Attention and Executive Systems Abnormalities in Adults with Childhood ADHD: A DT-MRI Study of Connections

Attention-deficit/hyperactivity disorder (ADHD) is hypothesized to be due, in part, to structural defects in brain networks influencing cognitive, affective, and motor behaviors. Although the current literature on fiber tracts is limited in ADHD, gray matter abnormalities suggest that white matter (WM) connections may be altered selectively in neural systems. A prior study (Ashtari et al. 2005), using diffusion tensor magnetic resonance imaging (DT-MRI), showed alterations within the frontal and cerebellar WM in children and adolescents with ADHD. In this study of adults with childhood ADHD, we hypothesized that fiber pathways subserving attention and executive functions (EFs) would be altered. To this end, the cingulum bundle (CB) and superior longitudinal fascicle II (SLF II) were investigated in vivo in 12 adults with childhood ADHD and 17 demographically comparable unaffected controls using DT-MRI. Relative to controls, the fractional anisotropy (FA) values were significantly smaller in both regions of interest in the right hemisphere, in contrast to a control region (the fornix), indicating an alteration of anatomical connections within the attention and EF cerebral systems in adults with childhood ADHD. The demonstration of FA abnormalities in the CB and SLF II in adults with childhood ADHD provides further support for persistent structural abnormalities into adulthood.

Keywords: ADHD, association fiber pathways, cingulum bundle, DT-MRI, pregenual and dorsal anterior cingulate white matter, superior longitudinal fascicle II

Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects approximately 8% of children (Faraone et al. 2003) and 4% of adults (Faraone et al. 2004; Kessler et al. 2006) and persists into adolescence and adulthood in a sizeable majority of afflicted children of both genders. Given its chronic morbidity and disability (Biederman and Faraone 2006; Biederman et al. 2006), management of ADHD is an important public health concern. ADHD is characterized primarily by behavioral symptoms of inattention, hyperactivity, and impulsivity beginning in childhood and often persisting across the life cycle (Biederman 2005). Although its etiology remains unclear, its strong familial nature and high levels of heritability (Faraone et al. 2005) support a genetic etiology. Importantly, the neurobiological abnormalities found in children with ADHD are also identified in adults (Seidman et al. 2005; Seidman et al. 2006; Makris et al. 2007).

ADHD has been hypothesized to be due, in part, to structural defects in brain networks influencing cognitive and motor behavior (Barkley 1997; Makris et al. 2007). A growing literature of magnetic resonance imaging (MRI)-based volumetric (Seidman et al. 2006; Valera et al. 2007) and cortical thickness (Makris et al. 2007) studies identify abnormalities in the dorsolateral prefrontal cortex (DLPFC), the frontoorbital cortex, the anterior cingulate cortex (ACC), the inferior parietal lobule (IPL), and the corticostriatal system, which are structures subserving attention and executive functions (EFs). The presence of this array of abnormalities raises a critical question as to whether ADHD is a syndrome that may involve disordered white matter (WM) connections.

There is currently evidence from MRI structural investigations that WM alterations are present in children, adolescents, and adults with ADHD (Hynd et al. 1990; Filipek et al. 1997; Overmeyer et al. 2001; Castellanos et al. 2002; Mostofsky et al. 2002; Seidman et al. 2006). However, results are inconsistent so far. Whereas the studies conducted in children and adolescents with ADHD showed a reduction in overall WM volume (Castellanos et al. 2002), in adults with ADHD, there was a trend toward an overall increase in WM volume (Seidman et al. 2006). Furthermore, these studies considered the cerebral WM in its entirety without investigating specific fiber pathways or adopting a neural systems perspective. To our knowledge, there is only one published study using diffusion tensor MRI (DT-MRI) in children and adolescents with ADHD (Ashtari et al. 2005) and none in adults. Ashtari et al. (2005) conducted an investigation of a number of WM structural regions of interest (ROIs); however, they did not address specifically a neural networks anatomical investigation to elucidate the alterations in brain organization that occur in adults with ADHD.

Because of strong theoretical considerations regarding the neuroanatomy of the attentional neural system (Mesulam 1990;
Posner and Petersen 1990, Makris et al. 2007), our laboratory has focused strongly on the role of the anterior cingulate in ADHD (Bush et al. 1999; Bush et al. 2005; Seidman et al. 2006; Makris et al. 2007). The ACC has strong connections to the DLPFC and is considered to play a critical role in complex cognitive processing (Bush et al. 2000), particularly in target detection, response selection, error detection, and reward-based decision making (Bush et al. 2002), functions that are thought to be impaired in ADHD. In addition to functional MRI abnormalities in the ACC (Bush et al. 1999), we found that adults with ADHD have a smaller ACC volume than controls by approximately 14% (Seidman et al. 2006), and in that same sample, the ACC in ADHD was significantly thinner than in matched controls (Makris et al. 2007). Similarly, portions of the lateral prefrontal cortex, especially the superior frontal gyrus component of the DLPFC, were also significantly reduced in volume (by approximately 11%; Seidman et al. 2006) and significantly thinner (Makris et al. 2007). Because, the cingulum bundle (CB) connects ACC with the DLPFC and the IPL, we were especially interested in these connections. We were also very interested in the superior longitudinal fascicle II (SLF II), as this WM pathway, particularly in the right hemisphere, is associated with attention (Heilman et al. 1970; Heilman et al. 1983; Mesulam 1990).

