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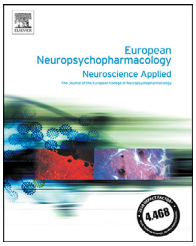

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Methylphenidate and atomoxetine normalise fronto-parietal underactivation during sustained attention in ADHD adolescents

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Abstract
Problems with sustained attention are a key clinical feature of Attention Deficit/Hyperactivity Disorder (ADHD) which also manifests in poor performance and abnormal fronto-striato-parietal activation during sustained attention. Methylphenidate and atomoxetine improve attention functions and upregulate abnormal fronto-cortical activation during executive function tasks in ADHD patients. Despite this, no functional Magnetic Resonance Imaging (fMRI) study has compared the effects of methylphenidate and atomoxetine on the neurofunctional substrates of sustained attention in ADHD. This randomised, double-blind, placebo-controlled, cross-over

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Vigilance;
Methylphenidate;
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study investigated the comparative normalisation effects of methylphenidate and atomoxetine on fMRI correlates and performance in 14 ADHD adolescents relative to 27 age-matched healthy controls during a parametric sustained attention/vigilance task with progressively increasing load of sustained attention. ADHD patients were scanned three times under a single clinical dose of either methylphenidate, atomoxetine, or placebo in pseudo-randomised order. Healthy controls were scanned once and compared to patients under each drug condition to test for potential drug-normalisation effects. Relative to controls, ADHD boys under placebo were impaired in performance and had underactivation in predominantly right-hemispheric fronto-parietal, and striato-thalamic regions. Both drugs normalised all underactivations, while only methylphenidate improved performance deficits. Within patients, methylphenidate had a drug-specific effect of upregulating left ventrolateral prefrontal/superior temporal activation relative to placebo and atomoxetine, while both drugs increased activation of right middle/superior temporal cortex, posterior cingulate, and precuneus relative to placebo. The study shows shared normalisation effects of methylphenidate and atomoxetine on fronto-striato-thalamo-parietal dysfunction in ADHD during sustained attention but a drug-specific upregulation effects of methylphenidate on ventral fronto-temporal regions.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by age-inappropriate levels of hyperactivity, impulsivity, and inattention (American Psychiatric Association, 2013). Sustained attention, the ability to voluntarily maintain the focus of attention on sporadically occurring stimuli, is consistently impaired in ADHD (Coghill et al., 2018; Rubia, 2011). In fMRI studies of attention functions, ADHD relative to controls, have reduced activation in the inferior frontal cortex (IFC), dorsolateral prefrontal cortex (DLPFC), insula, striatum, thalamus, inferior parietal lobe (IPL), and cerebellum and increased activation in regions of the default mode network (DMN; i.e. dorsal anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus) (Christakou et al., 2013; Hart et al., 2013; Rubia, 2018; Rubia et al., 2009b).

Stimulant medication like methylphenidate and amphetamines are the most effective treatments for ADHD with the non-stimulant atomoxetine showing slightly lower but good efficacy in reducing ADHD symptoms (Cortese et al., 2018). Nevertheless, these drugs' mechanisms of action in ADHD are not fully understood. At therapeutic doses, methylphenidate inhibits over 50% of dopamine transporters in the striatum (Volkow et al., 1998) and 70–80% of norepinephrine transporters in prefrontal regions (Hannestad et al., 2010), resulting in increased striatal dopamine levels and increased catecholamine levels in frontal and other cortical regions (Wilens, 2008). Atomoxetine selectively inhibits norepinephrine transporters, leading to increased levels of norepinephrine and dopamine in the prefrontal cortex (Bymaster et al., 2002), as well as in other norepinephrine transporter-rich regions such as ACC, thalamus, brain stem, midbrain, locus coeruleus, and cerebellum with, however, minimal striatal effects (Gallezot et al., 2011).

Both drugs improve the performance of ADHD patients in tasks of sustained attention (Coghill et al., 2014; Shang and Gau, 2012; Wehmeier et al., 2012). Direct drug comparisons showed larger effects of methylphenidate than atomoxetine on errors of omission, reaction times, and reaction time variability (Bédard et al., 2015), but comparable effects in reducing reaction time variability were also found (Ni et al., 2016).

Poor concentration and performance on sustained attention tasks are one of the most consistent behavioural (American Psychiatric Association, 2013) and cognitive (Coghill et al., 2018; Rubia, 2011) deficits in ADHD, respectively, and are underpinned by neurofunctional impairments (Christakou et al., 2013; Hart et al., 2013; Rubia et al., 2009c). Furthermore, both behavioural and cognitive inattention are key targets of methylphenidate and atomoxetine treatment. However, so far only one fMRI study has investigated the effect of methylphenidate in ADHD during sustained attention and found that a single clinical dose upregulated fronto-parietal activation in ADHD children and reduced activation deficits relative to controls in right ventromedial orbitofrontal, inferior prefrontal, and premotor cortices, as well as in bilateral subcortical regions including corpus striatum, thalamus, hippocampus, and cerebellum (Rubia et al., 2009b). Methylphenidate furthermore normalised brain underactivation in ADHD relative to controls in inferior parietal and temporal areas, along with all functional connectivity deficits between frontal, striato-thalamic, parietal, and cerebellar regions (Rubia et al., 2009b). However, no fMRI study has tested the effects of atomoxetine on sustained attention or compared both drugs.

fMRI studies that investigated the comparative effects of single doses of methylphenidate and atomoxetine on other cognitive functions showed shared normalisation and/or upregulation effects on right IFC during motor inhibition (Cubillo et al., 2014b) and time discrimination (Smith et al., 2013), with, however, only atomoxetine upregulating and normalising DLPFC activation during working memory relative to healthy controls (Cubillo et al., 2014a). During inhibition and time discrimination, methylphenidate had additional upregulation effects on dopaminergic-innervated regions such as basal ganglia and supplementary motor area (SMA) (Cubillo et al., 2014b; Smith et al., 2013). Furthermore, several studies of independent and comparative effects of single doses of methylphenidate and atomoxetine showed that both drugs improved and/or normalised

task-related DMN abnormalities in ADHD relative to controls (Cubillo et al., 2014a, 2014b; Rubia et al., 2009b; Smith et al., 2013).

Longer-term stimulant administration has also been associated with increased activation in ADHD patients during executive function and reward tasks in fronto-cingulo-striatal regions (Bush et al., 2008; Chou et al., 2015; Mizuno et al., 2013), although downregulation has also been observed during attention functions (Konrad et al., 2007) or in relation to treatment response in a motor inhibition task (Schulz et al., 2012). Similarly, longer-term atomoxetine administration in ADHD patients has been associated with upregulation of IFC in relation to treatment response during a motor inhibition task (Schulz et al., 2012), fronto-parieto-cerebellar regions during interference inhibition (Bush et al., 2013) and precuneus during visual processing (Fan et al., 2017). Downregulating effects of atomoxetine on IFC and ACC have also been observed during inhibitory control (Fan et al., 2017).

