belichenko et al 1997; Coleman et al 1985; Fehlow et al 1993; Guerin et al 1996; Kemper and Bauman 1998; Williams et al 1980). Although the reported type and location of cerebral abnormality vary from case to case, several cases have shown defects in the frontal lobe. These have included mild disruptions of laminar organization (Bailey et al 1998); thickened cortex (Bailey et al 1998); increased cell packing density, smaller cells, and a “less distinct laminar structure” in the anterior cingulate (Kemper and Bauman 1998); a minor malformation of the orbitofrontal cortex (Kemper and Bauman 1998); patches of decreased pyramidal cell density (Belichenko et al 1997); and reduced dendritic spine density (Williams et al 1980; note that only case 3 in this study fits criteria for autism).

In the imaging literature, two papers have examined cerebral cortical volume at the lobar level in autism. One found increased volume throughout the cerebrum that was maximal (13% increase) in the frontal lobe of autistic toddlers (Carper et al 2002). In contrast, a study of older children and adults (aged 12 to 30 years) detected enlargement in more posterior lobes but not the frontal lobe (however, see Discussion for a recent reanalysis) (Piven et al 1996). Finally, patients with autism also show metabolic (George et al 1992; Ohnishi et al 2000; Sherman et al 1984; Zilbovicius et al 1995) and electrophysiological (Giesies et al 1990; Dawson et al 1995; Townsend et al 2001) abnormalities in the frontal lobe.

Collectively, these behavioral, metabolic, neuropathologic, and neuroanatomic studies indicate that frontal lobe structure is often abnormal in autism. However, they do not address the localization of these defects in a systematic way. Behavioral and neuropathologic studies do not allow precise localization of abnormality, and out of necessity, neuropathologic studies generally only sample select areas of the frontal lobe rather than survey the entire region. Considering the large number of different cytoarchitectonic regions included in the frontal lobe (14 Brodmann’s areas), further localization of the abnormality is necessary to better characterize the neural bases of autism. Specifically, it is important to determine if the structure of the entire frontal lobe is affected or if abnormality is restricted to particular areas, such as association regions or motor regions. Such localization will help with the development and evaluation of hypotheses regarding possible causal factors such as abnormal protein expression.

We used magnetic resonance imaging (MRI) to examine the volumes of four subregions of the frontal lobe in young children with autism and in young normal control subjects. Neuroanatomic landmarks were used to designate the boundaries of the regions, which were the precentral gyrus (PCG), dorsolateral prefrontal cortex (DFC), orbitofrontal cortex (OFC), and the medial frontal cortex (MFC).

Methods and Materials

Parents of all subjects gave written informed consent for their child’s participation. Experimental procedures were approved by the Institutional Review Board of the San Diego Children’s Hospital Research Center. All patients and subjects were paid for their participation.

Patients with Autism

Twenty-five male patients with autism, aged 2.7 to 9.0 years (mean ± SD: 5.3 ± 1.6 years), were examined. Cerebral and frontal lobe volumes for all of these were included in previous
reports (Carper and Courchesne 2000; Carper et al 2002; Courchesne et al 2001). Frontal measures for eight subjects were also included as part of a report on possible neuroanatomic contributions to orienting deficits in children with autism (Harris et al 1999).

**Diagnostic Procedures.** All subjects were assessed by a trained psychologist and met criteria for the diagnosis of autism according to all of the following: DSM-IV (American Psychiatric Association 1994), Childhood Autism Rating Scale (CARS) (Schopler et al 1988), Autism Diagnostic Interview-Revised (ADI-R) (Lord et al 1994), and Autism Diagnostic Observation Schedule (ADOS) (Lord et al 1999) (Table 1). All subjects who were scanned prior to the age of 5 years met clinical criteria at that time and were also given a second diagnostic evaluation by Dr. Cathy Lord (an expert in the diagnosis of autism who was blind to the MRI measures) when they reached 5 years of age or older. These patients were included only if they met all of the above criteria after the age of 5. Patients diagnosed with pervasive developmental disorders other than autistic disorder were excluded. A complete neurological exam was given, including electroencephalogram (EEG) and brain stem auditory evoked response (BAER) testing. All who met diagnostic criteria were negative for Fragile X syndrome. Five of the patients showed seizure-like activity on EEG, although only one of these had known seizures (7-year-old with brief tonic-clonic episodes). That individual had been treated with Tegretol (carbamazepine) for approximately 8 months prior to imaging and behavioral evaluation.