The goal of this study was to extend our previous work on the neuroimaging of ADHD in an independent sample of adults with childhood-onset ADHD. The principal focus of this study was to investigate putative alterations of the connections believed to subserve attention and EFs in adults with ADHD using DT-MRI. Our driving hypothesis was that the WM associated with these neural networks would be different in ADHD subjects compared with controls. These WM structures include the CB and the SLF II. The current study sought to extend beyond measurements of regional WM volume and focused on looking for decreases in fractional anisotropy (FA) values for CB and the SLF II as a measure of potentially disordered connectivity within the attention and executive networks.

Methods

Subjects

Study subjects were adults, aged 37–66 years, who were participants in the longitudinal National Collaborative Perinatal Project (NCPP). The NCPP was initiated 40 years ago to investigate prospectively the prenatal and familial antecedents of pediatric, neurological, and psychological disorders of childhood (Niswander and Gordon 1972). Twelve university-affiliated medical centers participated in this national study, including 2 in New England (Harvard Medical School and Brown University). Obstetrical intake occurred between 2 January 1959 and 31 December 1965. Cases were selected on the basis of a sampling frame defined for each study center. At the conclusion of the study, a total of 55,908 births were recorded nationally, approximately 17,000 of which occurred in Boston/Providence ("New England Cohorts"). The sample for this paper was derived from a larger project, funded by the March of Dimes Foundation (L.J.S., principal investigator), designed to investigate the prenatal and early development antecedents of neuroimaging profiles of adults with and without childhood ADHD. The current investigation is a preliminary report that focuses on cross-sectional data based on neuroimaging assessment of WM using DT-MRI among 12 adults with childhood ADHD and 17 control subjects.

In this paper, we used intelligence and achievement test data collected in the NCPP at age 7 years to select subjects who are unlikely to manifest developmentally based learning disabilities (LDs). This approach was used to study ADHD independent of the frequent comorbid LDs that may contribute independent neurobiological abnormalities (Seidman et al. 2001). The assessment in childhood used a battery of 13 psychological measures obtained when the child was of age 7 years that are relevant to the study of cognition (Seidman et al. 2000). The tests that comprise Full Scale IQ are 7 subtests from the Wechsler Intelligence Scale for Children (Wechsler 1949) (Vocabulary, Comprehension, Information, Digit Span, Picture Arrangement, Block Design, and Digit Symbol Coding). We also report the reading subtest of the Wide Range Achievement Test (WRAT; Wilkinson 1995). Other tests and social history information were obtained from the mother at study intake (during pregnancy) and when the child was of age 7 years, including socioeconomic status (SES) of the family and ethnicity. Parts of the Wechsler Adult Intelligence Scale—Third Edition (WAIS-3; Wechsler 1997)—and WRAT—Third Edition (Wilkinson 1993)—were also administered at the adult assessment.

Adult assessments, including brain imaging, were obtained when the subjects were 37–46 years of age. All subjects completed the Diagnostic Interview Schedule IV (DIS-IV) for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and a supplementary DSM-IV instrument called the "Longitudinal Instrument for Symptoms of Attention (LISA)." The LISA uses the 18 ADHD items from DSM-IV (9 "inattentiveness," 9 "hyperactivity-impulsivity") to supplement the ADHD module of the DIS-IV. The LISA expands upon the DIS items for ADHD by asking about the age of onset and duration of each symptom, consistency of symptom expression across home and school, persistence into the present, and includes questions about past psychiatric treatments and hospitalizations and lifetime use of medications. The 12 subjects with ADHD all met DSM-IV criteria for childhood-onset ADHD (6 or more of either inattentive or hyperactive symptoms). Five persons with childhood ADHD continued to meet criteria for the disorder when interviewed in adulthood. All subtypes of ADHD are included. Additional inclusion criteria are at least 8th grade education, native English speaking, IQ of at least 75 in childhood, and willingness to participate in all procedures. Exclusion criteria include sensory-motor handicaps (e.g., severe visual problems), psychosis, neurological disorders (e.g., epilepsy, traumatic brain injury with cognitive sequelae or loss of consciousness, history of brain surgery), medical illnesses that significantly impair neurocognitive function (e.g., severe diabetes, kidney disease), current substance abuse (during the past 6 months), or history of alcohol or drug dependence. Reading disability in childhood (defined by WRAT Reading or Spelling scores below 80 at age 7 years) or adulthood (defined by Woodcock Johnson Letter Word, Passage Comprehension, or Word Attack scores below 80 when tested at adult entry to the imaging study) were exclusions. Exclusions also include conditions incompatible with MRI scanning (e.g., certain types of metal in the body, cardiac pacemakers, claustrophobia, pregnancy).

Controls were adults who met all the above inclusion criteria, who met none of the not-drawn criteria, and who were not diagnosed with childhood-onset ADHD. One of 12 persons with childhood ADHD had been treated with a stimulant, compared with none of the controls. Human subjects approval was granted by Institutional Review Boards at Brown University, Harvard University, the National Institute of Child Health and Human Development, the Massachusetts Mental Health Center, and Massachusetts General Hospital. Written consent was obtained from all interviewed/tested study participants.

