Shared and Drug-Specific Effects of Atomoxetine and Methylphenidate on Inhibitory Brain Dysfunction in Medication-Naive ADHD Boys

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The stimulant methylphenidate (MPX) and the nonstimulant atomoxetine (ATX) are the most commonly prescribed medications for attention deficit hyperactivity disorder (ADHD). However, no functional magnetic resonance imaging (fMRI) study has as yet investigated the effects of ATX on inhibitory or any other brain function in ADHD patients or compared its effects with those of MPX. A randomized, double-blind, placebo-controlled, crossover pharmacological design was used to compare the neurofunctional effects of single doses of MPX, ATX, and placebo during a stop task, combined with fMRI within 19 medication-naive ADHD boys, and their potential normalization effects relative to 29 age-matched healthy boys. Compared with controls, ADHD boys under placebo showed bilateral ventrolateral prefrontal, middle temporal, and cerebellar underactivation. Within patients, MPX relative to ATX and placebo significantly upregulated right ventrolateral prefrontal activation, which correlated with enhanced inhibitory capacity. Relative to controls, both drugs significantly normalized the left ventrolateral prefrontal underactivation observed under placebo, while MPX had a drug-specific effect of normalizing right ventrolateral prefrontal and cerebellar underactivation observed under both placebo and ATX. The findings show shared and drug-specific effects of MPX and ATX on performance and brain activation during inhibitory control in ADHD patients with superior upregulation and normalization effects of MPX.

Keywords: atomoxetine, attention deficit hyperactivity disorder, functional magnetic resonance imaging, methylphenidate, motor response inhibition, stop task

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate levels of impulsivity, inattention, and hyperactivity (American Psychiatric Association 2000). One of the most consistent findings are deficits in motor response inhibition, in particular during a stop task (Alderson et al. 2007), underpinned by functional magnetic resonance imaging (fMRI) findings of reduced activation in key areas of motor response inhibition such as ventrolateral prefrontal cortex (VLPFC), supplementary motor area (SMA), and caudate (Rubia 2011; Cubillo et al. 2012).

The stimulant methylphenidate (MPX) and the nonstimulant atomoxetine (ATX) are the most frequently prescribed drugs for the treatment of ADHD. Recent meta-analyses show that both drugs have comparable efficacy rates in reducing ADHD symptoms (Hazell et al. 2010; van Wyk et al. 2012), with 1 meta-analysis showing the superior efficacy of the long-acting but not short-acting MPX preparation (Hanwella

et al. 2011). However, their mechanisms of action in ADHD are relatively unknown. In humans, at therapeutic doses, MPX blocks 60–70% of the dopamine transporter in the striatum (Volkow et al. 1998). However, MPX has also shown to block 70–80% of the norepinephrine transporter in noradrenaline transporter-rich brain regions, including the prefrontal cortex (Hannestad et al. 2010). In rodent studies, MPX has shown to enhance the extracellular levels of both noradrenaline and dopamine (Bymaster et al. 2002). ATX is a selective presynaptic noradrenaline transporter blocker, which at therapeutic doses has shown to occupy noradrenaline transporters almost completely in the anterior cingulate (ACC), thalamus, brain stem, midbrain, locus ceruleus, and cerebellum in nonhuman primates (Gallezot et al. 2011).

In healthy adults, a single dose of MPX has been shown to downregulate right VLPFC activation during successful inhibitory trials in the stop task (Pauls et al. forthcoming 2012) and to upregulate activation in the putamen during errors in a go/no-go task, without significant effects during successful inhibition on brain activation or performance (Costa et al. forthcoming 2012). In ADHD patients, however, the effects of a single-dose MPX challenge on brain networks of motor inhibition have been more pronounced. Thus, in previously medicated children with ADHD, MPX has been shown to upregulate activation in the frontal, ACC, striatal, and parietal areas during go/no-go tasks (Vaidya et al. 1998; Epstein et al. 2007) and to normalize all brain activation deficits in the VLPFC, SMA, parieto-temporal, and cerebellar regions in medication-naive children with ADHD during the stop task (Rubia, Halari, Mohammad et al. 2011). Furthermore, during other cognitive control, attention, and timing functions, single-dose MPX challenges in ADHD children have shown to upregulate or normalize most prominently fronto-striatal, but also temporo-parietal, cingulate, and cerebellar activations (Shafritz et al. 2004; Rubia, Halari, Christakou et al. 2009; Rubia, Halari, Cubillo et al. 2009; 2011).

However, no fMRI study has as yet investigated the effects of ATX in ADHD patients, or compared its effects with those of MPX during any cognitive function. In healthy adults, a single-dose challenge of ATX upregulated VLPFC, superior temporal gyrus (STG), and SMA activation during motor inhibition tasks (Chamberlain et al. 2009; Graf et al. 2011).

The aim of this study was therefore to compare the effects of a single dose of MPX and ATX in medication-naive ADHD boys during a challenging stop task using a randomized, double-blind, placebo-controlled, crossover design. To identify potential normalization effects, the brain activation in the

ADHD group under each drug condition was compared with that of a group of age-matched healthy boys. Based on previous studies on the stop task in children with ADHD, we hypothesized that medication-naive ADHD boys under placebo compared with healthy control boys would show reduced activation in the VLPFC, SMA/ACC, and caudate during successful inhibition (Rubia et al. 1999, 2005, 2008, 2010; Pliszka et al. 2006). Furthermore, we hypothesized that, based on previous upregulation and normalization findings in ADHD during fMRI inhibition tasks, MPX would enhance frontal, striatal, SMA/ACC, and parietal activation (Vaidya et al. 1998; Epstein et al. 2007; Rubia, Halari, Cubillo et al. 2011; Rubia, Halari, Mohammad et al. 2011). With regard to ATX, there are no data on ADHD patients to base our hypotheses on, but we expected that ATX would also enhance the activation of VLPFC and STG in ADHD patients to the same extent or in a more pronounced manner than in healthy controls (Chamberlain et al. 2009; Graf et al. 2011), parallel to the more pronounced effects of MPX in ADHD relative to healthy controls, due to lower baseline catecholamine levels in ADHD patients (Del Campo et al. 2011; Fusar-Poli et al. 2012).

