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ORIGINAL ARTICLE

Differential effects of methylphenidate and atomoxetine on intrinsic brain activity in children with attention deficit hyperactivity disorder

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Background. Methylphenidate and atomoxetine are commonly prescribed for treating attention deficit hyperactivity disorder (ADHD). However, their therapeutic neural mechanisms remain unclear.

Method. After baseline evaluation including cognitive testing of the Cambridge Neuropsychological Test Automated Battery (CANTAB), drug-naive children with ADHD ($n = 46$), aged 7–17 years, were randomly assigned to a 12-week treatment with methylphenidate ($n = 22$) or atomoxetine ($n = 24$). Intrinsic brain activity, including the fractional amplitude of low-frequency fluctuations (fALFF) and regional homogeneity (ReHo), was quantified via resting-state functional magnetic resonance imaging at baseline and week 12.

Results. Reductions in inattentive symptoms were related to increased fALFF in the left superior temporal gyrus and left inferior parietal lobule for ADHD children treated with methylphenidate, and in the left lingual gyrus and left inferior occipital gyrus for ADHD children treated with atomoxetine. Hyperactivity/impulsivity symptom reductions were differentially related to increased fALFF in the methylphenidate group and to decreased fALFF in the atomoxetine group in bilateral precentral and postcentral gyri. Prediction analyses in the atomoxetine group revealed negative correlations between pre-treatment CANTAB simple reaction time and fALFF change in the left lingual gyrus and left inferior occipital gyrus, and positive correlations between pre-treatment CANTAB simple movement time and fALFF change in bilateral precentral and postcentral gyri and left precuneus, with a negative correlation between movement time and the fALFF change in the left lingual gyrus and the inferior occipital gyrus.

Conclusions. Our findings suggest differential neurophysiological mechanisms for the treatment effects of methylphenidate and atomoxetine in children with ADHD.

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Key words: Atomoxetine, attention deficit hyperactivity disorder, fractional amplitude of low-frequency fluctuations, methylphenidate, resting brain imaging.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common and impairing childhood neuropsychiatric disorder, with long-term academic and social impairments that may persist into adolescence (Wu & Gau, 2013) and adulthood (Yang *et al.* 2013). The convergent evidence of medication treatment effect (Sharma & Couture, 2014) clearly suggests that imbalanced dopaminergic and noradrenergic dysregulations contribute to the pathophysiology of ADHD (Del Campo *et al.* 2011).

Methylphenidate and atomoxetine are both indicated for treating ADHD, although their primary effects differ in that methylphenidate blocks both the dopamine (DAT) and noradrenaline (NET) transporters (Han & Gu, 2006), while atomoxetine has a much higher affinity for NET than for DAT (Simpson & Perry, 2003). Despite their widespread use, the specific mechanisms mediating their therapeutic effects on human brain functions remain unclear. Comparison of these two medications with partially overlapping pharmacological profiles provides an opportunity to identify therapeutic mechanisms at the level of systems neuroscience.

Previous neurobiological studies have implicated the involvement of sensorimotor regions in the pathogenesis

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of ADHD. Children with ADHD showed markedly reduced cortical inhibition, which was correlated with deficiencies in motor performance (Gilbert *et al.* 2011). When performing simple motor tapping, children with ADHD exhibited decreased activation in primary motor cortex relative to controls (Mostofsky *et al.* 2006). In a study of adults with ADHD during paced and unpaced tapping, hypoactivations were found in the sensorimotor timing systems (Valera *et al.* 2010).

Most evidence for cerebral functional change elicited by medications for ADHD comes from single photon emission computerized tomography (SPECT) and positron emission tomography (PET) studies (Dickstein *et al.* 2006). The use of SPECT and PET techniques in youth population is, however, constrained by ethical considerations associated with ionizing radiation. Due to the non-invasiveness and a relatively high temporal and spatial resolution, functional magnetic resonance imaging (fMRI) techniques have been widely used to explore the functional abnormalities in ADHD (Paloyelis *et al.* 2007).

Task-based fMRI approaches have been applied to study the effects of medications on brain activation in patients with ADHD. During response inhibition tasks, acute administration of methylphenidate was associated with increased activation in the frontostriatal network in children with ADHD (Rubia *et al.* 2009, 2011; Cubillo *et al.* 2014*b*). Acute administration of atomoxetine was associated with increased activation in the dorsolateral prefrontal cortex (Cubillo *et al.* 2014*a*, *b*), and decreased activation in the anterior cingulate cortex in children with ADHD (Cubillo *et al.* 2014*a*). Concerning chronic effects, improvement in ADHD symptomatology was differentially related to increased activation for atomoxetine and decreased activation for methylphenidate in the right inferior frontal gyrus, left anterior cingulate cortex, left supplementary motor area, and bilateral posterior cingulate cortex (Schulz *et al.* 2012).

