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Cortical Thinning of the Attention and Executive Function Networks in Adults with Attention-Deficit/Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) has been associated with structural alterations in brain networks influencing cognitive and motor behaviors. Volumetric studies in children identify abnormalities in cortical, striatal, callosal, and cerebellar regions. In a prior volumetric study, we found that ADHD adults had significantly smaller overall cortical gray matter, prefrontal, and anterior cingulate volumes than matched controls. Thickness and surface area are additional indicators of integrity of cytoarchitecture in the cortex. To expand upon our earlier results and further refine the regions of structural abnormality, we carried out a structural magnetic resonance imaging study of cortical thickness in the same sample of adults with ADHD ($n = 24$) and controls ($n = 18$), hypothesizing that the cortical networks underlying attention and executive function (EF) would be most affected. Compared with healthy adults, adults with ADHD showed selective thinning of cerebral cortex in the networks that subserve attention and EF. In the present study, we found significant cortical thinning in ADHD in a distinct cortical network supporting attention especially in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal, and the anterior cingulate cortices. This is the first documentation that ADHD in adults is associated with thinner cortex in the cortical networks that modulate attention and EF.

Keywords: ADHD, attention, cerebral cortex, cortical thickness, executive function

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood onset, highly prevalent neurobehavioral disorder, with genetic and environmental etiologies that persists into adolescence and adulthood in a sizeable majority of afflicted children of both genders. Its prevalence is in the same range worldwide (Faraone and others 2003), estimated to affect 8–12% of children (Faraone and others 2003) and approximately 4% of adults (Faraone and others 2004; Kessler and Merikangas 2004). It is characterized primarily by behavioral symptoms of inattention, hyperactivity, and impulsivity across the life cycle (Biederman 2005). These developmentally inappropriate symptoms of inattention, impulsivity, and motor restlessness are typically discernible before the age of 7 years, pervasive across situations, persist to a substantial extent throughout adolescence and adulthood (APA 2000; Biederman 2005), and tend to develop within a scenario of psychiatric comorbidity (Biederman and others 1991; Pliszka 1998; Kessler and Merikangas 2004) and neuropsychological deficits, especially in attention and executive functions (EFs) (Seidman, Valera, and Bush 2004; Seidman 2006). Although its etiology remains unclear, its strong familial nature (Faraone and others 1995; Faraone and Doyle 2001) and high levels of heritability (0.77) (Faraone and others 2005) strongly support a genetic etiology.

ADHD was first described 100 years ago under the name "hyperactivity" or "hyperkinesis disorder in childhood" found mainly in boys (Still 1902) who were thought to grow out of the disorder by teenage years. Although in the 1960s it was renamed with the now outmoded term "minimal brain damage" or "minimal brain dysfunction" suggesting that this could be a brain disorder, it was actually in the 1970s that ADHD sparked a renaissance of interest in childhood maladies when the feature of inattention was introduced as its central defining feature (Douglas 1972). The renaming of the disorder and the focus on "attention" led to a more specific brain localization perspective (Mattes 1980; Barkley 1997), a drive catalyzed by novel insights in the neurological bases of attention (Heilman and others 1970, 1983; Mesulam 1990; Posner and Petersen 1990). Moreover, many studies in the last decade have supported the validity of the adult form of the disorder (Faraone and others 2004).

The neuroanatomy of ADHD is being actively investigated in many laboratories around the world, including ours. Convergent data from neuroimaging, neuropsychological, genetic, and neurochemical studies have implicated dysfunction of dorsolateral prefrontal (DLPFC) and dorsal anterior cingulate (dACC) cortical structures (Bush and others 1999, 2005; Castellanos and others 2002; Durston 2003; Sowell and others 2003; Seidman, Doyle, and others 2004; Seidman and others 2005), which constitute the cortical arm of the frontostriatal network supporting EF. In addition to DLPFC and dACC, other regions within a distributed cortical network supporting attention have been identified including posterior parietal cortex and centers at the temporo-occipitoparietal junction in the lateral surface of the right hemisphere, principally the angular (Brodmann's area

39 [BA 39]) and supramarginal (BA 40) gyri (Heilman and others 1970; Goldman-Rakic 1988; Mesulam 1990; Posner and Petersen 1990; Cabeza and Nyberg 2000; Duncan and Owen 2000; Corbetta and Shulman 2002).

We previously investigated volumetric alterations in adults with ADHD. Relative to controls, ADHD adults had significantly smaller overall cortical gray matter, PFC, and anterior cingulate cortex (ACC) volumes. ADHD adults also showed trends toward significantly greater overall white matter and nucleus accumbens gray matter volumes (Seidman and others forthcoming). Although these results are novel and the first substantial demonstration of volumetric abnormalities in ADHD adults, manually derived volumetric regions of interest (ROIs) (Filipek and others 1994) do not directly allow for measurement of cortical thickness. Thickness is an additional indicator of integrity of cytoarchitecture in the cortex. To expand upon our earlier results and further refine the regions of structural abnormality, we carried out a study of cortical thickness in the same sample of adults with ADHD and controls, hypothesizing that the cortical network underlying attention and EF would be most affected. The main aim of the present study was to determine if adults with ADHD displayed thinning of the cortex of the brain networks that subserve attention and EF. We hypothesized that ADHD might be associated with selective structural deficiencies in the cortical networks embodying these neural systems.

Methods

Subjects

The sample was identical to that previously reported (Seidman and others forthcoming). In brief, males and females between the ages of 18 and 59 were eligible for the study. ADHD ($n = 24$) and control ($n = 18$) adults were group matched on age, social economic status (SES), sex distribution, handedness, education, intelligence quotient (IQ), and standard measures of academic skills. These subjects were derived from a series of adults who agreed to participate in brain imaging, recruited from an ongoing study evaluating the validity of adult ADHD (Faraone and others, forthcoming). Exclusion criteria were deafness, blindness, psychosis, neurological disorder, sensorimotor handicaps, inadequate command of the English language, or a full-scale IQ estimate less than 75 as measured by the Wechsler Adult Intelligence Scale-III (Wechsler 1997). No ethnic or racial group was excluded. We used a number of ascertainment sources to recruit ADHD probands: referrals to psychiatric clinics at the Massachusetts General Hospital (MGH) and advertisements in the greater Boston area. We recruited potential non-ADHD probands through advertisements in the greater Boston area. Written informed consent was obtained for all subjects, and all participants received an honorarium for participating. The study was approved by the MGH Human Subjects Institutional Review Board committee.

Clinical Assessment Measures

ADHD adults were only included if they met full criteria for current ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), with childhood onset and persistence into adulthood. We conducted interviews with all subjects and, when possible, with subjects' mothers. We considered a disorder positive if DSM-IV diagnostic criteria were unequivocally met in either interview.

