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Alerting deficits in children with attention deficit/hyperactivity disorder: Event-related fMRI evidence

Qingjiu Cao[a], Yufeng Zang[b], Chaozhe Zhu[b], Xiaohua Cao[a], Li Sun[a], Xiaolin Zhou[c,*], Yufeng Wang[a,*]

[a]Institute of Mental Health, Peking University, Beijing 100083, China
[b]State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China
[c]Department of Psychology, Peking University, Beijing 100871, China

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ABSTRACT

Attention deficit/hyperactivity disorder (ADHD) is one of the most common but poorly understood developmental disorders in childhood. Although neuropsychological studies demonstrate that children with ADHD have attentional alerting deficits, the neurobiological bases of such deficits have not been examined extensively. In this study, by using functional magnetic resonance imaging (fMRI), we explored the neural correlates of intrinsic alertness and phasic alertness deficits in ADHD by comparing twelve boys with ADHD (13.4±1.7 years) with 13 age-matched normal controls (13.2±1.2 years) in a cued target detection task. Behaviorally, compared with the controls, the ADHD group showed a higher overall error rate and a larger reaction time variability in performing the task. At the neural level, children with ADHD showed less activation than the controls in frontal (middle and superior frontal gyrus), parietal (inferior parietal lobe, precuneus) and putamen regions. These results demonstrate that children with ADHD have deficits in alerting functions and these deficits are related to the abnormal activities in frontal and parietal regions subserving top-down attention control processes.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common behavioral disorders in childhood. It is characterized by symptoms of inattention, impulsivity and hyperactivity that cause significant functional impairments in multiple settings. According to the symptomatic phenomenology, DSM-IV (American Psychiatric Association, 1994) conceptualizes ADHD as having three subtypes: predominantly inattention (ADHD-I), predominantly hyperactivity/impulsivity (ADHD-HI) and combined (ADHD-C). Subtype classification is based on the presence of six or more symptoms of inattentive behavior (ADHD-I), hyperactive/impulsive behavior (ADHD-HI) or both (ADHD-C). In the inattention symptoms, three of the nine items either explicitly or implicitly refer to poor sustained attention, suggesting that the deficit in sustained attention is an important clinical feature for the diagnosis of ADHD. Although the concept of inattention in the diagnostic criteria of DSM revisions is not formally defined in cognitive terms, there are

* *Corresponding authors.* Y. Wang is to be contacted at the Institute of Mental Health, Peking University, Huanyuanbeilu 51, Haidian District, Beijing 100083, China. Fax: +86 10 6202 7314. X. Zhou is to be contacted at the Department of Psychology, Peking University, Beijing 100871, China. Fax: +867 10 6276 1081.
E-mail addresses: xz104@pku.edu.cn (X. Zhou), wangyf@bjmu.edu.cn (Y. Wang).

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evidences from neuropsychological studies demonstrating abnormalities in basic attentional processes in ADHD (Carter et al., 1995; Oberlin et al., 2005).

According to the attention theory of Posner and Rafal (1987), attention can be subdivided into two broad domains, the intensity and the selectivity. The intensity aspects of attention, which include alertness and sustained attention, are probably a prerequisite for the more complex and capacity-demanding aspects of attentional selectivity (Sturm and Willmes, 2001; Sturm et al., 2004). The alerting process operates to establish sustained attention (e.g., by maintaining a state of readiness to process nonspecific or repetitive stimuli; Swanson et al., 1998). Indeed functional imaging studies have indicated that alertness and sustained attention are subserved by similar brain regions, including right inferior parietal cortex and right frontal cortex (Sturm and Willmes, 2001).

Alertness comprises on the one hand the ability of the internal control of arousal in the absence of an external cue and on the other hand the ability to increase response readiness for a short period after receiving an external cue or stimulus (Sturm and Willmes, 2001). The former is called tonic or intrinsic alertness while the latter is called phasic alertness. Clearly phasic alertness is built upon the basis of intrinsic alertness, triggered by an explicit external stimulus. When compared with intrinsic alertness, phasic alertness confers a behavioral advantage (i.e., alerting effect), which has been linked to the beneficial arousing effect of the cue. In reaction time (RT) studies, the alerting effect is usually measured by $RT_{\text{intrinsic alertness}} - RT_{\text{phasic alertness}}$ (Fan et al., 2005). Several functional neuroimaging studies have shown that intrinsic alertness is related to activities in the right-sided fronto–parieto–thalamic network (Sturm and Willmes, 2001; Sturm et al., 2004), while phasic alertness is related, in addition, to activities in the left-hemisphere frontal and parietal structures (Sturm and Willmes, 2001; Weis et al., 2000). However, it is still controversial concerning the precise neuroanatomical substrates of the alerting effect (Coull et al., 2001; Thiel et al., 2004; Fan et al., 2005).

It is also controversial whether children with ADHD have deficits in their alerting functions. Several behavioral studies demonstrated that, compared with normal controls, children with ADHD have slower RTs and a larger RT variability in cued target detection tasks (McDonald et al., 1999; Oberlin et al., 2005; Swanson et al., 1991). However, a recent meta-analysis suggests that these deficits are rather small, if they do exist (Huang-Pollock and Nigg, 2003). Converging evidence concerning whether children with ADHD have alerting deficits may be collected from functional imaging studies.

