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·**Original Article**·

Effects of methylphenidate on resting-state brain activity in normal adults: an fMRI study

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ABSTRACT

Methylphenidate (MPH) is one of the most commonly used stimulants for the treatment of attention deficit hyperactivity disorder (ADHD). Although several studies have evaluated the effects of MPH on human brain activation during specific cognitive tasks using functional magnetic resonance imaging (fMRI), few studies have focused on spontaneous brain activity. In the current study, we investigated the effect of MPH on the intra-regional synchronization of spontaneous brain activity during the resting state in 18 normal adult males. A handedness questionnaire and the Wechsler Adult Intelligence Scale were applied before medication, and a resting-state fMRI scan was obtained 1 h after medication (20 mg MPH or placebo, order counterbalanced between participants). We demonstrated that: (1) there were no significant differences in the performance of behavioral tasks between the MPH and placebo groups; (2) the left middle and superior temporal gyri had stronger MPH-related regional homogeneity (ReHo); and (3) the left lingual gyrus had weaker MPH-related ReHo. Our findings showed that the ReHo in some brain areas changes with MPH compared to placebo in normal adults, even though there are no behavioral differences. This method can be applied to patients with mental illness who may be treated with MPH, and be used to compare the difference between patients taking MPH and normal participants, to help reveal the mechanism of how MPH works.

Keywords: methylphenidate; resting-state brain activity; male adults; functional magnetic resonance imaging; regional homogeneity

INTRODUCTION

Dysfunction of the frontal–striatal–cerebellar circuitry is thought to be the main pathological change in attention deficit hyperactivity disorder (ADHD). In structural imaging, the volumes of the whole brain, prefrontal cortex, left caudate nucleus, and cerebellum are all reduced[1-8]. Functional neuroimaging studies of patients with ADHD show the involvement of multiple neuronal systems in this disorder, including the prefrontal cortex, parietal cortex, striatum and cerebellum[9-15]. These regions are organized in circuits. Each circuit has projections both to and from the prefrontal cortex[16]. Methylphenidate (MPH) is the most commonly used stimulant to treat ADHD. It can relieve the main symptoms of inattention, inappropriate motor activity and impulsivity. The therapeutic effects of MPH are thought to be through its actions on the dopamine and norepinephrine systems[17]. Nonhuman studies also indicate that MPH affects both of these systems[18]. In most functional neuroimaging studies, MPH is found to influence various brain areas when per-

forming a task, especially the frontal–striatal–cerebellar circuitry. The results from positron emission tomography (PET) studies are as follows. In a spatial working memory task, the MPH-induced improvements in task performance are accompanied by task-related reductions in regional cerebral blood flow (rCBF) in the dorsolateral prefrontal cortex and posterior parietal cortex in healthy males[19]. MPH activates the anterior cingulate but not the striatum according to a [^{15}O]H_2O PET study in healthy volunteers[20]. There are also some studies in which the MPH effects were evaluated using functional magnetic resonance imaging (fMRI). In a Go/No-go task, MPH increases frontal cortical activity in children with and without ADHD, whereas it increases striatal activation in ADHD children but reduces it in healthy children[9]. In ADHD children, using a Stroop-like paradigm, only after MPH administration did the Stroop effect tend to appear. Under interference conditions, MPH improves the activation in prefrontal cortex, insula, cerebellum, thalamus, and midbrain[21]. Most of the above studies focused on the brain activation when participants were performing tasks. However, it is hard to compare data from different cognitive tasks and draw clinically helpful conclusions. Although all studies agree that there are differences in brain activity between ADHD patients and normal controls, and these can be changed by MPH, the direction of the abnormalities and the drug effect, i.e. hypoactivation *versus* hyperactivation, prove to be fairly inconsistent among studies[22]. Differences might also be due to different tasks, because most cortical increases in activation might be task-specific. Finally, to accomplish a task, we need some activations and also to suspend some activations. In task-related studies, when on-MPH, participants always do the task better, which means greater accuracy and a shorter response time. If the conditions before and after medication are not controlled, the interpretation of the activation differences may be complicated, because they may come from different levels of task performance. And in most MPH-related studies, it is hard to keep a balance between the task performance off- and on-MPH.

