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Neural hyperactivity related to working memory in drug-naive boys with attention deficit hyperactivity disorder☆

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ABSTRACT

Background: Impaired working memory is thought to be a core feature of attention deficit hyperactivity disorder (ADHD). Previous imaging studies investigating working memory in ADHD have used tasks involving different cognitive resources and ignoring the categorical judgments about objects that are essential parts of performance in visual working memory tasks, thus complicating the interpretation of their findings. In the present study, we explored differential neural activation in children and adolescents with ADHD and in healthy controls using functional magnetic resonance imaging (fMRI) with the categorical n-back task (CN-BT), which maximized demands for executive reasoning while holding memory demands constant.
Methods: A total of 33 drug-naive, right-handed male ADHD without comorbidity (mean age 9.9 ± 2.4 years) and 27 right-handed, healthy male controls (mean age 10.9 ± 2.7 years) were recruited in the present study. Event-related fMRI was used to study differences in brain activity during the CN-BT between the two groups.
Results: The two groups did not differ in their accuracy in the CN-BT, although the ADHD patients showed significantly shorter reaction times to correct responses than did the controls. During the CN-BT, both ADHD patients and controls showed significant positive and negative activations by the correct responses, mainly in the sensory-motor pathways and the striato-cerebellum circuit. Additionally, the ADHD patients showed significantly higher activation in the bilateral globus pallidus and the right hippocampus compared with the controls. There was also a positive correlation between hyperactivation of the left globus pallidus and the reaction time to correct responses in ADHD.
Conclusions: In contrast to controls, ADHD patients showed neural hyperactivation in the striatum and mediotemporal areas during a working memory task involving categorization. Hyperfunction in these areas might be the pathophysiological foundation of ADHD, related to the deficits of working memory and the impulsive symptoms.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, impulsiveness, and hyperactivity that arise in childhood and often persist into adolescence and adulthood (Biederman and Faraone, 2005). Previous studies have proposed that deficiencies in cognitive function, and particularly in executive functions, are the core features of children and adolescents with ADHD (Sergeant et al., 2002). Executive functions often include working memory, planning, organization, inhibitory control, sustained attention, and set shifting. Among these executive functions, working memory is one of the most consistently reported deficits and is a crucial cognitive process that is implicated in theoretical models of ADHD (Cortese et al., 2012; Willcutt et al., 2005). Working memory refers to time-limited processes of active representations of information and is accessible for recall or for further manipulation (Martinussen et al., 2005). Working memory is an outcome of sustained attention on task-relevant mental representations and on the suppression of competing distracting events (Sander et al., 2012). Working memory consists of the manipulation, maintenance, and storage of verbal, object, or spatial–visual material, and refers to processes that are involved in the control, regulation, and active representation of information that guides conduct (D'Esposito, 2007). Clinically, working memory impairment is important because it is strongly associated with academic under-achievement (Gathercole and Alloway, 2006). In fact,

Abbreviations: ADHD, attention deficit hyperactivity disorder; fMRI, functional magnetic resonance imaging; CN-BT, categorical n-back task; SCID, Structured Clinical Interview for DSM-IV; WISC-CR, Wechsler Intelligence Scale for Children — Chinese Revision; CPRS-R, revised Conners' Parent Rating Scale; FWHM, full width at half maximum; GLM, general linear model; BA, Brodmann area; DAT, dopamine transporter; RT, reaction time; FWE, family-wise error.

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there is evidence that poor academic achievement is more related to working memory impairment than to the behavioral symptoms of inattention and hyperactivity/impulsiveness in ADHD patients (Rapport et al., 1999).