Trained interviewers, blind to ascertainment status, interviewed all adults with the structured clinical interview for DSM-IV (First and others 1997) and modules from the Kiddie SADS-E (Orvashcel 1994). Before interviewing research participants, interviewers completed a 4-month training program that included mastery of the instruments, learning about DSM-IV criteria, watching training tapes, observing interviews performed by experienced raters, rating several subjects under the supervision of the project coordinator, and completing practice interviews. Throughout the study, they were supervised by board-certified child and adolescent psychiatrists or licensed psychologists. This supervision included weekly meetings and additional consultations as needed. During the study, all interviews were audiotaped for random quality control assessments.

The interviewers had been instructed to take extensive notes about the symptoms for each disorder. These notes and the structured interview data were reviewed by the diagnostic committee so that the committee could make a best estimate diagnosis as described by Leckman (Leckman and others 1982). Initial diagnoses were prepared by the study interviewers and were then reviewed by a diagnostic committee of board-certified child and adolescent psychiatrists or licensed psychologists. The diagnostic committee was blind to the subject's ascertainment group, all data collected from other family members, and all nondiagnostic data (e.g., brain imaging data). Diagnoses were made for 2 points in time: lifetime and current (past month). Diagnoses were considered definite only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful (i.e., the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture). We computed kappa coefficients of diagnostic agreement by having experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98. Kappa coefficients for individual diagnoses included ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), substance use disorder (1.0), and tics/Tourette's (0.89).

A neuropsychological battery was administered. For this paper, we include estimates of IQ, academic functions, and rates of learning disability (LD). An IQ was estimated from the block design and vocabulary subtests of the Wechsler Adult Intelligence Scale—Revised (Wechsler 1981). Academic achievement was assessed with the reading and arithmetic tests of the wide range achievement test—revised (Jastak J and Jastak S 1985). To assess the presence of LDs, we used the procedure recommended by Reynolds (Reynolds 1984) and others (Frick and others 1991), which we have used previously (Faraone and Doyle 2001). The definition of LDs under Public Law 94-142 requires a significant discrepancy between a child's potential and achievement (Federal Register 1977). We measured "potential" with estimated IQ and "achievement" with results from the reading and arithmetic tests. Full scale IQ and achievement scores are initially converted to the Z-scores Z_{IQ} and Z_A, respectively. Expected achievement score, Z_{EA}, is then estimated by the regression equation $Z_{EA}=r_{IQA}*Z_{IQ}$ in which r_{IQA} is the correlation between the IQ and achievement tests. Values from the control sample were utilized. Then, the discrepancy score is $Z_{EA} - Z_A$ and its standard deviation is $\sqrt{1-r^2_{IQA}}$. We defined as LD any participant who had a value greater than 1.65 on the standardized discrepancy score: $(Z_{EA}-Z_A)/\sqrt{1-r^2_{IQA}}$.

Magnetic Resonance Imaging

Whole brain magnetic resonance images were collected on a Siemens Sonata 1.5-T scanner at the MGH Martinos Center (Charlestown, MA). A sagittal localizer scan was performed for placement of slices, followed by a coronal T_2-weighted sequence to rule out unexpected neuropathology. Two sagittal 3-dimensional (3D) magnetization-prepared rapid gradient echo (T_1-weighted, nonselective, inversion prepared, spoiled gradient, echo pulse, no distortion correction) sequences were collected for a total imaging time of 18 minutes and used for morphometric analyses conducted at the MGH Center for Morphometric Analysis. The volumetric T_1-weighted images, which were used for the analysis were as follows: time repetition = 2730 ms, time echo = 3.39 ms, time to inversion = 7000 ms, flip angle = 7°, bandwidth = 190 Hz/pixel, field of view = 256 × 256 mm^2, sampling matrix = 256 × 192 pixels, 128 contiguous 1.33-mm slices, and averages = 2.

Image Preprocessing: Standard Orientation and Segmentation

The images were resampled into a standard coordinate system based upon the bicommissural line (anterior commissure–posterior commissure) and the interhemispheric fissure (Talairach and others 1967; Filipek and others 1988, 1994; Talairach and Tournoux 1988). Given this coordinate system, coronal slices were defined perpendicular to the bicommissural line and aligned with the interhemisperic fissure. This positional normalization procedure allowed the reconstruction of a new

set of coronal images at the slice thickness of the original acquisition (1.33 mm). The images were not rescaled.

Magnetic Resonance Imaging–Based Segmentation of Cerebral Cortex and White Matter

Neuroanatomical segmentation was performed using semiautomated intensity contour algorithms for external border definition and signal intensity histogram distributions for delineation of gray–white borders (Filipek and others 1989, 1994). This technique allows for border definition as the midpoint between the peaks of the bimodal distribution for any given structure and its surrounding tissue (Worth, Makris, Caviness, and Kennedy 1997; Worth, Makris, Meyer, and others 1997). Segmentation was performed on coronal images (Fig. 1*A*) and divided the brain into gray matter and white matter regions. The cerebrum was

