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Anterior Cingulate Volumetric Alterations in Treatment-Naïve Adults With ADHD:

A Pilot Study

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Abstract

Objective—We sought to examine preliminary results of brain alterations in anterior cingulate cortex (ACC) in treatment-naïve adults with ADHD. The ACC is a central brain node for the integration of cognitive control and allocation of attention, affect and drive. Thus its anatomical alteration may give rise to impulsivity, hyperactivity and inattention, which are cardinal behavioral manifestations of ADHD.

Method—Segmentation and parcellation of the ACC was performed on controls ($n = 22$), treated ($n = 13$) and treatment-naïve adults with ADHD ($n = 13$).

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Results—There was a 21% volume reduction in the left ACC of the treatment-naïve group relative to the control group. Also, there was a 23% volume reduction in the right ACC of the treated group relative to the control group.

Conclusion—These results raise the possibility that in ADHD there are volumetric deficits persistent into adulthood, that are independent of medical treatment.

Keywords

ADHD; treatment-naïve ADHD; ACC; volumetry; morphometry; MRI

Introduction

ADHD is estimated to affect 5% to 10% of children and 4% of adults (Kessler & Merikangas, 2004). Emerging evidence shows that like its pediatric counterpart ADHD in adults is a highly morbid disorder (Biederman et al., 2006). Given its severe morbidity, understanding the neural basis of ADHD is of high clinical, scientific, and public health importance.

Convergent data from neuroimaging, neuropsychological, genetics, and neurochemical studies have implicated dysfunction of the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and parietal cortex (together, the cingulo-frontal-parietal [CFP] cognitive-attention network), along with striatum and cerebellum, as contributing to the pathophysiology of ADHD (Bush et al., 2008). The ACC findings are particularly consistent, with many imaging studies reporting ACC hypofunction (Bush et al., 1999; Bush, Valera, & Seidman, 2005; Durston et al., 2003; Ernst et al., 2003; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Pliszka et al., 2006; Rubia et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004; Zametkin et al., 1990) or structural abnormalities (Makris, Biederman et al., 2007; Makris, Buka et al., 2008; Seidman et al., 2006; Shaw et al., 2006). The ACC plays key roles in cognition, attention, target detection, motor control (response selection and inhibition), error detection and feedback-based decision-making. Our own prior structural work has shown the ACC to have the largest volume reduction in adults with ADHD (13.9%) of any of the structures we investigated. However, because this literature is based on samples of largely treated subjects, uncertainties remain as to whether these findings reflect the neural underpinning of the disorder or the complications of its treatment. Thus, in this study, we focus in on the ACC in never-treated adults with ADHD.

To-date there is only one study showing volumetric decrease on the right ACC in treatment-naïve children with ADHD relative to treated children with ADHD and controls (Pliszka et al., 2006). However, there is currently no study to our knowledge regarding the nature of cerebral alterations in treatment-naïve adults with ADHD. This paucity of information represents a serious void in our knowledge base on ADHD calling for studies specifically addressing treatment-naïve subjects with ADHD.

The principal focus of this study was to delineate the nature of ACC alterations in treatment-naïve adults with ADHD. To this end, we hypothesized volumetric MRI reductions in ACC in treatment-naïve adults with ADHD compared to community controls using T1-weighted MRI. This is, to our knowledge, the first study reporting volumetric alterations in treatment-naïve adults with ADHD.

Method

Methods are described in detail in Biederman et al. (2008) and Seidman et al. (2006). This study consists of a subset of ADHD subjects from the previous reports and a larger study of

persons with ADHD varying on a number of dimensions, including use of medications. Briefly, males and females between the ages of 18 and 59 were eligible for the study. Treatment-naïve and treated subjects with ADHD as well as control adults were group matched to be comparable on age, sex, handedness, and education (Table 1). Exclusion criteria were deafness, blindness, psychosis, neurological disorder, sensorimotor handicaps, inadequate command of the English language, or an estimated Full Scale intelligence quotient (IQ) estimate <80 as measured by *Wechsler Adult Intelligence Scale–Revised* (*WAIS-R*; Wechsler, 1981). We recruited ADHD subjects from referrals to psychiatric clinics at the Massachusetts General Hospital (MGH) and advertisements in the greater Boston area, and control subjects through advertisements in the same geographical areas. After complete description of the study to the participants, written informed consent was obtained, and all participants received an honorarium for participating. The study was approved by the MGH Human Subjects Institutional Review Board (IRB) committee.

