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Differential Prefrontal Cortex Activation During Inhibitory Control in Adolescents With and Without Childhood Attention-Deficit/Hyperactivity Disorder

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The authors examined inhibitory control processes in 8 adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) during childhood and in 8 adolescent control participants using functional MRI with the Stimulus and Response Conflict Tasks (K. W. Nassauer & J. M. Halperin, 2003). No group differences in performance were evident on measures of interference control and/or response competition created by location and direction stimuli. However, the ADHD group demonstrated significantly greater activation of the left ventrolateral prefrontal cortex during interference control as well as greater activation of the left anterior cingulate cortex, right ventrolateral prefrontal cortex, and left basal ganglia during the dual task of interference control and response competition. The magnitude of the prefrontal and basal ganglia activation was positively correlated with severity of ADHD. Response competition alone did not yield group differences in activation.

Keywords: attention-deficit/hyperactivity disorder, functional MRI, inhibitory control, adolescents, prefrontal cortex, anterior cingulate gyrus, basal ganglia

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, impulsiveness, and hyperactivity that arise in early childhood and often persist through adolescence. These symptoms have been viewed as varied manifestations of a core deficit in inhibitory control of behavior and cognition (Barkley, 1997; Nigg, 2001). Inhibitory control is a self-regulatory function that encompasses the directed suppression of task-inappropriate response tendencies and interference from competing stimuli and responses, and it is critical for the effective adaptation of responses to context and the maintenance of goal-directed behavior (Pennington, 1997). Deficits in these inhibitory processes have been found in individuals with ADHD across the life span (Carter, Krener, Charderderjian, Northcutt, & Wolfe, 1995; Seidman, Biederman, Weber, Hatch, & Faraone, 1998; Sergeant, Geurts, & Oosterlaan, 2002).

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Convergent evidence indicates that inhibitory control involves several component processes that are subserved by a neural network distributed across the ventral prefrontal cortex, basal ganglia, and supplementary motor area (Casey, Durston, & Fossella, 2001). These regions are activated during a range of inhibitory control tasks in both children and adults (e.g., Casey, Thomas, Davidson, Kunz, & Franzen, 2002; Menon, Adleman, White, Glover, & Reiss, 2001; Peterson et al., 2002). The ventral prefrontal cortex seems to form a nexus in which processed sensory input is integrated with task-relevant context information, and this convergence of input is used to control and guide behavioral responding (Miller & Cohen, 2001). The basal ganglia structures receive extensive input from the frontal cortex (including the ventral prefrontal regions) and in turn suppress competing motor behaviors via polysynaptic connections with pyramidal and extrapyramidal motor areas (Mink, 1996). The ventral prefrontal cortex and basal ganglia both project to the supplementary motor area (Lu, Preston, & Strick, 1994; Middleton & Strick, 2000), which plays a critical role in motor mapping and timing (Cunnington, Windischberger, Deecke, & Moser, 2003; Hoshi & Tanji, 2004). Additional regions activated during inhibitory control tasks, such as the anterior cingulate gyrus (e.g., Peterson et al., 2002), may not be necessary for inhibition per se but may reflect such interrelated cognitive processes as monitoring conflict or response selection (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003). Patients with damage to any of these regions exhibit inhibitory control deficits (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Rieger, Gauggel, & Burmeister, 2003).

The similarity in inhibitory control deficits between individuals with ADHD and patients with frontal lobe lesions first implicated

frontostriatal abnormalities in the pathophysiology of ADHD (Konrad, Gauggel, Manz, & Scholl, 2000; Mattes, 1980). Neuroimaging studies have provided further evidence of such abnormalities in ADHD. Morphological studies have repeatedly found subtle volumetric reductions of the prefrontal cortex and caudate nucleus in children with ADHD (Castellanos et al., 2002; Filipek et al., 1997), the latter of which seems to normalize during adolescence (Castellanos et al., 2002). Functional MRI (fMRI) studies have reported decreased activation of the basal ganglia in children with ADHD during go/no-go tasks (Durston et al., 2003; Vaidya et al., 1998) and in adolescents with ADHD performing a stop task (Rubia et al., 1999). However, these studies differ regarding prefrontal activity during the same inhibitory tasks, with activation enhanced in children (Durston et al., 2003; Vaidya et al., 1998) but reduced in adolescents with ADHD (Rubia et al., 1999). Finally, adults with ADHD activated the prefrontal cortex and striatal regions during the Stroop task instead of the anterior cingulate, as seen in control participants (Bush et al., 1999).

These neuroimaging data provide compelling evidence that ADHD involves impairments of several frontostriatal regions that purportedly mediate inhibitory control processes. Nevertheless, the precise nature of the pathophysiology has remained elusive. Further, findings hint at developmental changes in the nature of the frontostriatal abnormalities in ADHD, comparable to the commonly noted age-dependent decline in core symptoms (Hill & Schoener, 1996). As such, investigation of adolescents who were diagnosed with ADHD during childhood and followed over time may help clarify the specific pathophysiological substrates of ADHD.

In this study, we used fMRI in conjunction with the Stimulus and Response Conflict Tasks (SRCT; Nassauer & Halperin, 2003) to examine inhibitory control in adolescents diagnosed with ADHD during childhood according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; *DSM–III–R*; American Psychiatric Association, 1987). The SRCT provides separate measures of interference control and response competition that use the same stimuli, responses, and paired control conditions and differ only in the context of the stimulus–response associations. In addition, the task assesses the capacity to integrate the two aforementioned inhibitory control processes as well as the ability to recruit higher order cognitive processes engaged during dual tasks (e.g., "cognitive branching"; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999). An initial validation study of the SRCT in college students found significant increases in reaction time (RT) during both interference control and response competition, with performance on the former correlated with the Stroop interference effect (Nassauer & Halperin, 2003). Poor response competition in preschoolers at risk for ADHD (Marks et al., 2003) and compromised interference control and response competition in adolescents with childhood ADHD (Marks et al., 2004) have been reported by researchers using the SRCT. Thus, it was expected that adolescents with childhood ADHD would have greater ventral prefrontal cortex activity during interference control and reduced striatal activation during response competition compared with control participants and that both of these group differences in activation would be present during the simultaneous task of interference control and response competition. Further, it was expected that activation of the anterior cingulate gyrus would be reduced in adolescents with childhood ADHD, especially during the dual interference and response competition task.