Various functional magnetic resonance imaging (fMRI) studies have been used to investigate the neural basis of working memory in children and adolescents (Fassbender et al., 2011; Silk et al., 2005; Vance et al., 2007). The neural patterns associated with working memory in healthy children involve the frontoparietal network in the classical n-back task (Owen et al., 2005). Deficits in working memory among children with ADHD are robust, with the largest impairments in tasks that require executive control in dealing with visual and spatial information (Martinussen et al., 2005; Willcutt et al., 2005). Previous studies indicate differential working memory-related activation patterns in distributed regions within the fronto-striato-parieto-cerebellar network of ADHD compared to healthy controls (Fassbender et al., 2011; Silk et al., 2005; Vance et al., 2007). However, these studies are characterized by inconsistent results, such as less activation in the right parieto-occipital areas of ADHD (Silk et al., 2005; Vance et al., 2007) or ADHD patients did not display working memory modulated brain activation that might be complicated by the medication exposure (Fassbender et al., 2011). Neuroimaging findings have shown a different location and amount of sustained activity dependent on the type of information held in working memory (Grossman et al., 2002; Zimmer, 2008), and previous spatial and verbal working memory studies (Massat et al., 2012, Vance et al., 2007) could not reflect the neural mechanism of visual-object working memory in ADHD.

Furthermore, categorical judgments about objects are essential parts of performance in visual working memory tasks. A new variant of the traditional n-back task, named the categorical n-back task (CN-BT), has been designed as a complex visual-object working memory paradigm comprising stringent attention focusing, active memory encoding, cognitive categorical judgment, and fast motor response. This visual working memory based paradigm maximizes demands for executive reasoning while holding memory demands constant (Ciesielski et al., 2006, 2010; Sander et al., 2012). Previous studies have shown that the CN-BT is more sensitive in detecting impairments in the executive domain of working memory (Ciesielski et al., 2006, 2010). To our knowledge, altered brain activation related to the CN-BT has not previously been reported in children and adolescents with ADHD.

The current study aimed to investigate the neural mechanisms of visual-object working memory in ADHD children during the early illness course without the confounding factor of medication using CN-BT. We hypothesized the following: that (i) ADHD patients would show hyperactivation involved in fronto-striatal and mediotemporal patterns, which may underlie the pathophysiology subtending working memory-related processes; and that (ii) the altered neural activation would associate with the expression of clinical symptoms of ADHD.

2. Methods

2.1. Participants

The study was approved by the local research ethics committee, and written informed consent was obtained from the guardians of all participants. A total of 33 drug-naive, right-handed male children and adolescents with ADHD (mean age 9.9 ± 2.4 years, range 6–15 years) and 27 right-handed, healthy control males (mean age 10.9 ± 2.7 years, range 8–16 years) were recruited at the Mental Health Center of West China Hospital. The Structured Clinical Interview for DSM-IV (SCID), patient edition, was used to determine and establish a diagnosis of ADHD without conduct disorder, oppositional defiant disorder and Tourette's disorder, or any other Axis I psychiatric comorbid disorder. Three experienced clinical psychiatrists (L.G., Y.L., N.H.) performed the psychiatric examination for all patients to diagnose ADHD and to make sure they were drug-naive to be eligible for the study. There were 22 combined-subtype and 11 inattentive-subtype ADHD patients in the present study. Healthy controls were recruited from the local area by means of a poster advertisement and were screened using the SCID, non-patient edition. The selected healthy controls had no known history of psychiatric illness in first-degree relatives. Handedness was assessed with Annett's Hand Preference Questionnaire (Dragovic and Hammond, 2007) The ADHD patients and healthy controls had a full-scale IQ above 90 according to an age-appropriate Wechsler Intelligence Scale for Children — Chinese Revision (WISC-CR) (Dai and Gong, 1990), and there was no significant difference in IQ between ADHD patients and healthy controls ($P > 0.05$). Primary behavioral measures were assessed using the impulsivity–hyperactivity factor and the hyperactivity index from the revised Conners' Parent Rating Scale (CPRS-R) (Conners et al., 1998) for all of the participants in the present study. The CPRS-R offered flexible administration options while also allowing the collection of varying perspectives on a child's behavior from parents to help assess ADHD and to evaluate problematic behavior in children and adolescents.

The following exclusion criteria were applied to all subjects: any neurologic disorders; psychosurgery; any substantial physical illness, such as a brain tumor, epilepsy, or hepatitis, as assessed on the basis of clinical evaluation and medical records; and magnetic resonance (MR) contraindications. Conventional MR images were inspected by two experienced neuroradiologists, and no gross abnormalities were observed for any participant.

