Smaller Prefrontal and Premotor Volumes in Boys with Attention-Deficit/Hyperactivity Disorder

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Background: *Anatomic magnetic resonance imaging (MRI) studies of attention-deficit/hyperactivity disorder (ADHD) have been limited by use of callosal rather than sulcal/gyral landmarks in defining cerebral lobes and functionally relevant sublobar regions (e.g., prefrontal cortex). We present an investigation of cerebral volumes in ADHD using a Talairach-based approach that uses cortical landmarks to define functionally relevant regions.*

Methods: *Volumes were compared between groups of 12 boys with ADHD and 12 age- and gender-matched control subjects, using a series of multiple analyses of variance.*

Results: *Boys with ADHD had (on average) 8.3% smaller total cerebral volumes. Significant reductions in lobar volumes were seen only for the frontal lobes. Within the frontal lobes, a reduction was seen in both gray and white matter volumes, with some evidence suggesting lateralization of these findings: reduction in frontal white matter volume was specific to the left hemisphere; there was a bilateral reduction in frontal gray matter volume but more so in the right hemisphere. Subparcellation of the frontal lobe revealed smaller prefrontal, premotor, and deep white matter volumes.*

Conclusions: *Findings suggest that ADHD is associated with decreased frontal lobe gray and white matter volumes. More than one subdivision of the frontal lobes appears to be reduced in volume, suggesting that the clinical picture of ADHD encompasses dysfunctions attributable to anomalous development of both premotor and prefrontal cortices.* Biol Psychiatry 2002;52: 785–794 © *2002 Society of Biological Psychiatry*

Key Words: Attention-deficit/hyperactivity disorder, ADHD, MRI, frontal lobe, Talairach, prefrontal, premotor

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by excessive impulsive, hyperactive, and off-task ("inattentive") behaviors, present either individually or in combination. The neuronal basis of ADHD remains unclear; however, primary hypotheses suggest that ADHD is secondary to abnormalities in frontal-subcortical circuits. Many investigators have been struck by the ways in which the behavioral phenotype of impaired allocation of attention and inadequate inhibitory control may suggest dysfunction of frontal-striatal-cerebellar circuits, analogous to that seen in adult patients with acquired lesions localized to these regions (Barkley 1997; Grodzinsky and Barkley 1999; Lazar and Frank 1998; Pennington and Ozonoff 1996). Evidence from both anatomic (Berquin et al 1998; Castellanos et al 1996, 2001; Filipek et al 1997; Hynd et al 1993; Mostofsky et al 1998) and functional (Amen and Carmichael 1997; Ernst et al 1998; Lou et al 1990; Rubia et al 1999; Vaidya et al 1998; Zametkin et al 1990) neuroimaging studies have lent support to these hypotheses, revealing abnormalities at both subcortical (including basal ganglia and cerebellum) and cortical levels and pointing to dysregulation of the dopaminergic neurotransmitter system in ADHD (Dresel et al 2000; Ernst et al 1998, 1999; Krause et al 2000).

Some of the earliest anatomic magnetic resonance imaging (aMRI) studies found abnormalities in the basal ganglia. One study reported decreased volume of the left globus pallidus (Aylward et al 1996). Reduced caudate volume is a replicated finding, although there is discordance among investigations with regard to right versus left preponderance of the decrement (Castellanos et al 1996; Filipek et al 1997; Hynd et al 1993). Abnormalities have also been reported in the cerebellar vermis, specifically in the posterior inferior vermis, lobules VIII–X (Berquin et al 1998; Castellanos et al 2001; Mostofsky et al 1998).

At the cortical level, indirect evidence suggesting neuroanatomic abnormalities in the cerebral cortex is derived from structural MRI studies of the corpus callosum, which is thought to be a sensitive indicator of cortical anatomy (Witelson and McCulloch 1991). Most investigators have

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reported reduced area of rostral/anterior corpus callosum in ADHD (Baumgardner et al 1996; Giedd et al 1994; Hynd et al 1991); one group reported decreased size of posterior regions (Semrud-Clikeman et al 1994).

Most recently, investigators have begun to use structural imaging techniques to examine quantitative differences at the level of the cerebral cortex. The most consistent findings from these studies are abnormalities in anterior cerebral regions, corresponding to frontal/prefrontal cortices (Castellanos et al 1996; Filipek et al 1997); abnormalities in posterior regions have also been reported (Filipek et al 1997). These studies used an approach reliant on callosal landmarks to subdivide ("parcellate") the cerebrum; they did not use traditional anatomic subdivisions (cerebral lobes or functional subdivisions). Because the regions defined using this technique (e.g., "anterior inferior region") were not based on cortical surface landmarks that define cerebral functional subdivisions, their functional significance was somewhat provisional.