Given that intrinsic brain activity unrelated to specific tasks consumes most of the brain's energy economy (Fox & Raichle, 2007), there may exist an interaction between drug action and intrinsic brain activity. In addition, since resting-state fMRI (RS-fMRI) is conducted without the need of giving explicit instructions to the participants, variability of data due to subtle differences in task compliance and performance is substantially reduced. It is hence paramount to explore the medication effects on the brain function of ADHD children using RS-fMRI techniques. So far, however, few studies have examined the modulations of spontaneous brain activity related to ADHD medications (Schweren *et al.* 2013). Two RS-fMRI studies examined a local functional connectivity index, i.e. regional homogeneity (ReHo). It is assumed that for a given voxel, its activity is usually correlated to that of its neighbors, and ReHo is used to characterize the degree of local synchronization of spontaneous brain activity (Zang *et al.* 2004). A single dose of methylphenidate (20 mg) increased ReHo in the left middle and superior temporal gyri and decreased ReHo in the left lingual gyrus in healthy men (Zhu *et al.* 2013). In boys with ADHD, methylphenidate (10 mg) increased ReHo in bilateral ventral prefrontal cortex and cerebellar vermis and decreased ReHo in the right parietal and visual areas (An *et al.* 2013*b*). Using arterial spin labeling (ASL) to measure regional cerebral blood flow, the acute administration of methylphenidate (30 mg) *v.* atomoxetine (60 mg) produced differential effects in thalamus, midbrain, and striatal-cerebellar circuits in healthy adults (Marquand *et al.* 2012). These relatively inconsistent results may be explained by methodological heterogeneity, including samples (ADHD patients *v.* healthy volunteers), age range (children *v.* adults), medication history (previously medicated *v.* drug-naive), and imaging measures (ReHo *v.* ASL).

Beyond the studies mentioned above, there have been no published data regarding long-term medication effects on intrinsic resting brain activity in drug-naive children with ADHD. Medications for ADHD are typically given over extended periods of time, with the maximal behavioral efficacy of methylphenidate and atomoxetine observed at 6 weeks (Biederman *et al.* 2006) and 12 weeks (Montoya *et al.* 2009), respectively. There are likely significant neuropharmacological differences between single-challenge doses of medication and treatment administered over an extended period. The lack of data linking chronic pharmacological actions to therapeutic improvements represents a missed opportunity to understand better how medications work, an essential step towards improving treatments.

Low-frequency fluctuations (LFF) in the resting-state blood oxygen level dependent (BOLD) signal are thought to reflect the spontaneous neural functioning of the brain (Biswal *et al.* 1995). The amplitude of LFF (ALFF) is a regional index of the intensity of spontaneous LFF in the BOLD signal (Zang *et al.* 2007). Previous studies have shown the clinical relevance of ALFF and ReHo, indicating that the changes in these neuroimaging markers were closely related to the severity of ADHD. For example, in comparison with controls, children with ADHD demonstrated higher ALFF values in the left sensorimotor cortex and lower ALFF values in the right middle frontal gyrus, with significant correlations between executive dysfunction and the peak ALFF in the left sensorimotor cortex and the right middle frontal gyrus (Yang *et al.* 2011). The ADHD symptom scores were correlated with the ReHo values in the right cerebellum, dorsal anterior

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cingulate cortex, and left lingual gyrus in children with ADHD (An *et al.* 2013*a*).

Despite a promising method for detecting spontaneous brain activity, ALFF has been shown significantly higher in some cistern areas (Zang *et al.* 2007), probably due to higher physiological noise in these areas. Fractional ALFF (fALFF), the ratio of the amplitude of specific low-frequency oscillations (between 0.1 and 0.01 Hz) to the amplitude of oscillations across the whole detectable frequency range, was developed to suppress non-specific noise associated with ALFF (Zou *et al.* 2008). fALFF is more specific for gray matter than ALFF and is more effective at minimizing artifactual contributions of cardiac and respiratory noise (Zuo *et al.* 2010). Previous studies demonstrated a significant fALFF increase in bilateral lingual gyrus, the right precentral gyrus, and the left cuneus, and a decrease in bilateral superior and middle frontal gyrus in patients with ADHD (Cheng *et al.* 2012). To date, the effects of methylphenidate and atomoxetine on fALFF in children with ADHD have not been examined.

The present study explored regional changes in fALFF and ReHo after treatment for 12 weeks with methylphenidate *v.* atomoxetine in children with ADHD. Based on earlier neuroimaging studies, we hypothesized that methylphenidate would increase brain activity in the superior temporal gyrus and decrease brain activity in the lingual gyrus. Although no studies to date have examined the effects of atomoxetine on fALFF or ReHo, the high density of norepinephrine transporter in the paracentral lobule and supplementary motor area (Hannestad *et al.* 2010) provided a network of regions that we hypothesized would be associated with atomoxetine treatment.

Method

Participants

We recruited 64 eligible drug-naive children who were clinically diagnosed with ADHD according to DSM-IV diagnostic criteria from the Department of Psychiatry, National Taiwan University Hospital (NTUH), Taipei, Taiwan. They and their parents were interviewed with the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Epidemiological Version (K-SADS-E) by the corresponding author (S.S.G.) to confirm the diagnosis of ADHD and to exclude all other psychiatric disorders.

Participants were excluded if they had a serious medical illness; full-scale IQ score <80; a history of bipolar disorder, psychosis, any substance abuse, or pervasive developmental disorder; depression or anxiety disorders based on the DSM-IV criteria at study entry; a history of seizure or prior electroencephalogram abnormalities related to epilepsy, or if they had ever used any psychotropic medications before the study. Informed consent was obtained after participants and their parents had received detailed information regarding the study purpose and protocol. The informed consent procedures were approved by the Research Ethics Committee at NTUH before study implementation (approved no.: 200903062R; ClinicalTrials.gov number NCT00916851).