Materials and Methods

Participants

Forty-eight right-handed boys in the age range between 10 and 17 years participated. Nineteen (mean age [years, months] [SD] = 13 years, 1 month [2 years, 6 months]) medication-naive right-handed boys, who had a clinical diagnosis of ADHD, inattentive/hyperactive-impulsive combined subtype, as assessed by an experienced child psychiatrist using the standardized Maudsley diagnostic interview that assesses ADHD according to diagnostic and statistical manual of mental disorders, 4th edition, text revision criteria (Goldberg and Murray 2002), were recruited from clinics. The diagnosis of ADHD was determined by a multidisciplinary clinical team. The assessment process included information from semi-structured clinical assessment interviews with parents/carers, questionnaires from parents and teachers, school reports, developmental history, cognitive assessments, and behavioral observation of the child. The presence of learning disability was excluded based on information provided by parents and schools during the clinical and cognitive assessments, or by the presence of significant discrepancies between verbal and performance intelligence quotient (IQ) subscores, which is considered an indicator of potential learning difficulties.

ADHD boys scored above the clinical threshold for hyperactive-impulsive/inattentive 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 a clinical threshold on the social communication questionnaire (SCQ; Rutter et al. 2003; Table 1). Patients were scanned in a double-

blind, placebo-controlled, crossover design. On each scanning session, they received a single dose of either placebo (Vitamin C, 50 mg), MPX (Equasym, 0.3 mg/kg, range 5–20 mg), or ATX (Strattera, 1 mg/kg, range 16–66 mg), in a pseudo-randomized order, and remained medication-free between scans. National Institute for Clinical Excellence (NICE) guidelines of clinical efficacious dosages with minimal side effects at the time of the study were followed (http://www.nice.org.uk/CG72). All 3 drug conditions were over-encapsulated using the same opaque capsules by the pharmacist. Based on pharmacokinetic evidence, both medications were administered 1.5 h before the scan to allow for maximum absorption (Chan et al. 1983; Witcher et al. 2003). The same or similar dosages and time lapses between drug administration and the scan have been shown to be sufficient to observe changes in brain activation and performance in ADHD patients (MPX; Rubia, Halari, Cubillo et al. 2011; Rubia, Halari, Mohammad et al. 2011) and healthy controls (ATX; Chamberlain et al. 2007, 2009).

Twenty-nine healthy control boys (mean age [years, months] [SD] = 13 years, 9 months [1 years, 7 months]) were recruited through advertisement in the same geographical area and scanned once, unmedicated. They scored below the clinical threshold on the SDQ, SCQ, and CPRS-R (Table 1).

Exclusion criteria for all participants were IQ <70 on the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999), history of substance abuse or neurological deficits, presence of other psychiatric disorder (except for conduct disorder/oppositional defiant disorder in the ADHD group, $N = 2$), learning disability, reading, speech, or language disorder.

One-way analyses of variance (ANOVAs) showed no between-group differences for age ($F_{1,46} = 1.16$; $P = 0.28$), but for IQ ($F_{1,46} = 28.07$; $P < 0.001$) (Table 1). Low IQ is associated with ADHD (Bridgett and Walker 2006). Although ANCOVA is commonly conducted in case–control studies, this is statistically illegitimate when the covariate is an attribute of the disorder and when, as in this study, groups were not randomly selected. It then becomes meaningless to "adjust" the group effects for differences in the covariate, and ANCOVA cannot be used to control group assignment independent of the covariate as it would alter the group effect in potentially problematic ways, leading to spurious results (Miller and Chapman 2001; Dennis et al. 2009). Therefore, all analyses were conducted without IQ as a covariate.

Participants received £50 per scanning session. Parental and child informed consent/assent and approval from the local ethical committee were obtained.

Experimental fMRI Design: Stop Task

Participants practiced once the 9-min mixed-trials, event-related fMRI stop task, which measures the ability to suppress an already triggered motor response (Rubia et al. 2003, 2005, 2008, 2010; Rubia, Smith, Taylor et al. 2007). The basic go task is a choice reaction time task with a mean intertrial interval of 1.8 s, where participants have to respond to go arrows of 500 ms duration (80% of trials, 236 trials) pointing either right or left with a right or left button response with the right/left thumb, followed by a blank of 1300 ms. In 20% of trials (60 trials), the go-signals are followed and sometimes interrupted (about 250 ms later) by stop-signals, and participants have to inhibit their motor responses (Fig. 1). A tracking algorithm changes the time interval between go-signal and stop-signal onsets according to each subject's performance on previous trials based on the average percentage of inhibition over previous stop trials, recalculated after each stop trial, resulting in 50% successful and 50% unsuccessful inhibition trials.