In this study, a semiautomated Talairach-based MRI volumetric approach was used to examine differences of functionally significant cerebral volumes in a group of boys with ADHD. The technique relies on grouping stereotactically defined volumetric units (i.e., voxels) according to cortical landmarks to parcellate the cerebrum into functionally significant volumes: the cerebral lobes (frontal, parietal, temporal, and occipital) and then functionally relevant lobar subdivisions. Gender-based differences in structural MRI findings have been reported in ADHD (Castellanos et al 2001); therefore, and in light of the increased incidence of ADHD in boys (Barkley 1997), we chose to limit our study to boys. Based on findings from previous neuroanatomic, neurophysiologic, and neuropsychologic studies, we hypothesized that in boys with ADHD, abnormalities would be localized to the frontal lobes and, more specifically, to the prefrontal cortex.

Methods and Materials

Subjects

Our study included 12 boys with ADHD (8 right-handed, 2 left-handed, and two ambidextrous) and 12 age- and gender-matched control subjects (10 right-handed, 2 left-handed). The mean age of the group with ADHD, which comprised 12 Caucasians (one of whom was Hispanic), was 10.1 years (range 8.1–13.8 years) with a mean full-scale IQ (FSIQ) of 115 (range 101–131). The mean age of the control group, which comprised 11 Caucasians and one Asian, was 10.2 years (range 8.3–13.6 years), with a mean FSIQ of 125 (range 112–136).

Children with ADHD were recruited from the Developmental Cognitive Neurology and the Neuropsychology outpatient clinics at Kennedy Krieger Institute, advertisements at local ADHD support groups meetings, and through "word of mouth." All children with ADHD met DSM-IV criteria for the disorder, which was confirmed by a child neurologist (SHM). Rating scales and questionnaires were completed by each child's parents and included the DuPaul ADHD Rating Scale (DuPaul 1991), the Conners' Parent Rating Scale—Revised (Conners 1997), and the DICA-R or DICA-IV (Reich et al 1991), a semistructured diagnostic interview. Children needed to meet criteria on at least two of the three rating scales/questionnaires to be included as participants with ADHD. Four children met criteria for the inattentive type of the disorder (ADHD, predominantly inattentive type); eight children had symptoms of hyperactivity and impulsivity as well as inattention and therefore met criteria for combined type ADHD (ADHD, combined type). Results from the DICA revealed comorbid oppositional defiant disorder in three of the subjects, one of whom also had a simple phobia. The presence of comorbid conduct disorder, mood disorder, generalized anxiety disorder, separation anxiety disorder, or obsessive–compulsive disorder served to exclude children from this study, as did the presence of a reading disability, based on discrepancy between full-scale IQ from the Wechsler Intelligence Scale for Children—III (Wechsler 1991) and the reading composite from the Wechsler Individual Achievement Test (Wechsler 1992). None of the subjects with ADHD had any history of other neurologic disorders, including Tourette syndrome. Medication history revealed that 10 of the 12 subjects had been treated with stimulant medications, one of whom had also been treated with clonidine; 2 of the 12 subjects had not been treated with medications to address behaviors associated with ADHD.

Children in the control group were selected from participants who responded to advertisements placed at community wide service groups, volunteer organizations, local schools, and medical institutions, as well as through "word of mouth" through other participants. Children included as control subjects were deemed free of ADHD if they did not meet criteria on all rating scales/questionnaires administered. For four of the control subjects, the questionnaires administered included the DICA-IV, DuPaul, and Conners'. For the other eight, they included the Achenbach Child Behavior Checklist (Achenbach 1991) and the Revised Behavior Problem Checklist (Quay and Peterson 1987). None of the control subjects had any other history of neurologic or psychiatric disorders; the latter was confirmed in all control subjects using either the DICA or both the Achenbach Child Behavior Checklist and Revised Behavior Problem Checklist.

The study was approved by the Johns Hopkins Joint Committee on Clinical Investigation. For all subjects, written consent was obtained from a parent or guardian, and written assent was obtained from participating children.

Image Acquisition and Processing

All children were evaluated with routine clinical brain MRI scans (T1-weighted and T2-weighted sequences) and three-dimensional volumetric radiofrequency spoiled gradient (SPGR) scans. Scans were performed on a 1.5-T General Electric Signa Scanner (Milwaukee, WI) using the standard GE quadrature head coil. The MR protocol consisted of the following series: sagittal T1 and axial spin-density/T2-weighted brain MRI, followed by SPGR with the following scan parameters: TR = 35–45, TE = 5–7, flip angle = 45, NEX = 1, matrix size = 256 × 128, field

of view = 20–24. Each SPGR series was partitioned into 124, 1.5 mm slices.

