Anterior Cingulate Cortex Dysfunction in Attention-Deficit/Hyperactivity Disorder Revealed by fMRI and the Counting Stroop

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Background: *The anterior cingulate cognitive division (ACcd) plays a central role in attentional processing by: 1) modulating stimulus selection (i.e., focusing attention) and/or 2) mediating response selection. We hypothesized that ACcd dysfunction might therefore contribute to producing core features of attention-deficit/hyperactivity disorder (ADHD), namely inattention and impulsivity. ADHD subjects have indeed shown performance deficits on the Color Stroop, an attentional/cognitive interference task known to recruit the ACcd. Recently, the Counting Stroop, a Stroop-variant specialized for functional magnetic resonance imaging (fMRI), produced ACcd activation in healthy adults. In the present fMRI study, the Counting Stroop was used to examine the functional integrity of the ACcd in ADHD.*

Methods: *Sixteen unmedicated adults from two groups (8 with ADHD and 8 matched control subjects) performed the Counting Stroop during fMRI.*

Results: *While both groups showed an interference effect, the ADHD group, in contrast to control subjects, failed to activate the ACcd during the Counting Stroop. Direct comparisons showed ACcd activity was significantly higher in the control group. ADHD subjects did activate a frontostriatal-insular network, indicating ACcd hypoactivity was not caused by globally poor neuronal responsiveness.*

Conclusions: *The data support a hypothesized dysfunction of the ACcd in ADHD.* Biol Psychiatry 1999;45: 1542–1552 © *1999 Society of Biological Psychiatry*

Key Words: Functional magnetic resonance imaging (fMRI), Stroop, cognitive interference, attention, attention-deficit/hyperactivity disorder, cingulate cortex

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Introduction

Attention-deficit/hyperactivity disorder is characterized by developmentally inappropriate symptoms of inattention, impulsivity, and motor restlessness. ADHD affects approximately 5% of school-age children, and persists to a lesser degree into adulthood (see Biederman 1998; Spencer et al 1998). Given the great morbidity associated with the disorder, including persistent neuropsychological impairments (Seidman et al 1998), determining the underlying neurobiology of ADHD is of great importance.

Recent reviews of data from neuroimaging, neuropsychological, genetic, and neurochemical studies have generally implicated frontostriatal network abnormalities as the likely cause of ADHD (Castellanos 1997; Ernst 1998; Lou 1996; Seidman et al 1998; Shaywitz et al 1997; Solanto 1998; Swanson et al 1998; Tannock 1998; Zametkin and Liotta 1998). Of particular interest, while Zametkin and colleagues' 1990 positron emission tomography (PET) study showed that global cerebral glucose metabolism was 8.1% lower in the ADHD group than in the control subjects, cingulate cortex was one of only four (out of a total of sixty) regions interrogated that still showed regional hypoactivity after global normalization. The current fMRI study was undertaken to specifically examine the hypothesis that dysfunction of the anterior cingulate cognitive division (ACcd), a region vitally important to the proper and efficient functioning of frontostriatal attentional networks, might contribute to producing the core deficits of ADHD.

The ACcd (cytoarchitectural areas 24b′/24c′/32′) is a functional subdivision of the anterior cingulate cortex that plays a critical role in complex cognitive/attentional processing (Badgaiyan and Posner 1998; Bush et al 1998; Casey et al 1997b; Devinsky et al 1995; Mayberg 1997; Mega et al 1997; Paus et al 1998; Posner and Petersen 1990; Vogt et al 1992; Vogt et al 1995). The functional neuroimaging literature on normal volunteers has shown the ACcd to be activated by numerous cognitive/atten-

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tional tasks, including Stroop and Stroop-like cognitive interference tasks, divided attention tasks, working memory tasks, and response selection/generation tasks (see Figure 5). Based on these convergent findings, the ACcd has been hypothesized to play a primary role in 1) stimulus selection when faced with competing streams of input; and/or 2) response selection via the facilitation of correct responses and/or the inhibition of incorrect actions. Impairments of these functions could produce the core clinical features of ADHD, namely 1) impaired attention; and 2) impulsivity (i.e., defective inhibition of inappropriate responses). Thus, we hypothesized that a dysfunction in the ACcd might lead to inattention/impulsivity, and therefore contribute to the pathophysiology of ADHD.

Given that the ACcd has been repeatedly activated by Stroop and Stroop-like tasks known to activate the ACcd (see Figure 5), a review of the literature pertaining to the performance of ADHD subjects on the traditional Color Stroop task strengthened our suspicion that the ACcd might be impaired, as a number of researchers have reported deficits on the performance of the Color Stroop in ADHD (Barkley et al 1992; Carter et al 1995; Seidman et al 1997).

The Counting Stroop (Bush et al 1998) was developed as a cognitive activation paradigm for probing ACcd function. The Counting Stroop is a Stroop variant (MacLeod 1991; Stroop 1935) that allows on-line response time measurements without requiring speech. Stroop and Stroop-like tasks produce cognitive interference by pitting two competing information processing operations against one another. During the Counting Stroop, reading and counting processes compete, as subjects are instructed to report via button-press the number of words (1 to 4) on the screen, regardless of word meaning. Neutral trials contain common animals (e.g., "dog" written three times, answer, "three"), while interference trials contain number words that are incongruent with the correct response (e.g., "two" written three times, answer, "three"). The Counting Stroop was created because speaking produces head movements that can exceed those tolerated by fMRI, preventing the collection of vital performance data. In a validation study, the Counting Stroop activated the ACcd in a group of nine normal volunteers, and the degree of ACcd activation paralleled the amount of cognitive interference, as measured by reaction time data (Bush et al 1998). Similar in concept to a cardiac stress test, we predicted that it would tax the ACcd, and thereby, reveal ACcd dysfunction in ADHD that might not otherwise be detectable.