Method

Participants

Participants were 8 adolescent boys (7 right-handed, 1 left-handed) who were diagnosed with ADHD according to *DSM–III–R* criteria when they were 7–11 years old and 8 adolescent boys (all right-handed) with no history of ADHD. Those with childhood ADHD were recruited from a study of ADHD conducted between 1990 and 1994 (Halperin et al., 1994, 1997). The childhood diagnosis was based on parental responses to the Diagnostic Interview Schedule for Children—Version 2.1 (Shaffer, Fisher, Piacentini, Schwab-Stone, & Wicks, 1989). Diagnoses of schizophrenia, pervasive developmental disorder, major affective disorder, and Tourette's Syndrome, or a Wechsler Intelligence Scale for Children (WISC–R: Wechsler, 1974; WISC–III: Wechsler, 1991) Full Scale IQ score below 70, were exclusionary criteria for the initial study. Although childhood diagnoses were made on the basis of *DSM–III–R* criteria, all would have met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychiatric Association, 1994) criteria for the combined type of ADHD. Two participants had a comorbid diagnosis of conduct disorder in childhood, and 1 participant also met diagnostic criteria for separation anxiety disorder.

Adolescents with childhood ADHD were reevaluated at the mean age of 18.2 years ($SD = 1.3$, range = 16.2–19.8). Their childhood evaluation ranged from 7.0 to 11.0 years ($M = 9.0$, $SD = 1.2$) ago. Adolescents and their parents were interviewed with the National Institute of Mental Health Diagnostic Interview Schedule for Children—Version IV (NIMH DISC–IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), and the two reports were combined with an either-parent-or-adolescent algorithm to increase diagnostic reliability (Schwab-Stone et al., 1996). Although the ADHD group was defined by the presence of ADHD during childhood, the psychiatric status of this group at adolescence reflects the diverse outcomes characteristic of the disorder (Mannuzza et al., 1991). Four adolescents met *DSM–IV* criteria for ADHD in partial remission, 1 met full criteria for the combined type of ADHD, 2 met criteria for the predominantly inattentive type of ADHD, and 1 met criteria for the predominantly hyperactive–impulsive type of ADHD. However, the latter 3 patients should not truly be considered to have the predominantly inattentive and hyperactive–impulsive types of ADHD. Rather, they were children with the combined type of ADHD who had a diminution of symptoms with age but still had high numbers of both inattentive and hyperactive symptoms and resembled adolescents with ADHD in partial remission. One adolescent also met criteria for conduct disorder; there were no reports of any other Axis I disorders. The Mean Attention Problems score on the Child Behavior Checklist (CBCL; Achenbach, 1991), completed by parents at follow-up, was 63.6 ($SD = 11.0$, range = 50.0–81.0). Intellectual ability was estimated with the Vocabulary and Block Design subtests of the WISC–III or the Wechsler Adult Intelligence Scale—Third Edition (WAIS–III; Wechsler, 1997), depending on age. Mean estimated IQ of the ADHD group was 88.4 ($SD = 15.1$, range = 74.0–120.0). Seven patients had a previous history of treatment with stimulant medications, but no patient received medication for ADHD in the 6 months prior to this study.

Eight adolescent boys with a mean age of 17.5 years ($SD = 1.2$, range = 16.1–19.9) were recruited from the same communities to serve as control participants. The control participants and their parents were interviewed with the Disruptive Behavior Disorders module of the NIMH DISC–IV (Shaffer et al., 2000). Control participants with a history of two or more symptoms of ADHD during any 6-month period were excluded. The control participants were not systematically interviewed for the presence of other psychiatric disorders. Thus, they most likely did not constitute a "super-normal" (i.e., free of all pathology and symptoms) group that is unrepresentative of the urban population from which the sample was

recruited. Nevertheless, control participants with a prior psychiatric diagnosis or history of treatment were excluded. Mean estimated IQ of the control group was 92.4 (SD = 11.8, range = 77.0–126.0). None of the control participants had been exposed to psychotropic medication. There were no significant differences in the age or estimated IQ of the ADHD and control groups (both $p > .10$).

The study was approved by the Institutional Review Boards of Queens College of the City University of New York and the Mount Sinai School of Medicine. Written informed consent was obtained from the adolescents and, when appropriate, from their parents. The adolescents were compensated for their participation.

SRCT

The SRCT generates separate measures of (a) interference control, (b) response competition, and (c) the ability to integrate these two inhibitory control processes. The task was shortened for use in the scanner and programmed to run continuously in a blocked design. As shown in Figure 1, the SRCT consisted of six 24-s blocks that were each preceded by 15 s of fixation and 5 s during which the task instructions (e.g., *Press where the arrow is pointing.*) were displayed. The six blocks each consisted of 12 trials in which the stimulus appeared along the vertical midline for 500 ms, with a 1,500-ms interstimulus interval demarcated by a central fixation-cross. The trials were randomized with regard to right and left responses to minimize the effects of handedness. Stimuli were generated on a personal computer and projected via a SVGA projector system onto a rear-projection screen that could be viewed through a mirror mounted on the head coil. Participants responded with optical buttons held in the right and left hands. Each run of the SRCT lasted 264 s, and each adolescent completed three runs.

Interference control. The first three blocks of the SRCT assessed interference control. Block 1 required responses to the direction of cen-