Altogether, these fMRI findings suggest both shared and drug-specific effects of methylphenidate and atomoxetine during cognitive functions; both drugs upregulate inferior frontal activation and improve DMN deactivation, while atomoxetine appears to have drug-specific effects of upregulating DLPFC and methylphenidate has drug-specific effects of upregulating striatum and SMA.

Given evidence for normalisation/upregulation effects of methylphenidate on neural networks of sustained attention in ADHD adolescents (Rubia et al., 2009b), the aim of this study was to investigate whether atomoxetine would have the same or different normalisation/upregulation effects. For this purpose, we conducted a pseudo-randomised, double-blind, placebo-controlled, cross-over fMRI study to test the effects of single clinical doses of methylphenidate and atomoxetine on brain function in medication-naïve ADHD adolescents while they performed a parametric sustained attention task with progressively different difficulty levels. Healthy age-matched controls were scanned once, without medication, to test for potential normalisation effects of the two drugs on brain dysfunctions in ADHD under placebo relative to controls. Based on previous findings using the same task, we hypothesised that under placebo, ADHD adolescents relative to healthy controls would have underactivation in prefrontal, pre- and postcentral, superior parietal, and striato-thalamic areas (Christakou et al., 2013). Given that both drugs improve behavioural and cognitive inattention, and the evidence that both drugs can upregulate/normalise underactivation in IFC and parietal regions, which are part of the ventral attention system, during related executive function tasks (Cubillo et al., 2014a, 2014b; Rubia et al., 2014; Smith et al., 2013), we hypothesised that both drugs would normalise and/or upregulate IFC-parietal regions. Based on evidence from previous comparative fMRI studies of single-dose methylphenidate and atomoxetine effects during other functions, we further predicted that there would be drug-specific effects of methylphenidate on normalisation and/or upregulation of striato-thalamic regions (Cubillo et al., 2014a, 2014b; Rubia et al., 2011a, 2009b; Smith et al., 2013) and drug-specific or stronger effects of atomoxetine on DLPFC upregulation/normalisation (Cubillo et al., 2014a).

2. Experimental procedures

2.1. Participants

Seventeen medication-naïve right-handed boys (10–17 years old) with a clinical diagnosis of combined type ADHD (including both inattentive and hyperactive/impulsive symptoms) as assessed by an experienced child psychiatrist using the standardized Maudsley diagnostic interview (DSM-IV-TR criteria) (Goldberg and Murray, 2002), were recruited from South London clinics. ADHD boys scored above clinical threshold for ADHD symptoms on the Strengths and Difficulties Questionnaire for parents (SDQ) (Goodman and Scott, 1999) and the Conners Parent Rating Scale (CPRS-R) (Conners et al., 1998), and below clinical threshold on the Social Communication Questionnaire (SCQ) to exclude participants with high autism traits (Rutter et al., 2003) (Table 1).

Twenty-nine right-handed healthy boys (10–17 years old) were recruited through advertisement in the same South London area. They scored below clinical cut-off for the SDQ, SCQ, and CPRS-R.

In addition to MRI-related contraindications, exclusion criteria for all participants were IQ < 70 on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), history of substance abuse, neurological deficits, presence of psychiatric disorders (except for conduct disorder(CD)/oppositional defiant disorder in the ADHD group, $N = 2$), learning disability, reading, speech, or language disorder.

Independent samples t-tests showed no significant group difference for age ($t(39) = 1.84$, $p = 0.073$), but a significant difference for IQ with ADHD participants scoring significantly lower than controls ($t(39) = 6.82$, $p < 0.001$), which is typical in this population (Rommel et al., 2015). Consequently, both age (which differed at trend-level) and IQ were included as covariates in the between-group analyses. Furthermore, as expected, ADHD participants scored significantly higher on the SDQ ($t(39) = 11$, $p < 0.001$) and SCQ ($t(17.09) = 5.96$, $p < 0.001$) (Table 1).

Participants were reimbursed for their time commitment (£50 for each scanning session). Parental/child informed consent/assent and Ethics Committee approval (07/H0807/84) were obtained.

Five participants ($N_{ADHD} = 3$, $N_{control} = 2$) were excluded from analysis due to high motion artefacts (maximum displacement in

Table 1 Participant characteristics for controls and ADHD patients.

	HC ($N = 27$)		ADHD ($N = 14$)		Group comparison $t(df)$, p-value
	Mean	SD	Mean	SD	
Age (months)	174.80	28.09	159.33	19.23	$t(39) = 1.84$, $p = 0.073$
IQ	113.04	8.93	91.36	10.97	$t(39) = 6.82$, $p < 0.001$
SDQ hyperactive-impulsive/inattentive subscale	2.01	1.71	8.14	1.66	$t(39) = 11$, $p < 0.001$
SCQ total	2.36	2.43	10.00	4.47	$t(17) = 5.96$, $p < 0.001$

ADHD = Attention Deficit/Hyperactivity Disorder; HC = Healthy Control; IQ = Intelligence Quotient; SDQ = Strengths and Difficulties Questionnaire; SCQ = Social Communication Questionnaire.