In the present study, the Counting Stroop task and fMRI were used to test the functional integrity of the ACcd in ADHD. Since the persistence of ADHD symptoms into adulthood and a positive family history of ADHD are potential indicators of a more neurobiologically mediated form of the disorder (Biederman et al 1998; Seidman et al 1995), we chose to limit our patient sample to adults with ADHD who had at least one first-degree relative with ADHD. To further maximize the chance of finding group differences in this pilot study, we attempted to improve sample homogeneity by excluding subjects with learning disabilities or other (non-ADHD) Axis I diagnoses. We hypothesized that dysfunction in the ACcd contributes to the attentional deficits observed in ADHD by impairing the ability to select relevant stimuli when processing multiple competing streams of information and/or by influencing response selection. Accordingly, we specifically predicted that: 1) the ADHD group would show a greater interference effect on the Counting Stroop compared to the matched control group, as measured by longer reaction times and/or decreased accuracy; and 2) the ACcd would show greater fMRI activation during the Counting Stroop in normal adults than in the group with ADHD.

Methods and Materials

Subjects

The study sample ($n = 16$) consisted of two groups: 8 adults with ADHD (5 men and 3 women), and 8 matched normal control subjects. The subjects ranged in age between 22 to 47 years. Group matching was based on age, gender, socioeconomic status, and education. Informed consent was obtained per Massachusetts General Hospital Subcommittee on Human Subjects guidelines.

Inclusion criteria for all subjects were: 1) age 18 to 55 years; 2) right-handedness (per the Edinburgh Handedness Inventory, Oldfield, 1971); 3) an estimated full-scale IQ > 80; and 4) normal or corrected-to-normal vision. All were native English speakers. Subjects entered the study with knowledge that they would be paid for each session.

Inclusion criteria specific for ADHD cases were a diagnosis of ADHD per DSM-IV criteria (American Psychiatric Association 1994), with childhood onset and persistence of symptoms into adulthood; and the presence of at least one first-degree relative with ADHD (DSM-IV diagnosis confirmed by administration of the ADHD symptom checklist either in person or via phone interview).

Exclusion criteria for all subjects were the presence of: 1) any current Axis I psychiatric diagnosis other than ADHD; 2) a learning disability; 3) a neurologic disorder; 4) medical illness; or 5) pregnancy (ruled-out by a urine beta-hCG). No subjects were receiving medication. ADHD subjects had undergone at least a 48-hour wash-out period prior to scanning if on methylphenidate or D-amphetamine. All eight ADHD subjects had been exposed to medications used in the treatment of ADHD (methylphenidate, D-amphetamine and/or pemoline). Three of eight ADHD subjects were unmedicated for at least a 3-month period prior to scanning, and the remaining five ADHD subjects underwent a five half-life medication wash-out period prior to scanning. In contrast to ADHD subjects, who had to have at least one first-degree relative with ADHD, control subjects could not have a first-degree relative with any Axis I psychiatric disorder, including ADHD.

Clinical, demographic, and cognitive assessments were performed at the Pediatric Psychopharmacology Clinic at the Mas-

Table 1. Demographic and Cognitive Test Characteristics for ADHD and Control Groups

	ADHD		Control Subjects	
	Mean	SD	Mean	SD
Demographic Data				
Age (years)	36.6	7.7	37.3	8.1
Hollingshead Index	1.4	0.5	1.3	0.5
Gender	5M/3F	n.a.	5M/3F	n.a.
Cognitive Test Data				
WRAT Arithmetic SS	103.6	12.2	108.0	14.7
WRAT Reading SS	106.8	9.5	113.1	8.0
Vocabulary IQ	105.6	9.5	114.7	8.6
Performance IQ	107.8	10.0	107.8	11.8
Full-Scale IQ	106.7	8.7	111.2	7.7
Vocabulary SS	11.1	1.9	13.0	1.7
Block Design SS	11.6	2.0	11.6	2.5
Digit Span SS	9.8	3.1	10.8	2.3
Oral Arithmetic SS	10.2	3.1	12.3	1.5
Digit Symbol SS	10.6	2.1	12.5	1.9
Freedom from Distractibility IQ	99.0	16.0	108.7	10.0

SS, subscale.

The ADHD and control groups did not significantly differ on any measure. Since the goal here was to quantitatively compare the groups, rather than to rigorously show that the groups differed on any one measure, use of a Bonferroni correction was thought to be too strict in that it might obscure potential group differences (i.e., use of a $p = 0.05 \times 13$ comparisons would have yielded a critical threshold of $p \leq .004$). Thus, to provide some measure of correction for multiple comparisons without obscuring potential group differences, all tests of significance are reported at an uncorrected $p \leq .01$ level.

sachusetts General Hospital. Assessment of ADHD cases included: 1) psychiatric, medical, and neurologic evaluation by a board certified child and adult psychiatrist; 2) structured diagnostic interview with the Structured Clinical Interview (SCID; Spitzer et al 1992) and an ADHD symptom checklist from DSM-IV (American Psychiatric Association 1994). Cognitive testing included subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Wide Range Achievement Test-3 (WRAT-3; Weschler 1981; Jastak and Jastak 1985) to assess intellectual functioning (with vocabulary and block design subtests of WAIS-R used to estimate full-scale IQ). Socioeconomic status was measured by means of the Hollingshead Four Factor Index of Social Status (Hollingshead 1975).

