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The relationship between regional cerebral blood flow and response to methylphenidate in children with attention-deficit hyperactivity disorder: Comparison between non-responders to methylphenidate and responders

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Abstract

In a sample of children with attention-deficit hyperactivity disorder (ADHD), a voxel based investigation of regional cerebral blood flow (rCBF) during resting state was conducted to identify functional differences between non-responders to methylphenidate (MPH) and responders. Thirty-four children with ADHD were examined by technetium-99m-hexamethylporphylenamine oxime (HMPAO) SPECT. According to clinical response after 8 weeks of treatment with MPH, they were classified as non-responders to MPH and responders. Using SPM analysis, we compared the SPECT images of non-responders to MPH with those of responders. Non-responders to MPH had higher rCBF in the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex, and the right putamen relative to responders. In addition, lower rCBF was found in the right superior parietal lobule in non-responders to MPH relative to responders. Further stepwise discriminant analysis revealed that 88.2% could be correctly classified as either non-responders to MPH or responders when considering the extracted rCBF values in the left anterior cingulate cortex, the left claustrum, and the right superior parietal lobule. The current findings suggest that non-responders to MPH may have different patterns of rCBF in brain regions, which have been known as a part of frontal-striatal circuitry and posterior attentional system, respectively.
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1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, impulsivity, and hyperactivity (American Psychiatric Association, 1994). Methylphenidate (MPH), the most prescribed stimulant in psychiatric practice, has been used for the treatment of core features of ADHD including inattention, impulsivity, and hyperactivity as well as substantial deficits on cognition and social function (Spencer et al., 1996). In addition, MPH has been reported to improve academic productivity and relationship with parents and teachers (Greenhill, 1992). Although most children with ADHD show symptomatic response to MPH, non-responders to MPH, who account for up to 30% of children (Elia et al., 1991; Spencer et al., 1996), have no benefit or only adverse side effects during treatment with MPH (Rapport et al., 1994).

The activity of MPH on the molecular level is linked to its blockades of dopamine and norepinephrine transporter

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(Krause et al., 2000; Solanto, 1998). However, the neurophysiologic mechanism of its therapeutic effect is not fully understood (Volkow et al., 2002). Although various brain areas on which MPH may have influences have been suggested (Gustafsson et al., 2000; Langleben et al., 2002; Lee et al., 2005; Mehta et al., 2000; Schweitzer et al., 2000; Shafritz et al., 2004; Szobot et al., 2003; Teicher et al., 1996; Vaidya et al., 1998; Volkow et al., 1997), there has been only a limited number of studies exploring biological markers that would predict response to MPH.

A review of the studies on predicting response to MPH reported only weak associations between either behavioral measures or neurochemistry and response to MPH (Gray and Kagan, 2000). However, several lines of evidence suggest that potential neurobiological differences may exist between non-responders to MPH and responders in a sample of subjects with ADHD. Low skin conductance level and EEG abnormalities, as possibly indicating cortical hypoarousal, have been reported as characteristics of responders to MPH (Satterfield et al., 1973; Satterfield and Cantwell, 1974; Clarke et al., 2002). In addition, prior structural imaging studies have reported smaller splenium of the corpus callosum (Semrud-Clikeman et al., 1994), reversed caudate asymmetry, and smaller retrocallosal white matter volumes (Filipek et al., 1997) in non-responders to MPH as well as smaller and symmetric caudate and smaller left anterior-superior frontal volumes in responders (Filipek et al., 1997).

Recently, in a sample of children with ADHD, Rohde et al. (2003) reported increased levels of brain perfusion in the medial frontal and the left basal ganglia area in 4 children with homozygosity for 10-repeat allele at dopamine transporter gene (DAT1), that is known to be associated with a poor response to MPH (Roman et al., 2002; Winsberg and Comings, 1999), relative to 4 children without this genotype using [^{99m}Tc] ECD SPECT (Rohde et al., 2003). In [^{99m}Tc] TRODAT-1 SPECT study in a sample of adults with ADHD, lower baseline availability of striatal dopamine transporter has been found in non-responders to MPH relative to responders (Krause et al., 2005), which were in contrast with findings in a sample of children with ADHD who had homozygosity for 10-repeat allele at dopamine transporter gene (DAT1) (Cheon et al., 2005).