MRI Image Acquisition

Gradient echo-planar MRI data were acquired on a GE Signa 3T Horizon HDx system (General Electric, Milwaukee, WI, United States of America) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, United Kingdom. A semi-automated quality control procedure ensured consistent image quality (Simmons et al. 1999). A quadrature birdcage headcoil was used for radiofrequency transmission and reception. In each of 28 noncontiguous

Table 1
Sample characteristics for healthy control boys and patients with ADHD

Variables	Mean (SD)	
	Controls (29)	ADHD (19)
Age (years, months)	13 years, 9 months (2 years, 6 months)	13 years, 1 month (1 years, 7 months)
IQ	110 (12)	92 (11)
SDQ hyperactive-impulsive/inattentive subscale	1.45 (1.63)	7.86 (2.53)
SDQ total	3.72 (3.95)	22.46 (6.90)
SCQ total	1.18 (1.40)	9.53 (4.54)
CPRS-R total t score	44.09 (4.74)	79 (11.37)

Note: SDQ = strengths and difficulties questionnaire; SCQ = social communication questionnaire; CPRS-R = Conners' Parent Rating Scale; SD = standard deviation.
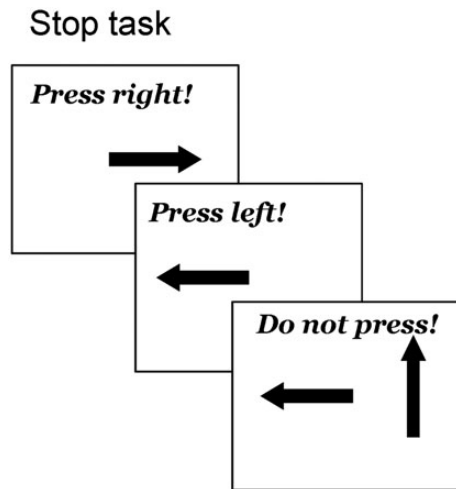
Stop task

Figure 1. Stop task. Subjects have to respond to go arrows (79.6% of trials, 294 trials) that point either right or left with a right/left button response. In 20.4% of trials (60 trials), the go-signals were followed (about 250 ms later) by stop-signals and subjects had to inhibit their motor responses. A tracking algorithm changed the time interval between go-signals and stop-signals according to each subject's performance on previous trials (average percentage of inhibition over previous stop trials, recalculated after each stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials.

planes parallel to the anterior–posterior commissure, 296 T_2*-weighted MRimages depicting blood oxygen level-dependent (BOLD) contrast covering the whole brain were acquired with echo delay time (TE) = 30 ms, repetition time (TR) = 1.8 s, flip angle = 75°, in-plane resolution = 3 mm, and slice thickness = 5.5 mm (including slice skip = 0.5 mm). In addition, a high-resolution gradient echo-planar image was also acquired in the intercommissural plane, with TE = 30 ms, TR = 1.8 s, flip angle = 90°, 43 slices, slice thickness = 3.0 mm, slice skip = 0.3 mm, and in-plane voxel size of 1.875 mm (matrix size 128 × 128), providing complete brain coverage.

For fMRI analysis, the software package of XBAM was used (http://www.brainmap.co.uk; Brammer et al. 1997), which makes no normality assumptions (violated in fMRI data), but instead uses median statistics to control outlier effects and permutation rather than normal theory-based inference. Furthermore, the most common test statistic is computed by standardizing for individual differences in residual noise before embarking on second-level, multi-subject testing using robust permutation-based methods. This allows a mixed-effects approach to analysis, recommended for fMRI (Thirion et al. 2007).

fMRI data were first processed to minimize the motion-related artifacts (Bullmore, Brammer et al. 1999). A 3-dimensional (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 time point was then realigned to this template by computing the combination of rotations (around the x, y, and z axes) and translations (in x, y, and z) that maximized the correlation between the image intensities of the volume in question and the template (rigid-body registration). Following realignment, data were then smoothed using a Gaussian filter (full width at half maximum, 7.2 mm) to improve the signal-to-noise characteristics of the images.

After motion correction, global detrending, and spin-excitation history correction, we first convolved the main experimental condition (successful inhibitory trials, contrasted with the go trials that formed the implicit baseline; Rubia et al. 2003, 2005, 2008; Rubia, Smith, Taylor et al. 2007) with two Poisson model functions (peaking at 4 and 8 s). We then calculated the weighted sum of these two convolutions that gave the best fit (least squares) to the time series at each voxel. A goodness-of-fit statistic [an sum of squares quotient (SSQ) ratio] was then computed at each voxel consisting of the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). The

appropriate null distribution for assessing the significance of any given SSQ ratio was established using a wavelet-based data resampling method for the functional MRI data (Bullmore, Brammer et al. 1999; Bullmore et al. 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of an SSQ ratio for each subject, which were combined to give the overall null distribution of SSQ ratio. The same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data.

At the individual-subject level, a standard general linear modeling approach was used to obtain estimates of the response size (beta) to the successful stop trials against an implicit baseline (go trials). After first-level analysis, the individual statistical maps were normalized into Talairach standard space (Bullmore et al. 2001).

A group activation map was then produced for the experimental condition (successful inhibition—go) by calculating the median SSQ ratio over all subjects at each voxel in standard space and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet resampled data (Brammer et al. 1997). ANOVAs were conducted using randomization-based tests for voxel- or cluster-wise differences (Bullmore, Suckling et al. 1999). The voxel-level threshold was first set to $P < 0.05$ to give maximum sensitivity and to avoid Type II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters such that the final expected number of Type I error clusters was <1 per whole brain. Thus, an expected cluster-level Type I error rate of <1 per brain was achieved by first applying a voxel-level threshold of $P < 0.05$, followed by thresholding the 3D clusters formed from the voxels that survived this initial step at a cluster-level threshold of $P < 0.01$. The cluster-level threshold of $P < 0.01$ was therefore not applied to the whole brain (which would be lenient), but rather to the data previously thresholded at a voxel-wise level of $P < 0.05$. The necessary combination of voxel- and cluster-level thresholds is not assumed from theory but rather determined by direct permutation for each data set. In large connected clusters, we identified local maxima that were farther apart than the upper bound of the likely Talairach mapping error (3 voxel radius: 10 mm; Thirion et al. 2007). Voxels were then assigned to the nearest local maximum with a statistical value that exceeded that of the voxels. A cluster mass rather than a cluster extent threshold was used, to minimize discrimination against possible small, strongly responding foci of activation (Bullmore, Suckling et al. 1999). These combined voxel/cluster tests coupled with permutation testing allow for Type I error control at the cluster level (Bullmore, Brammer et al. 1999; Bullmore, Suckling et al. 1999). Thus, for each analysis, <1 false-positive 3D cluster per map was expected at a P-value of <0.05 at the voxel level and <0.005 at the cluster level.