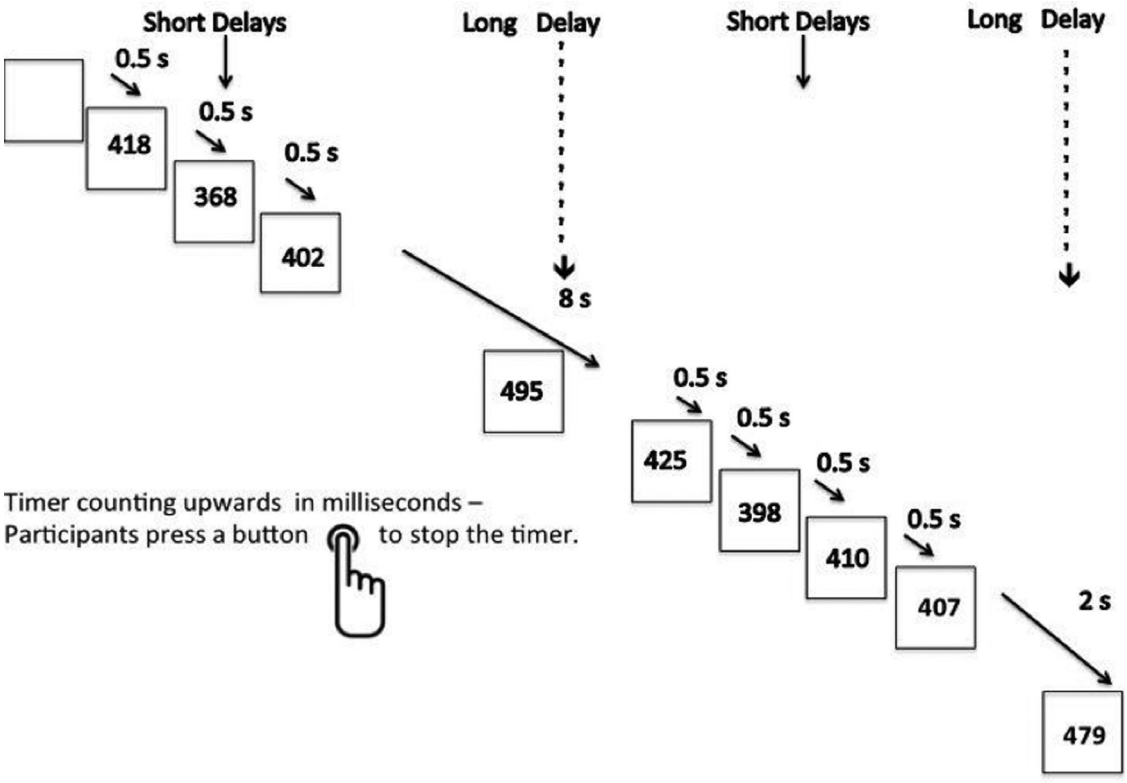


Fig. 1 Schematic representation of the sustained attention task. Subjects press a right-hand button once they see a timer appear on the screen counting milliseconds. The counter appears after either predictable short delays of 0.5 s in blocks of 3–5 stimuli, or after unpredictable long delays of 2 s, 5 s, or 8 s, pseudo-randomly interspersed into the blocks of 0.5 s delays (Christakou et al., 2013; Hart et al., 2017; Lim et al., 2016; Murphy et al., 2014).

x, y, z translation and rotation of >6 voxels), resulting in 14 ADHD and 27 healthy control boys.

2.2. Procedure

Patients were scanned in a double-blind, placebo-controlled, crossover design. On each scanning session, scheduled one week apart, they received a single dose of either placebo (Vitamin C, 50 mg), methylphenidate (Equasym, 0.3 mg/kg, range 5—20 mg), or atomoxetine (Strattera, 1 mg/kg, range 16–66 mg), in a pseudo-randomized order. Dosages were determined following National Institute for Health and Care Excellence (NICE) guidelines of clinical efficacious dosages with minimal side effects at the time of study (NICE, 2008). Based on pharmacokinetic evidence, both medications were administered 1.5-hour before scanning to allow maximum absorption (Chan et al., 1983; Witcher et al., 2003). Placebo was also administered 1.5-hour before scanning to preserve blinding. The same or similar dosages and time lapses between drug administration and scans have shown to be sufficient to observe changes in brain activation and performance in ADHD patients (Cubillo et al., 2014a, 2014b; Rubia et al., 2011a, 2011b; Smith et al., 2013). All three drugs were over-encapsulated using identical capsules by a pharmacist.

Controls were scanned once, unmedicated.

2.3. fMRI task: sustained attention task

Subjects practiced the task once in a mock scanner. The 12-minute sustained attention task is a variant of a psychomotor vigilance and delay tasks and requires sustained and focused attention. The task has been described in detail previously (Carlisi et al., 2017; Christakou et al., 2013; Hart et al., 2017; Lim et al., 2016; Murphy et al., 2014; Norman et al., 2017). Subjects respond as quickly as possible within 1 s via a right-hand button response to the appearance of a visual timer counting up in milliseconds from zero. The timer appeared either after short, predictable consecutive delays of 0.5 s, in series of 3–5 stimuli (240 in total) or after an unpredictable time delay of either 2 s, 5 s, or 8 s (20 each), pseudo-randomly interspersed into the blocks of 3–5 delays of 0.5 s. The three long, infrequent, unpredictable delays (2 s, 5 s, 8 s) place a higher load on sustained attention/vigilance while short, predictable 0.5 s delays are typically anticipated (Miyake et al., 2004), placing a higher demand on sensorimotor synchronisation (Fig. 1). The fMRI analysis contrasts each of the long delays with the short delays.

2.4. Analysis of performance data

Performance data were analysed using SPSS24 (IBM Corp., 2016). For the main performance measures of mean reaction time (MRT), intra-subject response variability of reaction time (SD intra-subject), number of omission errors, and number of premature errors (responses made before stimulus onset), repeated measures ANOVAs were conducted with drug condition (placebo, methylphenidate, atomoxetine) as within-subject factor and group as between-subject factor. For case-control comparisons, independent sample *t*-tests were used to compare ADHD participants under each drug condition (placebo, methylphenidate, atomoxetine) with controls on each of the performance outcomes. Due to the differential cognitive targets of the rare long (sustained attention)

and frequent short delays (sensorimotor synchronisation) and to match the fMRI analysis which used short trials as baseline condition, performance analyses were performed separately for means of all long delay trials (i.e. mean of 2 s, 5 s, and 8 s trials) and for short delay trials (i.e. 0.5 s).

One-way ANOVAs were used to test for potential scan order effects.

2.5. fMRI acquisition

fMRI images were acquired on a 3T General Electric Signa HDx TwinSpeed (Milwaukee, Wisconsin) MRI scanner using a quadrature birdcage headcoil at the Centre for Neuroimaging Sciences, King's College London. In each of 23 non-contiguous planes parallel to the anterior-posterior commissure, 480 T2*-weighted MR images depicting BOLD (Blood Oxygen Level Dependent) contrast covering the whole brain were acquired with echo time (TE) = 30 ms, repetition time (TR) = 1.5 s, flip angle = 70°, in-plane voxel size = 3.75 mm, slice thickness = 5.0 mm, slice skip = 0.5 mm). A whole-brain high resolution structural scan (gradient echo planar image) on which to superimpose the activation maps, was also acquired in the inter-commissural plane with TE = 30 ms, TR = 3 s, flip angle = 90°, in-plane voxel size = 1.88 mm, 43 slices, slice thickness = 3.0 mm, slice skip = 0.3 mm, providing complete brain coverage.

2.6. fMRI analysis

Event-related fMRI data were acquired in randomized trial presentation, and analysed using non-parametric imaging data analysis in XBAM (Brammer et al., 1997; www.brainmap.co.uk).

Data were first processed (Bullmore et al., 1999a) to minimize motion related artefacts. A 3D volume consisting of the average intensity at each voxel over the whole experiment was calculated and used as a template. The 3D image volume at each timepoint was then realigned to this template by computing the combination of rotations (around the *x,y,z* axes) and translations (in *x,y,z*) that maximised the correlation between the image intensities of the volume in question and the template. Following realignment, data were smoothed using a Gaussian filter (FWHM 8 mm) to improve the signal-to-noise characteristics of the images (Bullmore et al., 1999a). Participants with high motion (maximum displacement in *x,y,z* translation and rotation of >6 voxels) were excluded (2 control, 3 ADHD boys). Further preprocessing included slice timing correction and the residual effects of motion were regressed out from the time series (using the estimated motion parameters) before fitting a GLM.

Time series analysis for each individual subject was based on a previously published wavelet-based data resampling method for functional MRI data (Bullmore et al., 2001, 1999b). Using rigid body and affine transformation, the individual maps were then registered into Talairach standard space (Talairach and Tournoux, 1988). A group brain activation map (GBAM) was then produced for each experimental condition (three long delays of 2 s, 5 s, 8 s, each contrasted with the implicit baseline, i.e. the 0.5 s delays) and hypothesis testing was carried out at cluster level. A voxel-wise test at $p < 0.05$ was conducted to identify any voxels that might plausibly be activated followed by a subsequent test at cluster-level. Cluster-level statistical thresholds were chosen that resulted in less than one error cluster per map. This combined voxel/cluster tests coupled with permutation testing allowed for excellent type I error control at the cluster level (for correction of multiple comparisons see Supplement) (Bullmore et al., 2001, 1999b).