In such complicated neuronal activity, the baseline seems to be helpful. In contrast to the task-based approaches, examination of the resting-state functional connectivity enables the characterization of task-independent patterns of correlated activity[23]. The identification of a control or baseline state to which the condition of interest can be compared greatly helps to understand the changes during tasks and those due to the effects of a drug [24]**.** In recent years, resting-state imaging has been widely used and has yielded some findings in ADHD. In a single-photon emission computed tomography (SPECT) study, MPH increased the rCBF in bilateral prefrontal, caudate and thalamic areas in ADHD children[25]. In another SPECT study by Lee *et al.*[26], long-term MPH treatment affected the resting rCBF in ADHD children. After MPH treatment in ADHD children, the hyperperfusion in the somatosensory area (in comparison to normal control) was reduced; significant reduction of rCBF was found in the right striatum and bilateral ventral visual areas; and rCBF was increased in the superior prefrontal cortex[26]. It also indicated that ADHD symptom improvement after MPH is associated with the normalization of reduced orbitofrontal activity[26]. Using SPECT, Langleben *et al.* found that chronic MPH treatment decreased the extremely high rCBF in the motor, premotor, and anterior cingulate cortices in ADHD[27]. Based on resting-state SPECT, Cho *et al.*[28] found that non-responders to MPH had higher rCBF in the left anterior cingulate cortex, left claustrum, right anterior cingulate cortex, and right putamen, and lower rCBF in the right superior parietal lobule, compared to the responders. Another resting-state PET study indicated that in ADHD adults, the on-placebo condition was associated with relative increases in rCBF bilaterally in the precentral gyri, left caudate nucleus, and right claustrum compared to the on-MPH condition, while the on-MPH condition was associated with relative increases in the cerebellar vermis[29]. However, PET and SPECT are not readily acceptable for children, and SPECT has low spatial resolution.

The application of resting-state fMRI provides a new way to investigate the effect of MPH on the brain. It is non-invasive and convenient for clinical use. Using fMRI, Zang *et al.* found that patients with ADHD have decreased amplitude of low-frequency fluctuation (ALFF) in the right inferior frontal cortex, left sensorimotor cortex, bilateral cerebellum and vermis, as well as increased ALFF in the right anterior cingulate cortex, left sensorimotor cortex, and bilateral brainstem[30]. Cao *et al.* found decreased regional homogeneity (ReHo) in the frontal–striatal–cerebellar circuit and increased ReHo in the occipital cortex in ADHD pa-

tients[31]. Moreover, the resting-state activity index showed that ADHD patients exhibit more significant activity in basic sensory and sensory-related cortices[32]. Resting-state fMRI also helps to evaluate medication effects in both patients and normal adults. Teicher *et al.*[33], using T2 relaxometry, found that boys with ADHD have a higher T2 relaxation time in the bilateral putamen than healthy participants. After 1-week MPH treatment, the T2 relaxation times in the putamen change in ADHD children[33]. Anderson *et al.* found that moderate and high doses of MPH increase the T2 relaxation time in a rate-dependent manner—increasing it in the most active children with ADHD and reducing it in ADHD participants who are not objectively hyperactive[34]. Psychomotor stimulant treatment acts to normalize perfusion in the frontal cortex and the caudate nucleus with additional decreases in parietal and parahippocampal regions, as revealed by the continuous arterial spin labeling technique of MRI[35]. Other neurological and psychiatric diseases are also in focus. For instance, Wu *et al.* found that administration of levodopa relatively normalized ReHo in patients with Parkinson's disease[36]. Kelly *et al.* examined the effect of *L*-dopa on striatal resting-state functional connectivity (FC) in 19 healthy young adults and found that it increases FC in motor pathways connecting the putamen ROIs (regions of interest) with the cerebellum and brainstem[37]. Cao *et al.* examined the differences in functional connectivity of the putamen–ROIs between medication-naive children with ADHD and normal children[38]. Konrad *et al.* also summarized the structural connectivity of participants with ADHD[39]. In unmedicated unipolar depressed patients, after 6 weeks of treatment with sertraline, the low-frequency blood oxygen level-dependent fluctuations correlation between the anterior cingulate cortex and limbic regions is significantly increased when participants are at rest[40]. Resting-state fMRI has proved to be a suitable technique for studying drug effects.