Clinical Assessment Measures

ADHD adults were only included if they met full criteria for current ADHD according to the *DSM-IV*, with childhood onset and persistence into adulthood. We conducted direct interviews with all participants. Trained lay interviewers, blind to ascertainment status, interviewed all adults with the Structured Clinical Interview for *DSM-IV* (First, Spizer, Gibbon, & Willians, 1997) supplemented with modules from the Kiddie SADS-E (Orvashcel, 1994) to cover ADHD and other childhood disorders.

Magnetic Resonance Imaging

Whole brain Magnetic Resonance (MR) 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 T2-weighted sequence to rule out unexpected neuropathology. Two sagittal 3DMP-RAGE (T1-weighted, nonselective, inversion prepared, spoiled gradient, echo pulse, no distortion correction) sequences were collected and used for morphometric analyses conducted at the MGH Center for Morphometric Analysis (CMA). The volumetric T1-weighted images, which were used for the analysis were as follows: TR = 2730 ms, TE = 3.39 ms, T1 = 1,000 ms, flip angle = 7°, bandwidth = 190 Hz/pixel, FOV = 256 × 256 mm^2, sampling matrix = 256 × 192 pixels, 128 contiguous 1.33 mm slices, averages = 2.

Image Preprocessing: Standard Orientation and Segmentation

The images were resampled into a standard coordinate system based on the bicommissural line (anterior commissure–posterior commissure) and the interhemispheric fissure (Filipek, Kennedy, & Caviness, 1988; Filipek, Richelme, Kennedy, & Caviness, 1994; Talairach, & Tournoux, 1988). Given this coordinate system, coronal slices were defined perpendicular to the bicommissural line and aligned with the interhemispheric 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.

MRI Based Segmentation and Parcellation of Cerebral Cortex

Neuroanatomic segmentation was performed using semiautomated intensity contour algorithms for external border definition and signal intensity histogram distributions for delineation of gray–white borders (Filipek et al., 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. Segmentation was performed on coronal images and divided the brain into gray matter and white matter regions. The cerebrum was segmented into its principal gray matter and white matter structures and total cerebral white matter.

Specifically, the cortical ribbon was defined by two outlines, one external outline between the sub-arachnoid CSF and the cerebral cortex, and the other between the cerebral cortex and the underlying cerebral white matter (Filipek et al., 1994). The total number of voxels in each brain region determined its volume.

Cortical Parcellation

At the neocortex, which was defined by the aforementioned gray–white matter segmentation procedure, we parcellated the anterior cingulate gyrus (ACC or CGa) parcellation unit (PU) bilaterally (Caviness, Meyer, Makris, & Kennedy, 1996). This was based on the configuration of a specified set of cerebral landmarks, precisely the cingulate sulcus (anterior and superior border of ACC), the callosal sulcus (inferior border of ACC) and the plane passing though the dorsocaudal endpoint of the precentral sulcus (i.e., plane K; posterior border of ACC), and addresses interindividual topographic variability by preserving the morphological and topographic uniqueness of the individual brain. This method is explained extensively in Caviness et al. (1996). 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 ACC appeared. We selected a priori the ACC as the PU to investigate based on our previous work (Figure 1, Seidman et al., 2006).

Statistical Analysis

First, we compared the three groups on demographic, psychiatric, and neurocognitive factors, using the Chi square test and one-way ANOVAs for categorical and dimensional variables, respectively.

We tested the hypothesis that treatment-naïve and treated adults with ADHD would have morphometric abnormalities in the ACC relative to the controls using regression models. In each model, we estimate the volumetric outcome as a function of group status. We present the mean volumes within each group. All models were estimated using linear regression, and all tests were two-tailed. The alpha level was set at 0.05.

