Efficiency of the Prefrontal Cortex During Working Memory in Attention-Deficit/Hyperactivity Disorder

MARGARET A. SHERIDAN, M.A., STEPHEN HINSHAW, PH.D., AND MARK D'ESPOSITO, M.D.

ABSTRACT

Objective: Previous research has demonstrated that during task conditions requiring an increase in inhibitory function or working memory, children and adults with attention-deficit/hyperactivity disorder (ADHD) exhibit greater and more varied prefrontal cortical (PFC) activation compared to age-matched control participants. This pattern may reflect cortical inefficiency. We examined this hypothesis using a working memory task in a group of adolescent girls with and without ADHD. **Method:** Functional magnetic resonance imaging was used to investigate blood oxygenated level–dependent signal during a working memory task for 10 adolescents from each group, ages 11 to 17 years. We analyzed brain–behavior relationships with anatomically defined regions of interest in the PFC and primary motor cortex. **Results:** The relationship between brain activity in the dorsolateral PFC and ventrolateral PFC and memory retrieval speed differed by group membership, whereby comparison girls had a more efficient brain–behavior relationship than girls with ADHD. There were no such group differences in brain–behavior relationships for primary motor cortex. **Conclusions:** These findings lend support to the idea that cognitive and behavioral deficits experienced by children and adolescents with ADHD may in part be related to relatively low efficiency of PFC function. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(10):1357–1366. **Key Words:** attention-deficit/hyperactivity disorder, RT slope, working memory, prefrontal cortex, development.

Attention-deficit/hyperactivity disorder (ADHD) is believed to affect between 5% and 8% of school-age children in the United States, with persistence into adulthood for many of these children (Barkley, 1997; Mannuzza et al., 1998). Children with ADHD are characterized as having age-inappropriate levels of inattention, disinhibition, and hyperactivity. Their levels of impairment in academic, familial, peer-related domains and tests of executive functioning are substantial (Hinshaw et al., 2002; Klingberg et al., 2005; Martinusen et al., 2005; Nigg et al., 2004). Based on the deficits demonstrated by some children with ADHD on tests of executive functioning, it has been hypothesized that these children have a specific deficit in prefrontal cortex (PFC) function.

Support for this hypothesis has been generated by structural and functional imaging studies of ADHD. Castellanos and colleagues (1996) demonstrated that after controlling for total cerebral volume, boys with ADHD had smaller frontal cortical volumes than boys without ADHD. Numerous recent studies have reported greater activation in lateral PFC in ADHD patients during trials requiring inhibitory control in the go no-go paradigm (Durston et al., 2003; Schulz et al., 2004, 2005), the Stroop paradigm (Bush et al., 1999), and other cognitive tasks (Ernst et al., 2003; Schweitzer et al., 2000). Most of the studies examining PFC function in ADHD, described above, have used tasks tapping inhibitory control, given that this population is considered to have a specific deficit in inhibition (Nigg, 2001). Although these tasks have the benefit of addressing a primary deficit, they compare groups with unequal behavioral performance (e.g., reaction time, accuracy). In the present study we selected a task that taps PFC function but that is unlikely to yield differential performance in ADHD versus comparison

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Ms. Sheridan and Drs. Hinshaw and D'Esposito are with the Department of Psychology, University of California, Berkeley; Dr. D'Esposito is also with the Helen Wills Neuroscience Institute, Berkeley.

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Correspondence to Dr. Mark D'Esposito, Helen Wills Neuroscience Institute, 132 Barker Hall, #3190, Berkeley, CA 94720-3190; e-mail: despo@berkeley.edu.

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samples. This working memory task allows us to examine differences in PFC function not elicited by performance discrepancies.

Our sample constitutes adolescent females with and without ADHD. ADHD occurs more often in males than females, with a sex ratio of approximately 3:1 in community samples (Biederman et al., 2002). To our knowledge, this is the first study examining neural functioning in a group of girls with ADHD using functional magnetic resonance imaging (fMRI). Because this disorder is seriously impairing for girls as well as for boys (Arnold, 1996; Hinshaw et al., 2006), identifying the neural correlates of ADHD is important for individuals of both sexes.

Although many factors may be related to greater PFC activation in ADHD patients, we propose that individuals with ADHD have an inefficiency of neural processing in the PFC. No study to date has directly tested this hypothesis. In the present study we use a paradigm that has been used with older adults to show between-group differences in PFC efficiency (Rypma and D'Esposito, 2000).

The lateral PFC has been consistently implicated in behavioral regulation and executive control, with particular relevance for working memory processes (D'Esposito and Postle, 1999; Levy and Goldman-Rakic, 1999). Working memory refers to the temporary retention of information that was just experienced but no longer exists in the external environment or just retrieved from long-term memory. These internal representations are short-lived, but can be stored for longer periods of time through active maintenance or rehearsal strategies and can be subjected to various operations that manipulate the information in such a way that makes it useful for goal-directed behavior.