Statistical Analysis

For between-group comparisons, 3 ANOVAs were conducted comparing controls with patients under 1) placebo; 2) MPX; and 3) ATX. We were particularly interested in whether each drug would upregulate brain regions that were abnormally functioning in ADHD patients. For this purpose, to assess potential upregulation effects of either drug on brain regions that were impaired in ADHD patients, we created a mask of those activation clusters that differed between patients under placebo and controls and then conducted a within-patients repeated-measures ANOVA (drug condition: Placebo, MPX, ATX). Then statistical measures of the BOLD response were extracted for each participant in each of the clusters of within-group drug effects, and post hoc analyses were conducted to clarify the direction of these effects. To rule out the potential effects of training in the task on brain activation, repeated-measures ANOVAs on the extracted BOLD response measures were conducted within patients to test for potential scan-order effects. To assess whether brain regions, other than those that were abnormally functioning in ADHD patients relative to controls, were modulated by each drug, we also performed a whole-brain within-patients repeated-measures ANOVA (drug condition: Placebo, MPX, and ATX) at a stringent $P < 0.001$, allowing <1 error clusters.

Performance Data Analysis

Multiple univariate ANOVAs were conducted between controls and patients under each drug condition (separately) in the main performance variables: The stop-signal reaction time (SSRT), calculated by subtracting the mean stop-signal delay (SSD: Average time between the go- and stop-signal, at which the subject inhibited 50% of stop trials) from the mean reaction time (MRT) to go trials, that is, MRT − SSD (Rubia et al. 2003, 2005, 2008; Rubia, Smith, Taylor et al. 2007). Measures of the go process of the task are the MRT to go trials and intra-subject standard deviation (SD) of the MRT (SD of MRT). Repeated-measures ANOVAs were conducted within patients to test for drug-condition effects (placebo, MPX, and ATX) and for potential scan-order effects.

Results

Task Performance

There were no between-groups differences in the probability of inhibition ($F_{3,82} = 1.25$, $P < 0.3$), demonstrating that the tracking algorithm was successful (Table 2). There were no significant performance differences between controls and patients under placebo. Patients under MPX showed a significantly shorter SSRT than controls ($F_{1,46} = 5.32$, $P < 0.026$). Under ATX, patients relative to controls showed a reduced MRT to go trials ($F_{1,46} = 5.04$, $P < 0.03$; Table 2).

Within-patients repeated-measures ANOVA showed a significant drug-condition effect on MRT to go trials ($F_{2,36} = 3.28$, $P < 0.049$), which was significantly reduced when patients were under ATX compared with placebo ($P < 0.009$; Table 2). No significant differences in SSRTs were observed within patients under the different drug conditions. There were no scan order effects within patients.

Brain Activation

Motion

A multivariate ANOVA showed no significant differences between controls and patients under each drug condition in the extent of maximum rotation and translation movement parameters in the 3D Euclidean space ($F_{6,164} = 1.56$, $P = 0.16$).

Brain Activation Within Groups

Brain activation within each group for the contrast of successful stop relative to successful go trials is shown in Figure 2 and Supplementary Table 1.

Healthy boys showed activation in the bilateral VLPFC and premotor cortex, ACC extending to the SMA, left and right medial frontal cortex, putamen, thalamus and subthalamic nuclei, inferior and superior temporal and parietal cortices, and in the posterior cingulate, occipital cortex, and cerebellum.

Boys with ADHD under placebo showed activation in similar but less extensive bilateral VLPFC and premotor regions, insula, ACC/SMA, superior temporal, inferior and superior parietal regions, right putamen, right inferior and medial temporal regions, occipital and parahippocampal cortices, and in the cerebellum.

The group of ADHD boys under MPX showed activation in bilateral VLPFC, premotor regions, ACC, putamen, thalamus, posterior cingulate gyrus, medial and superior temporal cortices, inferior and superior parietal lobes, occipital cortices (including parahippocampal gyrus), and cerebellum.

When under ATX, boys with ADHD showed activation in the right medial and superior frontal areas, bilateral VLPFC, premotor regions, ACC/SMA, putamen, thalamus and subthalamic nuclei, posterior cingulate, medial and superior temporal regions, inferior and superior parietal cortices, occipital gyri, and cerebellum.

ANOVA Comparisons Between Controls and ADHD Boys Under Each Drug Condition

Controls Compared with ADHD Patients Under Placebo

Compared with healthy controls, ADHD boys showed under-activation in the left and right VLPFC, left middle temporal gyri (MTG)/inferior temporal gyri, and reaching into the inferior parietal lobe (IPL) and right anterior cerebellum/fusiform gyrus (Table 3, Fig. 3).

Patients showed enhanced activation compared with controls in a cluster comprising left posterior cerebellum/posterior cingulate gyrus (PCC), in the right STG, and reaching into the posterior insula and putamen (Table 3; Fig. 3). Given prior evidence for enhanced posterior cerebellum/PCC activation in ADHD patients to compensate for reduced VLPFC activation (Rubia, Smith et al. 2009; Cubillo et al. 2012), we used 1-tailed Pearson correlations within patients on the BOLD response in these two enhanced activation clusters to test whether they were negatively correlated with the reduced VLPFC clusters. Only activation in the right STG–putamen, but not the cerebellum, was negatively correlated with that of the left VLPFC ($r = -0.39$, $P < 0.05$).

