Differential Patterns of Striatal Activation in Young Children with and without ADHD

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Background: *Cognitive control, defined as the ability to suppress inappropriate thoughts and actions, is compromised in attention-deficit/hyperactivity disorder (ADHD). This study examines the neural basis of this deficit.*

Methods: *We used a paradigm that incorporates a parametric manipulation within a go/nogo task, so that the number of go trials preceding a nogo trial is varied to tax the neural systems underlying cognitive control with increasing levels of interference.*

Results: *Using this paradigm in combination with event-related functional magnetic resonance imaging (fMRI), we show that children without ADHD have increased susceptibility to interference with increasing numbers of go trials preceding a nogo trial, but children with ADHD have difficulty even with a single go trial preceding a nogo trial. In addition, children with ADHD do not activate frontostriatal regions in the same manner as normally developing children, but rather rely on a more diffuse network of regions, including more posterior and dorsolateral prefrontal regions.*

Conclusions: *Normal immature cognition may be characterized as being susceptible to interference and supported by the maturation of frontostriatal circuitry. ADHD children show a slightly different cognitive profile at 6 to 10 years of age that is paralleled by a relative lack of or delay in the maturation of ventral frontostriatal circuitry.*
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Key Words: ADHD, development, striatum, response inhibition, event-related fMRI, parametric

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neuropsychiatric disorder with onset in childhood. It is thought to affect 3% to 5% of all school-aged children and is characterized by age-inappropriate symptoms of hyperactivity, inattentiveness, and impulsivity (Buitelaar 2002; Kaplan et al 1994). Converging evidence implies the involvement of dopaminergic frontostriatal circuitry in ADHD. Anatomical imaging studies using magnetic resonance imaging (MRI) have demonstrated subtle reductions in volume in regions of the basal ganglia and prefrontal cortex (e.g., Castellanos et al 1996, 2001; Filipek et al 1997), whereas functional studies have suggested that these regions may be hypoperfused (e.g., Lou et al 1984). Cognitive functioning is mildly impaired in this disorder (for review, see Sergeant et al [2002]). In particular, cognitive control, the ability to inhibit inappropriate thoughts and actions, is affected. Several studies have shown that this impairment is related to the reduction in volume in frontostriatal regions (Casey et al 1997a; Semrud-Clikeman et al 2000), and functional studies have suggested that older children and adults with ADHD may activate these regions less than controls during tasks that require cognitive control (e.g., Bush et al 1999; Rubia et al 1999; Vaidya et al 1999).

We recently showed that development of this ability is related to the maturation of ventral frontostriatal circuitry in a sample of normally developing children relative to adults (Durston et al 2002b). We manipulated task difficulty within a go/nogo paradigm by parametrically varying the number of go trials preceding a nogo trial (Durston et al 2002a). Such manipulations allow for comparisons between groups on trials of similar performance. More importantly, this manipulation allows one to test the extent to which immature cognition is characterized by susceptibility to interference by varying the salience of the interfering information. Children demonstrated an increased susceptibility to interference compared to adults, as they made more errors overall. In addition, they displayed an increase in the number of errors they made to nogo trials as a function of the number of preceding go

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trials as adults did, demonstrating that their ability to inhibit an action was sensitive to the preceding context; however, whereas in adults activation in ventral prefrontal regions increased with increasing interference, this circuitry appeared to be maximally activated in children when suppressing a behavioral response regardless of the number of preceding responses. This pattern of ventral frontostriatal activity correlated with both age and performance, suggesting that changes in susceptibility to interference are paralleled by maturation in underlying frontostriatal circuitry (Durston et al 2002b).

In the present study, we used our go/nogo paradigm in combination with event-related functional magnetic resonance imaging (fMRI) to investigate the effect of increasing interference on both behavior (the suppression of the button press involved in the go response) and magnetic resonance (MR) signal in young children with ADHD and group-matched controls. We predicted that children with ADHD would demonstrate increased susceptibility to interference compared to control children, as the development of this ability is thought to be impaired in these children. Therefore, we hypothesized that children with ADHD would make more errors overall to nogo trials than control children. Second, we hypothesized that these differences would be paralleled by less efficient or focal patterns of frontostriatal activity than in children without ADHD.