For within-patient comparisons, an ANOVA 3×3 factorial design (3 drug conditions: placebo, methylphenidate, atomoxetine; 3 time delays) was conducted, testing for an effect of drug condition. Less than one false positive activation cluster was expected at $p < 0.05$ at voxel level and $p < 0.005$ at cluster level. Statistical measures of BOLD response for each participant were then extracted in each of the significant clusters and averaged across all three delays; post-hoc least significance difference t-tests were conducted to identify differences between the three drug conditions.

For the between-group comparisons, an ANOVA 2×3 split-plot design (2 groups, 3 time delays) was conducted to test for group effects across all 3 delays, using a randomisation-based test for voxel or cluster-wise differences as described elsewhere (Bullmore et al., 1999b). Less than one false positive activation cluster was expected at $p < 0.05$ at voxel and $p < 0.02$ at cluster levels. Statistical measures of BOLD response for each participant were then extracted in each of the significant clusters and averaged across all three delays; post-hoc least significance difference t-tests were conducted to identify between-group differences.

3. Results

3.1. Task performance

3.1.1. Within-patient performance

3.1.1.1. Long delays - sustained attention. Repeated measures ANOVAs within ADHD patients with drug condition as repeated measure showed a significant drug condition effect for MRT, but not for SD intra-subject, omission, or premature errors. Bonferroni corrected post-hoc *t*-tests showed that ADHD patients had significantly faster MRT under methylphenidate than under placebo ($p = 0.011$) (Table 2).

3.1.1.2. Short delays. Repeated measures ANOVAs within ADHD patients showed no significant drug condition effect on any of the performance measures in the short delay trials (Table 2).

3.1.2. Between-group performance

3.1.2.1. Long delays - sustained attention. Independent *t*-tests comparing ADHD patients under each drug condition to controls showed no significant group differences under placebo for omission errors, but for MRT, SD intra-subject, and premature errors, with ADHD patients scoring higher than controls on all measures. Under atomoxetine, ADHD patients had significantly higher MRT, SD intra-subject, and more premature errors, but did not differ from controls on omission errors. Comparisons between controls and ADHD patients under methylphenidate showed no significant differences for MRT or omission errors, but trend-level differences for SD intra-subject and premature errors (Table 2).

3.1.2.2. Short delays. Independent *t*-tests comparing controls with ADHD patients under each drug condition revealed significant group differences for all drug conditions for SD intra-subject and for premature errors, with ADHD patients scoring higher than controls. No other significant differences were observed (Table 2).

Performance findings remained identical when the two patients with comorbid CD were excluded with the exception that the higher premature errors in ADHD relative to controls under atomoxetine were only trend-level significant ($t(13) = 2$, $p = 0.06$).

Table 2 Performance measures and analyses for the sustained attention task for ADHD patients and controls. Long delay scores reflect means of all long delays combined (i.e. 2 s, 5 s, and 8 s).

	HC ($N=27$)		ADHD Placebo ($N=14$)		ADHD MPH ($N=14$)		ADHD ATX ($N=14$)		Group comparison	Analyses $t(df)$, p-value $F(df)$, p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
MRT										
Long delays	390.72	43.34	446.25	71.25	418.15	62.26	431.34	55.39	ADHD-Placebo>HC	$t(18.13)=2.67$, $p=0.016$
									ADHD-MPH vs HC	$t(39)=1.65$, $p=0.107$
									ADHD-ATX>HC	$t(39)=2.59$, $p=0.014$
									Within-ADHD drug condition: Placebo>MPH	$F(2, 26)=3.89$, $p=0.033$
Short delays	283.87	47.15	280.40	72.64	269.21	60.80	280.64	63.65	ADHD-Placebo vs HC	$t(39)=0.19$, $p=0.854$
									ADHD-MPH vs HC	$t(39)=0.85$, $p=0.398$
									ADHD-ATX vs HC	$t(20.62)=0.17$, $p=0.869$
									Within-ADHD drug condition	$F(2, 26)=0.52$, $p=0.604$
SD intra-subject										
Long delays	75.90	26.86	107.00	34.81	104.96	49.13	108.46	41.75	ADHD-Placebo>HC	$t(39)=3.18$, $p=0.003$
									ADHD-MPH vs HC	$t(17.14)=2.06$, $p=0.055$
									ADHD-ATX>HC	$t(39)=3.04$, $p=0.004$
									Within-ADHD drug condition	$F(2, 26)=0.17$, $p=0.848$
Short delays	86.71	40.22	141.79	58.21	134.13	61.81	133.19	56.03	ADHD-Placebo>HC	$t(39)=3.56$, $p=0.001$
									ADHD-MPH>HC	$t(18.88)=2.6$, $p=0.018$
									ADHD-ATX>HC	$t(39)=3.06$, $p=0.004$
									Within-ADHD drug condition	$F(2, 26)=0.92$, $p=0.411$
Number of omission errors										
Long delays	0.48	2.31	0.71	1.14	0.21	0.58	0.86	1.92	ADHD-Placebo vs HC	$t(39)=0.35$, $p=0.725$
									ADHD-MPH vs HC	$t(39)=0.42$, $p=0.674$
									ADHD-ATX vs HC	$t(39)=0.52$, $p=0.605$
									Within-ADHD drug condition	$F(1.37, 17.86)=1.03$, $p=0.349$
Short delays	0.56	1.50	2.71	4.73	1.79	4.51	2.36	4.99	ADHD-Placebo vs HC	$t(14.38)=1.67$, $p=0.118$
									ADHD-MPH vs HC	$t(14.52)=0.99$, $p=0.337$
									ADHD-ATX vs HC	$t(14.24)=1.32$, $p=0.207$
									Within-ADHD drug condition	$F(1.42, 18.44)=0.79$, $p=0.426$
Number of premature errors										
Long delays	22.48	29.02	49.21	43.05	63.14	81.01	59.29	65.05	ADHD-Placebo>HC	$t(39)=2.36$, $p=0.023$
									ADHD-MPH vs HC	$t(14.76)=1.82$, $p=0.089$
									ADHD-ATX>HC	$t(39)=2.52$, $p=0.016$
									Within-ADHD drug condition	$F(1.34, 17.40)=1.22$, $p=0.301$
Short delays	5.52	9.53	34.43	33.29	38.50	48.35	39.14	41.29	ADHD-Placebo>HC	$t(14.11)=3.18$, $p=0.007$
									ADHD-MPH>HC	$t(13.53)=2.53$, $p=0.025$
									ADHD-ATX>HC	$t(13.72)=3.01$, $p=0.01$
									Within-ADHD drug condition	$F(2, 26)=0.48$, $p=0.627$

ADHD = Attention Deficit/Hyperactivity Disorder; ATX = Atomoxetine; HC = Healthy Control; MPH = Methylphenidate; MRT = Mean Reaction Time (ms); SD intra-subject = Intra-subject Variability of MRT (ms).