After 12 were excluded (see Supplementary Fig. S1 for reasons), 52 children with ADHD, aged 7–17 years (mean age ± S.D. = 10.5 ± 2.4 years, 43 males) were randomly assigned to receive the treatment with either osmotic release oral system methylphenidate ($n = 26$) or atomoxetine ($n = 26$) for 12 weeks, determined by a computer-generated randomizing algorithm. All participants began medications the morning after visit 1 with an initial dosage of 18 mg/day methylphenidate or 0.5 mg/kg per day atomoxetine. Drug dosage was titrated at weeks 2, 4, and 8 depending on clinical response and adverse effects (methylphenidate maximum daily dosage 54 mg/day; atomoxetine maximum daily dosage 1.2 mg/kg per day).

Participants were scanned using RS-fMRI at baseline before treatment initiation and at week 12. In order to achieve maximum efficacy, considering the pharmacokinetics of both drugs, participants were requested to take medications as usual in the morning 2–4 h before the second RS-fMRI assessment. Additionally, the ADHD Rating Scale-IV – Parent Version: Investigator-Administered and Scored (ADHDRS-IV) and the Clinical Global Impression – ADHD Severity Scale (CGI-ADHD-S) were assessed by the investigators (C. Y.S. and S.S.G.) at baseline and week 12. Six participants discontinued medications (methylphenidate $n = 4$, atomoxetine $n = 2$) after week 2 and did not undergo the second RS-fMRI scan (Supplementary Fig. S1).

Measurements

ADHDRS-IV

The ADHDRS-IV (DuPaul *et al.* 1998) is an investigator-based validated 18-item semi-structured interview with the parents about the participants' ADHD symptoms over the past week. Each item, corresponding to one of the 18 DSM-IV ADHD behavioral items, is rated on a 4-point scale (0, never or rarely; 1, sometimes; 2, often; 3, very often). The inattention and hyperactivity/impulsivity subscales are the sum scores of the odd-numbered and the even-numbered items, respectively. The ADHDRS-IV is a reliable and valid instrument to assess ADHD symptom severity (Faries *et al.* 2001) and has been widely used in ADHD treatment studies (Gau *et al.* 2007). For example, in a

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randomized, double-blind, placebo-controlled clinical trial, the mean total scores of ADHDRS-IV were significantly lower for the atomoxetine group than the placebo group at week 6 (Gau *et al.* 2007). In an open-label, randomized trial of methylphenidate and atomoxetine treatment in children with ADHD, both treatment groups showed significant reductions in the scores of ADHDRS-IV at week 24 (Shang *et al.* 2015).

CGI-ADHD-S

The CGI-ADHD-S is a single-item rating of the clinician's assessment of the global severity of ADHD symptoms in relation to the clinician's experience with other patients with ADHD. The severity is rated on a 7-point scale (1, normal, not at all ill to 7, among the most extremely ill). The Chinese CGI-ADHD-S has been widely used in ADHD treatment studies in Taiwan (Gau *et al.* 2007; Gau & Shang, 2010*b*).

Reaction time (RTI)

Pre-treatment RTI was assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB), which is a computerized test battery with standardized procedures and solid psychometric properties widely used in Western (Luciana & Nelson, 1998) and in Taiwanese (Gau & Shang, 2010*a*) studies. The RTI, a simple single-choice task, is designed to measure participants' speed of response to a visual target. A large circle appears in the center of the screen, and a small yellow circle appears in the center of this circle when the participant pushes a button on the handheld device. The participant must then quickly touch the yellow circle on the screen. Two major indices are presented: (1) reaction time: the participant's response latency for releasing the press pad in response to the onset of a stimulus (minimal motor component); and (2) movement time: time taken to touch the stimulus after the press pad had been released (the motor component).

MRI data acquisition

Images were acquired using a 3-T Siemens Tim-Trio scanner with a 32-channel head coil. The imaging parameters were 180 echo planar imaging (EPI) volumes; TR = 2000 ms; TE = 24 ms; flip angle = 90°; field of view (FOV) = 256 × 256 mm^2; matrix size = 64 × 64; 34 axial slices acquired in an interleaved descending order; slice thickness = 3 mm; voxel size = 4 × 4 × 3 mm^3; imaging plane being parallel to the anterior commissure–posterior commissure (AC–PC) image plane. For spatial normalization, a high-resolution T1-weighted anatomical image was also acquired (MPRAGE, TR = 2000 ms; TE = 2.98 ms; TI = 900 ms; flip angle = 9°; FOV = 256 × 256 mm^2; matrix size = 256 × 256; isotropic voxel size = 1 mm).

Data preprocessing

Imaging preprocessing, including slice timing, head motion correction, within-subject registration of RS-fMRI data and T1 images, and spatial normalization, was performed using Statistical Parametric Mapping software (SPM8, http://www.fil.ion. ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF; Yan & Zang, 2010). The first ten volumes of the scanning sessions were removed to allow for scanner calibration and participants' adaptation to the scanning environment. For each subject, the functional images were slice timing corrected and realigned. Several nuisance variables, including linear trend, mean signals from white matter and ventricles, as well as the Friston-24 model motion parameters, were removed from the preprocessed time-courses by multiple linear regression analysis. Individual T1-weighted MPRAGE structural image was co-registered to the mean functional image after realignment using a linear transformation without re-sampling. The transformed structural images were then segmented into gray matter, white matter and cerebrospinal fluid, and generated information for spatial normalization in next step. The Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) tool was used to compute transformations from individual native space to MNI space, and then applied to functional images and resampled to 3 × 3 × 3 mm^3. For fALFF analysis, spatial smoothing with a 4.5 mm full-width at half-maximum (FWHM) Gaussian kernel was applied. For ReHo analysis, temporal filtering (0.01–0.1 Hz) was performed beforehand, while spatial smoothing was performed after ReHo calculation.