The ADHD and control groups did not significantly differ on any measure of demographic characteristics or cognitive abilities (Table 1).

Counting Stroop Task Methodology

Procedures for performing the Counting Stroop have been extensively described (Bush et al 1998) and are summarized in Figure 1.

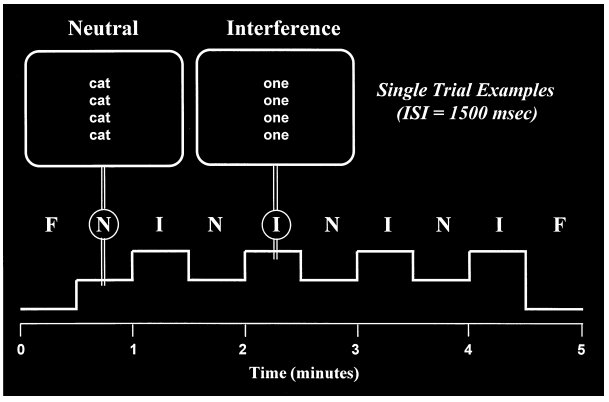

Figure 1. The Counting Stroop task: trial examples and block design. The top portion of this combination figure depicts examples of single trials for the two types of stimuli. Subjects were told that they would see sets of one to four identical words appear on the screen, and were instructed to report, via button-press, the number of words in each set, regardless of word meaning. During "neutral" trials, common animal names (dog, cat, bird, or mouse) were used. During "interference" blocks, the words consisted of number names (one, two, three, or four). Thus, both sets of stimuli were common words within a single semantic category, balanced for length of word. In both examples, the correct answer would be to press button number four. Subjects were instructed that the keypad buttons represented one, two, three, and four from left to right, and to use the index and middle fingers of each hand to respond. Subjects were explicitly told that the sets would change every 1.5 sec. Furthermore, they were 1) instructed to, "Answer as quickly as possible, but since getting the correct answer is important, do not sacrifice accuracy for speed"; and 2) told, "Do not blur your vision in an attempt to make the task easier—keep the words in sharp focus." After instructions were reviewed, subjects completed a 1 min computerized practice version of the task (20 neutral trials followed by 20 interference trials). The bottom half of the figure displays how these 1500 msec individual trials were blocked during fMRI scans. After a 30-sec period of fixation on a small dot (F), subjects completed 4 min of alternating 30-sec blocks of neutral (N) and interference (I) trials, and finished with 30 sec of fixation. Eye movements were not monitored. The order of presentation, regarding the neutral and interference blocks, was fixed for all subjects.

Functional MRI Scanning Techniques and Image Analysis

Functional MRI scanning techniques developed by the Massachusetts General Hospital NMR Center were used. These methods have been described and referenced previously (see Bush et al 1998; Whalen et al 1998) and are summarized here. Subjects were scanned in a General Electric Signa 1.5 Tesla high-speed echoplanar imaging device (Milwaukee, WI) using a quadrature head coil. Head stabilization was achieved using a plastic bite bar, molded to each subject's dentition. The subjects lay on a padded scanner couch in a dimly illuminated room and wore foam ear plugs and earphones that attenuate high-intensity scanner sounds, while allowing spoken instructions to be heard well.

Stimuli were generated on a Macintosh 100 MHz PowerPC™ (Cupertino, CA) and projected, via a Sharp XG-2000V color LCD projector (Osaka, Japan), through a collimating lens onto a rear-projection screen that was secured vertically in the magnet bore at neck level. Subjects viewed the images on a tilted mirror placed directly in front of their head. Individual words subtended

approximately 1 degree of the visual angle vertically, and a group of four words subtended a visual angle of approximately 6 degrees vertically.

Initially, a sagittal localizer scan [spoiled gradient recall (SPGR), 60 slices, resolution 0.898 $mm^2 \times 2.8$ mm) was done to provide both a reference for slice selection in later scans and a high-resolution scan for Talairach localization (Talairach and Tournoux 1988). Next, shimming was done to maximize field homogeneity. In the third scan series, subjects had an SPGR MR angiogram (resolution 0.78125 $mm^2 \times 2.8$ mm) to identify large and medium diameter blood vessels. The fourth series was a set of T1-weighted high-resolution axial anatomic scans (resolution 3.125 $mm^2 \times 8$ mm). For the functional series, asymmetric spin-echo (ASE) sequences (TE = 50 msec, TR = 2000 msec, flip angle 90°, FOV = 40 cm × 20 cm, matrix = 64 × 64, in-plane resolution 3.125 mm^2, slice thickness = 8 mm, 150 images/slice) were used to minimize macrovascular signal contributions. Twelve contiguous, interleaved slices, parallel to the anterior–posterior commissure line, were obtained for all studies. The angiogram, T1 anatomic, and ASE functional slices (series 3 to 5) were collected using identical slice plane prescriptions.

All data sets had the amount of motion quantified, and were then motion corrected. No difference was found between the mean displacement for the control group (.8 mm, SD .5 mm) and the ADHD group (1.6 mm, SD 2.4 mm; $t = .97$, *NS*). The functional scans were transformed into a standardized anatomic space (see Bush et al 1998; Talairach and Tournoux 1988).