2.2. CN-BT

The present CN-BT involved 57 commercially available color drawings of inanimate objects (buildings, cars, fruits, and plants) and animals (mammals, birds, reptiles, fish, and insects), which were presented consecutively and in random order. Small crosses were pseudo-randomly intermixed with the picture stimuli to provide a fixation point and an irregularity of timing to be as a control detection baseline. A drawing of a panda served as the n-back target. When the panda was presented, the subject was required to press a button with his/her right thumb only if at least two drawings prior to the panda belonged to the category of animals; alternatively, he/she was required to press a button with the left thumb for any other combinations of stimuli preceding the panda (Figure S1) (details in the Supplementary material according to the previous studies (Ciesielski et al., 2006, 2010)). All subjects were trained using a demo program before the scans and confirmed that they fully understood the procedures.

Visual stimuli were displayed on a white background using the E-prime 2.0 software package (http://www.pstnet.com/eprime.cfm) and were projected on a screen behind the MRI scanner. The subjects viewed the visual stimuli through a mirror attached to a head coil. Each run consisted of 124 stimuli (25% pandas, 23% other animals, 22% non-animals, and 30% crosses). Each stimulus of animals and non-animals lasted 500 ms, each stimulus of 18 crosses lasted 6 s, and each stimulus of 19 crosses lasted 4 s to provide time for the participants to press the button. In total, each run lasted 227.5 s.

2.3. fMRI data acquisition

All subjects underwent an fMRI scan using a 3 T Siemens Trio MRI system with an eight-channel phased-array head coil. A daily quality assessment was used to evaluate the stability of the MRI system and involved scanning a water phantom to achieve data quality assurance indexes. MR images sensitized to changes in blood-oxygen-level-dependent signal levels were obtained with a gradient-echo echo-planar imaging sequence: repetition time/echo time (TR/TE), 2000/30 ms; flip angle, 90°; slice thickness, 5 mm (no slice gap); matrix, 64 × 64; FOV, 240 × 240 mm^2; and voxel size, 3.75 × 3.75 × 5 mm^3. Each brain volume comprised 30 axial slices, and each functional run contained 114 image volumes, resulting in a total scan time of 228 s.

The participants were instructed to avoid moving their heads and to focus their eyes at the center of the screen during scanning. Earplugs were used to reduce noise interference during scanning for each participant. Additionally, we used foam cushions offered by the manufacturer to increase the comfort of the participants and decrease head motion. Head motions were evaluated at an MR workstation as soon as the scans ended. Participants with head movements greater than 2 mm or rotation more than 2° during fMRI scans were excluded. There was no significant difference in head motion between the ADHD patients and the controls, and no individuals were rejected due to excessive head motion.

To regress out the brain volume effects that might confound the neural functional activity, we also acquired a high-resolution, three-dimensional T1-weighted (3D-T1) image (TR/TE = 1900/2.26 ms, flip angle = 9°, 176 axial slices with thickness = 1 mm (without gap), voxel size = $1 \times 1 \times 1$ mm^3, FOV = 256×256 cm^2, and data matrix = 256×256). The 3D-T1 images were analyzed using VBM8 toolbox implemented in SPM8 with default parameters, and bias-corrected, tissue classified into gray matter and white matter and cerebrospinal fluid. The tissue segmentation procedure analyses were performed subsequently, which were multiplied by the non-linear components derived from the normalization matrix in order to preserve actual modulated brain volumes. The resulting tissue partition was spatially normalized to the Dartel template provided by VBM8 toolbox using linear (12-parameter affine) transformation and non-linear high-dimensional warping, within a unified model (Ashburner and Friston, 2005), and then was smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM). And there were no significant differences in total brain volume using a two-sample t test ($t = 0.386$, df = 58, $P = 0.701$) between ADHD patients (1430.3 ± 126.4 mm^3) and healthy controls (1417.3 ± 129.7 mm^3).