The delayed match-to-sample task, widely used in both animals and humans, was designed to probe working memory function (D'Esposito et al., 2000; Sternberg, 1966). This task has three processing stages: encoding, delay, and retrieval. In each trial, participants view a set of items to be remembered items (encoding). After a few seconds (delay), they indicate whether a newly presented item was a member of the earlier set (retrieval). In human fMRI and nonhuman primate single-cell recording studies, accuracy on the delayed match-to-sample task is associated with lateral PFC activity (Curtis and D'Esposito, 2003; D'Esposito and Postle, 1999; Fuster, 1989; Levy and Goldman-Rakic, 1999). In humans with specific damage to the lateral PFC, performance on delay match-to-sample tasks is impaired (D'Esposito and Postle, 1999).

Using fMRI, Rypma and D'Esposito (1999, 2000) demonstrated that among healthy young adults, individuals who retrieve items more quickly from working memory activate lateral PFC to a lesser extent during the response period than their slower counterparts. The rate of retrieval, or speed of memory search, can be determined by calculating the interpolated slope when plotting reaction time (RT) against memory load (i.e., remembering two versus six letters). This statistic, termed RT slope, is calculated under the hypothesis that items are retrieved from memory using a serial search strategy (Sternberg, 1966). In contrast to young adults, however, for healthy older adults a smaller RT slope is associated with greater PFC activation during retrieval (Rypma and D'Esposito, 2000). One interpretation of this finding is that older adults have less efficient PFC function than their young counterparts. Using the relationship between RT slope and PFC activation as a metric in this fMRI study, we used an identical delay match-to-sample task to examine PFC function for adolescents with and without ADHD.

The ability to temporarily hold an item in memory is well established by adolescence (Diamond, 2002), meaning that adolescents with and without ADHD should be able to perform this task well. We predict that during the response period of the working memory task, non-ADHD adolescents with a fast rate of retrieval (small RT slope) will show less PFC activation than those with a large RT slope. In contrast, we hypothesize that adolescents with ADHD will show a pattern of activation consistent with PFC inefficiency; that is, those with a small RT slope, who retrieve mnemonic information relatively quickly, are expected to show greater PFC activation than those with a large RT slope. In contrast to this group-specific relationship between RT slope and the PFC, we hypothesize that there will be no group differences in correlation between RT slope and neural activity for a control region, primary motor cortex (M1).

METHOD

Participants

Participants were adolescent girls (12–17 years), 10 with ADHD and 10 without ADHD (mean age 15.2 (SD 2) and 14.9 (SD 1.3) years, respectively). All of the participants had been initially evaluated and observed when they attended a research summer camp program approximately 5 years earlier, following a full diagnostic workup (see Hinshaw, 2002 for details). During this childhood phase of the research, girls with ADHD met full diagnostic criteria according to the standards of the *DSM-IV* (American Psychiatric Association, 1994); the comparison girls, matched for age, did not meet criteria for ADHD. Diagnoses were made through a combination of parent and teacher rating scale criteria (see Hinshaw, 2002) and were confirmed via the well-validated Diagnostic Interview Schedule for Children, 4th edition (Shaffer et al., 2000). At baseline, four subjects with ADHD met criteria for Inattentive type (ADHD/IA) and six met criteria for Combined type (ADHD/C). We reconfirmed the diagnosis at the follow-up time period 5 years later. At this follow-up assessment, in the group diagnosed with ADHD at baseline, one participant was one symptom short of meeting criteria for ADHD (see Hinshaw et al., 2006 for details of the diagnostic procedures). All of the analyses were conducted both with and without this participant. Because the pattern of findings was nearly identical, we report findings with her inclusion.

Although it has been hypothesized that the Combined and Inattentive types of ADHD differ qualitatively (Milich et al., 2001), there is almost no evidence that they differ in performance on neuropsychological and cognitive tasks such as the one used in this study (Chabildas et al., 2001; Hinshaw et al., 2002; Nigg et al., 2004). Two girls with ADHD met criteria for oppositional defiant disorder and two met criteria for a specific phobia. None of the participants in the present comparison group met diagnostic criteria for any disorder.

Adolescents with ADHD had significantly lower measures of baseline Verbal IQ (VIQ; $t_{18} = 2.317$; $p = .033$; ADHD mean 104, SD 17.2; control mean 120.1, SD 12.6), but not Performance IQ ($t_{18} = 0.228$; $p = .78$; ADHD mean 107.9, SD 13.9; control mean 109.4, SD 8.9; Wechsler, 1991). It is of note that adolescents with ADHD were in the normal range on VIQ and Performance IQ, but comparison adolescents had VIQ scores that were nearly 1 SD above the national mean. In subsequent analyses of brain/behavior correlations, we used VIQ as a covariate. In addition, we correlated VIQ with subjects' brain activation maps for every task period collapsed across load (encoding, delay, probe) and for encoding looking at the effect of load. VIQ did not correlate significantly with brain activity in any of these conditions, effectively eliminating VIQ as a possible explanation for brain activation in this study.