MRI Acquisition Parameters

Twenty-nine subjects (12 adult ADHD and 17 controls) were scanned as part of this study. All subjects received 3-dimensional T1-weighted anatomical magnetization prepared rapid gradient echo (MP-RAGE) and diffusion-weighted (DT-MRI) imaging on a 1.5-T scanner (Siemens Avanto, Munich, Germany). The MP-RAGE scans were acquired with the following parameters: TR = 2750 ms, TE = 3.31 ms, TI = 1000 ms, flip angle = 7°, slice thickness = 1.1 mm, in-plane resolution = 1 × 1 mm, acquisition matrix = 256 × 256 (field of view = 256 × 256 mm), 2 repetitions of 128 contiguous sagittal slices, and pixel bandwidth = 195 Hz/pixel. Due to the long duration of the study, the DT-MRI data were acquired using 2 different protocols. Protocol 1 (10/29 subjects) data were acquired using a 6-shot protocol and with a b value = 600 s/mm², TR = 9000 ms, TE = 67 ms, flip angle = 90°, 60 axial slices to cover the entire brain, slice thickness = 2 mm, no skip, in-plane...
resolution = 2 mm × 2 mm, data matrix = 128 × 128 (FOV = 256 mm × 256 mm), bandwidth = 1860 Hz/pixel, and diffusion sensitivity b = 600 s/mm². Protocol 2 (19/29 subjects) consisted of a 70-shot acquisition (10 T2 echo-planar or low b images with b = 0 s/mm² and 60 diffusion-weighted images with b = 700 s/mm²) with TR = 7200 ms, TE = 77 ms, flip angle = 90°, 60 axial slices to cover the entire brain, slice thickness = 2 mm, no skip, in-plane resolution = 2 × 2 mm, data matrix = 128 × 128 (FOV = 256 × 256 mm), bandwidth = 1630 Hz/pixel, and diffusion sensitivity b = 700 s/mm². As the target of the diffusion analysis for this report is the FA map, the differences in the number of diffusion-encoding directions is accounted for in the generation of the FAs (see below). Subjects in Protocol 1 (6 directions) consisted of 8 healthy controls and 2 adult ADHD subjects. Subjects in Protocol 2 (60 directions) consisted of 9 healthy controls and 10 adult ADHD subjects. To ensure that the differences between our 2 protocols would not affect our results, scanning protocol was included as a factor in all our statistical tests.

DT-MRI Analysis
By way of overview, our DT-MRI processing stream is as follows (Makris et al. forthcoming): 1) eddy current distortion corrections, 2) FA map generation for each subject (in its native space), 3) nonlinear registration of all FA volumes into a common space, 4) voxelwise group statistics based on the common space FA data, and 5) assessment of significant group differences in a priori defined anatomic regions, guided by statistical thresholding. Each of these steps is described in detail below.

Diffusion Tensor Calculations
For the DT-MRI processing, we used the FDT (FMRIB’s Diffusion Toolbox), which is part of FSL (FMRIB’s Software Library; Smith et al. 2004). A 12-degree affine mutual information cost function transformation (procedure available with FLIRT, FMRIB’s Linear Image Registration Tool) was applied to all volumes to help reduce eddy current distortions (i.e., reduce the image effects of the stretches and shears induced by the gradient coils during acquisition). FA images were created by fitting the diffusion tensor to the raw diffusion eddy-corrected data using FDT and then skull stripped using the Brain Extraction Tool (Smith 2002).

Spatial Normalization
All FA images were aligned into a common space using a nonlinear registration (BTRK; Rueckert et al. 1999; Smith et al. 2006). A high-quality target FA image available with the FSL distribution was used as the prespecified target for all nonlinear coregistrations. This target image was affine aligned into MNI152 standard space, and every image was transformed into 1 × 1 × 1 mm³ MNI152 space by combining the nonlinear transform to the target FA image with the affine transform from that target to MNI152 space. The transformed FA data were combined to create an overall average FA map (see Fig. 1).

Group Maps
Analyses examining the regional distribution of diagnostic group-related changes (i.e., controls vs. ADHD) were performed by a voxelwise 2-tailed t-test between groups. The resultant statistical maps were thresholded at P < 0.05. It was found that projecting the results onto the alignment-invariant tract representation (i.e., “mean FA skeleton”) using Tract-Based Spatial Statistics (Smith et al. 2006), part of FSL, did not allow us to examine all areas of interest in this study (e.g., the anterior part of the CB). We followed up our a priori anatomic regions using specific ROI-based between-group analyses. Specifically, our a priori hypotheses were tested as follows: anatomical ROIs were delineated, namely the CB and the SLF II, upon which we elaborate below in detail. Each ROI was filtered by excluding voxels when the mean FA of all subjects was below 0.15. The ROI-based mean FA for each individual subject was then calculated, and statistical analyses were performed (see below).