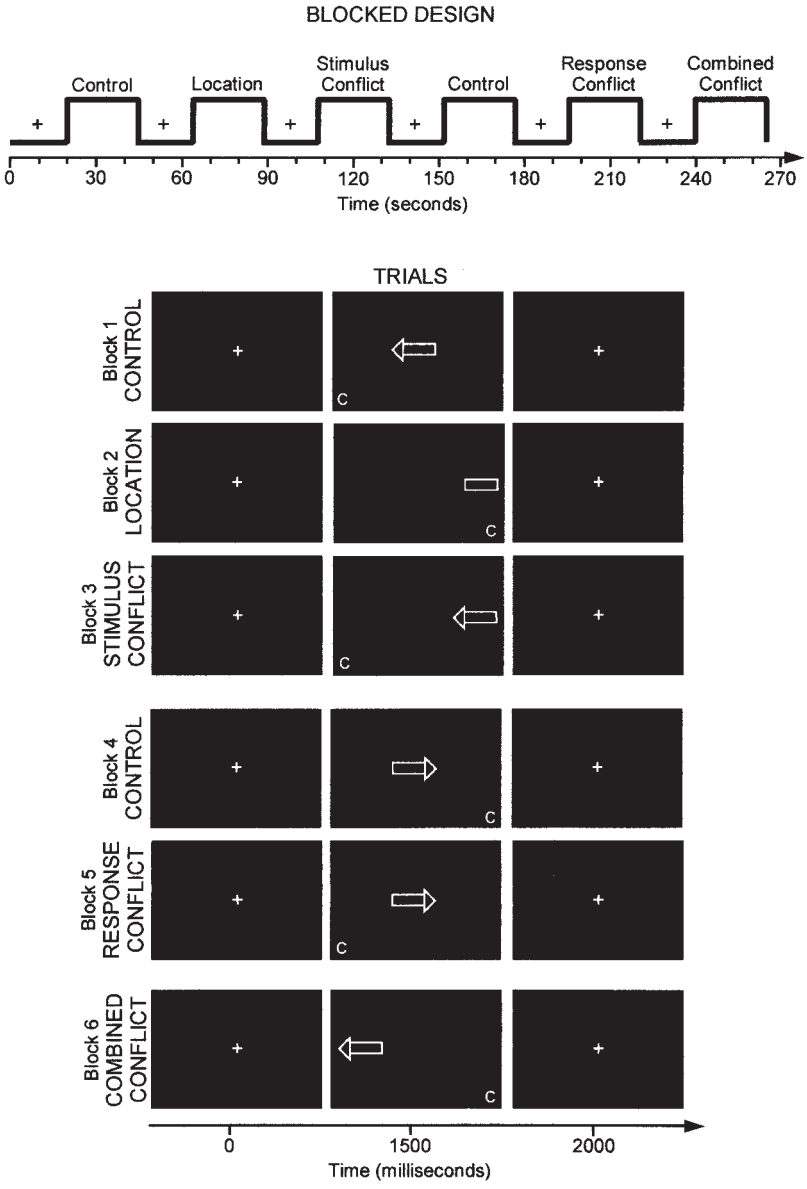

Figure 1. Schematic of the Stimulus and Response Conflict Tasks (Nassauer & Halperin, 2003) illustrating the blocked functional MRI design and the computer display changes across one trial in each of the six blocks. The *C* at the bottom of the frames indicates the correct response according to task contingencies.

trally displayed arrows (control condition). Block 2 involved responding to the location of rectangles on the left or right side of the screen and served to establish stimulus location as the prepotent response (location condition). Block 3 required participants to respond to the direction of arrows that appeared on the left and right side of the screen while ignoring the location of the arrow (stimulus conflict condition). Thus, this block entailed the suppression of interference from task-irrelevant location information that pilot data indicated were more salient (Nassauer & Halperin, 2003). The trials in Block 3 were randomized with regard to arrow direction and location, resulting in conflict between direction and location (e.g., right-pointing arrow on left side) on 50% of the trials. Brain activation associated with interference control was modeled by subtracting activation during the control and location conditions from that obtained during the stimulus conflict condition. This contrast was intended to isolate interference control by subtracting out the processing of location and direction cues.

Response competition. Blocks 4 and 5 tested response competition. Block 4 was identical to Block 1; participants responded to the direction of centrally displayed arrows (control condition). This condition was repeated to reestablish arrow direction as the prepotent response. Block 5 also involved centrally displayed arrows but required participants to inhibit the prepotent response to arrow direction and respond instead in the opposite direction (response conflict condition). Thus, all trials in this condition involved competition between the prepotent and correct responses. Brain activity related to inhibition of prepotent responses was modeled by subtracting activation during the control condition from that obtained during the response conflict condition.

Integration of interference control and response competition. Block 6 was similar to Block 3 in that left- or right-pointing arrows were presented on the left and right sides of the screen. However, participants were required to both ignore arrow location and inhibit the prepotent response to arrow direction, and instead they were to respond in the opposite direction (combined conflict condition). Trials in this block were randomized with regard to arrow direction and location, resulting in conflict between direction and location on 50% of the trials. Neural activation associated with simultaneous interference control and response competition was modeled by subtracting activation during the control (Blocks 1 and 4) and location (Block 2) conditions from that obtained during the combined conflict condition.

Image Acquisition

Structural and fMRI scans were acquired on a 1.5T GE Horizon scanner (General Electric, Milwaukee, WI) modified with hardware for echo-planar imaging. Firm foam padding and surgical tape were used to restrict head motion. Structural imaging consisted of an initial T1-weighted sagittal localizer sequence, followed by a T1-weighted series of the whole brain in the axial plane (three-dimensional spoiled-gradient recall echo in a steady state [3D-SPGR]; repetition time [TR] = 24 ms; echo time [TE] = 5 ms; flip angle = 40°, 23-cm field of view [FOV]; 256 × 256 matrix; 124 slices; 1.2-mm contiguous slices) and a series of T2-weighted axial images (TR = 600 ms, TE = 18 ms, 23-cm FOV, 256 × 256 matrix, 14 slices, 5-mm slice thickness, 2.5-mm skip). The latter two sequences were acquired for cross-participant registration, alignment of functional images to a reference brain, and localization of functional activity. Functional scans depicting the blood oxygenation level–dependent signal were acquired with a multislice gradient-echo echo-planar sequence with an FOV of 23 cm, a flip angle of 90°, a TE of 40 ms, and an acquisition matrix of 64 × 64. Each functional scan comprised a full brain volume of 14 axial slices with 5-mm slice thickness and 2.5-mm skip, acquired continuously over each run with a TR of 2,000 ms. This sequence results in an effective voxel resolution of 3.75 mm × 3.75 mm × 7.5 mm. Each participant completed three runs of 264 s, resulting in 132 time points.

Data Analysis

Mean RTs and percentages of correct responses were calculated for each condition (i.e., control, stimulus conflict, response conflict, and combined conflict) and served as the primary behavioral measures of inhibitory control. We analyzed group differences using repeated measures factorial analyses of variance (ANOVAs), with stimulus conflict (presence vs. absence) and response conflict (presence vs. absence) as within-subjects factors and group (ADHD participants vs. control participants) as the between-subjects factor. The two-tailed p value for significance was set at .05.

Image preprocessing and analyses were conducted with the use of statistical parametric mapping (SPM99) software developed by the Wellcome Department of Cognitive Neurology (Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997), which was implemented on a MatLab (Version 6.1, MathWorks, 2001) platform. The first 10 volumes of each functional time series were discarded. The functional scans were realigned to the remaining first volume as correction for interscan movements by means of a rigid body transformation with three rotation and three translation parameters. The functional scans, the T2-weighted anatomical scan, and the high-resolution T1-weighted image were coregistered. The functional scans were then spatially normalized to a standard template (Montreal Neurologic Institute [MNI] template, Montreal, Quebec, Canada), with normalization parameters estimated from the T1-weighted image. The functional images were resampled through a bilinear transformation, resulting in a voxel size of 2 mm × 2 mm × 2 mm. Finally, the functional images were spatially smoothed with a 7.5-mm × 7.5-mm × 15-mm full-width at half-maximum Gaussian kernel.