However, to the best of our knowledge, there have been no prior studies comparing regional cerebral blood flow (rCBF) of non-responders to MPH with that of responders. Thus, we conducted current study to compare rCBF of non-responders to MPH with that of responders and to explore neuroimaging markers that would predict response to MPH, using a voxel-based analysis, statistical parametric mapping (SPM) (Friston et al., 1994, 1995a,b, 1996). Based on prior imaging studies, we hypothesized that non-responders to MPH may have higher rCBF in the frontal and the basal ganglia areas. As an auxiliary hypothesis, we also expected that rCBF of non-responders to MPH may also be different from those of responders in such areas as the anterior cingulate cortex, the motor cortex, the premotor cortex, the parietal cortex, the somatosensory cortex, the ventral higher visual area, the claustrum, and the cerebellum.

2. Materials and methods

2.1. Subjects

Thirty-nine children with ADHD (35 boys and 4 girls) participated this study. Children with ADHD were recruited from the Attention-Deficit Hyperactivity Disorder Clinic of the Seoul National University Hospital, Seoul, South Korea. The diagnosis of ADHD was made according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994), confirmed by 2 board-certified child psychiatrists (J.W.H. and B.N.K.). Exclusion criteria were comorbid DSM-IV Axis I disorders, current or past neurologic illness, mental retardation or borderline intelligence, and substance abuse as evaluated by history, physical examination, and laboratory testing (complete blood count, urinalysis, liver function test, and serology). The severity of ADHD symptoms was estimated using the Clinical Global Impressions-Severity (CGI-S) scale (Guy, 1976), with ranges from 1 (normal) to 7 (among the most extremely ill patients). At the time of study entry, two (5.9%) of subjects had a history of prior use of stimulants and no participant was taking psychotropics including MPH 2 months before study entry. Of 39 children, 2 were excluded because of their tic disorder (one had chronic motor or vocal tic disorder and the other had Tourette disorder). In addition, two children with concurrent oppositional-defiant disorder and one with mild mental retardation were excluded in the analyses. Finally, thirty-four children with ADHD (mean age, 8.4 ± 2.5 years; male/female = 30/4) completed the study.

This study was conducted as a part of ''The Development of Biological Predictors of Medication Response in ADHD''. Current study protocol was approved by the Institutional Review Boards at Seoul National University Hospital. We also discussed any potential benefits and/or risks that were associated with procedures in the current study. We concluded that, although the risk of procedures including radiation exposure might be greater than minimal in children, it would be a minor increase and that results of this study would contribute much to our understanding of the subjects' disorder. After complete description of the study to both children and their parents, written informed consent was obtained.

2.2. Imaging protocol

All subjects laid in the supine position, with eyes closed, in a quiet room with dimmed lights. Based on body weight of children (7.4–11.1 MBq/kg), technetium-99m-hexamethylporphylenamine oxime (HMPAO) was administered. SPECT images were acquired using a triple head gamma

camera (Prism 3000; 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 twenty frames were acquired in step-and-shoot mode. Each frame continued for 20 s. Transaxial images were reconstructed as 128×128 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.

2.3. Procedures

After technetium-99m-HMPAO SPECT had been carried out, children with ADHD received 0.25–1.0 mg/kg/day MPH. Doses of MPH were individually titrated according to parents' reports of symptoms improvement and side effects and maintained for 8 weeks. The mean dose was 0.68 mg/kg/day. After 8 weeks, global improvement was rated for each child by the Clinical Global Impression-Improvement (CGI-I) Scale (Guy, 1976), ranging from 1 (very much improved) to 7 (very much worse). The CGI-I were assessed by the investigators, based on all information available from both children with ADHD and their parents at that time of rating. Children with a value of $\geqslant 3$ (minimally improved) in the CGI-I Scale were defined as non-responders to MPH. In addition, children with a value of 1 (very much improved) or 2 (much improved) in the CGI-I Scale were defined as responders.

2.4. Image analysis

Statistical parametric mapping (SPM) (Talairach and Tournoux, 1988; Friston et al., 1994, 1995a,b, 1996) was used to determine quantitative differences between the Tc-99m-HMPAO SPECT images of non-responders to MPH and responders. Using SPM 99 software, all images were spatially normalized onto the Tc-99m-HMPAO SPECT standard template provided with the SPM software to remove inter-subject anatomical variabilities (Friston et al., 1994, 1995a,b, 1996). 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 non-linear registration method using the weighted sum of the pre-defined smooth basis functions using a discrete cosine transformation. Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm Full-Width Half Maximum (FWHM). The aim of smoothing was to increase the signal-to-noise ratio and to account for variations in subtle anatomical structures. The count of each voxel was normalized versus the total brain count (proportional scaling in SPM) to remove global CBF differences between the individuals. After spatial and count normalization, significant differences between SPECT images of non-responders to MPH and responders were estimated at every voxel using t-statistics. Differences between groups were detected using a voxel threshold probability of 0.001, which has been commonly used in SPECT or PET data with hypothesized regional effects, and an extent threshold of 50 contiguous voxels.

