

Regional differences in cerebral perfusion associated with the α -2A-adrenergic receptor genotypes in attention deficit hyperactivity disorder

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Background: Neurobiologic studies have suggested that dysregulation of central noradrenergic systems may be involved in the pathophysiology of attention deficit hyperactivity disorder (ADHD), and it has been hypothesized that genetic changes in the norepinephrine pathways might contribute to dysfunction of the prefrontal cortex circuits in ADHD. We previously reported decreased cerebral blood flow in the right lateral prefrontal cortex and both orbitofrontal cortices in children with ADHD. Genetic investigations have shown that the α -2A-adrenergic receptor gene (*ADRA2A*) is associated with ADHD. Our aim was to examine whether the presence of a risk allele of the *ADRA2A* *MspI* polymorphism is associated with differences in regional cerebral blood flow in boys with ADHD. **Methods:** We recruited 21 Korean boys with ADHD (mean age 9.9, standard deviation [SD] 2.7 yr) and 11 age- and sex-matched controls (mean age 10.6 [SD 2.1] yr). Each participant underwent technetium-99m-hexamethylpropylene amine oxime (^{99m}Tc -HMPAO) single-photon emission computed tomography. We performed image analyses with voxel-wise *t* statistics using SPM2. **Results:** We found regional hypoperfusion in the prefrontal regions, including the right orbitofrontal and right medial gyri, and the bilateral putamen and cerebellum in boys with ADHD relative to controls ($p < 0.0005$, uncorrected for multiple comparisons). Boys with ADHD who carried the C allele ($n = 13$) at the *ADRA2A* *MspI* polymorphism had reduced perfusion in the bilateral orbitofrontal regions compared with those without the C allele ($n = 8$) ($p < 0.0005$, uncorrected for multiple comparisons). **Limitations:** This study was limited by the small sample size, and we did not obtain genetic data from the controls. **Conclusion:** Our findings suggest that regional differences in cerebral perfusion in the orbitofrontal cortex represent an intermediate neuroimaging phenotype associated with the *ADRA2A* *MspI* polymorphism; these data support the validity of the noradrenergic hypothesis regarding the pathophysiology of ADHD.

Introduction

Norepinephrine is involved in the modulation of attention, working memory, behavioural inhibition, planning, alertness, arousal and vigilance, and it has been suggested that norepinephrine improves prefrontal cortex function through action at postsynaptic α -2A-adrenergic receptors.^{1,2} Furthermore, guanfacine, an α -2A agonist, is believed to improve various prefrontal cortical functions, such as working memory, attention regulation and response inhibition.^{3,4} Recent single-photon emission computed tomography (SPECT)

studies have shown that the administration of guanfacine activates the dorsolateral prefrontal cortex in monkeys performing working memory tasks.^{5,6}

The prefrontal cortex guides behaviour and attention using working memory by applying representational knowledge to inhibit inappropriate actions, thoughts and feelings. These processes are the basis of executive functions, which include the regulation of attention, planning, impulse control and the initiation or monitoring of action.² Prefrontal cortical dysfunction contributes to neuropsychologic deficits, such as working memory and focused attention impairments, and in-

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hibitory control deficits in ADHD.⁷ Furthermore, it has been suggested that genetic changes in catecholamine pathways might contribute to the dysregulation of prefrontal cortex circuits in ADHD. It has been hypothesized that certain subcircuits within the prefrontal cortex are differentially sensitive to genetic alterations or neurodevelopmental abnormalities or both, and that these differential sensitivities may be associated with ADHD.^{2,8} Although genes in the dopaminergic system have been most extensively studied in ADHD, recent studies have focused on genes in the noradrenergic and serotonergic systems.^{9,10}