The functional images from each participant were analyzed individually by modeling the six blocks of the SRCT as delayed boxcar functions convoluted with the hemodynamic response function (individual threshold, $p < .001$) in the context of a general linear model. The effects of the three conflict conditions (i.e., stimulus, response, and combined) were tested by applying appropriate linear contrasts to the parameter estimates for each condition, resulting in three contrast maps for each participant. The contrast images of all participants were entered into second-level group analyses conducted with random-effects statistical models that accounted for intraindividual variability and permitted population-based inferences to be drawn. The effects of the three conflict conditions were first analyzed separately in the ADHD and control groups. The a priori hypotheses were subsequently tested with direct comparisons of the ADHD and control groups. The resultant voxelwise statistical maps were then thresholded for significance with the use of a cluster-size algorithm that protects against an inflation of the false-positive rate with multiple comparisons. For consistency with established functional imaging conventions, results for a priori regions of interest are reported at an uncorrected height (intensity) threshold of $p < .001$ and an extent threshold of $k = 50$ voxels. Coordinates of activation were converted from the MNI coordinates to the Talairach and Tournoux (1988) coordinates with a nonlinear transformation (Brett, 2000) prior to designation of anatomical localization. Finally, Pearson product–moment correlations between percentage of change in MRI signal intensity, CBCL Attention Problems score, and RT on the three conflict conditions were calculated for regions that differentiated the groups.

Results

Behavioral Data

Mean RTs and percentages of accuracy for all conditions are summarized in Table 1. As expected, the ANOVA assessing RT yielded significant main effects for stimulus conflict, $F(1, 14) = 10.94$, $p < .01$, $\eta^2 = .48$, and response conflict, $F(1, 14) = 10.00$, $p < .01$, $\eta^2 = .44$. There was a trend toward an interaction between the two conflicts in the combined conflict condition, $F(1, 14) = 3.12$, $p = .10$, $\eta^2 = .18$. However, there was

Table 1
Behavioral Performance on the Stimulus and Response Conflict Tasks by Adolescents Diagnosed With ADHD During Childhood and by Control Participants With No History of ADHD

	ADHD group				Control group			
	Accuracy (%)		Reaction time (ms)		Accuracy (%)		Reaction time (ms)	
Condition	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Control	97	3	484	137	96	9	470	32
Location	96	4	472	109	98	3	443	49
Stimulus conflict	88	6	601	184	88	15	581	70
Response conflict	93	10	538	133	93	8	520	63
Combined conflict	89	8	617	149	88	9	612	84

Note. ADHD = attention-deficit/hyperactivity disorder.

no significant main effect for group, $F(1, 14) = 0.21$, $p > .10$, $\eta^2 = .02$, and no Group × Stimulus Conflict, $F(1, 14) = 0.81$, $p > .10$, $\eta^2 = .06$, Group × Response Conflict, $F(1, 14) = 0.34$, $p > .10$, $\eta^2 = .02$, or Group × Stimulus Conflict × Response Conflict, $F(1, 14) = 1.38$, $p > .10$, $\eta^2 = .09$, interactions. The ANOVA assessing percentage of accuracy generated no significant main effects or interactions (all ps $> .10$). Analysis of the six parameters generated during motion correction revealed no significant group differences in mean translational movement (ADHD, .65 ± .46 mm; control, .61 ± .45 mm), $t(14) = 0.52$, $p > .10$, or mean rotational displacement (ADHD, .61 ± .45 mm; control, .51 ± .29 mm), $t(14) = 0.52$, $p > .60$, along the echo-planar time series.

fMRI Data

Interference control. The stimulus conflict minus control and location contrast was designed to isolate neural activation related to the suppression of interference from task-irrelevant information while controlling for motor activity (see Table 2 and Figure 2). The suppression of interference activated the ventrolateral prefrontal cortex in both groups. However, this activation was focused in Brodmann's area (BA) 44 of the left inferior frontal gyrus in the control group and distributed across BA 44 and 47 of the left inferior frontal gyrus in the ADHD group, with the peak activity located in the latter region. In addition, the ADHD group activated an anterior region (BA 46) of the right middle frontal gyrus. This task also engaged the left inferior parietal lobule (BA 40) in the ADHD group and the right lingual (BA 18) and inferior temporal gyri (BA 37) in the control group.

Direct voxel-by-voxel between-groups comparisons of activation during interference control are illustrated in Table 3 and Figure 3. These comparisons revealed significantly greater activation of the ventrolateral convexity of the left inferior frontal gyrus (BA 47) by the ADHD group relative to the control group. The robust activation of the left inferior parietal lobule in the ADHD group but not the control group did not emerge as a significant group difference because of relatively high activity in the control group during both control and experimental conditions. As depicted in Figure 3, the magnitude of signal change in the left ventrolateral prefrontal cortex of the ADHD group was positively correlated with the Attention Problems score of the CBCL in adolescence, $r(8) = .97$, $p < .001$, and to a lesser extent during childhood, $r(7) = .71$, $p = .07$. Activation and mean change score in RT were unrelated (all ps $> .10$). There were no significant clusters for which the control group produced greater activation than the ADHD group.

Response competition. The response conflict minus control contrast was intended to isolate neural activation associated with response competition while controlling for motor activity (see Table 2 and Figure 2). Response competition generated significant activation of the left globus pallidus and right superior temporal gyrus (BA 38) in the ADHD group and robust bilateral activation of the superior parietal lobule (BA 7) in control participants. However, no basal ganglia activation was seen in control participants. Direct between-groups comparisons revealed no clusters of significant differences in activation.

Integration of interference control and response competition. The combined conflict minus control and location contrast isolated activation related to the simultaneous suppression of prepotent (but incorrect) response and interference from task-irrelevant information (see Table 2 and Figure 2). The simultaneous task produced robust activation of the opercular region (BA 44) of the inferior frontal gyrus and anterior (BA 10/46) and dorsolateral (BA 6/8) regions of the middle frontal gyrus in both groups. However, this activation was evident bilaterally in the ADHD groups but was confined to the right hemisphere in control participants. Robust activation of the cingulate gyrus was also evident in both groups but varied from bilateral regions (BA 24) of the caudal cingulate in control participants to the rostral extent of the left anterior cingulate gyrus (BA 32) in the ADHD group. Further, the ADHD group exhibited widespread activation of the left caudate nucleus that was not seen in control participants. In contrast, large bilateral activation of the inferior parietal lobule (BA 40) was seen in control participants but not in the ADHD group.

