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Original article

Functional MRI in attention-deficit hyperactivity disorder: Evidence for hypofrontality

Yu-Feng Zang[a,h], Zhen Jin[b], Xu-Chu Weng[c], Lei Zhang[b], Ya-Wei Zeng[b], Li Yang[a], Yu-Feng Wang[a,*], Larry J. Seidman[d,e,f,g], Stephen V. Faraone[d,e,f,g]

[a]*Institute of Mental Health, Peking University, Huayuanbeilu 51, Haidian District, Beijing 100083, China*
[b]*Department of MRI, 306 Hospital, Beijng 100101, China*
[c]*Laboratory for Higher Brain Function, Institute of Psychology, The Chinese Academy of Sciences, Beijing 100101, China*
[d]*Massachusetts Mental Health Center, Boston, MA, USA*
[e]*Department of Psychiatry, Harvard Medical School, USA*
[f]*Psychiatry Service, Massachusetts General Hospital, Boston, MA, USA*
[g]*Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, USA*
[h]*National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, China*

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Abstract

Using event-related functional magnetic resonance imaging to study the Stroop effect on both behavioral and brain activation of ADHD children off or on methylphenidate (MPH). Nine ADHD boys (aged 9.8–14.5 years) and 9 age-matched normal controls were included. A Stroop-like paradigm was used. AFNI (Analysis of Functional NeuroImaging) and its Deconvolution Analysis were used in a descriptive comparison between ADHD and control groups. (1) Both behavioral reaction time and brain activation showed Stroop effect in controls but neither was found in ADHD children off MPH. When MPH was administered, the Stroop effect tended to appear. (2) The activation volume (AV) of prefrontal cortex (PFC) in both the neutral (NC) and interference conditions (IC) in ADHD children off MPH was smaller than in controls. AV of anterior cingulate cortex in the IC in ADHD children off MPH was smaller than that in controls, but was similar in the NC to that in controls. AV of the basal ganglia, insula and cerebellum was also smaller in the IC, but was larger in the NC for ADHD children off MPH compared with controls. These findings are consistent with prior findings of hypofrontality in ADHD children and implicate a compensatory network including basal ganglia, insula and cerebellum for relative lower cognitive load tasks.
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Keywords: Attention-deficit hyperactivity disorder; Functional magnetic resonance imaging; Stroop effect; Hypofrontality; Methylphenidate; Compensation

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) affects roughly 3–7.5% of school children (see Ref. [1] for review) and is characterized by inattention, hyperactivity and impulsivity. ADHD children show neuropsychological deficits on the Wisconsin Card Sorting Test [2,3], the Stroop test [2,3], the Matching Familiar Figures Test [2], response inhibition tests [4], and motor timing [5,6]. Many structural [7–14] and functional neuroimaging studies [15–17] have revealed abnormalities in the frontostriatal circuit. Due to its good spatial and temporal resolution, functional magnetic resonance imaging (fMRI) has been used to describe the activity of specific brain areas of ADHD subjects when performing specific cognitive tasks. Vaidya et al. [18] reported in an fMRI study with Go-No-Go paradigm and found methylphenidate (MPH) increased striatal activation in ADHD children but reduced it in healthy children. Two other fMRI studies demonstrated hypofrontality [6] and hypofunction of anterior cingulate cortex (ACC) [19] in ADHD subjects. With T2 relaxometry technique, Teicher et al. [20] found that cerebral blood volume was reduced in the putamen of ADHD children and normalized during treatment with methylphenidate.

* Corresponding author. Tel.: +86 10 82801969; fax: +86 10 62027314.
E-mail address: wangyf@bjmu.edu.cn (Y.-F. Wang).

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In addition to frontostriatal circuit abnormalities, the volumes of inferior posterior cerebellar lobe [21,22] and of posterior vermis [22] were found to be decreased in ADHD children. Nonmotor cognitive functions of the cerebellum have been well-documented by clinical [23,24] and neuroimaging studies [25,26].

