Event-Related fMRI Evidence of Frontotemporal Involvement in Aberrant Response Inhibition and Task Switching in Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: Response inhibition deficits are characteristic of individuals with attention-deficit/hyperactivity disorder (ADHD). Previous functional magnetic resonance imaging (fMRI) studies investigating the neural correlates of this dysfunction have used block designs, making it difficult to disentangle activation differences specifically related to response inhibition from activation differences related to subprocesses involved in task performance. The current study was designed to further enhance our understanding of this critical function in individuals with ADHD using event-related fMRI. Method: Ten adolescent boys diagnosed with ADHD, combined type, and 12 typically developing controls completed a Go/NoGo task modified to control for novelty processing. Results: The ADHD group made significantly more errors of omission and more errors of commission than the control group. Further, compared with controls, individuals with ADHD showed marked abnormalities in brain activation during response inhibition, including hypoactivation of the anterior/mid-cingulate cortex extending to the supplementary motor area and hyperactivation of the left temporal gyrus. Conclusions: The authors suggest that underactivation in frontal regions reflects core deficits in response/task-switching abilities for the ADHD group. J. Am. Acad. Child Adolesc. Psychiatry, 2004;43(11):1430–1440. Key Words: attention-deficit/hyperactivity disorder, functional magnetic resonance imaging, response inhibition, Go/NoGo.
magnetic resonance imaging (fMRI). Findings from the four published fMRI studies investigating response inhibition in ADHD suggest that there are identifiable differences in the profiles of brain activation between individuals with ADHD and typically developing controls. Cumulatively, these studies suggest that activation differences between ADHD and comparison groups are present in frontal and striatal areas (Durston et al., 2003; Rubia et al., 1999; Teicher et al., 2000; Vaidya et al., 1998), which correspond with mild to marked behavioral deficits in the ADHD group.

Vaidya et al. (1998), using two versions of a Go/NoGo task to control for the number of stimuli presented and motor movement, reported that children with ADHD showed less activation in striatal regions during the stimulus-controlled task and more activation in broadly defined frontal regions during the response-controlled task. Rubia et al. (1999) reported that individuals with ADHD demonstrated significantly decreased activation in the right mesial frontal cortex, right inferior and medial-inferior frontal lobe, and left caudate nucleus during performance of a stop-signal task. A third study reported longer T2 relaxation times bilaterally in the putamen of boys with ADHD than controls, which correlated significantly with behavioral performance measures on a continuous performance task (Teicher et al., 2000). Finally, Durston et al. (2003) showed in their group by condition analyses that children with ADHD activated less than controls in the caudate nucleus and more than controls in the right superior frontal gyrus (SFG), right middle frontal gyrus (MFG), right inferior parietal lobe, right superior temporal gyrus, and bilateral cingulate gyrus and precuneus. It would appear that frontal and striatal dysfunction is associated with executive impairments in ADHD. However, despite these initial advances in our understanding of the neural correlates of response inhibition in ADHD, a critical review of these studies reveals potential confounds and inconsistencies.

First, three of these studies used a block design, with alternating experimental (NoGo) and control (Go) conditions (Rubia et al., 1999; Teicher et al., 2000; Vaidya et al., 1998). Although providing potential statistical advantages, block designs can introduce uncertainty into the interpretation of the Go/NoGo findings. In particular, activation in the experimental blocks may not only reflect response inhibition but also changes in set, stimulus analysis, response preparation, processing of conflict and error, and novelty processing as well as mixed event types.

Confounds pertaining to novelty processing are also potentially relevant. The experimental tasks employed in these studies included a higher ratio of Go to NoGo trials, leading to the possibility that activation related to the NoGo trials was due to processing the novelty of the relatively rare event rather than inhibition per se. Block designs also are known to be susceptible to habituation and changes in behavioral strategies between blocks (e.g., Bush et al., 1998), and there are confounding differences in frequency of motor events (Liddle et al., 2001). Event-related designs are less susceptible to these problems and have the capacity to probe the time course of the signal change corresponding to inhibition (Leung et al., 2000). Durston et al. (2003) used an event-related design but were only able to analyze data on approximately 58% of their original sample due to movement artifacts and technical problems.