Head motion

Head motion was indexed by mean frame-wise displacement (FD) derived with Jenkinson's relative root mean square algorithm (Jenkinson *et al.* 2002). Mean FD (Jenkinson) was used due to its consideration of voxel-wise differences in motion in its derivation (Yan *et al.* 2013). Participants with mean FD exceeding 1 S.D. above the sample mean (0.25 ± 0.28 mm) were excluded from further analysis. Using this criterion, we excluded eight participants (four in each treatment group), yielding a final sample of 38 participants. The methylphenidate (n = 18) and atomoxetine (n = 20) groups did not differ significantly in mean FD (p = 0.1).

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fALFF and ReHo analyses

Analyses of fALFF and ReHo were conducted using DPARSF (Yan & Zang, 2010). Spatial smoothing was performed with a Gaussian kernel of 4.5 mm FWHM before fALFF calculation but after ReHo calculation, as smoothing before ReHo calculation greatly increased the regional similarity (Yan & Zang, 2010). To compute fALFF, the time series of each voxel was transformed to the frequency domain using a Fast Fourier Transform and the power spectrum was obtained. The square root was calculated at each frequency of the power spectrum, and the average square root was computed across 0.01–0.1 Hz at each voxel. The sum of the amplitudes across 0.01–0.1 Hz was divided by the amplitudes across the whole frequency range (0–0.25 Hz). To reduce the global effects of variability across participants, fALFF at each voxel was divided by the global mean fALFF within a brain mask for standardization (Zou *et al.* 2008).

Regarding computing the ReHo, individual ReHo maps were generated by calculating the Kendall coefficient of concordance (KCC) of the time series of a given voxel with those of its neighbors (26 voxels) in a voxel-wise way (Zang *et al.* 2004). Afterwards a whole brain mask was used to remove the non-brain tissues. Individual ReHo maps were then standardized by dividing by their own global mean KCC within the whole-brain mask. Then spatial smoothing was performed on the standardized individual ReHo maps with a Gaussian kernel of 4.5 mm FWHM.

Statistical analyses

SAS v. 9.4 (SAS Institute Inc., USA) was used to conduct data analyses. The mean scores and standard deviations were presented for continuous variables and percentage was used for categorical variables for the demographics and baseline assessments. Because of the repeated measures design, we used a linear multi-level model to test the behavioral symptoms measured by the ADHDRS-IV and CGI-ADHD-S at week 12 compared to baseline (week 0). Cohen's *d* was used to compute effect sizes on the inter-session variance for the comparisons between baseline and week 12, with small, medium, and large effect sizes as Cohen's *d* 0.2–0.5, 0.5–0.8, and >0.8, respectively.

To investigate the medication effects on fALFF and ReHo changes between the two treatment groups, we performed a two-sample *t* test on the individual post-treatment minus baseline contrast fALFF and ReHo maps. We included sex and individual mean motion estimates (i.e. mean pre-treatment and post-treatment FD) as nuisance covariates (Yan *et al.* 2013). The significance level was set at $p < 0.05$, corrected for multiple comparisons using Gaussian Random Field (GRF) theory (minimal $Z > 2.3$, cluster significance: $p < 0.05$).

To investigate differential effects of methylphenidate and atomoxetine on ADHD subtypes, we used the full factorial model in SPM8 to investigate a treatment by ADHD subtype interaction for the post-treatment minus pre-treatment changes in fALFF and ReHo. Owing to only one participant with the hyperactive-impulsive subtype in each treatment group, we only included the combined and inattentive subtypes in the subsidiary analysis.

Pearson's correlation (*r*) analyses were performed between ADHDRS-IV improvement scores and individual post-treatment minus baseline contrast fALFF and ReHo maps in the two treatment groups, including sex, mean pre-treatment and post-treatment FDs as covariates. The resultant correlation maps were set at a threshold of $p < 0.05$ (GRF corrected). In addition, clusters with significant correlations were identified as regions of interest (ROIs). Mean post-treatment minus baseline fALFF and ReHo values of these ROIs were extracted for further correlation analysis between fALFF and ReHo change and the pre-treatment RTI measures for the two treatment groups.

Results

Sample characteristics at baseline

The two treatment groups did not differ significantly in age, IQ, handedness, baseline symptom severity, ADHD subtype, or baseline fALFF and ReHo maps (covaried for sex, mean pre-treatment and post-treatment FDs) (Table 1). However, no female was in the methylphenidate group, while six were in the atomoxetine group ($p = 0.021$, Table 1).

Clinical improvement

Compared to baseline scores, both methylphenidate and atomoxetine produced statistically significant reductions in ADHDRS-IV and CGI-ADHD-S scores at week 12 with large effect sizes without significant between-group differences (Table 2). No significant adverse effect was reported. In addition, two-way ANOVA identified no significant treatment × subtype interactions in either changes in inattention ($p = 0.418$) or changes in hyperactivity-impulsivity symptoms ($p = 0.999$).