The raw, GE-Signa-formatted image data were transferred to Apple Macintosh Power PC workstations via network connections. The SPGR image data were imported into the program BrainImage (Reiss et al 1997) for visualization, processing, and quantitative analysis (Subramaniam et al 1997). The importation process creates a 124-slice image stack composed of spatially registered, 8-bit images that have been processed to minimize signal artifacts related to radio frequency (RF) field inhomogeneity. To prepare the stacks for measurement, nonbrain material (e.g. skull, musculature, and vasculature) was removed from these image stacks using a semiautomated edge detection routine that involves region growing as well as stepwise morphologic operations (Subramaniam et al 1997). These "skull stripped" images were resliced so that the interpolated slice thickness (z dimension) was the same as the x and y pixel dimensions, thereby converting the image stacks into cubic voxel data sets. The cubic voxel data sets were opened into the multiplanar visualization module of BrainImage so that three orthogonal representations of the data could be viewed simultaneously.

Image Measurements

Isolated brain tissue was segmented into gray, white, and cerebrospinal fluid (CSF) compartments by a fuzzy segmentation protocol that used an algorithm to assign voxels to one or more tissue categories based on intensity values and tissue boundaries. The segmentation method has previously been shown to be reliable for all gray matter, white matter, and CSF volumes (Reiss et al 1998).

The brain tissue was subdivided into cerebral lobes, subcortical, brainstem, and cerebellar regions according to a revised Talairach stereotaxic grid specific for measurement in pediatric study groups (Kaplan et al 1997; Kates et al 1999). This approach has been shown to yield high levels of sensitivity and specificity for all lobar brain regions (Kates et al 1999). For this study, only cerebral and lobar brain volumes were used (i.e., subcortical, brain stem, and cerebellar regions were not included). The lobar volumes that differed significantly between the groups were subdivided into functionally significant subdivisions also based on the Talairach grid.

We have developed a procedure for measuring fine-grained, functionally relevant Talairach-based subdivisions within all four lobes (frontal, parietal, temporal, and occipital). As we followed our analytic strategy, the only justifiable sublobar analyses were for the frontal lobe. (Descriptions of methodology for subdividing the other lobes are available by contacting WEK.)

The frontal lobe was subdivided into the following regions: motor, premotor, prefrontal, anterior cingulate, and deep white matter, as shown in Figure 1. The Talairach sector assignments for these subdivisions were based on the identification of landmarks and boundaries described below in a set of 10 "standard" pediatric brains chosen at random and which included both typically developing children as well as those with developmental disorders, as described in Kates et al (1999). Four major landmarks (gyri, sulci) were used for this parcellation strategy: the central sulcus, the precentral sulcus, the ascending ramus of the Sylvian fissure/anterior paraolfactory sulcus, and the cingulate sulcus, resulting in subdivisions defined as follows:

1. Motor cortex, the volume between the planes of the precentral and central sulci.
2. Premotor cortex: the volume between the planes of the precentral sulcus and the ascending ramus of the Sylvian fissure–anterior paraolfactory sulcus. The premotor cortex includes, among others, the supplementary motor area (SMA), the Broca's area, and the frontal eye fields (FEF).
3. Prefrontal cortex: the volume anterior to the plane defined by the ascending ramus of the Sylvian fissure/anterior paraolfactory sulcus. The prefrontal cortex includes, among others, the dorsolateral prefrontal, lateral orbitofrontal, and medial orbitofrontal cortices.
4. Anterior cingulate: the volume delineated by the cingulate and callosal sulci and, posteriorly, by the plane of the central sulcus.
5. Deep frontal white matter: the frontal volume of white matter that is "outside" or deep with respect to a line connecting adjacent sulcal cortices.

Research assistants, blind to the diagnostic status of every subject, carried out all measurements. Interrater reliability coefficients for tissue segmentation were .99, .99, and .96 for gray matter, white matter, and CSF volumes, respectively. Talairach parcellation, however, is based on a predefined grid, so reliability measurements are not applicable.

Data Analyses

Normality of data within each group was plotted and examined visually, then verified with the Kolmogrov–Smirnov test for age distribution (an important independent variable) and total cerebral tissue volumes (the overall dependent variable; $p > .9999$ for both groups). Volumes were compared between groups using a hierarchical approach by a series of two-tailed multiple analyses of variance (MANOVAs). These analyses were conducted in a stepwise fashion, from larger to smaller volumes as dependent variables, divided by the number of comparisons (with Bonferroni corrections for multiple comparisons at each step. Significance levels were set at p value less than .05, divided by the number of comparisons (Bonferroni correction). The sequential comparisons were determined by the significant findings in the preceding step; only those comparisons that were significant were analyzed in further detail. The sequence of analyses (with number of comparisons used in Bonferroni correction) was as follows:

1. Total cerebral tissue volume (TCV; Tissue volumes include both gray and white matter, but exclude CSF).
2. Total cerebral gray matter volume and total cerebral white matter volume (corrected for two comparisons).
3. Lobar tissue volumes: frontal, parietal, temporal, and occipital (corrected for four comparisons).
4. Any significant difference derived from step 3 to be analyzed with regard to differences specified in terms of left-side and right-side gray and white matter volumes (each corrected for two comparisons). In addition, compar-

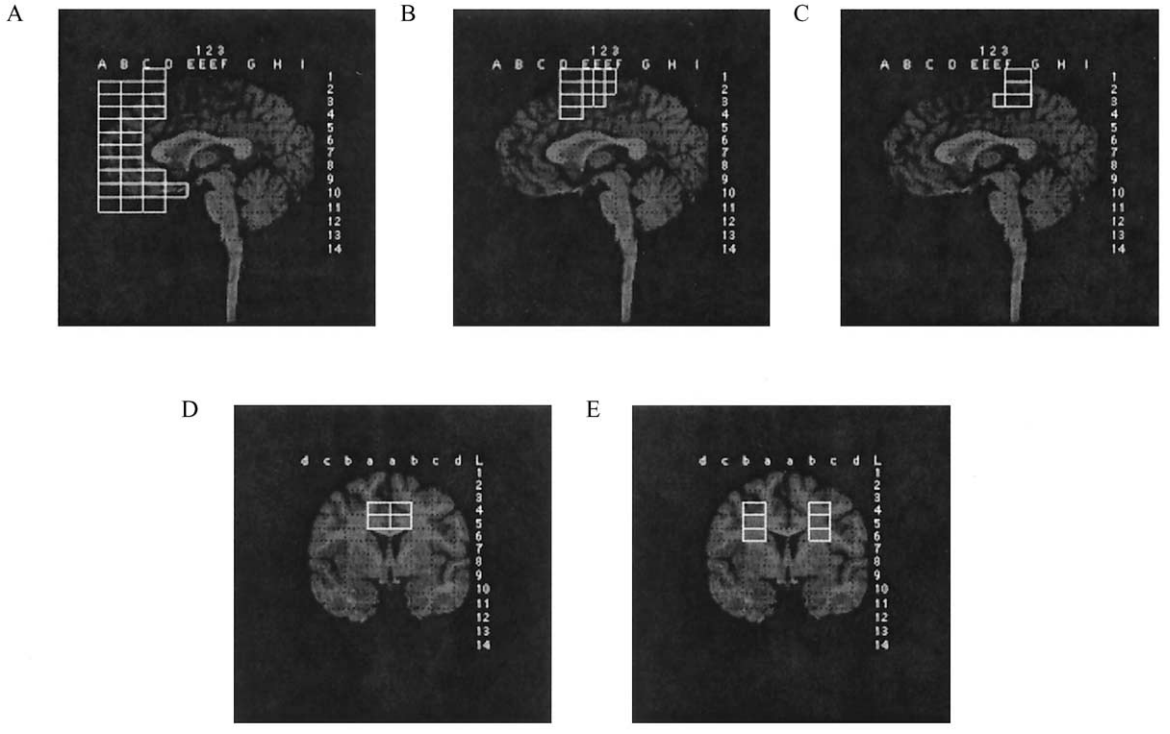

Figure 1. Delineation of frontal lobe subdivisions by Talairach coordinate system. The upper row of images depicts Talairach sectors corresponding to prefrontal **(A)**, premotor **(B)**, and motor **(C)** regions superimposed over midsagittal views of a "standard" brain. The lower row shows similar type of images in the coronal plane for Talairach sectors corresponding to the anterior cingulate **(D)** and deep white matter **(E)** frontal subdivisions. The assignment of sectors to a particular frontal subdivision followed the same general strategy that we reported in previous publications on lobar divisions (Kaplan et al 1997; Kates et al 1999), but also took into consideration individual landmarks detailed in Methods and Materials on a set of 10 brains from pediatric control subjects and children with developmental disorders ("standard" brains). Only sectors consistently included within the defined boundaries were assigned to a particular subdivision. Volumetric determinations were circumscribed to the appropriate tissue component of each sector.

isons of left–right volumetric symmetry were also conducted and were based on a symmetry coefficient (L–R) / [(0.5)(L + R)] followed by an analysis of variance (ANOVA) to assess the probability that the mean of the distribution differed significantly from zero.

5. Any significant difference derived from step 3 (i.e., lobar tissue volume) to be further analyzed with regard to lobar subdivisions (corrected for number of lobar subdivisions, e.g., five comparisons for frontal lobe subdivisions).
6. Any significant difference from step 5 (i.e., lobar subdivision tissue volume) to be analyzed with regard to differences specified in terms of right-side and left-side gray and white matter volumes (each corrected for two comparisons).