How MPH affects the resting-state fMRI signal in ADHD patients remains unknown. But ADHD patients have high inhomogeneity and some have bad responses to the drug. Therefore, in the present study, we carried out a pilot study in normal adults because they have higher homogeneity and there are fewer confounding factors. ReHo focuses on the similarities of intra-regional time series. It can be considered complementary to the model-driven method, and its major advantage is the ability to detect unpredicted hemodynamic responses that the model-driven method fails to reveal[41]. While functional connectivity measures the temporal synchronization of distinct brain regions, ReHo measures the local synchronization. We used the ReHo approach to analyze the fMRI data in normal adults, and to identify the differences in the resting pattern between off- and on-MPH states.

PARTICIPANTS AND METHODS

Participants

Eighteen healthy males (19–24 years; mean weight 66.8 ± 7.6 kg, range 54–85) participated in this subject-blind, medication-order randomized and placebo-controlled study. They were recruited through an advertisement in the university. The criteria were: (1) right-handed; (2) no history of neurological or psychiatric diseases; (3) no family psychiatric history; (4) no brain injury history; and (5) no history of any stimulant medication. After description of the study and its potential risks, the participants consented to participate and gave written informed consent. The study was approved by the Human Investigation Committee of Zhejiang University School of Medicine.

Testing Procedure

A questionnaire[42] was used to determine the handedness of each participant. The Wechsler Adult Intelligence Scale-Revised Chinese Edition[43] was used to obtain the full-scale IQ before scanning. Then the participants underwent two counterbalanced test sessions, one with a single dose of MPH (20 mg[44]) and the other with placebo. A resting-state fMRI scan was obtained 1 h after administration (oral MPH reaches peak concentration in the brain 60–90 min after administration[45]). The participants carried out a block-designed Go/No-go task[46] in the scanner after the resting scan. The task included 3 Go blocks and 3 No-go blocks. The Go block included 16 Go trials and the No-go block included 10 Go trials and 6 No-go trials. Each block lasted for 32 s and the interval between blocks was 20 s.

fMRI Scan Parameters

fMRI scans were acquired in a Siemens Sonata 1.5 T scanner equipped with gradients for echo planar. Each participant lay supine in the scanner, and the head was snugly

fixed with foam pads. We scanned each participant on two different days at an interval of one week. MPH (or placebo) was taken on the first day and one week after placebo (or MPH) was taken. The order of taking MPH first or placebo first was randomized (for a single participant taking MPH first or placebo first) and counterbalanced (among all the participants, half took MPH first and half took placebo first). One resting-state scan was run per session. In the fMRI scan, 2D, 3D and resting echo-planar images (EPIs) were obtained. In the resting-state scan, participants were instructed to close their eyes, to remain motionless as far as possible, and not to think of anything in particular. Twenty-five axial slices by spin echo sequence were acquired (thickness/gap, 5.0/1.0 mm; in-plane resolution, 128 × 128; FOV, 240 × 240 mm^2; TR, 510 ms; TE, 15 ms). Also, 25 axial slices with an EPI pulse sequence (thickness/gap, 5.0/1.0 mm; in-plane resolution, 64 × 64; FOV, 240 × 240 mm^2; TR, 2 000 ms; TE, 40 ms; flip angle, 90°), and 180 volumes were obtained. The resting state scan lasted 6 min. Each participant was scanned once. Finally, 144 whole-brain T1-weighted MP RAGE (magnetization-prepared rapid acquisition gradient echo) sagittal images were obtained with the following parameters: TR, 1 900 ms; TE, 3.93 ms; TI, 1 100 ms; flip angle, 15°; slice thickness/gap, 1.3 mm/0 mm; FOV, 240 × 240 mm^2.

fMRI Data Analysis

The first ten time points were deleted to provide a more stable resting dataset. The data were preprocessed by SPM5 (statistical parametric mapping 5, Wellcome Department of Cognitive Neurology, London, UK), including time alignment across slices, head-motion correction, voxel resampling to 3 × 3 × 3 mm^3, and spatial normalization. Datasets with >2.4 mm maximum translation or >2.4° maximum rotation along any axis were discarded (no participant's data was excluded).