To test whether areas of group differences were associated with inhibitory function, 1-tailed Pearson correlations were performed between BOLD responses in these regions and SSRTs within each group. Within healthy boys, the enhanced activation in the right cerebellum correlated with a shorter SSRT ($r = -0.45$, $P < 0.007$). Within patients, the (enhanced) activation in the right STG–putamen was negatively correlated with the SSRT ($r = -0.41$, $P < 0.04$).

Controls Compared with ADHD Patients Under MPX

ADHD boys under methylphenidate compared with controls showed reduced activation in the same left MTG cluster (Table 3; Fig. 3). All other previously reduced activation clusters were no longer observed.

Patients under MPX showed enhanced activation compared with healthy boys in 3 clusters: 1) bilateral occipital cortex, PCC, and precuneus, 2) left occipital cortex and cerebellum, and 3) left occipital and MTG/IPL (Table 3; Fig. 3).

Within patients, enhanced activation in the left cerebellum was negatively correlated with the SSRT ($r = -0.44$, $P < 0.03$).


Table 2

Performance data for 29 healthy control boys and 19 boys with ADHD under each medication condition

Performance variable	Controls mean (SD)	ADHD placebo mean (SD)	ADHD MPX mean (SD)	ADHD ATX mean (SD)
Pi (%)	51 (3)	51 (4)	53 (4)	53 (10)
MRT go trials (ms)	615 (117)	592 (77)	576 (79)	548 (71)
SD go trials (ms)	163 (56)	166 (50)	152 (42)	155 (65)
SSRT (ms)	165 (103)	126 (82)	93 (110)	133 (121)

Note: Pi = probability of inhibition; MRT = mean reaction time. SD = intrasubject standard deviation; SSRT = stop-signal reaction time.
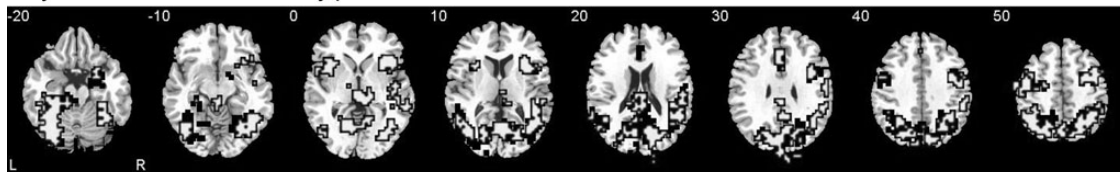
Within-group activations
Successful inhibition – go trials contrast
Healthy controls
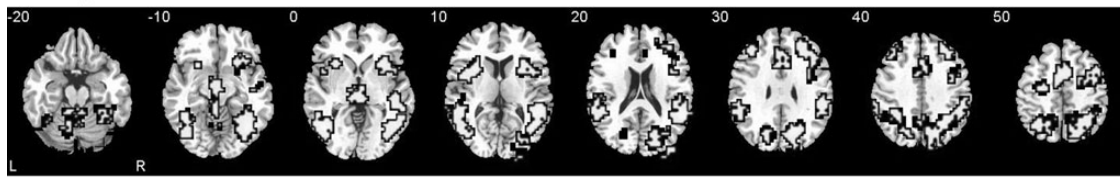
Boys with ADHD under placebo
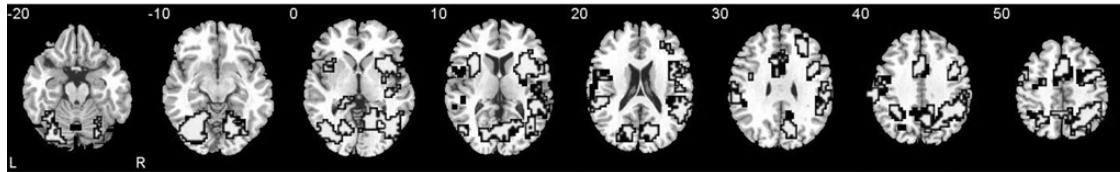
Boys with ADHD under methylphenidate
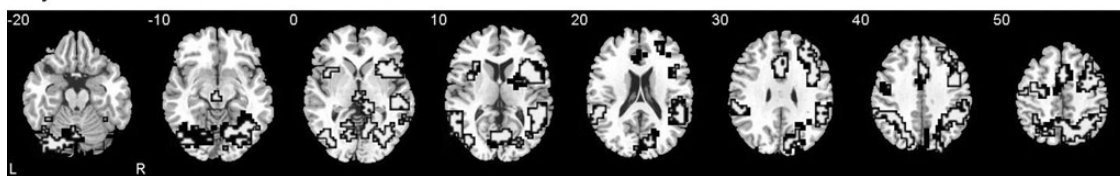
Boys with ADHD under atomoxetine

Figure 2. Within-group activation for healthy control boys and boys with ADHD under either placebo, MPX, or ATX. Axial sections showing within-group brain activation for the healthy control boys and boys with ADHD under each condition (placebo, MPH, and ATX) for the contrast Successful inhibition—go trials. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

Table 3
ANOVAs comparing controls and ADHD patients under each drug condition during successful motor response inhibition in the stop task