2.4. Statistical analysis

Analyses of demographics and behavioral and neuropsychological testing characteristics were performed using a two-sample t test in SPSS 16.0. We used a threshold of $P < 0.05$ to define significant differences between ADHD patients and healthy controls.

The fMRI data were analyzed using SPM8. For preprocessing, functional images were corrected for slice timing, with the middle slice as a reference, realigned to remove head motion, normalized onto the default echo-planar imaging template image with Montreal Neurological Institute (MNI) standard space coordinates provided by SPM8, and resampled with a $3 \times 3 \times 3$ mm^3 voxel size. Previous quantitative studies have indicated that the normalization of children's MR images to standard adult templates is useful and acceptable for statistical group comparisons (Burgund et al., 2002; Kang et al., 2003). Finally, images were spatially smoothed using a Gaussian kernel of 8 mm FWHM.

A general linear model (GLM) statistical analysis was performed in SPM8 based on the theory of Gaussian random fields (Frackowiak and Friston, 1994), and an event-related model was used in the present GLM analysis. fMRI responses were modeled by a canonical hemodynamic response function, and the realignment parameters, representing the degree of head movement (translation and rotation), were also included in the model to account for any variance associated with head motion (Friston et al., 1998). The responses to panda stimuli preceded by at least two consecutive animal stimuli were modeled in SPM8 as correct categorical n-back responses. Because the correct responses evoke stronger activation and coupling in distributed cortical networks (Pessoa et al., 2002) and provide clarity and validity across groups, only correct-response trials were submitted for the present analysis consistent with previous researches (Ciesielski et al., 2006, 2010). Using this model, a single contrast image was generated for each participant with a fixed-effects model, representing the difference between correct categorical n-back responses and baseline trials, which was then employed for group analyses using a random-effects model (Büchel et al., 1998).

For group statistical analysis, the first-level contrast images for each individual were entered into a random-effects analysis. With age, total brain volume and reaction time partialed out, single-sample t tests were separately used for the ADHD and healthy control groups to identify areas of significant activation during correct categorical n-back responses compared with the baseline trials. Two-sample t tests were used to identify areas showing significant differences in activation between ADHD patients and healthy controls, with age, total brain volume and reaction time partialed out. Significant activation was defined according to a two-tailed cluster-level threshold of $P < 0.05$ using family-wise error (FWE) correction for multiple comparisons and a cluster threshold of greater than 10 voxels, for both first and second level analyses. Areas of activation were described in terms of correspondence to standard Talairach coordinates, after conversion from the MNI space using mni2tal.m. To identify regions of activation correlated with performance and the speed of response, two-tailed Pearson correlations were performed in SPSS 16.0 using a statistical threshold of $P < 0.05$.

3. Results

3.1. Behavioral test and CN-BT analysis

Demographic variables, including age ($t = -1.392$, df = 58, $P = 0.169$), gender (male), and handedness (right handed), did not significantly differ between ADHD patients and healthy controls. The impulsivity–hyperactivity scores ($t = 5.609$, df = 58, $P < 0.001$) and hyperactivity index ($t = 6.564$, df = 58, $P < 0.001$) of CPRS-R were significantly higher in ADHD patients than in healthy controls. There was no significant difference between the two groups in the percent of correct responses in the CN-BT ($t = -0.354$, df = 58, $P = 0.724$), whereas the ADHD patients showed a significantly shorter reaction time to correct responses ($t = -2.123$, df = 58, $P = 0.038$) (Table 1).

3.2. fMRI results of within-group analysis

To explore the neural activation patterns related to working memory within ADHD and controls groups, we first performed the analyses with the threshold of $P < 0.001$ uncorrected, and found that the neural activations based on the CN-BT were involved in the fronto-parietal networks, sensory-motor pathways and the striato-cerebellum circuit (Figure S2) (details in the Supplementary material).