Anatomic ROIs—FA Values for Individual Subjects
Using the group average FA map method, we defined the following anatomical ROIs to test our a priori hypotheses: 1) the right and left CB and 2) the right and left SLF II. We also measured FA in the fornix, a control WM ROI, to test specificity of the attentional–executive connections. We did not predict a group difference for the fornix. Furthermore, for exploration we calculated the average FA value of the entire forebrain. We focused our analysis on the portions of the fiber tracts where the axons course in compact bundles from origin to termination. These compact portions are called stems (Makris et al. 1997) and mainly contain axons of a specific fiber tract as opposed to the corona radiata where such different types of axonal fibers as corticocortical, commissural, and projectional coexist in variable but balanced proportions. Precisely, the voxels pertaining to the stem portions of the CB and SLF II were determined by their location relative to other cerebral structures. This was done by one rater (N.M.), blind to group assignment, based on the mapping of these fiber pathways from the known literature (Papez, 1937; Yakovlev and Locke, 1961; Makris et al. 2002; Makris et al. 2005). The regions were evaluated as follows. For the CB ROI, voxels contained within the cingulate gyrus in front and above the corpus callosum were selected bilaterally. This ROI extended from the coronal plane at the inflection point of the callosal genu (Meyer et al. 1999) caudally to the anteriormost part of the cingulate gyrus contained within the cingulate sulcus rostrally (Figs 2, 4 and 5B-b). For the SLF II ROI, voxels in the region above the insula, the extreme capsule, the claustrum, the external capsule, the lenticular nucleus, and the internal capsule were selected bilaterally (Makris et al. 2005). This ROI was sampled within the core of the WM underlying the DLPCF in the frontal lobe (Figs 2 and 4). For the fornix, we selected the voxels pertaining to the body of the fornix (i.e., between the rostral bifurcation of the body into the columns and the caudal bifurcation of the body at the dorsal hippocampal commissure) below the corpus callosum. The anatomical locations were examined in each of the individuals to verify and guarantee the consistency and accuracy of
their placement. This procedure generated average FA values for ROIs in the right and left hemispheres for the CB and the SLF II in each subject.

Statistical Analyses
Mean FA values within anatomical ROIs were compared between groups (controls vs. ADHD) using an analysis of variance (ANOVA) that included scanning protocol as an additional factor as well as a group by protocol interaction term. If the interaction term was nonsignificant, it was dropped from the analysis. That is, we began with a model that contained 3 effects (group, scan protocol, and their interaction) and, finding a nonsignificant interaction, reduced it to a 2-factor model (group and protocol). Hemispheric symmetry of mean FA in CB and SLF II was determined by calculating a symmetry index (Galaburda et al. 1987) that expresses the difference in FA between corresponding regions as a percentage of the average FA of the regions: \((L - R)/(L + R) \times 1/2\). Positive values indicate higher FA in the left region. We examined group effects in symmetry coefficients of the CB and SLF II with a 2-group t-test with unequal variance estimates. Mean FA across the entire forebrain was also examined for group effects and (exploratory) as an additional covariate with the anatomical ROIs. The data analyses were performed using the JMP statistical software package, version 5.0.1.2 (SAS Institute Inc, Carey, NC). The significance level was 0.05.

Results

Demographic Characteristics
The groups were comparable on age at scanning, sex distribution, handedness, ethnicity, SES of origin, years of education, WAIS-3 Vocabulary score, and WRAT-3 Reading score. No significant differences were noted on any of these variables (see Table 1).

FA Differences
Initial ANOVA models showed a nonsignificant interaction between group and scanning protocol; therefore, the latter was excluded from subsequent statistical tests. FA values in the right CB and the right SLF II ROIs were decreased significantly in the ADHD group as compared with the control group, and no effect of scanning protocol was found (see Table 2). These results are shown in Figs 3-5. Significant values were superimposed on 2 templates: 1) a single-subject T1 (one of the...
subjects that participated in this study) affine transformed into MNI152 standard space (Fig. 3) and 2) the standard MNI152 T1 average atlas (Fig. 4). The orange/yellow areas indicate regions where the control group has significantly higher FA values than the ADHD group. ADHD subjects have lower FA in the right CB at the pregenual and dorsal regions of the anterior cingulate gyrus as well as in the right SLF II (Table 2). The mean symmetry index of FA in the CB was leftward in both groups, although significantly more so in the ADHD subjects [control mean = 20.4, ADHD mean = 28.4, $t(26.1) = 2.6$, $P = 0.02$]. Although the FA values for SLF II were lower bilaterally, this effect was significant only on the right side. Further, the symmetry index of the SLF II did not differ significantly between groups [control mean = –4.6, ADHD mean = –2.4, $t(21.8) = 0.5$, $P = 0.7$]. There were no significant FA differences between groups for the fornix, which was the control ROI. The
To our knowledge, this is the first study addressing WM integrity using DT-MRI in adults with childhood ADHD. It is also the first study where a systems approach has been applied to probe anatomical connectivity in the central nervous system of subjects with ADHD. The only other DT-MRI study in the extant literature focused on children and adolescents with ADHD (Ashtari et al. 2005) showed FA differences in the right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital region. That study, however, did not address specific neural networks to elucidate the alterations in brain organization that occur in subjects with ADHD. Neural networks are currently considered to be important in genotype-phenotyping (Hyman and Nestler 1993). Thus, the neural networks subserving self-regulatory, attention, and EF as well as the corticostriatal and corticocerebellar circuits could represent putative biomarkers for ADHD, and their quantification using DT-MRI may be relevant for diagnostic and therapeutic purposes in this condition. These ideas need to be tested in subsequent studies.