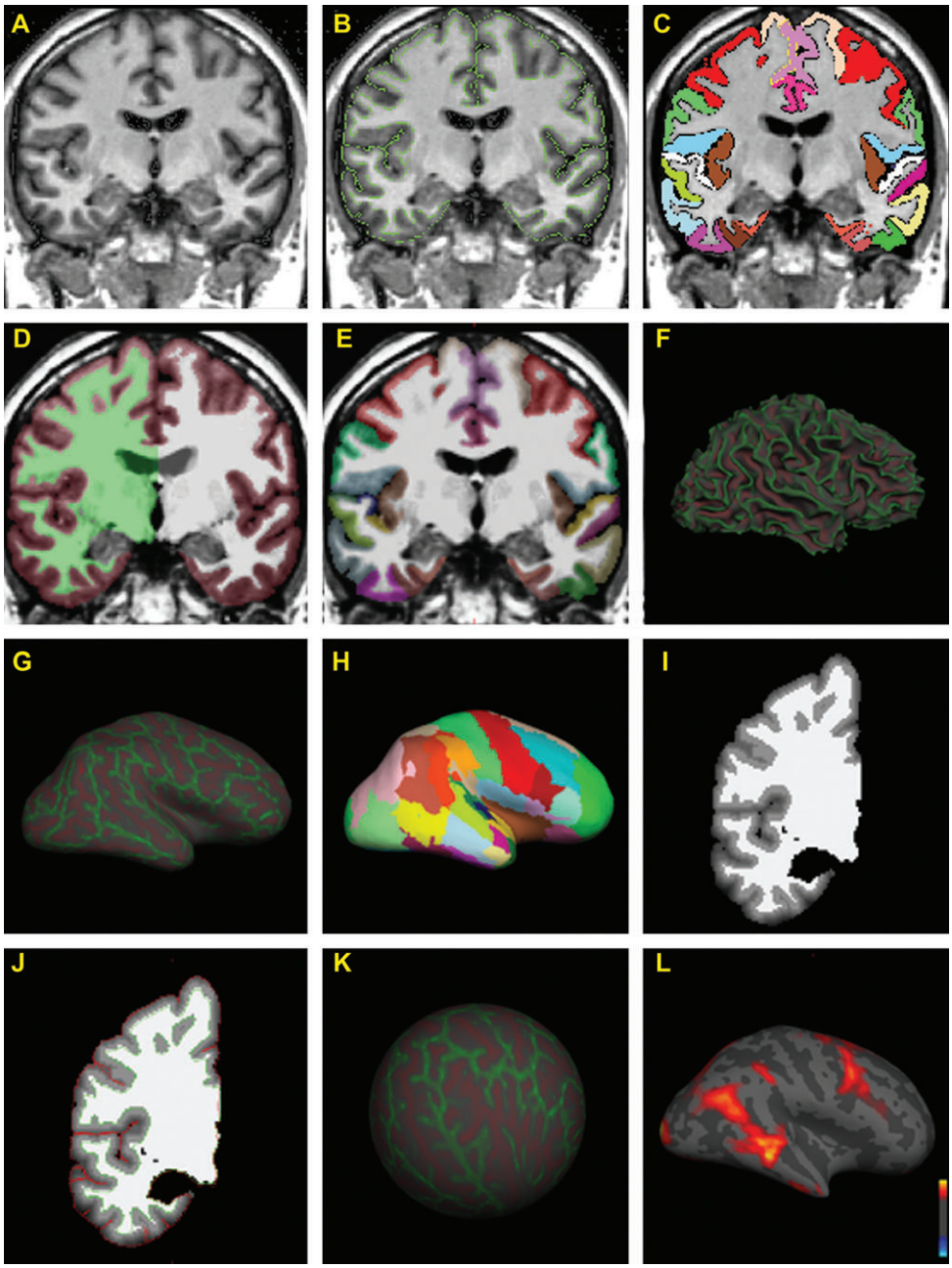


Figure 1. Illustration of the topological cortical parcellation (TCP) system. The overall approach is to segment and parcellate the cerebral cortex using "Cardviews" and then use "FreeSurfer" to compute cortical thickness differences. (*A*) shows an intensity normalized T_1-weighted magnetic resonance coronal image. Segmentation (*B*) and parcellation (*C*) of the cerebral cortex are executed in the Cardviews domain following mainly a manual procedure. The outline files created by the segmentation and parcellation procedures (using Cardviews) are converted to a FreeSurfer volume (*D* for segmentation and *E* for parcellation). A surface is tessellated (*F*), smoothed, and inflated (*G*) from the converted FreeSurfer volume. The cortical parcellation map is then overlayed on the inflated surface (*H*). An intensity gradient is created throughout the cortex as a function of the distance from the white matter surface according to the manual segmentation of the cerebral cortex (*I*). The exterior surface is generated to be consistent with the manual segmentation (*J*). With the white and gray surfaces in place, thickness maps are created across the cerebral cortex. The "pial" surface is created using a FreeSurfer algorithm to estimate the pial layer in the cerebral cortex. The white matter surface of each subject is transferred to spherical coordinates and registered to the average Montreal Neurological Institute brain (Evans and others 1993) (*K*). By registering each subject to a common space, each vertex on each subject can be mapped together to allow for intersubject averaging, and maps are then created showing the cortical thickness differences between groups of subjects; colored regions show significant differences in cortical thickness between the 2 groups with red representing $P < 0.05$ and yellow $P < 0.001$(*L*).

segmented into its principal gray matter and white matter structures and total cerebral cortex. Specifically, the cortical ribbon was defined by 2 outlines, one external outline between the subarachnoid cerebrospinal fluid and the cerebral cortex and the other between the cerebral cortex and the underlying cerebral white matter (Filipek and others 1994) as illustrated in Figure 1*B*. The total number of voxels in each brain region determined its volume.

Cortical Parcellation

The neocortex, which was defined by the aforementioned gray–white matter segmentation procedure, was parcellated further into 48 parcellation units (PUs) per hemisphere (Rademacher and others 1992; Caviness and others 1996) as shown in Figure 1*C*. This comprehensive system of cortical parcellation is based upon the configuration of a specified set of cerebral landmarks, mainly neocortical fissures, and addresses interindividual topographic variability by preserving the morphological and topographic uniqueness of the individual brain. Following cortical parcellation volumes were calculated for each PU by calculating the volume of the PU on each slice and then summing all slices on which the PU appeared.

The Topological Cortical Parcellation System

The topological cortical parcellation (TCP) system is a system of comprehensive analysis, which computes measurements of cortical surface topography, specifically of cortical thickness, surface area, curvature, folding, and curvature indices (Makris and others forthcoming). This method is different from other available techniques, which perform similar cortical measurements, in that it takes as its starting point volumetric segmentation data. This allows interoperation between volume-based and surface-based topographic analysis and extends the functionality of many existing segmentation schemes. The overall approach is to segment and parcellate the cerebral cortex using Cardviews and then use FreeSurfer to compute cortical thickness differences (Makris and others forthcoming). The derived measurements can be regionally specific and integrated with systems of cortical parcellation that subdivide the neocortex into gyral-based PUs and allows for quantitative analyses in terms of neural systems biology (Caviness and others 1999). In summary, this consists of the following procedural steps. After cortical segmentation and parcellation using Cardviews (Fig. 1*A–C*), the cortical surface analysis is done using FreeSurfer (Dale and others 1999; Fischl and others 1999; Fischl and Dale 2000). The manually segmented white matter volume is expressed by its topologically correct surface. A coregistered exterior surface is generated from the manually segmented (Filipek and others 1994) and parcellated (Caviness and others 1996) cortical ribbon. These surfaces (Dale and others 1999) enable the computation of cortical topographical measurements such as cortical thickness, curvature, gyrification index, and folding index (Dale and others 1999). This procedure is summarized in Figure 1.

Data Analyses

A priori and exploratory analyses were done using the cortical thickness data. The primary analyses tested a priori hypotheses derived from a wealth of published data on the network subserving attention (Heilman and Van Den Abell 1980; Mesulam 1990) and EF (Seron 1978; Damasio and Benton 1979; Damasio 1985) in humans. Based on the volumetric literature on ADHD, as well as our prior volumetric work on this sample (Seidman and others forthcoming), we expected the cortex to be thinner in ADHD than controls. Nevertheless, because we considered the possibility that there might be areas of larger cortex as well (Sowell and others 2003), we used 2-tailed tests. The "a priori analyses" consisted of group differences at each vertex within 18 (9 homotypic regions in the 2 hemispheres) a priori ROIs or PUs examined using a 2-group *t*-test and a 2-tailed significance level (alpha) of 0.05. The following 9 PUs were considered in this analysis: right and left F1 (superior frontal gyrus), F2 (middle frontal gyrus), FOC (orbital frontal cortex), CGa (anterior cingulate gyrus), CGp (posterior cingulate gyrus), AG (angular gyrus), SGa (anterior supramarginal gyrus), SGp (posterior supramarginal gyrus), and PO (parietal operculum) (Caviness and others 1996). More precisely, 1) prefrontal cortex (PFC) was included in F1, F2, and FOC, 2) cingulate cortex was included in the anterior cingulate gyrus (CGa, which approximates the perigenual ACC and the dACC of other authors) and CGp PUs, and 3) inferior parietal lobule (IPL) cortical areas were included in the AG, SGa, and SGp PUs as well as the PO.