Methods and Materials

Subjects

A total of 14 right-handed children completed the study[1], including 7 healthy controls (mean age = 8.68 [1.51] years, range 6.2–10.3 years, 1 female) and 7 children meeting DSM-IV criteria for ADHD (mean age = 8.55 [1.59] years, range 6.6–10.8 years, 1 female; 3 inattentive subtype, 4 combined subtype) (American Psychiatric Association 1994). A structured interview was used to establish diagnosis in the ADHD children and to confirm absence of diagnosis for the controls (Schedule for Affective Disorders and Schizophrenia for School-Age Children–Parent Version) (Orvaschel 1994). ADHD children with comorbid disorders other than opposition defiance disorder (ODD) and conduct disorder (CD) were excluded. The Conners rating scale (Conners 1969) and the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock 1983) were used to inventory ADHD symptomatology. Subjects were screened for any contraindications for MRI. All ADHD subjects were on stimulant medication, which they withheld from taking the day of the MRI. We obtained written assent from all subjects before scanning and written consent from a parent or legal guardian. The procedure was approved by the institutional review board at Weill Medical College of Cornell University. Ten children were excluded from the imaging study after having participated in a scanning session (including 7 subjects with ADHD) due to excessive motion in the scanner or technical problems; however, we were able to analyze the behavioral data for the larger sample of children (14 children with ADHD and 10 control children).

Paradigm

The subject's task was to press a button in response to visually presented stimuli but to avoid responding to a rare nontarget. The task consisted of five runs, which lasted 3 minutes and 56 seconds each. Each run contained a total of 57 trials, with 75% go trials, resulting in a total of 70 nogo trials, including 20 of each type (with 1, 3, or 5 preceding go trials) per subject. Foil trials (nogo trials after 2 or 4 go trials) were included to prevent learning of the pattern, but these trials were not included in the analysis. The order of presentation of the different types of nogo trials was pseudorandomized. To make the task more interesting for children, characters from the Pokemon cartoon series were used as stimuli. Stimulus duration was 500 milliseconds and the interstimulus interval was 3500 milliseconds (total trial length = 4000 milliseconds).

Scan Acquisition

Echo planar imaging (EPI) blood oxygenation level dependent (BOLD) images were acquired in 24 axial slices on a 1.5 T GE Signa scanner (Advanced NMR, Wilmington, MA), covering most of the brain (repetition time [TR] = 2000, echo time [TE] = 40, 64 × 64, 4-mm slice thickness, 3.125 × 3.125 mm in-plane resolution). Anatomical spin echo images were also collected (TR = 500, TE = min, 256 × 256, field of view [FOV] = 20, 4-mm slice thickness) in the same locations as the functional slices. Stimuli were presented using the integrated functional imaging system (IFIS) (MRI Devices Corporation, Waukesha, WI) that uses a liquid crystal display (LCD) video display in the bore of the MR scanner and a fiberoptic response collection device. Scanning sessions lasted no longer than 1 hour. The functional images were collected in 20–25 minutes, while the anatomical images were collected within a similar time frame. The participants were shown cartoons during the anatomical scans to prevent boredom and restlessness.

Analysis

Automated Image Registration (AIR) version 3.08 (Woods et al 1992) was used for motion correction, image smoothing (2 mm), and cross registration of data. Cross registration was checked by visual inspection of an overlay of each subject's brain with the brain chosen as the standard. There were no differences in variance between groups in MR signal. Foil trials were not included in the analyses. NeuroImaging Software (Laboratory for Clinical Cognitive Neuroscience, University of Pittsburgh and Princeton University) was used to perform a series of voxelwise, multifactorial analyses of variance (ANOVAs), beginning with a 14 (subjects) × 2 (condition: go vs. nogo) design, averaging

[1] At least three runs of the paradigm with less than one voxel of movement. Runs with too much motion were replaced with runs from the same subject to keep the number of runs per subject constant. At least one run was replaced for three subjects.