Although there is a paucity of data on WM alterations in ADHD using DT-MRI, there are substantial data showing WM (Hynd et al. 1990; Filipek et al. 1997; Overmeyer et al. 2001; Castellanos et al. 2002; Mostofsky et al. 2002; Seidman et al. 2006) and gray matter (Castellanos et al. 2002; Hesslinger et al. 2002; Durston 2003; Sowell et al. 2003; Seidman et al. 2006; Shaw et al. 2006; Makris et al. 2007) volumetric, intensity, and cortical thickness abnormalities using T1-weighted MRI. Additionally, our recent study in a different sample showed that ADHD adults have significantly smaller overall cortical gray matter, prefrontal, and ACC volumes as well as trends toward significantly greater overall WM volumes (Seidman et al. 2006). The reasons why the latter observation in adults with ADHD is discrepant with findings in children and adolescents with ADHD, which showed a reduction in overall WM volume (Castellanos et al. 2002), remain unclear and require further elucidation.

The findings of the present study showing abnormalities in the CB at the right anterior cingulate gyrus region and in the SLF II are consistent with volumetric and cortical thickness abnormalities observed in a different sample of adults with ADHD conducted by our group (Seidman et al. 2006; Makris

### Table 1
Demographic and neuropsychological variables in healthy controls versus adults with ADHD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 17)</th>
<th>Adults with ADHD (n = 12)</th>
<th>Statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at MRI</td>
<td>40.5 ± 2.1</td>
<td>41.3 ± 2.1</td>
<td>t = -0.98</td>
<td>0.4</td>
</tr>
<tr>
<td>SES (education)</td>
<td>45.6 ± 20.3</td>
<td>50.0 ± 21.2</td>
<td>t = -0.56</td>
<td>0.6</td>
</tr>
<tr>
<td>Education classification</td>
<td>4.8 ± 1.2</td>
<td>4.4 ± 1.3</td>
<td>t = -0.70</td>
<td>0.5</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>8.7 ± 2.2</td>
<td>8.3 ± 2.3</td>
<td>t = 0.43</td>
<td>0.7</td>
</tr>
<tr>
<td>WRAT-3 Reading</td>
<td>98.9 ± 7.7</td>
<td>93.2 ± 13.5</td>
<td>t = 1.27</td>
<td>0.2</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>47.1%</td>
<td>58.3%</td>
<td>( \chi^2 = 0.36 )</td>
<td>0.6*</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>76.5%</td>
<td>83.3%</td>
<td>( \chi^2 = 0.02 )</td>
<td>0.9**</td>
</tr>
<tr>
<td>Education classification</td>
<td>4.8 ± 1.2</td>
<td>4.4 ± 1.3</td>
<td>t = 0.70</td>
<td>0.5</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>88.2%</td>
<td>83.3%</td>
<td>( \chi^2 = 0.14 )</td>
<td>0.7**</td>
</tr>
</tbody>
</table>

Note: SD, standard deviation; WRAT-3, WRAT—Third Edition.

aTest statistic shows the group effect derived from an ANOVA model that includes scan protocol as an additional factor. The other values in the model are as follows: right CB: \( F_{2,26} = 5.5, P = 0.01 \) (protocol: \( t_{26} = -1.2, P = 0.2 \)); left CB: \( F_{2,23} < 0.1, P > 0.9 \) (protocol: \( t_{26} = -0.2, P = 0.8 \)); right SLF II: \( F_{2,26} = 2.5, P = 0.1 \) (protocol: \( t_{26} = 0.5, P = 0.6 \)); left SLF II: \( F_{2,26} = 3.8, P = 0.04 \) (protocol: \( t_{26} = -1.6, P = 0.12 \)); fornix: \( F_{2,26} = 2.7, P = 0.09 \) (protocol: \( t_{26} = 5.3, P = 0.03 \)).

**Table 2**
Mean FA values for 2 groups of subjects: Matched healthy controls versus adults with ADHD

<table>
<thead>
<tr>
<th>Region</th>
<th>Controls (n = 17)</th>
<th>Adults with ADHD (n = 12)</th>
<th>Group effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>t value</td>
</tr>
<tr>
<td>Right CB</td>
<td>2102.7 ± 154.0</td>
<td>1950.7 ± 92.3</td>
<td>-2.5</td>
</tr>
<tr>
<td>Left CB</td>
<td>2586.0 ± 240.9</td>
<td>2598.2 ± 143.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Right SLF II</td>
<td>3451.2 ± 285.8</td>
<td>3170.2 ± 399.5</td>
<td>-2.2</td>
</tr>
<tr>
<td>Left SLF II</td>
<td>3297.0 ± 269.8</td>
<td>3078.7 ± 255.1</td>
<td>-1.6</td>
</tr>
<tr>
<td>Fornix (control region)</td>
<td>3893.8 ± 862.9</td>
<td>3815.5 ± 645.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Note: SD, standard deviation.

