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ORIGINAL PAPER

Boong-Nyun Kim · Jae-Sung Lee · Min-Sup Shin · Soo-Churl Cho · Dong-Soo Lee

Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder

Statistical parametric mapping analysis

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Abstract *Objective* A voxel based investigation of cerebral blood flow was conducted to identify brain function differences in the resting state between children with Attention Deficit Hyperactivity Disorder (ADHD) and normal controls. *Method* Using DSM-IV criteria, we selected 40 children with pure ADHD by various assessment scales, psychometric tools and a neuropsychological battery. All patients were examined by ^{99m}Tc-HMPAO brain SPECT. Seventeen normal controls were recruited from age, sex, and IQ-matched children whose previous SPECT, MRI, EEG and psychometric and neuropsychological findings had been normal. Using SPM methods, we compared SPECT images of ADHD patients and those of 17 control subjects on a voxel by voxel basis using t-statistics. Voxels with a p-value of less than 0.01 were considered to be significantly different. *Result* Decreased cerebral blood flow in right lateral prefrontal cortex, right middle temporal cortex, both orbital prefrontal cortex and both cerebellar cortices were found in children with ADHD compared to the controls. In addition, the ADHD group showed increased blood flow in some parietal and occipital lobes (posterior brain regions) compared to the control group. *Conclusion* Although the results should be interpreted cautiously, this study confirms the presence of functional defects in the prefrontal cortex and reports new problems in the limbic area, somatosensory areas and in the cerebellum during the resting state of brains of ADHD children.

Key words ADHD · SPM · SPECT

B.-N. Kim (✉) · S.-C. Cho · M.-S. Shin
Division of Child & Adolescent Psychiatry
Department of Neuropsychiatry, Clinical Research Institute
Seoul National University Hospital
28 Yungundong, Chongrogu,
Seoul, Korea
Tel.: +82-02/760-2928
Fax: +82-02/747-5774
E-Mail: kbn1@snu.ac.kr

J.-S. Lee · D.-S. Lee
Department of Nuclear Medicine, Clinical Research Institute
Seoul National University Hospital
Seoul, Korea

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent pediatric behavioral disorders and affects 5–8 % of school-age children (American Psychiatric Association, 1994; Brown and Spencer, 1996; Biederman, 1998). A recent review of studies on ADHD suggested the importance of neurobiological pathophysiology (Castellanos, 1997). In this context, brain imaging techniques have rapidly developed and been applied to ADHD research since the late 1980s (Bonne et al., 1992; O'Tuama and Treves, 1993). Structural neuroimaging studies have shown volumetric abnormalities of the frontal lobe, basal ganglia, parietal lobe and cerebellum in ADHD (Giedd et al., 2001; Eliez and Reiss, 2000; Castellanos et al., 2001; Hale et al., 2000). Although the results of functional imaging studies have not been consistent, they have demonstrated lower brain activity by positron emission tomography (PET), single photon emission computerized tomography (SPECT), and electroencephalogram (EEG) in the superior and inferior prefrontal brain areas, caudate nuclei and parietal brain regions (Zametkin et al., 1990; Spalletta et al., 2001; Langleben et al., 2001; Gustafsson et al., 2000). In functional imaging studies, controlled studies of regional cerebral blood flow (rCBF) using SPECT have been performed in ADHD at rest (Lou et al., 1989; Sieg et al., 1995) or during cognitive tasks (Amen and Carmichael, 1997). However, subjects in SPECT rCBF studies to date have usually been few in number (range: 10–20 patients) and heterogeneous (i. e., have included neurologic patients, patients with other comorbid psychiatric diagnosis). All SPECT studies have used region of interest (ROI) based

methods to quantify the regional brain uptake of tracers. The ROI method has relatively a few limitations, such as, high observer dependence, low reliability and the limited examination of portions of the brain rather than entire areas of the brain. Furthermore, the ROIs are almost invariably large in size and lump together heterogeneous subregions within each brain structure (Busatto et al., 2000). Like ADHD, in the absence of established hypothetical regional cerebral abnormalities, SPM analysis is better suited for study than the ROI method.