Recent functional magnetic resonance imaging (fMRI) studies support the notion of frontostriatal network dysfunctions as the likely cause of ADHD and implicate also other brain regions, such as insular, parietal and temporal cortices (Rubia et al., 1999; Smith et al., 2006; Bush et al., 1999). Selective impairments of these circuits or regions may be related to different cognitive aspects of ADHD (Paloyelis et al., 2007). Different experimental tasks were used to reveal the neurobiological foundations of impulsivity (Rubia et al., 1999; Smith et al., 2006; Bush et al., 1999), working memory deficits (Valera et al., 2005; Sheridan et al., 2007), reward processing abnormality (Strohle et al., 2008) and so on in ADHD. The neural substrates of deficits in attentional components, such as selective or directed attention, were also examined recently (Booth et al., 2005; Shafritz et al., 2004; Tamm et al., 2006), but little is known about the neural substrates of deficits in alerting functions in ADHD. Using a modified version of attention network test (ANT; see Fan et al., 2005), Konrad et al. (2006) found that, compared with normal controls, children with ADHD showed significantly decreased neural activity in the right anterior cingulate gyrus and increased activity in brainstem for the alerting effect. However, this study did not explore directly the neural activities related to intrinsic alertness and phasic alertness, as the effects they obtained were for the subtraction of the no cue condition from the double cue condition. In a pilot fMRI study, Sunshine et al. (1997) reported that during sustained attention, brain regions activated in ADHD patients, including the bilateral middle frontal gyrus, the superior parietal lobules, and the inferior parietal lobules, were similar to those activated in normal individuals tested in a previous study (Lewin et al., 1996). They, however, did not compare directly brain activities in ADHD patients with those in the normals and hence could not reveal the potential deficits in ADHD.

Given that the previous studies did not investigate systematically the neurobiological basis of intrinsic alertness, phasic alertness, and their deficits in ADHD, we used a cued target detection task to explore to what extent children with ADHD would differ from the normal controls in their brain responses to the alerting processes during fMRI. In this task, participants were asked to detect the presence of a white dot target, which would or would not be preceded by a star cue. Brain activities responding to the target-only trials were taken as the neural correlates of intrinsic alertness while brain activities responding to the cue-plus-target trials were taken as the neural correlates of phasic alertness. The differential brain activation between the cue-plus-target condition and the target-only condition was taken as the neural correlates of the alerting effect of the cue. Previous studies have demonstrated that, for normal adults, the right-sided fronto–parieto–thalamic network is activated in intrinsic alertness (Sturm and Willmes, 2001; Sturm et al., 2004) and bilateral fronto-parietal structures are activated in phasic alertness (Sturm and Willmes, 2001; Weis et al., 2000). ADHD patients, on the other hand, show deficits in frontal and parietal activities in a number of different tasks (Rubia et al., 1999; Smith et al., 2006; Bush et al., 1999; Tamm et al., 2006; Vance et al., 2007). We predicted that, compared with normal controls, children with ADHD might show deficits in activation of the right-sided frontal and/or parietal lobe for intrinsic alertness and in activation of the bilateral frontal and/or parietal lobe for phasic alertness. As for the alerting effect, we predicted that the brain regions showing differential activities between children with ADHD and normal controls should be similar to those observed by Konrad et al. (2006). Given that the task used in this study was to reveal the alerting deficits in ADHD, it is possible that the fMRI signal changes in the abnormal regions revealed by this task in ADHD could have correlations with the symptoms severity of inattention as measured by behavioral scales. These signal changes, however, may not show correlations with the extent of hyperactivity/impulsivity because the task does not tap into the neurocognitive processes related to hyperactivity/impulsivity and all the tested children with ADHD had symptoms of inattention.

2. Results

2.1. Demographic and clinical data

Table 1 summarizes the major demographic and clinical data of the participants. The two groups were comparable on age [ADHD: 13.4±1.7 years, control: 13.2±1.2 years, $t(23)<1$]. The IQ was higher for the controls than for the ADHD patients [ADHD: 102.7±9.0; controls: 112.7±13.8, $t(23)=-2.32$, $p=0.04$]. Compared with the controls, the ADHD group got higher scores in the ADHD Rating Scale-IV (ADHD RS-IV), Conners' Parents Rating Scales (CPRS) and their subscales, including inattention, hyperactivity/impulsivity and cognitive problems/inattention subscales.

2.2. Behavioral results

Although children with ADHD showed numerically longer RTs (31 ms) for the target-only and cue-plus-target trials compared with the controls (see Table 2), the differences between the participant groups did not reach significance, as shown in the analysis of variance (ANOVA) with trial type as a within-participant factor and participant group as a between-participant factor, $F(1, 23)=1.53$, $p>0.1$. However, there was a significant main effect of trial type, $F(1, 23)=41.58$, $p<0.001$, with faster responses to cue-plus-target trials (406 ms) than to target-only trials (473 ms). This alerting effect did not interact with the participant group, $p>0.1$, indicating that children with ADHD and the normal controls had equivalent alerting effects. On the other hand, children with ADHD showed a larger RT variability than the controls, as demonstrated by the significant main effect of participant group in ANOVA over the variability, $F(1, 23)=5.54$, $p<0.05$. The group difference was larger for the cue-plus-target trials than for the target-only trials given the marginally significant interaction between participant group and trial type, $F(1, 23)=3.28$, $p=0.083$. These results demonstrated that children with ADHD could not maintain a stable alerting state in preparing for the target.