Subject contrast	Brain regions of activation	Brodman area (BA)	Peak Talairach coordinates (x, y, z)	N. of voxels	Cluster P-value	Cohen's d
C > ADHD placebo	R ventrolateral prefrontal cortex	47/11	32, 30, −10	156	0.009	0.67
	L ventrolateral prefrontal cortex	45/47	−22, 33, −13	110	0.01	1.16
	L middle/inferior/temporal/parietal gyri	21/37/22/40	−43, −52, 0	287	0.002	1.22
	R cerebellum/fusiform gyrus	36/37	36, −59, −10	97	0.01	1.06
ADHD placebo > C	L cerebellum/R + L posterior cingulate/occipital gyri	29/30/31/18/19	−25, −70, −16	637	<0.001	1.00
	R superior temporal/postcentral gyri/posterior insula/putamen	42/22/21/4	47, −15, 7	190	0.008	1.03
C > ADHD MPX	L middle temporal gyrus	21/37	−40, −59, −3	108	0.005	0.91
ADHD MPX > C	L cerebellum/parahippocampus/occipital gyri	36/37	−29, −37, −26	201	0.005	1.18
	L occipital/middle temporal/precuneus	39/22/40/7/19	−32, −70, 27	243	0.003	0.50
	L + R occipital gyri/posterior cingulate/precuneus	23/29/30/31/7/18/19	−11, −52, −3	624	<0.001	1.19
C > ADHD ATX	L middle temporal gyrus	21/37	−40, −56, −7	156	0.003	1.23
ADHD ATX > C	Nil					

Note: N voxels = number of voxels. L = left; R = right; the maps are thresholded to give less than 1 Type I error 3D cluster per map. Talairach coordinates, number of voxels, and areas are included underneath the corresponding cluster. Although both drugs normalized underactivation in the left and right VLPFC and cerebellum, rigorous effect size comparisons testing for normalization effects showed that the normalization was significant for both drugs in the left VLPFC but only significant for MPX and not ATX in the right VLPFC and cerebellum.

Within controls, there were no significant associations between brain activation and the SSRT.

Controls Compared with ADHD Patients Under ATX

After a single dose of ATX, patients relative to controls showed reduced activation in the same left MTG cluster and, as with MPX, all other previously reduced activation clusters were no longer observed (Table 3; Fig. 3). There were no areas of enhanced activation in patients and no significant associations between brain activation and SSRT within patients or controls.

Although covariation for IQ in nonrandomly selected groups violates the ANCOVA assumption (Miller and Chapman 2001; Dennis et al. 2009), and hence we do present noncovaried findings, we nevertheless wanted to assess the potential impact of IQ on group differences in brain
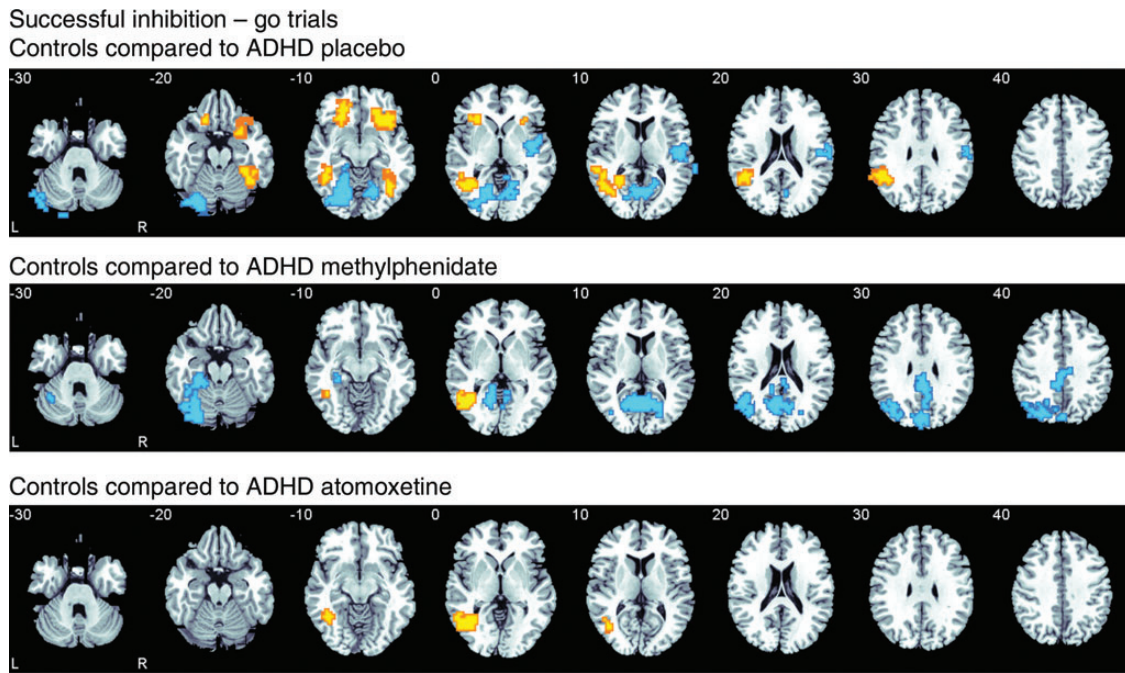
Figure 3. Between-group ANOVA comparisons between healthy control boys and boys with ADHD under placebo, MPX, or ATX. Axial sections showing the ANOVA between-group differences in brain activation between healthy control boys and boys with ADHD under each drug condition (placebo, MPX, and ATX) during successful inhibition in the stop task. Although both drugs normalized underactivation in the left and right VLPFC and cerebellum, rigorous effect size comparisons testing for normalization effects showed that the normalization was significant for both drugs in the left VLPFC, but only significant for MPX and not significant for ATX in the right VLPFC and cerebellum. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

activation. For this purpose, all case–control ANOVAs were repeated with IQ as a covariate. All findings remained significant at a more lenient P-value ($P < 0.03$).