Compared with block designs, event-related fMRI (ER-fMRI) design has the advantage of separating brain activity associated with correct responses from those associated with incorrect ones. ADHD children may show more errors in stimulus–response cognitive tasks than healthy controls. Subjects are usually aware when they have committed errors. Therefore, including these errors in a block design will add unknown variance to the data [27]. In the present study, ER-fMRI was used to explore the Stroop effect on ADHD children in both conditions on and off MPH.

2. Materials and methods

2.1. Subjects

There were 9 ADHD boys (aged 9.8–15, 13.03±1.64) and 9 age-matched normal boys (aged 10.1–14.3, 12.84±1.13) as a control group. ADHD inclusion criteria were: (1) diagnosis of ADHD based on both structured diagnostic interview (see Ref. [28], Chinese revised version see Ref. [29]) of the parent or the best informant and a teacher rating of DSM-IV criteria (6 children met the criteria for inattention-type and 3 met the criteria for combined-type. Seven children also had comorbid oppositional defiant disorder and one had comorbid dysthymic disorder); (2) no history of neurological disease and diagnosis of schizophrenia, affective disorder, pervasive development disorder; (3) no history of stimulant medication; (4) Standard Score from the Raven Standard Progressive Matrices greater than 25 percentile and full scale Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R) [30] score greater than 85; and (5) right-handed.

For the normal controls: (1) ADHD diagnosis was excluded based on the parent ratings of DSM-IV criteria; (2) Standard Score from the Raven Standard Progressive Matrices greater than 25 percentile. No WISSC-R criterion was used; (3) No history of neurological disease and diagnosis of schizophrenia, affective disorder, pervasive development disorder.

ADHD subjects underwent 2 fMRI scans with an interval of 1–2 weeks. In the first scan, 5 of the 9 ADHD children took 10 mg MPH 1.5 h beforehand and the remaining 4 did not take MPH. For the second scan, the original latter 4 took MPH but the other 5 did not. Informed consent was obtained from the subject's parent and was approved by the Research Committee of the Institute of Mental Health, Peking University.

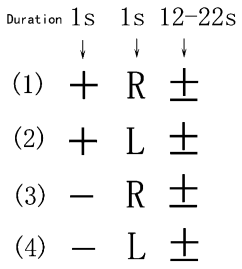

Fig. 1. Stroop-like paradigm of stimulus task. L and R mean the Chinese character 'left' and 'right', respectively. (1) and (2) are neutral conditions. (3) and (4) are interference conditions.

2.2. Cognitive tasks

A Stroop-like paradigm (Fig. 1) was used as the stimulus task that consists of a neutral condition (NC) and an interference condition (IC). The program was operated on a PC with DMDX (free software by K.I. Forster and J.C. Forster from Monash University and the University of Arizona). The background was white and the foreground was black. The visual angle was 6°. At the beginning, '±' was presented as the control at the center of the screen for 6 s. Then followed a cue '+' or '−' which lasted 1 s. This was followed by a word 'LEFT' or 'RIGHT' in Chinese, which was displayed for 1 s. Then followed the control '±'. The subject was asked to press the left or right button if 'LEFT' or 'RIGHT' followed the cue '+', respectively, and to press the right or left button if the 'LEFT' or 'RIGHT' followed the cue '−', respectively. The period from one cue to the next formed a trial. The trial beginning with '+' was NC and that with '−' was IC. The order of NC and IC was pseudo-randomly displayed. Each trial pseudo-randomly lasted for 14–24 s with the duration of '±' varied. Each session had 12 NCs and 12 ICs. And in each session, the left or right key should be pressed 12 times. The reaction time (RT) was recorded. Missing the target (RT > 1 s), wrong responses and impulsive responses (RT < 100 ms) were all taken as errors. Moderate training before scanning was done to ensure that all the subjects understood the tasks. The tasks were projected to a screen at the end of the scanner and then reflected to the subjects by a mirror over the head coil.