**Intelligence Estimates.** Subjects were administered one or more standardized tests of intelligence, depending on the child's level of cognitive functioning and cooperation. These included the Arthur adaptation of the Leiter International Performance Scale (Arthur 1980), the Stanford Binet Intelligence Scale (SBIS) (Thorndike et al 1986), and the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) (Wechsler 1991). Subjects were also administered the Peabody Picture Vocabulary Test-Revised (PPVT-R) (Dunn and Dunn 1981), a measure of receptive language ability. Nearly all of the subjects performed better on nonverbal portions of the tests than on the verbal portions, which is typical of patients with autism (Lincoln et al 1995). Because of this, the child's highest score from among the Leiter International Performance Scale, WISC-III performance intelligence quotient (IQ), or Stanford Binet Abstract Reasoning test was used for intelligence estimates.

**Normal Control Subjects**

Eighteen normal healthy male control subjects, aged 2.2 to 8.7 years (mean ± SD: 5.1 ± 1.8 years), were examined. Cerebral and frontal lobe volumes for all were included in previous reports (Carper et al 2002; Courchesne et al 2001) and frontal lobe measures for all but four were reported in a study of correlations between frontal lobe size and cerebellar size in autism (Carper and Courchesne 2000).

Control subjects were recruited through advertisements in the community and showed no evidence of developmental, educational, medical, or psychiatric abnormalities on a pre-MRI screening.

**Intelligence Estimates.** Control subjects were administered the PPVT-R and either the SBIS or the WISC-III, depending on their age at the time of testing. Nonverbal scores are shown in Table 1.

**Imaging and Image Processing**

Autistic patients were anesthetized with propofol by a licensed, board certified anesthesiologist prior to scanning. Control subjects were typically scanned during normal sleep, although some remained awake during scanning. All subjects were scanned on the same 1.5-T GE MRI scanner (Signa, General Electric, Milwaukee, Wisconsin) using a double-echo, proton density (PD) and T2-weighted axial protocol (repetition time [TR] = 3000 milliseconds, echo time [TE] = 30 and 80 milliseconds, 1 number of excitations [NEX], field of view [FOV] = 20 cm, matrix = 256 x 256, 3 mm slices, no gaps). Data were transferred to Silicon Graphics workstations (Mountain View, California) for analysis. Image sets from both subject groups were coded and internixed to ensure experimenter blindness to group.

Axial image sets were processed using an automated tissue classification program (SEGMENT) designed in our laboratory. The algorithms were similar to those described by other researchers in the semiautomated segmentation of nearly identical PD/T2 imaging protocols (Jackson et al 1994; Matsumae et al 1996). Skull and extracranial structures were removed from the T2-weighted images using a combination of thresholding and manual tracing. These images were then used as a mask on the tissue-classified images to create a data set containing only intracranial gray matter, white matter, and cerebrospinal fluid (CSF). Additional details regarding these algorithms and their validation are given in Courchesne et al (2000).

**Volume Measurements**

The volumes of individual brain structures were determined using a combination of manual tracing and computer algorithms. The software AREA (developed in our laboratory) allows the user to refer to the T2, PD, and tissue-classified axial images while tracing a structure, thereby maximizing the anatomical information available. The programs VoxelMath and VoxelView (Vital Images, Inc., Minneapolis, Minnesota) were used to create three-dimensional (3-D) reconstructions of the brain surface from the T2-weighted images, thereby allowing identification of surface landmarks. VoxelMath allows mathematical processing of images to maximize visualization of surface landmarks. VoxelView automatically displays landmarks and manual tracings in all orthogonal slice planes. Finally, LobeWorks (devel-