Statistical analysis of functional images for regions of significant change was accomplished using a multi-step process. Statistical maps were calculated using the Kolmogorov–Smirnov (KS) statistic, and displayed in pseudocolor, scaled according to significance, (after reslicing into coronal orientation) superimposed on (resliced) high-resolution sagittal localizer scans. The nonparametric KS test was used since fMRI data, both within and between groups, does not always approximate a normal distribution. As an objective measure of activated regions, an automated region-defining algorithm was used on smoothed KS maps (Bush et al 1996, Bush et al 1998). Smoothing was done using a Guassian filter with a sigma of 1.1, giving an effective resolution of 8.1 mm^2 full width at half maximum (FWHM). Significance values of local maxima within these identified regions are reported based upon the native (unsmoothed) statistical maps.

The anterior cingulate cognitive division [ACcd] was defined functionally and anatomically based upon a meta-analysis of prior functional neuroimaging studies that reported anterior cingulate activation in response to cognitively demanding tasks (see Figure 5). For this a priori defined ACcd region, encompassing ~500 voxels, statistical significance (of $p \leq .05$ corrected for the number of comparisons) was defined as $p \leq 1 \times 10^{-4}$.

In the Counting Stroop validation study (Bush et al 1998), using a separate cohort of normal volunteers, subjects improved performance with practice (as indicated by shorter RTs during scan two). Of critical import, ACcd activity paralleled the RT data. Specifically, robust ACcd activation was observed during scan one (during which RT interference effects were observed), but eliminated during scan two (during which no difference in RT between interference and neutral blocks existed). As the present study was started prior to the completion of the validation study, we conservatively performed two scans on each subject, and collected behavioral data during both scans. The RT data in the present study replicated those of our earlier validation study (Bush et al 1998) in that the subjects learned the task by the end of scan one. Thus, while two scans were performed on each individual, only the fMRI data from scan one was compared.

In the analysis of the fMRI data, four contrasts were examined. First, to determine if each of the groups significantly activated the ACcd (and other brain regions), a within-group statistical comparison of interference minus neutral condition maps was done on group averaged data for each group (ADHD and control subjects). Two comparisons were then done to more directly determine if the ACcd activity was higher in control subjects than in the ADHD group: comparisons were made between activity obtained solely during interference blocks (i.e., $\text{Interference}_{\text{Controls}}$ versus $\text{Interference}_{\text{ADHD}}$) after all scans were normalized to a common fixation condition baseline. This same $\text{Interference}_{\text{Controls}}$ versus $\text{Interference}_{\text{ADHD}}$ comparison was then also made after normalization of all scans to a common neutral condition (control task) baseline. A fourth comparison, done to assess the specificity of higher activation of ACcd in the control group, compared activity obtained solely during neutral task blocks (i.e., $\text{Neutral}_{\text{Controls}}$ versus $\text{Neutral}_{\text{ADHD}}$) after all scans were normalized to a common fixation condition baseline.

Results

Behavioral Data

Analysis of reaction time (RT) data (Figure 2) revealed that within groups, both control subjects and ADHD subjects displayed interference effects (i.e., showed longer RTs during interference trials as compared to neutral trials). Control subjects showed an overall increase in RT during interference blocks (720 msec ± SD 51 msec) as compared to neutral blocks (mean 691 msec ± 42 msec), and a repeated measures condition (interference versus neutral) by scan (scan one versus scan two) ANOVA demonstrated a significant main effect for condition ($F = 5.9$, df = 1, $p \leq .05$) and scan ($F = 14.8$, df = 1, $p < .01$). Similarly, the ADHD group showed an overall increase in RT during interference blocks (801 msec ± 135 msec) as compared to neutral blocks (mean 748 msec ± 104 msec), and a repeated measures condition (interference versus neutral) by scan (scan one versus scan two) ANOVA demonstrated a significant main effect for condition ($F = 8.5$, df = 1, $p < .05$) and scan ($F = 11.3$, df = 1, $p < .05$). Neither group displayed a significant condition by scan interaction. The decision to use only data from scan one was bolstered by two facts. First both the control and ADHD groups showed identical main effects for scan. Second, per the methodology of the Bush and co-workers (1998) validation study, planned block-by-block paired *t* test comparisons of interference minus neutral RTs only revealed significant differences ($p < .05$) in scan one (blocks two and three for both the ADHD and control subjects), while neither group showed significant differences in scan two RTs between interference and neutral conditions.

Mean accuracy (percentage correct) scores for scan one

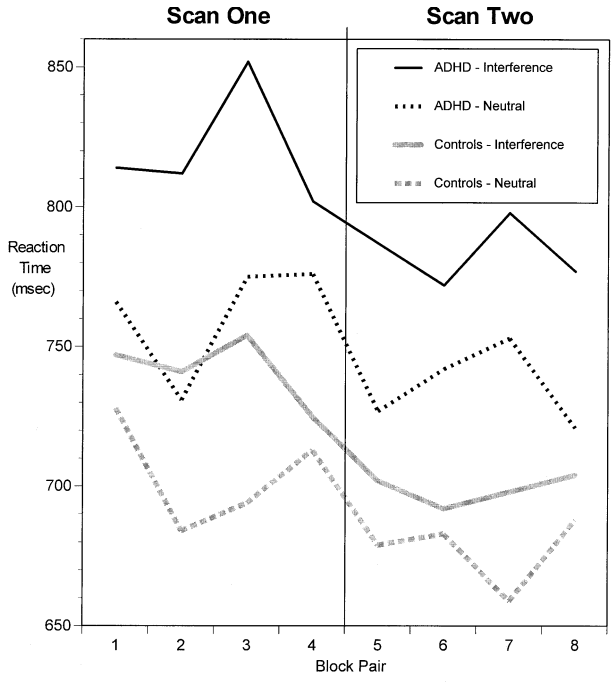

Figure 2. Reaction time data. Mean RTs for the eight interference-neutral word block pairs while ADHD and control subjects were being scanned. Note that the RT data for the normal control subjects in the present study replicated those of our prior study (Bush et al 1998) in that the control group learned the task by the end of the first scan. Thus, while two scans were performed on each individual, only the fMRI data from the first scan (i.e., the first four neutral/interference condition block-pairs, during which a robust cognitive interference effect could be demonstrated by a large RT disadvantage in both the ADHD and control groups during interference blocks versus neutral blocks) was compared.