Additional concerns with these studies include the use of restricted neuroanatomical localization with region of interest analyses rather than whole brain analyses. For example, restricting analyses to frontal (Vaidya et al., 1998) and striatal regions of interest (Teicher et al., 2000; Vaidya et al., 1998) precludes identification of other brain regions that may contribute to response inhibition impairments. This is relevant because fMRI literature on inhibition in normal controls does suggest involvement of regions other than the frontal and striatal regions, such as the inferior parietal cortex (e.g., Liddle et al., 2001).

Finally, there are concerns related to the diagnostic status of participants. The studies of Vaidya et al., Teicher et al., and Durston et al. included individuals with both the combined and inattentive subtypes of ADHD. Recent literature suggests that these subtypes may manifest differential deficits in executive function and inhibitory control (Carlson and Mann, 2000; Nigg et al., 2002). Thus, heterogeneity of subject group membership may be an additional confounding influence on the results.

Additional investigation to elucidate the extent and specificity of neural abnormalities underlying deficits in response inhibition in ADHD is needed, and the current study was designed to investigate these issues. A modified Go/NoGo task controlling for novelty processing was used. It has been argued that the Go/NoGo task most directly assesses the construct of inhibitory
control (Rubia et al., 2001a). Further, the task is thought to require “selective inhibition” because participants were required to respond differentially to two different infrequent stimuli, only one of which required inhibition (Bedard et al., 2003). We hypothesized that the ADHD group would demonstrate significantly more errors of commission and errors of omission than controls. We further hypothesized that the ADHD group would show less activation than controls in the inferior frontal cortex, anterior cingulate cortex, and basal ganglia, particularly in the right hemisphere.

**METHOD**

Fourteen adolescent boys diagnosed with ADHD and 12 typically developing male controls (group matched; ADHD group mean age 16.00 years, SD = 1.41, range 14–18; control group mean age 15.58, SD = 0.79, range 14–16), participated in the study. Subjects were recruited via mailings to local pediatricians, postings on the Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) and Stanford Psychiatry web sites, flyers, etc. Informed consent and assent were obtained from study participants and their parents, following procedures established by the Stanford Institutional Review Board. Subjects were compensated $100 for their participation in the study. Data from four subjects in the ADHD group were excluded due to excessive movement during fMRI acquisition (three subjects) and comorbid major depression (one subject). Subjects were all right-handed. Five subjects in the ADHD group reported current use of stimulant medication; all were subjected to an 18-hour washout before the fMRI scan. Subjects did not drink caffeine at least 2 hours before the scan.

ADHD diagnosis was determined via a structured interview conducted with a parent of each subject during the initial telephone screening and verified during the initial visit (parent completed Diagnostic Interview for Children and Adolescents and Conners ADHD/DSM-IV Scale [Table 1]). Subjects with a family history of bipolar disorder were excluded.

Typically developing controls were screened (via telephone interview with parent) for neurological, developmental, and psychiatric disorders and a family history negative for psychiatric disorders. Further, all controls scored in the normative range on the Child Behavior Checklist (Achenbach, 1991) and the Conners ADHD/DSM-IV Scale-Parent Version (CADS-P) (Table 1).

To minimize movement artifacts, a protocol using an MRI simulator was administered to the ADHD group. Specifically, a movie being viewed by the subject during the simulated scan would cut off for 3 seconds whenever the subject moved beyond a set criterion. Increasingly stringent movement criteria and time periods were selected until all ADHD subjects met a criterion of fewer than three movements exceeding 1 mm within 10 minutes. Exclusion criteria of head movement greater than 3 mm and rotation greater than 3 degrees during fMRI scanning resulted in the elimination of three subjects.

Cognitive functioning was assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and academic functioning was assessed using the Wide Range Achievement Test, Third Edition (Jastak and Wilkinson, 1993).

### Experimental Task

Stimuli were presented every 2 seconds using a fast, stochastic event-related design (Burock et al., 1998; Friston et al., 1999; Table 1).