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### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Autism</th>
<th>Control Subjects</th>
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<tbody>
<tr>
<td></td>
<td>n = 25</td>
<td>n = 18</td>
</tr>
<tr>
<td>Age at MR Scan (years)</td>
<td>5.24 ± 1.63</td>
<td>5.07 ± 1.81</td>
</tr>
<tr>
<td>Seizures (n)</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Mentally Retarded (n)</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>CARS scorea</td>
<td>41.26 ± 4.26</td>
<td>-</td>
</tr>
<tr>
<td>ADI Scoresb: Social</td>
<td>24.38 ± 3.56</td>
<td>-</td>
</tr>
<tr>
<td>Communication:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal subjects (n = 13)</td>
<td>17.92 ± 3.71</td>
<td>-</td>
</tr>
<tr>
<td>Communication:</td>
<td>12.45 ± 1.37</td>
<td>-</td>
</tr>
<tr>
<td>Nonverbal subjects (n = 11)</td>
<td>7.75 ± 1.92</td>
<td>-</td>
</tr>
<tr>
<td>Repetitive behaviors</td>
<td>7.75 ± 1.92</td>
<td>-</td>
</tr>
<tr>
<td>Nonverbal IQc</td>
<td>79.14 ± 22.01</td>
<td>112.76 ± 14.35</td>
</tr>
</tbody>
</table>

ADI, Autism Diagnostic Interview; CARS, Childhood Autism Rating Scale; IQ, intelligence quotient; MR, magnetic resonance.

aCARS scores were not available for two subjects.

bADI scores were not available for one subject.

cThree autistic subjects were unable to complete the nonverbal IQ test.
opened in our laboratory) translates landmarks made in VoxelView into the AREA software for calculation of regional volumes. All steps of volume measurement— including 3-D rendering, landmarking, manual tracing, and evaluation of automated processes—were performed by experienced neuroanatomists using neuroanatomical atlases (Carpenter 1976; Duvernoy 1988; Duvernoy 1991; Mai et al 1997; Nieuwenhuys et al 1988; Ono et al 1990). Five cases were recoded and measured a second time. Intraclass correlations were .88 for OFC, .99 for MFC, .98 for DFC, and .99 for PCG. Maximum absolute volume differences were OFC = 6%, MFC = 4%, DFC = 3%, and PCG = 2%.

**Frontal Cortex Subregions**

**Overview.** The boundary of the frontal lobe was delimited using the method described in Carper and Courchesne (2000), which uses the central sulcus as the primary posterior boundary of the frontal lobe. After the entire frontal lobe was identified in this way, the frontal gray matter was further divided into four subregions per side by one of the authors (R.A.C.) based on the method described by Semendeferi et al (1997). The subregions were orbitofrontal cortex, medial frontal cortex, precentral gyrus, and the remaining dorsolateral convexity. White matter was not subdivided, as it was considered unlikely that a reliable method could be devised. Boundary sulci were identified by viewing the 3-D surface display and sagittal, axial, and coronal slice displays in VoxelView (Figure 1). Note that the processing used to maximize surface image quality also reverses pixel intensity so that white matter appears brighter than gray matter on the T2 images and reduces the apparent thickness of gray matter (Figure 1). These processed images are used only for identification of boundary sulci. Once these were identified, their full extent was traced manually on the original T2 axial slices.

**Separating Orbitofrontal Cortex from Dorsal Convexity.** The orbital cortex was separated from the dorsal region by a boundary passing through the frontomarginal sulcus (FMS) and the lateral orbital sulcus (LOS, alternatively named the fronto-orbital sulcus by Ono et al 1990). The FMS is easily identified in coronal slices, while the LOS is best visualized sagittally. If the FMS and LOS did not connect directly, the surface endpoints of the two sulci were connected by a straight line, which was then used to mark boundary points on the axial slices. Similarly, if the LOS connected directly with the Sylvian fissure or with the horizontal ramus of the Sylvian fissure, the boundary was complete. Otherwise, a straight line was drawn from the surface endpoint of the LOS to the Sylvian fissure at the vertex of the inferior frontal gyrus pars orbitalis. This line was then used to mark boundary points on the axial slices. If the LOS was entirely absent, then the lateral most endpoint of the FMS rather than the LOS was connected to the Sylvian fissure.