This evidence suggests that noradrenergic dysregulation and, more specifically, alterations in α -2A-adrenergic receptor function are involved in the pathophysiology of ADHD. As a result, the α -2A-adrenergic receptor gene (*ADRA2A*) is potentially associated with this disorder. The C to G single nucleotide polymorphism (SNP) at position 1291, which creates an *MspI* site (rs1800544) in the promoter region of *ADRA2A*,¹¹ and the C to T polymorphism in the 3' untranslated region, known as the *DraI* site (rs553668),¹² are the 2 major polymorphisms that have been investigated in relation to ADHD. In our previous study,¹³ we performed family-based association analyses of these *ADRA2A* polymorphisms, using the transmission disequilibrium test and haplotype analyses. These analyses provided evidence for the involvement of the *ADRA2A MspI* and *DraI* polymorphisms in the etiology of ADHD in a sample of Korean ADHD patients and their families. In particular, the C alleles of the *MspI* and *DraI* polymorphisms were identified as putative risk alleles.¹³

Recent studies have used a strategy of examining both genetic and neuroimaging data in a single study. This converging strategy may advance our understanding of the pathophysiology of ADHD because it facilitates elucidating the relation between genetic factors and associated neurobiologic substrates.¹⁴ Imaging genetic approaches based on SPECT or positron emission tomography (PET) have primarily been used to investigate the effects of dopamine genes on regional cerebral perfusion and metabolism in ADHD. According to a recent SPECT study,¹⁵ patients with ADHD with risk alleles at both the dopamine D4 receptor gene (*DRD4*) and dopamine transporter gene (*DAT1*) loci showed significantly higher perfusion in the right middle temporal gyrus.

However, the association between regional brain perfusion or metabolism and noradrenergic system genes, specifically *ADRA2A* in ADHD, has not been previously investigated. Our previous SPECT study suggested functional impairment in the prefrontal and cerebellar regions in children with ADHD versus healthy controls.¹⁶ In this study, we sought to examine whether the presence of a risk allele of the *ADRA2A MspI* polymorphism is associated with differences in regional cerebral blood flow in Korean boys with ADHD.

Methods

Participants and clinical assessments

We recruited 21 Korean boys with ADHD who visited the Department of Child and Adolescent Psychiatry at Seoul

National University Hospital in Korea. Their diagnosis was based on the DSM-IV criteria using the Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version (K-SADS-PL).^{17,18} We excluded boys with a history of or a current neurologic disease, including convulsive disorder, or any evidence of a comorbid psychiatric condition, such as Tourette disorder, mental retardation, pervasive developmental disorder, bipolar disorder, psychosis, language difficulties or learning disabilities. We assessed intellectual and learning abilities using the Korean version of the Wechsler Intelligence Scale for Children (KEDI-WISC).¹⁹ Of the DSM-IV subtypes of ADHD, the combined subtype was the most common in our patients ($n = 8$), followed by the not otherwise specified ($n = 7$) and inattentive ($n = 4$) subtypes. Two patients also had oppositional defiant disorder, as diagnosed by DSM-IV. All ADHD patients were drug-naïve at the time of recruitment, and SPECT imaging was performed before any medication was given. The patients were genotyped for the *ADRA2A MspI* polymorphism; we divided the patients into 2 groups according to the presence of the C allele (i.e., C/C and C/G genotype group, and a G/G genotype group).

We retrospectively included control participants from among children who underwent brain SPECT studies at our institute during the past 3 years. The controls were mainly recruited from the Department of Pediatrics and were referred to our department because no specific organic causes were found by physical examination or brain imaging (including magnetic resonance imaging [MRI], SPECT and electroencephalography [EEG]). Upon referral, they were evaluated via psychiatric interview.

We selected 11 age-matched Korean boys who had no abnormal EEG, MRI or brain SPECT findings by expert visual decision, no evidence of ADHD or any other psychiatric problem as determined by psychiatric interview and no medical history related to a loss of consciousness, neurologic or psychiatric illness, or serious behavioural problem. The KEDI-WISC was administered to all controls. Among the 11 controls, the primary diagnoses were tension headache ($n = 6$), primary complaint was headache related to tension and stress, especially associated with academic examination). Five controls received no diagnoses (general complaints of mild discomfort after minor physical injuries from events such as traffic collisions).