REST software (http://www.restfmri.net)[47] was used to calculate Kendall's coefficient concordance (KCC)[48]. The ReHo or similarity of the ranked time series of a given voxel with its nearest 26 neighbor voxels was calculated in a voxel-wise manner. An individual KCC map was obtained for each participant. To make it more comparable between participants, the individual ReHo map was divided by the mean ReHo value of the whole brain. Then spatial smoothing (FWHM, 8 mm) was performed. A second-level random-effect one-sample *t*-test (P <0.001, uncorrected; P <0.05, after AlphaSim correction) was performed within the whole brain mask to show the ReHo results for each condition, including the MPH and placebo conditions. The paired-sample *t*-test was performed within the whole brain mask to show the difference between the two conditions. Single voxels with P <0.001, uncorrected (P <0.05, after AlphaSim correction), and cluster sizes >594 mm^3 were considered to show significant difference between conditions. Threshold correction was done using the AlphaSim program in REST.

RESULTS

The full-scale WAIS-RC IQ ranged from 108 to 130 (standard score) with an average of 121.3. No significant differences were found in the accuracy rates of the Go/No-go task on-placebo and on-MPH using the paired sample *t*-test (Go block, P = 0.33; No-go block, P = 0.83).

ReHo Results for On-Placebo and On-MPH Conditions

The ReHo results on-placebo and on-MPH are shown in Fig. 1 (one-sample *t*-test, single voxel threshold P <0.001, uncorrected and AlphaSim corrected threshold P <0.05; cluster size >594 mm^3; rmm = 6, df = 17). The default network, including the posterior cingulate cortex, medial prefrontal cortex, and inferior parietal lobe, displayed higher ReHo than other brain areas in both the on-placebo and on-MPH conditions.

ReHo Difference Map between On-Placebo and On-MPH Conditions

ReHo on-placebo and on-MPH were compared using the paired-sample *t*-test. The on-MPH condition had greater ReHo than on-placebo mainly in the left middle and superior temporal gyri, while the region where the on-MPH condition had lower ReHo than on-placebo was mainly in the left lingual gyrus. The single-voxel threshold was P <0.001, uncorrected. The map of differences was obtained after AlphaSim correction. The threshold was P <0.05 and cluster size was >594 mm^3; rmm = 6, df = 17 (Fig. 2, Table 1). The averaged ReHo values in the above areas that had differences between on-MPH and on-placebo for 18 participants were then calculated (Fig. 3).