#### TABLE 1

<table>
<thead>
<tr>
<th>Descriptive Statistics</th>
<th>ADHD Group (Mean, SD)</th>
<th>Control Group (Mean, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IQ/Achievement variables</strong></td>
<td>n = 10</td>
<td>n = 12</td>
</tr>
<tr>
<td>WASI Verbal Scale IQ</td>
<td>109.50 (14.92)</td>
<td>111.33 (14.84)</td>
</tr>
<tr>
<td>WASI Performance Scale IQ</td>
<td>107.40 (13.32)</td>
<td>110.92 (14.30)</td>
</tr>
<tr>
<td>WASI Full Scale IQ</td>
<td>109.20 (14.50)</td>
<td>111.58 (11.73)</td>
</tr>
<tr>
<td>WRAT-III Reading</td>
<td>108.10 (6.57)</td>
<td>111.00 (5.67)</td>
</tr>
<tr>
<td>WRAT-III Spelling</td>
<td>102.60 (11.89)</td>
<td>110.00 (10.44)</td>
</tr>
<tr>
<td>WRAT-III Arithmetic</td>
<td>105.90 (16.24)</td>
<td>106.25 (15.52)</td>
</tr>
<tr>
<td><strong>Conners ADHD/DSM-IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattentive</td>
<td>75.20 (7.91)</td>
<td>46.45 (6.23) b</td>
</tr>
<tr>
<td>Hyperactive/impulsive</td>
<td>82.30 (6.88)</td>
<td>51.18 (14.18) b</td>
</tr>
<tr>
<td>DSM-IV symptoms</td>
<td>81.80 (5.63)</td>
<td>47.36 (9.74) b</td>
</tr>
<tr>
<td><strong>Behavioral dependent variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors of commission</td>
<td>17.3 (11.7)</td>
<td>10.1 (7.9) b</td>
</tr>
<tr>
<td>Errors of omission to “B”</td>
<td>2.1 (1.6)</td>
<td>0.58 (0.8) b</td>
</tr>
<tr>
<td>Reaction time to “X”</td>
<td>201.98 (85.56)</td>
<td>235.45 (67.03)</td>
</tr>
<tr>
<td>Reaction time to “B”</td>
<td>218.35 (95.27)</td>
<td>265.03 (75.47)</td>
</tr>
</tbody>
</table>

*Note: ADHD = attention-deficit/hyperactivity disorder; WASI = Wechsler Abbreviated Scale of Intelligence; WRAT-III = Wide Range Achievement Test, Third Edition.

a Data missing for 1 subject in control group.

b Significant difference between groups.
Menon et al., 2001). The interval between two similar types of events (e.g., “A”) was jittered with a mean of 11.6 seconds and an SD of 11.6 seconds, which has been shown to be efficient for separating brain activation to individual events (Friston et al., 1999). To ensure that events could be statistically separated, we verified that the predicted responses for each pair of stimuli were mutually orthogonal. Expected waveforms for each of the two conditions were computed after convolution with a hemodynamic response function (Kruggel and von Cramon, 1999). The correlation between expected responses to each pair of conditions was less than 0.01, allowing independent assessment of brain activation to each condition (Clark et al., 1998).

The event-related Go/NoGo task consisted of a 4-second rest epoch at the beginning and a 6-second rest epoch at the end of the task, during which subjects passively viewed the word “rest.” The letters “X” (66% of trials), “A” (17% of trials), and “B” (17% of trials) were presented in random order every 2000 milliseconds for 200 milliseconds. Subjects were instructed to respond with a key press to every letter except “A,” to which they were instructed to withhold the response. The letter “B” was included to control for the novelty of the letter “A.” A higher percentage of “X” stimuli allowed for the build-up of a prepotent response. All subjects responded using the forefinger of the right hand. Errors of omission, errors of commission, and reaction times to the letter “X” and the letter “B” were recorded. Subjects completed this task in two runs of 7 minutes, 14 seconds, administered in a counterbalanced order and concatenated for analyses. In total, subjects completed 420 trials. After the scanning session, each subject reported on strategies adopted to successfully perform the task.

