

Atypical Pulvinar–Cortical Pathways During Sustained Attention Performance in Children With Attention-Deficit/Hyperactivity Disorder

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Objective: The neurobiological basis of inattentiveness, a core feature of attention-deficit/hyperactivity disorder (ADHD), is not yet well understood. Structural abnormalities in thalamus, especially the pulvinar nuclei, have recently been reported in ADHD. Pulvinar nuclei maintain reciprocal connections with cortical/subcortical areas, and play a central coordinating role during visual attention processing. The objective of this study was to test the hypothesis that children and young adolescents with ADHD would show atypical pulvinar–cortical functional pathways during sustained attention performance, and that these functional abnormalities would be associated with the inattentive symptoms of the disorder.

Method: Visual attention task-based functional magnetic resonance imaging (fMRI) data from 22 children and young adolescents with ADHD and 22 demographically matched, normal control subjects were analyzed. Cortical activation maps and temporal correlations of activity patterns between pulvinar nuclei and the remainder of brain were constructed for each participant. Correlations between activation magnitude of pulvinar and diagnostic measures were calculated in subjects with ADHD. **Results:** Compared to controls, subjects with ADHD showed significantly reduced pulvinar activations bilaterally, significantly decreased functional connectivity between bilateral pulvinar and right prefrontal regions, and significantly increased connectivity between the right pulvinar and bilateral occipital regions. In addition, the activation magnitude in the left pulvinar was negatively correlated with the *DSM-IV* inattentive index in ADHD group. **Conclusions:** Allied with previous evidence of structural abnormalities in pulvinar, the current data suggest that inappropriate development of pulvinar may lead to disrupted functional circuits for visual attention processing, and that these disruptions contribute significantly to the pathophysiological mechanisms of the inattentiveness symptoms in ADHD. *J. Am. Acad. Child Adolesc. Psychiatry*, 2012;51(11): 1197–1207. **Key Words:** ADHD, functional MRI, pulvinar, thalamo-cortical connectivity, attention

Attention-deficit/hyperactivity disorder (ADHD), characterized by cognitive deficits in attention and inhibitory processing, is the most common psychiatric disorder of childhood with a prevalence rate of 5% to 8%.¹ It is frequently associated with lifelong impairment

affecting both quality of life and learning. The development of objective biomarkers for this syndrome is a major goal of the neuroimaging research community.²

A large number of neuroimaging studies in ADHD have focused on the impulsive tendencies, implicating dysfunction within fronto-striatal circuits and other brain regions.³ For example, reduced functional connectivity between right inferior fronto-frontal, fronto-striatal, and fronto-parietal networks has been associated with performance of motor inhibition and task-switching tasks in this population.⁴ Reduced activity in right prefrontal cortex has been correlated with



This article is discussed in an editorial by Dr. Philip Shaw on page 1116.



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Clinical guidance is available at the end of this article.

reduced ability to inhibit motor responses during a think/no-think task.⁵ Decreased activations in regions associated with sensorimotor timing during finger tapping has also been observed, including prefrontal and precentral gyri, cerebellum, inferior parietal lobule, and superior temporal gyrus.⁶

Inattention is the other well-recognized component of ADHD; yet the neurobiological underpinnings of inattention have not been nearly as well studied as those associated with impulsivity.¹ Nonetheless, neuroimaging studies have reported functional deficits in prefrontal, anterior cingulate, and parietal cortices, regions well known to play important roles in attentional deployment.⁷ Recent studies have also reported aberrant cerebellar activation in ADHD during attention tasks⁸ and at rest.⁹ Increasingly, studies have also implicated cortico-striato-thalamo-cortical (CSTC) loops in attentional and cognitive processing, and evidence suggests that disturbances of CSTC loops may be associated with the inattention symptom of ADHD.¹⁰

The thalamus is an important component of the CSTC loops.¹¹ Functional magnetic resonance imaging (fMRI) studies have shown abnormal blood-oxygen-level dependence (BOLD) activation in the thalamus in patients with ADHD during task switching¹² and selective attention,¹³ as well as abnormal functional connectivity between thalamus and cortical regions during the resting state.^{14,15} However, findings of these two resting-state functional connectivity studies are not fully consistent, probably because of the location difference of the region-of-interest (ROI) selected from the entire thalamus.

One key nucleus of the thalamus consistently implicated in attentional function is the pulvinar.^{16,17} As the largest of the thalamic nuclei, and given its extensive connectivity with the superior colliculus and visual cortices, the pulvinar plays a central role in modulating visual processing and orienting of the eyes to salient visual events.¹⁸ Lesions of pulvinar can cause hemispatial neglect syndrome in humans¹⁹ and primates.²⁰ Injections of γ -aminobutyric acid (GABA)-related drugs into the pulvinar cause inhibition and facilitation of attention switches respectively, in nonhuman primates performing a spatial-cueing task.²¹ The pulvinar has connections with the prefrontal and inferior parietal lobes²² and the medial nucleus of the pulvinar sends projection fibers to the posterior cingulate gyrus, the retrosplenial area, and the posterior parahippocampal gyrus.²³ Functional

neuroimaging studies in both monkeys and humans showed that networks including pulvinar, posterior parietal cortex, superior temporal cortex, and dorsolateral prefrontal cortex were associated with attention-related functions.^{16,24,25} Positron emission tomography (PET) studies across species make it clear that the pulvinar plays a central role in spatial attention orienting and in the filtering of distracting information.¹⁶

Very recently, two vertex-based shape analysis studies, one by Ivanov *et al.*²⁶ and the other from our research group,²⁷ reported significant structural atrophy in bilateral pulvinar nuclei in youth with ADHD. Given these findings of anomalous anatomy and the clear role of pulvinar during attentional processing, we set out here to examine functional activation in the pulvinar nuclei and to assess pulvinar-cortical connectivity during a visual sustained attention task, acquiring functional imaging measures in a cohort of children with ADHD combined type, and comparing their responses to those of age-matched control participants. We recognized the possible neural heterogeneities associated with the sub-phenotypes of ADHD would affect the brain activation and connectivity patterns. In this study, we focused our research on children with ADHD combined-type, who had both inattention and hyperactivity symptoms that confirm the diagnosis of ADHD. We did not include those who were diagnosed with inattentive subtype, considering that children with ADHD inattentive subtype are often argued with their diagnoses. We predicted functional deficits within the pulvinar nuclei and the relevant extending connections to the cerebral cortices, deficits that are likely associated with the neurobiological underpinnings of inattention that is a hallmark symptom of ADHD in children.