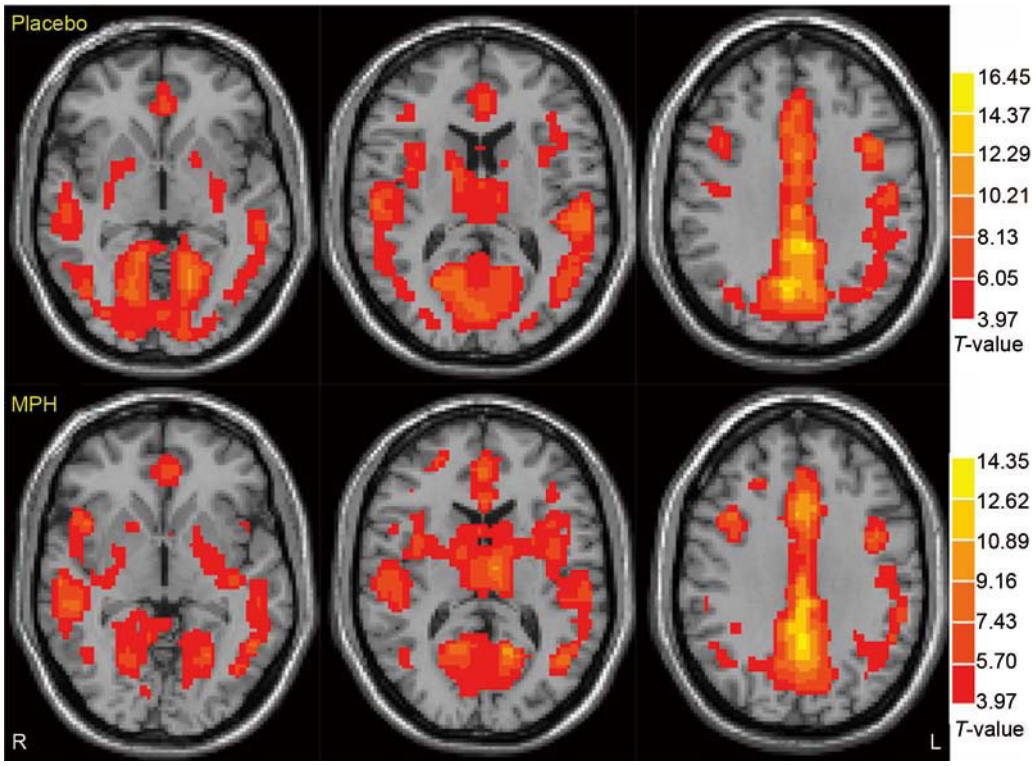

Fig. 1. Results of regional homogeneity on-placebo and on-MPH in the resting state. Maps are superimposed on axial sections of the ch2 template of REST (http://www.restfmri.net). The *Z* values of the three images in each condition are −3, 12, and 33 mm in the Montreal Neurological Institute system.

Table 1. Differences in regional homogeneity (ReHo) between on-MPH and on-placebo conditions

Brain regions	MNI coordinates			*t* value	Volume (mm^3)
	x	y	z		
Left lingual gyrus (BA 19)	–15	–54	–3	–5.12	648
Left middle and superior temporal gyrus (BA 39)	–30	–57	21	6.48	648

BA, Brodmann area. MNI, Montreal Neurological Institute. The coordinates are given as stereotaxic coordinates referring to the atlas of MNI and Tournoux (positive coordinate values indicate right, anterior and superior). *t* value, statistical value of peak voxel showing ReHo differences between on-MPH and on-placebo states (positive *t* value means increased ReHo on-MPH; negative *t* value means increased ReHo on-placebo).

DISCUSSION

MPH is popular in ADHD therapy. Detecting the neuronal changes after using MPH is important for understanding how it works to treat ADHD. The ReHo of the left superior and middle temporal gyri and left lingual gyrus was reorganized on-MPH.

We found that the main brain areas that had higher ReHo in the resting state both on-placebo and on-MPH were the posterior cingulate cortex, medial prefrontal cortex, and inferior parietal lobe. These areas seem to match the activity in the four major brain areas included by Raichle and Gusnard *et al.* in the resting state, the posterior medial cortices, posterior lateral cortices, ventral medial prefrontal cortex, and dorsal medial prefrontal cortex[24,49]. ReHo is an effective resting-state fMRI index to evaluate the similarity of the time series of one voxel to its nearest neighbors[41]. It shows the basic state inside an area before specific cognitive process, and is an important supplement to the method of functional connectivity which detects the connectivity between regions. ReHo is supposed to change in many psychiatric or neurological diseases. Abnormal ReHo has been