The study was approved by the institutional review board at the Seoul National University Hospital. Parents provided written informed consent, and the children provided verbal assent regarding participation in this study.

Genotyping

We extracted genomic DNA from whole blood lymphocytes using a G-DEXTM II Genomic DNA Extraction Kit (iNtRON Biotechnology). We detected the genotypes by analyzing primer-extension products generated from previously amplified genomic DNA using a chip-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform (Sequenom Inc.). In brief, oligonucleotide primers (5'-ACG TTG GAT GTT CTC CCA AGA

TCC AGC TTC and 5'-ACG TTG GAT GCC TGC TGG GAG TTG GCC AT for *MspI* [rs1800544]) were used to generate polymerase chain reaction (PCR) products. The PCR was performed in a volume of 5 μ L containing 1 \times PCR buffer (Takara), 2.5 mM MgCl₂, 0.2 mM of each dNTP, 0.1 U HotStar Taq Polymerase (Qiagen GmbH), 8 pM of each primer and 4.0 ng of genomic DNA. The reaction consisted of denaturation at 95°C for 15 minutes, followed by 45 cycles of 95°C for 20 seconds, 56°C for 30 seconds and 72°C for 1 minute, with a final extension at 72°C for 3 minutes. Following PCR, unincorporated dNTPs were removed by the addition of 0.3 U of shrimp alkaline phosphatase and incubation for 20 minutes at 37°C, followed by incubation for 5 minutes at 85°C for enzyme inactivation.

The extension primer was 5'-TTC TGC TCC GTC GGC CC for *MspI*. The total volume of each reaction was 9 μ L, including hME enzyme (Thermo Sequenase; GE Healthcare), ACT termination mix and 5 μ M of the extension primer. The primer extension protocol was incubation at 94°C for 2 minutes, followed by 55 cycles of 94°C for 5 seconds, 52°C for 5 seconds and 72°C for 5 seconds. After desalting the reaction products with SpectroCLEAN (Sequenom Inc.), we analyzed the samples in the fully automated mode with the MALDI-TOF MassARRAY system (Sequenom Inc.). If the C allele of the *MspI* polymorphism is present, there is no *MspI* restriction site. The C to G transversion at position 291 creates the *MspI* restriction site.

SPECT imaging protocol

Technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO) was administered intravenously while the participants were lying in a supine position with both eyes closed in a quiet room under dim lights; doses were based on body weight (7.4–11.1 MBq/kg). We obtained SPECT images using a triple-head gamma camera (Prism 3000; Picker International) with a high-resolution fan beam collimator. The energy window was set at 159 keV with a width of 9%, and the intrinsic spatial resolution was 3.5 mm. In all, we obtained 120 frames in step-and-shoot mode at 20 seconds/frame. Transaxial images were reconstructed as 128 \times 128 matrices and filtered with a Metz filter ($x = 1.5$ – 2.0). We corrected all images for attenuation using the Chang method.²⁰ The total-body radiation absorbed dose after a 99mTc-HMPAO study is 2.1 mGy (0.21 rad) per 500 MBq of 99mTc, which is less than 10% of the radiation absorbed from a conventional contrast-enhanced brain radiographic computed tomography scan.²¹

Statistical analyses

We converted all reconstructed images to the Analyze format and spatially normalized them to the SPECT standard templates provided with the SPM2 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK). We performed affine transformation to determine the optimal parameters to minimize the least squares distances between individual scans and

templates. We performed nonlinear registration using the weighted sum of the predefined smooth basis functions, and discrete cosine transformation was used to remove global nonlinear differences between images. The spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm full-width at half-maximum to increase the signal-to-noise ratio. We removed the global effects, such as arbitrary changes in global signals due to scan (participant) variations in radioactivity delivered, by normalizing the scan voxel counts by proportional scaling.