fMRI Acquisition

Images were acquired on a 1.5-T GE Signa scanner with Echospeed gradients using a custom-built whole-head coil that provides a 50% advantage in signal-to-noise ratio over that of the standard GE coil (Hayes and Mathias, 1996) and prevents head movement. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 2 seconds using a T2*-weighted gradient echo spiral pulse sequence (TR = 2000 milliseconds, TE = 30 milliseconds, flip angle = 89 degrees and one interleave) (Glover and Lai, 1998). The field of view was 240 mm and the effective in-plane spatial resolution was 3.75 mm. To aid in localization of functional data, high-resolution T1-weighted inversion recovery spoiled gradient-recalled three-dimensional MRI sequence with the following parameters was used: TR = 9, TE = 1.9, flip angle = 15 degrees, 124 slices in coronal plane, 256 x 192 matrix, acquired resolution = 1.5 x 0.9 x 1.2 mm. The images were reconstructed as a 124 x 256 x 256-matrix with a 1.5 x 0.9 x 0.9-mm spatial resolution.

The task was programmed using PsyScope (Cohen et al., 1993) on a Macintosh laptop. Initiation of the scan and task was synchronized using a TTL pulse delivered to the scanner timing microwave from a CMU Button Box connected to the Macintosh. Letters were presented visually at the center of a screen using a custom-built magnet compatible projection system (Resonance Technology, Northridge, CA).

Image Preprocessing

Images were reconstructed by inverse Fourier transform for each of the 120 time points into 64 x 64 x 18 image matrices (voxel size: 3.75 x 3.75 x 7 mm). fMRI data were preprocessed using SPM99 (Wellcome Department of Imaging Neuroscience, 2002). Images were corrected for movement using least-square minimization without higher order corrections for spin history and normalized to the Montreal Neurological Institute template provided with SPM. Images were then resampled every 2 mm using sinc interpolation.

Statistical Analysis

Statistical analysis was performed on group data using a random effects model (Holmes and Friston, 1998) along with the theory of gaussian random fields as implemented in SPM99, which takes advantage of multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data (Friston et al., 1995).

Confounding effects of fluctuations in global mean were removed by proportional scaling in which, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. A temporal smoothing function (4-mm gaussian kernel corresponding to dispersion of 8 seconds) was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Voxel-wise t statistics were computed using the random effects model and normalized to Z scores to provide a statistical measure of activation independent of sample size. Finally, to determine the presence of significant clusters of activation, the joint expected probability distribution of height (Z > 1.67, p < .05) and extent (p < .05) threshold (Poline et al., 1997) was used to correct for spatial correlations in the data.

For group analysis, a random effects model was used to determine voxel-wise t statistics contrasting specific conditions of interest. This model estimates the error variance for each condition of interest across subjects rather than across scans (Holmes and Friston, 1998) and provides better generalization to the subject population, albeit with some loss in power due to averaging in the time domain. Analysis proceeded in two steps. In the first step, adjusted images corresponding to the conditions/events of interest were determined. For each condition, a weighted average of the images was computed taking into account the hemodynamic response. In the second step, these condition-specific images were contrasted in a general linear model to determine appropriate t statistics. The t statistics were normalized to Z scores to determine significant clusters of activation. The following events were examined: A versus B events and B versus A events. An initial examination of within-group activation was made for each group on the comparison of interest, A versus B events. A between-group analysis was then conducted to examine differences in activation. To control for the potentially confounding influences of deactivation (B versus A events) in the ADHD group, a deactivation mask (Z = 1.67, p < .05) was created; only data that survived this masking are reported for the between-group analyses. For discussion regarding the influence of deactivation on between-group comparisons, see Tamim et al. (2002a).

Neuroanatomical locations of activation were determined using the standard Talairach atlas (Talairach and Tournoux, 1988) and refined using the more detailed Duvernoy neuroanatomical atlas (Duvernoy et al., 1999).

RESULTS

IQ/Achievement and Rating Scales

The two groups did not significantly differ with regard to IQ or achievement scores. The two groups
differed significantly on all subscales of the CADS-P. Means and standard deviations for these variables are reported in Table 1.

Behavioral Data

Exploration of the dependent variables (errors of commission, errors of omission to the “B,” reaction time to “X,” and reaction time to “B”) revealed an outlier in the control group for errors of commission. To prevent any confounds in the data resulting from nonnormality of the data, nonparametric Mann-Whitney tests were conducted to compare the groups on the errors of commission variable. Independent samples t tests were conducted for the errors of omission and reaction time variables.