We collapsed the participants' false responses to catch trials (i.e., commission errors) and their omission of responses to targets (i.e., omission errors) to give overall response error rates (Table 2). Children with ADHD had higher overall error rates than the controls, $t(23)=2.58$, $p<0.05$. Further analyses showed that the commission error rate was higher for children with ADHD than for the controls, $t(23)=2.464$, $p<0.05$, and so the omission error rate, $t(23)=2.024$, $p=0.054$.

Table 1 – Demographic and clinical characteristics of the ADHD and the control groups

Variables/group	ADHD ($n=12$)	Controls ($n=13$)
Age	13.4 (1.7)	13.2 (1.2)
Full scale IQ	102.7 (9.0)	112.7 (13.8)[a]
ADHD RS-IV		
Total scores	44.9 (11.6)	25.5 (6.8)[b]
Inattention	24.4 (4.8)	14.0 (5.4)[b]
Hyperactivity/impulsivity	20.5 (7.9)	11.5 (2.1)[b]
CPRS		
Total scores	36.2 (15.6)	6.5 (7.3)[b]
Cognitive problems/inattention	6.2 (2.4)	1.2 (2.2)[b]

Note: ADHD RS-IV = ADHD rating scale-IV; CPRS = Conners' parents rating scales.
[a] $p<0.05$.
[b] $p<0.001$.

Table 2 – Task performance in children with ADHD and in the normal controls

Variable/group	ADHD ($n=12$)	Controls ($n=13$)
Target-only trials		
Mean RT (ms)	487 (55)	458 (91)
RT variability	97 (24)	86 (27)
Cue-plus-target trials		
Mean RT (ms)	423 (60)	389 (64)
RT variability	116 (41)	80 (26)
Alerting effect (ms)	64 (44)	69 (58)
Overall error (%)	11.93 (8.33)	5.19 (4.21)
Commission for the catch trial (%)	7.55 (6.73)	2.47 (3.21)
Omission for target (%)	12.07 (10.41)	6.11 (5.56)

Numbers in parentheses represent standard deviations.

2.3. Functional MRI results

Fig. 1 shows the results of within-group analyses on the three types of effects for each participant group. As can been seen, brain activation related to the three experimental conditions appears to be less diffusing for the ADHD group than for the controls. Regions showing activation in both participant groups for both target-only and cue-plus-target trials included left primary sensorimotor cortex, right visual cortex, and right cerebellum. Frontal and parietal lobes in the right hemisphere, including cingulate gyrus, paracentral lobe and inferior parietal lobe, were activated for the controls on target-only trials. Children with ADHD, however, did not show activation in cingulate gyrus although they did show significant activation in left putamen, left inferior temporal gyrus and right precuneus. For phasic alertness, the normal controls showed activation mainly in a left frontal network, including middle frontal gyrus and inferior frontal gyrus, while children with ADHD showed activation in the left visual cortex and parahippocampal gyrus.

For the alerting effect (brain activation for cue-plus-target trials minus brain activation for target-only trials), the normal controls showed extensive activation in bilateral middle frontal gyrus, right superior frontal gyrus, bilateral precuneus, bilateral insular, right middle temporal gyrus, left superior temporal gyrus, and left middle occipital gyrus. The ADHD group, on the other hand, showed activation mainly in posterior brain areas (i.e., bilateral occipital gyrus) and right cerebellum. Reversed contrasts with brain activation for target-only trial minus brain activation for cue-plus-target trials did not show significant effects.

Group comparison revealed that, for all the three types of contrasts, there were no regions where activation was greater for the ADHD group than for the controls. Table 3 shows brain regions with decreased activation in children with ADHD compared to the controls. On target-only trials, activation was greater for the controls than for children with ADHD in the

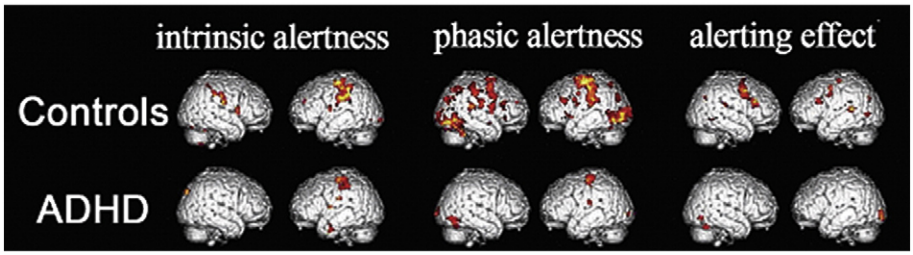

Fig. 1 – Brain activations for the three within-group contrasts in the two participant groups.

right precuneus, right middle frontal gyrus, and left inferior parietal lobe. Percentage signal changes for voxels within these regions having maximally different activations between the two groups are shown in Fig. 2A. On cue-plus-target trials, relative to children with ADHD, the controls showed increased activation in the right middle frontal gyrus, left middle frontal gyrus and left superior frontal gyrus (Fig. 2B). It is clear from the figures that while the signal changes related to the intrinsic (Fig. 2A) and phasic (Fig. 2B) effects were positive for the controls, they were negative for children with ADHD.