Subsequently, brain regions of significant rCBF difference subjected to a stepwise discriminant function analysis in order to evaluate the potential to classify correctly non-responders to MPH and non-responders on an individual basis. To discriminate between groups, discriminant function analysis was performed with a forward selection mechanism based on Wilks' lamda (λ) as selection criteria for potential predictors, i.e. the extracted rCBF values. An F-value of 3.84 and 2.71 was used for inclusion and removal of variables, respectively. For group membership, the same a priori probability was assumed for all cases. For validation of the model, we used a leave-one-out procedure. These statistical analyses were conducted using the window version of SPSS 11.0.

2.5. Statistical analysis

Differences in demographic and clinical variables between non-responders to MPH and responders were tested using an independent t-test for continuous variables and a Fisher's exact test for $2 \times k$ table. P-value of 0.05 was used the significance criteria. All statistical analyses were two-tailed and conducted using the window version of SPSS 11.0.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics were presented in Table 1. While 10 children were classified as non-responders to MPH, 24 children were classified as responders according to the CGI-I Scale. There were no significant differences between non-responders to MPH and responders except the CGI-I scores (independent t-test, $df = 32$, $t = 8.978$, $p < 0.001$).

3.2. Comparison between non-responders to MPH relative to responders

As shown in Fig. 1 and Table 2, non-responders to MPH had higher rCBF in the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex, and the right putamen (Talairach coordinates $x = -8$, $y = 38$, $z = 15$, voxel numbers: 223, $z = 4.23$, $p < 0.001$; Talairach coordinates $x = -24$, $y = 20$, $z = 3$, voxel numbers: 355, $z = 4.09$, $p < 0.001$; Talairach coordinates $x = 12$, $y = 32$, $z = 13$, voxel numbers: 103, $z = 3.72$, $p < 0.001$; Talairach coordinates $x = 24$, $y = 19$, $z = -6$, voxel numbers: 63, $z = 3.60$, $p < 0.001$) relative to responders. In addition, as shown in Fig. 2 and Table 3, lower rCBF was found in

Table 1
Demographic and clinical variables between non-responders to MPH and responders

Variables/group	Non-responders ($N = 10$)	Responders ($N = 24$)
Age	9.7 ± 2.9	7.9 ± 1.3
Sex	Boys (9): Girls (1)	Boys (21): Girls (3)
ADHD subtype		
Combined type	8	12
Predominantly inattentive type	1	7
Predominantly hyperactive-impulsive type	1	5
Intelligence		
Mean FSIQ	105.3 ± 8.5	110.5 ± 15.3
Mean VIQ	102.5 ± 13.3	110.5 ± 15.4
Mean PIQ	107.3 ± 4.9	108.2 ± 14.0
Mean CGI-S Scale Score	5.1 ± 0.7	5.1 ± 1.1
Treatment		
Mean MPH dose (mg/day)	22.0 ± 13.1	20.7 ± 8.4
Mean body weight (kg)	37.9 ± 12.4	29.2 ± 8.7
Mean CGI-I Scale Score[a]	3.5 ± 0.5	1.9 ± 0.3

FSIQ = full-scale intelligence quotient; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; CGI-S = the Clinical Global Impression-Severity; CGI-I = the Clinical Global Impression-Improvement.
[a] $p < 0.001$.

the right superior parietal lobule (Talairach coordinates $x = 32$, $y = -68$, $z = 49$, voxel numbers: 51, $z = 3.67$, $p < 0.001$) in non-responders to MPH relative to responders.

3.3. Discrimination between non-responders to MPH and responders

Stepwise discriminant function analysis including the extracted rCBF values in the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex, the right putamen, and the right superior parietal lobule were applied to predict the response to MPH (Table 4). Three variables (the extracted rCBF values in the left anterior cingulate cortex, the left claustrum, and the right superior parietal lobule) appeared in the final model. The sensitivity of this mathematical model was assessed by calculating probability scores. Overall, 30 (88.2%) out of 34 subjects were classified correctly (Wilks' $\lambda = .356$, $\chi^2 = 31.46$, $p < 0.001$). For non-responders to MPH, 9 out of 10 subjects were classified correctly. On the other hand, three responders were classified wrongly into non-responders to MPH. The validation of the model by the leave-one-out procedure showed the same classification error as the training model (11.8%).