METHOD

Participants

A total of 48 children and young adolescents, ranging from 9 through 15 years of age, were involved in this study. Three were excluded from analyses because of heavy head motions, and one was excluded because of low (<80%) response accuracy during fMRI acquisition. Finally, 22 children with ADHD combined type and 22 control subjects were included in analyses. All of the subjects were strongly right-handed, evaluated using the Edinburgh Handedness Inventory,²⁸ and had estimated full-scale IQ ≥ 80 , measured by Wechsler Abbreviated Scale of Intelligence (WASI),²⁹ to minimize neurobiological heterogeneity.

The patient group included children who met current *DSM-IV* criteria for ADHD combined type, by combining the Conners Rating Scale—Revised-L for both parent and self reports.³⁰ This was confirmed with a parent interview using the Schedule for Affective Disorders and Schizophrenia for Children—Present and Lifetime Version (K-SADS-PL).³¹ The normal control group included children who had T-scores <60 (<1 SD) on all Conners parent and self-reports.

For both groups, we included the K-SADS-PL screening questions and supplements to rule out pervasive developmental disorders, substance use and abuse, and posttraumatic stress disorder. Similarly, oppositional defiant disorder with physical aggression (using *DSM-IV* diagnostic criteria), and all other current Axis I disorders (except for fear of the dark) were exclusionary. Children with any specific learning disorders were also excluded. The basic reading, mathematical reasoning, reading comprehension, and numerical operations subtests of the Wechsler Individual Achievement Test 2nd ed. (WIAT-II)³² were administered to determine the presence of impairments in reading or math.

General exclusion criteria for both groups also included the following: chronic medical/neurological illness or was taking systemic medication; specific or focal neurological disorder including epilepsy; treatment with any nonstimulant psychotropic within the past month; contraindications to magnetic resonance imaging (MRI) scanning; and heavy head motions (any of the six translation and rotation parameters >1.5 mm) during the fMRI data acquisition.

We avoided including siblings, considering that genetic and family factors might influence brain activation patterns during the fMRI tasks. Nine of the subjects with ADHD were taking short-acting Ritalin, whereas the others were not medicated. To eliminate the medication effects on brain activations during the fMRI tasks, we requested a 48-hour wash-out period before the study.

The children and young adolescents with ADHD were recruited from the Children's Evaluation and Rehabilitation Center at the Albert Einstein College of Medicine, and the Max and Celia Parnes Family Psychological and Psychoeducational Services Clinic at the Ferkauf Graduate School of Psychology. The controls were recruited from local schools through newspaper advertisements. This study received Institutional Review Board approval for human subjects' research at the Albert Einstein College of Medicine. Written informed consents were provided by all participants and their parents after the nature of the study and its procedures were carefully explained. All procedures were conducted in keeping with the tenets for the ethical conduct of research as outlined in the Declaration of Helsinki.

MRI Data Acquisition Protocol

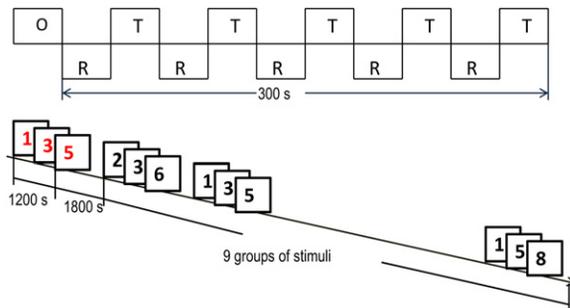
Imaging data were obtained using a 3.0 Tesla 32 Channel FreewaveAchieva MRI Scanner (Philips Medical Systems, Best, the Netherlands). All data acquisition protocols exceed the Biomedical Informatics Research Network (BIRN) recommendations for functional and morphometric data acquisition (<http://www.nbirn.net/>). High-resolution T1-weighted whole-head structural MRI data for each subject was acquired and used for image registration and head motion correction (240-mm field of view [FOV] with 240 × 240 in-plane matrix and 1 mm isotropic resolution, time echo [TE] = 4.6 milliseconds, repetition time [TR] = 9.8 milliseconds, $\alpha = 8^\circ$, sensitivity encoding [SENSE] factor = 2. Total scan time is 3 minutes). fMRI acquisition used whole-brain gradient echo-planar imaging (EPI) acquired over a 230-mm FOV on a 230 × 128 acquisition matrix with 2-mm slice thickness, and 2 × 2 mm² in-plane resolution, 41 slices, TE = 28 milliseconds, TR = 2000 milliseconds.

Experimental Task for fMRI Acquisition

Sustained attention is impaired in patients with ADHD combined type. The continuous performance task (CPT) is one of the most widely used measures of impaired sustained attention, allowing for a parametric design that can systematically challenge sustained attention abilities.³³ Studies have reported acceptable reliability and validity of the CPT,³⁴ and strong correlation between the omission error rates and teacher ratings of inattention.³⁵ The CPT tasks have also shown behavioral and functional brain impairments associated with inattention in previous fMRI studies of patients with ADHD.^{36,37}

To achieve maximal measurement power in relatively brief periods, in the present study we designed a three-digit stimulus set and used a block design CPT task. Multi-digit stimuli evoke more attentional demands than single-digit stimuli. Block designs have superior measurement characteristics in a given time period relative to event-related designs (at a cost of experimental flexibility). Briefly, the block design is shown in Figure 1. In each of the five task blocks, a white box appeared in the center of the computer screen. A target sequence of three digits (1-3-5, 2-4-6, 3-5-7, 4-6-8, and 5-7-9 respectively) were shown in red at the rate of one digit per 400 milliseconds. Then after 1.8 seconds' recalling time, nine sequences of three digits, from 1 to 9, appeared in black in a pseudo-random order, at the rate of 1 digit every 400 ms. A 1.8-second reaction period ensued after each sequence. In this period, participants were instructed to quickly use the right hand to press the left button when the sequence matched the target sequence, and to press the right button otherwise. During the rest blocks, participants were instructed to keep their eyes open, and to remain as relaxed and motionless as possible. Each participant was asked to perform two

FIGURE 1 Block design structure and the sequence of one task block of the visual attention task. Note: O = 8 seconds' initial fixation period; R = 30 seconds' rest block; s = seconds; T = 30 seconds task block.



runs of the task, and the duration of each run was 5 minutes. Before the MRI scans, participants were provided a set of task training blocks to ensure that they understood the requirements of the task.