Eight of the a priori PUs, specifically the right F1, F2, CGa, CGp, AG, SGa, SGp, and PO, constitute the core of the attentional neural network (Heilman and Van Den Abell 1980; Mesulam 1990), whereas 10 PUs, namely, the right and left F1, F2, FOC, CGa, and CGp compose the EF neural network (Seron 1978; Damasio and Benton 1979; Damasio 1985). Thus, at the cortical level, the system dedicated to attention involves principally the right frontal and parietal lobes in contrast to the EF system, which is principally located within the right and left frontal lobes.

For descriptive purposes, we obtained the mean thickness and standard deviation for both groups at the vertex showing the largest absolute *t*-value. Second, we tested the average thickness of the significant clusters within a PU. Third, in a more conservative test (because of the size of the PUs), we tested as well the average thickness in each one of the 9 a priori PUs for each subject in each hemisphere. A multivariate analysis of variance (MANOVA) was used to see if overall a priori PUs were different in the ADHD group with follow-up analysis of variance tests for each cluster and each PU. Finally, average thickness within each network (i.e., the attention and EF networks) was compared. This was relevant given that this analysis would determine a general group effect of the PUs constituting the attention and EF networks over and above an effect at each individual PU.

In the "exploratory analyses," we did as follows: 1) Each vertex in regions outside the 18 a priori ROIs was examined with a corrected significance level of $P = 0.00064$ (0.05/78) (corresponding to the significance level correcting for 78 PUs [96 – 18 = 78] that were not part of the a priori set of ROIs). 2) Group differences in thickness at each vertex were re-examined with a general linear model that included an estimate of the average thickness of the entire neocortex of each subject as a covariate to see if individual ROIs were significantly different against a backdrop of possible generalized cortical thinning.

Results

Demographic Characteristics, Intellectual Functioning, and Symptoms

As Table 1 shows, compared with non-ADHD adults, adults with ADHD were not significantly different on age, SES, sex distribution, handedness, or education. All subjects were Caucasian. The groups were statistically comparable on IQ, reading and arithmetic achievement, and frequency of LDs (which was low in both groups). Both groups were highly educated and were above average in general intellectual ability. There were no significant differences between groups on lifetime rates of mood, anxiety, substance, or antisocial disorders. The only significant difference in these well-matched groups was in number of ADHD symptoms, which, of course, was significantly higher in persons with ADHD.

Cortical Thickness

A Priori Analyses

Virtually all a priori ROIs were significant using the maximum *t*-value in the predicted regions, except for a few marginal trends in PO, left AG, and left SGp. MANOVA analyses related to the average thickness of the significant clusters within the 18 a priori PUs showed a group effect in both the right ($P = 0.048$) and the left ($P = 0.03$) hemispheres, indicating cortical thinning in attention and EF networks in the ADHD group. Follow-up univariate tests for each PU demonstrated that the subjects with ADHD had significantly decreased thickness of their DLPFC bilaterally (F1 and F2) (corresponding to BAs 8, 9, 46),

Table 1
Demographic, psychiatric, and cognitive characteristics of adults with ADHD and controls

	Controls (N = 18) Mean (SD) or (%)	ADHD (N = 24) Mean (SD) or (%)	Test statistic (df), P value
Demographic characteristics			
Age, time of scan (years)	34.8 (± 2.5)	38.0 (± 2.2)	$t_{40} = -1.0$, $P = 0.333$
SES	1.8 (± 0.4)	1.9 (± 0.9)	$z = -0.1$, $\|z\| = 1.0$
Sex (number of males)	9 (50)	12 (50)	χ^2_1=0.0, $P = 1.000$
Ethnicity (number of Caucasian)	18 (100)	24 (100)	χ^2_1=0.0, $P = 1.000$
Handedness (number of right)	16 (89)	22 (96)	χ^2_1=0.7, $P = 0.409$
Education (number of Bachelor's degree)	13 (72)	15 (63)	χ^2_1=0.4, $P = 0.508$
Psychiatric characteristics			
ADHD symptoms	1.7 (± 0.6)	14.0 (± 0.6)	$t_{38} = -15.0$, $P < 0.001$*
Persons medicated, entry to study	4 (22)	7 (29)	χ^2_1=0.3, $P = 0.612$
Persons medicated, time of scan	1 (6)	1 (4)	χ^2_1=0.0, $P = 0.834$
Mood disorders	5 (28)	4 (17)	χ^2_1=0.8, $P = 0.385$
Multiple anxiety disorder	0 (0)	4 (17)	χ^2_1=3.3, $P = 0.069$
Antisocial personality disorder	0 (0)	0 (0)	χ^2_1=, $P = 1.000$
Substance use disorders	6 (33)	12 (50)	χ^2_1=1.2, $P = 0.280$
Cognitive/academic performance			
Full scale IQ estimate	117.9 (± 3.0)	117.5 (± 2.8)	$t_{40} = 0.1$, $P = 0.924$
WRAT-R arithmetic	105.6 (± 3.0)	101.5 (± 2.2)	$t_{40} = 1.2$, $P = 0.256$
WRAT-R reading	108.6 (± 2.2)	109.3 (± 1.5)	$t_{40} = -0.3$, $P = 0.791$
Learning disorders	1 (6)	2 (8)	χ^2_1=0.1, $P = 0.729$

df, degrees of freedom; SD = standard deviation; WRAT-R, wide range achievement test—revised. Asterisk (*) highlights $P < 0.05$.

FOC (BAs 11 and 47), and CGa or ACC and CGp areas (BA 24 and BA 23, respectively) bilaterally. Cortical thickness decreases were also observed in the right lateral inferior parietal cortical areas at the temporo-occipitoparietal junction, specifically the right AG (BA 39) and right SGa and SGp (BA 40) (Table 2 top part, Fig. 2). The mean cortical thickness of the network subserving attention across its 8 member PUs was significantly decreased in the ADHD group (t_{40} = 2.19, P = 0.034). Similarly, the mean cortical thickness of the EF network across its 10 member PUs was significantly decreased in the ADHD group ($t_{39.6}$ = 2.11, P = 0.042). Given that the T_1 magnetic resonance imaging (MRI) data at hand do not allow the identification of cytoarchitectonic patterns, any association to BAs is meant to be a gross approximation and serving the purpose of an anatomical reference to the topographic system of parcellation (Rademacher and others 1992).

Exploratory Analyses

When areas outside the a priori units were analyzed at a more stringent significance level of P = 0.00064, the only area that still showed significance was in the right occipital pole (BA 17). We also reanalyzed the data while covarying for each subject's average cortical thickness. In the right hemisphere, F2, AG, and CGa were still significantly thicker in the control group than in the adult ADHD group at P= 0.05. In the left hemisphere, CGa and CGp remained significant at P = 0.05. Additionally, there was a significant increase in thickness in the right CGp in the ADHD group.