The results of these analyses revealed significant group differences, with the ADHD group making significantly more errors of omission ($t_{12.65} = 2.74, p < .05$, one-tailed test) and significantly more errors of commission than controls (Mann-Whitney $U = 34.5, p < .05$, one-tailed test). The two groups did not differ for the two reaction time variables (“X”: $t_{20} = -0.60$, no significance; “B”: $t_{20} = -0.89$, no significance). Means and standard deviations are reported in Table 1.

In the ADHD group, 60% reported adopting a verbally mediated strategy for the task (i.e., silently reading letter to self before responding and/or silently reminding self of instructions), compared to 50% in the control group.

Brain Activation

A Versus B. Controls showed significant activation in the right angular gyrus extending to the supramarginal gyrus and superior temporal sulcus. In addition, they showed significant activation in the SFG, extending to the anterior/mid-cingulate cortex, MFG/supplementary motor area (SMA), and inferior frontal gyrus (IFG) (Table 2, Fig. 1).

The ADHD group showed significant activation bilaterally in the middle/inferior temporal gyrus, bilaterally in the IFG extending to insula and frontal operculum, and in the left anterior cingulate gyrus extending to the SFG and SMA (Table 2, Fig. 1).

Group Differences. Between-group comparisons for A versus B events revealed significantly more activation for the ADHD group than controls in the left middle/inferior/superior temporal gyrus (Table 3, Fig. 2). In contrast, the control group showed significantly more activation than the ADHD group in the right middle temporal gyrus (BA20)/inferior temporal gyrus/superior temporal gyrus.

### Table 2

<table>
<thead>
<tr>
<th>Activated Regions</th>
<th>Voxels</th>
<th>Maximum Z Score</th>
<th>Peak Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>A versus B Controls</td>
<td>Right angular gyrus (BA7/39) extending to supramarginal gyrus and superior temporal sulcus</td>
<td>1,464</td>
<td>4.65</td>
</tr>
<tr>
<td>Males With ADHD</td>
<td>Right inferior frontal gyrus (BA47) extending to insula, middle frontal gyrus, and frontal operculum</td>
<td>598</td>
<td>3.41</td>
</tr>
<tr>
<td></td>
<td>Left middle temporal gyrus (BA20)/inferior temporal gyrus/superior temporal gyrus</td>
<td>871</td>
<td>3.84</td>
</tr>
<tr>
<td></td>
<td>Right middle temporal gyrus (BA21) extending to superior temporal sulcus gyrus/inferior temporal gyrus and insula</td>
<td>2,154</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Right inferior frontal gyrus (BA44/47) extending to frontal operculum and insula</td>
<td>657</td>
<td>3.49</td>
</tr>
<tr>
<td></td>
<td>Right inferior frontal gyrus (BA47) extending to frontal operculum and insula</td>
<td>734</td>
<td>3.54</td>
</tr>
<tr>
<td></td>
<td>Left anterior cingulate cortex (BA32) extending to superior frontal gyrus and supplementary motor area</td>
<td>1,135</td>
<td>3.26</td>
</tr>
</tbody>
</table>

*Note: For each significant cluster ($p < .05$), region of activation, number of voxels activated, maximum Z score, and location of peak (Talaraich coordinates) are shown. BA = Brodmann’s area.*
DISCUSSION

To our knowledge, this study is amongst the first to use an event-related Go/NoGo fMRI task to investigate the neural correlates of response inhibition in individuals with ADHD. Unlike previous fMRI studies, we used a task that controlled for processing of infrequent events and isolated brain activation directly related to response inhibition. Individuals with ADHD made significantly more errors of omission and errors of commission than controls accompanied by significant between-group brain activation differences. Controls showed significantly greater activation than individuals with ADHD.
with ADHD in the right anterior/mid-cingulate cortex extending to the SMA and MFG. In contrast, the ADHD group demonstrated an abnormal pattern of activation that included the left middle and superior temporal gyri. Our results suggest that individuals with ADHD show aberrations in brain activation in association with response inhibition.

