Localized Enlargement of the Frontal Cortex in Early Autism

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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.

Neuroanatomic 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 (Ciesielski et al 1990; Dawson et al 1995; Townsend et al 2001) abnormalities in the frontal lobe.

Collectively, these behavioral, metabolic, neurophysiologic, 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 neurophysiologic studies do not allow precise localization of abnormality, and out of necessity, neuropathological 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

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Table 1. Subject Characteristics

	Autism $n = 25$	Control Subjects $n = 18$
Age at MR Scan (years)	5.24 ± 1.63	5.07 ± 1.81
Seizures (*n*)	5	—
Mentally Retarded (*n*)	6	—
CARS score[a]	41.26 ± 4.26	—
ADI Scores[b]: Social	24.38 ± 3.56	—
Communication: Verbal subjects ($n = 13$)	17.92 ± 3.71	—
Communication: Nonverbal subjects ($n = 11$)	12.45 ± 1.37	—
Repetitive behaviors	7.75 ± 1.92	—
Nonverbal IQ[c]	79.14 ± 22.01	112.76 ± 14.35

ADI, Autism Diagnostic Interview; CARS, Childhood Autism Rating Scale; IQ, intelligence quotient; MR, magnetic resonance.
[a]CARS scores were not available for two subjects.
[b]ADI scores were not available for one subject.
[c]Three autistic subjects were unable to complete the nonverbal IQ test.

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 seizurelike 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 intermixed 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-