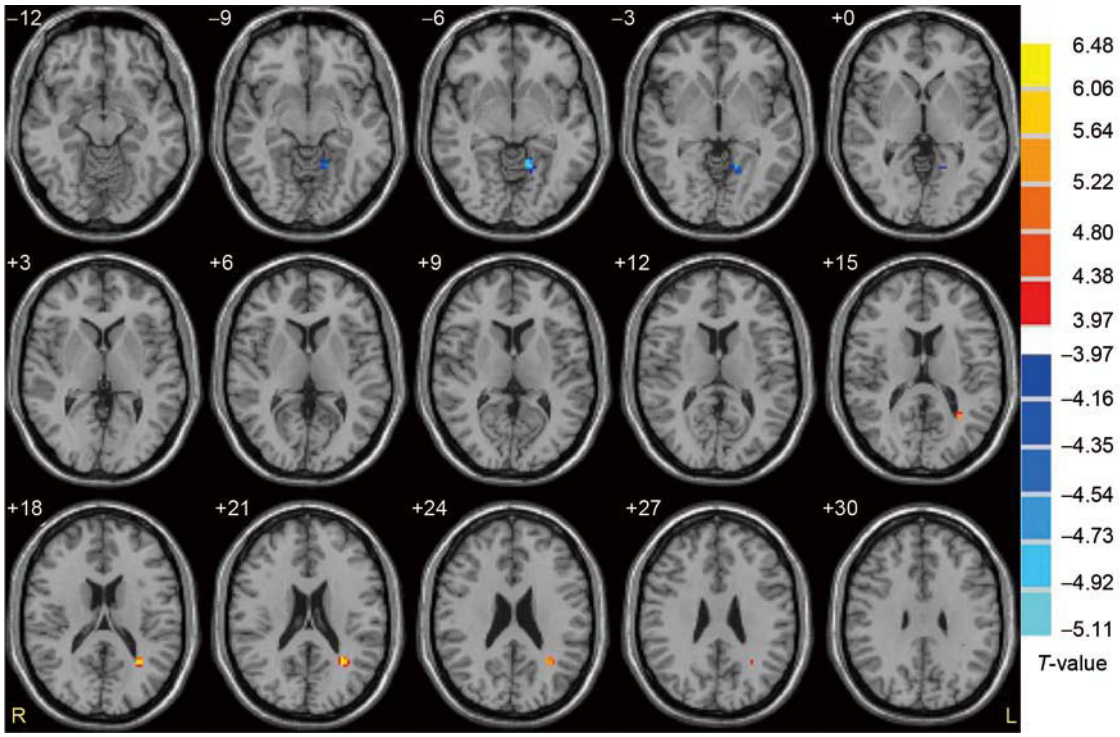

Fig. 2. Difference map of resting-state brain ReHo pattern. Warm color indicates ReHo higher on-MPH than on-placebo, while cold color indicates ReHo lower on-MPH than on-placebo. Maps are superimposed on the ch2 template of REST (http://www.restfmri.net) from z = −15 mm to z = 30 mm in the Montreal Neurological Institute system, and the coordinate increment between slices was 3 mm.

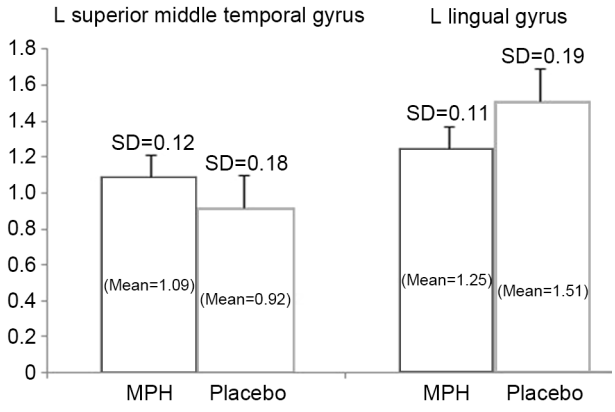

Fig. 3. Mean ReHo on-MPH and on-Placebo in left superior and middle temporal gyri and left lingual gyrus of all participants. Y-axis indicates the mean ReHo value. L, left.

observed in the resting state in ADHD[31,50], schizophrenia[51], Alzheimer's disease[52], Parkinson's disease[36], and major depressive disorder[53]. Particularly, increased ReHo has been found in the medial temporal lobe in patients with temporal lobe epilepsy[54] and in the thalamus in patients with generalized tonic-clonic seizures[55]. These findings are consistent with the hypothesis of increased neuronal synchronization of epileptiform discharge in the epileptic focus or zone. MPH has affects on task performance both in ADHD and normal participants[9,56,57]. In this study, we found differences in ReHo in the left superior and middle temporal gyri (on-MPH > on-placebo) and left lingual gyrus (on-MPH < on-placebo) in normal adults.

