Reduced Prefrontal Efficiency for Visuospatial Working Memory in Attention-Deficit/Hyperactivity Disorder

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Objective: Visuospatial working memory impairments have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). However, most ADHD research has focused on the neural correlates of nonspatial mnemonic processes. This study examined brain activation and functional connectivity for visuospatial working memory in youth with and without ADHD. **Method:** Twenty-four youth with ADHD and 21 age- and sex-matched healthy controls were scanned with functional magnetic resonance imaging while performing an N-back test of working memory for spatial position. Block-design analyses contrasted activation and functional connectivity separately for high (2-back) and low (1-back) working memory load conditions versus the control condition (0-back). The effect of working memory load was modeled with linear contrasts. **Results:** The 2 groups performed comparably on the task and demonstrated similar patterns of frontoparietal activation, with no differences in linear gains in activation as working memory load increased. However, youth with ADHD showed greater activation in the left dorsolateral prefrontal cortex (DLPFC) and left posterior cingulate cortex (PCC), greater functional connectivity between the left DLPFC and left intraparietal sulcus, and reduced left DLPFC connectivity with left midcingulate cortex and PCC for the high load contrast compared to controls ($p < .01$; $k > 100$ voxels). Reanalysis using a more conservative statistical approach ($p < .001$; $k > 100$ voxels) yielded group differences in PCC activation and DLPFC-midcingulate connectivity. **Conclusion:** Youth with ADHD show decreased efficiency of DLPFC for high-load visuospatial working memory and greater reliance on posterior spatial attention circuits to store and update spatial position than healthy control youth. Findings should be replicated in larger samples. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(9):1020–1030. **Key Words:** ADHD, fMRI, spatial working memory, prefrontal cortex, children

Working memory impairments are considered a primary neurocognitive deficit and candidate endophenotype for attention-deficit/hyperactivity disorder (ADHD).[1,2] A substantial proportion of children with ADHD demonstrate impaired ability to temporarily hold and manipulate information in mind,[2-4] with greater deficits found for visuospatial than auditory-verbal information.[3] Deficits in storage and manipulation of visuospatial information have been linked to the childhood presentation of ADHD[5] and may contribute to the development of later psychopathology[6] and academic difficulties, which in turn are associated with long-term difficulty in quality of life.[7] As such, there is considerable interest in identifying the neuropathophysiology underlying visuospatial working memory impairments in ADHD.

Visuospatial working memory is supported by a core network that includes a central executive in dorsolateral prefrontal cortex (DLPFC) and areas along the intraparietal sulcus (IPS) that control spatial attention.[8,9] The columnar organization and intrinsic connectivity of DLPFC provide the functional architecture to store and update visuospatial information in mind.[10,11] Local intracolumnar connections between pyramidal neurons

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that respond to the same visual location create microcircuits that engage in recurrent excitation to maintain neural representations in the absence of extrinsic cues and/or in the presence of interference.[8,12] Greater DLPFC and IPS activation have been associated with increased working memory load,[13] as well as with improvements in performance,[14] whereas disruption of DLPFC activity has been linked to visuospatial working memory deficits[15] and may underlie the difficulty that children with ADHD have using internal representations to regulate behavior.[16]

Little is known about the neural correlates of visuospatial working memory impairments in ADHD. Research has focused overwhelmingly on nonspatial, object-related processes and has implicated ventral prefrontal cortex in nonspatial working memory deficits in patients with ADHD, but has found little evidence of DLPFC abnormalities.[17-21] These findings may reflect the specialization of dorsal and ventral subdivisions of lateral prefrontal cortex for spatial and nonspatial information, respectively.[8,22] One study linked deficits in working memory for spatial position to prefrontal cortex hyperactivation, but more information on the specific localization of this abnormality is warranted.[23] The lack of data on the contributions of DLPFC to visuospatial working memory impairments is striking, given the fact that DLPFC is a well-established target of most effective medications for ADHD.

This study used functional magnetic resonance imaging (fMRI), together with a well-established and validated N-back task, to compare visuospatial working memory in children with ADHD and healthy control children. The N-back task used nonverbal stimuli to test working memory for spatial position and has previously shown sensitivity for DLPFC abnormalities in pediatric populations.[24] We predicted that children with ADHD would show impaired visuospatial working memory and reduced DLPFC activation compared to controls. Further analyses explored the functional connectivity of regions that differed in activation between children with and without ADHD.

METHOD

Participants

Forty-five children 9 to 15 years of age (mean = 12.78, SD = 1.94) were recruited from an industry-funded treatment study, via e-mail announcements and ads/flyers posted throughout the hospital and on online volunteer sites. All parents/children gave informed consent/assent to participate in the study, and the institutional review board of the medical school approved all study procedures. Children and parents were compensated for participation.