across all runs, to look for common patterns of activation between groups. Secondly, a 14 (subjects) × 2 (group) × 2 (condition: go vs. nogo) ANOVA was performed to look for differences in pattern of activation between groups. Post hoc analyses were performed for each group separately. For each trial type, two 2-second scans were included in the analyses taken at the peak of the hemodynamic response (4 and 6 seconds after stimulus presentation), yielding 40 data points per trial type per subject. In each analysis, regions of three or more contiguous voxels ($p < .05$ for each voxel in the cluster) were identified (Forman et al 1995). To separate clusters that had more than one maximum with contiguous voxels, analyses were also performed at more conservative p-values, ranging from $p < .005$ to $p < .01$ to examine whether these regions were behaving similarly by comparing their response over go trials and the three levels of nogo trials. If they did not display the same pattern, they were treated as separate clusters. Images were warped into stereotaxic space using Analysis of Functional Neuroimages (AFNI) (Cox 1996) to localize regions of activity, based on the coordinate system of the Talairach atlas (Talairach and Tournoux 1988). Only correct trials were analyzed. A post hoc scan by scan analysis similar to one we have used previously (Casey et al 2000; Durston et al 2002b) was performed on brain regions identified as having significant signal change by the omnibus group × condition ANOVA to test for a differential response between groups on the three different types of nogo trials. Correlations between MR signal change, age, and accuracy were calculated for regions that differentiated the two groups.

Results

Behavioral Results

Across all subjects that participated in the behavioral study, children with ADHD made significantly more errors on nogo trials (mean accuracy = 90.4 [8.1]% for controls; 79.1 [14.4]% for ADHD; $t = 2.43$, $p < .032$). Differences in reaction time (RT) and accuracy on go trials did not reach significance (mean RT = 677 [112] milliseconds for controls; 758 [102] milliseconds for ADHD; $t = 1.87$, $p < .09$; mean accuracy = 97.8 [1.8]% for controls; 95.8 [3.7]% for ADHD; $t = 1.71$, $p < .12$). For the group of children with usable imaging data, there were no differences between the children with and without ADHD in reaction time (mean RT = 678 [140] milliseconds for controls; 719 [133] milliseconds for ADHD; $t = .02$, $p < .99$) or accuracy (for go trials: mean accuracy = 97.8 [1.8]% for controls; 95.8 [3.7]% for ADHD; $t = .71$, $p < .49$; for nogo trials: mean accuracy = 86.4 [8.8]% for controls; 74.9 [9.6]% for ADHD; $t = 1.19$, $p < .26$.); however, the number of errors made on the nogo trials increased as a function of the number of preceding go trials for the control children (10.2%, 17.2%, 17.9%, $r = .90$, $p < .02$) but not for the children with ADHD (15.6%, 22.7%, 21.7%, $r = .79$, $p < .07$). Thus, ADHD children's performance on nogo trials preceded by only one go trial was more similar to control children's performance on nogo trials preceded by as many as three to five go trials (see Figure 1). Average motion was no different between groups used in the final analysis (x = .02 mm, y = .00 mm, and $z = .42$ mm for controls; x = .23 mm, y = .01 mm, and $z = 1.10$ mm for ADHD; $t = 1.3$, $p < .22$ for x; $t = .1$, $p < .92$ for y; $t = 1.91$, $p < .09$ for z).

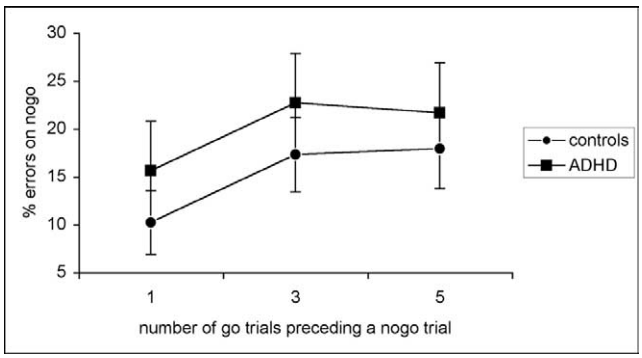

Figure 1. Percentage of errors on nogo trials as a function of the number of preceding go trials (mean ± SE). ADHD, attention-deficit/hyperactivity disorder.

fMRI Results

EFFECTS OF CONDITION (GO TRIALS VS. NOGO TRIALS). Significant regions of activation for the ANOVAs comparing go to nogo trials across groups are summarized in Table 1. The most robust activation for the 14 (subjects) × 2 (condition) ANOVA was in the left primary motor cortex (Brodmann Area [BA] 4), where MR signal increased for go trials (motor response) compared to nogo trials (no motor response). MR signal increased for nogo trials compared to go trials for regions in the right inferior parietal lobe and bilateral posterior cingulate gyrus and posterior hippocampus (see Table 1).