Correlation of fALFF or ReHo changes with ADHDRS-IV symptom improvement

Correlation analyses (Table 3) revealed that improvement on the ADHDRS-IV inattention subscale was correlated with increased fALFF in the left superior temporal gyrus and left inferior parietal lobule for

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Table 1. *Demographics, baseline ADHD symptoms, and baseline neuropsychological functions between the methylphenidate group and the atomoxetine group*

	Methylphenidate ($N = 18$)		Atomoxetine ($N = 20$)		
	Mean or N	S.D. or %	Mean or N	S.D. or %	p
Age, years	10.61	2.25	10.45	2.44	0.83
Gender					
Male	18	100.00	14	70.00	0.021[a]
Hand					
Right	17	94.44	18	90.00	0.61
IQ					
Verbal IQ	108.00	13.10	107.80	9.49	0.96
Performance IQ	112.00	15.20	109.25	12.92	0.55
Full-scale FIQ	111.17	15.69	108.25	8.52	0.48
ADHD subtype					
Combined type	10	55.56	11	55.00	
Inattentive type	7	38.89	8	40.00	0.99
Hyperactive-impulsive type	1	5.55	1	5.00	
ADHDRS-IV					
Visit 1					
Inattentive	22.00	3.68	23.65	2.85	0.13
Hyperactivity	15.56	7.11	15.00	6.24	0.80
CGI-ADHD-S					
Visit 1	5.61	0.61	5.90	0.64	0.16
Pre-treatment RTI					
Reaction time (ms)	370.36	123.60	376.95	97.85	0.86
Movement time (ms)	453.06	181.09	423.98	158.68	0.60
End-dose of medication (mg)	30	15.12	31.75	7.66	–

ADHD, Attention deficit hyperactivity disorder; IQ, intelligence quotient; ADHDRS-IV, ADHD Rating Scale-IV – Parent version: Investigator-Administered and Scored; CGI-ADHD-S, Clinical Global Impression – ADHD Severity Scale; RTI, reaction time.
[a] $p < 0.05$.

methylphenidate ($r = 0.88$ at peak voxel, $p = 0.000002$) (Fig. 1*a*), and in the left lingual gyrus and inferior occipital gyrus for atomoxetine ($r = 0.76$, $p = 0.00009$, Fig. 1*b*). The improvement of ADHDRS-IV hyperactivity/impulsivity subscale was correlated with increased fALFF in the bilateral precentral and postcentral gyri for methylphenidate treatment ($r = 0.78$, $p = 0.0001$, Fig. 1*c*). By contrast, improvement of the ADHDRS-IV hyperactivity/impulsivity subscale correlated with decreased fALFF in the left precentral and postcentral gyri ($r = -0.67$, $p = 0.001$), right precentral and postcentral gyri ($r = -0.81$, $p = 0.00001$), and left precuneus ($r = -0.82$, $p = 0.000008$) for atomoxetine treatment (Fig. 1*d*). Changes in ReHo did not correlate significantly with improvement in ADHDRS-IV inattention or hyperactivity/impulsivity subscale for either medication.

Correlations between pre-treatment RTI measures and fALFF change

Supplementary Table S1 presents the Pearson's correlations between pre-treatment RTI measures (reaction time and movement time) and fALFF change (the difference between pre- and post-treatment) for the two treatment groups after the age was accounted for in the correlation analysis. For atomoxetine, there was a significant negative correlation between reaction time and fALFF change in the left lingual gyrus and the left inferior occipital gyrus, whereas there were significant positive correlations between movement time and fALFF change in bilateral precentral and postcentral gyri and left precuneus, with a negative correlation between movement time and the fALFF change in the left lingual gyrus and the inferior occipital gyrus. In contrast, pre-treatment RTI measures did not correlate significantly with fALFF change after methylphenidate treatment.

Differential medication effects on neuronal activity

Compared with the atomoxetine group, the methylphenidate group showed significantly increased fALFF in the right precentral and postcentral gyri in the post-treatment minus pre-treatment contrast map

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Table 2. *Symptom change from baseline to week 12 in the methylphenidate and atomoxetine groups*

	Methylphenidate ($N = 18$)				Atomoxetine ($N = 20$)				Group comparisons			
	Week 12	Week12- baseline			Week 12	Week12- baseline			Week 12		Week12- baseline	
	Mean (S.D.)	Mean (S.D.)	Cohen's *d*	*p*	Mean (S.D.)	Mean (S.D.)	Cohen's *d*	*p*	Cohen's *d*	*p*	Cohen's *d*	*p*
ADHDRS-IV												
Inattention	9.89 (5.58)	−12.11 (5.44)	−2.56	<0.001	10.50 (5.92)	−13.15 (5.82)	−2.83	<0.001	0.11	0.746	−0.18	0.575
Hyperactivity-impulsivity	6.33 (5.44)	−9.22 (5.45)	−1.46	<0.001	5.80 (5.17)	−9.20 (6.26)	−1.61	<0.001	−0.10	0.759	0.004	0.991
CGI-ADHD-S	3.22 (0.94)	−2.39 (0.92)	−3.01	<0.001	3.20 (1.11)	−2.70 (1.13)	−2.99	<0.001	−0.02	0.948	−0.30	0.361

ADHDRS-IV, ADHD Rating Scale-IV – Parent version: Investigator-Administered and Scored; CGI-ADHD-S, Clinical Global Impression – ADHD Severity Scale.

(Fig. 2). For fALFF, we identified a significant treatment by subtype interaction in the right precentral gyrus (Supplementary Table S2, Supplementary Fig. S2). For ReHo, we did not identify any significantly differential effect of medications on this intrinsic measure of resting state functional MRI as a function of ADHD subtype.

