The acute effect of methylphenidate on cerebral blood flow in boys with attention-deficit/hyperactivity disorder

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Abstract. Methylphenidate (MPH) is the most commonly prescribed treatment for attention-deficit/hyperactivity disorder (ADHD). The therapeutic mechanisms of MPH are not, however, fully understood. We studied the effects of MPH on brain activity in male children and adolescents with ADHD, using the blood flow radiotracer technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) and single-photon emission tomography (SPET) . The study was randomized, double blind, and placebo controlled (MPH group, *n*=19; placebo group, *n*=17), Radiotracer was administered during the performance of the Continuous Performance Test and before and after 4 days of MPH treatment. Statistical parametric mapping (SPM99) analysis showed a significant reduction in regional cerebral blood flow in the left parietal region in the MPH group compared with the placebo group (P<0.05, corrected for multiple comparisons). Our findings suggest that the posterior attentional system, which includes the parietal cortex, may have a role in the mediation of the therapeutic effects of MPH in ADHD.

Keywords: Attention-deficit/hyperactivity – disorder – ADHD – Parietal cortex – SPET – Methylphenidate

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Introduction

Methylphenidate (MPH) is the most commonly prescribed medication for attention-deficit/hyperactivity disorder (ADHD), and its clinical efficacy is well established [1]. It has been proposed that the therapeutic effect of MPH is achieved via an increase in the synaptic concentration of dopamine through blockade of the dopamine transporter (DAT) [2].

Although some neuroimaging studies of the MPH effect on brain activity have reported prefrontostriatal effects, a significant minority have reported changes in the partietal cortex [3, 4, 5, 6]. While the prefrontostriatal findings support the prevailing hypothesis of the aetiology of ADHD, the importance of the posterior brain regions in certain types of attention suggests that MPH is likely to modulate the parietal as well as the prefrontal cortex. In a positron emission tomography (PET) study of normal adults, Mehta et al. [7] reported that MPH-induced improvements in working memory performance were associated with reductions in regional cerebral blood flow (rCBF) in the dorsolateral prefrontal and posterior parietal cortices. Using carbon-11 raclopride PET in healthy adults, Volkow et al. [8] demonstrated that, while oral MPH increased extracellular dopamine in the striatum, there was no correlation between MPH-induced DAT blockade and the increase in dopamine, suggesting that mechanisms other than DAT blockade may be important for the therapeutic effect of MPH [9]. Much of the available data on the effects of MPH is derived from case control studies of adults with and without ADHD, many of which were not placebo controlled.

The goal of our study was to evaluate the effect of MPH on brain activity in children with ADHD in a randomized clinical trial. Our hypothesis was that MPH modulates rCBF in the prefrontostriatal and occipitoparietal cortices.

Materials and methods

Participants were recruited from the ADHD outpatient clinic at Hospital de Clínicas de Porto Alegre (HCPA-UFRGS). Parents provided written informed consent and the subjects gave their verbal assent to participation. This investigation was approved by the Ethics Committee of the hospital.

The inclusion criteria for the study were: (a) diagnosis of ADHD according to the DSM-IV criteria [10], (b) age between 8 and 18 years, and (c) male sex. The exclusion criteria were: (a) presence of any neurological or significant clinical disease, (b) presence of bipolar disorder or any substance abuse/dependence disorder, (c) use of any psychotropic medication in the previous 6 months, and (d) estimated WISC-IQ less than 70.

This was a 4-day, double-blind, placebo-controlled, randomized, fixed dose escalating, parallel-group trial. On the first day, subjects received 0.35 mg/kg of MPH or placebo (twice a day). The dose was increased to 0.70 mg/kg daily on the second day, and kept at this level until the fourth day. The clinical severity of ADHD was measured by the 10-item Conners Abbreviated Rating Scale (ABRS) at baseline and after the second single-photon emission tomography (SPET) study.