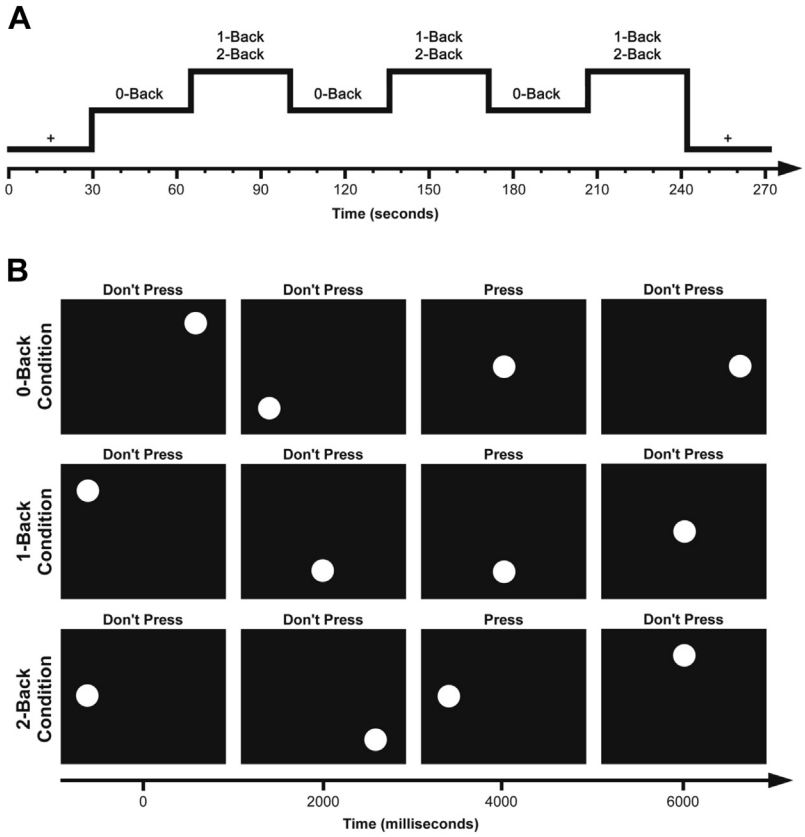
Participants were evaluated using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version (K–SADS–PL),[25] supplemented with ratings on the clinician-administered ADHD Rating Scale-IV (ADHD-RS)[26] and the parent-completed Child Behavior Checklist (CBCL).[27] Participants with ADHD met *DSM-IV* criteria on the K-SADS-PL and scored $\geq$1.5 SD above the mean for age and gender on the ADHD-RS. Healthy control children all scored within 1 SD of the mean for age and gender on the ADHD-RS and reported $\leq$4 current symptoms of ADHD on the K-SADS-PL. Children with an estimated IQ of $<$80, as estimated using the 2-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI),[28] a primary psychiatric diagnosis other than ADHD, or any medical disorder that could affect brain function, were excluded. Nine youth with ADHD had a history of stimulant medication (3 also had tried nonstimulant medications). Two of the 9 youth were on medication (1 stimulant and 1 nonstimulant) when they entered the study and completed the requisite 2-week prestudy washout.

Participants were acclimated to the scan experience using an fMRI simulator and completed a 15-minute N-back training session outside of the scanner, which provided visual and verbal feedback on a trial-by-trial basis. Once comfortable with the task, participants were accompanied to the MRI scanner.

Visuospatial Working Memory Task

We adapted the N-back task from Chang *et al.*[24] to test working memory for spatial position in the MRI scanner. The task consisted of 4 runs; each lasted approximately 4.5 minutes and included 30-second fixation periods at the beginning and end of each run (Figure 1). Each run contained 6 blocks that alternated between control (0-back) and experimental (1-back or 2-back) conditions; there were two 0-back/1-back runs and two 0-back/2-back runs. The 1-back and 2-back conditions were presented in different runs to minimize confusion. Run order (i.e., 0-back/1-back and 0-back/2-back) was counterbalanced across participants. Each block had 16 trials and began with the instructions displayed for 4 seconds. All trials included the stimulus (a circle) presented for 500 milliseconds in 1 of 9 positions in a 3 $\times$ 3 matrix, followed by a blank screen for 1,500 milliseconds (Figure 1B). For the control (0-back) condition, participants had to press a button if the circle was in the center position of the 3 $\times$ 3 matrix. For the experimental conditions, participants had to press the button if the circle was in the same position as the

FIGURE 1 Schematic representation of the visuospatial N-back task. Note: (A) Each of 4 runs contained 6 blocks that alternated between control (0-back) and experimental (1-back or 2-back) conditions, and included 30-second fixation periods at the beginning and end. Each block had 16 trials and began with the instructions displayed for 4 seconds. (B) Examples of stimuli for 4 trials in the experimental and control conditions.



previous trial (1-back) or 2 trials previous (2-back). The total task duration was 18 minutes.

Image Acquisition and Preprocessing

Scans were performed on a Siemens Alegra 3.0 Tesla (Siemens, Erlangen, Germany) head-dedicated MRI scanner. A high-resolution, T2-weighted anatomical volume of the whole brain was acquired in the axial plane with a turbo spin-echo pulse sequence (repetition time [TR] = 4,050 ms, echo time [TE] = 99 ms, flip angle = 170°, field of view [FOV] = 240 mm, matrix = 512 × 336, 40 slices, slice thickness = 4 mm, in-plane resolution = 0.41 mm^2). Four series of 110 functional T2*-weighted images were acquired at the same 40 slice locations with gradient-echo echo-planar imaging sensitive to the blood oxygenation level–dependent (BOLD) signal (TR = 2,500 ms, TE = 27 ms, flip angle = 82°, matrix = 64 × 64, slice thickness = 4 mm, no gap = 4 mm, in-plane resolution = 3.75 mm^2). All images were acquired with slices positioned parallel to the anterior commissure–posterior commissure plane.

Functional images were preprocessed with SPM8 software (Wellcome Trust Center for Neuroimaging, London, England). The functional images for each participant were separately corrected for the staggered acquisition of slices and realigned to the first image in the time series to correct for head movements. Functional series with more than 1 voxel (4 mm) of motion were discarded. The groups did not differ in translational movement, rotational displacement, or number of functional series included in the analysis ($p > .05$). Functional time series were co-registered to their respective T2-weighted anatomical images, normalized to a standard template (Montreal Neurological Institute [MNI]), using normalization parameters estimated from the high-resolution T2-weighted image, and resampled with a 2-mm^3 voxel size. The resultant images were smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel.