Groupwise differences in activation during the combined conflict minus control and location contrast are depicted in Table 3 and Figure 4. The ADHD group had significantly greater activation of the left anterior cingulate gyrus (BA 32), anterior regions of the right middle frontal gyrus (BA 10), and ventrolateral regions of the right inferior frontal gyrus (BA 47), as well as a large region of the left basal ganglia that included both the caudate nucleus and the globus pallidus. Further, as illustrated in Figure 5, the magnitude of the signal change in the latter three regions of the ADHD group

Table 2
Local Maxima and Extent of Activation During the Stimulus and Response Conflict Tasks for Adolescents Diagnosed With ADHD During Childhood and for Control Participants With No History of ADHD

Contrast and region	BA	Hemi	No. of voxels	Coordinates			t^a
				x	*y*	*z*	
Control group							
Stimulus conflict + control + location							
Inferior frontal gyrus	44	L	121	−50	17	23	4.90
Inferior temporal gyrus	37	R	259	50	−51	4	5.81
Lingual gyrus	18	R	370	24	−78	−3	5.31
Response conflict + control							
Superior parietal lobule	7	R	1,072	18	−44	54	7.30
Superior parietal lobule	7	L	1,004	−24	−40	47	7.21
Combined conflict + control + location							
Middle frontal gyrus	46	R	72	42	40	18	4.56
Inferior frontal gyrus	44	R	82	53	16	3	4.56
Middle frontal gyrus	8	R	246	30	14	44	5.12
Cingulate gyrus	24	R	130	6	−4	43	4.98
Cingulate gyrus	24	L	343	−12	−8	43	4.55
Inferior parietal lobule	40	R	1,593	34	−32	50	6.88
Inferior parietal lobule	40	L	193	−38	−31	46	4.98
ADHD group							
Stimulus conflict − control + location							
Middle frontal gyrus	46	R	355	36	41	3	4.52
Inferior frontal gyrus	47	L	554	−38	39	−5	4.55
Inferior parietal lobule	40	L	63	−40	−28	25	5.92
Response conflict − control							
Globus pallidus		L	154	−10	1	−10	7.42
Superior temporal gyrus	38	R	355	40	6	−26	5.46
Combined conflict − control + location							
Middle frontal gyrus	10	R	83	38	47	−1	6.45
Inferior frontal gyrus	44	R	608	46	14	5	6.40
Inferior frontal gyrus	44	L	54	−52	8	8	5.45
Middle frontal gyrus	8	R	211	30	19	29	5.29
Middle frontal gyrus	6	L	266	−36	2	31	5.84
Anterior cingulate gyrus	32	L	423	−6	34	13	6.63
Caudate nucleus		L	336	−6	16	8	7.98

Note. Values under *x, y,* and *z* are coordinates from Talairach and Tournoux (1988); *t* values represent peak activation in the cluster ($p < .001$, uncorrected). ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann's area; Hemi = hemisphere; L = left; R = right.
[a] Degrees of freedom for the control group are 1 and 6; for the ADHD group, 1 and 7.

was positively correlated with the Attention Problems score of the CBCL in adolescence: anterior prefrontal cortex, $r(8) = .74$, $p < .05$; ventrolateral prefrontal cortex, $r(8) = .72$, $p < .05$; and basal ganglia, $r(8) = .79$, $p < .05$. The magnitude of the signal change in the basal ganglia was also correlated with childhood ratings on the Attention Problems score, $r(7) = .86$, $p < .05$, and there were trends toward similar correlations in the anterior prefrontal cortex, $r(7) = .73$, $p = .07$, and ventrolateral prefrontal cortex, $r(7) = .73$, $p = .06$. No significant correlations were found between activation and RT (all ps $> .10$). There were no clusters for which the control group produced greater activation than the ADHD group.

Discussion

Adolescents who were diagnosed with ADHD during childhood exhibited differential responses to inhibitory control tasks in several brain regions previously implicated in the pathophysiology of ADHD relative to age-, gender-, and IQ-matched adolescents with no history of ADHD. Specifically, adolescents with childhood ADHD generated more robust and diffuse activation of the left ventral prefrontal cortex during interference control than did control participants, with this difference most prominent in the ventrolateral convexity of the inferior frontal gyrus. The more cognitively demanding task of simultaneous interference control and response competition also produced more robust and widespread frontal activation in those with childhood ADHD that extended medially to the anterior cingulate gyrus, rostrally to the ventrolateral and anterior prefrontal regions, and subcortically to the basal ganglia. Further, activation of the latter three regions was positively related to severity of ADHD ratings. Response competition created by location and direction cues alone produced little activation in either group. It is surprising that groupwise differences in task performance were not detected, although this may reflect the small sample size or the relatively short nature of the task.

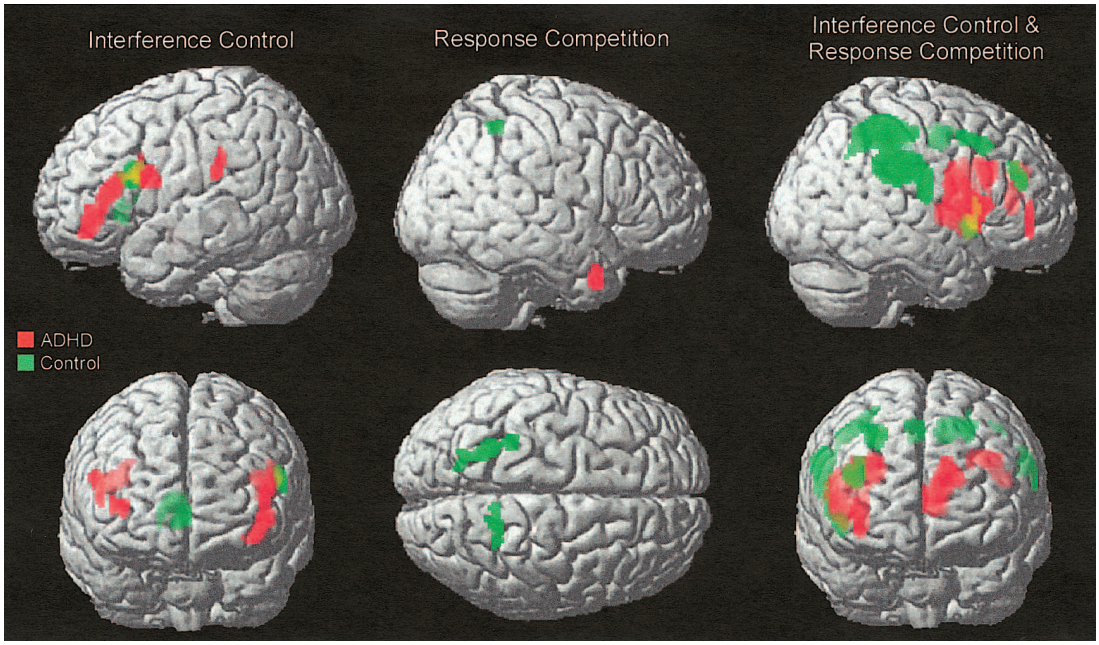

Figure 2. Lateral, superior, and anterior views of the brain depicting regions of activation during interference control, response competition, and simultaneous interference control and response competition in adolescents with childhood attention-deficit/hyperactivity disorder (ADHD) and in adolescent control participants (display threshold, $p < .001$).