Results

Prerequisite Analyses of Independent Variables

Significant differences were found between the groups in FSIQ, but not age. The FSIQ of the control group was significantly higher than that of the ADHD groups [$F(1,22) = 7.849$, $p = .01$]; however, we elected not to covary for IQ. Our rationale for this was that it seems circular to control for IQ measurements that may be substantially determined by anatomic variations or differences. For instance, IQ test scores may be lowered by ADHD-associated deficits in executive functions, including motor response preparation, and working memory, which have their bases in frontal lobe circuitry (Barkley 1997).

Main Analyses

Results from analyses of cerebral, lobar, and lobar subdivision volumes for ADHD and control subjects are summarized in Table 1 (with Bonferroni corrected p values reported). The analyses for total cerebral volume, including gray and white matter but excluding CSF, revealed that the cerebral volume of the control group was 8.3% larger than that of ADHD group [$F(1,22) = 9.632$, $p = .0052$]. Both total cerebral gray [$F(1,22) = 7.262$, $p = .0264$] and

Table 1. Cerebral and Lobar Volumes for ADHD and Control Subjects

	ADHD (n = 12)	Control subjects (n = 12)	Statistics (Dx: $F_{1, 22}$)	Probability (Bonferroni corrected)	Mann–Whitney (Bonferroni corrected)
Cerebral volumes					
Total cerebral volume	1137.955 ± 101.701	1241.420 ± 54.713	9.632	.0052	.0111
Total GM	694.828 ± 50.702	745.625 ± 41.148	7.262	.0264	.0188
Total WM	443.127 ± 56.396	495.795 ± 26.469	8.577	.0156	.0358
Lobar volumes					
Frontal tissue	412.604 ± 38.187	462.495 ± 27.541	13.475	.0052	.0108
Parietal tissue	296.204 ± 32.317	317.918 ± 23.488	3.545	*ns*	*ns*
Temporal tissue	210.993 ± 18.110	227.347 ± 16.615	5.314	*ns*	*ns*
Occipital tissue	129.991 ± 12.885	139.923 ± 7.029	5.495	*ns*	*ns*
Frontal lobe GM/WM volumes					
Frontal GM	246.307 ± 19.030	270.838 ± 16.926	11.133	.0060	.0064
Frontal WM	166.296 ± 21.702	191.656 ± 14.179	11.484	.0052	.0306
Frontal GM-R	127.045 ± 9.267	141.533 ± 9.026	15.052	.0016	.0054
Frontal GM-L	119.262 ± 10.689	129.307 ± 8.455	6.518	.0362	.0486
Frontal WM-R	85.032 ± 12.277	95.635 ± 9.470	5.611	*ns*	*ns*
Frontal WM-L	81.263 ± 9.786	96.020 ± 6.409	19.098	.0008	.0030

All values are cm^3 and are reported as means ± standard deviation, *ns* (not significant p value set at .05 after Bonferroni correction).
ADHD, attention-deficit/hyperactivity disorder; GM, gray matter; WM, white matter; R, right side; L, left side.

total cerebral white [$F(1,22) = 8.577$, $p = .0156$] matter volumes were significantly smaller in the group of children with ADHD.

The MANOVA for lobar tissue volumes determined that the frontal tissue volume was smaller in the ADHD group [$F(1,22) = 13.475$, $p = .0052$], whereas the parietal, temporal, and occipital lobar tissue volumes were not significantly different from those of the control group. The decrease in frontal lobe volume accounted for 48% of the reduction in total cerebral volume. A ratio of frontal lobe tissue volume to nonfrontal tissue volume has been used in previous studies to help establish specificity of frontal findings (Kates et al 2001). The ratio of frontal lobe tissue volume to nonfrontal tissue volume in the ADHD group was smaller than that of the control group at a trend level of significance [$F(1,22) = 3.433$, $p = .0774$]; in contrast, there were no significant differences (or trends) for ratios of other lobar volumes (e.g., ratio of parietal lobe tissue volume to nonparietal tissue volume).

Within the frontal lobe, both gray [$F(1,22) = 11.133$, $p = .006$] and white [$F(1,22) = 11.484$, $p = .0052$] matter volumes were significantly smaller in the ADHD group. There appeared to be an effect of laterality for both gray and white matter frontal lobe volumes: left frontal white matter was significantly smaller in the group of boys with ADHD [$F(1,22) = 19.098$, $p = .0008$], whereas the right was not. In contrast, frontal gray matter volume was significantly smaller in the group of boys with ADHD bilaterally, more so on the right [$F(1,22) = 15.052$, $p = .0016$] than the left [$F(1,22) = 6.518$, $p = .0362$]. There were, however, no significant group differences in symmetry of frontal volumes.