EFFECTS OF GROUP BY CONDITION. In the 14 (subjects) × 2 (group) × 2 (condition) ANOVA, only one region in the left caudate nucleus displayed more activation for control children than for children with ADHD. In contrast, children with ADHD displayed more activation in a number of regions, including the right superior frontal gyrus (BA 10), the right middle frontal gyrus (BA 9/46), the right inferior parietal lobe (BA 40), the bilateral posterior cingulate gyrus (BA 31), the bilateral precuneus (BA 7), the right superior temporal gyrus (BA 22), and the bilateral occipital cortex (BA 18) (see Table 1).

EFFECTS OF CONDITION FOR CONTROL CHILDREN. The results from the individual group ANOVAs are summarized in Table 2. Control children showed an increase in MR signal in the left primary motor cortex for go trials compared to nogo trials. For nogo trials, MR

Table 1. Regions Activated in Comparisons Including All Subjects

Area	Brodmann Area	Side	Talairach	Maximum *F*
Condition (go versus nogo) for All Subjects				
Primary Motor	4	left	(−35, −15, 49)	40.37
Posterior Hippocampus		bilateral	(21, −46, 0) (−20, −47, 0)	9.98
Inferior Parietal Lobe	40	right	(53, −32, 26)	8.20
Posterior Cingulate Gyrus	31	bilateral	(8, −49, 35) (−8, −46, 35)	6.60
Group by Condition (go versus nogo)				
More Activation in Control Subjects				
Caudate Nucleus		left	(−10, 25, −5)	8.73
More Activation in ADHD Subjects				
Superior Frontal Gyrus	10	right	(11, 57, 21)	23.92
Occipital Cortex	18	bilateral	(−20, 84, 3) (14, 87, −1)	17.95
Inferior Parietal Lobe	40	right	(28, −42, 24)	16.89
Precuneus	7	bilateral	(5, −53, 48) (−3, −55, 48)	13.89
Superior Temporal Gyrus	22	right	(38, −35, 4)	12.68
Middle Frontal Gyrus	46	right	(41, 30, 25)	9.73
Posterior Cingulate Gyrus	31	bilateral	(19, −43, 28) (−7, −49, 26)	9.61
Middle Frontal Gyrus	9/46	right	(53, 17, 25)	9.49

Activation is greater for nogo trials than for go trials in all areas except primary motor cortex, where activation is greater on go trials.
ADHD, attention-deficit/hyperactivity disorder.

signal increased relative to go trials in the inferior frontal gyrus (BA 44/45), caudate nucleus, right globus pallidus, anterior cingulate gyrus (BA 32), right middle frontal gyrus (BA 8), and right inferior parietal lobe (BA 40) (see Table 2 and Figure 2).

EFFECTS OF CONDITION FOR CHILDREN WITH ADHD. Children with ADHD showed an increase in MR signal in the left primary motor cortex for go trials compared to nogo trials similar to the controls. For the comparison of nogo trials relative to go trials, they showed an increase in activation in the right superior frontal gyrus (BA 10), right inferior parietal cortex (BA 40), bilateral posterior cingulate gyrus (BA 31), bilateral precuneus (BA 7), and bilateral occipital cortex (BA 18) (see Table 2 and Figure 3).

POST HOC ANALYSES. The post hoc scan by scan analysis revealed no effect of preceding context on MR signal in any region for either group. Correlations between MR signal change, age, and accuracy were not significant for any region in this sample.