Interference Control

The present findings point to both commonalities and differences in the contribution of the prefrontal cortex to interference control in adolescents with and without a childhood history of ADHD. Both groups recruited the left ventral prefrontal cortex during the suppression of task-irrelevant information. However, this activity was more diffuse and changed in its anatomic distribution in adolescents with childhood ADHD relative to control participants, such that peak activation in the former group was localized more rostrally in the ventrolateral convexity of the prefrontal cortex. This region is unique among prefrontal cortical areas in that it contains neurons that convert sensory input into commands for the inhibition, not execution, of responses (Sakagami et al., 2001). The firing patterns of these neurons seem to code for sensory cues that signal the suppression of responses on the basis of the salience or association of these cues with reward (Sakagami et al., 2001; Schoenbaum et al., 1998) and are influenced by interference from past stimulus–response associations (Lauwereyns et al., 2001). Neuroimaging studies have reported

Table 3
Local Maxima and Extent of Significantly Greater Activation During the Stimulus and Response Conflict Tasks in Adolescents Diagnosed With ADHD During Childhood Compared With Control Participants With No History of ADHD

Contrast and region	BA	Hemi	No. of voxels	Coordinates			t[a]
				x	y	z	
Stimulus conflict − control + location							
Inferior frontal gyrus	47	L	193	−38	40	−7	5.35
Combined conflict − control							
Inferior frontal gyrus	47	R	155	32	21	−8	4.32
Middle frontal gyrus	10	R	73	38	45	−1	4.61
Anterior cingulate gyrus	32	L	67	−8	43	7	4.58
Caudate nucleus		L	1,593[b]	−6	16	7	4.44
Globus pallidus		L		−10	−2	−10	4.94

Note. Values under *x, y,* and *z* are coordinates from Talairach and Tournoux (1988); *t* values represent peak activation in the cluster ($p < .001$, uncorrected). ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann's area; Hemi = hemisphere; L = left; R = right.
[a] Degrees of freedom are 1 and 14. [b] The peaks of these regions were part of the same, larger cluster.

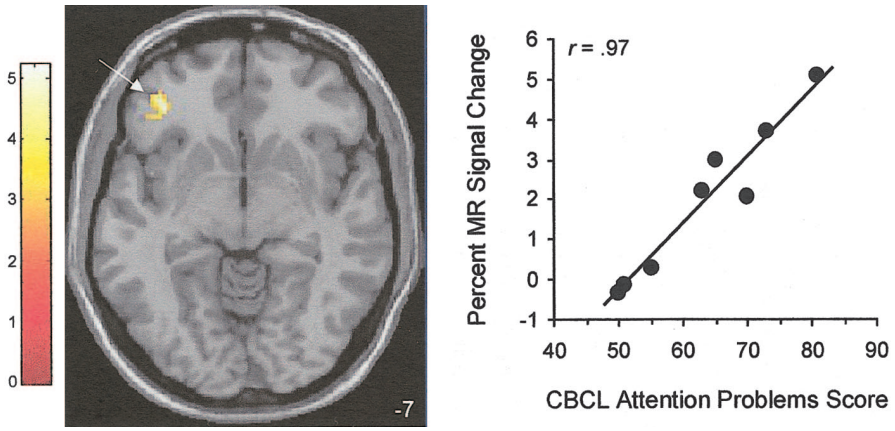

Figure 3. Left: Greater activation of the left ventrolateral prefrontal cortex during interference control in adolescents with childhood attention-deficit/hyperactivity disorder relative to that of adolescent control participants, depicted on a standardized axial magnetic resonance (MR) image (display threshold, $p < .001$). The value in the lower right corner indicates the Talairach coordinate (Talairach & Tournoux, 1988). Right: Correlation of percentage of change in activation of this region with the Attention Problems score of the Child Behavior Checklist (CBCL) in adolescents with childhood attention-deficit/hyperactivity disorder.

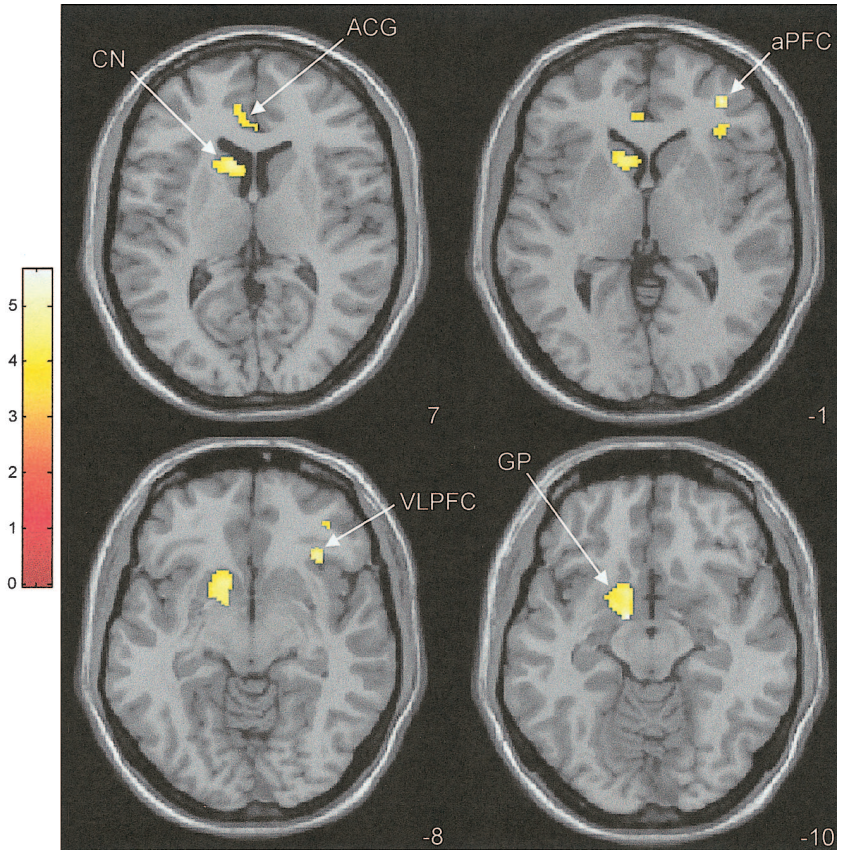

Figure 4. Regions of greater activation during simultaneous interference control and response competition in adolescents with childhood attention-deficit/hyperactivity disorder compared with those of adolescent control participants, depicted on standardized axial magnetic resonance images (display threshold, $p < .001$). The values in the lower right corner of the images indicate Talairach coordinates (Talairach & Tournoux, 1988). CN = caudate nucleus; ACG = anterior cingulate gyrus; aPFC = anterior prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; GP = globus pallidus.