For the alerting effect, compared with the controls, children with ADHD showed decreased activation in right precentral gyrus, right supplementary motor area, and left putamen. The plot of percentage signal changes at the maximally activated voxels indicated that, in left putamen nucleus, the normal controls had increased BOLD activity for phasic alertness than for intrinsic alertness while children with ADHD showed a reversed pattern (Fig. 2C).

2.4. *Correlation between fMRI signal intensity and ADHD symptom severity*

Pearson correlation analysis was conducted between percentage signal changes at the maximally activated voxels within brain regions showing significant between-group differences and the ADHD symptom severity indicated by the scores in ADHD RS-IV (i.e., inattention symptoms and hyperactivity/impulsivity symptoms) in ADHD group. For intrinsic alertness, a significant negative correlation was observed between percent signal changes in the right precuneus and scores of inattention symptoms in ADHD RS-IV ($r=-0.587$, $p<0.05$; Fig. 3A), with more severe the inattentive symptoms the less activation in the right precuneus in ADHD group. This correlation was confirmed by another analysis in which activities in the same region correlated negatively with the factor scores of cognitive problems/inattention in CPRS ($r=-0.621$, $p<0.05$; Fig. 3B). However, the specificity of the reduced activity in precuneus for inattention was not robust, as the correlation was reduced in the partial correlation analysis controlling for the hyperactivity/impulsivity symptoms ($r=-0.466$, $p=0.148$). Analyses of other correlations, including the one between signal changes at precuneus and the scores of hyperactivity/impulsivity symptoms, did not find significant effects.

3. Discussion

This study explored the neural correlates of intrinsic and phasic alertness deficits in children with ADHD. Consistent with our hypotheses, we found significant behavioral as well as brain activation differences between children with ADHD and the normal controls. Relative to the controls, children with ADHD had significantly more overall response errors and a larger RTs variability in performing the cued target detection task. Indeed, it has been suggested that the measurement of RT variability is more sensitive to ADHD symptoms than the measurement of

Table 3 – Brain regions showing decreased activation in the ADHD group compared with the normal controls

Hemisphere	Brain area	Talairach coordinates (x, y, z)	BA	Volume	Z score
Intrinsic alerting					
R	Precuneus	9,−53, 50	7	837	4.08
R	Middle frontal gyrus	24, 25, 35	8	567	3.90
L	Inferior parietal lobe	−56, −39, 41	40	432	3.60
Phasic alerting					
R	Middle frontal gyrus	24, 2, 44	6	1944	4.20
R	Middle frontal gyrus	24, 43, −10	11	648	4.12
L	Middle frontal gyrus	−33, 22, 24	9	1269	3.82
L	Superior frontal Gyrus	−18, 31, 29	9	459	3.58
Alerting effect					
R	Precentral gyrus	18, −29, 57	4	297	3.83
R	Supplementary motor area	12, 6, 58	6	468	3.59
L	Putamen	−21, 3, 3		432	3.40

Note: R, right; L, left; BA, Broadmann area.