were not significantly different between the two groups for either interference trials (control subjects: 97.1% ± 2.3%; ADHD: 90.7% ± 12.2; N.S.) or neutral trials (control subjects: 97.3% ± SD 2.3%; ADHD: 95.4% ± 4.4%; N.S.). The behavioral results are in line with those of prior studies, which show that ADHD subjects perform cognitively demanding tasks accurately but at slower speeds than control subjects (Carter et al 1995; Seidman et al 1997).

Functional MRI Results

As predicted, significant fMRI activation was seen in the ACcd of the matched normal control group, but not in the group with ADHD, when comparing interference trials with neutral trials (Figure 3). The dynamic time course of this activity in the ACcd of the control subjects, shown in Figure 4, reliably increased during interference epochs as compared to neutral epochs. This ACcd activation, found in the control group, was in close proximity to those found in other neuroimaging studies that used a host of cognitively demanding tasks (Figure 5). While our specific ROI was limited to the ACcd, it should be emphasized that no activation was found anywhere in the cingulate cortex of the ADHD group.

Direct between group comparisons confirmed greater ACcd activity in control group than in the ADHD group. An $\text{Interference}_{\text{Controls}}$ versus $\text{Interference}_{\text{ADHD}}$ contrast done after all scans were normalized to a common fixation condition baseline, showed that the ACcd of the normal control group indeed displayed greater activation than that of the ADHD group ($p = 1.65 \times 10^{-6}$). A similar comparison of $\text{Interference}_{\text{Controls}}$ versus $\text{Interference}_{\text{ADHD}}$ blocks, made after normalization of all data to a neutral task baseline, also revealed greater activation in the normal control group ($p = 8.6 \times 10^{-9}$). No difference in fMRI activity was found in the ACcd region when comparing $\text{Neutral}_{\text{Controls}}$ versus $\text{Neutral}_{\text{ADHD}}$, after all scans were normalized to a common fixation condition baseline.

For completeness, while our main interest lay in testing ACcd response, loci of activation in all other regions meeting the same threshold as the ACcd (i.e., $p \leq 1 \times 10^{-4}$) are reported (Table 2).

Discussion

The Counting Stroop was used in conjunction with fMRI to examine the functional integrity of the cognitive division of the anterior cingulate cortex in adults with ADHD. While both the ADHD group and the control group showed an interference effect, the Counting Stroop fMRI data revealed a relative hypofunctionality of the ACcd in ADHD. The control group showed significant fMRI activation in the ACcd, while the ADHD group did not. In two direct comparisons, the controls showed greater activation than the ADHD group in response to the interference task. Furthermore, this activity was shown to be specifically different during the interference condition, as there was no difference found in ACcd activation when comparing group responses to the neutral task.

We focused upon ACcd in this study hypothesizing that it plays a central role in cognitive and attentional tasks by allocating attentional resources when confronted with competing information processing streams and/or by mediating response selection. While the exact role this portion of anterior cingulate cortex plays in distributed attentional networks is debated, with different authors emphasizing its role in modulating attention/executive functions by influencing sensory and/or response selection, monitoring competition, complex motor control, motivation, novelty, error detection, working memory, and anticipation (Badgaiyan and Posner 1998; Bush et al 1998; Carter et al 1998; Casey et al 1997b; Casey 1997c; Devinsky et al 1995; Drevets and Raichle 1998; Goldman-Rakic 1988; Mayberg 1997; Mega et al 1997; Murtha et al 1996; Paus et al 1998; Petit et al 1998; Picard and Strick

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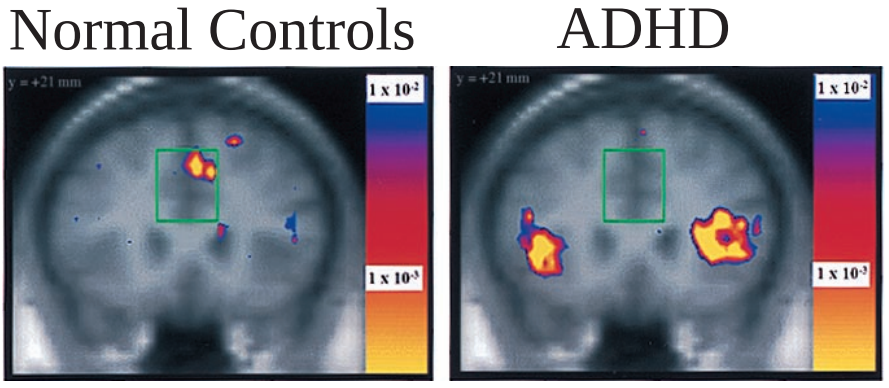

Figure 3. Anterior cingulate cognitive division activates in the normal control group but not in the ADHD group during the counting Stroop. The coronal slices (y = +21 mm) for the control and ADHD groups show the KS statistical map data (for interference blocks minus the neutral blocks of scan one) superimposed on the group averaged Talairach and Tournoux (1988) transformed high-resolution structural scans. These coronal slices pass through the ACcd activation depicted in Figure 5 for the normal control subjects in the present study (represented by the anterior green triangle in Figure 5). The ACcd showed significantly higher activity in the normal control group during the interference blocks minus the neutral blocks ($p = 6.0 \times 10^{-5}$). In contrast, while the ADHD group did display significant activity in a frontostriato–insular–thalamic network (as evidenced by the bilateral insular activation seen in this slice and in Table 2b), they did not show significant activation anywhere in cingulate cortex.