The MANOVA for frontal lobe subdivisions determined that both prefrontal [$F(1,22) = 15.203$, $p = .004$] and premotor [$F(1,22) = 13.01$, $p = .008$] tissue volumes were smaller in the ADHD group (Figure 2), as was the volume of the deep white matter [$F(1,22) = 9.778$, $p = .0245$]. The motor and anterior cingulate tissue volumes

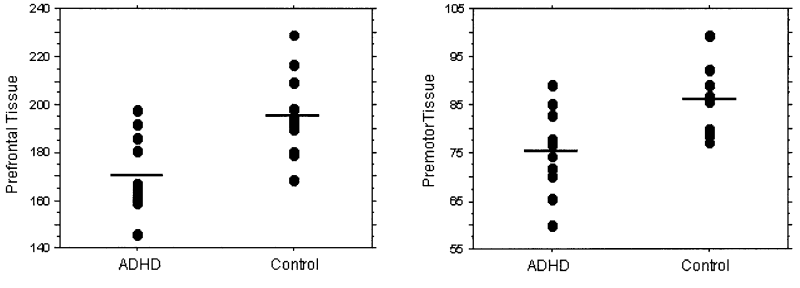

Figure 2. Bivariate plots showing smaller prefrontal and premotor tissue volumes (cm^3) in 12 boys with attention-deficit/hyperactivity disorder (ADHD) compared with 12 age-matched male control subjects.

Table 2. Frontal Lobar Subdivision Volumes for ADHD and Control Subjects

	ADHD (n = 12)	Control subjects (n = 12)	Statistics (Dx: $F_{1, 22}$)	Probability (Bonferroni corrected)	Mann–Whitney (Bonferroni corrected)
Frontal subdivision volumes					
Prefrontal tissue	170.367 ± 15.294	195.849 ± 16.692	15.203	.0040	.0090
Premotor tissue	75.618 ± 8.169	86.175 ± 6.005	13.010	.0080	.0090
Motor tissue	46.637 ± 5.317	51.210 ± 3.469	6.227	*ns*	*ns*
Anterior cingulate tissue	31.547 ± 3.648	34.036 ± 1.412	4.859	*ns*	*ns*
Deep WM	50.743 ± 6.114	56.871 ± 2.951	9.778	.0245	.0395
Subdivision GM/WM					
Prefrontal GM	118.528 ± 9.291	133.608 ± 11.389	12.631	.0036	.0064
Prefrontal WM	51.837 ± 7.663	62.241 ± 7.458	11.360	.0056	.0158
Premotor GM	53.509 ± 4.869	60.354 ± 3.685	15.078	.0016	.0024
Premotor WM	51.837 ± 7.663	62.241 ± 7.458	5.259	*ns*	*ns*
Subdivision hemispheric volumes					
Prefrontal GM-R	61.730 ± 4.684	69.998 ± 6.634	12.438	.0038	.0122
Prefrontal GM-L	56.798 ± 5.194	63.608 ± 5.242	10.219	.0084	.0112
Prefrontal WM-R	26.626 ± 4.811	31.545 ± 3.880	7.599	.0230	.0188
Prefrontal WM-L	25.211 ± 3.329	30.698 ± 4.117	12.882	.0032	.0112
Premotor gray GM-R	27.411 ± 2.743	31.203 ± 1.872	15.645	.0014	.0014
Premotor gray GM-L	26.098 ± 2.428	29.152 ± 1.963	11.471	.0054	.0078
Premotor WM-R	26.626 ± 4.811	31.545 ± 3.880	1.481	*ns*	*ns*
Premotor WM-L	25.211 ± 3.329	30.698 ± 4.117	12.974	.0032	.0102
Deep WM-R	26.302 ± 3.260	29.094 ± 1.861	6.635	.0344	.0418
Deep WM-L	24.440 ± 2.921	27.775 ± 1.515	12.330	.0040	.0134

All values are cm^3 and are reported as means ± standard deviation, *ns* (not significant p value set at .05 after Bonferroni correction).
ADHD, attention-deficit/hyperactivity disorder; GM, gray matter; WM, white matter; R, right side; L, left side.

were not significantly different from those of control subjects.

Within the prefrontal subdivision, both gray [$F(1,22)$ = 12.631, p = .0036] and white matter [$F(1,22)$ = 11.36, p = .0056] volumes were significantly smaller in the ADHD group. Prefrontal gray matter volumes were significantly smaller bilaterally in the group of children with ADHD [left: $F(1,22)$ = 10.219, p = .0084; right: $F(1,22)$ = 12.438, p = .0038], as were prefrontal white matter volumes [left: $F(1,22)$ = 12.882, p = .0032]; right [$F(1,22)$ = 7.599, p = .023]. There were no significant group differences in symmetry of prefrontal volumes.

Within the premotor subdivision, gray matter volume [$F(1,22)$ = 15.078, p = .0016] was significantly smaller in the ADHD group, and these differences were seen bilaterally [left: $F(1,22)$ = 11.471, p = .0054]; right: [$F(1,22)$ = 15.645, p = .0014]. There was no significant difference in total premotor white matter volume; however, left premotor white matter volume was significantly smaller in the group of boys with ADHD [$F(1,22)$ = 12.974, p = .0032]. There were no significant group differences in symmetry of premotor volumes.