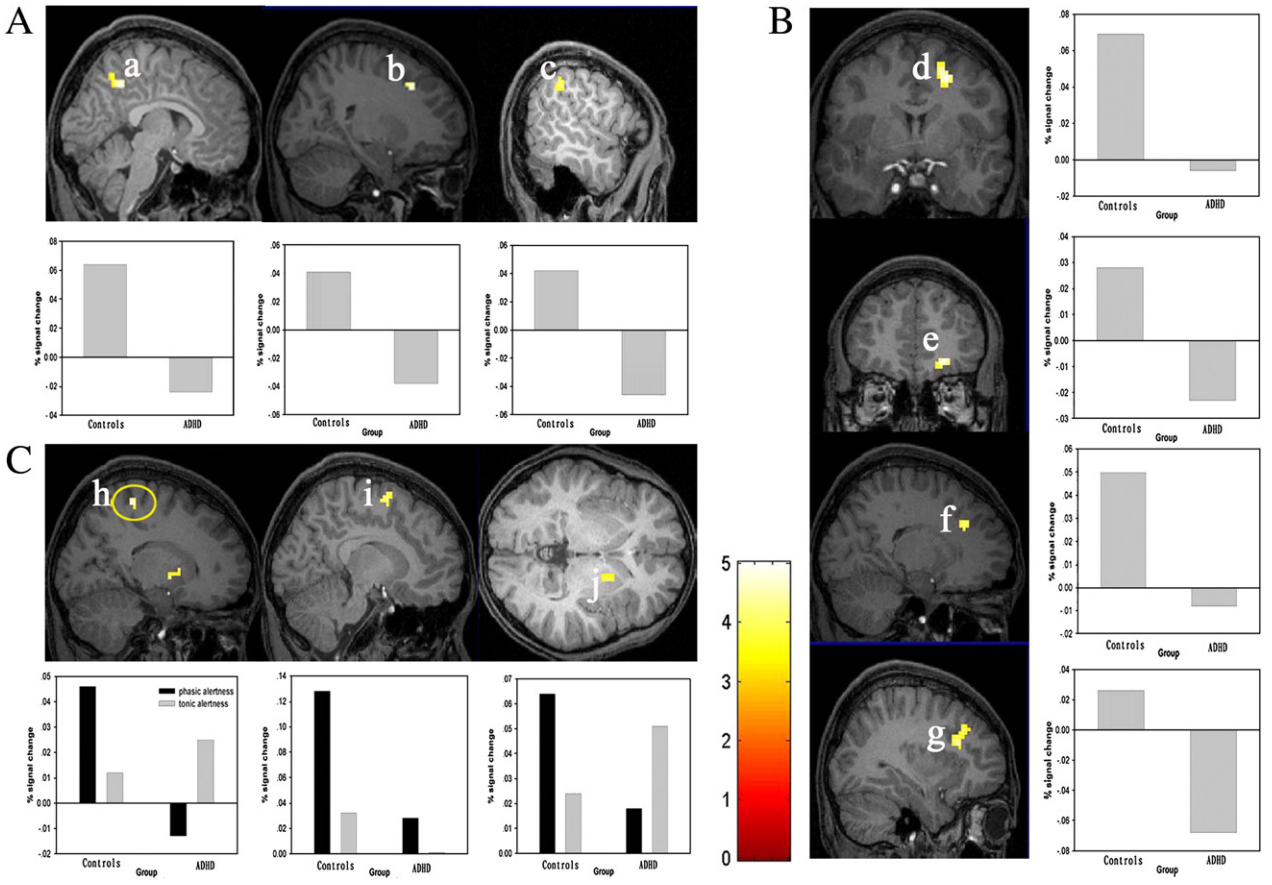

Fig. 2 – Brain regions showing decreased activation in the ADHD group compared with the controls for A) intrinsic alertness, B) phasic alertness and C) alerting effect (thresholded at $p < 0.001$, uncorrected, extend threshold 10 voxels). a, right precuneus; b, right middle frontal gyrus; c, left inferior parietal lobe; d, right middle frontal gyrus; e, right middle frontal gyrus; f, left middle frontal gyrus; g, left superior frontal gyrus; h, right postcentral gyrus; i, right supplementary motor area; j, left putamen nucleus. Plots of the percentage blood oxygen level dependent (BOLD) signal changes are shown for the participant groups for the maximum activation voxels in different regions.

mean RT (Epstein et al., 2003). Children with ADHD also exhibited significantly less activation than the controls in frontal, parietal and striatum regions. These findings suggest that deficits in the attentional alerting functions in children with ADHD are related to the abnormal activities in frontal and parietal regions subserving top-down attention control processes.

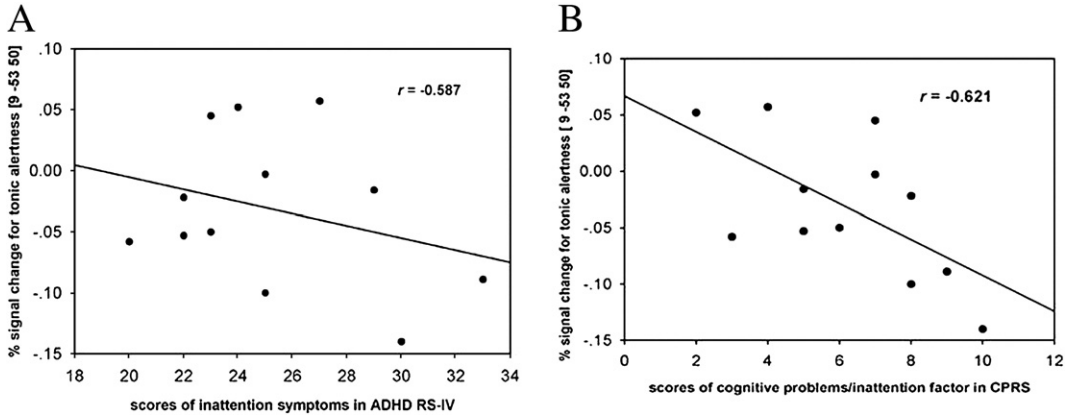

Fig. 3 – Correlations for the ADHD group in the intrinsic alertness condition between the percentage signal change in the maximum activation voxel within right precuneus and (A) scores of inattention symptoms in ADHD RS-IV and (B) the factor scores of cognitive problems/inattention in CPRS.