To correct the multiple comparisons, we then used the threshold of $P < 0.05$ with FWE correction, which is conservative and therefore less likely to yield false positive findings (Nichols, 2012). For the healthy controls, task-positive activation was found in the right precentral gyrus (Brodmann area [BA] 4) and postcentral gyrus (BA3), the bilateral paracentral lobule (supplementary motor area) (BA6), and the left cerebellum (anterior lobe), and task-negative activation was found in the bilateral caudate nucleus, bilateral globus pallidus, and right hippocampus, related to the baseline trials of the CN-BT. For the ADHD

Table 1
Characteristics of ADHD patients and healthy controls based on a behavioral test and the CN-BT.

Characteristics	ADHD patients (n = 33) Mean (SD)	Healthy controls (n = 27) Mean (SD)	P value
CPRS-R			
Impulsivity–hyperactivity	6.0 (3.0)	2.1 (2.1)	<0.001
Hyperactivity index	10.7 (5.1)	3.6 (2.7)	<0.001
CN-BT			
% cor	70.9 (14.8)	76.2 (17.9)	0.724
RT (ms) to correct	704.3 (487.9)	988.8 (549.6)	0.038

Abbreviations: CPRS-R, revised Conners' Parent Rating Scale; CN-BT, categorical n-back task; % cor, percentage of correct responses; RT, reaction time.

Table 2
Brain regions of positive and negative activations by the correct responses during performance of the categorical n-back task in ADHD patients and healthy controls using a one-sample *t* test at a cluster level of significance of $P < 0.05$ with family-wise error correction and a cluster threshold greater than 10 voxels.

Group	Task-positive					Task-negative				
	Areas of activation	Talairach			No. of voxels	Areas of activation	Talairach			No. of voxels
		x	y	z			x	y	z	
ADHD patients	Right precentral gyrus (BA4) and postcentral gyrus (BA3)	42	−15	56	561	Left parietal lobe (angular gyrus) (BA39)	−45	−71	28	88
	Bilateral paracentral lobule (supplementary motor area) (BA6)	−6	8	52	240	Bilateral subgenual anterior cingulated cortex (BA32)	3	31	−12	27
	Left cerebellum (anterior lobe)	−18	−53	−15	58	Bilateral ventral medial prefrontal cortex (BA10)	3	58	−5	26
	Right globus pallidus	18	−9	−5	33					
	Left globus pallidus	−17	−2	−2	20					
	Right hippocampus	33	−4	−15	15					
Healthy controls	Right precentral gyrus (BA4) and postcentral gyrus (BA3)	39	−24	45	432	Right caudate nucleus	3	6	−3	60
	Bilateral paracentral lobule (supplementary motor area) (BA6)	−2	2	50	180	Left caudate nucleus	−8	15	−2	72
	Left cerebellum (anterior lobe)	−15	−53	−20	13	Right globus pallidus	24	−4	−5	15
						Left globus pallidus	−21	−5	−5	18
						Right hippocampus	27	−7	−22	129

Abbreviations: BA, Brodmann area.

patients, task-positive activation was found in the right precentral gyrus (BA4) and postcentral gyrus (BA3), the bilateral paracentral lobule (supplementary motor area) (BA6), the left cerebellum (anterior lobe), the bilateral globus pallidus, and the right hippocampus, and task-negative activation was found in the left parietal lobe (angular gyrus) (BA39), the bilateral subgenual anterior cingulate cortex (BA32), and the bilateral ventral medial prefrontal cortex (BA10), related to the baseline trials of the CN-BT (Table 2 and Fig. 1).

3.3. fMRI results of between-group analysis

Regarding correct responses during performance of the CN-BT, ADHD patients showed higher activation in the right hippocampus ($t = 4.8$, df = 58, $P = 0.001$), right globus pallidus ($t = 4.19$, df = 58, $P = 0.021$), and left globus pallidus ($t = 4.3$, df = 58, $P = 0.017$) compared with healthy controls (Table 3 and Fig. 2). The analyses of the whole-brain image data between the two groups kept experiment-wise type I error rates protected at $P < 0.05$, with an FWE correction procedure that considered the intercorrelation of the data structure. In the ADHD patient group, there was a significant negative correlation between activation of the left globus pallidus and the reaction time to correct responses in the CN-BT ($r = -0.369$, N = 33, $P = 0.038$, two tailed).