Results

The treatment-naïve group showed significant volume decrease in the left anterior cingulate gyrus as shown in Table 2, with a large effect size ($d = .71$, 21% smaller). On the other hand, the treated group showed significant volumetric decrease in the right anterior cingulate gyrus with a large effect size ($d = .85$, 23% smaller; Table 2). There were no significant group differences in whole brain or total cerebral volume or in the right ACC (Table 1).

Discussion

This pilot analysis showed a volumetric decrease in the cortex of the left ACC in treatment-naïve adults with ADHD. This finding suggests that volumetric abnormalities in the ACC in adults with ADHD represent alterations reflecting the neural underpinnings of the disorder.

Consistent with our results are the results from a recent study by Pliszka et al. (2006) that showed an alteration in the right ACC of treatment-naïve children with ADHD. Although these two studies are not directly comparable given the determining influence developmental forces may have on brain structure as a function of time, it is interesting to note that both studies have identified a change related to the ACC.

The anterior cingulate gyrus is an important regulator of other cortical and subcortical brain regions, and its disconnection seems to be consistent with the symptoms encountered in ADHD. The ACC is connected with other cortical areas ipsilaterally and contralaterally as

well as with subcortical structures. This mesh of connections converging to and diverging from the neuronal bodies of the ACC constitutes a central networking node within the overall connectional map of the brain critical for the interface of drive, emotion, cognition and motor function (Paus, 2001) as well as for the modulation of cognitive control (Cohen, Botvinick, & Carter, 2000). An abnormality of ACC could produce derangement of attention and executive neural networks in adults with ADHD. Importantly, a deficit of the ACC network may cause breakdown in modulation of cognitive control and allocation of attention, which may result in impulsivity, hyperactivity, and inattention.

The finding that in adults with ADHD the left ACC is abnormal volumetrically is critical to elucidate a concept that has recently been raised in ADHD clinical research. A study by Shaw et al. (2007) reported that children with ADHD show a “delay” in maturation of brain structures as compared to controls (Shaw et al., 2007). It is unclear from this study, however, whether the brain abnormalities will eventually “normalize” or not. In a previous study by Shaw et al. (2006), the authors showed that certain aspects of the morphometric profile of children with “better outcome ADHD” (such as the right inferior parietal lobule) tend to “normalize” as they progress into late adolescence (Shawet al., 2006). The results of our study, although preliminary, bear evidence that there are abnormalities in the anterior cingulate gyrus of ADHD participants that persist well into adulthood.

Our study showing abnormalities in the ACC in medication-naïve ADHD participants add to a very limited literature on this topic. Although the stimulant drugs have been proven to be relatively safe and highly effective for the treatment of ADHD, there is very limited and equivocal information on how they affect brain structure. Castellanos et al. (2002) found that medication-naïve children and adolescents with ADHD showed *smaller* white matter volumes relative to both ADHD children and adolescents with previous history of stimulant treatment and control participants (Castellanos et al., 2002). In contrast, a recent study by our group showed that white matter volume was *increased* in adults with ADHD relative to controls (Seidman et al., 2006). However, the two studies investigated different samples of individuals with ADHD, that is, Seidman et al. (2006) studied adults, whereas Castellanos et al. (2002) studied children and adolescents. Although Seidman et al. (2006) studied adults with ADHD, they did not investigate treatment effects in ADHD.

Regarding the effect of treatment on gray matter in ADHD, a recent study by Pliszka et al. (2006) showed bilateral volumetric decreases in the caudate nucleus in treatment-naïve and treated ADHD children relative to controls suggesting that medication may not have an effect on this subcortical structure in children with ADHD (Pliszka et al., 2006). However, they did show volumetric decrease on the right ACC in treatment-naïve children with ADHD relative to treated children with ADHD and controls. The treated children instead, did not show significant differences from controls suggesting a possible protective effect of medication on this cortical structure. In contrast, our preliminary data showing a significant volumetric decrease of the right anterior cingulate gyrus in the group of treated adults with ADHD would suggest that medication may not have a protective effect on this structure. More work in needed to be done to confirm these findings and clarify this important issue.