We performed intergroup analyses with voxel-wise *t* statistics using SPM2. We made comparisons between patients with ADHD and controls and between patients with ADHD with and without the C allele (C/C and C/G genotypes v. G/G genotype). We analyzed our data at different threshold levels to attain an adequate statistical inference. Voxel-level inference was performed at a height threshold of $p < 0.0005$ (uncorrected for multiple comparisons) and cluster-level inference at $p < 0.05$ (corrected for multiple comparisons, extent threshold = 125 voxels, which has been reported to be an appropriate spatial resolution for SPECT in tissue).²² We converted the Montreal Neurological Institute (MNI) coordinates to the Talairach space (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>). We determined the anatomic locations using the Talairach and Tournoux atlas.²³

Results

Participant characteristics

The demographic and clinical characteristics of the ADHD participants are presented in Table 1. There were no significant differences in the age, intelligence quotient (IQ) or ADHD subtype between patients with ADHD with and without the C allele at the *ADRA2A MspI* location. The mean age of the ADHD patients was 9.9 (standard deviation [SD] 2.7) years, and the mean age of the controls was 10.6 (SD 2.1) years. The mean estimated IQ was 112 (SD 14) in the controls, which was not significantly different from that of the patients with ADHD.

Table 1: Demographic and clinical characteristics of patients with attention deficit hyperactivity disorder

Characteristic	Genotype; mean (SD)*	
	C/C or C/G, <i>n</i> = 13	G/G, <i>n</i> = 8
Age, yr	10.2 (3.1)	9.5 (1.7)
Intelligence quotient		
Full-scale	110 (10)	115 (15)
Verbal	112 (15)	113 (16)
Performance	106 (9)	114 (12)
ADHD subtype, no. of patients		
Combined	5	3
Inattentive	3	1
Hyperactive-impulsive	1	1
Not otherwise specified	4	3

SD = standard deviation.

*Unless otherwise indicated.

Comparisons between ADHD patients and controls

Significant reductions in perfusion were found in the prefrontal regions, including the right orbitofrontal and right medial gyri, bilateral putamen and cerebellum in ADHD patients compared with controls at the voxel-level inference ($p < 0.0005$; Fig. 1, Table 2). Hypoperfusion in the left putamen and cerebellum were significant at the cluster level threshold of $p < 0.001$. A trend toward a reduction in perfusion was found in the right orbitofrontal gyrus at the cluster-level inference ($p = 0.056$). Regional hyperperfusion was observed in the bilateral precentral gyri and left postcentral gyrus in ADHD patients compared with controls at the cluster-level inference ($p < 0.05$).

Comparisons between ADHD patients with and without the C allele

In total, 13 ADHD patients (mean age 10.2 [SD 3.1] yr) carried the C allele, and 8 (mean age 9.5 [SD 1.7] yr) were homozygous for the G allele. The genotype frequencies (C/C homozygous, C/G heterozygous and G/G homozygous) were 4.8%, 57.1% and 38.1%, respectively. These frequencies were under Hardy–Weinberg equilibrium ($p = 0.19$).

A significant reduction in perfusion was observed in the bilateral orbitofrontal regions in ADHD patients with the C allele compared with those without the C allele at the voxel-level inference ($p < 0.0005$; Fig. 2, Table 3). In particular, the right orbitofrontal gyrus showed a trend toward hypoperfusion at the cluster-level inference ($p = 0.06$). No significant increase in regional perfusion was observed in the ADHD patients with the C allele compared with those without the C allele.

Discussion

In this study, boys with ADHD showed lower perfusion than controls in the prefrontal regions, including the right orbitofrontal and right medial gyri, and the bilateral putamen and cerebellum. These results are consistent with our previous SPECT findings in children with ADHD,¹⁶ who were found to have lower regional cerebral blood flow than healthy controls in the right lateral prefrontal cortex, right middle temporal cortex, both orbitofrontal cortices and both cerebellar cortices.