4. Discussion

To our knowledge, the exploration of working memory-related brain activation using the CN-BT has not been previously reported in children and adolescents with ADHD. In addition to having activation within the sensory-motor pathways and the striato-cerebellum circuit similar to that of healthy controls with related visual-object and action cognitive strategies, the ADHD patients also showed task-negative activation in the fronto-cingulate-parietal network involved in working memory. Additionally, the higher activation of the bilateral globus pallidus and right hippocampus in ADHD patients compared to healthy controls revealed an important role in the pathophysiology of ADHD related to working memory.

Before attempting to interpret the differences in neural activation between ADHD patients and healthy controls, it is important to determine whether the differences resulted from a higher task difficulty. In this study, we excluded event-related fMRI signals to error responses, which may confound the results (Pessoa et al., 2002). ADHD patients performed with a level of accuracy similar to that of healthy controls (70.9% vs 76.2%), yet the involved networks of activation were different. This finding suggested that the different networks in the two groups did not result from general task difficulty. Nevertheless, we expected the children and adolescents with ADHD to exhibit a lower accuracy in the CN-BT than healthy controls, given that working memory is a key cognitive function that is impaired in ADHD (Martinussen et al., 2005). In the present study, ADHD patients did demonstrate the expected trend, making 5.3% more errors on average than healthy controls, although there was no significant difference in total accuracy in the CN-BT between the two groups. Furthermore, overall performance was highly variable in both groups, with a standard deviation of ±14.8% for ADHD patients and ±17.9% for healthy controls. Thus, given the high variability in the performance of the young children and adolescents and the relatively small sample sizes with matched IQs, the present study may not have been sensitive enough to detect behavioral performance differences (Martinussen et al., 2005). Nonetheless, the present study was more sensitive in terms of functional brain imaging than the behavioral data, as our findings are consistent with the results of several other ADHD imaging studies, in which functional differences were found despite no significant differences in behavioral performance in a working memory task (Valera et al., 2010; Vance et al., 2007).

Conceptualized as the interplay of low-level feature-binding processes and top-down control (Sander et al., 2012), the working memory functions of healthy controls are thought to be highly dependent on brain regions within the fronto-striatal circuit (Bunge et al., 2001; Kondo et al., 2004; Lewis et al., 2004) and cerebellum (Gottwald et al., 2003), with interactions of an extended network including the mediotemporal and parietal areas (Lee and Rudebeck, 2010; Todd and Marois, 2004), which are also reflected by the present study. Furthermore, it has been demonstrated that the dopaminergic and noradrenergic systems modulate working memory processes (Chamberlain et al., 2006). Because working memory processes have been implicated in theoretical models of ADHD (Rapport et al., 2001), previous evidence has suggested that children and adolescents with ADHD might exhibit working memory deficits because of dysfunction in fronto-striato-cerebellar networks and/or because of dopaminergic and noradrenergic dysregulation (Chamberlain and Robbins, 2013; Levy and Swanson, 2001).