Individual Imaging Data Preprocessing

The task-based fMRI and T1-weighted structural MRI data pre-processing was carried out using tools from the FMRIB Software Library (FSL)/fMRI Expert Analysis Tool (FEAT) and ART2.³⁸ For the fMRI data from each participant, slice timing was corrected, spatial intensity was normalized, head motion was corrected, and each image was smoothed with an 8-mm full-width-at-half-maximum (FWHM) Gaussian spatial filter. Nonbrain structures in both the fMRI and T1-weighted data were extracted using the Brain Extraction Tool. The T1-weighted image was normalized to ICBM152 template in the Montreal Neurological Institute (MNI) space.³⁹ The resulting transformation parameters were applied to the fMRI data to ensure accurate spatial normalization. Voxel-based functional activation maps responding to the fMRI task were generated using the FEAT tool from FSL. The Z statistic image was thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$.

Pulvinar Seed Region Processing

An average image was generated by averaging the 44 high-resolution T1-weighted structural images, which had been registered to the T1-weighted standard MNI template during pre-processing. In the high-resolution (voxel size = $1 \times 1 \times 1 \text{ mm}^3$) Automated Anatomical Labeling (AAL) template image provided by the Wake Forest University (WFU)-PickAtlas software⁴⁰; the brain voxels were labeled by names of the anatomical structures in the standard MNI space. We thus investigated the locations and the number of the voxels (the approximate size) of the pulvinar nuclei, to determine

the locations and size of the ROIs. Two spherical regions from both hemispheres (Origins [$\pm 14, -26, 8$] and radius $R = 4 \text{ mm}$) were identified accordingly, and were verified from the average image. For the task-based functional image from each individual, the average time series inside each seed region was calculated by using Featquery (FSL tool).

Functional Connectivity Analyses

Functional connectivity between each seed region and the remainder of the brain was examined by calculating the temporal correlation coefficient between the average time series of the seed region and the time series of the voxels from the whole brain using the FILM tool in FSL, where the average time series of the seed region was applied as the basic shape of the real event and was compared to the time series for the whole brain by a linear correlation model. Correlation coefficients were normalized by Z (Gaussianized T/F) transformation. The Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < .05$.

Statistical Analyses

The group comparisons of the demographic and task performance data were analyzed using a general linear model (GLM-SPSS 17.0.2). Analyses were false discovery rate corrected for multiple comparisons ($p < .05$).

Group comparisons of the images were analyzed using the GML by adding sex as a fixed-effect covariate, task performance accurate rate, and omission error rate as random-effect covariates. The Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$.

Pearson partial correlations were carried out to measure the degree of associations among the task performance measure, the activation magnitudes within the pulvinar nuclei (Z value within each ROI), and the diagnostic features (*DSM-IV* Inattentive and Impulsive/Hyperactive Indices), while controlling for the possible effect of sex in the subjects with ADHD.

RESULTS

Analyses of the demographic and task performance data showed no significant between-group differences (Table 1), except the omission error rate for performing the fMRI task ($p = .04$).

Group comparisons of the task-responsive activation maps are shown in Figure 2. As in Figure 2D, subjects with ADHD showed significantly reduced task-negative (the time series of those

TABLE 1 Demographic Characteristics and Functional Magnetic Resonance Imaging (fMRI) Task Performance Measures in Both Groups

	NC (N = 22)	ADHD (N = 22)	Statistic	p
Age (y)	12.1 ± 2.23	11.6 ± 2.86	t = 2.35	.07
Male/female	10/12	12/10	$\chi^2 = 3.50$.71
Education (y)	6.2 ± 2.21	5.8 ± 2.81	t = 2.25	.07
Mother's education	16.1 ± 3.46	14.7 ± 4.02	t = 2.09	.08
Father's education	16.5 ± 3.55	14.8 ± 4.37	t = 1.77	.06
IQ	114.7 ± 14.92	106.6 ± 16.21	t = 0.06	.73
Race/ethnicity			$\chi^2 = 4.33$.11
Caucasian	11	9		
Black	3	3		
Hispanic	6	8		
Asian	1	1		
Mixed	1	1		
fMRI Task performance measures (normalized)				
Accuracy rate	0.89 ± 0.07	0.86 ± 0.05	t = 2.45	.09
Omission error	0.08 ± 0.05	0.12 ± 0.08	t = 4.18	.04
Commission error	0.03 ± 0.01	0.01 ± 0.02	t = 3.22	.35
Reaction time	88.05 ± 9.4	76.39 ± 16.3	t = 2.78	.15

Note: Accuracy rate = number of correct responses/number of requested responses; ADHD = patients with attention-deficit/hyperactivity disorder; commission error = number of wrong responses/number of requested responses; NC = normal controls; omission error = number of missed responses/number of requested responses; y = years.

voxels were significantly negatively correlated with the design of the task) BOLD activations in bilateral superior temporal gyri (Heschl's gyri) (left side: Coordinates of Maximum [−44, −28, 18] Z = 3.61; right side: [54, −4, 4] Z = 3.94). From Figure 2E, children with ADHD also showed significantly reduced task-positive (the time series of those voxels were significantly positively correlated with the design of the task) BOLD activations in right thalamus ([12, −8, 24] Z = 3.53), right hippocampus ([26, −34, 12] Z = 4.66), right precuneus ([24, −59, 24] Z = 3.48), right angular gyrus ([30, −62, 44] Z = 4.59), left inferior occipital gyrus ([−44, −68, −12] Z = 3.92), and left cerebellum ([−38, −72, −28] Z = 4.17).