2.3. Imaging procedure

Images were acquired on a 2T Elscint/Prestige scanner. Seven functional images were acquired by T_2*-weighted echo-planar sequence (TE, 60 ms, TR, 1000 ms, flip angle, 90°, in-plane resolution, 2.96×2.94 mm, thickness/skip, 8/4 mm). Seven images were acquired axially from 26 mm below to 46 mm above the anterior commissure to posterior commissure (AC–PC) line at an angle of 3° to the AC–PC line (Fig. 2). Each session contained 383 images. After that, 7 T1-weighted anatomy images were acquired (TE, 96 ms, TR, 5000 ms) at the same position of T_2*. Finally, a fast SPoiled GRass (SPGR) sequence was used to obtain

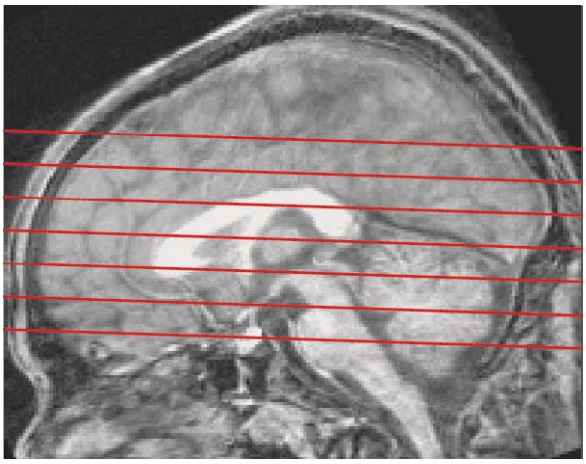

Fig. 2. Location of fMRI scanning.

the whole brain structure (TE, 6 ms, TR, 25 ms, Thickness, 2 mm). Image reconstruction was performed off-line.

2.4. Data analysis

AFNI ([31], latest version of 2001) was used on a workstation. FMRI data were 3D motion corrected and spatially calibrated to structural images. Based on cinematic viewing, only the correct response fMRI data with no perceptible head movements were taken into further analysis. There were totally six conditions, three Ics and three NCs, within a matched set of subjects, which contains one ADHD boy off MPH, same ADHD boy on MPH and one control boy. Among these six conditions, the number of selected correct response trials was equal to each other. For example, within a matched set, the ADHD child off MPH made only four correct responses in the IC and it was the least in either the three ICs or three NCs. Then four correct response trials were picked out randomly from all the other ICs and NCs. These selected fMRI data were then spatially normalized by Talairach and Tournoux coordinates [32], voxel volume re-sampled ($3\times3\times3$ mm), spatially filtered (FWHM, 5 mm), and temporally smoothed (three points linear filter).

The fMRI data of all the nine subjects in a matched group (ADHD children off MPH, same ADHD children on MPH or controls) were concatenated for generating the activation maps using Deconvolution Analysis of FMRI Time Series Data in AFNI [31] voxel by voxel. First, the impulse-response functions were estimated based on the input stimulus functions and the observed fMRI time series data. The impulse-response functions were then convolved with the stimulus functions to yield the estimated response. Finally, the F statistic was calculated for each voxel to test the 'goodness' of the fit between the observed time series and the estimated response. Voxels with $F_{(14,687)}>2.776$ ($P<0.0005$) and a cluster of at least seven contiguous voxels with $P<0.03$ (corrected by Monte Carlo simulation in AFNI) was taken as activation. The volume of activated brain areas was descriptively compared within group (NC vs IC) and between groups (ADHD children off MPH, same ADHD children on MPH or controls). The activated volume (AV) of each region of interest (ROI), including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, basal ganglia (BG, including only putamen and globus pallidus here), and cerebellum, were calculated.

In addition to the statistical procedures above, SPSS software was used to test the behavioral results. RT difference within group (NC vs IC) was tested with paired t-tests, and differences between groups (ADHD children off MPH, same ADHD children on MPH and controls) was tested with ANOVA. The Kruskal–Wallis test was used to test for error number difference among the three groups.