Effect Size Comparisons of Case–Control Conditions to Test for Significant "Normalization" Effects

To establish whether the group differences between controls and patients under each drug condition were significantly different, we directly compared the effect sizes of the group differences from the 3 case–control comparisons (Matthews and Altman 1996). We used a rigorous effect size comparison test of normalization, which is necessary to avoid spurious results. For example, it could be that differences between cases and controls are no longer observed, simply because the underactivation is below the statistical threshold, spurious, or underpowered. This effect size comparison procedure was also used to test for the significance of the upregulation effects of MPX on the two brain activation clusters that were significantly enhanced under MPX relative to controls. When comparing two effect sizes, the z-test can evaluate the likelihood of whether they are significantly heterogeneous. The difference between the two effect sizes can be considered a normalized variable, where the standard error of the difference is a combination of the standard errors of the two comparisons. Based upon this, the probability of a Type I error can be calculated using the formula

$$ p(\alpha) = \frac{(es_1 - es_2)}{\sqrt{(se_1^2 + se_2^2)}}. $$

The z-test showed that the effect sizes differed significantly between all case–control contrasts in the left VLPFC, so that the "normalization effect" of this underactivation under placebo was significant for both drug conditions ($P < 0.03$). In the right VLPFC, the normalization effect was significant for the comparison between the case–control comparison effect size under MPX relative to the case–control comparison effect size under placebo ($P < 0.02$) and relative to the effect size of the case–control comparison under ATX ($P < 0.05$), while the case–control comparison under ATX did not differ in effect size from that under placebo, suggesting that only MPX had a significant and drug-specific normalization effect on this region. For the right cerebellum, only the case–control contrast under MPX showed a significant difference in effect size relative to the case–control comparison under placebo ($P < 0.04$), while the ATX case–control comparison relative to the placebo case–control comparison only showed a trend for differing in effect sizes ($P < 0.1$; Table 4).

ANOVA Within-Patients Comparison Between Placebo, MPX, and ATX Conditions

Within-group effects of each drug were tested in region of interests (ROIs) that differed between ADHD patients under placebo and controls to assess whether each drug would upregulate the areas that are abnormally functioning in ADHD patients. There was a main effect of drug condition within patients in a cluster in the right VLPFC, reaching into STG (11 voxels, peak Talairach coordinates [x, y, z]: 29, 7, −26; Brodman area [BA] 47/38; $P < 0.037$), which was significantly enhanced in patients under MPX compared with ATX ($P < 0.008$) and placebo ($P < 0.002$), the latter of which did not differ between each other ($P < 0.73$; Fig. 4).

Furthermore, activation in this cluster was negatively correlated with the SSRT only when patients were under MPX ($r = -0.37$, $P < 0.05$). There were no scan-order effects on brain activation. To assess whether other areas that were not

Cluster	BOLD signal	Comparison	z-value	P-value
R VLPFC	Controls: 0.0100	C-placebo C-MPX	−2.09411	0.018
	ADHD placebo: −0.0072	C-placebo C-ATX	−0.85536	0.20
	ADHD MPX: 0.0129	C-MPX	1.61795	0.05
	ADHD ATX: 0.00007	C-ATX		
L VLPFC	Controls: 0.0052	C-placebo C-MPX	−2.43858	0.01
	ADHD placebo: −0.0227	C-placebo C-ATX	−1.89561	0.03
	ADHD MPX: 0.0008	C-MPX	0.59397	0.28
	ADHD ATX: −0.0048	C-ATX		
R CB-OCC	Controls: 0.0330	C-placebo C-MPX	−1.7201	0.04
	ADHD placebo: −0.0007	C-Placebo C-ATX	−1.29872	0.1
	ADHD MPX: 0.0244	C-MPX	0.47343	0.32
	ADHD ATX: 0.0174	C-ATX		
L premotor/basal ganglia	Controls: 0.0018	C-placebo C-MPX	2.227558	0.01
	ADHD placebo: −0.0013	C-placebo C-ATX	−0.23371	0.40
	ADHD MPX: −0.03101	C-MPX	−2.27584	0.01
	ADHD ATX: 0.0017	C-ATX		
SMA/ACC	Controls: 0.0159	C-placebo C-MPX	2.929462	0.002
	ADHD placebo: 0.0359	C-placebo C-ATX	0.556187	0.29
	ADHD MPX: −0.0232	C-MPX	−2.39568	0.008
	ADHD ATX: 0.02464	C-ATX		

Note: C = healthy control boys; placebo = ADHD boys under placebo; MPX = ADHD boys under MPX; ATX = ADHD boys under ATX; R = right; L = left; VLPFC = ventrolateral prefrontal cortex; OCC-CB = occipito-cerebellum; SMA = supplementary motor area; ACC = anterior cingulate gyrus; BOLD = blood oxygen level-dependent.
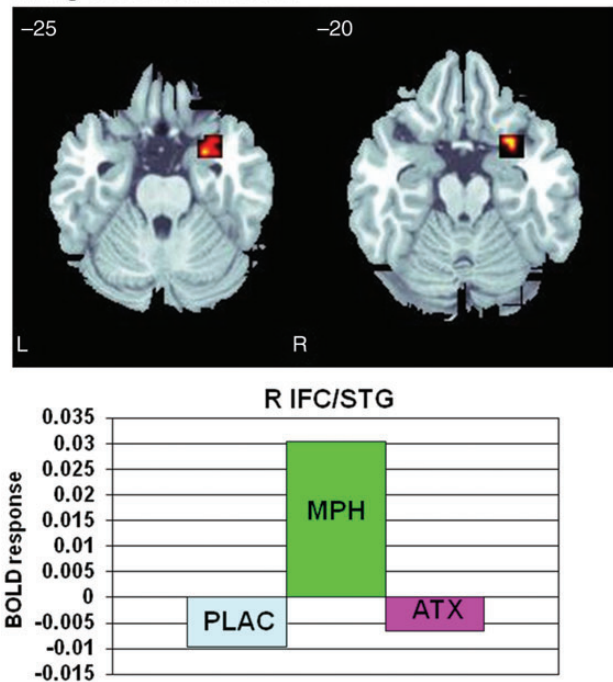