From the larger pool of subjects in the follow-up investigation, adolescents were excluded based on a number of criteria: history of brain trauma, birth mother drug or alcohol use during pregnancy, and birth complications. In addition, adolescents could be taking no psychoactive medication other than stimulants, could not be frequently using drugs or abusing alcohol, and had to have had a Full Scale IQ >80. In addition, no adolescent could have met criteria for reading disorder at either baseline or adolescent follow-up. These rigorous exclusion criteria limited the fMRI subsample to 22 adolescents. One participant was excluded based on claustrophobia discovered in the scanner and one on excessive movement during the scanning.

All of the adolescents came to the Henry H. Wheeler, Jr. Brain Imaging Center at the University of California, Berkeley, with a parent. During the initial session, parents read and signed a consent form, approved by the University of California, Berkeley Committee for the Protection of Human Subjects, allowing their daughter to participate in the study. Adolescents read and signed a similar but more simply written assent describing study procedures. Of the 10 adolescents in the ADHD group, two were medication free for 24 hours before the scan, three were medication naïve, and five had stopped receiving stimulant medications for at least 1 year before the scan.

Cognitive Task

Adolescents performed a delayed match-to-sample task, using letter stimuli, with a memory load manipulation (high = six letters, low = two letters [Sternberg, 1966]). Half of the trials were high load and half were low load. A single trial consisted of three distinct periods: encoding, delay, and retrieval. During the encoding period, adolescents viewed upper case letters, projected on a screen, for 2.2 seconds. They were instructed to remember the letters because they would be tested on them in a few seconds. Next, during the delay period (13.2 seconds), they were instructed to maintain fixation and to hold in mind the letters they had just seen. During the retrieval period (2.2 seconds), adolescents were shown a lower case letter and asked to press the right button if the letter matched and the left button if the letter did not match one of the encoding stimuli. Although the probe item was only displayed for 2.2 seconds, participants' responses were recorded for up to 5 seconds after the onset of the response period. The intertrial interval was 13.2 seconds in length. Each participant completed up to 80 trials in total. The task was divided into 10 blocks (4 minutes, 30 seconds each) for the purpose of fMRI scanning. Load was fully counterbalanced within each fMRI run.

Analyses

Behavioral Data. Nine girls with ADHD and nine comparison girls were included in the analysis of the behavioral data. One ADHD participant and one comparison participant were excluded because of technical problems with the recording of their behavioral responses. For the remainder, mean reaction time and accuracy were computed for each trial type. These means were then entered into a 2 (group: ADHD, comparison) × 2 (load: high, low) mixed analysis of variance test for between-subject and within-subjects effects, respectively. In addition, for each participant with behavioral data, RT slope and reaction time intercept (RT intercept) were calculated. The RT slope statistic effectively calculates the rate at which participants can retrieve items from memory (Sternberg, 1966). The RT intercept is the intercept of the line delineated by the RT slope, indicating the overall speed at which participants respond in this task.

Imaging Data. All of the images were acquired using a 4.0-T Varian INOVA MR scanner. A two-shot T2-weighted gradient-echo echo-planar image sequence (effective TR 2200 ms, TE 28 ms, FOV 22.4 cm^2, matrix size 64 × 64) was used to acquire blood oxygenated level –dependent (BOLD) signal. Each functional volume acquisition contained 20 axial slices of 5 mm with a 0.5-mm interslice gap, voxels were 3.5 × 3.5 × 5.5 mm. Between-slice timing was corrected.

Image processing and analysis were completed using a statistical parametric mapping program (SPM2; Friston et al., 1991). Data were spatial smoothed using 10-mm full width at half-maximum Gaussian kernel. Motion correction was accomplished using a six-parameter rigid-body transformation algorithm (Friston et al., 1995). Before statistical analyses, echo-planar image data were normalized to Montreal Neurological Institute space using a high-resolution three-dimensional T1-weighted structural scan. A total of

1,230 whole-brain volumes were collected for each subject. For each participant, there were 1,130 usable whole-brain volumes. For each participant, total time in the scanner was approximately 1 hour, 30 minutes.