Superior and Middle Temporal Gyri

In the present study, we also demonstrated that MPH significantly increased the ReHo in the temporal lobe. Structural and functional changes in this area are always associated with psychiatric diseases, such as ADHD. In a voxel-based morphometric study, the temporal lobe and cerebellum were found to have a lower grey matter volume in ADHD children than in control participants[58]. Structural studies show a correlation between specific phenotypes and alterations in brain structure, especially in frontal–striatal–cere-

bellar circuits[59]. In functional studies, under-activation in the temporal lobe was observed in adult ADHD patients in working memory and decision-making tasks. Superior temporal lobe dysfunction is also important in many attention-allocation tasks, such as oddball tasks and visual-spatial attention tasks[10,60-62]. Attention allocation is typically measured in the oddball task, which requires the detection of non-standard "oddball" stimuli in a string of standard stimuli. Children with ADHD are impaired in target detection and discrimination, by showing more errors, slower responses and more variable responses[63,64]. Evidence from ERP studies shows abnormalities in the temporal lobe in ADHD children during oddball tasks[65]. In an fMRI study, activation related to successful performance of oddball trials was observed bilaterally but predominantly in the left superior middle temporal lobe and also in the cerebellum in healthy boys. The analysis of covariance between normal and ADHD children shows increased activation mainly in healthy participants in the left superior and middle temporal gyrus in an oddball task[61]. MPH is associated with a robust normalization of low-frequency EEG activity during the resting brain state, but has less impact on the oddball task in ADHD patients[66]. In our study, ReHo increased in the superior and middle temporal lobe after MPH. MPH is helpful in improving attention. Increased ReHo in this area in the resting state may help in the execution of attention-related tasks.

Studies reflect increased recognition that the temporal and parietal cortices likely contribute to ADHD-related cognitive deficits[67]. Silk *et al.* reported that the superior and middle temporal regions are preferentially activated in ADHD patients in a mental rotation task[68]. These lateral temporal areas are involved in the ventral visual stream for object recognition, particularly for manipulable objects[69]. Individuals with ADHD use alternative strategies and brain regions compared to normal controls during working memory tasks due to impaired prefrontal functioning. Healthy control participants show greater activation of regions associated with verbal strategies [e.g., left superior temporal gyrus, Brodmann area (BA) 22], while adults with ADHD are more likely to report using visual strategies and activation of brain regions associated with visual imagery[13]. In both normal controls and ADHD adults, the activation associated with the Paced Auditory Serial Addition Task includes the left superior temporal gyrus as well as additional activation in the left middle temporal gyrus. But the activation in normal controls is greater than in ADHD patients[44]. The low activation in these areas may be related to the worse performance in the task. In our study, MPH improved the ReHo in these two areas and thus may improve the task performance. This area is associated with motor inhibition in normal children. An event-related fMRI study showed that in a group of normal children, when performing a Go/No-go task, left middle temporal gyrus activation is correlated with the No-go condition[70]. So, the temporal lobe seems to be more involved in cognitive tasks in normal participants than in ADHD patients. Patients may have functional disorders in this area and are unable to perform some tasks well. In our study, MPH improved the ReHo in this area. In the default mode network, this area is thought to be related to conscious awareness[49]. This may be why MPH helps to improve task performance. People may have better conscious awareness and respond to the stimulus well. In ADHD patients, MPH usually improves the symptoms of inattention and impulsivity. This may relate to the functional increase in this area. There is a pity in this result that white matter occupies a large part in the significant brain region. However, what we concern is grey matter, because ReHo, which was used in this study, is only related to grey matter.

Lingual Gyrus

In a resting-state fMRI study, ADHD children showed significantly increased ReHo in the bilateral lingual gyrus, and also in the occipital cortex[31]. Several resting-state SPECT studies demonstrated that the occipital cortex is relatively hyperperfused in ADHD and that MPH tends to decrease flow in this area. The abnormality in these regions may be the cause of the inhibition disorder in ADHD patients[26,71,72]. In task-related neuroimaging studies, hyperactivation is found in the lingual gyrus in ADHD. ADHD adults engage the lingual gyrus more strongly during task switching than normal adults[73]. In Go/No-go tasks using ERPs, significant increases were detected in the lingual gyrus in ADHD adults during the N2 time frame. This supports the theory that ADHD patients have to inhibit their reactions more strongly than healthy controls[74]. In our study, MPH decreased ReHo in the lingual gyrus in normal adults and this may also be related to improvement of attention and inhibition. It is quite consistent with the SPECT study of MPH in the occipital cortex. Similar results were also found in the

cerebellum in some resting studies. In ADHD adolescents, increased functional connectivity with the dorsal anterior cingulate cortex was found for the bilateral cerebellum in an ADHD compared to a control group[75]. Children with ADHD also show an increased ALFF in the left lateral cerebellum[30]. These results are partly consistent with ours.