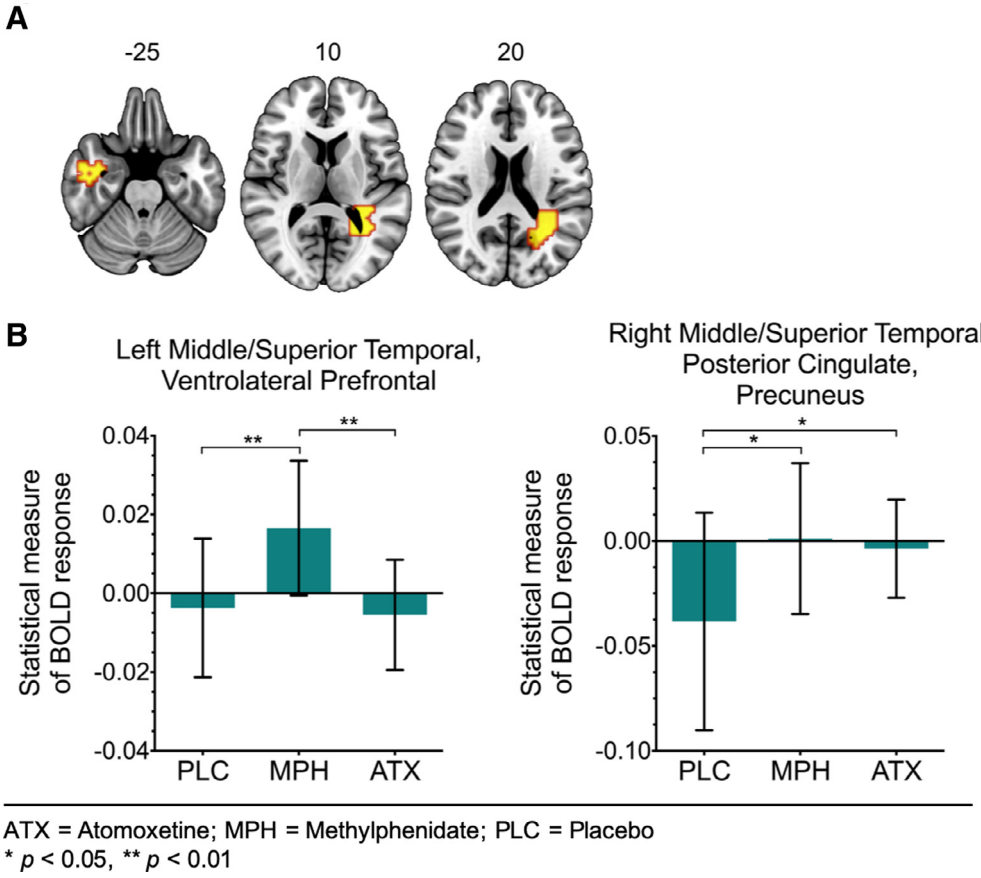


Fig. 2 Within-group ANOVA effects of drug condition on brain activation in ADHD adolescents during sustained attention at $p < 0.05$ for voxel and $p < 0.005$ for cluster levels. (A) Axial slices marked with z coordinate as distance in millimetres from the anterior-posterior commissure. (B) Graphs representing the statistical measure of BOLD response in two activation clusters across drug conditions. Error bars represent standard deviations of the means.

3.2. Brain activation

3.2.1. Motion

Multivariate ANOVA showed no significant differences between controls and ADHD patients under each drug condition in the extent of mean rotation and translation movement parameters in the 3-dimensional Euclidean space ($F(6, 152) = 1$, $p = 0.43$).