Statistical Analysis

Behavioral Data Analysis. Percent correct, reaction time (RT), reaction time variability (RTSD) for correct responses, and percent false alarms for each load (0-back, 1-back, 2-back) served as the primary behavioral measures. Signal detection variables d-prime (d′) and criterion (c) were calculated to provide pooled measures of discriminability and response bias, respectively.[29] Higher

TABLE 1 Sample Characteristics

	Controls (n = 21)		ADHD (n=24)		*p*-Value
Age, y, mean, SD	12.44	(1.95)	13.07	(1.93)	.28
Range, y	9.52	15.40	9.02	15.70	
Male, n, (%)	16	(76.19)	21	(87.5)	.44
Right-handed, n (%)	19	(90.48)	22[a]	(95.65)	.50
Full-Scale IQ, mean (SD)	111.14	(15.11)	110.00	(15.96)	.81
Race/ethnicity, n (%)					.44
African American	7	(33.33)	6	(25.00)	
White	7	(33.33)	6	(25.00)	
Hispanic	6	(28.57)	7	(29.17)	
Other	1	(4.77)	5	(20.83)	
CBCL attention T score, mean (SD)	50.71	(1.82)	65.33	(9.07)	<.001
ADHD-RS-IV total score, mean (SD)	3.14	(3.84)	30.13	(8.99)	<.001
ADHD Subtype, n (%)					
Combined			8	(33.33)	
Inattentive			16	(66.66)	
Comorbid disorders, n (%)					
Oppositional defiant disorder	0	(0)	2	(8.33)	.18
Conduct disorder	0	(0)	1	(4.17)	.34
Anxiety disorder	0	(0)	4	(16.67)	.05

Note: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale—IV; CBCL = Child Behavior Checklist.
[a]*Data unavailable for 1 participant.*

d′ values indicate greater discriminability, whereas negative c values indicate a bias to respond.[30] Differences in working memory performance were tested using mixed analyses of variance (ANOVAs), with load (0-back, 1-back, 2-back) as the within-subjects factor and group (ADHD versus Control) as the between-subjects factor. The 2-tailed p value for significance was .05.

Standard Convolution Model for BOLD Analysis. Functional images from each participant were analyzed individually by modeling the 3 load conditions as delayed boxcar functions convoluted with the hemodynamic response function (individual threshold, $p < .001$) in the context of a general linear model. Six motion correction parameters generated during realignment and a regressor for the condition instructions were entered as covariates of no interest.[31] The neural effects of visuospatial working memory were tested by applying planned linear contrasts to the parameter estimates for the alternating control and experimental conditions within each run, resulting in separate 1-back minus 0-back (low load) and 2-back minus 0-back (high load) contrast maps for each participant. In addition, a linear contrast was applied to the parameter estimates for the 0-back, 1-back, and 2-back conditions across runs as an approximation of an omnibus test and to identify activation related to the parametric increase in working memory load, yielding a third contrast map for all participants. This analysis was informed by the behavioral results and was therefore considered secondary.

The individual contrast images for all participants were entered into second-level group analyses conducted with random-effects models. One-sample t tests were performed to define activation related to visuospatial working memory and the parametric increase in processing demands in each group. Group differences in activation related to working memory and the parametric increase in processing demands were examined with 2-sample t tests. The resultant voxelwise statistical maps were thresholded for significance using a cluster-size algorithm that protects against false-positive results in spatially continuous data.[32] Statistical significance was set at a height (intensity) threshold of $p < .01$ and an extent (cluster) threshold of $k > 100$ voxels. This threshold combination offers a desirable balance between type I and type II errors for fMRI studies of complex cognitive processes.[33] On the recommendation of the reviewers, additional secondary analyses were performed using a more restrictive statistical significance threshold of $p < .001$ with an extent (cluster) threshold of $k > 100$ voxels. A mask was created of significant group differences in working memory–related activation in DLPFC from the 2-back minus 0-back 2-sample t test.

Psychophysiological Interaction Analysis. Psychophysiological Interaction (PPI) analyses were conducted to further define group differences in working memory–related function in left DLPFC. PPI tests for variations in physiological connectivity between brain regions as a function of changes in the psychological context.[34,35] The method computes whole-brain connectivity between the time series of the seed region of interest (ROI) and the time series of all other voxels. The seed ROI was defined

TABLE 2 Behavioral Performance

	Controls n = 21		ADHD n = 24				
	Mean	(SD)	Mean	(SD)	Group	Statistics Load	Group × Load
Reaction Time (ms)							
0-Back	542.65	(129.56)	497.07	(96.34)	$F_{1, 43} = .04$	$F_{2,86} = 16.99$	$F_{2,86} = 1.31$
1-Back	583.01	(161.34)	556.05	(129.51)	$p = .55$	$p < .001$	$p = .28$
2-Back	602.22	(173.93)	602.40	(164.95)	$\eta^2_p = .001$	$\eta^2_p = 0.28$	$\eta^2_p = .03$
Reaction Time SD (ms)							
0-Back	165.17	(68.29)	179.01	(53.56)	$F_{1, 43} = 3.03$	$F_{2,86} = 20.14$	$F_{2,86} = .30$
1-Back	191.80	(66.60)	222.78	(73.74)	$p = .09$	$p < .001$	$p = .55$
2-Back	230.72	(99.28)	271.61	(72.05)	$\eta^2_p = .07$	$\eta^2_p = 0.32$	$\eta^2_p = .01$
Percent Correct							
0-Back	93.54	(8.11)	94.88	(4.75)	$F_{1, 43} = .04$	$F_{2,86} = 37.07$	$F_{2,86} = 0.30$
1-Back	86.55	(11.80)	84.63	(19.45)	$p = .84$	$p < .001$	$p = .74$
2-Back	74.65	(16.99)	72.92	(22.61)	$\eta^2_p = .001$	$\eta^2_p = 0.46$	$\eta^2_p = .01$
Percent False Alarms							
0-Back	1.66	(2.13)	2.79	(3.18)	$F_{1,43} = 3.88$	$F_{2,86} = 19.22$	$F_{2,86} = 2.99$
1-Back	3.22	(2.00)	8.23	(9.24)	$p = .06$	$p < .001$	$p = .06$
2-Back	6.59	(6.02)	8.29	(6.15)	$\eta^2_p = .08$	$\eta^2_p = 1.00$	$\eta^2_p = 0.55$

Note: ADHD = attention-deficit/hyperactivity disorder.

by the mask created of the group differences in left DLPFC activation for the 2-back minus 0-back contrast (MNI: x = −42, y = 28, z = 40). The time series of the first eigenvariate of the BOLD signal, adjusted for the effects of 0-back, 1-back, and 2-back conditions, were separately extracted from the ROI in the left DLPFC. The volume of the left DLPFC ROI was 2,472 mm^3.