Patients with other psychiatric or neurological diseases also have abnormal resting signals in the lingual gyrus. In major depressive disorder patients, ReHo in the left lingual gyrus is decreased[53]. This is somewhat inconsistent with results in ADHD[31]. This difference may come from differences between the diseases. Depression is characterized by a decline of mood and activity and looks like the opposite of ADHD. Compared to normal controls, schizophrenia patients show decreased ALFF in the lingual gyrus[76]. Similar results are also seen in Schneiderian symptoms, and the severity of the symptoms is negatively correlated with rCBF in the left lingual gyrus in resting PET. In neuromyelitis optica patients, the ALFF is decreased in the lingual gyrus and this might be related to the cognitive impairment[77]. Using a resting PET scan covariance pattern, AD patients were found to have hyperperfusion in the lingual gyri[78]. From the above studies in different diseases, we find inconsistencies in resting lingual gyrus signals. Sometimes they increase and sometimes decrease. The brain is an integrated network, so hyperperfusion in one area may be related to hypoperfusion in another[78]. The pathology in different diseases may display different changes in the same area.

The lingual gyrus is considered to be recruited in dreaming, visual processing and visual memory[79]. The resting-state signal changes in this area in ADHD patients and MPH has some influence on the signal.

Basal Ganglia

The basal ganglia are always found to have abnormal activation in ADHD patients. For instance, striatal hypoperfusion is found in ADHD at rest using SPECT, and the right striatum has low activation in a verbal awareness task in ADHD[80]. In a stop signal task, patients show lower power of response in the left caudate[10]. These abnormal activations are thought to be due to the abnormality in dopamine level. In the current study, we found almost no change in resting-state activity in these regions on-MPH compared to on-placebo. This may be for the following reasons. First, the basal ganglia are most involved in motor execution. So, in our normal participants, due to their resting state, there might be no MPH effect in these areas. In a resting fMRI study, MPH only had an effect on patients who were objectively hyperactive when on placebo and unaffected in ADHD children who were not hyperactive[33]. Furthermore, it might be due to the relatively slight signal in this area. Finally, it might be due to the threshold of the statistics, because in fMRI studies, the threshold is a little bit arbitrary and different thresholds may lead to different activated brain regions or different sizes of activated brain regions.

Prefrontal Cortex

The importance of the prefrontal cortex in ADHD has been shown in many studies[2,9,19,21]. But in our study there was no notable activity in this area. Actually, with certain parameters, a difference between the on- and off-MPH conditions appeared in the left superior frontal gyrus. A combination of individual voxels at P <0.05, cluster size >6939 mm^3 and rmm = 6 corresponding to a corrected P <0.05 by AlphaSim together with a grey matter mask (threshold P >0.3) was used to get the above difference. But these parameters were too lenient and stricter ones were finally used. Then the difference was not statistically significant. In previous studies, activation in the bilateral frontal lobes was also inconsistent in ADHD patients. In a cued target-detection task, Cao *et al.* found that children with ADHD show less activation than controls in the left superior frontal gyrus[81] and in the STOP task, Li *et al.* found that the left superior frontal gyrus is one of the main activation regions in normal children, but not in ADHD children[82]. However, Almeida *et al*. found that the cortical thickness of the right superior frontal gyrus is reduced in children, adolescents and adults with ADHD in contrast to healthy controls[83]. Overmeyer *et al.* found that hyperkinetic children have significant grey matter deficits in the right superior frontal gyrus[84]. Thus, further studies of this area are needed.

The primary goal of this study was to investigate the basic state-change between the on-MPH and on-placebo conditions, using ReHo to evaluate the drug effect. The results help us to better understand why MPH reduces the symptom of ADHD. Here, we used the resting-state mode, which focuses on a broad state of information-gathering but not a specific task. Further studies should focus on how MPH affects the resting-state signals in ADHD patients.

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About the Cover

Chinese-Caucasian differences in a gene contributing to the risk of developing mood disorders: Long's findings call for ethnic population-based drug development and treatment of depression and anxiety. For details, see pages 4–15. (Cover designed by Yefei Li)