3. Results

3.1. Behavioral data

There were 3–10 correct response trials selected in each matched set of subjects. As shown in Table 1, the RT of the IC in normal controls was significantly longer than that of NC. But no such difference was found in the ADHD children off MPH. After the MPH administration, the RT in IC tended to be longer than that of NC. Across groups, the RT difference (ANOVA) was not significant either in NC ($P=0.708$) or in IC ($P=0.110$). The error number made by ADHD children was higher ($P=0.039$ in IC) and tended to be higher ($P=0.052$ in NC) than that of normal controls (Table 2).

Table 1
Difference of RT (ms) between NC and IC (paired t-test, df = 8, two-tailed)

Group and condition		*Mean*	*N*	*SD*	*t*	*P*
Control	NC	588.36	9	109.47	−2.706	0.027
	IC	648.58	9	85.62		
ADHD off MPH	NC	541.57	9	92.51	0.116	0.91
	IC	532.58	9	173.34		
ADHD on MPH	NC	516.74	9	131.04	−1.217	0.258
	IC	554.79	9	114.7		

RT, reaction time; NC, neutral condition; IC, inference condition.

Table 2
Difference of Error number between groups (Kruskal–Wallis test, df = 2)

Condition	Group	Mean	SD	Chi-square	*P*
NC	Control	1.44	1.01		
	ADHD off MPH	4.56	3.00	5.901	0.052
	ADHD on MPH	4.11	3.10		
IC	Control	1.44	1.74		
	ADHD off MPH	5.33	4.18	6.472	0.039
	ADHD on MPH	4.56	3.36		

NC, neutral condition; IC, interference condition.

Table 3
Activation volume (cm^3) of ROI

	Controls		ADHD off MPH		ADHD on MPH	
	NC	IC	NC	IC	NC	IC
PFC-R	20.57	26.77	11.89	0	0	2.39
PFC-L	11.13	27.25	8.59	0	0	0.9
ACC	3.51	7.48	3.28	0.17	0	0
BG-R	0.12	3.94	1.56	0	0	0
BG-L	0.54	1.91	4.27	0	0	0
Insula-R	3.22	6.84	6.65	0	0	0.51
Insula-L	3.79	8.36	5.15	0	0	0.07
Cerebellum-R	3.22	9.47	15.01	0.64	0	2.38
Cerebellum-L	8.14	16.14	13.3	0.85	0	2.81

ROI, region of interest; NC, neutral condition; IC, interference condition; -R, right; -L, left; PFC, prefrontal cortex; ACC, anterior cingulate cortex; BG, basal ganglia.

3.2. Activation maps

3.2.1. Activation in the control group

In NC of the control group, PFC (Brodmann area [BA]: right 47, bilateral 10 and bilateral 9), ACC (BA, 24), bilateral insula (BA, 13, 14), right temporal pole (BA, 38), right angular gyrus (BA, 39), bilateral fusiform (BA, 37, 19), bilateral supplementary motor area (SMA), bilateral BG, bilateral thalamus, bilateral cerebellum, and brain stem, all were activated. In IC of the control group, right Broca gyrus (BA, 46), bilateral supramarginal gyrus (BA, 40) and right precuneus (BA, 7) were activated. AV of each ROI in IC of controls was larger than that in NC (Table 3).

3.2.2. Activation in ADHD off MPH

In IC, only small parts of PFC and cerebellum were activated (Fig. 3 and Table 3). All the areas activated in NC of the control group were also activated in NC of ADHD children off MPH, though AV varied. AV of ROIs in IC of ADHD children off MPH was found to be smaller than that in NC.

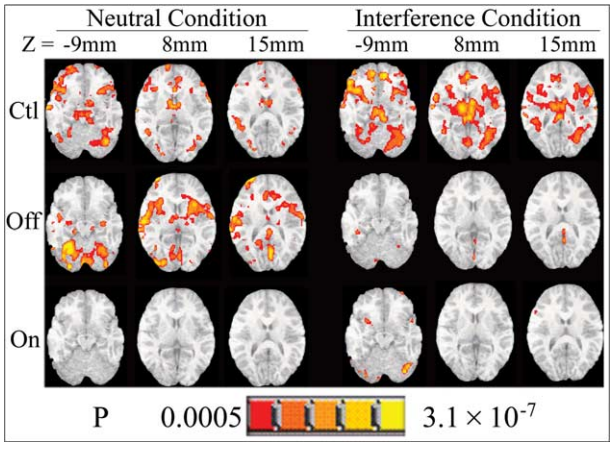

Fig. 3. Activation map. *Z*, *Z* axis in Talairach and Tournoux coordinates; Ctl, controls; Off, ADHD off MPH; On, ADHD on MPH; In controls, activation volume was larger in IC than in NC, i.e. Stroop effect existed. But it disappeared in ADHD off MPH. When the MPH was administered, Stroop effect appeared again.