The time-series data of the first eigenvariate of the seed ROI were temporally filtered and mean corrected as in conventional SPM analysis. Bayesian estimation was used to deconvolve the time series of the BOLD signal to generate the time series of the neuronal signal for the ROI. Separate time series of the neuronal signals were then created for the 0-back/1-back and 0-back/2-back runs, generating 2 sets of regressors for the following: the psychological variables (P-regressors), representing the main effects of the 1-back minus 0-back or 2-back minus 0-back contrasts; the physiological variable (Y-regressor), denoting the baseline time courses for the DLPFC ROI (Y-regressors); and the PPI regressors, representing interactions between the psychological and physiological variables. These regressors were forward-convolved with the hemodynamic response function and then entered into a regression model along with effects of no interest, including the 6 motion correction parameters. The specific effects of the 1-back minus 0-back and 2-back minus 0-back contrasts on functional connectivity were tested by applying the appropriate linear contrasts to the parameter estimates for the PPI regressors. The individual contrast images for all participants were then entered into second-level group analyses conducted with random-effects statistical models, as described above.

RESULTS

Participants

Demographic and clinical data are shown in Table 1. There were no group differences in age, sex, handedness, race/ethnicity, or Full-Scale IQ (all $p > .20$).

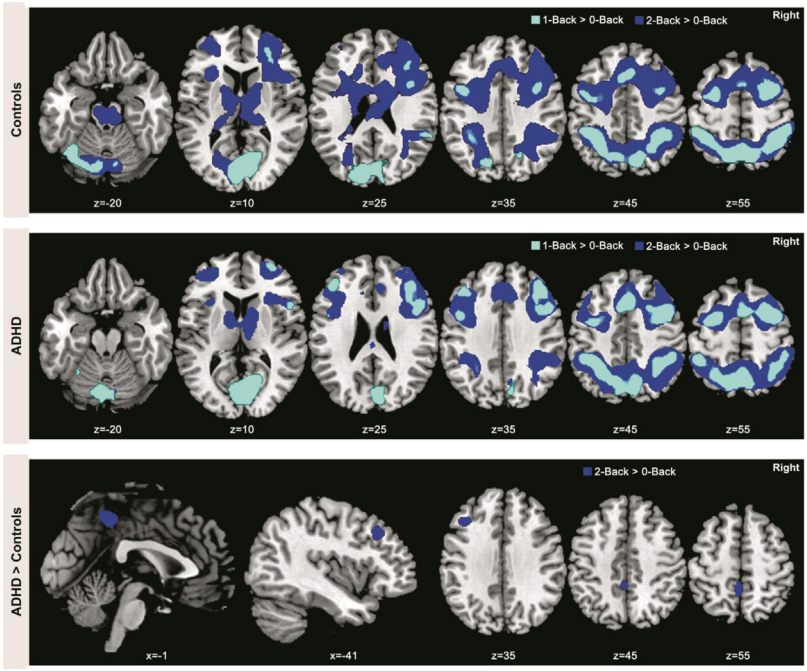
Behavioral Data

As shown in Table 2, there were significant main effects of load for several behavioral measures, but there were no significant main effects of group or group × load interactions.

Working Memory–Related Activation

Children with ADHD and controls had similar patterns of activation for both working memory conditions compared to the control condition in a distributed frontoparietal network that extended to the cerebellum (Figure 2). However, this activation was more extensive for the high load (2-back minus 0-back) than the low load contrast (1-back minus 0-back; Tables S1 and S2, available online). Both groups had robust bilateral frontal activation, centered in a supplementary motor area and ventrolateral prefrontal cortex for the low working memory load contrast, but extended to the anterior insula cortex, inferior frontal gyrus, and more widely in the ventrolateral prefrontal cortex for the high load contrast. Furthermore, children with ADHD activated

FIGURE 2 Neural activation for low (1-back minus 0-back) and high (2-back minus 0-back) working memory load contrasts in typically developing controls (top row) and youth with attention-deficit/hyperactivity disorder (ADHD; middle row). Note: Youth with ADHD showed greater activation in left dorsolateral prefrontal cortex and left posterior cingulate cortex for the high working memory load contrast than controls (bottom row). Figures thresholded at $p < .01$ (cluster corrected for multiple comparisons > 100 contiguous voxels).



bilateral DLPFC for both working memory contrasts, whereas controls activated only the right DLPFC for the high load contrast. Both groups also showed overlapping bilateral activation centered in the left IPS for the low load contrast, which was more prominent in the right IPS for controls and in the right precuneus for children with ADHD for the high load contrast. Significant activation was also seen in the cerebellum for both working memory contrasts and in thalamus for the high load contrast.

Direct comparison of the 2 groups yielded no significant differences in activation for the low load contrast. However, children with ADHD had significantly greater activation than controls for the high load contrast in left DLPFC and left posterior cingulate cortex (PCC) (Figure 2, bottom row). There were no regions of significantly greater activation for controls than for children with ADHD.