Imaging was performed using a GE Starcam 4000i SPET camera with a 64×64 matrix. The images were acquired after an intravenous injection of technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD). The first SPET study was done before the pharmacological intervention, and the second was done on the fourth day of intervention. The radiotracer was injected 1.5 h after the second daily dose of the medication. Immediately before the injection, the patient was placed in a quiet, dimly lit room where he had one minute's training in a standardized attention test (Continuous Performance Test; CPT) [11]. The CPT was used prior to imaging to standardize blood flow. After training, the CPT was applied for 12 min. During the 6th minute, the radiotracer was injected.

Statistical analysis of the imaging data was performed on every voxel using statistical parametric mapping (SPM99) [12]. Statistically significant differences between sets of images were assessed at each voxel with a threshold of $P<0.001$. To correct for correlated multiple comparisons, clusters of voxels that survived this threshold were assessed further using the random Gaussian fields theory, which calculated the significance of clusters based on their peak height and spatial extent ($P<0.05$). Finally, clusters of voxels that survived these statistical tests were overlaid on template images to indicate the brain regions which exhibited significant changes.

The comparison among all categorical variables was performed using the chi-square test. The continuous data were compared through a Student's *t* test or Mann-Whitney *U* test. A 5% significance level was accepted in all these comparisons.

Results

There were 19 subjects in the MPH group and 17 in the matched placebo group. Table 1 summarizes the sociodemographic and clinical variables, and shows no statistical difference between the groups.

There were no significant differences between the groups with respect to the mean dose of MPH or placebo, the mean dose of radiotracer injected during the two SPET studies or the time interval between the injection of ^{99m}Tc-ECD and the acquisition of the images. After 4 days of treatment, the MPH group had a significantly larger reduction in the scores of the ABRS (ABRS1–ABRS2) than the placebo group ($P<0.01$) (data not shown but available upon request).

Table 1. Demographic and clinical characteristics, IQ, and basal scores on the ABRS and the TRF attention problem scale in the MPH and placebo groups

Characteristics[a,b]	MPH (n=19)	Placebo (n=17)
Age (years)	11.5 (2.4)	11.8 (2.7)
Ethnicity (European-Brazilian)	18 (94.7)	14 (82.4)
Education (median grade)	5 (2–9)	5 (3–10)
Estimated IQ	97.5 (12.3)	91.5 (11.8)
Monthly family income (number of minimum wages per family member[c])	3.0 (0.4–9.9)	2.5 (1–8.5)
Baseline ABRS	22.4 (4.9)	20.8 (5.0)
Baseline TRF attention problem scale (T score)	66.9 (11)	70.3 (11.1)
ADHD type (combined)	16 (84.2)	13 (76.2)
Main co-morbidity (DBD)	11 (58.8)	12 (68.4)

ABRS, 10-item Conners Abbreviated Rating Scale; TRF, Teacher Report Form; MPH, methylphenidate; ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behavior disorders

[a] Mean and standard deviation (in parentheses) are reported for continuous variables with normal distribution; median and range (in parentheses) are reported for continuous variables without normal distribution;*n* and percent (in parentheses) are reported for categorical variables

[b] There was no significant difference between the groups in any variable assessed

[c] Total amount of money earned by all persons in the family living in the house (transformed into the number of minimum wages) divided by the number of family members living in the house

Regional cerebral blood flow

In within-group comparisons, a significant reduction in the rCBF of the left posterior parietal cortex was found between the first and the second SPET study in the MPH group only (Z=5.29, P=0.019, corrected for multiple comparisons; MNI coordinates −40 mm, −52 mm, 56 mm).

This finding was complemented by the results of the between-group comparison: Although no significant difference was found in the rCBF in any area between the two groups before the administration of the medication or placebo (scan 1), a significantly higher reduction in the rCBF was found in the left posterior parietal region in the MPH group than in the placebo group when differences in the rCBF between scans 1 and 2 were analyzed (Z=4.95, P=0.015, corrected for multiple comparisons; MNI coordinates −38 mm, −52 mm, 50 mm) (Fig. 1). No other significant rCBF differences were found on the within- and between-group comparisons.