3.2.3. Activation in ADHD on MPH

AV of some ROIs in IC was found to be larger than that in NC (Fig. 3 and Table 3), but similar to that of controls. No activation was found in NC at the given threshold ($P < 0.03$). But in IC, the PFC, insula, cerebellum, thalamus, and midbrain were activated.

3.2.4. Activation compared across groups

In IC, AV of each ROI of ADHD off MPH was smaller than that of controls (Fig. 3 and Table 3). Also in IC, AV of some ROIs was larger in ADHD on MPH than off MPH. Comparing AV of each ROI in NC of ADHD children off MPH to that of controls, AV was found smaller in PFC, similar to that in ACC, but larger than that in BG, insula and cerebellum. In NC, as no activation was seen in ADHD on MPH, AV of ROIs in ADHD off MPH was much larger than that on MPH.

4. Discussion

4.1. Stroop effect in ADHD children

In the present study, the Stroop effect (in which the RT in IC is longer than that in NC) was found in the behavioral performance of the control children, but no such Stroop effect was found in that of ADHD children off MPH. However, a Stroop effect tended to appear in the ADHD children when MPH was administered. The brain activation was similar to the case in behavioral performance. AV of each ROI in the IC of controls was larger than that in NC. Here we take this activation effect, as what Bush et al. [19] did, to be the Stroop effect. But in ADHD subjects off MPH, AV of each ROI in the IC was smaller than that in NC, and the Stroop effect disappeared. When MPH was administered to ADHD subjects, AV of some ROIs in IC was slightly larger than that in NC and thus the Stroop effect tended to appear. This result of increased activation of PFC in the IC after MPH is consistent with the results of the other fMRI study, in which Vaidya et al. [18] found that MPH increased frontal activation in both ADHD and control groups.

The Stroop task, a paradigmatic measure for selective attention, has often been employed to investigate attention deficits in schizophrenia [33], obsessive–compulsive disorder [34], as well as ADHD [19,35]. And the Stroop task was widely used to evaluate the impairment of executive function in those patients [2,36]. In an fMRI study in which the Counting Stroop version of the Stroop was used, Bush et al. [19] found that normal controls showed significant activation (Interference > Neutral) in ACC, while the ADHD adults did not. The activation effect observed in the current study is quite consistent with what Bush et al. [19] has found. The Stroop effect of behavioral performance

also disappeared in ADHD children off MPH in the present study. But in Bush's study, both of the ADHD adult group and control group exhibited Stroop effect in behavioral performance. The incongruent results of the two studies may be due to the age difference of subjects enrolled. We presume that the ADHD adults enrolled in Bush's study could exhibit higher inhibitory control than that of the younger ADHD subjects enrolled in the current study.

Carter et al. [35] used a basic Stroop Color-Word Naming paradigm (e.g. naming a color word 'RED' in blue ink vs naming the color of this word in red ink) and found increased Stroop interference in ADHD children. This seems to be contrary to the behavioral performance observed in ADHD children off MPH in the current study. The main cause may relate to the different paradigms. The examiners' verbal regulation may help the ADHD children operate more 'carefully and seriously' in the Stroop Color-Word Naming task. But in the current study, ADHD children tend to make more errors and to respond more rapidly while subjects were asked to simply press the left or right button when no examiner is on the scene to supervise them. Different Stroop paradigms may dominantly reveal different aspects of executive function. In the current study, the higher impulsiveness of ADHD children may account for the disappearance of Stroop effects both in behavioral performance and in brain activation.