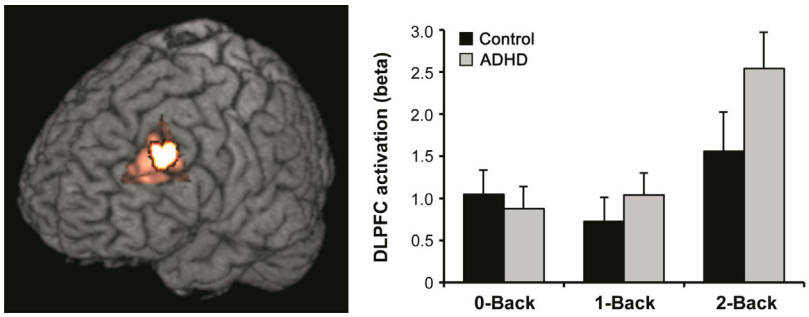
Parametric Effect of Working Memory Load on Activation

Secondary analyses revealed increases in frontoparietal activation across the 3 working memory load conditions (Table S3 and Figure S1, available online). Frontoparietal activation increased linearly as load increased and task accuracy decreased. However, as illustrated for left DLPFC in Figure 3, the increase in task-related activation was most prominent for the 2-back condition; the difference between 0-back and 1-back was limited in comparison. Direct comparison of children with ADHD and controls found no significant differences in linear trends across load conditions.

Working Memory-Related Functional Connectivity

PPI analyses revealed distinct patterns of left DLPFC connectivity for children with and without ADHD that were more extensive for the high load than the low load contrast (Tables S4 and S5, available online). Youth with ADHD had significantly greater left DLPFC connectivity with bilateral posterior insula and right temporal cortex for the low load contrast and with left IPS and cerebellum for the high load contrast compared to controls (Figure 4, top row). In contrast, controls showed significantly greater left DLPFC connectivity with left PCC for the low load contrast and with both left midcingulate cortex and PCC for the high load contrast (Figure 4, bottom row).

FIGURE 3 Surface view of enhanced left dorsolateral prefrontal cortex (DLPFC) activation for the high working memory load contrast in youth with attention-deficit/hyperactivity disorder (ADHD) compared to controls. Note: Left DLPFC activation (in β values) increased linearly with working memory load, most prominently in the 2-back condition.



Secondary analyses using a threshold of $p < .001$ and a cluster extent of $k > 100$ voxels found that the frontoparietal activation for the low load contrast was restricted to the supplementary motor area and IPS in controls, but extended beyond these areas to the DLPFC, lingual gyrus, and cerebellum in youth with ADHD (Table S1, available online). The patterns of frontoparietal activation for the high load contrast and across the 3 working memory load conditions were essentially unchanged for the 2 groups at the higher threshold (Tables S2 and S3, available online). However, only the group differences in left PCC activation and the connectivity of the left DLPFC with the midcingulate cortex, both for the high load contrast, were significant at this more conservative threshold (Tables S4 and S5, available online).

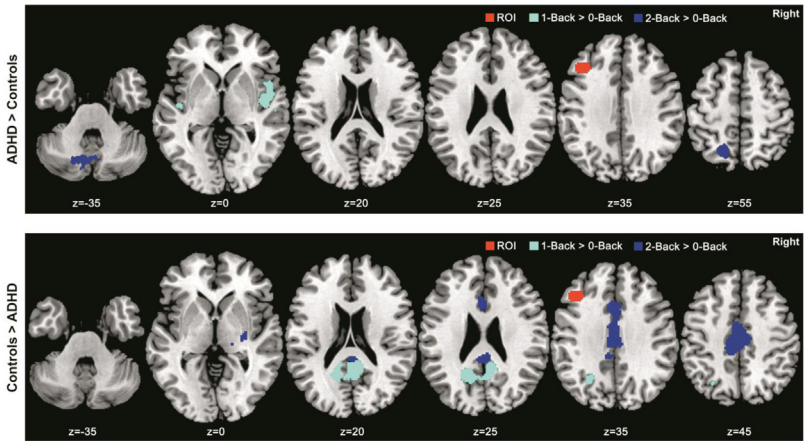
DISCUSSION

These findings provide evidence of functional anomalies in DLPFC associated with visuospatial working memory in youth with ADHD. Youth with ADHD performed comparably to controls on a visuospatial N-back task and demonstrated similar patterns of frontoparietal activation, indicating that the 2 groups used similar mechanisms to store and update spatial positions of visual targets. Increases in working memory load yielded linear decreases in accuracy and response speed in both groups, and were associated with equivalent linear gains in frontoparietal activation. Nonetheless, youth with ADHD activated bilateral DLPFC for both load contrasts and showed greater left DLPFC activation for the high load contrast than controls, who activated only the right DLPFC in the high load contrast. Enhanced left DLPFC activation in youth with ADHD might have been partially driven by differences in functional connectivity of this prefrontal region, providing clues about the nature of DLPFC abnormalities for visuospatial working memory in youth with ADHD.

The enhanced left DLPFC activation in youth with ADHD, in the context of N-back performance comparable to that in controls, suggests reduced efficiency of this prefrontal region for visuospatial working memory. Greater DLPFC activation is associated with better working memory performance[13] and larger memory capacity,[36] with practice reducing activation but not necessarily improving performance.[37] Our findings may thus indicate that youth with ADHD required greater mental effort to achieve performance levels similar to controls in the highest working memory load condition. The localization of the group difference in DLPFC activation to the left hemisphere likely reflects the bilateral activation of this region for both load contrasts in youth with ADHD; controls used only the right DLPFC, commonly associated with visuospatial processing, to address the increased working memory demands in the high load contrast. Also possible but less likely, given the relatively short task blocks, is that the difference in left DLPFC activation reflects practice-related reductions in activation in controls that were not present in youth with ADHD. Both scenarios suggest that youth with ADHD exert greater mental effort to regulate behavior using internal representations than typically developing youth.[38,39]

Differences in functional connectivity of left DLPFC suggest that youth with and without ADHD engaged distinct neural mechanisms to store and update spatial positions of visual