By calculating the functional connectivity between both pulvinar seed ROIs (Figure 2) and the remainder of the brain, we found that functional connectivities between the pulvinar nuclei of both hemispheres and right prefrontal lobe were significantly decreased relative to those in controls, whereas functional connectivities between the right pulvinar nuclei and bilateral occipital lobes were significantly increased in subjects with ADHD compared with controls (Figure 3 and Table 2).

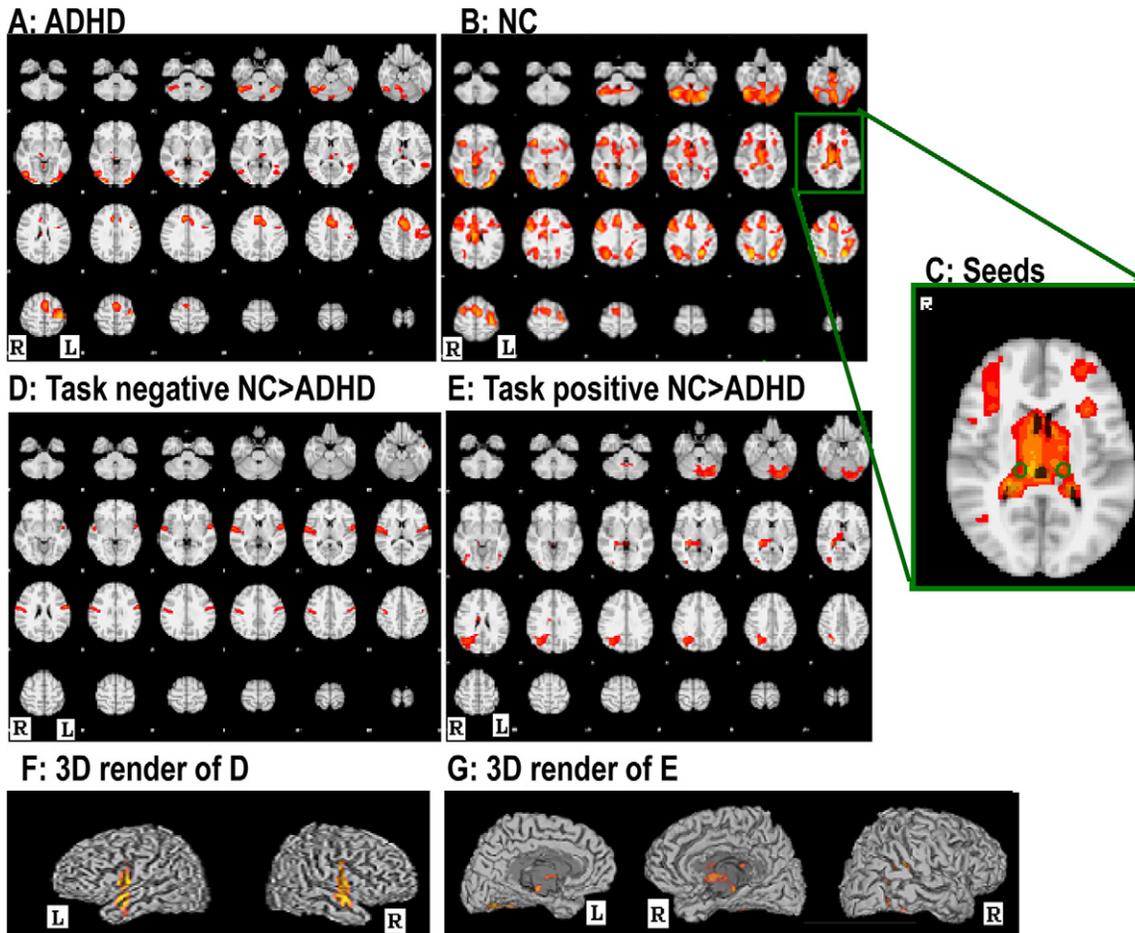
In the patient group, a significant negative correlation was shown between the activation

magnitude of the left pulvinar nuclei and the DSM-IV inattentive index ($r = -0.87$; $p = 0.009$). This result is shown in Figure 4. The fMRI performance measures did not show significant correlations with the DSM-IV diagnostic indices or with the pulvinar activation measures.

DISCUSSION

During performance of a sustained visual attention task, children with ADHD showed significantly decreased functional activations in a large area of the thalamus in the right hemisphere, significantly decreased functional connectivity between the right pulvinar and right prefrontal cortex, and significantly increased functional connectivity between the right pulvinar and bilateral occipital regions. Reduced activation in an ROI within the left pulvinar was also observed in the patient group, although between-group differences did not reach predetermined significance levels. Nonetheless, children with ADHD showed significantly decreased functional connectivity between the left pulvinar and the right prefrontal lobe. This study also found significant negative correlation between activation magnitude of the left pulvinar and the DSM-IV inattentive index in the 22 children with ADHD.

FIGURE 2 Within-group averages and between-group differences of whole brain functional activations. Note: Images A and B show the group averages of the task-responsive brain activations in controls and patients, respectively; C shows the locations of the bilateral pulvinal seed regions; D and E showed the between-group differences of the task-negative and task-positive brain activations, respectively. ADHD = attention-deficit/hyperactivity disorder; L = left hemisphere; NC = normal controls; R = right hemisphere.