Discussion

The present study provides the first fALFF evidence of distinct therapeutic mechanisms of methylphenidate and atomoxetine in children with ADHD in addition to the comparable clinically meaningful reduction in clinical symptoms after 12-week treatment. Our principal findings are that inattention improvement was correlated with increased fALFF in the left superior temporal gyrus for methylphenidate, and in the left lingual gyrus and inferior occipital gyrus for atomoxetine. In contrast, hyperactivity/impulsivity improvement was differentially correlated with increased fALFF for methylphenidate and with decreased fALFF for atomoxetine in bilateral precentral and postcentral gyri. We did not detect previously reported medication effects on ReHo (An *et al.* 2013*b*; Zhu *et al.* 2013) for either methylphenidate or atomoxetine. The divergent fALFF effects of these two treatments in association with clinical improvement highlight the importance of adopting an RS-fMRI approach to understanding medication-related changes in intrinsic brain activity in children with ADHD.

Consistent with previous head-to-head studies in Western countries (Kratochvil *et al.* 2002) and Taiwan (Ni *et al.* 2013), both methylphenidate and atomoxetine treatments were associated with a clinically meaningful reduction in inattention and hyperactivity/impulsivity symptoms. Symptom severity decreased to 'mildly-to-moderately ill' for both treatment groups. In addition, no significant group differences were noted with respect to the changes of the ADHDRS-IV and CGI-ADHD-S ratings, suggesting the similar efficacy of methylphenidate and atomoxetine in reducing symptoms in children with ADHD.

Our findings of fALFF changes in bilateral precentral and postcentral gyri associated with hyperactivity/impulsivity improvement in both groups strongly implicate the sensorimotor systems in the therapeutic reactions of both methylphenidate (Shaw *et al.* 2009; Schulz *et al.* 2012) and atomoxetine (Schulz *et al.* 2012) for children with ADHD. Moreover, the opposing effects of these two medications in sensorimotor systems suggest different processes underlie the differential therapeutic mechanisms of methylphenidate and atomoxetine. Such opposite effects were also noted in task-based fMRI studies (Marquand *et al.* 2011;

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Table 3. *Significant clusters of fALFF change correlated with ADHDRS-IV improvement in the methylphenidate and atomoxetine groups*

	Methylphenidate ($N = 18$)						Atomoxetine ($N = 20$)						
			MNI							MNI			
Brain area	L/R	Volume (mm^3)	x	y	z	*t*	Brain area	L/R	Volume (mm^3)	x	y	z	*t*
IA subscale of ADHDRS-IV													
Superior temporal gyrus, inferior parietal lobule	L	1566	−54	−45	21	3.82	Lingual gyrus, inferior occipital gyrus	L	3159	−18	−90	−9	3.52
HI subscale of ADHDRS-IV													
Precentral and postcentral gyri	R + L	13 986	33	−27	57	4.58	Precentral and postcentral gyri	L	2781	−33	−21	69	−3.47
							Precentral and postcentral gyri	R	2187	39	−36	66	−3.59
							Precuneus	L	1917	−21	−57	69	−3.9

ADHDRS-IV, ADHD Rating Scale-IV – Parent version: Investigator-Administered and Scored; fALFF, fractional amplitude of low-frequency fluctuation; HI, hyperactivity/impulsivity; IA, inattention; L, left; R, right; MNI, Montreal Neurological Institute.

Schulz *et al.* 2012). For example, opposing effects of methylphenidate and atomoxetine on activated and deactivated networks were found in healthy volunteers performing a rewarded working memory task (Marquand *et al.* 2011). Differential chronic drug effects in the inferior frontal gyrus, anterior cingulate gyrus, supplementary motor area, and posterior cingulate cortex were observed in children with ADHD during a go/no-go task (Schulz *et al.* 2012). In these clusters, greater medication benefit on methylphenidate was associated with decreased activation, whereas greater benefit on atomoxetine was associated with increased activation (Schulz *et al.* 2012). In non-human primates, methylphenidate and atomoxetine both increased neuronal signal-to-noise ratio (SNR), albeit through distinct complementary mechanisms (Gamo *et al.* 2010). Specifically, methylphenidate enhanced SNR by suppressing non-specific information, whereas atomoxetine increased the intensity of specific signals (Gamo *et al.* 2010). Given the complex indirect links between the fMRI BOLD signal and underlying neural events, further studies are warranted to identify the molecular mechanisms of the differential effects of methylphenidate and atomoxetine on fALFF in the sensorimotor systems.

For methylphenidate, we found that increased fALFF in the left superior temporal gyrus was associated with improvement in inattention. Previous imaging studies have implicated the superior temporal gyrus in the pathogenesis of inattention problems in patients with ADHD (Mulas *et al.* 2006). Previous studies showed that a single dose of methylphenidate was associated with increased ReHo in the left superior temporal gyrus in healthy adults (Zhu *et al.* 2013). We speculate that methylphenidate improves inattention symptoms by altering neuronal information in the superior temporal gyrus which in turn increases fALFF.