Within-group analyses for the normal controls revealed significant activation for intrinsic alertness in frontal (anterior cingulated gyrus, middle frontal gyrus), parietal (inferior parietal gyrus, precuneus), thalamus and brainstem structures. This finding is similar to those reported in functional imaging studies for intrinsic alertness in normal adults (Sturm and Willmes, 2001; Sturm et al., 2004), suggesting that the task used here captured the construct of intrinsic alertness. For phasic alertness, there was significant bilateral frontal (middle frontal gyrus) activation, consistent with findings in Weis et al. (2000). For the alerting effect, bilateral middle frontal gyrus, right superior frontal gyrus, bilateral precuneus, bilateral insular, right middle temporal gyrus, left superior temporal gyrus, and left middle occipital gyrus were activated for the normal controls. This finding is inconsistent with Coull et al. (2001) and Fan et al. (2005) who found primarily left-hemisphere activation. The discrepancy may be caused partly by the different experimental paradigms since stimuli in this study were presented at the center of the screen while stimuli in Coull et al. (2001) and Fan et al. (2005) were presented peripherally, involving attentional shift. In addition, differences in participants' age may have also contributed to the discrepancy as a previous study showed that the brain network for the top-down attentional modulation process is not fully established in children (Konrad et al., 2005).

Compared with the controls, children with ADHD appeared to have less diffusing activation in frontal and parietal areas for both intrinsic alertness, phasic alertness and the alerting effect. They tended to recruit the posterior brain regions (i.e., posterior occipital lobe) and cerebellum for the alerting processes. It has been proposed that frontal and parietal regions are the neuroanatomical substrates of top-down processes of attention (e.g., Hopfinger et al., 2000; Corbetta and Shulman, 2002). Failure to activate these regions suggests that children with ADHD may have deficits in these processes, although this suggestion should be substantiated in further, more systematic studies.

Although the two participant groups had no significant differences in mean RTs to the target and in the alerting effect, direct comparisons found that the two groups have deviant brain activation patterns related to these comparisons. These apparent differences between behavioral and neural data suggest that RT measures might be less sensitive to attentional deficits than brain activation measures under some circumstances.

For intrinsic alertness, direct comparisons revealed that, compared with the controls, children with ADHD had decreased activation in right precuneus, right middle frontal gyrus and left inferior parietal lobe. A recent study (Tamm et al., 2006) using the oddball detection task demonstrated that children with ADHD had significantly less activation in bilateral parietal lobe (including the superior parietal gyrus and supramarginal and angular gyri of the inferior parietal lobe) and right precuneus. In an attentional switch task, Smith et al. (2006) found that boys with ADHD showed decreased activation in right parietal lobe. Similar findings of decreased activation in parietal lobe, especially in precuneus and inferior parietal lobe, were also obtained for children with ADHD in this study. Consistent with our hypothesis that the fMRI signal changes in abnormal regions could correlate with the symptoms severity of inattention but not with the extent of hyperactivity/impulsivity, the correlation analysis suggested that activation of the right precuneus correlated with the severity of inattention symptoms in ADHD, although this decreased activation in the right precuneus could be influenced by the hyperactivity/impulsivity symptoms. The precuneus and inferior parietal lobe are thought to be associated with goal-directed attention and to code for top-down signals of visual expectancy (Corbetta and Shulman, 2002; Hahn et al., 2006). For intrinsic alertness, because of the absence of external cues, participants had to modulate the level of alertness in a top-down mode in self-initiated preparation for a subsequent response to an expected stimulus (Sturm and Willmes, 2001). The abnormality of parietal lobe in ADHD during the intrinsic alertness suggests that children with ADHD may have impairment in the posterior parietal attentional system (Tamm et al., 2006), especially in the function of top-down modulation.

Compared with the controls, children with ADHD also showed decreased neural activity in bilateral middle frontal gyrus and left superior frontal gyrus for phasic alertness. Using the cued target detection paradigm, several studies demonstrated that activation of bilateral middle frontal gyrus and left superior frontal gyrus is associated with cue processing (Hahn et al., 2006; Hopfinger et al., 2000). Processing of the cue could increase phasic arousal or even the ability to prepare for a motor response in advance (Coull et al., 2001). The dysfunction of these regions could interfere with the following target-related activity. Hence the dysfunction in bilateral middle frontal gyrus and left superior prefrontal gyrus in children with ADHD in the present study might explain their poorer behavioral performance associated with phasic alertness, including the larger RT variability. Indeed, further analyses indicated that there were significant correlations between the SDs of phasic alertness RT and the changes of the BOLD signal in the maximum activation voxels within these brain regions.

For the alerting effect, children with ADHD showed less activation in the right precentral gyrus, right supplementary motor area and left putamen than the controls. Many studies have observed the anatomical and functional abnormalities of putamen in ADHD (see Bush et al., 2005, Seidman et al., 2005 for reviews), indicating that the putamen is one of the primary structures in the pathology of ADHD (Teicher et al., 2000). In our study, the patterns of BOLD activity at putamen were different between the two participant groups for target-only and cue-plus-target trials, adding further support for the view that children with ADHD may be closely tied to functional abnormality at putamen. Moreover, the finding of less activation in the supplementary motor area is consistent with Tamm et al. (2004) who observed that this region was hypoactivated for children with ADHD in a response inhibition task.