*Test statistic shows the group effect derived from an ANOVA model that includes scan protocol as an additional factor. The other values in the model are as follows: right CB: \( F_{2,26} = 5.5, P = 0.01 \) (protocol: \( t_{26} = -1.2, P = 0.2 \)); left CB: \( F_{2,23} < 0.1, P > 0.9 \) (protocol: \( t_{26} = -0.2, P = 0.8 \)); right SLF II: \( F_{2,26} = 2.5, P = 0.1 \) (protocol: \( t_{26} = 0.5, P = 0.6 \)); left SLF II: \( F_{2,26} = 3.8, P = 0.04 \) (protocol: \( t_{26} = -1.6, P = 0.12 \)); fornix: \( F_{2,26} = 2.7, P = 0.09 \) (protocol: \( t_{26} = 5.3, P = 0.03 \)).

### Discussion

In this study, we demonstrated that WM associated with neural networks subserving attention and executive processing was different in adults with ADHD than in their matched controls. This WM included long association corticocortical fiber pathways, namely the CB and the SLF II. Of the above WM structures, the right CB and right SLF II are especially involved in attention processing (Makris et al. 2002), whereas the CB and the SLF II bilaterally are involved in executive functioning (Makris et al. 2005). In these WM regions, the FA values were lower in adults with ADHD than in matched controls indicating disruptions in WM integrity. Overall, these novel findings demonstrate a structural abnormality of these neural systems in the cerebrum of adults with ADHD. The absence of fornix abnormality suggests some specificity for the SLF II and CB findings. In addition, there was no significant group difference in the mean FA across the entire forebrain \([t(27) = -1.3, P = 0.2]\), and, in an exploratory analysis, including forebrain FA as a covariate in the ROI analysis did not change the results reported in Table 2.
et al. 2007). Taken together, these findings suggest abnormal anatomical connectivity between the anterior cingulate gyrus and other prefrontal regions, a putatively central disconnection between cortical regions regulating attention and EF. Interestingly, although the cortical network steering attention utilizes right lateral frontal and anterior cingulate areas, it is also driven by more posterior cortical centers at the temporo-occipito-parietal junction in the lateral surface of the right hemisphere, principally the angular (BA 39) and supramarginal (BA 40) gyr (Critchley, 1966; Heilman et al. 1970; Heilman et al. 1983; Heilman and Valenstein, 1985; Mesulam 1990; Posner and Petersen 1990; Breiter et al. 2006). The specific WM fiber pathways connecting these cortical areas are the SLF II and the CB, which in the right hemisphere would be responsible for processing information related to attentional functions. The fact that the results were significant in the right hemisphere is consistent with models of attention (Heilman et al. 1983; Mesulam 1990).

The EF circuitry principally involves the prefrontal regions and has been anatomically simplified as primarily representing the interplay of frontostriatal activity (e.g., 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 et al. 1999; Mayberg, 2002; Tamm et al. 2004). The ACC in particular has recently attracted considerable attention as one of the principal structures implicated in ADHD (Bush et al. 1999; Tamm et al. 2004). The ACC is connected with the prefrontal cortex, the IPL, and subcortical centers such as the amygdala, thalamus, striatum, and the brain stem. These connections transfer information to and from the ACC vital for monitoring, balancing, and deciding how and when to allocate cognitive control (Carter et al. 1998; Botvinick et al. 1999; Carter et al. 2000; Cohen et al. 2000; Gehring and Knight 2000; Paus, 2001; Bush et al. 2002). It is also known that these deficits exist independently of hemispheric lateralization and that bilateral alterations increase the severity of EF symptoms (Damasio 1985). The CB is one of the principal fiber tracts mediating these connections bilaterally (Mufson and Pandya 1984; Makris et al. 2002). The functional role of the CB has been associated principally with the limbic system (Papez 1937; Yakovlev and Locke 1961). Fibers originating in the cingulate cortex project rostrally to the premotor and prefrontal cortices. Caudally, they project to the posterior parietal cortices and project around the splenium of the corpus callosum to the parahippocampal gyrus. Other cortical areas that send fibers through the CB are the frontal, parietal, and superior temporal areas, as well as the parahippocampal gyrus and the insula. Its relationships with the parahippocampal gyrus, the presubiculum, the retrosplenial area, the insula, the perirhinal region, the cingulate cortex, and the anterior and mediiodorsal nuclei of the thalamus suggest a central role of this fiber tract in the integration of visuospatial and motivational processes (Papez 1937; Pandya and Veteran 1985; Schmahmann and Pandya 2006). The behavioral affiliations of the CB are heterogeneous including memory, attention, learning, pain perception, motivation, emotion, and visceral function (Papez 1937; Pandya and Veteran 1985; Devinsky et al. 1996; Casey et al. 1997; Mesulam 2000; Schmahmann and Pandya 2006). Thus, its structural failure may disrupt the normal processing and communication of ACC with other prefrontal cortical and subcortical centers and could result in disarming of fundamental cortical properties that mediate such symptoms of ADHD as abnormal decision making and control of drives, as well as inattention.