Discussion

In this first study of cortical thickness measurement in adults with ADHD, we found an overall decrease of cortical thickness in the cerebrum as well as selectively localized cortical thinning in prefrontal, lateral inferior parietal, and cingulate regions. More precisely, cortical thinning in the lateral superior and middle frontal gyri and the FOC was bilateral. Instead, AG and supramarginal gyrus cortical thinning was lateralized in the right hemisphere. Right ACC and left posterior cingulate cortex were thinner as well. These cortical areas are richly

Table 2
Cortical thickness measurements (mm) in adults with ADHD

PU	Controls (n = 18) Mean ± SD	ADHD (n = 24) Mean ± SD	Group differences		Number of vertices
			T-value	P value	
Average thickness of vertices in significantly different regions inside a PU					
R.F1	4.0 ± 0.4	3.6 ± 0.5	2.35	0.024*	819
R.F2	3.6 ± 0.4	3.3 ± 0.5	2.59	0.013*	1608
R.FOC	3.5 ± 0.5	3.1 ± 0.4	2.36	0.024*	45
R.AG	3.3 ± 0.3	3.0 ± 0.3	2.87	0.007*	733
R.SGp	3.2 ± 0.3	2.9 ± 0.3	2.75	0.009*	375
R.SGa	3.4 ± 0.3	3.1 ± 0.4	2.48	0.018*	329
R.PO				N/A	0
R.CGa	2.0 ± 0.3	1.8 ± 0.2	2.78	0.008*	355
R.CGp	2.5 ± 0.3	2.2 ± 0.3	2.47	0.018*	34
L.F1	4.2 ± 0.4	3.8 ± 0.5	2.25	0.030*	1298
L.F2	3.7 ± 0.4	3.4 ± 0.4	2.52	0.016*	1997
L.FOC	3.2 ± 0.4	3.0 ± 0.4	2.35	0.024*	68
L.AG				N/A	0
L.SGp				N/A	0
L.SGa	3.4 ± 0.4	3.2 ± 0.4	2.07	0.045*	21
L.PO				N/A	0
L.CGa	2.0 ± 0.2	1.8 ± 0.2	3.10	0.004*	451
L.CGp	2.4 ± 0.2	2.2 ± 0.2	4.15	0.0002*	879
Average thickness of all vertices in the PU					
R.F1	4.2 ± 0.5	3.9 ± 0.7	1.74	0.090	3103
R.F2	3.7 ± 0.4	3.4 ± 0.6	2.05	0.048*	3389
R.FOC	3.0 ± 0.3	2.9 ± 0.3	1.39	0.172	1919
R.AG	3.2 ± 0.3	3.0 ± 0.3	2.24	0.031*	1559
R.SGp	3.3 ± 0.3	3.1 ± 0.3	1.96	0.057	1127
R.SGa	3.4 ± 0.3	3.2 ± 0.4	2.08	0.044*	732
R.PO	3.3 ± 0.4	3.1 ± 0.4	1.32	0.196	501
R.CGa	2.4 ± 0.3	2.2 ± 0.3	1.83	0.074	2018
R.CGp	3.0 ± 0.3	2.9 ± 0.3	1.29	0.204	2825
L.F1	4.2 ± 0.5	3.9 ± 0.6	1.91	0.063	3301
L.F2	3.7 ± 0.4	3.4 ± 0.5	2.13	0.040*	3650
L.FOC	3.6 ± 0.3	3.5 ± 0.3	1.37	0.178	1597
L.AG	3.3 ± 0.3	3.2 ± 0.4	1.38	0.174	1268
L.SGp	3.4 ± 0.3	3.2 ± 0.4	1.20	0.235	2090
L.SGa	3.4 ± 0.3	3.2 ± 0.4	1.89	0.066	230
L.PO	3.5 ± 0.3	3.4 ± 0.4	0.70	0.490	317
L.CGa	2.5 ± 0.3	2.4 ± 0.2	0.95	0.350	2158
L.CGp	2.8 ± 0.3	2.6 ± 0.2	2.38	0.022*	2594
Average thickness of entire hemisphere					
Right	3.3 ± 0.1	3.1 ± 0.1	2.20	0.033*	72270
Left	3.3 ± 0.1	3.1 ± 0.1	2.15	0.038*	71217

SD, standard deviation; Asterisk (*) highlights $P < 0.05$.

interconnected by corticocortical association fiber systems and form the cerebral cortical core of the attentional and EF circuitries in the human brain. We also observed cortical thinning in the left SGa; however, we do not feel confident for the significance of this result considering its relatively modest *P* value (0.045) and the low number of statistically significantly different vertices ($N = 21$). Furthermore, we found statistically significant thinning in both the attention and EF neural networks. Thus, these findings support the hypothesis that adults meeting criteria for ADHD are characterized by selective structural deficiencies at the principal centers of the cortical networks embodying attention and executive functioning and suggest that brain properties related to these networks are preserved from infancy into adulthood. Notably, these circumscribed areas showing abnormal cortical thinning in ADHD closely match the cortical topography of attention and EF networks that have repeatedly been identified in published functional imaging studies (see Fig. 2 and Goldman-Rakic 1988; Posner and Petersen 1990; Cabeza and Nyberg 2000; Corbetta and Shulman 2002).

To our knowledge, other than our previous volumetric analyses with this sample (Seidman and others forthcoming), there is only one published structural volumetric MRI study in adults with ADHD (Hesslinger and others 2002) and that sample was small ($n = 8$ ADHD and 17 healthy males). Moreover, no prior studies reported cortical thickness measurements. Therefore, it is difficult at this time to compare the results of our study with currently existing structural studies of ADHD. Hesslinger and others (Hesslinger and others 2002), who examined total brain volume and FOCs, found significant volumetric reduction only in the left FOC. Previous volumetric MRI reports in children with ADHD have implicated alterations of lateral prefrontal cortical and dACC structures, either on the right or on the left hemisphere, as well as corpus callosum and cerebellum (Castellanos and others 2002; Durston 2003; Seidman, Valera, and Bush 2004; Bush and others 2005; Seidman and others 2005). Furthermore, in a surface-based study in children and adolescents with ADHD, Sowell and others (Sowell and others 2003) showed decreases in size of the inferior dorsal prefrontal and anterior temporal cortices bilaterally as well as bilateral increases in the posterior temporal and inferior parietal regions. Another recent study (Shaw and others 2006) indicated a trend of decrease in thickness of the right parietal cortex in children with ADHD, which tends to normalize by late teenage years. Our novel findings in adults with ADHD are in agreement with the localizations of structural cerebral cortical deficits encountered in children and adolescents with ADHD, which relate to the frontostriatal circuitry deficiency in ADHD showing alterations of the DLPFC and dACC bilaterally. There is also agreement with Hesslinger and others (Hesslinger and others 2002) in that we observed alterations in the FOC in adults with ADHD.