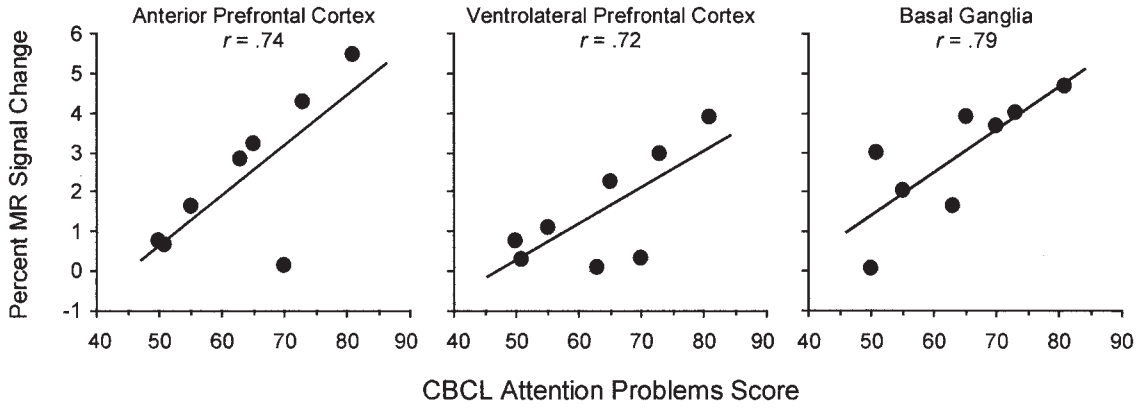

Figure 5. Correlation of the Attention Problems score of the Child Behavior Checklist (CBCL) in adolescents with childhood attention-deficit/hyperactivity disorder with the percentage of change in activation of the right anterior prefrontal cortex, right ventrolateral prefrontal cortex, and left basal ganglia during simultaneous interference control and response competition. MR = magnetic resonance.

similar ventrolateral prefrontal cortex activity during cognitive paradigms that entail processing the outcomes of stimulus–response associations to guide the suppression of task-irrelevant responses, mnemonic traces, and stimulus features (Casey et al., 2002; Kostopoulos & Petrides, 2003; Menon et al., 2001).

The greater and more diffuse ventrolateral prefrontal activation in those with childhood ADHD is reminiscent of immature brain function associated with greater susceptibility to interference in healthy children relative to adults (Casey et al., 2002; Durston et al., 2002). It also suggests greater cognitive effort to suppress interference from task-irrelevant information at comparable levels to those of adolescent control participants. Further, the positive correlation of ventrolateral prefrontal cortical responses with severity of clinical ratings suggests that difficulty with interference control is involved in the manifestation of inattentive and hyperactive symptoms. This is consistent with the finding of ventrolateral prefrontal cortex activation in adults with ADHD, who demonstrated greater Stroop interference effects than did control participants (Bush et al., 1999).

Differential patterns of activation during interference control were also found in more posterior brain regions that provide input to the ventral prefrontal cortex. Control participants activated occipital and inferotemporal regions of the ventral visual pathway that mediate feature-selective processing (Mishkin, Ungerleider, & Macko, 1983). This activity may represent attentional tuning to directional aspects of the stimuli during response selection (Schumacher, Elston, & D'Esposito, 2003; Thiel, Zilles, & Fink, 2004). In contrast, adolescents with childhood ADHD engaged posterior parietal regions that are part of the dorsal visual pathway, which mediates spatial-selective processing (Mishkin et al., 1983). This activity suggests either greater reliance on or interference from localization cues rather than directional cues.

Response Competition

The response conflict task is similar to stimulus–response compatibility tasks that have been used to examine response selection in prior functional imaging studies (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Maclin, Gratton, & Fabiani, 2001; Schumacher et al., 2003). Both paradigms compare trials with compatible stimulus–response pairs to trials with incompatible stimulus–response pairs. In neuroimaging studies of the stimulus-compatibility tasks in healthy adults, researchers have reported activation of the dorsal prefrontal, premotor, and posterior parietal cortices with spatial stimuli (Bunge et al., 2002; Maclin et al., 2001; Schumacher et al., 2003). In contrast, the response conflict task in the current study produced surprisingly little activation of regions associated with either response inhibition or selection in both groups, with activity found bilaterally in the superior parietal lobule of control participants and in the left globus pallidus and right superior temporal gyrus in adolescents with childhood ADHD. No activation was seen in the striatum or premotor and prefrontal cortices, and no significant group differences in activation were found. The paucity of activation generated by this task may be related to the trial parameters of the response conflict condition. The occurrence of conflict between prepotent and correct responses on all trials in this condition potentially allowed participants to establish a behavioral set that did not result in much conflict. Thus, the response conflict task may not have been sufficiently stimulating to generate group differences, particularly given evidence of such deficits in children and adolescents with ADHD (Durston et al., 2003; Rubia et al., 1999; Vaidya et al., 1998).

Integration of Interference Control and Response Competition

The divergent patterns of neural activation in those with and without a childhood history of ADHD during the dual inhibitory task suggest differential processing of competing stimulus features and/or motor programs despite similar task performances. The cingulate gyrus, dorsolateral and ventral prefrontal cortices, and posterior parietal regions activated by control participants during this task are all interconnected (Bates & Goldman-Rakic, 1993; Cavada & Goldman-Rakic, 1989), and they form a network specialized for processing response conflict in visuospatial tasks (Bunge et al., 2002; Schumacher et al., 2003). The cingulate and dorsolateral prefrontal activation during this task likely reflected

the increased processing and response selection demands imposed by conflicts in both the preresponse and response stages of processing (Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003), whereas the robust activation of the bilateral posterior parietal regions may represent increased attentional tuning to spatial features of the stimuli (Thiel et al., 2004). The fact that activation was limited to this frontoparietal network suggests efficient processing of interference from competing stimulus features and responses.

Adolescents with childhood ADHD instead exhibited a pattern of widespread bilateral activation of the frontal cortex regions, with no corresponding activity in the posterior regions. Robust activation was seen in ventrolateral prefrontal cortical regions that were recruited during interference control, with significantly greater activity in these adolescents compared with that of control participants, results again suggesting increased interference from task-irrelevant information (Lauwereyns et al., 2001). Of interest, adolescents with childhood ADHD also activated premotor cortical areas that subserve visuomotor mapping (Hoshi & Tanji, 2004), which were expected to be engaged during the response conflict task (Bunge et al., 2002; Schumacher et al., 2003). The activation of these prefrontal and premotor regions is indicative of interference from both task-irrelevant stimulus features and prepotent responses.