1996; Posner and Petersen 1990; Posner and Rothbart, in press; Raichle et al 1994; Taylor et al 1997; Vogt et al 1992; Vogt 1993), the important point is that the cortical territory here referred to as the ACcd is incorporated into all these models of complex cognitive and motor control. Further focused study of the ACcd is, therefore, vitally important to the understanding of the pathophysiology of many neuropsychiatric disorders, especially ADHD.

It must be emphasized that while the current study focuses attention on the ACcd, it does not presume that the ACcd is the only structure relevant to performance of cognitive interference, response selection, or attentional tasks; or that a single lesion in this region is the sole cause of ADHD. Neuropsychological studies have reported that ADHD patients also show deficits on other tasks that have been associated with lateral prefrontal cortex, such as continuous performance tasks, response inhibition tasks, and the Wisconsin Card Sorting Test (see Barkley 1997; Casey et al 1997a; Schachar et al 1995; Seidman et al 1998; Vaidya et al 1998). Also, the weight of evidence from neuroimaging and neuropsychological studies of ADHD suggests that abnormalities exist in other parts of the frontostriatal network and/or the connections between them (Castellanos 1997; Ernst 1998; Heilman et al 1991; Lou 1996; Shaywitz et al 1997; Swanson et al 1998; Tannock 1998; Zametkin and Liotta 1998).

Given these findings, valid alternative hypotheses that should be tested in future work include the possibilities that the pathophysiology of ADHD is related to dysfunction in the ACcd, frontostriatal circuitry, corpus callosum, and/or some combination of these and other structures. In light of the extensive reciprocal connections the ACcd maintains with lateral prefrontal cortex, parietal cortex, and lower motor areas in humans and other primates (see Devinsky et al 1995), it is likely that the pathophysiology of ADHD involves a dysfunctional interaction between ACcd and frontostriatal circuitry. However, a role for specific ACcd dysfunction in a parallel distributed network (Cohen et al 1990; Goldman-Rakic 1988; Goldman-

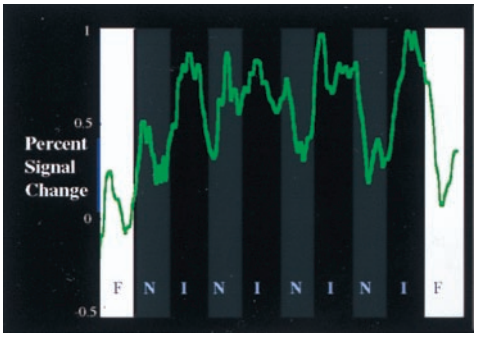

Figure 4. Time course of activity in the anterior cingulate cognitive division of normal control subjects during the counting Stroop. Presentation of dynamic changes in fMRI signal intensity in the ACcd of normal control subjects (shown in Figures 3 and 5) during performance of the counting Stroop. The y-axis values represent percent change from the mean fMRI signal intensity during the initial fixation period. Functional MRI activity in the ACcd of the normal control group reliably rose during the interference blocks and fell during the neutral blocks.