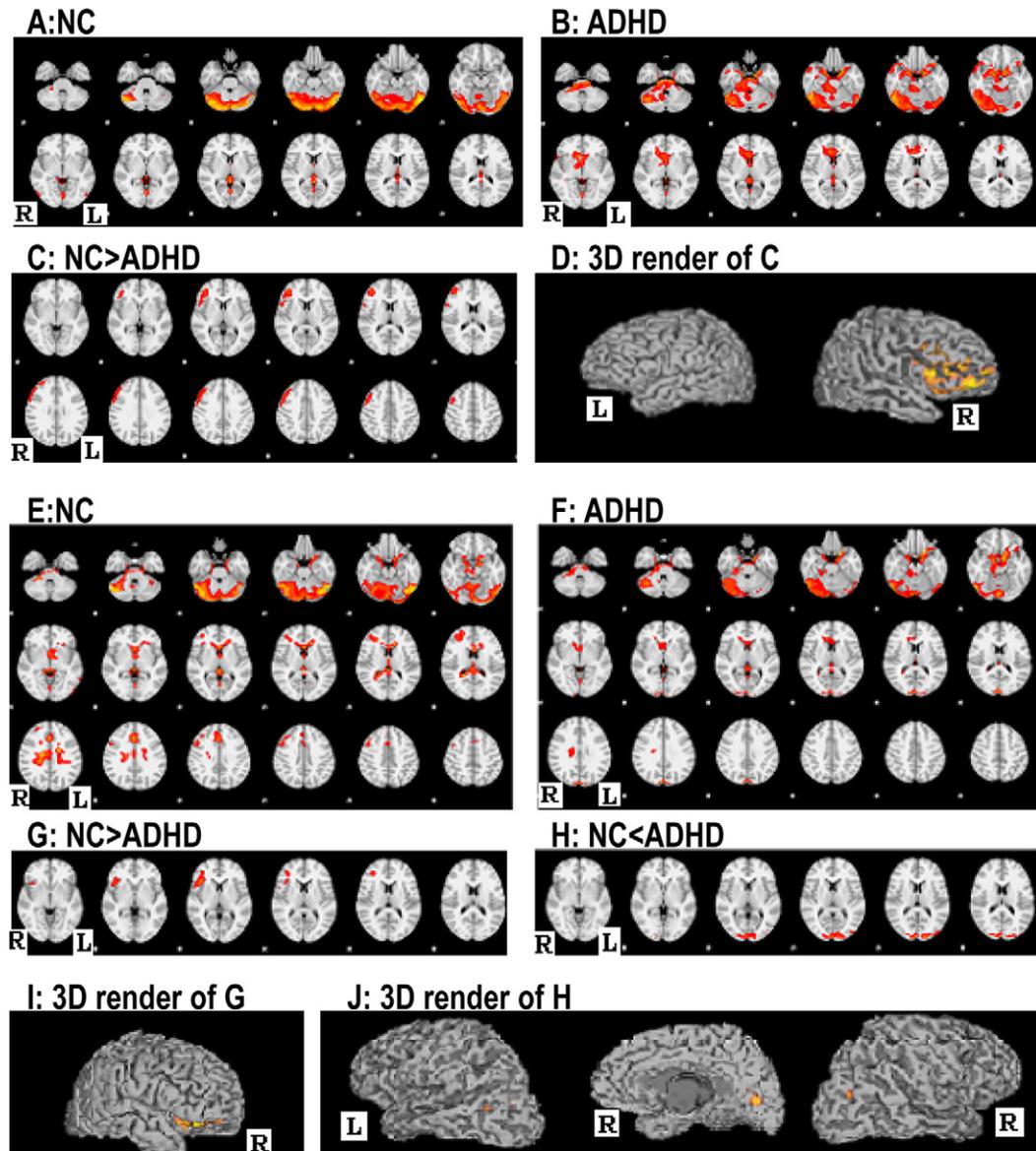


The decreased functional activations of bilateral pulvinal, their under-communication with the right prefrontal cortex, and the over-communication between right pulvinal and bilateral occipital lobes suggests that functional abnormalities within the occipital-pulvinal-prefrontal circuit may play an important role in the inattentiveness that is seen in the children with ADHD. These findings are in agreement with existing fMRI studies that have reported reduced thalamic activations during various tasks in ADHD.^{4,7} Furthermore, decreased BOLD activation and blood flow perfusion in the prefrontal lobe and increased blood flow perfusion in bilateral occipital lobes during various visual tasks has been consistently reported in patients with ADHD.^{9,10} Structural imaging studies have consistently shown decreased frontal

volume,^{41,42} reduced prefrontal cortical convolution complexity,⁴³ dramatic delay of cortical maturation in terms of cortical topography and thickness in ADHD,⁴⁴ and severe structural atrophy in bilateral pulvinal in youth with ADHD.^{26,27} Delayed or inadequate development of these crucial structures may well contribute to significant disturbances across the functional circuits for visual attention processing, and may play an important role in the pathophysiology of inattentiveness in ADHD.

Consistent with the results of a recent study in ADHD,⁴⁵ we found significantly reduced brain activations in the right hippocampus and precuneus during sustained visual attention. However, findings of structural abnormalities in these regions are not always consistent in ADHD. As reviewed by Shaw and Rabin,⁴⁶ many MRI studies have reported no

FIGURE 3 Images A–D show the within-group averages and between-group differences of functional connectivity between the left pulvinar nuclei and the remainder of whole brain, whereas images E–J show those of the right pulvinar nuclei and the remainder of the whole brain in controls and patients. Note: ADHD = Attention-Deficit/Hyperactivity Disorder; L = Left hemisphere; NC = Controls; R = Right hemisphere.



significant structural differences in the precuneus of ADHD children. A recent study reported enlarged subregions of bilateral hippocampi in subjects with ADHD compared with controls.⁴⁷ Shaw and Rabin suggested that ADHD in childhood may be characterized by a delay in subcortical maturation, and that different clinical outcomes may be associated with different developmental trajectories in adolescence and beyond.⁴⁶

The current study also demonstrated significant activation reductions in cerebellum in children

with ADHD. An increasing number of studies have now reported functional and structural deficits in the cerebellum.⁴⁸⁻⁵⁰ Together with these existing findings, the current study suggests that cerebellum plays an important role in attention processing, and that functional and structural anomalies in cerebellum may contribute to the cognitive and behavioral impairments seen in ADHD.