How a volumetric decrease of the left anterior cingulate gyrus in treatment-naïve adults with ADHD can be reconciled with the observation by Pliszka et al. (2006) of a volumetric decrease on the right ACC in treatment-naïve children with ADHD is a notion that needs further clarification. In a previous volumetric study of our group (Seidman et al., 2006) we documented statistically significant volume differences in treated adults with ADHD, in total anterior cingulate gyrus (13.9%) and right anterior cingulate gyrus (13.2%). Although it did not reach statistical significance, the left anterior cingulate gyrus was also much smaller in the adult ADHD group (14.8%). Thus a decrease in size left anterior cingulate gyrus

would have been expected to be present in treatment-naïve adults with ADHD. A smaller total anterior cingulate gyrus may not be surprising in treatment-naïve children with ADHD as well. A developmental shift of laterality from childhood to adulthood would be also an interesting possibility, however, to the best of our knowledge there is currently no information to explain this scenario. More work is needed to confirm these findings and clarify this important issue.

Our findings must be interpreted in light of some limitations. One is that ADHD is clinically heterogeneous. We cannot test hypotheses about heterogeneity without markedly increasing the sample size of the study. Another issue relates to the limitations of the naturalistic treatment history used in our study. A naturalistic study design has some limitations inherent to it. Specifically, adults with ADHD will have been treated with several medications at the time of study entry, which could impact gray and white matter biology in different ways. However, the alternate study design, a randomized, controlled trial, has important limitations as well. A controlled trial would only be able to evaluate the effect of medications over a relatively short duration because attrition rates would increase to unacceptable levels, especially in a placebo group. Thus, we considered the naturalistic design to be the more efficient and feasible design to address our main aims at this point in time. Furthermore, given the absence of studies on treatment-naïve adults with ADHD and the small number of participants in the present study we are considering this result as preliminary until replicated in larger, better powered studies.

Conclusion

In this pilot study, we found preliminary evidence suggesting that in treatment-naïve adults with ADHD the left ACC is altered volumetrically, showing a decrease in its volume as compared with healthy controls. If confirmed in larger studies, these findings suggest that ADHD is associated with persistent brain abnormalities localized at the left ACC, a region central to cognitive control, drive and affect modulation that appear to be independent of medication treatments.

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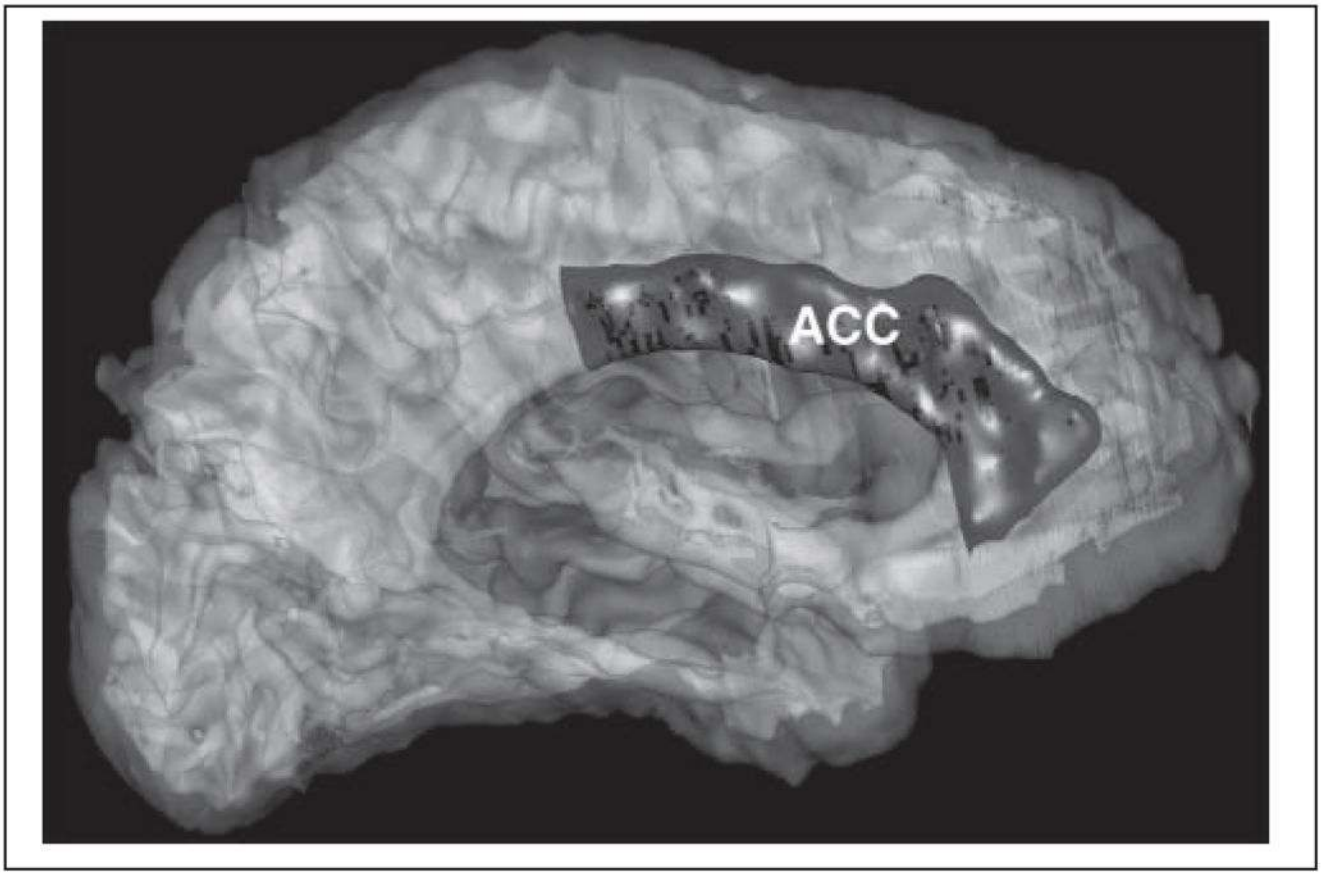