Control group activation to A versus B events is quite consistent with the existing literature from event-related fMRI studies and suggests that our task is capturing response inhibition as measured by Go/NoGo tasks. Significant regions of activation for the control group included the right angular gyrus extending to the supramarginal gyrus, right SFG extending to the anterior/mid-cingulate cortex and SMA, and right IFG. Previous event-related Go/NoGo studies of typically developing controls have reported activation to NoGo events in the right IFG and MFG (although more anterior in the Garavan et al. study) (Garavan et al., 1999; Liddle et al., 2001; Menon et al., 2001), SFG (Liddle et al., 2001) and SMA (Menon et al., 2001), and right angular gyrus (Garavan et al., 1999; Menon et al., 2001). Liddle et al. (2001) also reported activation in the right inferior parietal lobes including the supramarginal gyrus, although not specifically in the angular gyrus. Thus, the convergence of data seems to suggest a critical role for prefrontal cortex and inferior parietal regions, particularly the right hemisphere, in response inhibition.

Within-group analyses of activation to A versus B events for the ADHD group diverged from that observed in the control group, which suggests abnormalities in the recruitment of brain resources for task performance. Significant activation associated with response inhibition for the ADHD group was observed bilaterally in the IFG and temporal cortex and in the left anterior cingulate cortex extending to the SMA. The fact that the ADHD group generally demonstrated more widespread and bilateral activation patterns suggests that they may have been recruiting more resources to perform the task and/or they found the task more effortful. Activation in the anterior cingulate is likely related to experiencing response conflict (Braver et al., 2001), and SMA activation is probably related to motor planning and response execution (Humberstone et al., 1997). Temporal lobe activation for the ADHD group was unexpected and has not previously been reported. We suggest that activation in this region may reflect the adoption of verbally mediated strategies (Gaillard et al., 2001; Price, 2000). The location of this activation is consistent with a role in verbal working memory (Cabeza et al., 2002; Henson et al., 2000; Na et al., 2000) and may reflect an attempt to either rehearse or hold the instructions in mind to enhance task performance. Additionally, activation in this region may be associated with visual recognition of objects (Kim et al., 2000;Passingham and Toni, 2001). Further investigation and replication of left temporal cortex activation are warranted, however. Although the temporal region has not typically shown aberrations in an ADHD population, the regions activated in the left temporal cortex in the current study are extensive. Further, our tentative hypothesis that activation in this region is associated with verbally mediated strategies needs further investigation and confirmation because there was not a significant between-group difference in the number of subjects reporting using verbally mediated strategies. Notably, the only region in which both groups showed significant activation to A versus B events was in the right IFG. This region, particularly in

### TABLE 3

<table>
<thead>
<tr>
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<th>Voxels</th>
<th>Maximum Z Score</th>
<th>Peak Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>A versus B</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control group versus ADHD group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right anterior/mid-cingulate cortex extending to supplementary motor area/superior frontal gyrus (BA6) and middle frontal gyrus</td>
<td>1,501</td>
<td>3.97</td>
<td>10, 8, 40</td>
</tr>
<tr>
<td>ADHD group versus Control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left middle temporal gyrus (BA20/21)/inferior temporal gyrus/superior temporal gyrus extending to superior temporal gyrus</td>
<td>873</td>
<td>4.20</td>
<td>-52, -34, -12</td>
</tr>
</tbody>
</table>

Note: For each significant cluster (p < .05), region of activation, number of voxels activated, maximum Z score, and location of peak (Talaraich coordinates) are shown. BA = Brodmann’s area.
the right hemisphere, is thought to play a significant role in inhibition (Liddle et al., 2001; Menon et al., 2001; Tamm et al., 2002b).