To our knowledge, this is the first study to evaluate the different resting brain perfusions of ADHD and normal children using an automatic voxel-based statistical parametric mapping (SPM) method instead of an ROI method. We measured resting rCBF with SPECT in a relatively large (n = 40) number of drug naive, homogeneous pure ADHD patients and compared their results with those of a group of normal controls.

Methods

Subjects

Patients and clinical assessment

Before the study, its nature and purpose were fully explained to the patients and their parents, and a written informed consent was obtained from each child's parent and a written assent from each child for the entire procedure. The Ethics Committee of the Department of Nuclear Medicine and Neuropsychiatry, Seoul National University (Seoul, Korea), approved the protocol.

A total of 40 right-handed ADHD patients including 32 boys and 8 girls (mean age: 9.7 ± 2.1 y) participated in this study. All subjects had been living in ordinary family environments and attending regular schools. At least one certified child psychiatrist and child psychologist evaluated each subject. All patients included in this study were clinically diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994). Patients with any comorbid psychiatric diagnoses, such as depression, anxiety, conduct disorder or learning disorders were excluded. All ADHD subjects were free from any general medical condition. This was confirmed by medical and neurological examination and laboratory tests.

Intellectual and learning abilities were assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974). and the Luria-Nebraska Neuropsychological Battery (LNNB) (Golden, 1987). ADHD subjects who were suspected of being afflicted with mental retardation and learning disorders were excluded.

Behavioral and emotional problems were assessed using the Child Behavior Checklist (CBCL) (Achenbach, 1991), Yale Children's Inventory (YCI) (Shaywitz, 1988), Conners' Parent Rating Scale (CPRS) and Conners' Teacher Rating Scale (CTRS) (Goyette et al., 1978), which have all been previously standardized in Korea. The clinical characteristics of ADHD subjects are presented in Tables 1 and 2.

Controls and assessment

Control subjects were collected retrospectively from children who had undertaken brain SPECT studies during the past 3 years at our institute. The control subjects were mainly recruited from the department of pediatrics. All the patients, however, were referred to the department of child psychiatry because there were no specific organic causes during P/E and brain imaging (including MRI, SPECT and EEG) and were evaluated via psychological assessment and psychiatric interview. At that time all the subjects were screened by the parental version of DuPaul ADHD scale and CBCL (Table 2). No definite meaningful T-scores in the CBCL and ADHD scales were found. All subjects also received WISC-R; no one showed attentional problems in the subsets of results of the IQ test. Finally 17 age-matched subjects who met the following criteria were selected as controls. The criteria for normal controls were that 1) the subject had no abnormal findings on EEG, MRI, and brain SPECT by expert visual decision, 2) the subject had already been neuropsychologically assessed and that

Table 1 Demographic and psychometric variables in patients and controls

Variables/group	ADHD (n = 40)	Controls (n = 17)
Age		
Mean (S. D.*)	9.7 (2.1)	10.4 (2.2)
Range	8–12	8–12
Sex	Boys (32) : Girls (8)	Boys (15) : Girls (2)
Grade		
Mean (S. D.)	5.4th Gr. (2.7)	5.6th Gr. (1.2)
Range	primary school 1–6	primary school 1–6
KWIS		
Mean (S.D)	99.7 (10.8)	101.3 (11.2)
Range	90–123	100–121
LNNB-C	T-score	
C1	62.6 (11.2)	Not performed
C2	61.1 (10.5)	
C3	54.8 (12.1)	
C4	59.9 (10.2)	
C5	52.4 (3.5)	
C6	52.2 (4.7)	
C7	54.7 (5.8)	
C8	56.2 (13.2)	
C9	62.9 (12.7)	
C10	53.8 (13.7)	
C11	60.6 (10.4)	
S1	61.4 (12.3)	
S2	60.4 (13.5)	
S3	69.5 (14.1)	