Furthermore, within the core of the attention network in the right hemispheric cerebral cortex, the principal connecting fiber pathways are the SLF II and the CB (Mufson and Pandya 1984; Petrides and Pandya 1984; Petrides 1986; Makris et al. 1997; Mori et al. 1999; Makris et al. 2002; Makris et al. 2005; Schmahmann and Pandya 2006). SLF II can be viewed as a major link providing the prefrontal cortex with information from the parietal lobe concerning the perception of visual space. Because the SLF II pathway is bidirectional, the fibers originating from the prefrontal cortex and directed back to the posterior parietal region could provide a mean by which the prefrontal cortex can regulate the focusing of attention in different parts of space. Another possible role of the SLF II pathway may be in selecting between competing locations on the basis of conditional rules (Petrides 1986). In addition, damage to SLF II could result in disorders of spatial working memory by virtue of interrupting relationships with prefrontal area 46 (Preuss and Goldman-Rakic 1989; Petrides and Pandya 2002). The importance of temporal, parietal, and frontal cortical regions for attention has been documented experimentally in monkeys (see e.g., Watson et al. 1978). Interestingly, it has been also shown that experimental frontoparietal disconnections produce alterations in spatial processing and directed attention in rats (Burgham et al. 1997).

In a recent study with another sample of adults with ADHD (Makris et al. 2007), we found that the ACC, the frontal multimodal association area (i.e., the DLPFC), and the orbital frontal regions show cortical thinning in adults with ADHD. In the ADHD literature, these alterations have been associated with deficit of the EF network, which involves frontostriatal structures bilaterally, that is, the prefrontal cortex, dorsal ACC, caudate, and putamen (Barkley 1997; Bush et al. 1999; Castellanos et al. 2002; Durston 2003; Sowell et al. 2003; Seidman et al. 2004; Bush et al. 2005; Seidman et al. 2005; Seidman et al. 2006). Furthermore, we observed that the cortical network subserving attention was altered as well showing cortical thinning (Makris et al. 2007). Moreover, in the present hypothesis-driven study we demonstrated that WM fiber abnormalities of adults with ADHD are associated with the expected attentional and executive neural systems. Remarkably, these fiber alterations also match the cortical thickness and volumetric as well as the functional alterations observed in the cerebrum of adults with ADHD (Bush et al. 1999; Giedd et al. 2001; Durston 2003; Bush et al. 2005; Seidman et al. 2006; Makris et al. 2007). Thus, it appears that the observed FA abnormalities within the prefrontal and dorsal anterior cingulate gyrus WM as well as the SLF II, could contribute to the phenomenology of this disorder. These connectional deficits among the cingulate cortex, the DLPFC, and orbitofrontal and parietal cortices seem to be syndrome congruent and consistent with the cardinal symptoms of adults with ADHD, namely impulsivity, hyperactivity, and inattention. Overall, dysfunction of the joint attentional and EF networks could have a powerfully disabling effect on the fundamental cerebral properties that might mediate the symptoms of ADHD. Of course, future work will need to address whether the abnormalities are selectively localized to these ROIs or whether a wider range of locations are altered. In this study, the absence of a significant difference in a control region (the fornix)
provides preliminary support for the hypothesis that it is the attentional and executive network connections that are impaired.

Although in the present investigation, emphasis was placed on the WM structures and interpretations on their abnormalities, information regarding the gray matter structures is relevant in order to interpret our observations in WM and fiber tract alterations given that the gray matter centers are processing the information conveyed to them by their fiber connections. It is the overall integrity of the neural networks (composed by ensembles of neuronal bodies and axonal systems) that is ultimately relied upon by the self-regulatory, attention, EF, and motor control systems. The proliferative mechanisms that give rise to the projection neurons of the neocortex operate with precision (Takahashi et al. 1999; Caviness et al. 2000), giving rise to tightly regulated numbers of an overlapping succession of laminar neuronal classes. The earliest formed are the projection neurons of layers VI then V with those of the successively more superficial layers IV—II following in order (Angevine and Sidman, 1961; Rakic, 1974; Bisconet and Marty 1975a, 1975b; Caviness 1982; Sidman and Rakic 1982). The molecular events that specify neuronal class as well as those that determine a protomap of ultimate neocortical architectonic organization appear to take place concurrently with the proliferative process, whereas mechanisms of cell differentiation and the assembly of neural systems go forward after the young neurons are assembled within their respective layers in the cortex following the completion of their migrations (OLeary 1989; Miyashita-Lin et al. 1999; Grove and Fukuchi-Shimogori 2003). The fundamental molecular and genetic operations that govern this critical early stage of cortical development are as yet little understood. The proposed work is directed at an early formative stage of the differentiation process that is ultimately expressed as ADHD.

Limitations

Our findings must be interpreted in light of methodological limitations. Our sample was not referred specifically for ADHD, and our results may not generalize to clinically referred ADHD samples. On the other hand, these results are unique in terms of reflecting a community sample of adults with childhood-onset ADHD. The diagnoses of ADHD relied on the self-report of adult subjects derived from structured interviews. Thus, these findings may not generalize to diagnoses defined using data from informants. However, this is a standard procedure for diagnosing ADHD in adults, and there is substantial data showing that it can be done reliably and that it is a valid methodology (Faraone et al. 2000; Biederman et al. 2006). The sample size was modest and requires replication and extension. Furthermore, it has to be clarified that because in the current study we do not have neuropsychological testing, considerations regarding functions of fiber pathways are based on existing knowledge of functional neuroanatomy and thus are inferential. Future work with larger samples should also look at the relationship of neuropsychological measures, FA, and subtypes of ADHD.