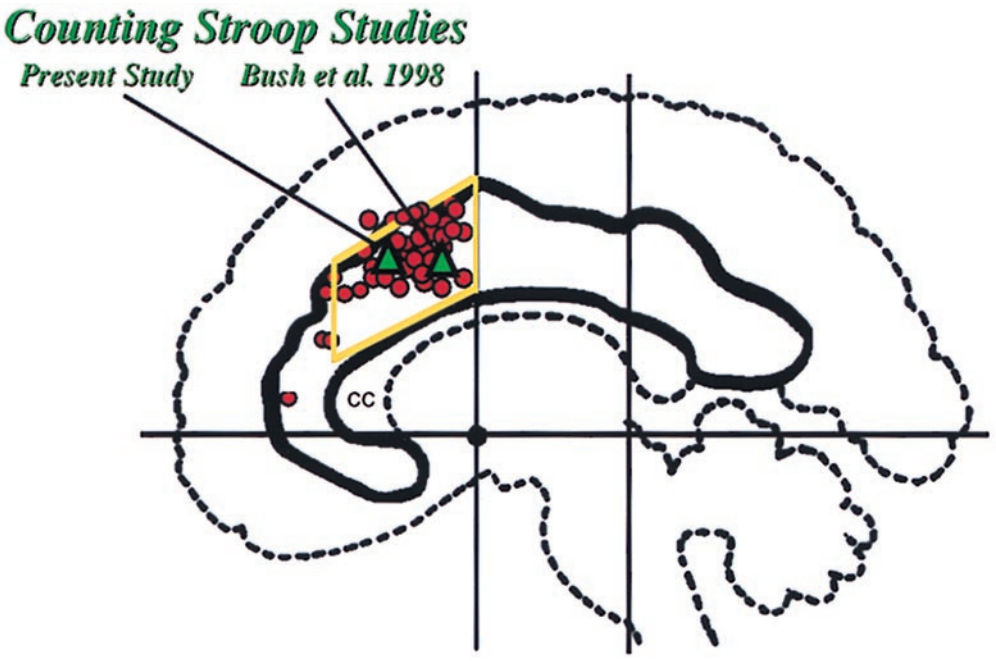

Figure 5. Functional neuroimaging localizes the anterior cingulate cognitive division. Locations of local maxima from selected functional neuroimaging studies involving complex cognitive processing are superimposed on a schematic parasagittal view of cingulate cortex. The local maxima are represented by red dots that cluster in the dorsal anterior cingulate cognitive division (ACcd). All points were reported to represent activations in anterior cingulate cortex anterior to $y = 0$ mm (Talairach and Tournoux 1988). Based on a review of these cognitive challenge studies, the ACcd ROI for the present study (represented by the yellow parallelogram) was defined on the averaged Talairach transformed high-resolution anatomic scan prior to scan analysis. The ACcd ROI included anterior cingulate cortex anterior to $y = 0$ mm, posterior to $y = 30$ mm, and within 15 mm of the midline. The superior/inferior extents of this ROI varied by slice due to the shape of cingulate cortical surface. The ACcd activation from the normal control subjects in the present study (anterior green triangle) and the counting Stroop validation study (posterior green triangle, Bush et al 1998) lie at the center of the cognitive division cluster. The figure includes local maxima from studies using Stroop and Stroop-like cognitive interference stimuli in healthy volunteers (Bench et al 1993; Bush et al 1998; Carter et al 1995; Derbyshire et al 1998; George et al 1994; George et al 1997; Larrue et al 1994; Pardo et al 1990; Taylor et al 1994; Taylor et al 1997) and tasks involving divided attention (Bush et al 1995; Corbetta et al 1991), response inhibition (Kawashima et al 1996; Paus et al 1993), verbal generation (Frith et al 1991; Petersen et al 1988; Raichle et al 1994), spatial working memory (Petit et al 1998; Smith et al 1995), nonspatial working memory (Cohen et al 1997; Courtney et al 1996; Jonides et al 1997; Petit et al 1998; Schumacher et al 1996; Seidman et al 1998; Smith et al 1995; Smith et al 1996), and anticipation (Murtha et al 1996). It should be noted that the territory described here as the ACcd encompasses the same cortical region described by Picard and Strick (1996) as the "rostral cingulate (motor) zone." Since studies have reported activation in this region in response to tasks that have not involved a motor response or even motor preparation (Murtha et al 1996), and as Picard and Strick (1996) have described the "rostral cingulate zone" as a region involved in complex (i.e., cognitively challenging) tasks, we retain the AC "cognitive division" nomenclature. CC, corpus callosum.

Rakic et al 1993) is not entirely eliminated, as apparent "frontostriatal" deficits may just be "downstream" effects of ACcd dysfunction. Future network analysis of regional interactions (Friston et al 1996; Mattay et al 1996; Nyberg et al 1996) should be able to definitively answer this question surrounding the specificity of ACcd dysfunction in ADHD.

Notably, the normal control subjects in the present study and the normal volunteers in the initial validation study (Bush et al 1998) both showed activation in a network including the ACcd, lateral prefrontal cortex (BA 9), and superior parietal cortex (BA 7). In contrast, the ADHD group showed robust activity in a different network, including bilateral activity in a different region of lateral prefrontal cortex (BA 45) and insular cortex, as well as unilateral activation of caudate, putamen, thalamus, and pulvinar. One possible explanation that potentially incorporates and/or reconciles these findings is that ADHD subjects might compensate for impairment of the ACcd (or an ACcd-frontostriatal network) by recruiting a different, less efficient, response pathway. Supporting this view, Raichle and co-workers (1994), using PET, have indeed reported evidence that two (verbal) response selection pathways exist—one for nonautomatic processes including ACcd and left lateral prefrontal cortex; and another, including bilateral sylvian-insular cortex, for more automatic (practiced) tasks. However, it is also possible that the ADHD subjects were simply made more frustrated and anxious by a task that was extremely difficult for them, especially when they knew that their performance was being monitored. This could also account for the fronto-insular–striatal–thalamic network activation, as many of

Table 2a. Regions Activated During Counting Stroop: Control Subjects

Talairach Coordinates				
x	y	z	*p* Value	Region
−3	21	37	6.0×10^{-5}	Left anterior cingulate (BA 32/a32′)
6	15	43	6.3×10^{-4}*	Right anterior cingulate (BA 32/a32′)
6	0	40	1.4×10^{-4}*	Right anterior cingulate (BA 24/a24b′–c′)
−43	6	37	6.1×10^{-7}	Left middle frontal gyrus (BA 9)
−31	−48	46	6.0×10^{-5}	Left superior parietal lobule (BA 7)
−43	−57	37	6.0×10^{-5}	Left inferior parietal lobule (BA 40)
−34	−69	9	2.6×10^{-5}	Left medial/inferior occipital gyrus (BA 39/37)

Table 2b. Regions Activated During Counting Stroop: ADHD Subjects

Talairach Coordinates				
x	y	z	*p* Value	Region
43	36	0	4.2×10^{-6}	Right inferior frontal gyrus (BA 45)
−28	21	9	1.6×10^{-6}	Left inferior frontal gyrus (BA 45)
−43	18	6	6.0×10^{-5}	Left insula
−43	−3	9	2.6×10^{-5}	Left insula
−34	−15	12	1.1×10^{-5}	Left insula
37	9	9	2.2×10^{-7}	Right insula
43	−12	18	6.1×10^{-7}	Right insula
−6	3	6	6.1×10^{-7}	Left caudate
25	−3	9	1.6×10^{-6}	Right putamen
9	−12	9	6.1×10^{-7}	Right thalamus
−18	−21	9	2.6×10^{-5}	Left pulvinar