FIGURE 4 Significantly greater functional connectivity of left dorsolateral prefrontal cortex for low (1-back minus 0-back) and high (2-back minus 0-back) load contrasts in youth with attention-deficit/hyperactivity disorder (ADHD) compared to controls (top row) and in controls compared to youth with ADHD (bottom row). Note: Figures thresholded at $p < .01$ (cluster corrected for multiple comparisons > 100 contiguous voxels). ROI = region of interest.



targets. The incremental transition in functional connectivity of left DLPFC from interactions with left PCC for the low load condition to left midcingulate cortex for the high load condition suggests that control youth engaged executive processes and enhanced effortful control to address the increased processing demands.[40,41] Youth with ADHD instead showed a pattern of enhanced DLPFC interaction with ipsilateral IPS in the high load condition, indicating greater reliance on core visuospatial processes to resolve the increased mnemonic demands. The area surrounding IPS regulates the spatial focus of attention[42] and mediates shifts in spatial attention to temporarily maintain positional information in mind,[43] but the contribution of these attentional resources to visuospatial working memory are limited when mnemonic demands are highest,[13] especially in children.[44] Reliance on inefficient parietal attention mechanisms and the failure to integrate the function of lateral and midline executive regions when processing demands are highest may have driven left DLPFC to compensate in youth with ADHD.

Similar effects of load on frontoparietal activation in both groups raise the possibility that the group difference in left DLPFC activation reflects processes specific to the high load condition. Load-sensitive activation that represents processes specific to working memory (e.g., manipulation of stimuli in mind) and load-insensitive activation that reflects supporting functions (e.g., attention regulation) have both been found in DLPFC.[45] The absence of group differences in the effect of load on performance and activation suggests that the enhanced left DLPFC response found in youth with ADHD reflects processes engaged specifically to manage the increased processing demands in the high load condition, rather than processes specific to visuospatial working memory. However, it is also possible that the short blocks used in our task may not have been sufficiently challenging to reveal activation decrements in the low load condition.

The unexpected findings of enhanced PCC activation and reduced DLPFC connectivity with PCC in youth with ADHD suggest that the inefficiencies in visuospatial processing extend beyond the core frontoparietal network for working memory. The PCC contains neurons that encode visuospatial events in allocentric space,[46] is robustly activated for top-down shifts in spatial attention,[47] and may serve to coordinate egocentrically and allocentrically directed attention.[48] The current finding of enhanced PCC activation in the high load condition in youth with ADHD is thus consistent with the notion that these youth need to exert greater mental effort to achieve performance similar to that of controls. However, the functional interaction between the DLPFC and PCC that controls demonstrated in both load conditions has been linked to the selection of salient items in working memory,[49] and may reflect adaptive changes that optimize future behavior.[50]

These findings further implicate the interaction of attention and working memory in the difficulties that youth with ADHD have regulating behavior using internal representations.

The possibility that the frontoparietal network specialized for visuospatial working memory is inefficient rather than deficient in capacity in ADHD has implications for the treatment of ADHD. The need to exert greater neural/mental effort to achieve normal levels of performance may render working memory in youth with ADHD particularly susceptible to motivational influences, arousal level, and affect.[51] Thus, manipulation of these factors may improve working memory.[52] Furthermore, since youth with ADHD relied on capacity-limited spatial attention processes and failed to recruit executive processes when mnemonic demands were high, our research suggests that neuropsychological interventions for ADHD that target working memory should focus on developing more efficient executive strategies to store and update spatial information, rather than on increasing memory capacity itself.[53]

This study has some limitations. First, the 7-year age range of our sample was large, and although balanced between groups, it may have confounded the results with the development of visuospatial working memory. Second, the ADHD sample comprised mainly the predominantly inattentive subtype, which may limit generalization of our findings to youth with combined-type subtype. Third, the sample size, although comparable to most task-based fMRI studies in the literature, may not have provided sufficient power to detect small or even medium-sized differences in activation and behavior. Fourth, the current set of findings exemplify the conundrum of choosing a statistical threshold that balances type I and type II error for random-effects analyses of fMRI data. For example, the finding of greater activation in left DLPFC for youth with ADHD than controls at the relatively more liberal threshold of $p < .01$ may represent a false-positive (type I error), whereas the absence of this difference in DLPFC activation at the more rigorous threshold of $p < .001$ may reflect a false-negative (type II error). Our findings must therefore be considered preliminary until replicated in larger samples. Finally, the design of the N-back task without a manipulation to differentially activate the right and left hemispheres precluded us from testing possible laterality effects.

Overall, our results provide evidence of functional anomalies in the DLPFC associated with visuospatial working memory in youth with ADHD. Their enhanced left DLPFC activation, despite performance comparable to typically developing controls, points to inefficiency in updating of spatial information, requiring greater mental effort to maintain performance. This may be partially driven by a reliance on capacity-limited posterior spatial attention circuits when task demands are high. &

CG Clinical Guidance

- Working memory is an important neuropsychological process to evaluate in youth with ADHD.
- Deficits in working memory may describe only a subpopulation of youth with ADHD.
- Research such as this, which evaluates aspects of working memory or other neuropsychological tasks among youth with ADHD, may help to identify refined phenotypes (i.e., more homogeneous subgroups), which might theoretically provide an avenue for developing a more individualized understanding of psychopathology or treatment response.

Accepted June 16, 2014.

This article was reviewed under and accepted by deputy editor Ellen Leibenluft, MD.

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Research was supported by the Klingenstein Third Generation Foundation (A.C.B.), the Canadian Institutes of Health Research (A.C.B.), and a Mount Sinai Robin Chemers Neustein Postdoctoral Fellowship Award (A.C.B.).

The authors thank Hanna Oltarzewska, BS, Cara Rabin, BA, and Joanne Philips, MS, of the Icahn School of Medicine for their invaluable support in data acquisition.