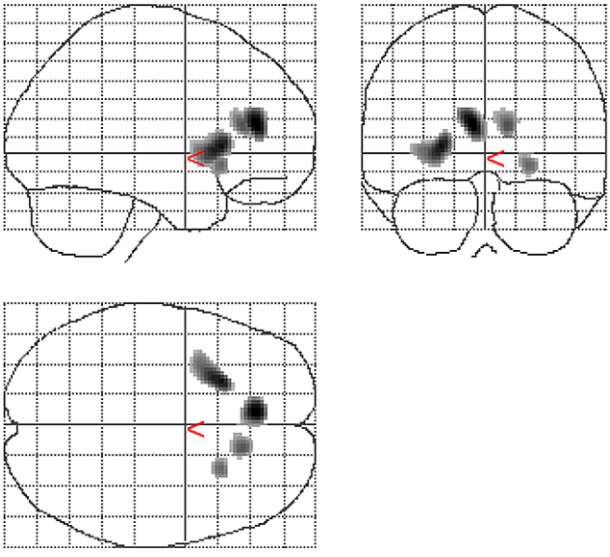

Fig. 1. Brain areas with significantly higher rCBF in non-responders relative to responders ($P < 0.001$). In this figure, four large clusters are shown: the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex, and the right putamen.

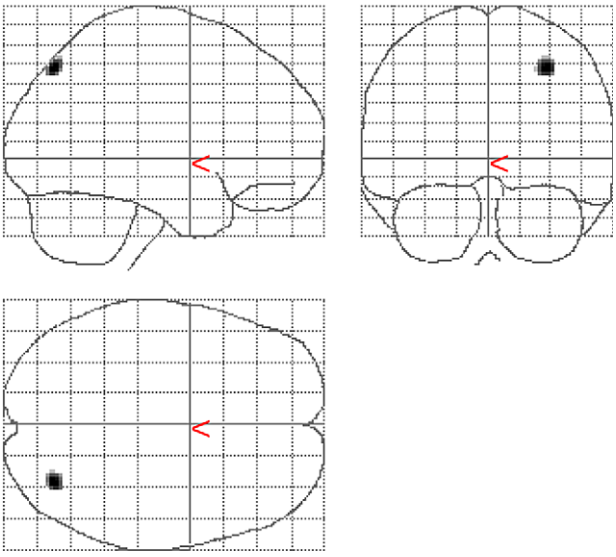

Fig. 2. Brain areas with significantly lower rCBF in non-responders relative to responders ($P < 0.001$). In this figure, one cluster is shown: the right superior parietal lobule.

Table 2
Brain areas with significantly higher rCBF in non-responders to MPH relative to responders

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	P value (uncorrected)
223	Anterior cingulate cortex	Left	−8, 38, 15	4.23	<0.001
355	Claustrum	Left	−24, 20, 3	4.09	<0.001
103	Anterior cingulate cortex	Right	12, 32, 13	3.72	<0.001
63	Putamen	Right	24, 19, −6	3.60	<0.001

Table 3
Brain areas with significantly lower rCBF in non-responders to MPH relative to responders

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	P value (uncorrected)
51	Superior parietal lobule	Right	32, −68, 49	3.67	<0.001

Table 4
Clinical classification matrix, based on the extracted rCBF values

Clinical classification	Predicted group by the extracted rCBF values	
	Non-responders	Responders
Non-responders ($N = 10$)	9 (90.0%)	1 (10.0%)
Responders ($N = 24$)	3 (12.5%)	21 (87.5%)

rCBF = regional cerebral blood flow.
The classification of subjects' the extracted rCBF values in the left anterior cingulate cortex, the left claustrum, and the right superior parietal lobule with respect to their clinical response has been calculated by stepwise discriminant function analysis. Rows represent the clinical response and columns the responses predicted by the extracted rCBF values.

4. Discussion

In a sample of children with ADHD, we report higher rCBF in the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex, and the right putamen and lower rCBF in the right superior parietal lobule in non-responders to MPH relative to responders. In addition, further stepwise discriminant analysis revealed that 88.2% (i.e. 30 out of 34 subjects) could be correctly classified as either non-responders to MPH or responders when considering the extracted rCBF values in the left anterior cingulate cortex, the left claustrum, and the right superior parietal lobule. To the best of our knowledge, the current report is the first functional neuroimaging study in children with ADHD investigating differences in rCBF between non-responders to MPH and responders. Our results concur partially with results of structural neuroimaging studies (Filipek et al., 1997; Semrud-Clikeman et al., 1994) and the study of Rohde et al. (2003), who also demonstrated higher rCBF in medial frontal and basal ganglia areas in children with homozygosity for the 10-repeat allele at DAT1 gene, that is known to be associated with a poor response to MPH (Roman et al., 2002; Winsberg and Comings, 1999).