**Separating Precentral Gyrus from Dorsal Convexity.** The precentral gyrus was separated from the remainder of the dorsal convexity by a boundary passing through the precentral sulcus (PCS). The PCS generally has two more separate segments. Since these segments frequently intersect with the superior and inferior frontal sulci, only branches that traversed the brain surface in a primarily inferior to superior direction, rather than a posterior to anterior direction, were used. If two segments of the PCS could be visualized on a single axial slice, the boundary line was drawn through both segments so that the posterior aspect of each was classified with the precentral gyrus region of interest.
Comparing Frontal Cortical Regions Between Groups. Repeated measures ANOVA was used to compare regional volumes between the two subject groups in more restricted age ranges. Both groups were separated into two equal age bins by a cutpoint at 5.0 years. This age cutpoint was chosen because it separated subjects into equal-sized bins. This minimized the age-related variability within groups, thereby increasing statistical power. This cutpoint differs from the 4.0-year cutpoint used in our previous report. There is no single exact age at which the rate of brain growth suddenly changes for all individuals (see Figure 2). Therefore, the age cutpoint is somewhat arbitrary. With the current sample of subjects, a cutpoint of 5.0 years provided the largest possible sample size in each age bin. Mean values of age and ROI volume for each of these age bins are shown in Table 2.

The first analysis for each age bin was a three-factor repeated measures ANOVA with ROI (DFC, OFC, MFC, PCG) and hemisphere (left, right) as repeated measures and subject group as the between-subjects variable. If this first analysis did not show effects of laterality (i.e., an interaction between subject group and hemisphere), volumes for the left and right were added together and a second ANOVA was performed using the bilateral volumes. This was a group by ROI analysis. As would be expected, the ROI variable showed significant main effects in all comparisons (e.g., DFC volume is 2.5 to 3 times larger than OFC, so that there is always a main effect of ROI); therefore, main effects of ROI are not described. Results listed below used the Huynh-Feldt adjustment (Box adjustment) to degrees of freedom to correct for failures of sphericity.

Results

Growth of Frontal Cortical Regions

Regression analyses were significant for the DFC [R = .539; F(5,37) = 3.03; p = .02] and MFC [R = .570; F(5,37) = 3.56; p = .01] but not for the other ROIs. Both of these regions showed significant linear relationships with age (DFC: contribution to $R^2$ = .18; p = .004; MFC: contribution to $R^2$ = .26; p = .001), but only DFC showed a significant difference in age effects between groups (i.e., a group by linear age interaction: contribution to $R^2$ = .08; p = .04). In normal control subjects, a DFC volume increase of 48% was predicted from 2 years of age to 9 years of age, but only a 10% increase was predicted in autistic patients (Figure 2). As seen in Figure 2, before age 5, DFC volumes for the two subject groups are strikingly different with very little overlap between the two groups. However, because of the different age effects between the two groups, volumes are fairly similar after about 5 years of age. We performed additional tests to assess whether similar effects might be present, but more subtle, in the other regions of interest. In other words, perhaps the other regions also show enlargement in the youngest subjects but not of sufficient magnitude to be detected in a regression analysis across a broad age range.

Comparing Frontal Cortical Regions Between Groups

Subjects Aged 2.2 to 5.0 Years. Three-way ANOVA for the youngest subjects showed a significant main effect of hemisphere [right > left; F(1,19) = 4.29; p = .05] but no significant
interactions between hemisphere and any other variable. A two-way ANOVA of bilateral volumes revealed a significant group by ROI interaction \( F(3,57) = 6.89; p = .003 \) and a significant main effect of group \( F(1,19) = 8.54; p = .009 \), suggesting that the ROIs were differentially affected in autism. T-tests showed that patients with autism had significantly larger DFC \( (t[19] = 3.22; p = .005) \) and also MFC volumes \( (t[19] = 2.66; p = .02) \) but did not differ significantly on OFC or PCG volumes (Figure 3A).

Finally, to determine if DFC and MFC volumes were differentially affected, the two regions were compared directly. Since the range of volumes differs between these two regions regardless of subject group, volumes were first transformed into z scores based on the mean values and standard deviations of the control subjects. A t test performed in the autism group then revealed a significant difference \( (t[11] = 2.25; p = .05) \), indicating greater abnormal enlargement of DFC than of MFC (Figure 3A).

**Subjects Aged 5 to 9 Years.** Three-way ANOVA for the older children did not reveal significant main effects or interactions related to hemisphere. Subsequent two-way ANOVA of bilateral volumes showed neither a main effect of group nor a group by ROI interaction. Additional analyses were not performed (Figure 3B).