Functional neuroimaging studies using SPECT or PET have reported reduced perfusion in the prefrontal cortices of

children with ADHD.^{24,25} In a meta-analysis of 16 functional neuroimaging studies in ADHD, Dickstein and colleagues²⁶ concluded that significant frontal hypoactivity patterns were present in patients with ADHD that affect the dorsolateral prefrontal, inferior prefrontal and anterior cingulate cortices. Bush and colleagues,²⁷ in their review of functional neuroimaging (PET, SPECT, functional MRI) studies in ADHD, found a consistent pattern of frontal dysfunction, including altered patterns of activity in the anterior cingulate and dorsolateral or ventrolateral prefrontal cortices and in associated striatal and cerebellar regions, which supports the findings of our study. Furthermore, it has been suggested that neuropsychologic deficits underlying ADHD, such as impairments in response inhibition, delay aversion or working memory, are associated with structural or functional brain abnormalities or both in the frontal–striatal–cerebellar circuits.²⁸

In the present study, we found that regional cerebral perfusion depended on the presence of the C allele of the *ADRA2A* *MspI* polymorphism in ADHD. Patients with ADHD who carried the C allele had lower perfusion in the bilateral orbitofrontal regions than ADHD patients without the C allele. The *ADRA2A* gene is an attractive candidate gene in ADHD.

With respect to the *MspI* and *DraI* polymorphisms of *ADRA2A* in ADHD, we previously observed a trend toward overtransmission of the C/C haplotype in Korean patients with ADHD.¹³ This is in line with the results of the study by Wang and colleagues,²⁹ which also showed a tendency toward C/C haplotype overtransmission in a sample of Chinese ADHD patients. However, studies involving Western populations have reported that the G allele of the *MspI* polymorphism and the T allele of the *DraI* polymorphism in *ADRA2A* are putative risk alleles in ADHD.^{30,31} Ethnic differences in allele frequencies may be responsible for the discrepancies between populations,²⁹ and there is also a possibility that the pattern of linkage disequilibrium might differ among populations.³² Divergent results among studies might also reflect methodologic issues, such as sample size, inclusion or exclusion criteria, or instruments used to assess symptom characteristics. The results of our study suggest that the presence of the C allele of the *ADRA2A* *MspI* polymorphism, at least in the Korean population, is associated with decreased regional cerebral blood flow in both orbitofrontal cortices in patients with ADHD.

Arnsten and colleagues³³ proposed that noradrenergic inputs into the prefrontal cortex modulate dopaminergic function in this area by stimulating the α -2-adrenergic receptors in dopamine-containing neurons, which increases the signal-

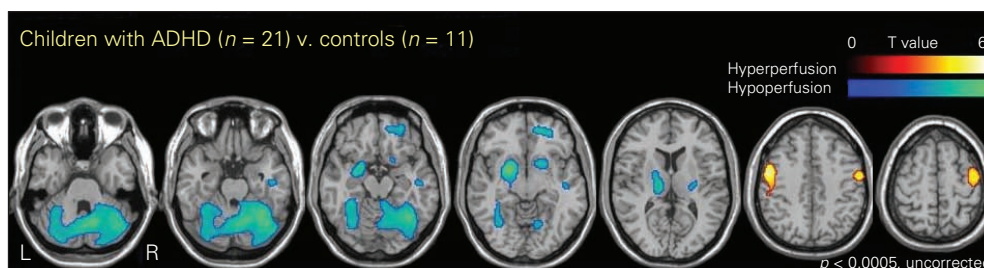


Fig. 1: Brain areas with significantly increased or decreased cerebral blood flow in patients with attention deficit hyperactivity disorder compared with healthy controls at the voxel-level inference ($p < 0.0005$).

to-noise ratio of these neurons. Of the several types of α -2-adrenergic receptors, the α -2A-adrenergic receptor is the most prevalent noradrenergic receptor in the prefrontal cortex.³³ Recent studies in animals indicate that norepinephrine enhances “signals” through postsynaptic α -2A-adrenergic receptors in the prefrontal cortex, whereas dopamine reduces “noise” via dopamine D1 receptor stimulation.³⁴ It has also been suggested that elevated cyclic adenosine monophosphate signalling in the prefrontal cortex is associated with impairments in working memory and that α -2A-adrenergic receptor stimulation strengthens the functional connectivity of microcircuits in the prefrontal cortex by inhibiting intracellular cyclic adenosine monophosphate signalling.³⁵