Between-group comparisons further emphasize significant aberrations in brain activation during response inhibition for the ADHD group. Individuals with ADHD activated less than controls in the right anterior/mid-cingulate cortex extending to the SMA and MFG and more than controls in the left temporal cortex to A versus B events. Hypoactivation for the ADHD group in the right cingulate cortex and SMA is likely to be directly linked to behavioral performance because these regions have been shown to play a specific role in task/response switching (Rushworth et al., 2002). In particular, the activation observed in the current study corresponds with the cognitive division of the anterior cingulate cortex, thought to be critically involved in stimulus-response selection in the face of
competing streams of information (Bush et al., 2000), a demand inherent to the Go/NoGo task. Interestingly, Rubia et al. (1999) also reported hypoactivation in the right mesial frontal cortex (BA 8/32) for a group of adolescents with ADHD on a stop-signal task that involved strong task-switching demands. Further, Bush et al. (1999) reported that individuals with ADHD failed to activate the anterior cingulate cortex cognitive division to the same extent as controls on an interference task, the counting Stroop. These findings suggest that the frequently reported response inhibition deficits in individuals with ADHD are actually symptomatic of a more general deficit in task or response switching rather than deficient response inhibition per se.

We hypothesized that individuals with ADHD would show deficits in striatal functioning because all four previous fMRI studies of Go/NoGo tasks reported aberrations in these regions for the ADHD group (Durston et al., 2003; Rubia et al., 1999; Teicher et al., 2000; Vaidya et al., 1998). However, no activation in these regions was observed in the within- or between-group comparisons. One explanation is that striatal regions do not play an integral role in response inhibition per se but may play a role in other executive processes related to task performance detected in block designs versus event-related designs. For example, successful performance in a Go/NoGo task involves several subprocesses including target detection, novelty processing, working memory, and vigilance, which are not easily disentangled in block designs. Alternatively, the lack of activation in the striatal regions may reflect methodological difficulties in activating these structures using fMRI (Menon et al., 1998).

Interestingly, the behavioral data did not reveal between-group differences for the reaction time variables. This was somewhat unexpected given that many studies of inhibition in the neuropsychological assessment literature report that the performance of individuals with ADHD is characterized by slow and variable reaction times (Castellanos and Tannock, 2002; Kuntsi et al., 2001). However, a review of the fMRI studies investigating response inhibition in ADHD does not support the finding of slower and more variable reaction times in individuals with ADHD. In the Durston et al. (2003) study, the ADHD group did not differ in reaction time from the control group. In the Rubia et al. (1999) study, the ADHD group was faster than the control group. The Teicher et al. (2000) study reported more reaction time variability in the ADHD group, but this difference did not meet statistical significance. Thus, our data are consistent with those of other fMRI studies of response inhibition in ADHD. Clearly, additional investigation is warranted to explicate the apparent inconsistency between the fMRI literature and the neuropsychological assessment literature.

In summary, our results demonstrate that adolescents with ADHD have impairments in response inhibition associated with abnormalities in brain activation. The two groups activated essentially different networks during response inhibition, overlapping only in the right IFG, with the ADHD group activating a more extensive bilateral network, suggesting recruitment of additional resources for task performance. The ADHD group exhibited particular difficulties in task/response switching as indicated by more errors of commission and omission, and this appeared to be related to hypoactivation in the anterior/mid-cingulate cortex and SMA regions. Further, individuals with ADHD exhibited more activation than controls in the left temporal lobe, possibly related to the adoption of verbally mediated strategies or visual processes. This latter finding is intriguing but requires replication.

Limitations

Although parents endorsed significant impairment in multiple settings during the diagnostic interview, we were unable to obtain teacher ratings. Thus, pervasiveness of symptomatology cannot be verified, somewhat limiting generalizability of these findings. These findings should also be replicated using alternative tasks requiring response inhibition, e.g., the Stop Signal task, to further confirm and clarify the brain regions contributing to problems with task switching and response inhibition in ADHD. Although we attempted to control for as many variables as possible, it should be noted that the A versus B contrast compares withholding a response with performing a motor response and that this may interact with diagnosis. Finally, it should be noted that no conclusions can be drawn related to error-related neuronal activation because the between-group analyses included both correct and incorrect responses.

Clinical Implications

The current study findings, when taken together and interpreted in the context of the existing fMRI re-
sponse inhibition literature for ADHD, suggest that task or response switching, rather than response inhibition per se, is deficient in ADHD. Further, the current findings suggest a critical role for cingulate regions in this function. Future studies may investigate the veracity of this hypothesis using other experimental paradigms that are more explicitly designed to investigate task switching. In addition, it may be fruitful to examine the impact of intervening directly with task switching (e.g., training this specific function repeatedly) in individuals with ADHD.

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