KWIS Korean version of Wechsler Intelligence Scale for Children
Non-significant differences in age, grade and KWIS score by Students' T-test
LNNB-C Luria-Nebraska Neuropsychological Battery for children, T score > 60: clinically meaningful impairment; *C1* motor function; *C2* rhythm; *C3* tactile function; *C4* visual function; *C5* receptive speech; *C6* expressive speech; *C7* writing; *C8* reading; *C9* arithmetic; *C10* memory; *C11* intellectual process; *S1* pathognomonic; *S2* left sensory motor; *S3* right sensory motor

Table 2 Scores in rating scales in patients and controls

Variables/group	ADHD (n = 40)	Controls (n = 17)
CBCL		
Attention problems**	6.45 (5.8)	1.44 (2.2)
Delinquent behavior*	1.05 (3.2)	0.55 (1.1)
Aggressive behavior*	2.02 (2.2)	0.75 (1.8)
DuPaul ADHD scale**	24.6 (6.8)	3.8 (4.2)
DSM-IV diagnostic criteria	11.3 (5.4)	NC
Yale Child Inventory		NC
Attention problems	13.9 (4.0)	
Impulsivity	8.5 (2.5)	
Hyperactivity	9.0 (2.9)	
Conners		NC
Conners-parent	20.3 (4.6)	
Conners-teacher	16.2 (4.5)	

CBCL Korean version of Child Behavior Checklist
* statistically significant ($p < 0.05$)
** statistically highly significant ($p < 0.01$)

no evidence of ADHD or any other psychiatric problem was found in the psychiatric interview and clinical scales, and 3) the subject had no medical history of loss of consciousness, no neurological illness, and no serious behavioral problem. Most of the normal controls had a diagnosis of tension headache. Among these 17, primary diagnosis of 11 children was the somatoform disorder (their chief complaint is tension headache related with tension, stress, especially academic examination). Five children received no diagnosis (their chief complaints were examination after mild physical injury including traffic accident), 1 received adjustment disorder with mild degree depressive symptom (she also complained about frequent headache and received play therapy).

Image processing and analysis by statistical parametric mapping

SPECT imaging protocol

All subjects lay in the supine position, with their eyes closed, in a quiet room with dimmed lights. 555 MBq Tc–99m-HMPAO was administered and the SPECT image was acquired using a dual head gamma camera (Prism 2000; Picker International, Cleveland, OH) with a low-energy, high-resolution parallel hole collimator. The energy window was set at 140 keV with a 15 % width. One hundred and twenty frames were acquired, in the step-and-shoot mode, with each frame acquired for 20 seconds. Frames were 128 × 128 pixels in size, transaxial images were reconstructed as 64 × 64 matrixes and filtered with a Metz filter (x = 1.5~2.0); all images were corrected for attenuation using Chang's method (Chang, 1978). Finally, 40–50 images from the top of the cerebral cortex to the bottom of the cerebellum perpendicular to the orbito-meatal line were reconstructed.

Statistical parametric mapping analysis

Statistical parametric mapping (SPM) (Talairach and Tournoux, 1988; Friston et al., 1989, 1990, 1991, 1995a, 1995b) was used to determine the quantitative differences between the Tc–99m-HMPAO SPECT images of the ADHD patients and the age-matched controls. Using SPM 99 (Statistical Parametric Mapping 99, Wellcome Department of Cognitive Neurology, London, UK) software, all the images were spatially normalized onto the Tc–99m-HMPAO SPECT standard template provided SPM software to remove inter-subject anatomical variability (Friston et al., 1991, 1995a, 1995b). Affine transformation was performed to determine which 12 optimal parameters to use to register the brain on the template. Subtle differences between the transformed image and the template were removed by the nonlinear registration method using the weighted sum of the pre-defined smooth basis functions used in discrete cosine transformation. Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm FWHM. The aim of smoothing was to increase the signal-to-noise ratio and to account for the variations in subtle anatomical structures. The count of each voxel was normalized versus the total count for the brain (proportional scaling in SPM) to remove global CBF differences between the individuals. After spatial and count normalization, significant differences between the SPECT images of ADHD patients and age-matched controls were estimated at every voxel using t-statistics. Voxels with a p-value of less than 0.01 were considered to be significantly different.