### Removal of Mentally Retarded Patients and Patients with Seizure Disorders

Many patients with autism have IQs in the mentally retarded range. Some researchers prefer to restrict their analyses to either mentally retarded or nonretarded autism patients to simplify. We therefore repeated our comparisons with the mentally retarded subjects \( n = 6 \) removed to make our results more easily comparable to a broader range of other studies. (There were not enough mentally retarded patients to examine this group separately.) Age regressions were significant for OFC, MFC, and DFC \( F(5,31) \geq 2.85; p \leq .03 \), but none of these regions showed significant interactions between group and age; that is, there was no longer evidence of groupwise differences in DFC age effects. However, four of the six retarded patients were over 6.5 years of age, so their removal substantially reduced the group representation at the older end of the age range. This would make it more difficult to achieve a significant regression. Thus, the absence of a significant groupwise difference may be due to the decreased sample size rather than a true lack of effect.

Results of groupwise comparisons were very similar to those described for the full subject sample. Among subjects under age 5 years, there was a significant group by ROI interaction \( F(3,51) = 4.96; p = .01 \) and a significant main effect of group \( F(1,17) = 5.74; p = .03 \). T-tests showed that patients with autism had significantly larger DFC \( (t[17] = 2.79; p = .01) \) and also MFC volumes \( (t[17] = 2.14; p = .05) \) but did not differ significantly on OFC or PCG volumes. However, direct comparison of DFC and MFC did not show significant differences. In patients older than 5 years, two-way ANOVA did not reveal any significant results related to group, although all mean volumes were smaller than normal.

A similar repetition of analyses was performed after eliminating patients with seizure disorder or seizure activity on EEG \( (n = 5) \). Results were very similar to those derived previously. Age-based regression analyses were significant for MFC and DFC regions \( F(3,52) \geq 2.59; p \leq .05 \). The MFC did not show any group-related effects, while the DFC now showed only a trend toward a group by age interaction (contribution to \( R^2 = .078; p = .07 \)). In groupwise analyses of subjects under age 5, there was a significant group by ROI interaction \( F(3,45) = 3.53; p = .05 \) and a significant main effect of group \( F(1,15) = 5.70; p = .03 \). T-tests again showed that patients with autism had significantly larger DFC \( (t[15] = 2.35; p = .03) \) and also MFC volumes \( (t[15] = 2.38; p = .03) \) but did not differ significantly on OFC or PCG volumes. However, there was no significant difference in the degree of abnormality between DFC and MFC. In patients older than 5 years of age, two-way ANOVA did not reveal any significant results related to group.

### Discussion

The present analyses demonstrated that DFC volume increased less with age in the autism group than in normal control subjects. This effect was not detected in the other frontal lobe regions. In addition, the DFC and MFC regions of the frontal lobe are larger than normal in young children with autism (those under age 5). The age effect was not seen when subjects with mental retardation were removed, but this was likely due to the decreased statistical power; all other findings remained the same.

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**Table 2. Mean Volumes and Standard Deviations for Regions of Interest**

<table>
<thead>
<tr>
<th>Region</th>
<th>Autism ( n = 12 )</th>
<th>Control Subjects ( n = 9 )</th>
<th>Autism ( n = 13 )</th>
<th>Control Subjects ( n = 9 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFC</td>
<td>21.46 (2.22)</td>
<td>21.66 (2.96)</td>
<td>22.48 (2.35)</td>
<td>24.31 (2.35)</td>
</tr>
<tr>
<td>MFC</td>
<td>37.25 (3.43)</td>
<td>32.89 (3.35)</td>
<td>40.96 (4.4)</td>
<td>41.35 (4.25)</td>
</tr>
<tr>
<td>DFC</td>
<td>66.11 (6.81)</td>
<td>58.19 (4.36)</td>
<td>69.85 (9.91)</td>
<td>73.2 (7.32)</td>
</tr>
<tr>
<td>PCG</td>
<td>17.86 (2.68)</td>
<td>15.99 (2.37)</td>
<td>17.34 (2.35)</td>
<td>18.14 (3.01)</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFC</td>
<td>21.94 (2.47)</td>
<td>20.59 (3.09)</td>
<td>22.56 (2.24)</td>
<td>23.13 (1.7)</td>
</tr>
<tr>
<td>MFC</td>
<td>37.29 (3.26)</td>
<td>34.12 (3.2)</td>
<td>40.44 (4.72)</td>
<td>40.91 (3.65)</td>
</tr>
<tr>
<td>DFC</td>
<td>66.01 (6.81)</td>
<td>58.32 (4.07)</td>
<td>71.45 (9.58)</td>
<td>74.44 (8.63)</td>
</tr>
<tr>
<td>PCG</td>
<td>18.41 (2.69)</td>
<td>16.77 (2.4)</td>
<td>17.52 (1.55)</td>
<td>18.63 (3.52)</td>
</tr>
<tr>
<td>Total</td>
<td>43.4 (4.07)</td>
<td>42.25 (5.51)</td>
<td>45.03 (4.37)</td>
<td>47.44 (3.69)</td>
</tr>
</tbody>
</table>