Movement for subjects was restricted by the use of a plastic neck brace, soft cushions, and plastic structural supports that reminded subjects not to move. Mean movement parameters after the exclusion criteria were applied were small and did not differ between groups (ADHD: mean 0.159 mm (SD 0.11), mean 0.003 degrees (SD 0.003); comparison: mean 0.09 mm (SD 0.07), mean 0.003 degrees (SD 0.003). Movement correction parameters were included as covariates in each individual's general linear model analysis; any scan containing movement >5.5 mm was excluded from analysis. As a result, several adolescents had fewer than 1,130 acquisitions. The smallest number of acquisitions allowed was 452 for one participant. This participant performed 40 working memory trials out of a possible 80. After excluding runs with excessive movement, adolescents with ADHD had a mean of 62 (SD 19) runs included; comparisons had a mean of 72 (SD 12). The number of trials excluded was not significantly different between groups: $t(18) = -1.57$, $p = .13$.

To specifically investigate group differences that are unrelated to task performance effects, only correct trials were used in statistical analyses of fMRI data. When there were no behavioral data due to technical complications (two participants), analysis was performed on all of the data. Analyses were completed with and without these two participants. Any changes in results related to the exclusion of these participants' data are noted in Table 1.

To identify areas of task-related BOLD activation, a whole-brain analysis was completed using multiple regression. A statistical parametric map was calculated for each participant based on linear combinations of the covariates modeling each task period. For the whole-brain random effects analysis, covariates were entered separately for all task period and load combinations (e.g., high-load encoding, low-load encoding). Covariates are used to model task-related changes in blood flow in the brain. A single covariate is an impulse function, representing the presentation of a single stimulus, convolved with a canonical hemodynamic response function, representing the slow change in blood flow to that stimulus (Friston et al., 1995). See Figure 1 for an illustration of this method.

For each of the task periods (encoding, delay, retrieval) and conditions (high load, low load), contrast maps of BOLD signal were created that identified areas of BOLD signal associated with a particular covariate. The results of these individual analyses were combined into a group analysis. The BOLD response for

TABLE 1

All Significantly Active Regions in the Random Effects Analysis for Both Groups Collapsed Across Load

ADHD Encoding			Control Encoding		
t	Coordinates	Area	*t*	Coordinates	Area
11.38	(−22 −82 −8)	BA 17/18/19: L lingual	5.82	(12 −82 −10)	BA 17/18/19:R and L lingual
			4.74	(−46 −56 −26)	
7.26	(18 −68 50)	BA 7: R and L parietal	6.03	(38 −42 44)	BA 7: R and L parietal
5.03	(−22 −62 46)		4.87	(−34 −60 34)	
7.04	(−10 −12 14)	L thalamus/putamen	6.87	(16 16 22)	R caudate
6.75	(−44 28 10)	BA 44/45: L IFG	5.97	(30 38 16)	BA 45: R IFG
6.85	(−10 18 36)	BA 32: SMA	5.87	(−38 36 22)	BA 45: L IFG
			4.93	(−8 32 16)	BA 24: ACC
Delay			Delay		
4.95	(0 22 50)	BA 8: SMA			
4.18	(−42 12 30)	BA 44: L IFG			
Retrieval			Retrieval		
7.38	(−34 −52 −38)	L and R cerebellum	4.71	(36 −58 −20)	R cerebellum[a]
6.48	(28 −50 −28)				
6.08	(−14 −68 −16)	BA 18: L lingual	5.31	(−22 −46 −10)	BA 37: L lingual gyrus
7.34	(22 −62 32)	BA 7: R and L parietal	4.48	(−18 12 14)	L caudate[a]
7.16	(−16 −64 30)				
9.64	(−10 −10 14)	L and R thalamus	4.27	(−12 −18 4)	L and R thalamus
8.08	(18 −12 18)		3.49	(6 −14 2)	
12.32	(8 18 44)	BA 24/32: ACC/SMA[a]	5.59	(8 28 20)	BA 24: ACC
9.79	(−38 14 16)	BA 47: L and R IFG	5.60	(−32 16 6)	L and R[a] IFG/insula
5.90	(42 14 14)		4.88	(38 12 −8)	
10.10	(−38 14 58)	BA 2/3: L and R postcentral gyrus	6.37	(−54 −10 −4)	BA 45: L and R IFG
9.15	(36 −16 56)		5.33	(32 42 16)	
			5.29	(−52 36 4)	BA 46: L MFG
			5.30	(−48 −26 38)	BA 2/3: L precentral gyrus

Note: ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann's area; L = left; R = right; IFG = inferior frontal gyrus; ACC = anterior cingulate cortex; SMA = supplementary motor area; MFG = middle frontal gyrus.

[a] Indicates areas which are no longer significant at $p = .05$ corrected when participants with no behavioral data are excluded from the analysis.