Result

Regions of cerebral perfusion defect in the ADHD group

As shown in Fig. 1 and Table 3, four voxel clusters were found to have significantly reduced HMPAO uptake in ADHD patients relative to control subjects ($p < 0.01$, two-tailed). These were the large middle frontal gyrus and medial orbito-frontal gyrus (voxel numbers: 594, z value = 3.16, p = 0.001) in the right hemisphere, the small middle temporal gyrus (voxel numbers: 130, z

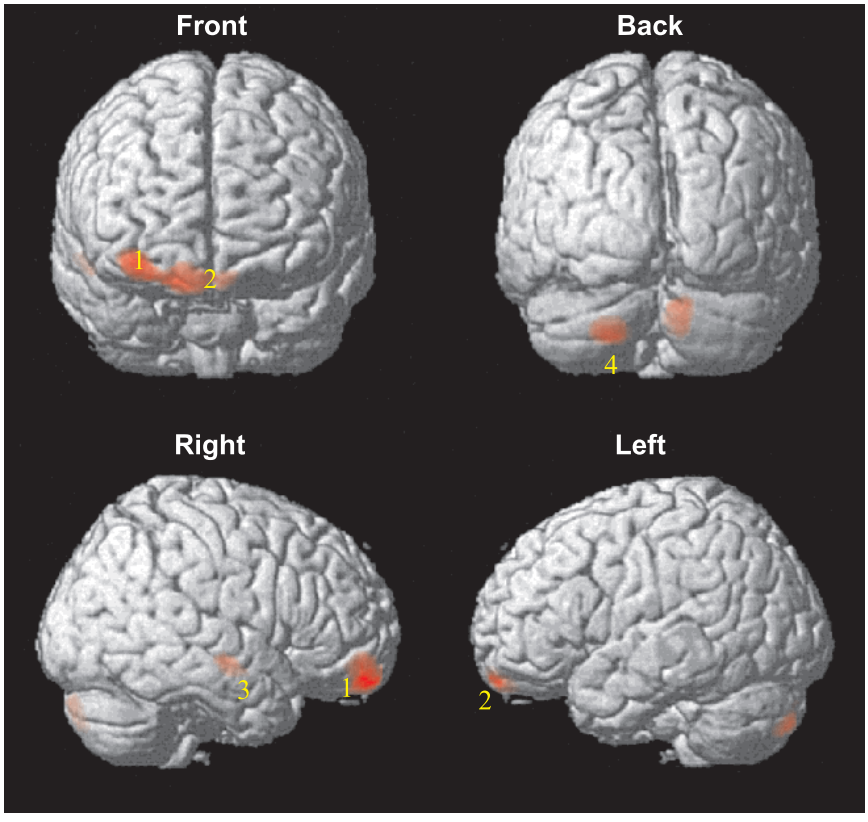

Fig. 1 Brain areas with significantly decreased perfusion in ADHD patients compared to normal controls (threshold: $P = 0.01$, uncorrected). In this figure, four clusters labeled with numbers are shown: right lateral prefrontal cortex (number 1); large right and small left orbitofrontal cortices (number 2); right middle temporal cortex (number 3); right and left cerebellar cortex (number 4)

Table 3 Brain areas with significantly decreased perfusion in ADHD patients compared to normal controls (threshold: P = 0.01, uncorrected)

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	*P* value (uncorrected)
594	Middle frontal gyrus	Right	36, 54, –12	3.16	0.001
	Medial frontoorbital gyrus	Right	8, 58, –20	2.89	0.002
146	Cerebellum	Left	–22, –84, –44	3.15	0.001
131	Cerebellum	Right	10, –88, –34	3.03	0.001
130	Middle temporal gyrus	Right	54, –12, –12	2.73	0.003

value = 2.73, p = 0.003) in the right hemisphere; and medial cerebellar cortices in the right (voxel number: 131, z = 3.03, p = 0.001) and left hemisphere (voxel number: 146, z = 3.15, p = 0.001).