Previous studies have shown the deficits of the fronto-striatal circuit and their interaction in a distributed neural network involved in the top-down central executive control of working memory functioning (Sander et al., 2012). The children with ADHD reported significantly higher level of prefrontal activation than the control children performing a working memory task (Tsujimoto et al., 2013), suggesting that the impairment in the fronto-striatal circuit is responsible for the working memory deficits observed in ADHD children. The original CN-BT research showed healthy children exhibited higher neural activation in the globus pallidus than healthy adults (Ciesielski et al., 2006), and previous researches also reported activated specific subcomponents including the globus pallidus in healthy participants during other paradigms of working memory (McNab and Klingberg, 2008; Schulze et al., 2011), suggesting that the globus pallidus plays a role in the working memory. As a core component in striatum, the globus pallidus remains a brain area of significant interest in research in the pathophysiology of ADHD. The striatum is a critical area in the dopamine theory of ADHD, which posits that patients with ADHD have a significantly high level of dopamine transporter (DAT) binding in the striatum. DAT blockers, such as methylphenidate, which targets the striatum, can improve the symptoms of ADHD (Ma et al., 2012). A structural MRI study also showed that the globus pallidus decreased in volume in children with ADHD (Nakao et al., 2011). In the present study, the healthy controls demonstrated task-related negative activation in the striatum, whereas the ADHD patients displayed task-positive activation in the bilateral globus pallidus. Recent studies have found that top-down control of working memory indeed results in both an enhancement of relevant information and a suppression of irrelevant information (Gazzaley et al., 2005), and the amount of top-down modulation is related to individual working memory performance (Zanto and Gazzaley, 2009). The dysfunction of top-down modulation seems to lead to the excessive processing of irrelevant information and that is in turn detrimental to working memory (Berry et al., 2009). Thus, the higher activation of the globus pallidus in the CN-BT might reflect the impaired brain function of children and adolescents with ADHD. In addition, previous studies proved that the impulsivity was related to higher striatal DAT availability in healthy males (Costa et al., 2013) and demonstrated that patients with ADHD exhibited significantly higher specific DAT binding in the striatum compared with normal subjects. In this study, there was a significant negative correlation between hyperactivation of the left globus pallidus and a shorter reaction time to correct responses in the CN-BT, showing impulsivity behavior and supporting the interpretation of impaired suppressive function in the working memory of ADHD patients.

The medial temporal lobe has been conceptually linked to the maintenance of bound representations, which is also critical for working memory performance when processing and maintaining complex objects (Lee and Rudebeck, 2010; Ranganath et al., 2005), underlining the important role of medial temporal lobe involvement in intra- and inter-item binding (Piekema et al., 2010). Because the noradrenergic systems project to the frontal cortex, cerebellum, and hippocampus to modulate working memory processes (Chamberlain and Robbins, 2013), as a major component of the medial temporal lobe, the hippocampus has been thought to be involved in working memory (von Allmen et al., 2013) and to play a critical role in processing complex spatial representations (Lee and Rudebeck, 2010). Previous studies have found that in rat models of ADHD, amino acid levels are higher in the hippocampus (Ruocco et al., 2009) and that methylphenidate might change the molecular levels in the hippocampus (Scaini et al., 2008). A neuroimaging study also suggested the hippocampus as a potentially important locus of abnormalities in children with ADHD

Table 3
Brain regions showing significantly higher activation by the correct responses during performance of the categorical n-back task in ADHD patients than in healthy controls.

Brain regions	Talairach			No. of voxels	*t*-Score	*P* value[a]
	x	y	z			
Right hippocampus	30	−9	−12	139	4.80	0.001
Right globus pallidus	18	−2	−4	45	4.19	0.021
Left globus pallidus	−16	−3	−2	55	4.30	0.017

[a] Using family-wise error correction at cluster level and a cluster threshold greater than 10 voxels.