It is also worth noting the potential functional significance of the *ADRA2A* *MspI* polymorphism. In a previous study,³⁶ the presence of a single haplotype block spanning *ADRA2A* was reported. This haplotype block contained 9 different SNPs in *ADRA2A*, including the *MspI* site and a nonsynonymous amino acid change at position 251, a position with known functional relevance to *ADRA2A*. The authors demonstrated that the *ADRA2A* haplotype block was capable of capturing and representing the information content of the known functional locus, even when that locus was not included.³⁶ It is worth considering the possibility that the *MspI* polymorphism may affect the expression and function of *ADRA2A* or that it serves as a marker for another functionally relevant locus of the *ADRA2A*.

Based on the findings of these neurobiologic studies and our own study, we believe that genetic alterations in *ADRA2A* may exert differential effects on prefrontal cortical dysfunction in ADHD and, thus, contribute to ADHD symptomatology by influencing endogenous α -2A-adrenergic

receptor signalling. However, because ADHD is considered to be a complex polygenic disorder with a genetic etiology involving the combined effects of multiple genes,³⁷ it should be noted that our results of regional cerebral perfusion differences may be related to interactions between *ADRA2A* and other genes that contribute to the dysregulation of the central noradrenergic or dopaminergic systems in ADHD.

Reports about structural and functional abnormalities of the cerebellum in ADHD are a relatively recent phenomenon. In the present study, patients with ADHD had regional cerebellar hypoperfusion compared with controls. This is in agreement with previous reports of regional cerebral blood flow abnormalities in the cerebellum of ADHD patients.^{16,38} Furthermore, animal and human research has suggested that cerebellar structures and circuitries may play roles in the cognitive processes that lie beyond the traditional view of their involvement in motor coordination.³⁹ Our results support the hypothesis of cerebello-thalamo-prefrontal circuit dysfunction in ADHD and suggest that this dysfunction might underlie the motor impairments and executive function deficits encountered in ADHD.⁴⁰

Limitations

Several limitations of this study should be noted. First, our ADHD sample was selected based on participation in genetic

Table 2: Regions with significant differences in perfusion between patients with attention deficit hyperactivity disorder and healthy controls

Comparison; brain region	Talairach coordinates			Cluster size*	Z
	x	y	z		
Controls > ADHD					
Putamen	-22	4	-5	1934	4.98
Thalamus	-18	-19	3		4.15
Cerebellum, posterior lobe	32	-53	-14	10857	4.62
Cerebellum, anterior lobe	8	-61	-20		4.56
Fusiform gyrus	-36	-61	-7		3.90
Medial frontal gyrus/ orbitofrontal gyrus, BA 11	26	44	-12	402	4.13
Medial frontal gyrus/ orbitofrontal gyrus, BA 11	10	48	-9		3.97
Putamen	18	10	-4	315	3.86
Inferior temporal gyrus	46	-16	-16	159	3.71
Lentiform/internal capsule	26	-13	8	118	3.56
Putamen	32	-10	2		3.50
ADHD > controls					
Precentral gyrus	-53	0	41	582	4.69
Postcentral gyrus	-53	-23	44		3.40
Precentral gyrus	51	-4	46	544	4.20

ADHD = attention deficit hyperactivity disorder; BA = Brodmann area.
*Local maxima clusters composed of more than 100 significant voxels ($p < 0.0005$, height-threshold).