Stereotactic coordinates and statistical significance values are reported for local maxima meeting threshold criteria (see Methods). It should be noted that the statistical threshold ($p \leq .05$, Bonferroni corrected for the number of comparisons) was defined for the a priori defined ACcd region, which encompassed ~500 voxels, thus yielding a threshold of $p \leq 1 \times 10^{-4}$. For completeness, however, loci of activation are reported for all other regions meeting the same threshold as the ACcd, with the caveat that rigorous correction for the larger number of voxels within whole brain would require activation surpassing $p \leq 1 \times 10^{-7}$ to establish post hoc significance. Coordinates are expressed in millimeter units. The origin (0,0,0) is the anterior commissure at the midsagittal plane, with $x > 0$ corresponding to right of midsagittal, $y > 0$ corresponding to anterior, and $z > 0$ corresponding to superior (Talairach and Tournoux 1988). Two regions (denoted with asterisks, Table 2a) displayed a trend towards significance in right anterior cingulate cortex of the control group. Cytoarchitectonic areas are indicated after the named structure in parentheses. Generally, these are listed as Brodmann areas (BA), with the additional refined specifications of areas 32′ and 24b′/c′ for the anterior cingulate activations (consistent with more recent nomenclature, Vogt et al 1995).

these same structures have been implicated in anxiety/distress in both healthy volunteers and across different anxiety disorders (see Rauch et al 1997 for review). Future studies might consider using questionnaires, galvanic skin response, and heart rate measurements to characterize the level of stress experienced by subjects during task performance, and try to relate these measures to neural structures activated.

While convergent data from neuroanatomic, connectionist, electrophysiologic, and functional neuroimaging studies strongly supports the existence of two functional subdivisions of anterior cingulate cortex specialized for processing "cognitive/attentional" and "affective/emotional" information (Bush et al 1998; Devinsky et al 1995; Drevets and Raichle 1998; Drevets et al 1997; Mayberg 1997; Mega et al 1997; Lane et al 1997; Vogt et al 1992; Whalen et al 1998); the mechanisms by which the ACcd and other cingulate subdivisions function in normal cognitive and emotional processing have not been definitively established; making it impossible to determine with certainty how ACcd dysfunction might contribute to ADHD pathophysiology. At first glance, the fact that anterior cingulate cortical abnormalities have been linked to other psychiatric disorders such as obsessive-compulsive disorder (Rauch et al 1994), schizophrenia (Benes 1993; Carter et al 1997; Dolan et al 1995), depression (see Drevets and Raichle 1998; Mayberg 1997), and anxiety disorders (Rauch et al 1997) might appear to argue against the specificity of AC abnormalities in ADHD. However, this point actually underscores the need to consider the existence of anterior cingulate's functional subdivisions when interpreting findings, as the majority of these studies report abnormalities in the more rostral affective subdivision, or can alternatively be explained by symptom overlap (i.e., the existence of attentional dysfunction in ADHD, schizophrenia, and depression).

Potential limitations do limit the ability to generalize our findings. Due to the limited number of subjects studied, and the fact that our study included restrictive criteria designed to increase sample homogeneity (i.e.,

familial ADHD persistent into adulthood without comorbid learning disabilities), it is difficult to generalize our findings to all patients with ADHD. Also, the fact that the data are group averaged makes it possible that increased anatomic variability in the ADHD group could have made it appear that the ADHD individuals do not activate the ACcd to the same degree as a spatially more homogeneous control group. Development of a task (or version of the Counting Stroop) which activates the ACcd more robustly in individuals is therefore needed to more definitively establish a defect in ACcd in ADHD. Also, the findings should be replicated using a large group of children with ADHD.

With respect to medication status, while the wash-out procedure was adequate to produce nearly complete elimination of the medications, the long-term effects of medication on cognitive processing cannot be ruled-out as a potential confound. Subsamples defined by recency of medication exposure were too small to permit meaningful supplementary analysis. Thus, the present results will need to be verified in either medication-naive samples, or those in which a longer wash-out period is used in order to rule-out the possible influence of long-term effects of medication exposure on cognition.

An interesting question arises as to whether the ADHD subjects possess the same volume of ACcd tissue (activated to a lesser extent) or whether they had smaller volumes of ACcd tissue. As has been shown, the anterior cingulate cannot be treated as a homogeneous region, and the ACcd is only one part of anterior cingulate cortex, so it would not necessarily be informative to simply correlate total anterior cingulate volumes with the fMRI data. At this point in time, the ACcd is only defined functionally (i.e., based upon its activation in response to various cognitively demanding tasks in PET and fMRI studies) and on its connections to other brain areas. Thus, since we cannot define ACcd volumes based on available imaging techniques (which do not delineate cytoarchitectural areas), the issue as to potential differences in ACcd volume between groups must remain an open question for future studies to resolve.

The data support the hypothesis that the ACcd is dysfunctional in ADHD. The control group showed significant fMRI activation in the ACcd, while the ADHD group did not. In two direct comparisons, the controls showed greater activation than the ADHD group did during the interference task. Furthermore, ACcd activity was shown to be specifically different during the interference condition, as no difference in ACcd activation was found when comparing group responses to the neutral task. The fact that a different activation pattern was observed in the ADHD group establishes that the observed hypoactivity in ACcd of the ADHD group was regionally specific, and not indicative of a global failure to respond to a cognitive challenge.

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