DFC, dorsolateral prefrontal cortex; MFC, medial frontal cortex; OFC, orbital frontal cortex; PCG, precentral gyrus.

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Implicit in these results is the notion that very early in life, children with autism must have experienced an abnormally rapid rate of brain growth in the DFC, but that this rate decreased to slower than normal by around age 2. This is supported by our previous findings using retrospective analysis of longitudinal head circumference measures (Courchesne et al 2003). In that study, we found that children who later receive diagnoses of autism have smaller than normal head circumferences (and presumably brain sizes) at birth. Head circumference measures then increase very rapidly in the first year so that by 6 to 14 months of age, head circumferences average in the 95th percentile. The present data emphasize both the transient nature of this accelerated growth, which is followed by slower than normal growth, and the possible regional localization of this effect.

In considering the apparent regional restriction of frontal cortex overgrowth, we must keep in mind the timing of normal brain growth in these areas. Throughout the brain, primary and secondary motor and sensory regions tend to develop more rapidly than regions of association cortex. Dendritic length reaches adult levels earlier in visual sensory cortex than in middle frontal gyrus (association area) (reviewed in Huttenlocher 1990), and in humans, the maximum number of synapses is reached earlier in auditory cortex than in middle frontal gyrus (Huttenlocher and Dabholkar 1997). Similarly, MRI studies suggest that the degree of axonal myelination increases more rapidly in sensory and motor cortex (e.g., precentral, postcentral, and calcarine regions) than in association areas (Barkovich et al 1988; Eckert et al 1996). This heterochronicity of development may make it difficult to detect cerebral hyperplasia in the earliest developing regions. As seen in the DFC and MFC, the pattern of early overgrowth followed by abnormally slow growth can result in regional volumes that are indistinguishable from normal by 5 to 9 years. A similar phenomenon could occur in brain regions that normally develop earlier, such as the PCG. That is, it may be that early hyperplasia does occur in the PCG in autism but that continuing growth in control subjects makes it impossible to detect a volumetric abnormality without examining subjects under 2 years of age. If the OFC region develops more rapidly than other association regions of frontal cortex, then it is also possible that early hyperplasia could have been missed in this region. In any case, it appears clear that there are regional differences in the characteristics of structural frontal lobe abnormality. This is either a true spatial difference, i.e., the dorsolateral region is more deviant than other regions in the autistic frontal cortex, or it may be a temporal difference, i.e., all areas are affected but development of different frontal regions goes away at different time points in development and therefore at different points in the child's learning and experience. Longitudinal studies and studies examining even younger children with autism will be needed to disentangle these two possibilities.

Both within the frontal cortex and across the larger cerebral lobes (Carper et al 2002), we have found early cerebral overgrowth in autism to be more robust in association areas than in regions that are predominantly sensory or motor. These areas have several features in common: They develop comparatively later ontogenetically (as described above); they have developed more recently phylogenetically, which often correlates with common expression of developmental molecules; and they are broadly connected with multiple cerebral areas and multiple modalities. Each of these features compliments recent experimentation or theory in autism, emphasizing the complexity of deciphering this disorder.

A study by Herbert et al (2004) examined cerebral white matter volume in boys with autism, reporting an enlargement of what they classified as “superficial” white matter (white matter immediately beneath the cortex). As with our earlier report (Carper et al 2002), this enlargement had the greatest magnitude in the frontal lobe. They also found that white matter underlying the frontal pole, their area closest to our DFC and OFC regions, was 1.2 standard deviations larger than normal, while white matter close to our PCG region was enlarged by only .8 standard deviations. Thus, their regional findings were again consistent with ours. Based on these and other results, Herbert et al (2004)
conjecture that the ontogenetic timing of myelination is a major driving force in the regional differences in enlargement. Similarly, it may be possible that later developing frontal cortical regions are more susceptible to the processes that cause cerebral overgrowth in autism.