Novelty and Significance

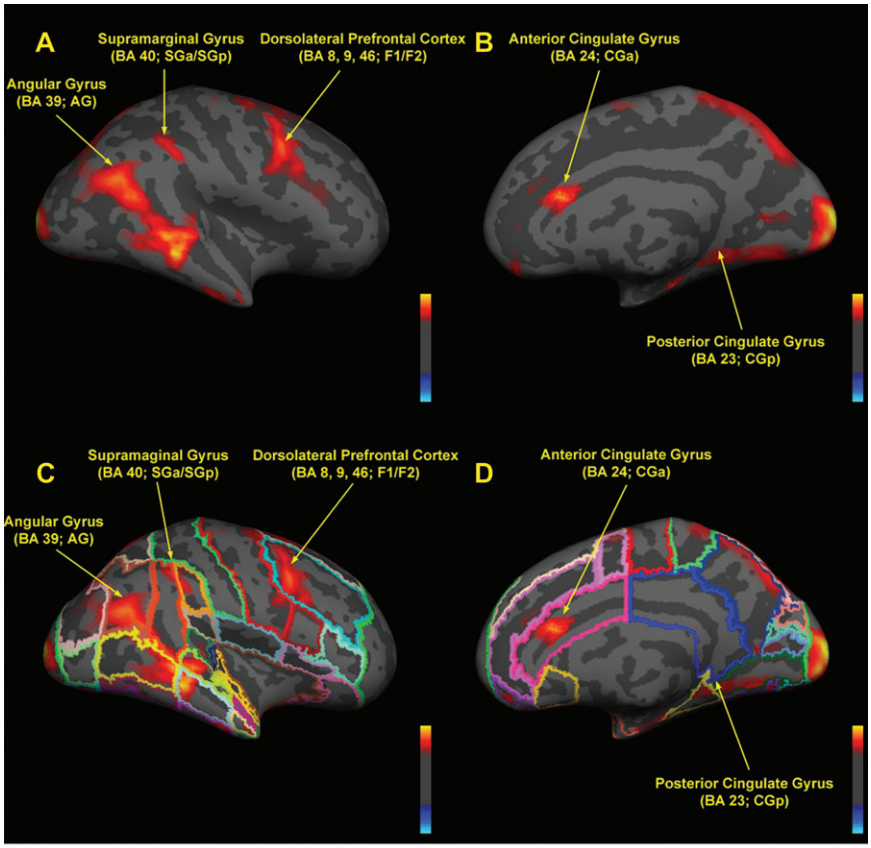
The present study differed from prior investigations in ADHD in a number of aspects not previously shown: 1) The cortical structures associated with the attention and EF neural networks were clustered together and treated as groups in the statistical analysis. Thus, we measured differences of the overall group of the structures constituting the anatomical circuits under investigation between the adult ADHD and control populations. 2) We were able to determine statistically significant differences of the attention and EF cortical networks in adults with ADHD. These differences were in terms of cortical thinning in the ADHD population as compared with healthy controls. Overall, our novel findings demonstrate a localized deficiency of the attention and EF cortical networks. Specifically, for the cortical network dedicated to attention, selective and rightward lateralized cortical thickness decreases were found in the dorsolateral prefrontal, IPL, and anterior cingulate regions. This is the first investigation reporting selective attention and EF structural neural network deficiencies in adults with ADHD.

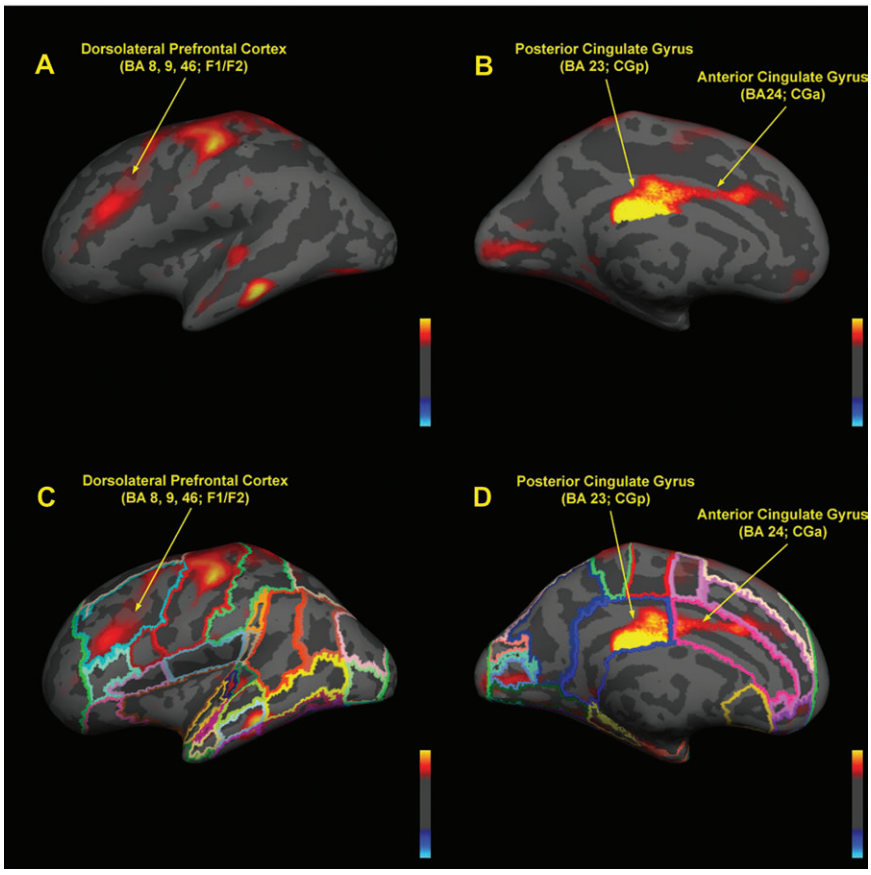
Studying multiple anatomical regions, which are components of a structural and functional circuit may be an important avenue to identify a biomarker for a disease (Hyman and Nestler 1993; Breiter and others 2006). Specifically, in ADHD, the neural networks subserving attention and EF are putative biomarkers. Thus, their structural quantification using MRI may ultimately be relevant for diagnostic and therapeutic purposes in ADHD.

Neurobiology of ADHD

The demonstration that ADHD is a neurobiological disorder fueled interest in the basic brain properties that might mediate its phenotypic expression. Based on the success of stimulant medications in humans and animal experimentation, the "frontostriatal" model implicating dopamine pathways (Shaywitz and others 1978) suggested that amelioration of dopaminergic and noradrenergic functions is necessary for the clinical efficacy of pharmacological treatment of ADHD (Elia and others 1990). Current insights emphasize the role of attentional and executive dysfunction in this disorder (Pennington and Ozonoff 1996; Seidman, Doyle, and others 2004; Seidman, Valera, and Bush 2004). Consequently, there has been a focus on the brain structures related to these behavioral correlates as well as the neural networks in which these structures are assembled. Prefrontal hypotheses of ADHD have principally implicated the DLPFC and FOC. DLPFC lesions are associated with organizational, planning working memory and other executive dysfunctions, whereas FOC lesions are related to social disinhibition and impulse dyscontrol. Given the persistence of EF deficits in adults with ADHD, the DLPFC is likely affected. Furthermore, behavioral inhibition is thought to be a core deficit in ADHD, which is related primarily to orbital frontal dysfunction (Barkley 1997).