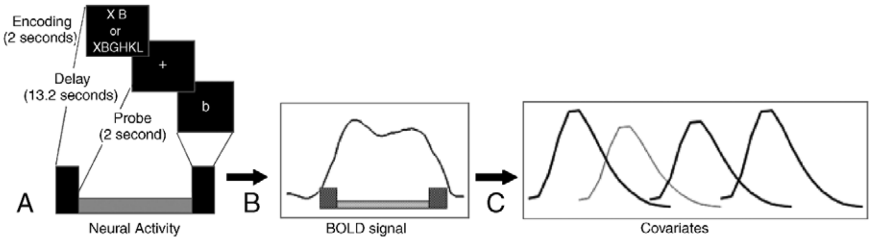


Fig. 1 Experimental design and analysis. A, The behavioral paradigm, timing, and associated neural activity. B, The relationship between changes in blood flow in the brain (BOLD) and neural activity elicited by the behavioral task. C, The use of covariates to sample the BOLD response in the delayed match to sample design. The 3 highlighted canonical hemodynamic responses are used to sample encoding, delay, and response activity, respectively. The second covariate was not used in the analysis because the early delay activity is contaminated by the encoding response.

adolescents with ADHD during each task period, and condition was directly compared to that of adolescents without ADHD, using independent-sample *t* tests. Results for all of the group analyses are reported for each task period (encoding, delay, retrieval) and within task period for each load condition (high, low). Significance for the group map-wise random effects analysis was set at $p = .05$ corrected for a cluster level threshold using gaussian random field theory as implemented by the fmristat program (Cao and Worsley, 2001; see also *http://www.math.mcgill.ca/keith/fmristat*). We used a voxel level threshold of $t = 2.82$ and a search volume corresponding to the actual brain volume of each group. The use of this combination of smoothing and threshold is supported by simulation studies of cluster size tests (Hayasaka and Nichols, 2003).

To examine a priori hypotheses about the relationship between RT slope, RT intercept, and PFC activation, a group-level region of interest (ROI) analysis was performed for three areas: left dorsolateral PFC (DLPFC), left ventrolateral PFC (VLPFC), and bilateral M1. Because RT slope is a measure of memory function that does not require motor control, M1 was considered a control region in which no differences were expected. ROIs were determined anatomically using a Montreal Neurological Institute normalized automated anatomical labeling map (Tzourio-Mazoyer et al., 2002). Each ROI was considered a single region. ROI analysis was performed using the MarsBaR toolbox in SPM2. Because this delayed match-to-sample task used letter stimuli, left PFC was preferentially activated, consistent with previous literature (D'Esposito and Postle, 1999; Fletcher and Henson, 2001). Consequently, we consider the left DLPFC and left VLPFC. The DLPFC was defined anatomically as the middle frontal gyrus and included BA 8/9/46; the VLPFC was defined as the inferior frontal gyrus and included BA 44/45/47. M1 was defined as the postcentral gyrus (BA 4). The mean β values extracted from these ROIs for each subject were correlated with RT slope and RT intercept for each group separately while covarying for VIQ. The difference between the group correlations was tested for significance using Fisher *Z* statistic. A final exploratory analysis was conducted in which RT slope was correlated with every voxel in the brain, with correlations exceeding $p = .01$ within the DLPFC and VLPFC reported. This allowed for localization of the retrieval-related activity that was correlated with RT slope. Because we are considering three ROIs, we use a multiple comparison correction for these three tests, setting the significance level at $p = .0167$ for the RT slope correlations with left DLPFC, left VLPFC, and M1. For the behavioral analyses, the significance was set to $p = .05$.

RESULTS

Behavioral Data

No main effect of group on either accuracy or response times was found (Fig. 2). There was a

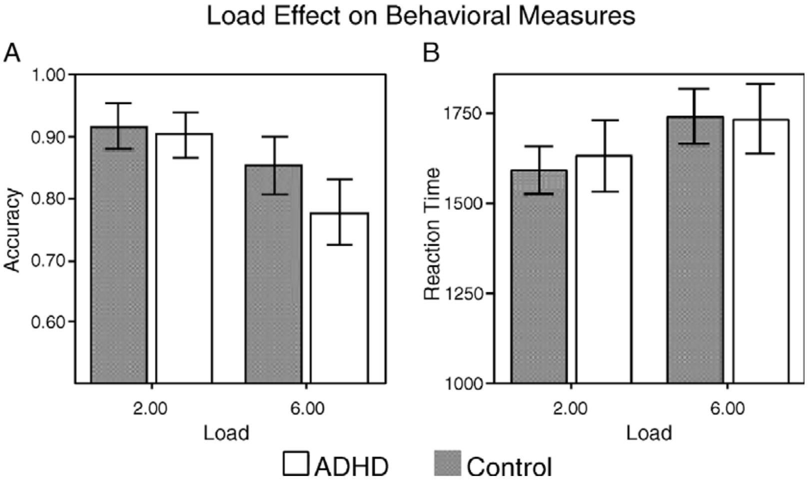


Fig. 2 Effect of load on accuracy (A) and reaction time (B) for adolescents with attention-deficit/hyperactivity disorder (ADHD; open columns) and comparison adolescents (shaded columns).

significant main effect of load on accuracy ($F_{1,16}$ = 12.22; $p = .003$) and RT ($F_{1,16}$) = 8.53; $p = .010$). Both groups performed less accurately and more slowly at high load, but the group × load interaction was not significant.