Abnormalities in the expression or effectiveness of developmentally relevant molecules are another possible source of regional differences. It has been reported that brain-derived neurotrophic factor (BDNF) messenger RNA (mRNA) is more densely expressed in dorsomedial than ventral (e.g., orbital) areas of primate prefrontal cortex (Huntley et al 1992), and neurotrophins can affect tissue volume through their effects on neurotrophin expression and neuronal connectivity (Conover et al 1995; Wassink et al 1999). Given the report that levels of BDNF, along with neurotrophic factor 4 (NT-4) and other brain-related substances, may be increased in newborns who later develop autism or mental retardation without autism (Nelson et al 2001), this might be one mechanism contributing to the differences in regional frontal enlargement.

Changes in neurotrophin expression might also contribute to other neuroanatomic abnormalities. Substantial evidence from postmortem studies indicates that Purkinje cell numbers are reduced in the cerebellum in autism (Bailey et al 1998; Fehlow et al 1993; Guerin et al 1996; Kemper and Bauman 1998; Ritvo et al 1986; Williams et al 1980). It is particularly interesting to note that Purkinje cell-granule cell cocultures treated with BDNF or NT-4 show reduced Purkinje cell survival, apparently through excito-toxic mechanisms (Morrison and Mason 1998). So, it is possible that pervasively elevated levels of a neurotrophin such as BDNF or NT-4 could increase the survival of cortical neurons or neuronal processes, as we may have seen in the current study, and simultaneously decrease the survival of Purkinje cells, as is seen in postmortem studies.

Another possible source of regional differences in overgrowth is the effect of abnormal neural activity during development. As described above, a reduction in Purkinje cell numbers is a frequent finding in the autistic cerebellum. It has been suggested that this cellular reduction might lead to a disinhibition of neurons of the deep cerebellar nuclei and that the increased activity that would likely result could alter both structure and function during early brain development via cerebello-thalamocortical projections (Courchesne 1995). This increased activity could rescue cells or processes that would otherwise be pruned during early development (Carper and Courchesne 2000) or it could alter individual cortical maps (Müller et al 2001).

An important question that still remains is the cellular nature of the frontal overgrowth. Is the increased volume due to lateral expansion of certain cytoarchitectonic regions in the autistic brain, such as through an increase in the number of cortical columns or an increase in the width of columns? One study suggests that column width is actually reduced in children and adults with autism (Casanova et al 2002) but the study only sampled one area within the frontal cortex (area 9) and does not examine the overall number of columns. In addition, our previous findings of increased cerebral white matter volume (Carper et al 2002; Courchesne et al 2001) cannot be fully explained by this finding. Is tissue enlargement due to increased cortical thickness, perhaps from the expansion of particular layers or increased numbers of cells per column? Or is it perhaps due to increased complexity and extent (and therefore volume) of dendritic trees? Some of these questions may be directly answerable with MRI, but others will require more systematic examination of the cerebrum in postmortem studies of autism. However, the current results and other MRI-based characterizations of the brain in autism can help to direct these studies, by suggesting clear regions of interest for detailed examination.

To the best of our knowledge, the present study is the first published study to examine the volumes of restricted regions of frontal cortex in autism. Herbert et al (2002) have examined asymmetry indices in this area and volumes of restricted white matter regions (Herbert et al 2004), as described above. Piven et al (1996) had previously reported a lack of enlargement of the frontal lobe in patients aged 12 to 30 years, but after a recent reanalysis using upgraded software, now find frontal enlargement (Piven, unpublished data).

Our results indicate that a substantial portion of the frontal cortex is enlarged very early in autism. Some regions, the orbital cortex and precentral gyrus, are not affected the same way, varying either in degree or in timing of maldevelopment. Due to the pattern of volumetric change across age, these effects may not be evident in older autistic children or adults, although neural connectivity or responsivity might still be abnormal in such patients. Additional research will be needed to determine the timing and cellular characteristics of this cerebral overgrowth.

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