Disclosure: Dr. Newcorn is a recipient of research grants from Shire and is or has been an advisor/consultant for Alcobra, Biobehavioral Diagnostics, Enzymotec, GencoSciences, Neos, Shire, and Sunovian. Drs. Bédard, Clerkin, Krone, Fan, Halperin, and Schulz report no biomedical financial interests or potential conflicts of interest.

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http://dx.doi.org/10.1016/j.jaac.2014.05.011

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FIGURE S1 Parametric analyses of the effect of working memory load on neural activation in youth with attention-deficit/hyperactivity disorder (ADHD) compared to typically developing controls. Note: Neural activation (in β values) in the left intraparietal sulcus (IPS) area, left posterior cingulate cortex, left supplementary area, and left inferior frontal gyrus increased linearly as working memory load increased. Error bars = standard deviation.

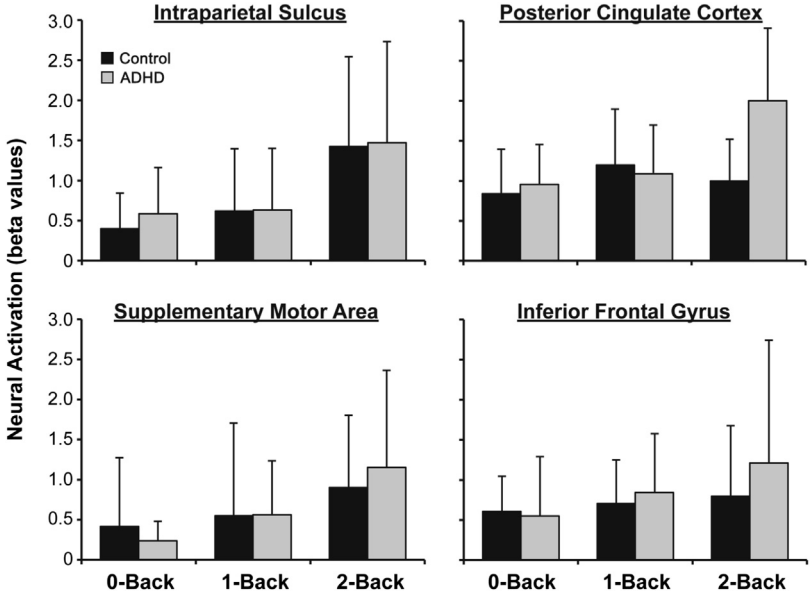

TABLE S1 Regions of Significantly Greater Activation During 1-Back Compared to 0-Back

Region	Hemi	BA	Cluster (Voxels)	MNI Coordinates			*t*
				X	Y	Z	
Controls:							
Intraparietal sulcus[a]	Left	7	9,271	−26	−54	48	6.86
Supplementary motor area[a]	Right	6	1,059	26	2	60	4.81
Supplementary motor area	Left	6	775	−26	−2	52	4.50
Presupplementary motor area	Right	8	301	2	18	46	3.83
Temporoparietal cortical junction	Right	22	111	58	−44	20	3.76
Ventrolateral prefrontal cortex	Right	46	254	28	44	8	3.70
Participants With ADHD:							
Lingual gyrus[a]	Right	18	6,898	14	−66	0	7.70
Supplementary motor area[a]	Left	6	773	−24	0	66	6.04
Supplementary motor area/dorsolateral prefrontal cortex[a]	Right	6/46	3,285	24	10	60	5.88
Cerebellum[a]	Left	—	279	−28	−58	−28	4.48
Intraparietal sulcus[a]	Right	7	918	34	−48	46	4.39
Ventrolateral prefrontal cortex	Right	10	165	32	58	14	4.33
Dorsolateral prefrontal cortex	Left	46	294	−42	36	26	4.20
Premotor cortex	Left	6	152	−44	4	34	3.31

Note: Data are presented at $p < .01$*, with the extent threshold fixed at* $k > 100$ *voxels. ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann area; Hemi = hemisphere; MNI = Montreal Neurological Institute.*

[a]*Significant at* $p < .001$*, with the extent threshold fixed at* $k > 100$ *voxels.*

TABLE S2 Regions of Significantly Greater Activation During 2-Back Compared to 0-Back

Region	Hemi	BA	Cluster (Voxels)	MNI Coordinates			*t*
				X	Y	Z	
Controls:							
Intraparietal sulcus[a]	Right	7	6,905	32	−52	52	12.68
Supplementary motor area/anterior insula/inferior frontal gyrus/dorsolateral prefrontal cortex[a]	Left	6/—/45/46	13,696	−8	14	50	9.58
Cerebellum[a]	Left	—	1,979	−28	−60	−28	7.43
Ventrolateral prefrontal cortex[a]	Left	10	249	−32	50	18	6.96
Cerebellum[a]	Right	—	384	34	−58	−34	5.66
Anterior insula[a]	Left	—	413	−30	24	10	5.65
Primary visual cortex[a]	Left	17	205	−16	−74	10	4.22
Participants With ADHD:							
Precuneus[a]	Right	7	7,285	8	−60	50	8.82
Thalamus[a]	Right	—	717	8	−6	10	7.47
Anterior insula/dorsolateral prefrontal cortex/inferior frontal gyrus[a]	Right	—/46/45	7,579	32	24	−2	7.47
Ventrolateral prefrontal cortex/dorsolateral prefrontal cortex[a]	Left	10/46	367	−32	52	8	6.63
Ventrolateral prefrontal cortex[a]	Right	10	264	30	56	8	5.97
Thalamus[a]	Left	—	187	−12	0	6	5.74
Anterior insula[a]	Left	—	236	−30	20	0	5.60
Participants With ADHD > Controls:							
Dorsolateral prefrontal cortex	Left	46	160	−42	28	40	3.52
Posterior cingulate cortex[a]	Left	23	192	−2	−40	52	3.52

Note: Data are presented at p < .01, with the extent threshold fixed at k > 100 voxels. ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann area; Hemi = hemisphere; MNI = Montreal Neurological Institute.