Discussion

In this study, we show that, behaviorally, children with and without ADHD are susceptible to behavioral interference during performance of a go/nogo task, with children

Table 2. Regions Activated in Comparisons for Individual Groups

Area	Brodmann Area	Side	Talairach	Maximum *F*
Condition (go versus nogo) for Control Children				
Primary Motor	4	left	(−25, 22, 54)	180.04
Inferior Parietal Lobe	40	right	(60, −25, 27)	39.06
Middle Frontal Gyrus	8	right	(33, 35, 39)	34.43
Caudate Nucleus		right	(8, 25, −5)	29.00
Inferior Frontal Gyrus	44/45	left	(−43, 23, 38)	18.27
Caudate Nucleus		left	(−15, 4, 16)	12.66
Globus Pallidus		right	(25, −6, −6)	11.58
Anterior Cingulate Gyrus	32	medial	(−2, 2, 25)	6.58
Condition (go versus nogo) for ADHD Children				
Superior Frontal Gyrus	9/10	right	(17, 50, 22)	78.48
Posterior Cingulate Gyrus	31	bilateral	(19, −35, 31) (−16, −43, 35)	33.37
Primary Motor	4	left	(−32, 16, 54)	26.71
Inferior Parietal Lobe	40	right	(48, −45, 25)	17.08
Occipital Cortex	18	bilateral	(18, −82, −1) (−13, 82, 6)	16.45
Precuneus	7	bilateral	(12, −40, 45) (−11, −38, 42)	10.21

Activation is greater for nogo trials than for go trials in all areas except primary motor cortex, where activation is greater on go trials.
ADHD, attention-deficit/hyperactivity disorder.

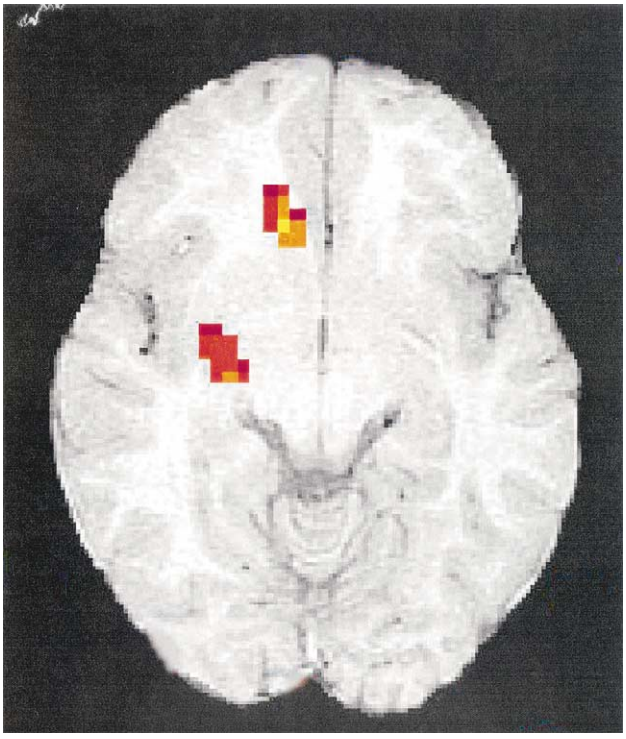

Figure 2. Increased activation of the right caudate nucleus and globus pallidus to nogo trials compared to go trials for control children but not for children with attention-deficit/hyperactivity disorder ($z = -6$; $p < .05$).