Another relevant cortical structure in ADHD is the dACC, which currently is considered to have a role in cognition and motor control and to be involved in processes underlying the arousal/drive state of the organism (Dum and Strick 1993; Paus 2001). The dACC plays a role in complex cognitive operations (Bush and others 2000) such as target detection, response selection, error detection, action monitoring, and reward-based decision making (Carter and others 1998, 2000; Botvinick and others 1999; Cohen and others 2000; Gehring and Knight 2000; Bush and others 2002), functions that are thought to be impaired in ADHD. Functional neuroimaging reports on normal subjects have shown that cognitive interference tasks such as the Stroop and Stroop-like tasks engage the dACC activating it (Paus and others 1998). Furthermore, the dACC has been shown to be functionally abnormal in adults with ADHD using the counting Stroop task (Bush and others 1999), a continuous performance test (Zametkin and others 1990) and response inhibition tasks (Rubia and others 1999; Tamm and others 2004). Currently there is one study reporting right posterior cingulate volume reduction in children with ADHD (Overmeyer and others 2001).





The IPL is a multimodal association area related to cognitive functions such as attention and language (Riddoch 1935; Brain 1941; Paterson and Zangwill 1944; McFie and others 1950; Denny-Brown and Banker 1954; Sperry 1961; Geschwind and Kaplan 1962; Geschwind 1965a, 1965b; Critchley 1966; Heilman and others 1970; Mesulam 1981; Posner and others 1984; Geschwind and Galaburda 1987; Caplan 1990; Caplan 1992; Goodglass and Wingfield 1993). Humans with damage in the right caudal inferior parietal area, that is, the AG (BA 39), usually exhibit severe impairment in spatial attention referred to as hemi-inattention (Heilman and Van Den Abell 1979, 1980; Mesulam 1981; Posner and others 1984), which is also one of the major behavioral manifestations of the neglect syndrome (Heilman and Van Den Abell 1980). Alternatively, humans with lesions in the left AG usually show some type of language impairment (Geschwind and Kaplan 1962; Geschwind 1965a, 1965b; Caplan 1990; Caplan 1992; Goodglass and Wingfield 1993). Commonly, these manifestations are associated with right handedness in humans (Annett 1967; Geschwind and Galaburda 1987). Through its connections, the AG provides the PFC with information concerning the perception of the visual space as well as linguistic information. Similarly, the PFC via bidirectional connections directed back to the posterior parietal region could provide a means by which it can regulate the focusing of attention in different parts of space. Although this region is theoretically important, there are no structural studies of the IPL in adults with ADHD. There is one study reporting increased size of cortex in the IPL of children and adolescents with ADHD (Sowell and others 2003). This finding contrasts somewhat with the results of our present study, which showed a decrease in cortical thickness in adults with ADHD. However, volumetric and cortical thickness measures are distinct measures and may not correlate with one another, and Sowell and others did not specifically report cortical thickness measures.

Distinct cortical circuits directing attention and EF appear to be selectively altered in adults with ADHD. Thus, the notion of cognitive dysfunction in ADHD can be reflected biologically in the 2 cortical networks operating attention and EF. This combined network deficiency is a powerful instantiation engaging fundamental cortical properties thus mediating the symptoms of this highly heritable disorder.

The EF network principally involves the prefrontal regions and has been anatomically simplified as primarily representing the interplay of frontostriatal activity (Luria 1966, 1973; Hecaen and Albert 1978; Seron 1978; Damasio and Benton 1979). However, several components of the EFs may be associated with cortical limbic structures such as the cingulate cortex (Damasio 1985; Bush and others 1999; Tamm and others 2004). It is also known that these deficits exist independently of hemispheric lateralization and that bilateral alterations increase the severity of EF symptomatology (Damasio 1985). Much focus has been placed on the executive, frontostriatal circuitry in terms of neural network alterations in ADHD. This is largely due to the fact that dopaminergic compounds (i.e., the stimulants), which are mediated by frontostriatal networks, have proven to be effective treatments for patients with ADHD (Shaywitz and others 1978). We contrast the EF circuitry with the attention circuitry, which we discuss below.

The Attention Network in ADHD

Given that a neural network is an assembly of centers and the fiber tracts that interconnect them, a complete discussion of the attention circuitry in ADHD would require quantitative information about all the above structures. In the absence of information on fiber tracts, we are here inferring only from the quantitative data of cortical thickness and the known function of the cortical centers that are major components of the attention circuitry. With the exception of the nucleus accumbens septi, which was enlarged in patients, volumetric analyses showed no significant differences in subcortical structures in adults with ADHD (Seidman and others forthcoming). The core of the attention network in the cerebral cortex is within a distributed network including lateral and medial PFC areas, posterior parietal cortex, and centers at the temporo-occipitoparietal junction in the lateral surface of the right hemisphere (Heilman and Van Den Abell 1980; Heilman and others 1983; Heilman and Valenstein 1985; Mesulam 1998). More precisely, these areas are the middle and superior lateral frontal gyri (BAs 8, 9 and 46), the angular (BA 39) and supramarginal (BA 40) gyri, and the cingulate gyrus (BAs 23 and 24) (Critchley 1966; Heilman and others 1970; Goldman-Rakic 1988; Mesulam 1990; Posner and Petersen 1990; Cabeza and Nyberg 2000; Duncan and Owen 2000; Corbetta and Shulman 2002). Lesions in any of these 3 cortical areas can cause some type of neglect behavior (Mesulam 1990). In addition, these 3 regions are interconnected with other cortical areas, which are related to attention processing as well. These additional areas are the cortices of the banks of the anterior superior temporal sulcus, the inferior temporal area, and the medial parietal region. Although the latter cortical areas are considered as part of the broader attentional network, they are not equally essential for attention processing (as the 3 core cortical areas mentioned previously) because their lesions alone cannot cause neglect behavior in humans (Mesulam 1990). Perceptual information such as visual, auditory, and tactile is processed through successive stages of intermodality elaboration in cortical unimodal association and multimodal regions for intermodality integration. Precisely, from their primary areas of arrival (i.e., the calcarine area, the Heschl's gyrus and the primary somatic sensory cortex in the postcentral gyrus), they converge on the right AG in the IPL (Pandya and Kuypers 1969; Jones and Powell 1970) where the different sensory modalities are put together meaningfully (Denny-Brown and Banker 1954;