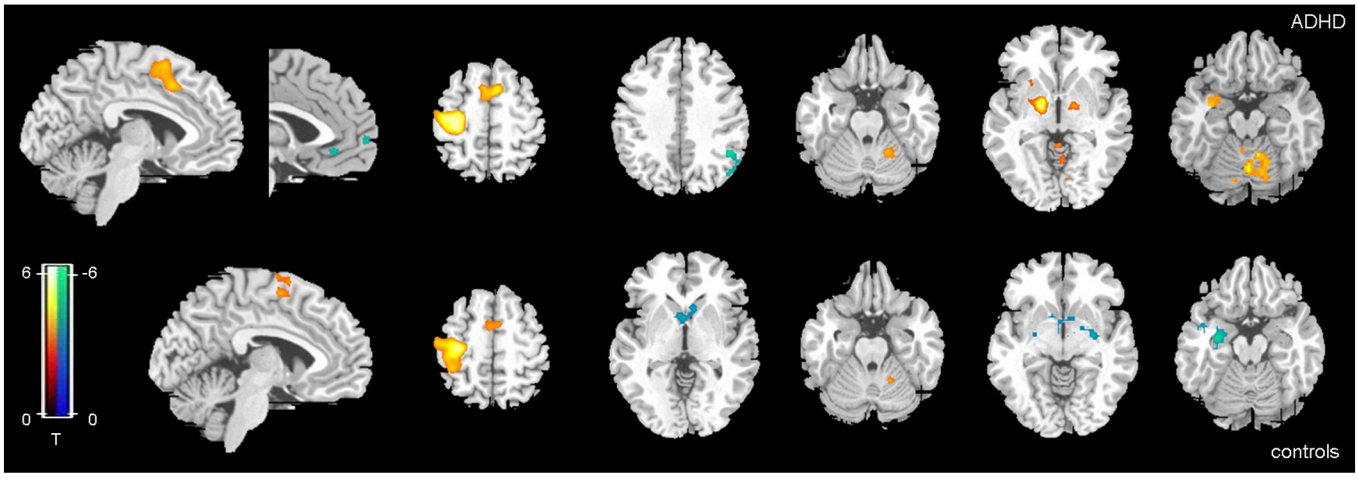

Fig. 1. Brain regions of significantly positive (warm color) and negative (cool color) activations by the correct responses during performance of the categorical n-back task in ADHD patients and healthy controls respectively.

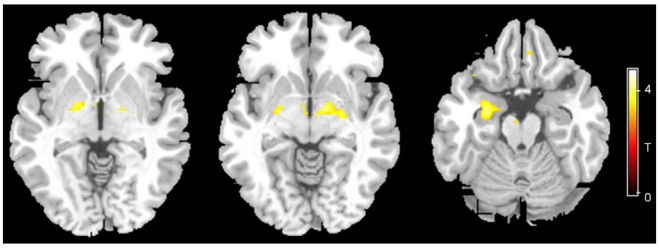

Fig. 2. Compared with healthy controls, ADHD patients showed significantly higher activation by the correct responses in the bilateral globus pallidus and right hippocampus during performance of the categorical n-back task.

(Kobel et al., 2010). Consistent with these studies, the hyperfunction of the hippocampus in ADHD patients during a working memory task in the present study might indicate either impairment or higher efficiency of the hippocampus due to compensational effects. Furthermore, the globus pallidus and hippocampus are working consistently to update the information to the prefrontal cortex that is an executive function center (Lee and Rudebeck, 2010; Nakao et al., 2011), the dysfunction of which is important in the pathophysiology of ADHD (Biederman and Faraone, 2005). And there is a balance between updating and maintenance within the prefrontal cortex, too much updating and it cannot maintain information relevant to the task, too much maintenance and overload occurs (Sander et al., 2012). What the present results about hyperactivation are indicating, theoretically, is that updating circuitry in the context of ADHD may be driven by hyperactivity/impulsivity so that relevant representations are not maintained in working memory to perform the CN-BT as well.

However, although the present study revealed hyperactivation of the striatum and mediotemporal areas in children and adolescents with ADHD during a working memory task, additional questions should be considered. Previous study suggested the right-hemisphere brain activation during a spatial working memory task in ADHD patients (Vance et al., 2007), whereas in the present study, we did not find lateralization activation, which is consistent with the original study using the CN-BT (Ciesielski et al., 2006). One possible interpretation might be that patterns of brain activation are known to depend on the nature of information maintained in the working memory (Tsujii et al., 2009), and our working memory task involved not only visual information but also categorical judgments about objects, making the task much more complex. Furthermore, the mixed subtypes in the ADHD group in the present study might have had confounding effects on the results. Future studies should examine the neural nature of subgroups of ADHD patients to unravel the underlying mechanisms.

5. Conclusion

In summary, children and adolescents with ADHD cannot suppress hyperactivation in the bilateral globus pallidus and the right hippocampus during a working memory task involving categorization compared with healthy controls. Hyperfunction in these areas may be the pathophysiological foundation of ADHD and relate to the deficits of working memory processing and the impulsive symptoms.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2014.03.013.

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