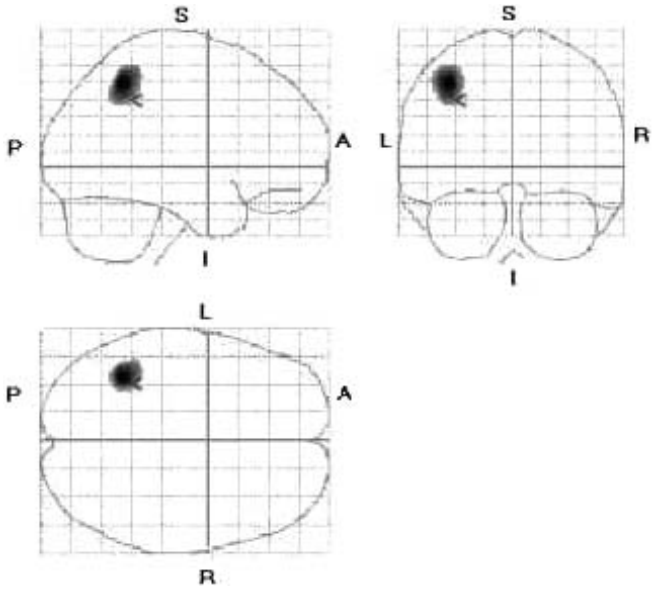

Fig. 1. Statistical parametric mapping showing foci of reduced rCBF in the left posterior parietal lobe in the MPH group compared with the placebo group, at the threshold of Z=4.95. Peak Z score in this region was significant at the P=0.015 level, corrected for multiple comparisons. *A*, Anterior; *I*, inferior; *S*, superior; *P*, posterior; *L*, left; *R*, right

Discussion

In a sample of boys with ADHD, we documented a reduction in the rCBF in the left posterior parietal region after the acute administration of MPH. Although most studies evaluating the effect of MPH on the brain activity in patients with ADHD have reported prefrontostriatal effects [3, 5, 8, 9, 13], our results concur partially with those from the study of Mehta et al. [7], who demonstrated MPH effects on both the dorsolateral prefrontal and the posterior parietal cortex.

Methodological issues could explain the differences among studies. Some investigations have studied only adults [6, 7, 8, 9, 13]. Symptoms of ADHD might differ between adults and children and some brain imaging studies have demonstrated different findings according to age [14]. The duration of treatment has ranged from several weeks [4, 13] to a single dose [6, 7, 8, 9]. Also, studies have varied in the extent of prior MPH exposure, with some including drug-naïve subjects [4] and others enrolling patients chronically treated with stimulants [5]. Differences in image analysis approaches (region of interest vs whole brain SPM) could also have contributed to the variability of results [3, 5]. Imaging techniques have varied from blood flow-related contrast to metabolic and receptor-based imaging [3, 13]. In addition, the type of radiotracer used has varied across studies.

Attention is modulated by distributed neural networks and the posterior parietal cortex integrates this complex system [15]. Recently, Levy and Farrow [16] proposed that dorsolateral prefrontal/parietal connections allow maintenance of working memory required for goal completion. PET studies have suggested that a posterior attentional system modulated by noradrenaline is normally involved in the preparation of the posterior cortex for processing of external stimuli. In ADHD, this system seems to be dysregulated, possibly via deficits in the locus coeruleus [16]. Since imaging in our study was preceded by an attention task, the parietal areas involved in attention circuits could have been activated. Thus, the group that received MPH treatment in our study, besides showing significant clinical improvement, could have presented improved functionality in the region, with a consequent reduction in the need for recruitment;this suggests that the left posterior parietal lobe might be important in the mediation of the clinical effects of MPH.

Our study has some limitations. First, statistical parametric mapping as implemented in SPM 99 is a conservative approach that could have led to false negative findings in the right parietal and bilateral frontostriatal regions. Second, our sample was clinically referred and included only males, so the findings may not be generalizable to females with ADHD. Third, we evaluated only the effect of a relatively brief treatment, and other areas may be affected by a longer course of MPH administration. Lastly, our subjects performed CPT before imaging. This is a common approach intended to standardize brain activity across subjects; however, the rCBF pattern might be different if images were preceded by other activation procedures or rest.

In conclusion, our findings indicate that brief administration of MPH is associated with reduced activity in the left posterior parietal cortex. These findings support the emerging role of the posterior attentional system in both the pathophysiology of ADHD and the therapeutic mechanism of MPH in the disorder.

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