The effects of atomoxetine on fALFF in visual cortex highlight a region that tends to be overlooked in ADHD studies (Castellanos & Proal, 2012). Structural neuroimaging studies have found significant reduction in gray-matter volume in the occipital lobes in drug-naive adults with ADHD (Ahrendts *et al.* 2011). Children with ADHD showed decreased small-world network nodal efficiency in occipital cortex in a resting-state study (Wang *et al.* 2009). Animal studies demonstrated that atomoxetine increased noradrenaline levels in the occipital cortex of rats (Swanson *et al.* 2006), and human participants showed significantly greater stop-related BOLD activity in the left inferior and middle occipital regions during atomoxetine treatment compared to placebo (Nandam *et al.* 2014). Occipital cortex interacted with the dorsal attention network to maintain attention (Shulman *et al.* 2009)

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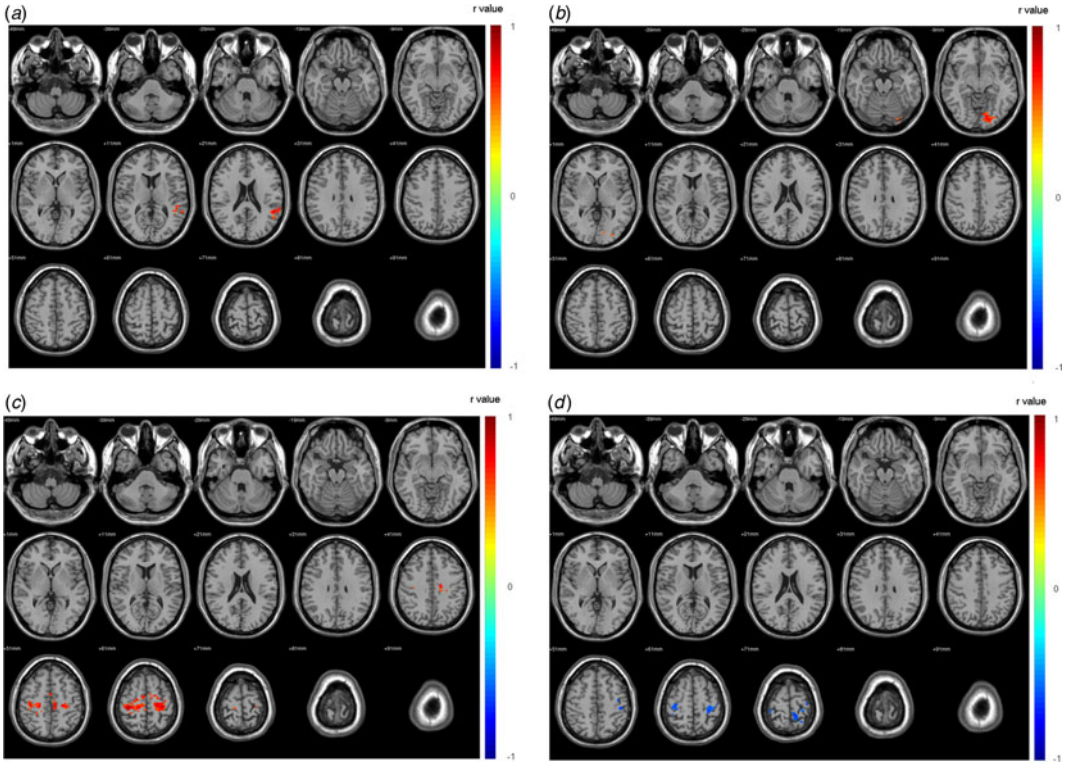

Fig. 1. Voxel-wise correlation map. (*a*) The fALFF change after methylphenidate administration in left superior temporal gyrus and inferior parietal lobule was positively correlated with ADHDRS-IV Inattention (IA) Subscale improvement. (*b*) The fALFF change after atomoxetine administration in left lingual gyrus and inferior occipital gyrus was positively correlated with ADHDRS-IV IA Subscale improvement. (*c*) The fALFF change after methylphenidate administration in bilateral precentral and postcentral gyri was positively correlated with ADHDRS-IV Hyperactivity/Impulsivity (HI) Subscale improvement. (*d*) The fALFF change after atomoxetine administration in bilateral precentral and postcentral gyri and left precuneus was negatively correlated with ADHDRS-IV HI Subscale improvement. Left in the figure indicates the right side of the brain. fALFF, Fractional amplitude of low-frequency fluctuation; ADHDRS-IV, ADHD Rating Scale-IV – Parent version: Investigator-Administered and Scored.

and to suppress attention to irrelevant stimuli (Capotosto *et al.* 2009). Our findings of the link between inattention improvement and increased fALFF in the left lingual and inferior occipital cortex further supported the relevance of posterior brain areas in the pathophysiology of inattentive symptoms in ADHD (Castellanos & Proal, 2012).

For the medication-related fALFF changes, we found a significant treatment by ADHD subtype interaction in the right precentral gyrus. Future studies are needed to replicate our findings.

In contrast to fALFF, we did not detect significant regional changes in ReHo after treatment with methylphenidate or atomoxetine. The inconsistency with the findings of previous studies (An *et al.* 2013*b*; Zhu *et al.* 2013) which demonstrated ReHo change after methylphenidate treatment could be accounted for by methodological heterogeneity, including age, gender, recruitment of drug-naive patients and treatment duration. fALFF indexes spontaneous activity at the single-voxel level (Zou *et al.* 2008), while ReHo reflects local synchrony of spontaneous activity among neighboring voxels (Zang *et al.* 2004). The characterization of intrinsic brain activity is in its infancy, and studies with larger samples and greater temporal and spatial resolution will be needed to further evaluate the sensitivity of methods to detect pharmacological effects in brain.