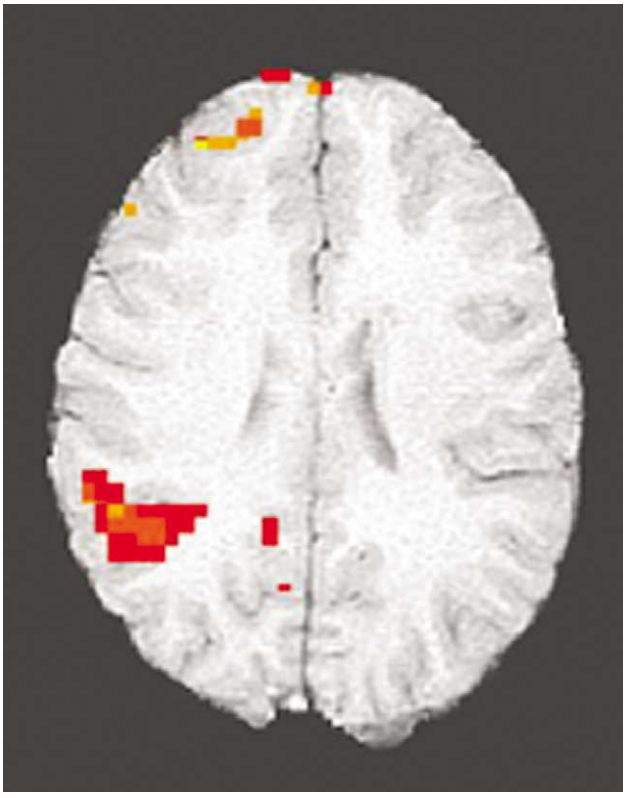

Figure 3. Increased activation of the right inferior parietal lobe and posterior cingulate gyrus to nogo trials compared to go trials for children with attention-deficit/hyperactivity disorder compared to healthy controls ($z = 24$; $p < .05$).

with ADHD being more susceptible to our parametric manipulation. Using the same task, we previously showed that children and adults differ in their susceptibility to interference (with children making more errors overall), but that both age groups showed a behavioral effect of preceding context, with a greater number of false alarms on nogo trials that were preceded by more go trials (Durston et al 2002b). In the current study, children with ADHD did not show a significant effect of preceding context, with a single go trial being sufficient to interfere with inhibiting a response on the next trial. Thus, children with ADHD had similar accuracy for the nogo trials after one preceding go trial as children without ADHD had on nogo trials after three to five go trials. It has been suggested that children with ADHD have a different developmental trajectory in impulse control (Barkley 1997), with normally developing children exhibiting more control earlier in development. Our current sample is between 6 and 10 years of age, one of the younger age groups tested with fMRI to date. Clearly, cognitive control continues to develop over this age range (Carver et al 2001; Casey et al 1997b, 2001; Diamond 1990; Diamond et al 1994; Diamond and Taylor 1996; Enns and Akhtar 1989; Enns and Cameron 1987; Enns et al 1998; Gerstadt et al 1994; Luria 1961; Passler et al 1985; Ridderinkhof and van der Molen 1997; Ridderinkhof et al 1997; Tipper et al 1989; Van der Meere and Stemerdink 1999), so the divergence in developmental trajectories between groups may just be beginning in our current sample. This may explain the lack of differences in overall accuracy for the children who participated in the imaging study. Alternatively, the sample of ADHD children with usable imaging data for this study may have been too small to detect group differences. In our overall sample (including those without usable scan data), there were significant differences in accuracy between children with and without ADHD. The use of a subsample in the imaging study raises the question of whether there was a selection bias in the ADHD sample, with more inattentive rather than hyperactive ADHD children; however, most of the subjects included in the imaging analysis were of the combined subtype.

Of primary interest in the current study is what neural systems distinguish young children with and without ADHD when overriding an inappropriate action. The basal ganglia were the primary area discriminating groups, with normally developing children activating this region more than children with ADHD (see Figure 2). This replicates a

previous study that showed atypical frontostriatal function in children with ADHD, whereby normally developing children activated regions in the basal ganglia during a go/nogo task and children with ADHD did not (Vaidya et al 1998). In the present study, children with ADHD also activated the ventral prefrontal cortex and the anterior cingulate gyrus less than control children. These findings are consistent with imaging literature on ADHD showing abnormal patterns of activity, symmetry, and volume of frontostriatal regions (Casey et al 1997a; Castellanos et al 1996; Ernst et al 1999; Vaidya et al 1998; Zametkin et al 1990) and anterior cingulate gyrus (Bush et al 1999; Vaidya et al 1998). Studies of the development of cognitive control have demonstrated the importance of the maturation of this circuitry in the development of this ability (Bunge et al 2002; Casey et al 1997b; Durston et al 2002b), and less activation of this circuitry in children with ADHD supports the hypothesis that a delay in or lack of development of this circuitry may be involved in the poor cognitive control associated with ADHD.