Some of the earliest functional neuroimaging studies noted that performing a focused visual attention task caused a decrease in blood flow in

TABLE 2 Regions That Had Significant Functional Connectivity with the Pulvinar Nuclei, and Had Significant Between-Group Differences During the Functional Magnetic Resonance Imaging (fMRI) Tasks

	Z	Coordinate			BA	Anatomical Location
		X	Y	Z		
Left pulvinar nuclei						
NC	5.96	±38	-35	-30		Bilateral cerebellum
	3.11	±25	15	-25	38	Bilateral inferior frontal gyrus
	4.23	±52	-55	-25	37	Bilateral temporal lobe
	3.37	±47	-76	-16	19	Bilateral occipital lobe
	3.32	±12	-35	7	0	Bilateral hippocampus
	3.11	0	-55	16	19	Left precuneus
ADHD	6.29	±50	-54	-22		Bilateral cerebellum
	5.65	48	-50	-22	20	Right inferior temporal lobe
	4.45	±4	-40	10	29	Bilateral posterior cingulum
	3.09	±3	-50	15	30	Bilateral precuneus
NC>ADHD	3.91	39	44	-14	45/47	Right inferior frontal gyrus
	3.79	47	19	45	9	Right middle frontal lobe
Right pulvinar nuclei						
NC	5.49	±52	59	-34		Bilateral cerebellum
	3.81	30	46	26	46	Right middle frontal lobe
	3.81	38	32	10	45	Right inferior frontal gyrus
	3.61	52	12	36	34	Left inferior orbital frontal gyrus
	3.31	15	-34	7	27	Right hippocampus
ADHD	5.36	-22	18	-22	11	Left orbital frontal gyrus
	4.55	12	-6	-12	34	Right hippocampus
	4.49	±2	-94	20	19/19	Bilateral cuneus
	3.1	14	-30	24		Right precuneus
	3.77	-52	-66	-22	29	Right cerebellum
NC>ADHD	3.97	40	22	4	47	Right prefrontal lobe
NC<ADHD	3.96	±4	-94	14	19/19	Bilateral occipital lobe

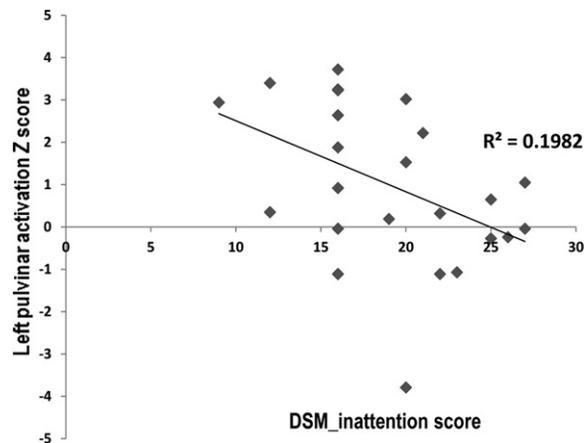
Note: ADHD = patients with attention-deficit/hyperactivity disorder; BA = Brodmann area; NC = normal controls.

the auditory cortex and its associated areas, even though no explicit auditory stimulation was presented.⁵¹ Clearly, in the magnet environment, the ongoing noise of the scanner is a potential source of distracting input, and it is perhaps not surprising that a relative suppression of processing within auditory cortex has often been observed, although similar blood flow suppressions have been reported in visual cortices during attention-demanding somatosensory⁵² and auditory tasks.⁵³ An interesting study, during which participants performed a sustained auditory attention (vigilance) task, also showed initial suppression of activity in the visual cortex, but this suppression declined as a function of the time participants spent engaged in the task.⁵⁴ The fall-off in suppression was not, however, accompanied by a decrement in ongoing performance, and the authors interpreted this pattern as reflecting a withdrawal of resources as the auditory task became more automated. Electrophysiological

data also suggest that auditory cortex activity is actively suppressed during performance of a visual demanding task.⁵⁵

In the current study, the finding of significant functional connectivity between the pulvinar and bilateral auditory cortices in controls also suggests that an important aspect of focusing visual attention involves attentional modulation of ongoing auditory processing. In addition, it was evident from the voxel-based whole-brain activation maps (Figure 2D) that subjects with ADHD showed significantly reduced deactivation in bilateral temporal lobes. To verify this primary result, an ROI-based supplementary analysis was carried out (Supplement 1 and Figure S1, available online). It revealed that the hemodynamic signals from bilateral Heschl's gyri, during the visual attention task, showed significantly less negative correlations in the ADHD cohort compared with controls. Thus, these data point to an

FIGURE 4 Significant negative correlation between left pulvinar activation and inattentive index in the patient group.



apparent attenuation of constitutively activated cross-sensory attentional suppression mechanisms in ADHD. Although there is a tendency to focus on the mechanisms by which attention is focused on “to-be-attended” inputs, clearly the mechanisms by which “to-be-ignored” stimulation streams are selected against deserve equal emphasis, and the current data point to potentially important deficits in these suppressive mechanisms that will require further study. Altered attentional suppression mechanisms may play an important role in the distractibility that is often seen in this phenotype.

There are some issues of this study that need to be considered. First, this study included both male and female subjects. Clinical studies have reported differences in the symptoms and profiles of comorbidities between male and female individuals with ADHD. It is unclear yet whether the neuropathological mechanisms of ADHD have gender differences. This study matched the number of male and female participants within and between groups, and included sex as a fixed-effect covariate for between-group analyses. We further tested the data by comparing the imaging results between the 12 male and 10 female patients with ADHD, and did not find significant differences. However, considering the limited sample size in each subgroup, the statistical power of this test was limited. Future studies can focus on investigations in the trajectories of the neurocognitive function, symptom profiles, neural development, and sex effect in ADHD, by recruiting a very large study sample

and using longitudinal follow-ups. Second, several subjects with ADHD had been taking short-acting medications, whereas the others were medication naive. We requested a minimum of a 48-hour wash-out period to eliminate the medication effects on the brain activations. Whole-brain activations did not differ significantly between the medicated and medication-naive patients. Third, the patient group showed significantly higher omission error rate and a trend of lower accuracy rate for the fMRI task performance. These items had been controlled during group comparisons to remove potential confounders. For any task-based fMRI data, response errors contribute to the signal noise. Altered brain activations and connectivity could be the result of high-response errors. We thus requested >80% response accurate rate as an inclusion criterion. In this study, temporal correlations (functional connectivities) between the pulvinar nuclei and the remainder of the whole brain were investigated during the visual sustained attention task. In Supplement 2 and Figure S2 (available online), we also carried out a Psychophysiological Interactions (PPI) analysis to investigate the group differences of the effective connectivities between the pulvinar nuclei and other brain regions. In addition, head motion can significantly affect the BOLD signals during fMRI acquisition. Framework head motion analyses and comparisons between the head motion measures and the BOLD signals are detailed in Supplement 3 and Figure S3, available online). &

CG Clinical Guidance

- Inappropriate development of the pulvinar nuclei in subjects with ADHD may contribute significantly to disruption of cortical–pulvinar–cortical circuits for attention processing, and further contributes to the pathophysiological mechanisms of inattention of this disorder.
- Future studies may assess the impact of treatment strategies on the connectivity and efficiency of the pulvinar–cortical circuits for attention processing, which will help in the formulation of more effective intervention strategies.