RT slope and RT intercept were calculated for each participant. The groups did not differ significantly in RT slope (ADHD mean 25.5 [SD 42.6]; control mean 37.8 [SD 49.1]; $t = 0.56$; $p = .58$) or RT intercept (ADHD mean 1,582 [SD 339]; control mean 1,516.5 [SD 254]; $t = -.46$; $p = .65$]. One participant from the control group was an outlier (RT slope = 155 ms/item); this value was >2 SDs from the control mean. In addition, this RT slope was larger than any RT slope in previous studies (Gibbs and D'Esposito, 2005). Thus, we dropped this participant's data from further analyses involving RT slope.

Imaging Data: Main Effect of Task Period

Encoding Period. Collapsed across load, adolescents both with and without ADHD activated cortical and subcortical regions during the encoding period, consistent with previous studies (Table 1). There were no brain regions that were significantly more active for either group.

Delay Period. Collapsed across load, adolescents with ADHD showed significant activation in supplementary motor area and left inferior frontal gyrus during the delay period. When the two groups were compared directly, there were no areas that were significantly more active for either group.

Retrieval Period. Collapsed across load, the ADHD and comparison groups activated cortical and subcortical regions that were consistent with previous studies during the retrieval period (Table 1). There were no brain regions that were significantly more active for either group.

Imaging Data: Effect of Load

For each task period, main effects of load (6 letters > 2 letters) and differences in response to load by group (ADHD, comparison) were explored. During the encoding period, there was an expected main effect of load for both groups in extrastriate cortex. In addition, comparison adolescents activated the inferior frontal gyrus and extrastriate cortex more than adolescents with ADHD during high load (Table 2). During the delay and retrieval periods, there was no main effect load and no difference in response to load by group.

TABLE 2
BOLD Activation Associated With the Effect of Load

Encoding		
t	Coordinates	Area
ADHD		
6.81	(−24 56 36)	BA 19: extrastriate
Control		
13.39	(22 −72 −10)	BA 18: extrastriate
10.3	(38 28 2)	BA 47: R IFG/insula
Control > ADHD		
3.44	(38 26 4)	BA 47: R IFG/insula
3.21	(48 −36 46)	BA 40: R superior parietal

Note: Significantly active regions for the random effects analysis are shown for both groups when encoding 6 letters was compared to encoding 2 letters compared to baseline as well as direct group comparisons. BOLD = blood oxygenated level–dependent; R = right; IFG = inferior frontal gyrus.

ROI Analyses

Average activity from ROIs of the left DLPFC, left VLPFC, and M1 were correlated with RT slope while controlling for VIQ via partial correlations. As predicted, group differences emerged in these correlations for both left DLPFC and left VLPFC, but not M1 (Fig. 3). For ADHD subjects, as RT slope decreased (faster retrieval), left VLPFC activation at the retrieval period increased ($r_6 = -0.80$; $p = .02$). A similar pattern was found in left DLPFC, but this did not reach statistical significance ($r_6 = -0.58$; $p = .13$). For comparison adolescents, the opposite pattern emerged: as RT slope decreased (faster retrieval), left VLPFC activation at the retrieval period decreased as well ($r_5 = 0.60$; $p = .16$) as did left DLPFC activation ($r_5 = 0.63$; $p = .13$), although these correlations did not reach significance. Correlations in a control region, M1 were nonsignificant and small for both groups ($r_6 = 0.02$; $p = .95$; $r_5 = 0.28$; $p = .55$). Finally, there was no relationship between RT intercept and activation in left VLPFC, left DLPFC, or M1, nor were there differences in the relationship between these outcomes in the two groups.