Figure 2. Cerebral cortical thickness differences between a group of 24 adults with ADHD and a group of 18 matched normal controls. In (*a*), the right hemisphere is represented, whereas the left hemisphere is shown in (*b*). (*a*) Lateral (*A*, *C*) and medial (*B*, *D*) views of right cerebral surfaces, showing differences in cortical thickness between a group of the ADHD patients and the group of normal controls. Colored regions show significant differences in cortical thickness between the 2 groups with red representing $P < 0.05$ and yellow $P < 0.001$. More specifically, red and yellow show the locations where the cortex of the ADHD group of subjects is thinner compared with the cortex of the group of their matched controls. Anatomical localization was performed in (*C*, *D*), by superimposing the parcellated cortex of the Montreal Neurological Institute 305 average brain onto the cerebral surfaces (*A*, *B*). In the lateral view of the right hemispheric surface (*A. C*), these areas are located in the dorsolateral prefrontal areas (superior and middle frontal gyri, F1 and F2, respectively), as well as the inferior parietal areas (SGa and SGp, as well as AG). In (*B*, *D*), the medial view of the right hemispheric surface areas of cortical thickness differences between the group of ADHD patients and the group of their matched normal controls are located in the CGa. (*b*) Similarly, in the lateral view of the left hemisphere (*A*, *C*), the differences are localized in the dorsolateral prefrontal areas (superior and middle frontal gyri, F1 and F2, respectively). The medial view of the right hemispheric surface areas (*B*, *D*) of cortical thickness differences between the group of ADHD patients and the group of their matched normal controls are localized in the posterior cingulate gyrus (CGp).

Geschwind 1965a, 1965b). In turn, information is relayed to paralimbic and limbic structures, for investment with affective tone, hedonic valence to experience and for memory consolidation (Yeterian and Pandya 1985; Mesulam 1998). It is of relevance to keep in mind that in directed attention, the 3 principal cortical areas (i.e., the DLPFC, the cingulate cortex, and the IPL) are engaged simultaneously to operate as an ensemble in an orchestrated and coherent fashion. The resultant phenomenon is an emergent quality of the network as a whole (Mesulam 1998). Action is then directed toward the hypothalamus and brain stem for balancing of the internal milieu and toward the supplementary motor and premotor frontal areas in preparation for executive behavior appropriate to environmental and internal factors (Yeterian and Pandya 1985; Mesulam 1998).

In the present study, we found that the ACC, the frontal multimodal association area, that is, the DLPFC and the orbital frontal regions show cortical thinning in adults with ADHD. In ADHD literature, these alterations have been associated with deficit of the EF network, which involves frontostriatal structures bilaterally, that is, the PFC, dACC, caudate, and putamen (Barkley 1997; Bush and others 1999, 2005; Castellanos and others 2002; Durston 2003; Sowell and others 2003; Seidman, Doyle, and others 2004; Seidman and others 2005, forthcoming). In this investigation, our primary focus has been the study of the attentional cortical system, and we demonstrated selective cortical thinning of this neural network and of its member structures in adults with ADHD. Overall, failure of the joint attentional and EF networks can have a powerfully disabling effect on the fundamental cerebral properties that might mediate the symptoms of this disorder.

Cortical thinning of the right occipital pole cortex (BA 17) could be of relevance as well. This was the only a posteriori ROI that remained statistically significant after correcting for multiple comparisons. This primary visual processing area in the right hemisphere feeds visual information to the right AG. Thus, we should consider the possibility that this visual input modality may be impaired in ADHD. Failure in the primary visual input in the right hemisphere may accentuate a deficit of integration of sensory stimuli at the right AG where they are meant to be combined and become meaningful. Thus, other sensory modalities such as auditory and tactile may be considered to be more efficient avenues for communicating with patients affected by ADHD.

The cortical thickness alterations of the PFC, cingulate, and IPL cortices observed in this investigation may reflect a change in size, shape, number, pattern of arrangement and densities of cells, volume of the neuropil or individual cells, or synaptic densities. It could also reflect an alteration of a particular type of cells in the cortex. It is of interest that most of the cortical regions showing thinning were multimodal association areas. It may be that the coticocortical association fiber pathways originating and terminating in these cortical regions are altered as well. A diffusion tensor MRI investigation targeting these long association fiber tracts could elucidate this hypothesis. These neurobiological changes could be due to a number of conditions such as genetic, metabolic, toxic, infectious, or vascular. Postmortem research would be helpful in clarifying the nature of the pathology.

Integration of Data and Limitations

Data generated from multiple procedures need to be integrated into a common coordinate space to give a holistic representation of the brain as well as to understand differences between individuals and populations. It is important that computational models investigating variability of structure be able to integrate these multiple data representations. The representation of the human neocortex is particularly complex, due to its constrained topology and highly curved topography and high degree in interindividual variability. This complexity can lead to trade-offs between automated procedures (which can increase the speed of analyses and lower costs) and manual techniques (which can increase accuracy at the potential expense of topological constraints and cost) in terms of the errors readily observable when mapping into a common database or coordinate system. Registration errors are inherently present in all procedures involving intersubject mapping. Limitations are due in part to the finite number of degrees of freedom allowed in the transformation procedure, as well as the ill-posed nature of intersubject correspondence in topology with respect to detailed topography and function. The ultimate sensitivity of a method is constrained to identification of regions of change that are large with respect to the unaccounted for intersubject anatomical variability. Despite these limitations, the current methods of registration employed in this study represent state-of-the-art technology in this domain. The TCP system capturing such current modular package designs as "FreeSurfer" is interoperable within an integrated processing environment. In this context, interactiveness and integration between morphometric volumetric data and surface data sets become of particular interest in order to precisely characterize the neocortex of the individual cerebrum. It is known that although generally consistent overall, the detailed results of volumetric analysis can be substantially different between differing segmentation methods. Given that each different segmentation technique has embedded within it a set of anatomical and operative rules and conventions, it is crucial to preserve a constant representation of anatomy between the volumetric and surface-based measurements. Precisely, thickness and volume measures should optimally be consistent within a given subject. Thus, to perform a set of thickness measures that are guaranteed to be concordant with the prior literature on these subjects, a procedure that operates from the identical segmentation starting point is required (Makris and others forthcoming; Seidman and others forthcoming).

Note that other parcellation schemes could be used to interrogate the localization of cortical thickness differences (Talairach and Tournoux 1988; Tzourio-Mazoyer and others 2002); however, the current presentation is anatomically consistent with previous volumetric analyses with this sample (Seidman and others forthcoming). The parcellation scheme can be used both for localization of the thickness differences and as ROIs for summary analysis, as shown in Table 2. However, depending on the matching of the extent of the biological effect relative to the extent of the anatomical region, the power of the regional analysis to detect the biological changes can be variable. This "dilution" effect can be seen in Table 2 as the difference in effect size of the results of the regional analysis of significant vertices compared with the total region.

Conclusion

Although executive and attentional deficiencies have been emphasized in ADHD, this is the first documentation showing that in adults with ADHD, the brain is affected in the distinct

cognitive cortical networks that support attention and EF. These results suggest that discovery of a selective difference in cortical thickness of the attention and EF networks in adults with ADHD relative to controls might be regarded as the MRI profile of the brain and, as such, a potential structural biomarker for the attention and executive phenotypic deficiency in this disorder. Further research with larger samples is needed to confirm this hypothesis.

Human Research Statement

The experiments undertaken in this paper were performed with the understanding and written informed consent of each subject.

Notes

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