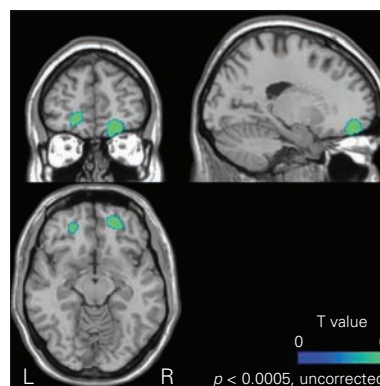


Fig. 2: Brain areas with significantly decreased cerebral blood flow in patients with attention deficit hyperactivity disorder with the C/C or C/G genotype compared with those with the G/G genotype at the voxel-level inference ($p < 0.0005$).

Table 3: Regions with significant differences in perfusion between patients with attention deficit hyperactivity disorder with the G/G genotype and the C/C or C/G genotypes

Comparison; brain region	Talairach coordinates			Cluster size*	Z
	x	y	z		
G/G > C/C or C/G					
Orbitofrontal gyrus	-22	44	-9	178	4.11
Orbitofrontal gyrus	18	48	-12	304	4.10

*Local maxima clusters composed of more than 100 significant voxels ($p < 0.0005$, height-threshold).

and neuroimaging studies, and this may have resulted in skewed demographic and clinical characteristics. Second, we did not obtain genetic data from the healthy controls. Thus, although the ADHD children had lower regional cerebral blood flow in the prefrontal regions than controls, we cannot rule out the possibility that the observed group difference might be attributable to the presence of the C allele of the *ADRA2A* *MspI* polymorphism in the control group. Third, 6 of the controls had tension headache, which might have increased regional cerebral blood flow⁴¹⁻⁴³ and led to greater regional brain perfusion differences between ADHD and control participants. However, regional cerebral blood flow increases have been found in regions such as the amygdala, anterior cingulate, insula and thalamus, which are generally activated in functional imaging studies in patients with pain or headache.⁴²

Finally, it is important to note that regional hypoperfusion was observed in the right orbitofrontal gyrus, left putamen and right cerebellum in ADHD patients compared with controls at an FDR-corrected threshold of 0.05. Additionally, significant hyperperfusion was found in the bilateral precentral gyri. However, no significant decrease in regional perfusion was observed in ADHD patients with the C allele compared with patients without the C allele at the FDR-corrected threshold. Therefore, the orbitofrontal SPECT results should be interpreted with caution and further work is needed to confirm the findings of this study.

Conclusion

Our findings confirm those of our previous report,¹⁶ namely, that regional cerebral blood flow is decreased in the prefrontal regions, including both orbitofrontal cortices, in boys with ADHD compared with healthy controls. This study provides evidence that the presence of the risk allele of the *ADRA2A* *MspI* polymorphism is associated with lower perfusion in bilateral orbitofrontal regions measured by SPECT in ADHD. Furthermore, our results suggest that regional differences in cerebral perfusion in the orbitofrontal cortex represent an intermediate neuroimaging phenotype associated with the *ADRA2A* *MspI* polymorphism and, thus, support the noradrenergic hypothesis about the pathophysiology of ADHD.

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Competing interests: None declared.

Contributors: Drs. B.-N. Kim and J.-W. Kim contributed to the study's conception and design. They, along with Drs. Cho, Shin and Yoo acquired the data. Drs. B.-N. Kim, J.-W. Kim, Kang, Hong and Lee analyzed the data. Drs. B.-N. Kim, J.-W. Kim and Kang wrote the manuscript, which was critically revised by all of the authors. All of the authors approved the final version submitted for publication.

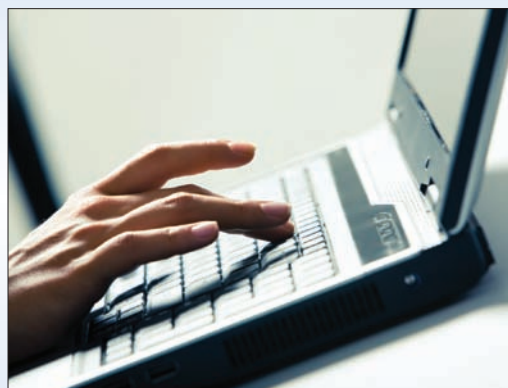
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