In summary, the correlations between RT slope and PFC activation (and not motor cortex) were in opposite directions between comparison adolescents and those with ADHD. Even though only one of the within-group correlations reached statistical significance (left

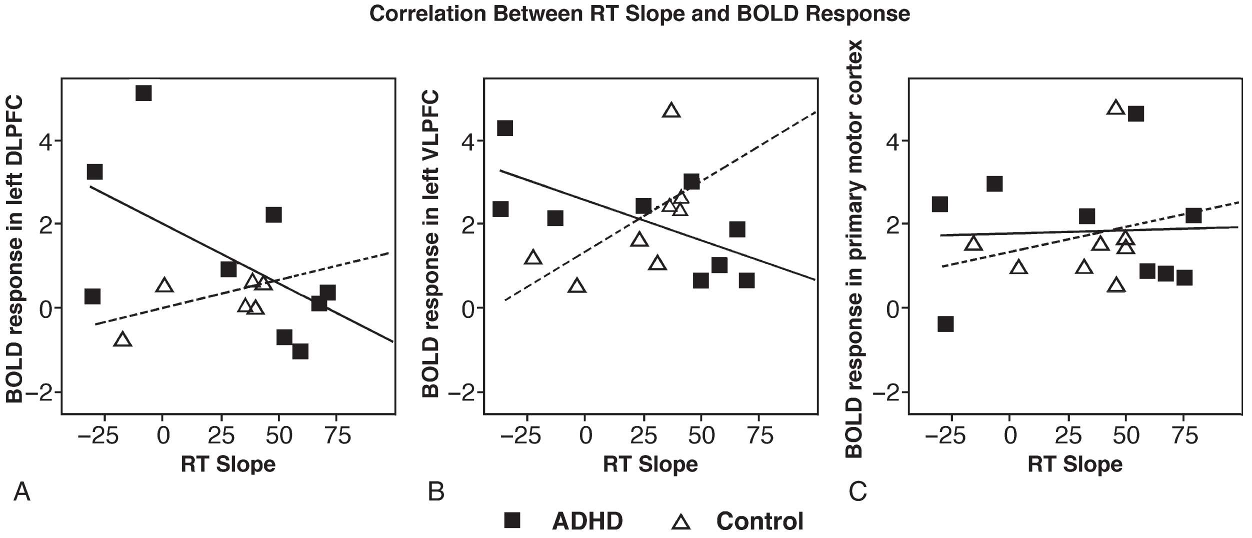


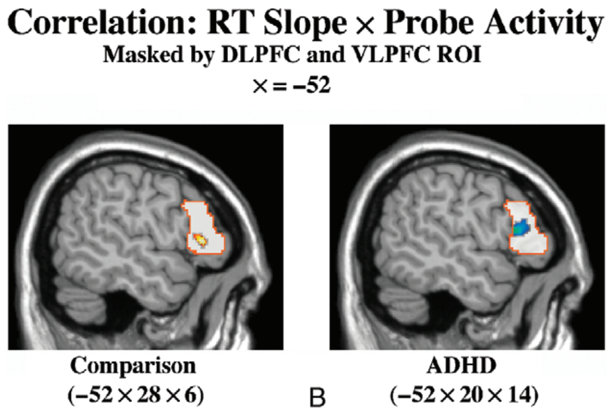
Fig. 3 Correlations in adolescents with and without attention-deficit/hyperactivity disorder (ADHD) between RT slope and left DLPFC (A), left VLPFC (B), and primary motor cortex (C). Solid line shows linear regression for adolescents with ADHD and dashed line shows linear regression for controls. DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex.

VLPFC in ADHD subjects), the RT slope–PFC activation correlations were significantly different between comparison adolescents and those with ADHD for both the VLPFC ($Z_{2,15} = 2.95$; $p = .002$) and DLPFC ($Z_{2,15} = 2.33$; $p = .01$) (Fig. 3). In contrast, there were no significant differences between the correlations in primary motor cortex between comparison adolescents and those with ADHD.

To provide further support for our predictions, RT slope was entered into a correlation matrix with the contrast map of retrieval-related activity for comparison adolescents and those with ADHD. The correlation map was then masked with the left-lateralized PFC ROIs (Fig. 4). This analysis yielded clusters of voxels within VLPFC that were negatively correlated with RT slope for adolescents with ADHD and positively correlated with RT slope for comparison adolescents. No areas within the PFC showed the opposite pattern of correlation for adolescents with or without ADHD.

DISCUSSION

This investigation demonstrated that while performing a delayed match-to-sample task, female adolescents with ADHD and without ADHD show marked differences in the relationship between their RT slope, a measure of memory retrieval rate, and the activation of lateral PFC (but not primary motor cortex). We interpret this finding as a population difference in neural efficiency. Adolescents without ADHD who have a faster retrieval use less PFC, whereas adolescents with ADHD who have a faster retrieval rate use more PFC. The ability of individuals to perform a task more quickly while recruiting less cortex can be thought of as efficient. One other study



A Comparison (−52 × 28 × 6)

B ADHD (−52 × 20 × 14)

Fig. 4 Correlations in comparison adolescents (A) and those with ADHD (B) between RT slope and every voxel in the lateral prefrontal cortex at probe. Only positively correlated voxels were found for comparison adolescents (VLPFC: −52 × 28 × 6; $t = 4.63$; voxels, 72) and only negatively correlated voxels were found for adolescents with ADHD (VLPFC: −52 × 20 × 14; $t = 6.99$; voxels, 125 and DLPFC: −26 × 38 × 16; $t = 3.71$; voxels, 31). DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex.

has reported similar differences in brain–behavior relationships in adolescents with ADHD: While performing a go/no-go task, adolescents with ADHD activated the VLPFC more than adolescents who had never been diagnosed with ADHD (Schulz et al., 2005). Although these authors do not describe this pattern as indicative of differences in neural efficiency, such an interpretation could apply.