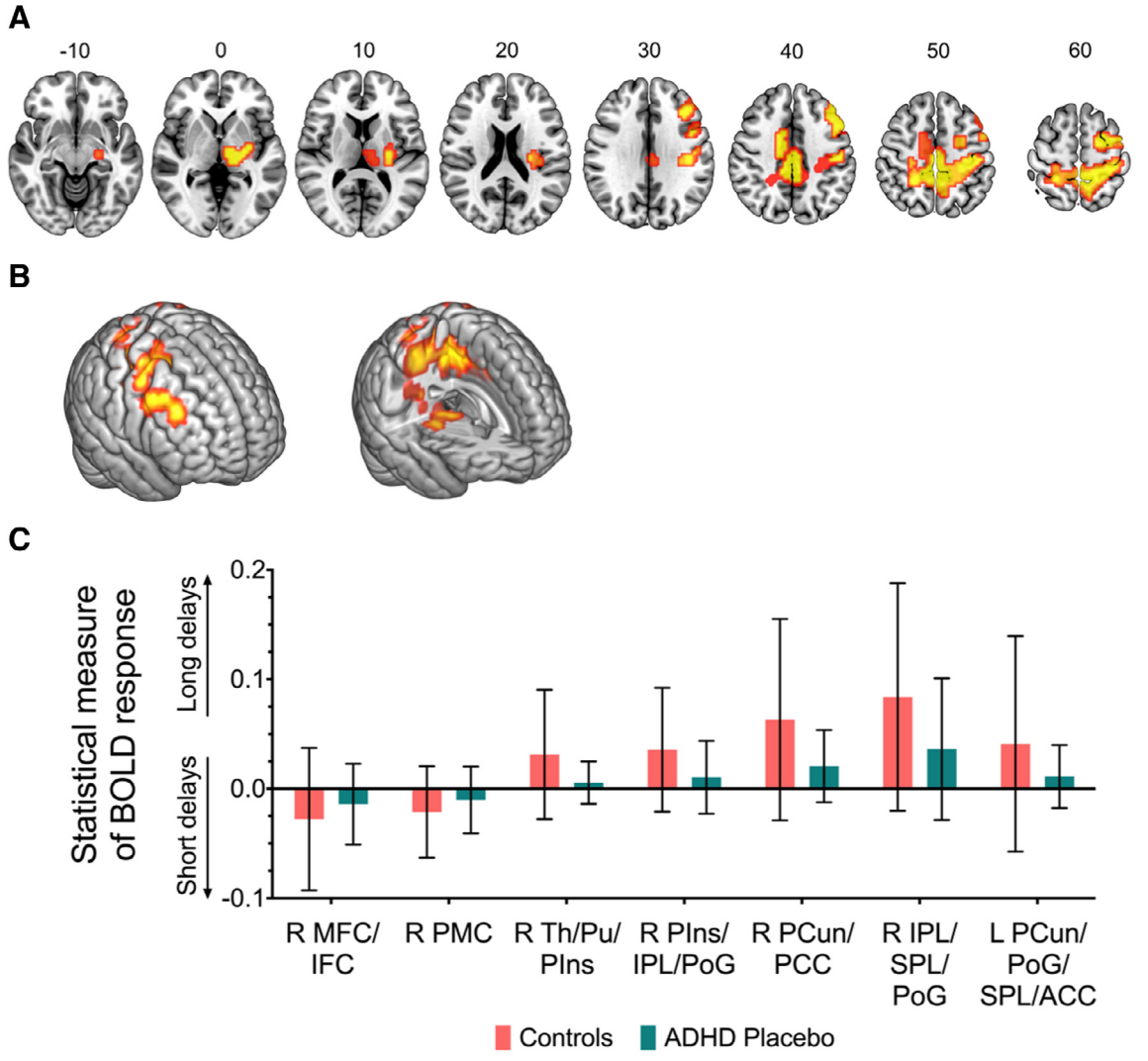
3.2.2. Within-patient activation

Within-patient comparison showed significant drug effects in two clusters in the left middle/superior temporal/ventrolateral prefrontal (VLPFC) cortex (BA 21/38/47; 31 voxels; peak Talairach coordinates [x,y,z]: −36, −4, −29; $p = 0.004$) and the right middle/superior temporal/PCC/precuneus (BA 21/22/39/23/31; 58 voxels; peak Talairach coordinates [x,y,z]: 36, −48, 9; $p = 0.003$). The activation of the left middle/superior temporal/VLPFC cluster was significantly increased under methylphenidate compared to placebo ($p = 0.007$) and compared to atomoxetine ($p = 0.003$), while atomoxetine and placebo did not differ significantly. The activation of the right middle/superior temporal/PCC/precuneus cluster was significantly higher under both methylphenidate ($p = 0.024$) and atomoxetine ($p = 0.012$) relative to placebo, while the two drug conditions did not differ ($p = n.s.$) (Fig. 2). Both clusters survived at a more lenient $p < 0.01$ when two patients with comorbid CD were excluded (Supplementary Figure S1).

To test for correlations between drug-induced differences in BOLD response and task performance in the long delay trials, we extracted average scalar measures of the BOLD response in the clusters of within-group drug condition differences in ADHD patients and conducted Pearson correlations with the main performance measures of MRT and SD intra-subject. False discovery rate (FDR) correction was applied for multiple comparisons. The only correlations that survived correction were between SD intra-subject and right middle/superior temporal/PCC/precuneus activation under placebo ($r = 0.66$, $p = 0.03$) and left middle/superior temporal/VLPFC activation under methylphenidate ($r = -0.72$, $p = 0.024$)

3.2.3. Between-group activation

Patients with ADHD under placebo relative to controls showed reduced activation in right DLPFC and IFC, premotor and inferior parietal cortices, thalamus/putamen, posterior insula, PCC, left ACC, as well as in bilateral postcentral and superior parietal cortices, precuneus (Fig. 3, Table 3). The underactivation in right DLPFC/IFC/premotor cortex was driven by differences during the short delay trials, while all other underactivations were related to the long delay trials. Patients under placebo showed no



ACC = Anterior Cingulate Cortex; IFC = Inferior Frontal Cortex; IPL = Inferior Parietal Lobule; L = Left; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex; PCun = Precuneus; PIns = Posterior Insula; PMC = Premotor Cortex; PoG = Postcentral Gyrus; Pu = Putamen; R = Right; SPL = Superior Parietal Lobule; Th = Thalamus.

Fig. 3 ANOVA comparison of controls and ADHD patients under placebo during sustained attention at $p < 0.05$ for voxel and $p < 0.02$ for cluster levels. (A) Axial slices are marked with *z* coordinate as distance in millimetres from the anterior–posterior commissure. (B) Three-dimensional rendering of activation differences. (C) Graph showing statistical measure of BOLD response in controls and ADHD patients under placebo in clusters that differed between groups. Error bars represent standard deviations of the means.

enhanced activation relative to controls. Findings remained at a more lenient $p < 0.04$ when the two patients with comorbid CD were excluded with exception of the thalamus/putamen cluster (Supplementary Figure S2).

To test the association between case-control differences in BOLD response and task performance on the long delay trials, we extracted average scalar measures of the BOLD response in the clusters of between-group differences and conducted Pearson correlations with MRT and SD intra-subject within each group, applying FDR correction for multiple testing.

After FDR correction, the only remaining (negative) correlations were for controls between the activation of the right parietal/postcentral cluster and MRT ($r = -0.54$, $p = 0.019$) and SD intra-subject ($r = -0.49$, $p = 0.025$), the right precuneus/PCC and MRT ($r = -0.54$, $p = 0.042$) and SD intra-subject ($r = -0.54$, $p = 0.028$), and the left parietal/ACC cluster and SD intra-subject ($r = -0.53$, $p = 0.018$).

To assess whether subtle, non-significant differences in motion could have affected the analysis, we tested whether motion parameters were correlated with any of

Table 3 ANOVA showing brain activation differences between ADHD patients under placebo and controls in relation to long and short delay trials.

Cerebral region	BA	Peak Talairach coordinates			Cluster size (voxels)	*p*
		x	*y*	*z*		
HC > ADHD-Placebo						
Long delays						
R Precuneus/Posterior Cingulate	31/7/5	7	−37	42	279	0.00014
R Inferior/Superior Parietal/Postcentral	40/7/5	40	−26	42	122	0.0002
L Precuneus/Postcentral/Superior Parietal/Anterior Cingulate	7/5/6/24	−18	−37	48	86	0.01
R Thalamus/Putamen/Posterior Insula	-	18	−15	−7	49	0.01
R Posterior Insula/Inferior Parietal/Postcentral	40/1/2/3	33	−22	15	39	0.02
Short delays						
R Medial/Inferior Frontal Cortex	9/8/6/46/44	58	19	37	101	0.004
R Premotor Cortex	6	29	4	48	66	0.0003

ADHD = Attention Deficit/Hyperactivity Disorder; BA = Brodmann Area; HC = Healthy Control; L = Left; R = Right.

the between-group activation differences. For this purpose, we extracted the statistical measures of BOLD response for each subject for the clusters that differed between controls and ADHD patients under placebo and correlated these with the estimated maximum displacement motion parameters for *x*, *y*, and *z* for each subject. We found no significant correlations between motion parameters and statistical measures of BOLD response in any clusters ($r < 0.5$, $p = n.s.$).

No differences in brain activation were observed when comparing controls with ADHD patients under methylphenidate or under atomoxetine. Findings remained when patients with comorbid CD were excluded.

3.3. Scan order effects

One-way ANOVAs revealed no scan order effects for MRT ($F(2, 39) = 0.13$, $p = 0.883$), SD intra-subject ($F(2, 39) = 0.01$, $p = 0.99$), omission errors ($F(2, 39) = 0.07$, $p = 0.932$), or premature errors ($F(2, 39) = 0.22$, $p = 0.806$), nor for the extracted BOLD response measures in the two clusters that showed a within-patient drug effects (left VLPFC/superior/middle temporal cluster, $F(2, 39) = 0.77$, $p = 0.47$; right middle/superior temporal/PCC/precuneus cluster, $F(2, 39) = 0.56$, $p = 0.577$).