Figure 1.
The anterior cingulate gyrus (ACC) is shown on a 3-D reconstruction of the medial aspect of the left hemisphere

Table 1

Demographic Characteristics

Demographic Characteristic	Controls (*n*=22)	Treatment Naïve ADHD (*n*=13)	Treated ADHD (*n*=13)	Test Statistic, *p* value
Age in Years	34.5±9.5	40.5±11.3	33.3±10.0	F (2, 45)=1.95, p=0.154
Sex (male)	12 (55)	7 (54)	6 (46)	$\chi^2_{(1)}$=0.25, p=0.881
Handedness (right)	20 (91)	13 (100)	12 (92)	$\chi^2_{(1)}$=1.22, p=0.544
Race (Caucasian)	18 (82)	13 (100)	13 (100)	$\chi^2_{(1)}$=5.16, p=0.076
Education (BA or more)	17 (77)	6 (50)	9 (75)	$\chi^2_{(1)}$=2.95, p=0.228
Full scale IQ estimate	114.6±11.3	114.9±13.0	119.4±14.2	F (2, 45)=0.65, p=0.524
Whole brain volume	1300.3±142.8	1313.7±96.5	1271.1±81.7	F (2, 45)=0.45, p=0.637
Total cerebral volume	1136.8±129.1	1153.2±90.5	1107.6±75.3	F (2, 45)=, p=0.61, p=0.547

Values in table represent *mean±standard deviation* or *frequency(percent)*

1 Social class as measured by the Hollingshead scale; 2 Psychotropic medications taken on the day of the scan, other than stimulants;

Table 2

Adjusted mean MRI volumes for the anterior cingulate cortex (ACC)

ADHD ROIs	Controls (*n*=22)	Treatment Naïve ADHD (*n*=13)	Treated ADHD (*n*=13)	Omnibus Test Statistic, *p* value
Anterior Cingulate Cortex (L)	5.8±1.8	4.6±1.4 *a**	5.0±1.3	F (2, 45)=2.76, p=0.074
Anterior Cingulate Cortex (R)	6.7±1.8	6.4±1.7	5.2±1.5 *a**	F (2, 45)=3.49, p=0.039

*Remains significant after adjustment for SES

*a*p<0.05 versus Controls

(L) = left hemisphere, (R) = right hemisphere

Stats for text in Results section:

Comparison of treatment naïve versus controls on left ACC: effect size=0.71, percent change=21%

Comparison of treated ADHD versus controls on right ACC: effect size=0.85, percent change=23%