The baseline RTI measures complemented the changes in clinical ratings, but only for atomoxetine. After 12-weeks of atomoxetine treatment, children with shorter pre-treatment RTI reaction time, i.e. more attentive responding, had greater increased fALFF in the visual cortex, left lingual gyrus and inferior occipital gyrus. Children with shorter pre-treatment RTI movement time had more decreased fALFF in the sensorimotor cortex, bilateral precentral and postcentral gyri, and left precuneus. Independent replication of these results could facilitate identification of atomoxetine responders via relatively inexpensive reaction time measures (Elliott *et al.* 2014).

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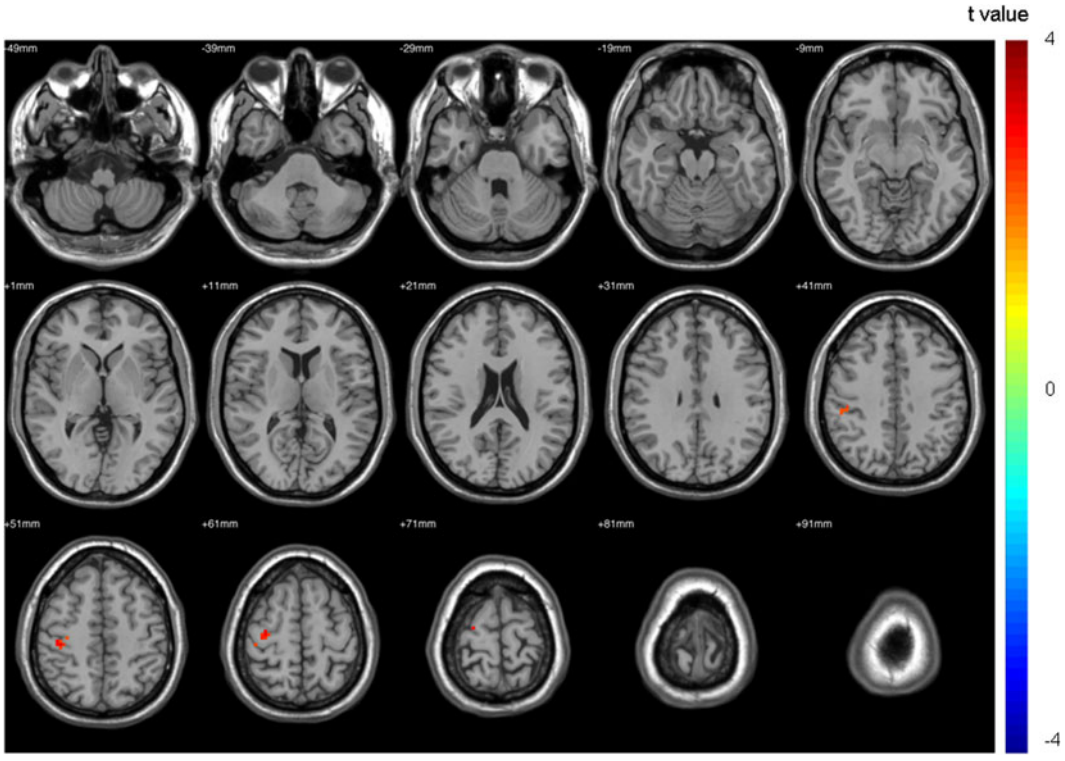

Fig. 2. The cluster showing significant differences in post-treatment minus baseline fractional amplitude of low-frequency fluctuation (fALFF) change between the two treatment groups is located in right precentral and postcentral gyri and consists of 59 voxels (Montreal Neurological Institute coordinates of peak voxel: 39, −24, 45; $t = 3.89$). Warm colors indicate higher fALFF change in the methylphenidate group than in the atomoxetine group; $p < 0.05$, Gaussian Random Field-corrected. Left in the figure indicates the right side of the brain.

Our findings should be interpreted in light of limitations. First, given the moderate sample size, further research with larger sample size is warranted to replicate our results and to extend the generalizability of our results. Second, we study a highly selected medication-naive patient population with minimal psychiatric co-morbidities to avoid confounding by co-morbid disorders and past medication history. Future studies with similar methods need to be carried out in ADHD patients with other psychiatric co-morbid conditions. Third, our findings of medication effects on resting-state brain activity need to be supported by studies incorporating task designs that allow identifying specific neurocognitive processes to clarify the underlying pharmacological mechanisms of medications treating ADHD. Fourth, this study is limited by a relatively wide age range (7–17 years) of the participants. Since brain maturation and development may introduce variability into the medication effects, further studies with a narrower age range are warranted. Fifth, the absence of a placebo arm is another limitation of this study while it is ethically questionable to withhold medication from children with ADHD who have been indicated for pharmacotherapy.

Despite the preceding potential limitations, the present study has the methodological strengths including drug-naive patients, chronic administration of medication, and novel measures of regional resting-state brain activity.

In conclusion, this is the first study using fALFF to investigate differential neural correlates of symptom improvement in drug-naive children with ADHD who are randomized into treatment with methylphenidate or atomoxetine. We find that comparable clinical improvement appears to be mediated by distinct effects of methylphenidate and atomoxetine on intrinsic functional brain architecture. These results provide an initial window into the possible neurophysiological mechanisms of drug response in children with ADHD. In addition, our findings demonstrate the feasibility of using fALFF as a tool to access the medication effect on intrinsic brain activity in individuals with ADHD.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716001938.

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Declaration of Interest

None.

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