The direct between-group comparisons showed that there was no activation of additional brain regions in children with ADHD, compared with the normal controls. This finding is consistent with the results of recent reports (Booth et al., 2005; Vance et al., 2007) but is different from some other studies (Durston et al., 2003; Konrad et al., 2006). The hypoactivation in regions specified in Fig. 2 for children with ADHD may result from the decreased activation in the alerting conditions and/or the increased activation in the baseline, which was defined as the averaged brain activity occurring during the intervals between experimental tasks (Friston et al., 1999). Our previous study has indicated that,

compared to the normal controls, children with ADHD exhibited higher brain activities during the resting-state (Tian et al., 2008). In the scanner, while waiting for the stimulus, it is probably easier for children with ADHD to be attracted by the irrelevant stimuli, such as the noise of the scanner, resulting in higher brain activities in the "baseline" for them than for the controls. It is possible that the resting-state brain activity is intrinsically related to the no-stimulus baseline activity in an experimental setup; and the negative fMRI signal changes for children with ADHD (see Fig. 2) may have something to do with the higher-level baseline, although this issue should be addressed in further studies. In any case, we were interested in whether there are differences between the differential brain activities induced by experimental conditions across the two groups of individuals. It is almost impossible to find optimal baselines that are equivalent to individuals with ADHD and their normal controls.

The present study has a few limitations. Firstly, the sample size in this study was relatively small and that, no ADHD children with predominantly hyperactive-impulsive subtype and female children with ADHD were included. Secondly, several individuals in the ADHD group met diagnostic criteria for oppositional defiant disorder (ODD) and conduct disorder (CD), which may have confounded the findings to some extent. Thirdly, in our sample children with ADHD had lower IQ than the controls, although the IQ scores were not found to correlate with either behavioral data or MR signal changes. Nevertheless further studies may use ADHD patients and the controls that are better matched in IQ and other aspects even though the relatively lower IQ maybe intrinsic to individuals with ADHD (Castellanos et al., 1996). Fourthly, the findings concerning the alerting effect in our study were somewhat different from Konrad et al. (2006) who found decreased activation in the right anterior cingulated gyrus and increased activation in the brainstem for ADHD. The reasons for the discrepancies are unknown at the moment, as the two studies differed in a number of aspects, including the experimental task, the age of participants, and the comorbidity. Further studies are needed to examine the contributions of these factors to the pattern of brain activation for the alerting effect.

In summary, our results demonstrate that children with ADHD have impairments in alerting functions associated with abnormalities in brain activation. They are hypoactive in frontal and parietal lobes that subserve the top-down attentional control processing.

4. Experimental procedures

4.1. *Participants*

Participants included 15 boys with ADHD and 14 age- and gender-matched controls, all aged between 11 and 16 years. Three patients and 1 normal boy were excluded from further analysis because of their excessive head motion (see Statistical analyses). All the participants met the following criteria: (1) right-handed, (2) no lifetime history of head trauma with loss of consciousness, (3) no history of neurological illness or other serious physical diseases, and (4) the full score of Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R, Gong and Cai, 1993) higher than 85. This study was approved by the Research Ethics Review Board of Institute of Mental Health, Peking University.

Children with ADHD were recruited from the outpatients of Peking University Institute of Mental Health. A structured diagnostic interview, the Clinical Diagnostic Interviewing Scales (CDIS) (Barkly, 1998), which is based on DSM-IV criteria, was administered to diagnose ADHD. The inclusion criteria for children with ADHD were: (1) ADHD-I or ADHD-C, (2) no history of emotional disorders, affective disorders, Tourette disorder and other Axis I psychiatric disorders, and (3) no evidence of severe language development delay or communication problems as determined through clinical history, parent interview, and observation of the child. Boys with ADHD comorbid CD or ODD were included. Seven patients met the criteria for ADHD-C and 5 for ADHD-I. Nine of the 12 patients were stimulants naive and the other 3 patients were withheld from stimulants at least 2 weeks before the MRI scanning. Five had comorbid ODD and 2 had comorbid CD. Controls were recruited from a local middle school. The inclusion criteria for them were the same as the ADHD group except that they were not diagnosed as ADHD according to CDIS. Other information collected from the participants included the CPRS and the ADHD RS-IV reported by parents. The ADHD RS-IV contains all the inattention and hyperactivity/impulsivity symptoms of ADHD according to DSM-IV. Each symptom is scored according to how often it occurred (i.e., "never" is rated as 1, "occasionally" is 2; "often" is 3; and "always" is 4). Potential control participants who had 6 or more items of inattention or hyperactivity/impulsivity symptoms scored higher than 2 according to ADHD RS-IV were excluded.

All the participants were asked, for at least 24 h prior to fMRI scanning, to abstain from medication, foods, liquids containing caffeine or other substances which may influence the level of arousal. After the complete description of study procedures, written informed consents were obtained from parents or guardians of the participants. All children recruited agreed to take part in the experiment.

4.2. *Experimental task*

During the fMRI scanning, each child performed a randomized event-related version of the cued target detection task, with the inter-trial intervals (ITI) being jittered from 6 to 10 s (6, 8 and 10 s, mean = 6.6 s). We used a relatively long ITI, making it unlikely that a preceding stimulus acted as a warning signal (cue) for the subsequent trial. This time separation would be crucial for trials without the preceding cue (i.e., target-only trials) and make it possible to isolate the intrinsic effect (Sturm et al., 2004).