Both left [$F(1,22)$ = 12.330, p = .004] and right [$F(1,22)$ = 6.635, p = .0344] frontal deep white matter was significantly smaller in the ADHD group; there was no significant difference in symmetry of frontal deep white matter.

Because of the relatively small sample size, lobar and sublobar analyses were also conducted using nonparametric (Mann–Whitney) tests to ensure validity of our findings. Results confirmed findings from parametric analyses and are shown in Tables 1 and 2.

Discussion

In this study, MRI volumetric measurement was used to assess cerebral cortical abnormalities in boys with ADHD. Consistent with our hypotheses, we found that, compared with age- and gender-matched control subjects, boys with ADHD had smaller absolute frontal lobe volumes. The findings appear to be specific to the frontal lobe. First, there were no significant differences seen in other cerebral lobes. Second, the decrease in total cerebral volume in boys with ADHD was primarily accounted for by smaller frontal lobe volume. Finally, the ratio of the frontal lobe tissue volume to the nonfrontal tissue volume in the ADHD group tended to be smaller than that of the control group, suggesting specificity of frontal lobe findings.

Within the frontal lobes, we observed a reduction in both gray and white matter volumes. There was suggestion of laterality in these findings: reduction in frontal white matter volume was specific to the left hemisphere; there was a bilateral reduction in frontal gray matter volume, but more so on the right than the left. Lateralized findings

have been reported in previous aMRI studies (Aylward et al 1996; Castellanos et al 1996; Filipek et al 1997; Hynd et al 1993; Mataro et al 1997), as well as functional imaging (Ernst et al 1998; Lou et al 1989; Rubia et al 1999; Seig et al 1995; Vaidya et al 1998), electrophysiology (Oades et al 1996; Silberstein et al 1998), and neuropsychological (Epstein et al 1997; Nigg et al 1997; Sheppard et al 1999; Voeller and Heilman 1988) studies. For instance, in one previous study in which aMRI was applied to cerebral cortical measurements in ADHD (Castellanos et al 1996), decreased volume was localized to the "right anterior frontal" region. In a separate study (Filipek et al 1997), investigators found decreased volume of the right "anterior-superior (frontal)" region (both en bloc and white matter) with bilateral reduction of the "anterior-inferior" region.

Observations of right hemisphere dominance for sensory-attentional (Damasio et al 1980; Gainotti et al 1972; Heilman and Van Den Abell 1980) and for motor intentional systems involved in response inhibition (Kertesz et al 1985; Verfaellie and Heilman 1987), along with observations from the previously mentioned studies, have led some to hypothesize that ADHD is a "right-hemisphere syndrome" (Heilman 1991; Stefanatos and Wasserstein 2001). Others, however, have suggested that ADHD may involve bihemispheric dysfunction (Malone et al 1994). The findings from our study appear to suggest a differential contribution of both the right and left hemisphere, with gray matter abnormalities (most likely reflecting anomalies in neuronal structure) being present bilaterally, although to a greater degree in the right hemisphere, and white matter abnormalities (possibly reflecting disrupted efferent or afferent connections of the frontal lobe, including those with the basal ganglia) being lateralized to the left hemisphere.

Our findings of smaller total cerebral and frontal lobe volumes are consistent with previous aMRI studies of children with ADHD (Castellanos et al 1996; Filipek et al 1997), both of which revealed primarily "anterior" abnormalities within the cerebral cortex, with one study (Filipek et al 1997) also revealing decreased volume of bilateral retrocallosal region white matter. Both of the aforementioned studies used callosal landmarks to parcellate the cerebral lobes, generating subdivisions that only roughly approximated established functional cerebral demarcations. The semiautomated technique outlined in this study relied on cortical surface landmarks to define cerebral lobar subdivisions. In doing so, we were able to show that the frontal lobes themselves (rather than more arbitrarily defined "anterior" regions of the cerebrum) are indeed smaller in boys with ADHD. Limitations of Talairach-based parcellation need to be pointed out. In particular, it does not take into account the gyral–sulcal landmarks of each individual subject's brain; rather, it bases those landmarks on a set of "standard" brains and therefore is though to be less accurate than "gold standard" manual delineation. Talairach-based parcellation has, however, been shown to yield high levels of sensitivity and specificity for all lobar brain regions in both adults (Andreasen et al 1996) and children (Kates et al 1999).