It can be argued that the 2 different diffusion protocols have differing sensitivity for resolving diffusion-based alterations in this patient population. As we have "reduced" the high-dimensional diffusion acquisition in the summary scalar value (i.e., the FA), we are making our comparisons on a property that is over sampled (albeit differently) in these 2 acquisitions. It can be expected that this calculation will not result in a systematic difference in FA, and in fact, the scanning protocol did not factor in our results. Moreover, there is not a systematic selection of either subject population in these protocols, and because the methodological variation would tend to decrease power (rather than increase power), we feel that this acquisition difference is not a factor in the observed FA differences. Finally, our DT-MRI acquisition was sensitive enough to detect FA differences in subsections of the most densely packed fibers, such as the CB and SLF II. Regardless of the underlying pathophysiology, this DT-MRI method can discern a class of abnormality at certain locations within a tract. However, it has limited sensitivity for assessing the entire tract and lacks the sensitivity to indicate if WM abnormalities are due to a lack of coherence in the tracts and/or due to a difference in direction of tracts.

Finally, the current study investigated adults with ADHD and did not address the developmental course of the CB and SLF II. Given that the capacity of the EF and attention function subserved by CB and SLF II could well be related to maturation of these fiber bundles, as has been shown for a different circuitry, that is, the frontostriatal circuitry (Liston and others, 2006), future studies should be conducted with a larger age range of children and adults with ADHD and include behavioral testing for EF and attention function.

In this report of DT-MRI analysis in adults with ADHD, we demonstrated significantly different FA values in the anatomical connections of the attention and EF cerebral systems. These results expand upon previous findings demonstrating cortical abnormalities in the attentional and executive systems, thus supporting the idea of a comprehensive abnormality in the cerebral neural networks subserving attention and EFs in adults with ADHD. Furthermore, these observations are congruent with the clinical picture of ADHD and consistent with the putative neuroanatomy of the well-documented attentional and executive symptomatology characterizing this disorder.

Human Research Statement

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

Funding

March of Dimes Foundation (to L.J.S.); National Association for Research in Schizophrenia and Depression (to N.M.); National Institutes of Health National Center for Complementary and Alternative Medicine (to N.M.); National Alliance for Research on Schizophrenia and Depression (Distinguished Investigator Award to J.B.), Janssen Pharmaceuticals (to J.B.); Johnson and Johnson Center for the Study of Psychopathology (to J.B.); Fairway Trust (to D.K.); National Research Service Award (NIMH F32 MH065040-01A1) (to E.M.V.); Harvard Medical School Department of Psychiatry (Peter Livingston Fellowship to E.M.V.); Clinical Research Training Program Fellowship in Biological and Social Psychiatry (MH-16259 to E.M.V.); National Center for Research Resources (P41RR14075 to J.B.); National Institute of Mental Health (NIMH MH/HD 62152 to L.J.S.); Mental Illness and Neuroscience Discovery Institute (to L.J.S.).
Notes

The authors would like to thank Denise Boriel, Scott Sorg, Jessica Coop, Kym Goyette, Lou Lipsitt, PhD, Amlia Papazoglou, Nicole Peace, Anne Peters, Russell Poldrack, PhD, Chris Provencal, Paul Satz, PhD, and Michael Schiller for their contributions to this study. Conflict of Interest: Eve M. Valera, Ph.D. has been a speaker for Shire Pharmaceuticals. George Bush, M.D., M.M.Sc. receives/d research support from, is has been a speaker for, or is has been on the advisory board for the following pharmaceutical companies: Eli Lilly and Company, Pfizer, Inc., Shire U.S. Inc., Novartis Pharmaceuticals, Janssen Pharmaceuticals, McNeil Pharmaceuticals, and Johnson & Johnson. He does not have a financial interest in any of these entities. Larry J. Seidman, Ph.D. received research or educational support from, and has been a speaker in an industry sponsored symposia for, Eli Lilly, and Janssen. Joseph Biederman, M.D. has received research support from Bristol-Myers Squibb, Eli Lilly and Co., Janssen Pharmaceutical Inc., McNeil, Otsuka America Inc., Shire, NICHHD, MIMH, NIDA. He has also served as an Ad-board/consultant for Cephalon Inc., Eli Lilly and Co., Janssen Pharmaceutical Inc., McNeil, Novartis, Novon, and Shire. Additionally, he spoke for Cephalon Inc., Eli Lilly and Co., Janssen Pharmaceutical Inc., McNeil, Novartis, Shire, UCB Pharma, Inc., and Wyeth. Research support received 2001-2006: Abbott, Astra-Zeneca, Celtech, Cephalon Inc., Forrest, Glatice, NARSAD, New River Pharmaceuticals, Novartis, Noven, Pharmacia, Pfizer, Stanley Pharmaceuticals, Wyeth.

Address correspondence to Nikos Makris, MD, PhD. Email: nikos@cma.mgh.harvard.edu.

References