Stimuli consisted of a white star cue and a white dot target presented against a black background, with the cue and the dot subtending about 1.5° of the visual angle. A fixation cross was presented at the center of the screen all the time, and the participants were required to fixate the cross throughout the runs. There were three types of task conditions: 1) intrinsic alertness, which consisted only of a target presented at the center of the screen for 200 ms (i.e., target-only trial); 2) phasic alertness, which consisted of a cue and a target (i.e., cue-plus-target trial); and 3) the catch condition in which the cue was

presented but it was not followed by a target. In cue-plus-target trials, the cue was displayed at the center of the screen for 100 ms. After a variable stimulus-onset-asynchrony (SOA) of 200 or 500 ms, the target was presented for 200 ms. We used two different SOAs to minimize the potential impact of temporal orienting and anticipation. The catch condition was used to prevent the participants from responding without attending to the target. Each condition has 52 trials, which were presented in a pseudorandom order. Each participant was tested for two runs, each containing 26 trials for each condition and lasting 8.5 min.

The stimuli were presented through a LCD projector onto a rear projection screen located at the participant's head. The screen was viewed with an angled mirror positioned on the head-coil. Before scanning, the participants were informed of the different trial types. They were instructed to respond to the target as fast and as accurately as possible, with the right thumb pressing the button of a keypad placed on the right of their body. A 3-minute training session was performed before scanning.

4.3. *Data acquisition*

MRI data were acquired using a SIEMENS TRIO 3-Tesla scanner (Siemens, Erlangen, Germany) in the Institute of Biophysics, Chinese Academy of Sciences. Participants lay supine with head snugly fixed by a belt and foam pads to minimize head movement. The functional images were acquired by using an echo-planar imaging (EPI) sequence with the following parameters: 30 axial slices, thickness/skip = 4.0/1.0 mm, in-plane resolution = 64 × 64, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm, 256 volumes each run. In addition, a T1-weighted, sagittal three-dimensional spoiled gradient-recalled sequence was acquired covering the whole brain (176 slices, TR = 1700 ms, TE = 3.03 ms, slice thickness = 1.0 mm, skip = 0 mm, flip angle = 15°, inversion time = 1100 ms, FOV = 240 × 240 mm, in-plane resolution = 256 × 256).

4.4. *Statistical analyses*

The fMRI data were analyzed with Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London; Friston et al., 1995). The first 4 volumes were discarded to remove saturation effects. The remaining fMRI images were corrected for the acquisition delay between slices and for the head motion. Individual runs exhibiting more than 3 mm maximum displacement in any direction of x, y, and z or 3° of any angular motion throughout the course of the scan were excluded from further analysis. Four participants (3 ADHD and 1 control) were rejected based on this criterion and three participants (2 ADHD and 1 control) had only one run for further analysis. There were no significant differences in total translation and rotation in remaining fMRI data between two groups. The fMRI data were then normalized to the standard MNI template, re-sampled to 3-mm cubic voxels, and then spatially smoothed with a Gaussian kernel of 6 × 6 × 6 mm^3 full-width at half-maximum.

Four event types were defined at the first level, consisted of two conditions of interest (phasic alertness, intrinsic alertness) and two conditions of no interest (catch trials and errors responses). Correct trials in the two interested conditions were taken into analysis in each run for each participant with six head movement parameters as confounds. For the individuals who had two runs for further analyses, the minimum number of trials included in each condition for analysis was 36. For the controls, the average correct trials used for analysis were 48, 49 and 49 respectively for the target-only, the cue-plus-target and the catch conditions. For children with ADHD, these numbers were 45, 46 and 47, respectively. When using SPM2 to construct design model, the baseline in general refers to the averaged brain activity occurring during the intervals of experimental tasks, which need not to be explicitly modeled in SPM (Friston et al., 1999). The event types were time-locked to the onset of stimuli by a canonical synthetic haemodynamic response function (HRF) and its first-order temporal derivative. The parameter estimates for the canonical HRF and linear contrasts of these estimates comprised the data for the second stage of analyses.

For the second-level analysis, random effect analyses were firstly performed for the ADHD and the control groups separately. In each group, three planned one-sample *t*-tests were conducted to identify neural correlates of 1) phasic alertness (i.e., cue-plus-target trials — baseline), 2) intrinsic alertness (i.e., target-only trials — baseline) and 3) alerting effect of the cue (i.e., cue-plus-target — target-only). Two-sample *t*-tests were then performed to investigate group differences in activation between the ADHD group and the controls. Activations for one-sample and two-sample *t*-tests were all reported at a level of significance $p < 0.001$, uncorrected and a cluster threshold of greater than 10 voxels. MNI stereotactic was transformed to Talairach and Tournoux space (Talairach and Tournoux, 1988).

We compared the ADHD and the control groups on demographic, psychiatric, and cognitive factors, using AVOVA, the Student's *t*-test and chi-square test. Correlation analyses were performed to explore the relationship between brain activation and ADHD symptom severity in the ADHD group. Brain regions in which the two groups showed significantly different activation were identified firstly, and then Pearson correlations between the changes of the BOLD signal in the maximum activation voxels within these regions and the ADHD symptom severity were computed. A two-tailed *p* level of 0.05 was used as the criterion of statistical significance.

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