In our study, Talairach-based parcellation proved advantageous in that it provided an efficient means for subparcellating the frontal lobes into functionally significant regions of interest. We hypothesized that within frontal lobes, abnormalities would be specific to prefrontal cortex. We did find significantly smaller prefrontal tissue volume in boys with ADHD; however, we also found reduced premotor tissue volume and reduced deep white matter volume. The results suggest that, at the cortical level, frontal abnormalities associated with ADHD are not restricted to the prefrontal cortex (defined in this study to include, among others, dorsolateral and orbitofrontal cortices), where most research has focused.

Our finding of smaller prefrontal and premotor size in boys with ADHD could be explained by the presence of broadly distributed abnormalities throughout these brain regions. Alternatively, it is possible that the findings could be driven by more localized abnormalities within both premotor and prefrontal subdivisions. We are currently developing manual techniques to further subparcellate these frontal lobe subdivisions, which might help to answer this question. In either case, the findings appear to indicate that abnormalities in ADHD exist within both premotor and prefrontal cortices.

Parallel frontal-striatal circuits that mediate motor, oculomotor, cognitive "executive" functions and socially responsive behavior have been described (Mega and Cummings 1994). A similar parallel organization may also exist for frontal-cerebellar circuits (Middleton and Strick 1997; Schmahmann 1997), which have also been hypothesized to contribute to the pathophysiology of ADHD (Berquin et al 1998; Castellanos et al 2001; Mostofsky et al 1998). Although some investigations have emphasized abnormalities in specific circuits, in particular those originating in lateral orbitofrontal regions, thought to mediate inhibition of inappropriate socioemotional behavior (Lichter and Cummings 2001), our findings suggest that the abnormalities in ADHD may not be entirely restricted to a single circuit. Rather, there may be a common developmental abnormality that encompasses a number of parallel circuits, particularly those within premotor (which includes the "supplementary motor area" and "oculomotor" circuits described by Mega and Cummings) and prefrontal regions (which includes the "dorsolateral prefrontal" and "lateral orbitofrontal" circuits also described).

Motor, oculomotor, and cognitive findings appear to support our observation that abnormalities in ADHD involve more than one of these circuits. Investigations of individuals with ADHD have shown prolonged and excessive variability in reaction time (Reader et al 1994; Teicher et al 1996), excessive overflow movements on motor examination (Barker et al 2001; Denckla and Rudel 1978), and deficits on motor response inhibition tasks (Mostofsky et al 2001a; Mostofsky et al 2001b; Shue and Douglas 1992). These findings point to abnormalities within circuits originating in supplementary and other premotor areas. Consistent with these limb-motor findings, oculomotor studies of ADHD have revealed excessive variability in saccade latency/reaction time and deficits in tasks requiring inhibition of eye movements (e.g., excessive directional errors on antisaccade task) (Mostofsky et al 2001a; Mostofsky et al 2001b; Munoz et al 1999; Ross et al 2000). Involvement of prefrontal circuits in ADHD is implicated by abnormalities in working memory associated with circuits originating in the dorsolateral prefrontal cortex; lateral orbitofrontal regions, important in control of socially responsive behavior (Adolphs 2001) are hypothesized to contribute to socially disinhibited ("impulsive") behavior that is a prominent impairment associated with ADHD.

Deficits in response inhibition in ADHD can be attributed to SMA/premotor (overflow movements; deficits in motor response inhibition), oculomotor (e.g., directional errors on antisaccades), and prefrontal (behavioral disinhibition) circuits. Impaired response inhibition has been hypothesized to be the most fundamental developmental deficit in ADHD (Barkley 1997), and our findings of decreased volumes of both premotor and prefrontal regions suggest impairment of more than one type of inhibition in ADHD, each an inhibitory component of a response capability dependent on its own specialized frontal-subcortical circuit. Thus, parallel deficits in motor, oculomotor, cognitive, and social response preparation/inhibition in ADHD may be manifestations of neighboring, but separate, abnormalities of parallel neural circuits. Examination of brain–behavior relationships through correlations of behavioral and aMRI findings, further linked by functional imaging analyses, will help to confirm this multiple domain model of response inhibition.

In this article, we have reported ADHD-related frontal volume reductions; these are both in prefrontal (encompassing, among others, the dorsolateral prefrontal, lateral orbitofrontal, and medial orbitofrontal cortices) and premotor (encompassing, among others, the SMA, Broca's area, and the FEF) regions. The study is limited by its small sample size and by the inclusion of only male subjects. In the future, we intend to confirm these findings with a larger sample, as well as explore whether the findings are relevant to girls with ADHD. It would also be important to determine whether the findings are consistent across ADHD subtypes (inattentive, hyperactive/impulsive, and combined type). Future studies with larger numbers of subjects will not only allow us to address the influence of gender and subtype but also of comorbid diagnoses on anatomic MRI findings in ADHD. Increasing the number of subjects will also allow us to examine differences specific to functionally relevant subdivisions (e.g., dorsolateral prefrontal and SMA) within prefrontal and premotor regions.

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