4. Discussion

This study shows that during a sustained attention task, single clinical doses of methylphenidate and atomoxetine both normalise the placebo-related underactivation in medication-naïve ADHD adolescents relative to healthy controls in a typical, right hemispheric dorsal and inferior fronto-cingulo-parieto-striato-thalamic sustained attention network. Within patients, methylphenidate had a drug-specific effect of upregulating left VLPFC superior temporal activation, while both drugs upregulated right middle/superior temporal activation and slightly more rostral parts of a PCC/precuneus location that was reduced in function in patients under placebo relative to controls and which was normalised with both drugs. At the performance level, however, only methylphenidate normalised MRT and reduced significant group differences between controls and ADHD patients under placebo in SD intra-subject and premature errors to trend-level significance, while atomoxetine had no effects. Main findings remained when the two patients with comorbid CD were excluded.

The underactivation in ADHD patients under placebo compared to controls was in predominantly right-hemispheric, typical regions of sustained attention, including DLPFC/IFC, inferior and superior parietal regions, precuneus, cingulate, insula and striato-thalamic areas. These areas are typically activated in healthy children and adults during sustained attention paradigms (Langner and Eickhoff, 2013; Smith et al., 2011), including the identical task (Christakou et al., 2013; Lim et al., 2016; Murphy et al., 2014). Furthermore, underactivation of several of these regions has been reported previously in ADHD adolescents relative to controls during the same (Christakou et al., 2013; Norman et al., 2017) and other sustained attention tasks (Rubia et al., 2009b). A meta-analysis of fMRI studies of selective and sustained attention in 171 ADHD patients also reported reduced activation relative to controls in predominantly right-hemispheric DLPFC, inferior parietal cortex, precuneus, superior temporal areas, thalamus, and basal ganglia (Hart et al., 2013). Fronto-parietal and striato-thalamic underactivation in ADHD adolescents relative to age-matched controls could reflect a delay in functional brain maturation given that the same frontal and striato-thalamic regions have been shown to be progressively more recruited with increasing age during development between childhood and adulthood during similar (Smith et al., 2011) and the same sustained attention paradigms (Murphy et al., 2014). This suggests that the activation pattern in ADHD relative to age-matched healthy controls is like the activation pattern of a younger relative to an older child, suggesting a maturational delay (Rubia, 2018). This would resonate with evidence for a delay in the functional maturation of the ventral attention network, shown by an ADHD by age interaction in the functional connectivity within this network and its anti-correlation with the DMN in large resting state fMRI data of ADHD patients ($N = 133$) (Sripada et al., 2014).

The reduced activation in thalamus and striatum was no longer observed when we excluded two patients with comorbid CD. However, given that we found this cluster to be reduced in ADHD in previous studies on the same and similar sustained attention tasks (Christakou et al., 2013; Rubia et al., 2009b), this is likely due to reduced power rather than to a CD-specific deficit.

While reduced activation in ADHD patients relative to controls in inferior and superior parietal, PCC, and striato-thalamic regions was observed during the long delay trials, underactivation of the DLPFC/IFC and premotor cortex was observed during the short delay trials. The long delays are less frequent (20%) and, given the three different delay periods of 2, 5, and 8 s, also less predictable than the short consecutive 0.5 s delays (3–5 in a row). Consequently, the long delays place a higher load on sustained attention than the short delays, which are typically anticipated and trigger sensorimotor synchronisation (Miyake et al., 2004). The reduced activation in ADHD patients relative to controls in right DLPFC/IFC and premotor cortex during short delays, triggering sensorimotor synchronisation, is in line with previous reports of reduced activation in ADHD patients relative to controls during tasks of sequential finger tapping and motor timing in typical regions mediating sensorimotor synchronisation, such as pre-SMA, motor and premotor cortex (Gaddis et al., 2015; Mostofsky et al., 2006; Rubia et al., 1999; Valera et al., 2010), and IFC (Valera et al., 2010) (Noreika et al., 2013). While most fMRI studies of sensorimotor synchronisation in ADHD showed underactivation relative to controls in regions contralateral to the side of the motor response (Mostofsky et al., 2006; Rubia et al., 1999; Valera et al., 2010), bilateral reduction was also observed (Gaddis et al., 2015). The ipsilateral premotor activation reduction in this study suggests either sensorimotor synchronisation problems in ADHD or, together with the underactivation in right DLPFC/IFC, it could also reflect a combination of abnormalities in attention processing and sensorimotor synchronisation.

Underactivation of IPL and PCC/precuneus in ADHD patients relative to controls during the long delay trials, with a higher load on sustained attention, is in line with the role of these regions in mediating visuospatial attention (Small et al., 2003; Ungerleider, 2000). This is further supported by our findings of inverse correlations in healthy controls between MRT/SD intra-subject and brain activation in precuneus, ACC, parietal and postcentral regions, suggesting that increased activation of these regions is associated with faster and less variable responses in controls. ADHD patients have typically reduced activation of PCC and precuneus during salient stimuli in visual-spatial tasks, such as during attention allocation (Rubia et al., 2007), motor timing (Rubia et al., 1999), and error detection (Rubia et al., 2008, 2005). Our findings of PCC/precuneus underactivation during sustained attention extend these prior findings and support the notion that these regions are under-functioning in ADHD during different tasks requiring visual-spatial attention.

Importantly, both drugs normalised the underactivation in ADHD patients under placebo relative to controls in all regions. These findings extend previous evidence of normalisation effects of methylphenidate during another sustained attention task (i.e. continuous performance task) on inferior parietal areas, and upregulation effects on inferior frontal, premotor, and subcortical regions, such as the thalamus (Rubia et al., 2009b). Furthermore, in this study, methylphenidate not only reduced the activation difference between ADHD patients and controls as in the previous study (Rubia et al., 2009b), but also normalised all fronto-parieto-striato-thalamic brain dysfunctions. These findings extend previously observed normalisation/upregulation effects of single doses of methylphenidate on fronto-cingulo-parietal, striato-thalamic, and cerebellar underactivation in youth with ADHD relative to controls during sustained and selective attention (Rubia et al., 2009b; Shafritz et al., 2004), time estimation (Rubia et al., 2009a) and executive functions (Epstein et al., 2007; Rubia et al., 2011a, 2011b). The normalisation effects of right IFC, insula, ACC, and putamen underactivation in the current study are also in line with a meta-analysis of single-dose effects of methylphenidate in fMRI studies of cognitive functions in 212 ADHD patients that showed a consistent upregulation of right IFC/insula, followed by putamen and ACC (Rubia et al., 2014).

Most importantly, this study shows for the first time that a single atomoxetine dose has comparable effects to methylphenidate in normalising fronto-striato-thalamo-parietal brain abnormalities during sustained attention. These results are further supported by our within-patient analysis showing that both methylphenidate and atomoxetine significantly upregulated the activation of slightly more ventral parts of the PCC/precuneus than those that were underactivated and normalised by both drugs. These findings extend previous research showing shared normalisation effects of methylphenidate and atomoxetine of IFC dysfunction during other functions including response inhibition (Cubillo et al., 2014b) and time discrimination (Smith et al., 2013).