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SUPPLEMENT 1

Analysis

In a supplementary analysis, we specifically targeted auditory cortical regions along Heschl's gyrus and asked whether the classically observed suppression of auditory cortical activity was attenuated in our attention-deficit/hyperactivity disorder (ADHD) cohort. Two spherical regions of interest (ROI) located in bilateral Heschl's gyri (Origins $[-52, -4, 12]$ for left and $[54, -4, 4]$ for right, with radius $R = 5$ mm) were identified in the Montreal Neurological Institute (MNI) space, then mapped back to the individual structural magnetic resonance imaging (MRI) and, in turn, to the functional magnetic resonance imaging (fMRI) scans. For each participant, we quantitatively calculated the two-tailed Pearson temporal correlation between the average time series of each ROI and the time series of the task design. Group differences were compared using the General Linear Model, with normal controls and patients with ADHD as groups, and hemisphere (left and right ROIs) as repeated measures, the two-tailed correlation coefficient as dependent variables, and age and gender as random-effect and fixed-effect covariates, respectively. Significant group differences were revealed ($p = .041$). A post hoc *t* test also showed significant group differences in the correlation coefficients within both hemispheres (left side Heschl's gyrus: controls $[-0.101 \pm 0.108]$, ADHD $[-0.055 \pm 0.116]$, $p = .030$; right side Heschl's gyri: controls $[-0.199 \pm 0.178]$, ADHD $[-0.103 \pm 0.210]$, $p = .046$). Also from Figure 4, the ADHD cohort showed significantly reduced suppressive activity relative to controls in both Heschl's gyri.

SUPPLEMENT 2

Analysis

Psychophysiological Interactions (PPI) analysis was also carried out in each individual, using the fMRI Expert Analysis Tool (FEAT) PPI analysis tool as implemented in functional magnetic resonance imaging (fMRI) Expert Analysis Tool (FEAT) (<http://www.fmrib.ox.ac.uk/Members/joreilly/how-to-run-a-ppi-analysis-in-feat>). The two regions of interest (ROIs) from bilateral pulvinar nuclei defined in the main text were used in this PPI analysis. The psychological regressor was set up by defining the task condition as 1 and the rest as -1 . The physiological regressor was the time-course extracted from each ROI

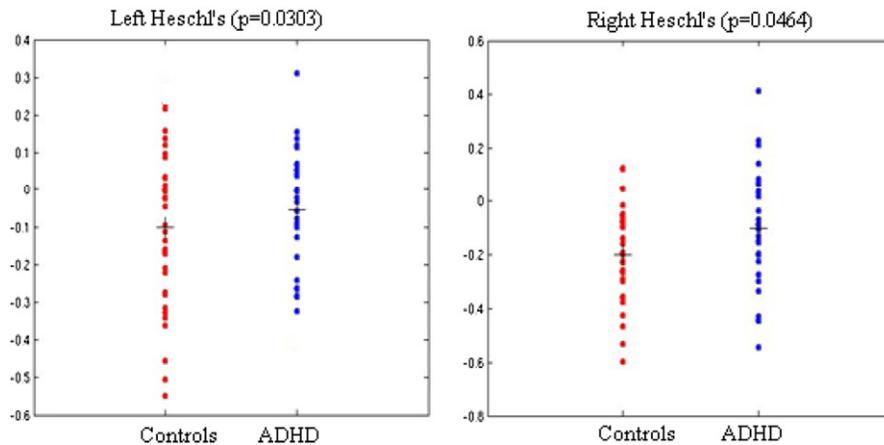
after preprocessing. Interaction between these two regressors was then assessed. The Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < .05$. Group comparisons were analyzed using the GML by adding sex as a fixed-effect covariate, and accuracy and omission error rates as random-effect covariates. The Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$. Figure S2 (available online) shows the results of the between-group comparisons. Significantly decreased effective connectivities between bilateral pulvinar nuclei and right prefrontal cortex were found in subjects with attention-deficit/hyperactivity disorder (ADHD) compared to normal controls. Also, significantly increased effective connectivity between the right pulvinar nucleus and bilateral occipital regions were found in subjects with ADHD compared to controls. These results further support the findings from the main study, and suggest disruption of cortical-pulvinar-cortical circuits for attention processing in individuals with ADHD.

SUPPLEMENT 3

Analysis

Head motion in functioning magnetic resonance imaging (fMRI) data often causes position shifts of the brain structures, and can induce artifacts in the blood-oxygen level-dependent (BOLD) signals at each voxel that cannot be fully corrected. Severity of head motion is a key issue to be considered for inclusion criteria in any fMRI study. Traditional measurement of head motion uses six parameters generated from the rigid body transformation for head realignment. Recent studies using resting-state fMRI data collected from large cohorts have demonstrated that patterns of head movement can have a significant impact on the dynamic patterns of resting-state BOLD signals,¹ and are significantly associated with decreased functional connectivity between long-distance seed regions. In contrast, these motion effects serve to increase measures of short-distance local functional coupling,² even after head motion spatial correction. These studies suggest that head motion-induced artifact may be a critical component of resting-state BOLD signals, and may confound spontaneous brain dynamics.

FIGURE S1 Group comparisons of the task-responding correlation coefficients in bilateral Heschl's gyri. Note: ADHD = attention-deficit/hyperactivity disorder.