Our findings of higher rCBF in the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex, and the right putamen in non-responders to MPH are in partial accordance with suggested brain areas where MPH may have neurophysiologic effects in prior studies (Langleben et al., 2002; Lee et al., 2005; Shafritz et al., 2004; Schweitzer et al., 2000; Teicher et al., 1996; Vaidya et al., 1998; Volkow et al., 1997), although results were not consistent and dependent on age of subjects, protocol of MPH treatment, imaging techniques, and method of image analyses. Prior studies on the effects of MPH in subjects with ADHD have reported higher perfusion or metabolism in the prefrontal cortex and the cerebellum (Lee et al., 2005; Schweitzer et al., 2000; Volkow et al., 1997). In addition, lower perfusion or metabolism during MPH treatment has also been reported in such areas as the anterior cingulate cortex, the motor cortex, the premotor cortex, the parietal cortex, the somato-sensory cortex, the ventral higher visual area, the striatum, and the claustrum (Langleben et al., 2002; Lee et al., 2005; Schweitzer et al., 2000; Szobot et al., 2003).

The changes in metabolism during MPH treatment have been reported to correlate positively with dopamine activity and negatively with extracellular dopamine availability (Volkow et al., 1997; Rohde et al., 2003). Treatment with MPH amplifies dopamine signals by blocking DAT (Volkow et al., 1998). Because dopamine is known to decrease background firing of striatal neurons while strengthening corticostriatal signals in striatal cells, its amplification increases the signal-to-noise ratio in target neurons (Kiyatkin and Rebec, 1996). Moreover, the MPH-induced amplification of the striatal dopamine signal may improve ADHD symptoms including inattention and distractibility. Although we cannot rule out contributions owing to other effects of MPH, e.g., effects on the noradrenergic systems, our findings suggest that non-responders to MPH have a higher DA activity and lower extracellular DA availability in brain regions, which have been known as a part of frontal-striatal circuitry and associated with working memory and inhibitory behavior (Giedd et al., 2001), relative to responders. In addition, our results suggest that more MPH may be needed to achieve a response in non-responders to MPH.

In partial accordance with previous studies (Mehta et al., 2000; Szobot et al., 2003), we also report lower rCBF in the right superior parietal lobule in non-responders to MPH relative to responders. Along with the prefrontal cortex, the parietal cortex may be involved in attention, working memory, episodic memory retrieval, and visual awareness (Naghavi and Nyberg, 2005). Especially, the superior parietal lobule is engaged when the source of the attentional signal is goal-directed (Yantis and Serences, 2003). PET studies have suggested that a posterior attentional system, which includes the parietal cortex and is modulated by noradrenaline, seems to be dysregulated in subjects with ADHD (Levy and Farrow, 2001). Therefore, the current finding of rCBF decrease in the right superior parietal lobule may reflect higher impairment of a posterior attentional system in non-responders to MPH.

The limitations of the current study are as follows. The first originates from the status of patients during the

imaging process. The findings of the current study were based on the resting state, but individual emotional and behavioral reactions to the imaging process could have affected our findings. We made an effort to control for patient status by creating a calm environment and by making mothers to attend during the imaging acquisition process. During acquisition of SPECT data, no children showed anxiety or behavioral changes; however, functional neuroimaging study using active cognitive tasking would be needed to overcome the limitation. The second limitation is the contemporaneous nature of the current study. Since we evaluated clinical response to MPH and then compared the pre-treatment imaging data, we could not examine specific relationship between the changes of rCBF and clinical responses. In future, it would be useful to compare pre- with post-treatment imaging data of non-responders to MPH and responders. Third, a less conservative level of threshold, that is uncorrected p value of 0.001, was used in our SPM analysis, which had the potential risk of giving unquantified error control (Brett et al., 2003). Fourth, in the current study, the judgment about clinical response was made by the investigators, based on information from children with ADHD and their parents. However, we could not include information from their teachers, which might be useful to assess the clinical response in more integrative way. Finally, because of small number of non-responders in the current study, current findings may not be replicated in the future, large-scale studies.

Better understanding the functional differences between non-responders to MPH and responders may lead to earlier detection of clinical response in children with ADHD. In the future, studies with high-resolution imaging modality including PET or MEG would be helpful to identify functional differences between non-responders to MPH and responders and to predict response before treatment. In addition, it would be interesting to examine the relationship among clinical characteristics including results of various cognitive tasks, genetic markers such as DAT1 or the dopamine receptor gene, and specific brain areas where MPH has an effect.

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