Regions of cerebral perfusion overactivity in the ADHD children group

As shown in Fig. 2 and Table 4, four large voxel clusters of significantly elevated HMPAO uptake were found in ADHD patients. The largest clusters were areas including the postcentral gyrus and angular gyrus (voxel number 4289, z = 2.94, p = 0.002) in the left hemisphere. The

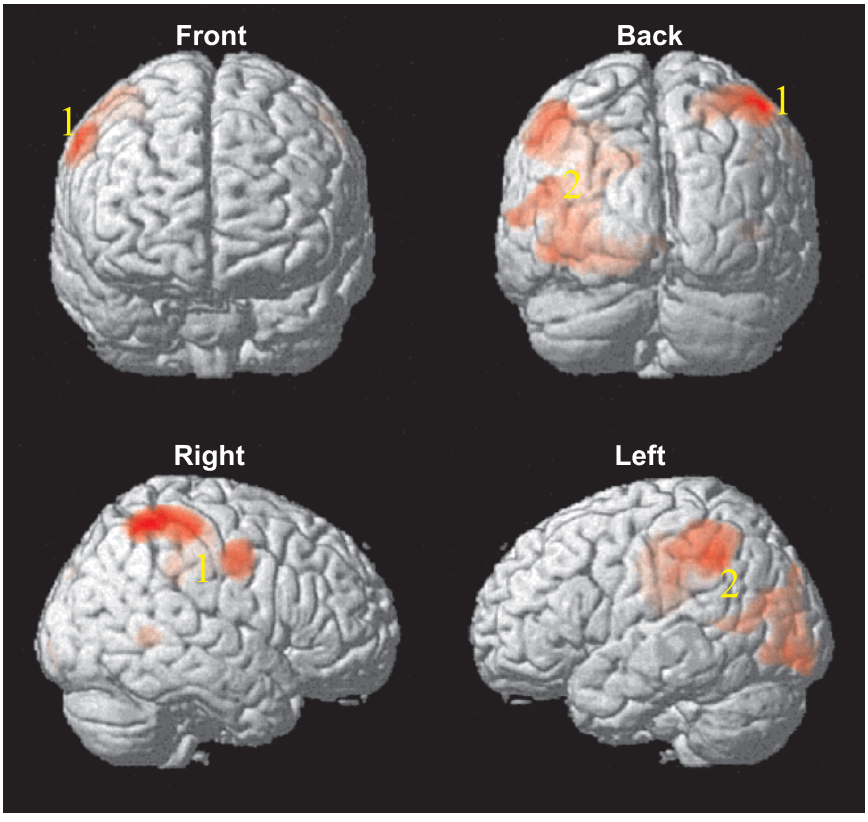

Fig. 2 Brain areas with significantly increased perfusion in ADHD patients compared to normal controls (threshold: *P* = 0.01, uncorrected). In this figure, four large clusters labeled with numbers are shown: right upper parietal cortices (number 1) and left parieto-occipital cortices (number 2)

Table 4 Brain areas with significantly increased perfusion in ADHD patients compared to normal controls (threshold: P = 0.01, uncorrected)

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	*P* value (uncorrected)
4289	Angular gyrus	Left	–42, –50, 40	2.94	0.002
	Postcentral gyrus	Left	–56, –28, 46	2.46	0.007
2629	Postcentral gyrus	Right	46, –36, 60	3.15	0.001
	Angular gyrus	Right	42, –50, 60	3.07	0.001
1121	Inferior occipital gyrus	Left	–40, –88, –2	3.82	0.000
	Superior occipital gyrus	Left	–22, –90, 30	2.79	0.003
335	Precentral gyrus	Right	58, –6, 40	3.34	0.000

second largest clusters were also areas including the postcentral gyrus and angular gyrus (voxel number: 2629, $z = 3.15$, $p = 0.001$) in the right hemisphere. Other clusters are inferior and superior occipital gyrus in the left hemisphere (voxel number: 1121, $z = 3.82$, $p = 0.000$) and the precentral gyrus in the right hemisphere (voxel number: 335, $z = 3.34$, $p = 0.000$).