Both groups of children activated posterior regions, including the right parietal lobe, the posterior cingulate gyrus, and the posterior hippocampus. These patterns of activity may reflect specific aspects of our task design. For example, the activation in parietal and posterior regions areas may reflect vigilance. Although the stimuli occurred frequently and regularly, they only occurred once every 4 seconds. Likewise, the activation of the posterior hippocampus may be related to the frequency of the nontarget being relatively rare and novel when compared to the regularly and frequently occurring targets. The activation of these regions across both groups suggests that these regions may be more intact or mature in both children with and without ADHD than other neural systems examined in this study.

Although children with ADHD activated ventral frontostriatal circuitry and the anterior cingulate gyrus less than control children, they activated other regions more than the normally developing children. These regions were predominantly located in posterior regions of the parietal and occipital cortex (see Figure 3) but also in prefrontal regions previously shown not to correlate with performance on these tasks (Casey et al 1997b; Konishi et al 1999). The present finding is in line with a previous report of increased activation in posterior areas in boys with ADHD during a task involving motor inhibition (Rubia et al 1999). It appears that children with ADHD rely on a more diffuse network of neural systems in performance of tasks that tax cognitive control, such as go/nogo and Stroop tasks (Bush et al 1999). The recruitment of additional areas suggests that a deviation from the normal maturational process in ventral frontostriatal development may be causing children with ADHD to rely on alternative strategies. The increased activation of dorsolateral prefrontal areas may, for instance, reflect an increased involvement of working memory, and the activation in parietal and posterior regions areas may reflect an increased need for or reliance on vigilance or sustained visual attention.

Both the normally developing children and children with ADHD did not show an effect of preceding context on patterns of brain activity. Furthermore, for this sample, there were no correlations between activated brain regions and age or accuracy. These findings are not surprising given our previous report that even in normally developing children, activation associated with inhibiting a response is maximal in the easiest conditions of this task. Thus, if activation is effectively at ceiling level for both groups in even the easiest conditions, there is no range for activation levels to further increase.

Although our results are consistent with the ADHD literature, there are inherent limitations of our study. First, the sample size is small and may have resulted in reduced power, limiting our ability to detect subtle differences between groups. That said, this sample size is not atypical of the functional neuroimaging literature, particularly in the case of patient populations where compliance and motion can result in a high postscan exclusion rate, as was the case for this young sample of children with ADHD (all less than 11 years). A second potential confound is that we used group averages, where differences between groups may be due to increased anatomic variability in the ADHD sample rather than functional differences. An approach that combines anatomical and functional imaging could better tease apart anatomical and functional differences in the neurobiological substrate of ADHD. A related concern is the use of the Talairach atlas in pediatric populations, as adult neuroanatomy does not necessarily generalize well to children; however, there is recent evidence to suggest that anatomic differences between school-aged children and adults are only modest in their effects on detecting functional differences (Burgund et al, in press). Third, although subjects with ADHD were taken off medication for the scan, none were stimulant-naive, and so we cannot rule out long-term effects of medication on patterns of brain activity, especially in dopamine-rich areas as the basal ganglia. Issues such as these stress the need for studies of medication-naive subjects, preferably including larger samples and multiple methodologies to tease apart these issues. Finally, our ADHD subjects included children with diagnoses of both combined and inattentive subtypes. There is evidence that there are multiple etiologic pathways to ADHD (Castellanos and Tannock 2002), and subtypes diagnosed according to DSM-IV may represent different groups. Sample size does not allow for the separation of these subsets in this study, but future

studies including larger numbers of subjects may be able to separate subgroups.

In sum, we have shown that children with and without ADHD display an increased susceptibility to interference, where even the easiest condition of our go/nogo task produced a high level of behavioral interference for the children with ADHD. Normally developing children activate a network including ventral frontostriatal regions during successful performance of this task, whereas children with ADHD appear to rely more on a more diffuse network involving more posterior regions of the inferior parietal lobe and posterior cingulate, as well as dorsolateral prefrontal regions. This differential pattern of activation may represent compensatory mechanisms, in response to aberrant or delayed development of ventral frontostriatal circuitry that may underlie the poor cognitive control associated with this disorder.

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