4.2. Dysfunction of various brain area and cognitive load in ADHD

In the paradigm we have used, the cognitive load in IC is higher than that in NC. We found that AV differences between ADHD children off MPH and controls are correlated to cognitive loads. In the PFC, AV of ADHD children off MPH was smaller than that of controls in both low cognitive load NC and high cognitive load IC. This is consistent with the hypofrontality result of other ADHD studies [6,37]. In the ACC in the present study, AV in IC of ADHD children off MPH was smaller than that of controls. This hypofunction of ACC is similar to that observed by Bush et al. [19]. But in NC, AV of the ACC in ADHD children off MPH was similar to that of controls. This suggests that the ACC dysfunction is apparent in high cognitive load condition. Within regions of the BG, insula and cerebellum in IC, AV of ADHD children off MPH was smaller than that of controls, but larger than that of controls in the NC. In an fMRI study with two versions of Go-No-Go paradigm, Vaidya et al. [18] found that striatal activation of ADHD children was weaker than that of controls in a stimulus-controlled task, but was marginally greater than that of controls in response-controlled task. Both Vaidya's and the current results indicate that BG of ADHD subjects showed various responses to different cognitive tasks when compared to the control subjects. In the current study, the insula and cerebellum of ADHD children off MPH exhibited task-dependent activation, i.e. smaller AV in IC and larger AV in NC, similar to BG. Bush et al. [19] suggested that the greater activation in the insula in ADHD adults compared with controls could be of a compensatory reaction. We agree with Bush's idea and propose that the BG, insula and cerebellum show a hypofunction in a higher cognitive load but a compensatory hyperfunction in a lower cognitive load in ADHD boys.

Using a new technique of fMRI, named T2 relaxometry, Teicher et al. [20] measured the blood volume (BV) in putamen of ADHD boys in steady-state. They found that MPH increased BV of putamen in ADHD boys with objective hyperactivity, but reduced BV in ADHD boys with no objective hyperactivity. Contrary to changes of BV in putamen in the former study, another study [26] from the same research group with same approach reported that MPH reduced BV of vermis in ADHD with objective hyperactivity, but increased it in ADHD without objective hyperactivity. These results suggested that putamen and vermis plays distinct role in ADHD.

It seems quite difficult for interpreting the fMRI results in ADHD on MPH. It is noticed that less (in IC) and no (in NC) activation were seen at the given threshold in ADHD on MPH (Fig. 3). FMRI-BOLD signal is relative rather than absolute. That means so-called activation is a measure of amplitude of difference between baseline and task condition. A probable interpretation to the current result is that MPH elevated fMRI baseline level in ADHD and that the lower load NC did not change such baseline very much. Further studies using PET might elucidate such result better.

Despite the advantage of ER-fMRI, some limitations to the current study should be indicated. It is clear that ER-fMRI allows fewer trials in a session than block design, and much fewer than behavioral study. In addition, ADHD children usually make more errors than normal controls in behavioral performance. Therefore, there were only 3–9 correct trials for the NC or the IC of each ADHD subject in this study. Too few correct trials will weaken the power of results. More subjects and more scanning sessions within the tolerance of ADHD subjects are expected to uncover more definitive results. Another limitation is the confounding effect of subjects. Two subtypes of ADHD have been included in this study. And no specific psychological test, for example, metaphor and sarcasm scenario test [38], was used to exclude high functioning autism. Keeping the subject group more homogeneous could reveal the mechanism more accurately.

4.3. Conclusions

In both behavioral and brain activation data, no Stroop effect was observed in the ADHD children off MPH but appeared after MPH was administered. The PFC of ADHD children off MPH exhibited hypofunction in either high or low cognitive load. The ACC, BG, insula and cerebellum exhibited hypofunction in the high cognitive load. In the low cognitive load, the ACC remained normal, while the BG,

insula and cerebellum showed compensatory hyperfunction. These findings confirmed the hypofrontality in ADHD children and suggested a compensatory network of the basal ganglia, insula and cerebellum when ADHD children have a relatively lower cognitive load.

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