[a]*Significant at p < .001, with the extent threshold fixed at k > 100 voxels.*

TABLE S3 Regions With Significant Linear Trends in Activation Across the 0-Back, 1-Back, and 2-Back Conditions

Region	Hemi	BA	Cluster (Voxels)	MNI Coordinates			*t*
				X	Y	Z	
Controls:							
Intraparietal sulcus/precuneus	Right	7	4,909	32	−52	52	9.59
Anterior cingulate cortex/supplementary motor area/dorsolateral prefrontal cortex	Left	32/6/46	6,668	−4	20	48	7.90
Supplementary motor area	Left	6	800	−24	4	58	7.32
Cerebellum	Left	—	317	−32	−42	−36	7.29
Inferior frontal gyrus	Left	44	227	−44	8	38	6.03
Anterior insula cortex	Left	—	360	−32	18	12	5.42
Cerebellum	Right	—	102	40	−46	−36	5.35
Participants With ADHD:							
Intraparietal sulcus	Right	7	1,622	30	−56	66	8.96
Inferior frontal gyrus/dorsolateral prefrontal cortex	Left	44/46	979	−44	16	32	7.63
Cerebellum	Left	—	510	−28	−60	−30	7.52
Caudate nucleus	Left	—	209	−14	2	16	6.77
Caudate nucleus	Right	—	184	14	0	16	6.69
Supplementary motor area	Left	6	650	−24	0	58	6.26
Pre-supplementary motor area	Right	8	536	2	30	44	6.21
Precuneus/intraparietal sulcus	Right	7	1,858	6	−60	50	6.15
Dorsolateral prefrontal cortex	Right	46	256	42	34	36	5.95
Ventrolateral prefrontal cortex	Left	10	129	−42	50	14	5.18
Ventrolateral prefrontal cortex	Right	10	108	32	60	12	5.13

Note: Data are presented at $p < .01$*, with the extent threshold fixed at* $k > 100$ *voxels. All clusters of activation are significant at* $p < .001$ *and an extent threshold of* $k > 100$ *voxels. ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann area; Hemi = hemisphere; MNI = Montreal Neurological Institute.*

TABLE S4 Regions of Significantly Greater Functional Connectivity With Left Dorsolateral Prefrontal Cortex During 1-Back Compared to 0-Back

Region	Hemi	BA	Cluster (Voxels)	MNI Coordinates			*t*
				X	Y	Z	
Controls:							
Cuneus	Left	18	875	−6	−86	38	3.80
Participants With ADHD:							
Intraparietal sulcus	Right	7	703	24	−74	50	4.71
Dorsolateral prefrontal cortex	Left	9	423	−52	16	34	4.6
Dorsolateral prefrontal cortex	Right	46	324	42	28	30	4.16
Insula	Right	—	232	32	20	2	4.16
Cuneus	Left	19	124	−4	−80	32	3.45
Cerebellum	Right	—	102	40	−46	−36	5.35
Participants With ADHD > Controls:							
Middle temporal gyrus	Right	21	103	58	22	−6	3.66
Superior temporal gyrus	Right	22	127	60	−48	8	3.56
Insula	Left	—	119	−42	−16	4	3.23
Controls > Participants With ADHD:							
Posterior cingulate cortex	Left	23	587	−18	−54	24	3.61

Note: Data are presented at p < .01, with the extent threshold fixed at k > 100 voxels. No activation was significant at p < .001, with the extent threshold fixed at k > 100 voxels. ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann area; Hemi = hemisphere; MNI = Montreal Neurological Institute.

TABLE S5 Regions of Significantly Greater Functional Connectivity With Left Dorsolateral Prefrontal Cortex During 2-Back Compared to 0-Back

Region	Hemi	BA	Cluster (Voxels)	MNI Coordinates			*t*
				X	Y	Z	
Controls:							
Anterior cingulate cortex	Left	32	123	−22	34	26	4.22
Caudate nucleus	Left	—	503	−6	22	6	4.18
Inferior frontal gyrus	Left	44	120	−30	10	24	4.16
Cuneus/precuneus	Right	7	184	12	−74	24	4.13
Caudate nucleus (tail)	Right	—	285	10	−2	18	4.09
Middle occipital gyrus	Left	19	245	−28	−76	16	3.82
Caudate nucleus (tail)	Left	—	145	−14	−8	18	3.41
Participants With ADHD:							
Inferior frontal gyrus	Right	45	566	50	20	18	5.32
Inferior frontal gyrus	Left	46	897	−26	42	16	5.01
Cerebellum	Left	—	318	−26	−74	−46	4.45
Anterior insula	Right	47	149	36	24	−4	3.86
Inferior parietal lobule	Right	40	293	38	−40	52	3.65
Intraparietal sulcus	Left	7	172	−18	−54	66	3.26
Participants With ADHD > Controls:							
Intraparietal sulcus	Left	7	297	−14	−62	60	3.86
Cerebellum	Left	—	258	−20	−72	−44	3.48
Controls > Participants With ADHD:							
Midcingulate cortex[a]	Bilateral	24	1,031	0	−18	40	4.39
Hippocampus	Right	—	198	22	−24	−6	3.38
Posterior cingulate cortex	Right	23	141	4	−40	24	3.14

Note: Data are presented at $p < .01$*, with the extent threshold fixed at* $k > 100$ *voxels. ADHD = attention-deficit/hyperactivity disorder; BA = Brodmann area; Hemi = hemisphere; MNI = Montreal Neurological Institute.*

[a]*Significant at* $p < .001$*, with the extent threshold fixed at* $k > 100$ *voxels.*