In other respects, we found a large degree of similarity between female adolescents with and without ADHD in this study. For instance, there were no group differences in behavioral performance on our task. Such equivalent behavioral performance allowed us to draw conclusions about group differences in neural activity without the confound of between-group behavioral performance differences. When task period–specific activation, collapsed across load, was compared between groups, there were no significant group differences, highlighting the subtlety of the differences in PFC function between these two groups.

We found that both groups were less accurate and slower to respond at high load when compared with low load, but there was no load × group interaction. Load effects in the fMRI data were found only during the encoding period. Both groups activated a greater extent of visual processing areas during the high versus low load trials, reflecting the difference in visual input between these conditions. A between-group comparison found that non-ADHD adolescents also exhibited greater activation in the VLPFC than did the ADHD group during high-load trials. In the face of a high-load working memory task, adolescents with ADHD may not have recruited sufficient resources to properly encode these items.

Clinical Implications

The results of this study further support a theory of ADHD that posits PFC dysfunction as a core deficit, emphasizing the VLPFC and connected regions. Pharmacological and behavioral interventions that target efficiency in neural processing could result in greater gains. Furthermore, recent studies of behavioral interventions aimed at training children with ADHD on tasks of working memory have met with some success (Klingberg et al., 2005). The present investigation supports the import of those findings and allows a possible mechanism by which to test the effects of such interventions.

Limitations

There are several important limitations to this study. Similar to previous imaging studies with this population, we report a small sample size, which was further reduced for certain analyses because of equipment failure, movement artifacts, and outlier status. The small sample size precluded the statistical significance of correlations between prefrontal cortex activation and RT slope, which, although strong, did not uniformly attain statistical significance. Also, some subjects in both groups (ADHD and comparison) had negative RT slopes, indicating that their speed increased as they recalled more items from memory. This finding is not commonly found in adult populations and may reflect slight differences in strategy for adolescents compared with adults across diagnostic status. Because the possible presence of a different search strategy for these participants raises questions about the relevance of an RT slope × brain activity correlation, we conducted these analyses with and without subjects who had a negative RT slope. When RT slope correlations with brain activity were examined without these subjects, ADHD and control correlations were nonsignificantly different for the DLPFC but continued to be significantly different in the VLPFC ($Z_{2,15} = 2.19$; $p < .05$). Finally, our sample was heterogeneous in terms of subtype and comorbid diagnosis, which may have increased our type II error rate.

In conclusion, we have demonstrated that those adolescent females diagnosed with ADHD who showed faster memory retrieval rates revealed greater activation in lateral PFC than their slower counterparts. In contrast, adolescents without ADHD who had faster memory retrieval rates showed less activation in lateral PFC than their slow counterparts. These data suggest that for adolescents with ADHD, speeded memory retrieval is associated with PFC activation in a less efficient manner than it is for control adolescents. This finding replicates, in a new population, extant literature demonstrating a parallel pattern of decreased neural efficiency in aging populations (Rypma and D'Esposito, 2000). It is possible that both findings are due to differences in synaptic connections. Unlike other areas of cortex, the PFC continues to develop from childhood to young adulthood, making it a prime target for dysfunction in developmental disorders. This growth is related to a continued pruning of synaptic connections (Diamond, 2002; Fuster, 2000). Perhaps either disrupted synaptic pruning (ADHD) or degeneration of synaptic connections (aging) results in the recruitment of more pathways to complete the same neural computations.

Group differences in brain–behavior relationships were strongest in the VLPFC. Also, during the encoding period of the task, under conditions of high load, adolescents with ADHD failed to activate the VLPFC compared to age-matched controls. Thus, our findings emphasize the importance of specific subregions of the lateral PFC in the pathophysiology of ADHD (see Aaron et al., 2004 for another discussion). In addition, this is the first investigation to characterize the nature of the difference between prefrontal cortex activation in participants with and without ADHD as a difference in neural efficiency.

We used a small subsample of the girls who participated in the longitudinal studies by Hinshaw et al. (2002, 2007). In the larger investigations it was demonstrated that participants with ADHD have deficits in executive function during both childhood and early adolescence. We extend and develop these findings by using neuroimaging to directly examine PFC activation for this group in a task tapping executive functioning.

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