Discussion

This study aimed to identify cerebral perfusion differences using images of an ADHD and a control group in the resting state, in order to determine the functional differences of the resting ADHD brain and to speculate upon the pathophysiology of ADHD. Our results reveal specific, different perfusion patterns in ADHD patients compared to controls. Specifically, perfusion was found to be decreased in the right anterior cerebrum and cerebellum and to be increased in the bilateral posterior cerebrum of subjects with ADHD relative to the normal controls. The areas of reduced perfusion were mainly the right lateral prefrontal and large right and small left orbitofrontal cortices. Perfusion of the small right middle temporal cortex was significantly lower than in the control group. In addition, regional blood flow of the cerebellar cortex in both hemispheres, which is known to be connected functionally with frontal cortex, was significantly lower in ADHD patients. Hyperactive perfusion areas, which are mainly posterior brain regions, include the right upper parietal cortex and the left parieto-occipital cortex.

Over the last decade, the number of brain imaging studies carried out on ADHD has increased significantly (Giedd et al., 2001). Structural imaging studies have relied on MRI, and have revealed a loss of normal asymmetry and brain volume in ADHD patients (Castellanos, 1997). These changes were mainly found in the prefrontal cortex, the basal ganglia and the cerebellum. The prefrontal cortex and the basal ganglia are rich in dopamine receptors and the cerebellum is functionally connected with the prefrontal cortex (Hale et al., 2000). Castellanos et al. (1996) reported a smaller right anterior frontal volume and a reversal of normal (left > right) lateral ventricles asymmetry in ADHD patients. Amen et al. (1997) noted decreased perfusion in the prefrontal cortex in 54 children with ADHD relative to 18 controls at rest and during a concentration exercise with SPECT. These results are consistent with the findings of the present study, namely that prefrontal and orbitofrontal functional defects are present and that right-sided defects are more prominent in ADHD children. A recent fMRI study evaluated task-related blood flow changes, and suggest a lower activation in the prefrontal cortex of ADHD children and adults versus their respective controls (Rubia et al., 1999).

Many investigators have shown with reasonable consistency that abnormal asymmetry of basal ganglia structures is found in ADHD in MRI studies (Pueyo et al., 2000). Using PET, Ernst et al. (1994, 1997) reported a lower regional cerebral metabolic rate of glucose (rCMRGlc) in the left subcortical regions in girls with ADHD; however, in this study, no perfusion defect or overactivity was found in basal ganglia. When compared to controls using a p-value of 0.05, we found perfusion defects in striatal areas in the present study. At the 0.05 p-value level, however, there were many other unexplained and unexpected areas of perfusion defect or increase that seemed to be false positive. In addition, one of the possible explanations of undetection of striatal dysfunction might be the lower resolution power of SPECT compared to MRI or PET.

Reports about the structural and functional abnormalities of the cerebellum in ADHD are a relatively recent phenomenon. Evidence from animal and human research suggests that the cerebellum may play a role in cognitive process. This includes the domain of executive function that is normally attributed to the prefrontal cortex and is typically deficient in an individual with ADHD. One study (Mostofsky et al., 1998) reported that the volume of the inferior posterior lobe (lobule VIII-X) was reduced. Another study (Berquin et al., 1998) revealed that the vermian volume was significantly lower in boys with ADHD, and that this reduction involves mainly the posterior inferior lobe and not the superior lobe. Our present functional imaging study strengthened the validity and reliability of the results of previous structural imaging studies, which suggested that hypothetical cerebello-thalamo-prefrontal circuit dysfunction may subserve the motor control, inhibition, and the executive function deficit encountered in ADHD (Sanchez-Carpintero and Narbona, 2001). To our knowledge, the result of the present study was the first report of functional impairment in the cerebellar cortex in ADHD.