Our finding of shared normalisation of the right DLPFC underactivation during the short delay trials is inconsistent with the drug-specific upregulation/normalisation effects of atomoxetine on the right DLPFC during working memory in the same ADHD adolescents (Cubillo et al., 2014a). This disparity in results may reflect task-dependency of the neurofunctional effects. It is thus possible that methylphenidate has greater effects in normalising motor-related (sensorimotor synchronisation) rather than working memory related right DLPFC deficits, given the importance of dopamine in movement control (Joshua et al., 2009).

Although not directly comparable, longer-term stimulant administration has also been associated with increased activation in ADHD patients in similar regions as the ones observed here, including IFC, DLPFC, ACC, and basal ganglia, both in individual studies of interference inhibition and reward tasks (Bush et al., 2008; Chou et al., 2015; Mizuno et al., 2013) and in meta-regression analyses testing for an association between brain activation and long-term stimulant use in meta-analyses of fMRI studies of attention (Hart et al., 2013), timing (Hart et al., 2012) and cognitive control (Hart et al., 2013; McCarthy et al., 2014; Norman et al., 2016), although downregulation has also been observed in individual studies of attention (Konrad et al., 2007) or in relation to treatment response during motor inhibition (Schulz et al., 2012). Similarly, longer-term atomoxetine administration in ADHD patients has been associated with upregulation of IFC during motor inhibition (Schulz et al., 2012), DLPFC, parietal, and cerebellar regions during

interference inhibition (Bush et al., 2013), and precuneus during visual processing (Fan et al., 2017). Although downregulating effects on IFC and ACC activation during inhibitory control was also observed in ADHD adults (Fan et al., 2017).

The shared normalisation effects likely reflect the increased availability of both dopamine and norepinephrine, potentially mediated primarily by norepinephrine transporters, which are inhibited by both drugs (Bymaster et al., 2002; Gallezot et al., 2011; Hannestad et al., 2010; Wilens, 2008).

Within patients, both methylphenidate and atomoxetine significantly upregulated the activation of a right-lateralised middle/superior temporal, PCC, and precuneus cluster located more ventrally to the PCC/precuneus cluster that was underactivated in ADHD boys under placebo and normalised by both drugs in the between-group analysis. This is in line with our previous work on other tasks showing upregulation effects of methylphenidate relative to placebo in PCC and precuneus during sustained attention (Rubia et al., 2009b) and response inhibition (Rubia et al., 2014), precuneus (Rubia et al., 2011b), PCC, and superior temporal lobe during error processing (Rubia et al., 2014), and middle and superior temporal lobe during interference inhibition (Rubia et al., 2011a).

Additionally, only methylphenidate, but not atomoxetine, upregulated activation of the left-hemispheric VLPFC/superior/middle temporal cluster. Upregulation of VLPFC has been observed with a single dose of methylphenidate relative to placebo during executive function (Cubillo et al., 2014a, 2014b; Epstein et al., 2007) and timing tasks (Rubia et al., 2009a), and was found to be drug-specific compared to atomoxetine (Cubillo et al., 2014a, 2014b). Interestingly, a meta-analysis showed that long-term stimulant medication treatment was associated with increased activation in bilateral VLPFC in ADHD patients relative to controls during cognitive control tasks (Norman et al., 2016). Together these results suggest that methylphenidate has a drug-specific effect relative to atomoxetine in upregulating VLPFC. This might be related to methylphenidate's action on the dopaminergic system which innervates the VLPFC (Arnsten and Rubia, 2012). Alternatively, it may also be related to the role of VLPFC in motivation processes (Haber, 2016), which have shown to play a key role in methylphenidate's mechanism of action (Volkow et al., 2004).

The findings of performance improvement (MRT, SD intra-subject, and premature errors) under methylphenidate, but not atomoxetine, are in line with the previously observed higher affinity of methylphenidate than atomoxetine in improving attention performance (Bédard et al., 2015). Studies that showed improved sustained attention performance with atomoxetine tested the effects of 4- and 12-week treatment, rather than a single dose (Gau and Shang, 2010; Shang and Gau, 2012). Given that atomoxetine reaches its highest clinical efficacy at 12 weeks (Montoya et al., 2009), it is likely that long-term treatment is necessary to observe performance improvement. Furthermore, this study was designed primarily to test single-dose drug effects on neural correlates of ADHD and hence used a task optimised for fMRI testing. fMRI tasks typically lose behavioural sensitivity relative to behavioural tasks. Also, the sample size was relatively small, which limited the power of the neurocognitive analyses. The performance data should therefore be interpreted with caution.

The strength of this study is the use of a double-blind, placebo-controlled design and the recruitment of medication-naïve ADHD children, given that long-term treatment is associated with brain structure and function changes (Hart et al., 2013; Nakao et al., 2011; Norman et al., 2016).

A limitation of this study is the relatively small subject numbers, which has particularly limited the performance analysis. Testing acute effects of drugs avoids confounds associated with long-term treatment, such as symptomatic improvement, side effects, and effects on brain activation and structure (Hart et al., 2013; Nakao et al., 2011; Norman et al., 2016). However, this has limitations. While methylphenidate offers immediate effects on ADHD symptoms (Greenhill et al., 2001), atomoxetine reaches highest clinical efficacy at approximately 12 weeks (Montoya et al., 2009). Consequently, the study design could have favoured methylphenidate, which might explain its greater effects on performance. Although this and other studies (Cubillo et al., 2014a, 2014b; Smith et al., 2013) have shown immediate effects of atomoxetine on brain activation, studying the effects of long-term drug treatments may be clinically more relevant. Another limitation is that, due to the within-subject design for drug effects, ADHD patients completed the task three times, while controls only once, for ethical and financial reasons. Scanning controls three times would have controlled for practice effects in patients and allowed more powerful modelling. Nevertheless, the lack of scan order effects on performance and brain activation suggests that it is unlikely that findings were confounded by practice effects. Last, to increase the homogeneity of this sample, we recruited only right-handed combined-type ADHD boys which does not generalise to other ADHD subtypes, females, or left-handed participants.

In conclusion, to our knowledge this is the first fMRI study in ADHD patients that directly compared single-dose effects of methylphenidate and atomoxetine on neurofunctional correlates of sustained attention. The findings offer first evidence of comparable effects of methylphenidate and atomoxetine in upregulating and normalising attention-related fronto-parieto-striato-thalamic dysfunction in ADHD. Furthermore, they show drug-specific upregulation effects of methylphenidate on left ventrolateral and superior temporal regions. The shared normalisation effects on attention network dysfunction in ADHD may underlie their clinical efficacy in improving behavioural inattention symptoms in ADHD. They could also potentially indicate that patients with behavioural or cognitive sustained attention problems may benefit from either medication. However, longer-term medication administration studies will need to test this.

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Contributors

KR obtained funding, designed the study, wrote the protocol and supervised the study. OSK, AIC, and KR wrote the manuscript. VG, MB, AS, and NB conducted a critical revision of the manuscript for important intellectual content. AIC, KR, VG, and OSK conducted the statistical analyses. AIC and AS coordinated participant recruitment, testing and data collection. NB prescribed the drugs and overlooked clinical issues. AS supervised the MRI acquisition. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

KR has received speaker's honoraria from Shire, Medice, and Lilly. No other conflicts of interests need to be declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.07.139.

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