Head motion effects in the BOLD signals and their putative effects on functional connectivity patterns in our block-designed, visual attention task-based fMRI data were assessed in this supplementary document. The framewise measurements of the six realignment parameters, the absolute values of the differentials of the time-courses (Diff), the sum of the absolute values of the differentials of the six realignment parameters (FD) (calculation details provided in Power *et al.*¹), and the Mean Motion (mean of the absolute values of the displacements along x-, y-, and z-axes compared to the previous volume) were calculated from the 44 fMRI data sets. Three spherical ($R = 4$ mm) regions of interest (ROIs) were located in the right pulvinar nucleus [14, -26, 8], the right prefrontal lobe [45, 30, 4], and the left occipital lobe [-12, -94, 7], given that the main hypothesis and resultant significant findings were associated with these brain regions. Functional connectivities in the pulvinar-prefrontal pairing and in the pulvinar-occipital pairing were calculated from the time series of the three ROIs (after all preprocessing steps introduced in main text). We did not see any pattern of significant relationship between head motion and

changes in the BOLD signals in any of the 44 data sets. Figure S3, panels A–F (available online), demonstrate the framewise head motion measures and comparisons with the BOLD signals and derivatives in a randomly selected subject. In addition, we did not find significant between-group differences in Mean Motion, and there were no significant correlations between Mean Motion and the functional connectivities in the pulvinar-prefrontal and pulvinar-occipital pairings across the whole sample (shown in Figures S3G and S3H, available online). These results suggest that BOLD signals collected during active visual attention tasks, such as the one used here, are much less sensitive to head motion-induced noise signals compared to the spontaneous brain dynamics recorded during resting-state scans.

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FIGURE S2 (A) Brain regions with significantly decreased effective connectivity with the left pulvinar nuclei in participants with attention-deficit/hyperactivity disorder (ADHD); (B and C) brain regions with significantly decreased/increased effective connectivity with the right pulvinar nucleus in participants with ADHD compared to neurotypical controls. Note: R = right hemisphere.

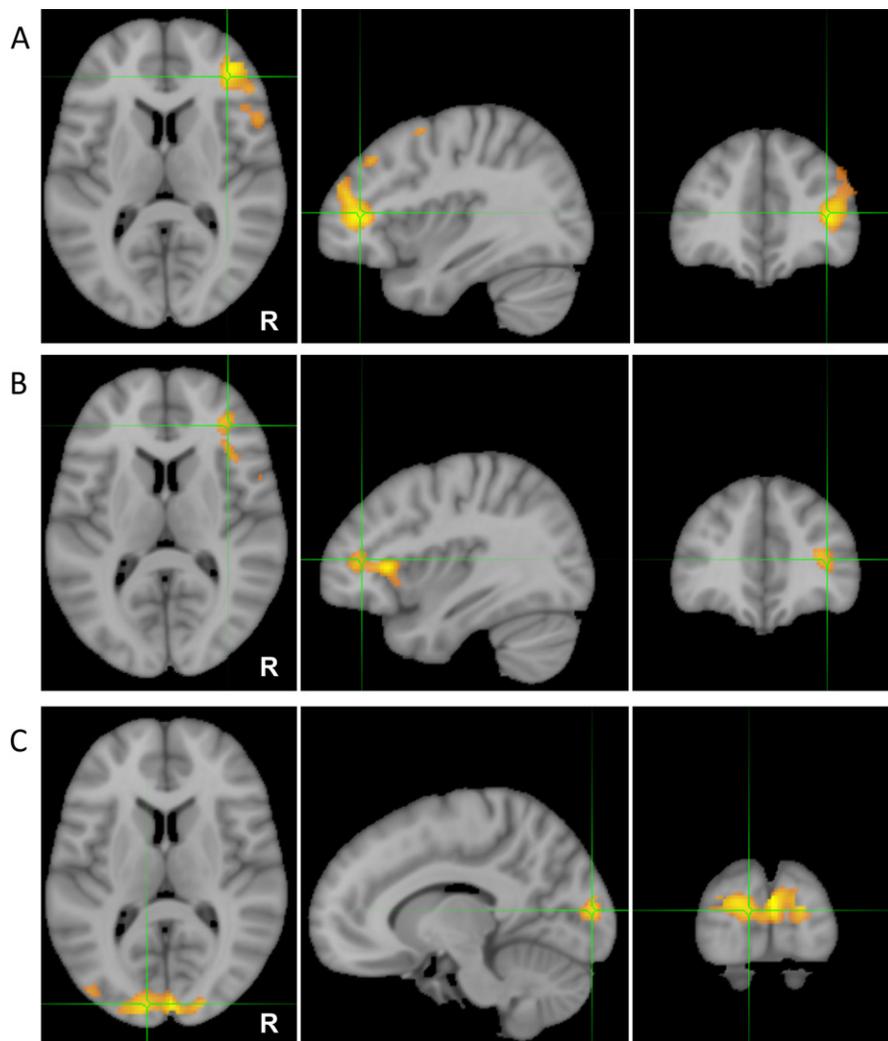


FIGURE S3 Framewise changes in the functional magnetic resonance imaging (fMRI) signals during the block-design visual attention task are not related to the framewise changes of head position after head motion correction. Note: (A to C) fMRI timecourses from 3 regions of interest (ROIs) in a randomly selected participant. The ROIs are 8-mm-diameter spheres centered on the coordinates of [14, -26, 8] (right pulvinar nucleus), [45, 30, 4] (right prefrontal lobe), and [-12, -94, 7] (left occipital lobe). (D) Six frame-by-frame realignment parameters. (E) Absolute values of the differential of each timecourse in the three ROIs. (F) Sum of the absolute values of the differentials of the six realignment parameters (FD). (G and H) These show that there are no significant correlations between Mean Motion and functional connectivity in either the pulvinar-prefrontal pairing (linear: $r = 0.20$, $p = .22$; nonlinear: $r = 0.22$, $p = .17$), or in the pulvinar-occipital pairing (linear: $r = 0.17$, $p = .28$; nonlinear: $r = 0.16$, $p = .34$). BOLD = blood-oxygen-level dependence.