The temporal lobe has been disregarded by ADHD studies using the ROI-based method, and previous MRI studies have revealed no abnormalities in ADHD patients. However, Ernst et al. (1997) reported lower absolute cerebral metabolic rate of glucose (CMRGlc) in the right medial temporal lobe in both women and girls with ADHD, and the same research group (Ernst et al., 1994) also reported a higher normalized metabolic rate in the medial temporal lobe of girls with ADHD than in normal girls. Our study group also included female subjects, but no specific difference was found in a subgroup analysis of female subjects. The present study is also the first to show perfusion defect in the right middle temporal cortex in children with ADHD.

A previous study using FDG-PET demonstrated that lateralization of the normalized CMRGlc of PET differed for ADHD and controls in the parietal lobes. ADHD patients showed lower normalized CMRGlc on the left than on the right, which was a reversal of the pattern found in the control group (Langleben et al., 2001). Another SPECT study, estimating regional cerebral blood flow, showed higher perfusion in the premotor and parieto-occipital sensory areas (Lou et al., 1984). These reports

are comparable with our results. Hyperperfusion in these regions of the brain might be due to a lack of inhibition of these areas, that is, these findings suggest that ADHD patients lack adequate filtering of sensory perception, which is consistent with the "hyperarousal theory" in ADHD (Aston-Jones et al., 1999).

Investigators have invoked a number of explanations for core deficit in ADHD. The models, as summarized by Hunt et al. (1994) and Jassen (2000), fall into five categories: 1) cognitive processing deficit-ADHD as a primary dysfunction of selective attention and hyperactivity, resulting from disturbance of the dopamine system; 2) impaired behavioral inhibition-ADHD as dysfunction of behavioral inhibition by the prefrontal cortex; 3) excessive arousal with associated hyperfunctional dysfunction in the locus ceruleus and the reticular activating system; and 4) deficient reward system caused by deficit in the limbic, prefrontal and association cortex. Our findings partially support theories 1, 2, 3, and 4. Recently a more complex hypothesis called 5) the cognitive-energetic theory has integrated simpler theories into a complex theory that involves three dysfunctional systems in ADHD children (Sergeant, 2000). According to this theory, ADHD children have abnormal functions at three distinct levels: First, a lower set of cognitive processes, including encoding, central processing, and response organization, second, arousal activation and, third, effort executive function system. Such a complex model may be necessary to understand the attentional process, which involves several levels and diverse brain circuits. Our findings are compatible with this cognitive energetic theory because the abnormalities found in the present study involve diverse brain circuits. Therefore, ADHD may be the end result of diverse dysfunctional areas mediating attention and behavioral inhibition.

In summary, our overall results suggest prefrontal and cerebellar regions, which perform the executive and supervisory function in attention, are impaired in ADHD children. Moreover, the parieto-occipital cortex, which perceives somatosensory sensation might be hypersensitive and hyperactive in ADHD children. In addition, the limbic cortex (right middle temporal cortex), which is associated with the reward and cognitive system, was also impaired in ADHD children.

One limitation of our study originates from the status of patients during the imaging process. Though the findings of this study were based on the resting state, patients' individual emotional and behavioral reactions to the imaging process could affect the findings. We made an effort to control patient status by creating a calm environment and by having mothers in attendance during imaging. No child showed anxiety or behavioral changes; however, SPECT study using active cognitive tasking would be needed to overcome the limitation. The second limitation is associated with the selection of the control group. For ethical reasons, we could not use healthy normal children as controls, and controls were found among children who had previously received SPECT. However, this seems to be an unavoidable limitation of SPECT study in children. Although results should be interpreted cautiously, this study confirms the presence of a functional defect in the frontal lobes and found new problems in the temporal lobe, the somatosensory areas and cerebellum in the resting state of the brains of ADHD children.

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