The increased conflict processing demands imposed by simultaneous interference control and response competition also activated the cingulate gyrus in adolescents with childhood ADHD. However, this activation was localized more rostrally in the anterior cingulate gyrus compared with that of control participants. More important, direct comparison of the two groups revealed significantly greater activation of the rostral extent of the anterior cingulate gyrus in adolescents with childhood ADHD than in control participants. This region of the cingulate gyrus purportedly serves to monitor for conflicts between stimuli and/or responses that signal changes in future actions (Botvinick et al., 2001; Fan et al., 2003; Weissman et al., 2003). Practice-related decreases in anterior cingulate activation (Milham, Banich, Claus, & Cohen, 2003) suggest that increased activation of this region in those with childhood ADHD may reflect greater interference from conflicting motor demands and/or greater processing effort to convert these conflicting demands into task-appropriate responses.

Adolescents with childhood ADHD also demonstrated robust bilateral activation of an anterior prefrontal cortex region that has been linked to higher order executive functions. This region is activated by dual tasks that involve interference between the processing of the tasks (e.g., Koechlin et al., 1999; Szameitat, Schubert, Müller, & Von Cramon, 2002) but not by tasks that do not engender such interference (e.g., Adcock, Constable, Gore, & Goldman-Rakic, 2000). The precise executive process subserved by the anterior prefrontal cortex is still debated, but the region may be specialized for processing multiple simultaneous task contingencies (cognitive branching; Koechlin et al., 1999) or for a more general role in coordinating the adaptation, inhibition, and switching of strategies and representations required to process competing task demands (Szameitat et al., 2002). These theories suggest that the significantly greater anterior prefrontal activation seen in adolescents with childhood ADHD reflected increased interference from the competing processing demands of the dual inhibitory tasks. Further, the positive relationship between anterior prefrontal activation and severity of clinical ratings implicates task-processing interference in the pathophysiology of the disorder.

The increased activation of the basal ganglia by adolescents with childhood ADHD during the dual-interference control and response competition task differs from previous reports in which children and adolescents with ADHD performed go/no-go and stop tasks (Durston et al., 2003; Rubia et al., 1999; Vaidya et al., 1998). This discrepancy may be related to differences between the tasks or to differences between the samples. The patients in this study were unique in that they were all diagnosed with ADHD as children but presented with varying degrees of symptomatology in adolescence. Many would not have qualified for the previous neuroimaging study of adolescents with ADHD (Rubia et al., 1999), which focused on the relatively selective group of adolescents who continue to present with the full disorder. The response conflict task of the SRCT involves the selection and execution of appropriate responses in addition to the inhibition of prepotent responses that is measured by go/no-go and stop tasks. Further, the stimulus conflict task seems to measure more cognitive aspects of inhibitory control than do the go/no-go and stop tasks, with performance on this task correlated with the interference effect of the Stroop task (Marks et al., 2004; Nassauer & Halperin, 2003). Thus, the increased basal ganglia activation seen in adolescents with childhood ADHD during the combined conflict is in fact consistent with the previous finding of caudate nucleus activation during the Stroop task in adults with ADHD but not in control participants (Bush et al., 1999). These data raise the possibility that altered caudate nucleus function may be involved in the deficits in interference suppression and more cognitive aspects of inhibitory control (Bush et al., 1999; Carter et al., 1995; Marks et al., 2004), in addition to the motor inhibition deficits characteristic of ADHD (Durston et al., 2003; Rubia et al., 1999; Sergeant et al., 2002; Vaidya et al., 1998). Further, the positive correlation between basal ganglia responses during the combined conflicts task and severity of clinical ratings of ADHD in both childhood and adolescence suggests that these difficulties play a central role in the manifestation of ADHD.

The pattern of frontostriatal activation seen in adolescents with childhood ADHD suggests that the competing stimulus features, responses, and task demands of the dual inhibitory task produced interference on multiple levels of processing that required greater executive and inhibitory effort to process at a level comparable to that of the adolescent control participants. Greater interference effects could also explain the lack of posterior cortex activation associated with attentional tuning to task-relevant stimulus features.

Caveats

These findings must be considered in the context of several methodological issues that may limit their generalizability. First, the small sample size likely limited statistical power to detect groupwise behavioral (i.e., task) differences as well as changes in activation of other brain regions. Second, the unique nature of the ADHD sample in this study makes it difficult to compare the results with previous imaging studies of adolescents and adults with ADHD (Bush et al., 1999; Rubia et al., 1999); our participants were not self-referred during adolescence but were instead diagnosed with ADHD as children and followed into adolescence, and

as such, they presented with varying degrees of symptomatology. Self-referral of adolescents with ADHD has consistently generated different findings from those reported in longitudinal studies (Marks, Newcorn, & Halperin, 2001). Third, the SRCT measures different cognitive processes than do the go/no-go and stop tasks that have been used previously to study children with ADHD (Durston et al., 2003; Rubia et al., 1999; Vaidya et al., 1998). The go/no-go and stop tasks measure the inhibition of prepotent and ongoing responses, respectively, whereas the SRCT seems to test interference control and the competition between prepotent and correct responses. The response conflict component of the SRCT involves the inhibition of the prepotent (but incorrect) response, but unlike the go/no-go and stop tasks, it also requires the selection and execution of a competing response. Thus, the discrepancy between findings may reflect the differences between the tasks.

The SRCT used in this study was adapted to be presented and analyzed in a blocked design rather than an event-related design in order to maximize power to detect changes in activation while minimizing time in the scanner. However, this approach has limitations. First, the blocked design precluded separate analysis of only those trials that involved conflict between arrow direction and location in the stimulus conflict and combined conflict conditions. Second, an event-related design would have permitted greater flexibility in counterbalancing the order of the conditions across runs while still maintaining the conditions required to establish the appropriate prepotent response. These issues are being addressed in ongoing studies.

Summary and Conclusions

In summary, in this study we provide preliminary evidence that differential processing of interference control and competition between prepotent and correct responses may represent a central neurocognitive outcome of ADHD. Robust activation of ventrolateral prefrontal regions that process stimulus–responses associations based on salience, basal ganglia structures that suppress competing motor programs, and anterior cingulate and anterior prefrontal cortical areas that may respectively monitor for conflict and integrate executive functions involved in processing task conflicts were seen in adolescents with childhood ADHD but not in adolescent control participants during inhibitory control tasks. Similar task performance in the two groups suggests that the increased activation in adolescents with childhood ADHD may reflect greater effort to overcome interference. Alternatively, the relatively short tasks used in this study may have enabled these adolescents to maintain sufficient motivation to perform and may account for the lack of group differences in performance. Positive correlations between the prefrontal and basal ganglia activation and ADHD ratings suggest that these difficulties with inhibitory control may represent core deficits in ADHD and raise the possibility that the increased frontostriatal activation will normalize with the continuing remission of symptomatology.

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