Figure 4. Results of the repeated-measures ANOVA analysis on drug effect within ADHD boys. Axial sections showing the repeated-measures ANOVA results for the drug effect within ADHD patients (placebo, MPX, and ATX). Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

dysfunctional in ADHD were also upregulated with either drug, we also conducted a whole-brain within-patients ANOVA. The whole-brain analysis showed a cluster in the right inferior parietal/superior temporal lobe (Talairach coordinates [x, y, z]: 46, −37, 9; $P < 0.001$) which was due to the fact that it was enhanced under ATX relative to placebo ($P < 0.05$), but not relative to MPH (Supplementary Fig. 1).

Inverse Contrast of Go–Successful Stop

No differences were observed between controls and patients under placebo or under ATX for the inverse contrast of go–successful stop trials. However, patients under MPX showed enhanced activation in the left insula/VLPFC and premotor cortex, reaching into caudate, putamen, and globus pallidus (187 voxels, peak Talairach coordinates [x, y, z]: −25, 19, 13; BA 45/6; $P < 0.006$), and also in ACC/SMA (162 voxels, peak Talairach coordinates (x, y, z): 4, 11, 43; BA 6/24/32; $P < 0.003$; Fig. 5).

There were no scan-order effects on brain activation or correlations with performance. There were significant differences in effect sizes for both clusters for the MPX case–control contrast relative to the placebo case–control comparison ($P < 0.01$) and relative to the ATX case–control comparison ($P < 0.01$).

Discussion

The study shows both shared and drug-specific normalization and upregulation effects on inhibitory brain regions in ADHD patients. ADHD relative to control boys showed no performance deficits but significantly improved in their inhibitory capacity relative to controls under MPX. Under placebo, patients had reduced activation in left and right VLPFC, left MTG, and right cerebellum. Within patients, MPX relative to ATX and placebo significantly upregulated right VLPFC/STG activation which was furthermore associated with improved inhibitory performance, which exceeded that of controls under this drug condition. Rigorous testing for shared or drug-specific differences in normalization effects using effect size comparisons of case–control differences under each drug showed that relative to controls, both drugs significantly normalized the left VLPFC underactivation that was observed under placebo. However, MPX showed a drug-specific normalization effect relative to ATX of significantly normalizing the right VLPFC and right cerebellar underactivations that were present under placebo.

The underactivation in ADHD patients in key areas of motor response inhibition in the right and left VLPFC and in parieto-temporal regions is in line with previous findings (Rubia et al. 1999, 2005, 2008, 2010; Epstein et al. 2007; Rubia 2011; Cubillo et al. 2012). The right VLPFC, together with the pre-SMA, is a key area of motor response inhibition in adolescents and adults, as has consistently been shown in lesion, fMRI and transcranial magnetic stimulation studies (Aron et al. 2003, 2004, 2007; Rubia et al. 2003; Aron and Poldrack 2006; Chambers et al. 2006, 2009; Chevrier et al. 2007; Rubia, Smith, Taylor et al. 2007; Goghari and MacDonald 2009), although recent fMRI evidence has argued for a more prominent role of the right VLPFC for attentional capture

Go – Successful inhibition trials
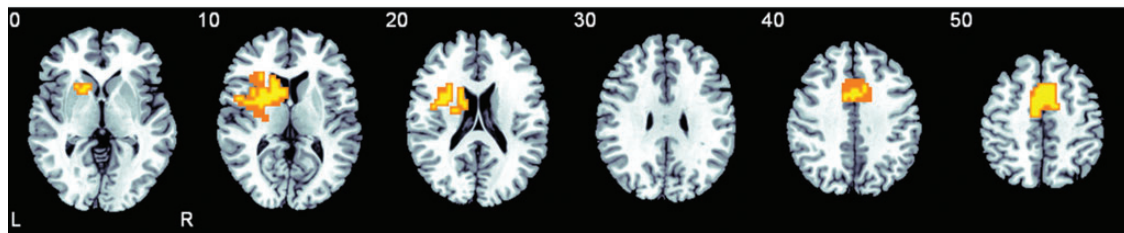ADHD methylphenidate > controls

Figure 5. Between-group ANOVA comparison between healthy control boys and boys with ADHD under MPX for the contrast of go–successful inhibition trials. Axial sections showing the ANOVA between-group difference effects in brain activation between healthy control boys and boys with ADHD under MPX. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.

rather than inhibition itself (Sharp et al. 2010; Pauls et al. forthcoming 2012). The left VLPFC forms also part of the inhibition network (Nee et al. 2007; Swick et al. 2008), but has been suggested to mediate performance monitoring, necessary for correct inhibitory task performance (Derrfuss et al. 2005; Stevens et al. 2009). Although less commonly reported, the cerebellum is also typically activated in the stop task in healthy adolescents and adults and correlated with the SSRT (Rubia, Smith, Taylor et al. 2007), which was also observed in this study. The finding of cerebellar underactivation replicates a previous finding of cerebellar underactivation during the stop task in ADHD children (Rubia, Halari, Mohammad et al. 2011). The enhanced activation in patients under placebo relative to controls in the right STG–putamen and the left cerebellum/occipital cortex was likely compensatory, as suggested by the negative association of STG–putamen activation with inhibitory capacity and with the (reduced) left VLPFC activation. This compensatory enhanced activation in STG that is considered a part of the inferior frontal–superior temporal junction that mediates inhibition (Rubia et al. 2003; Rubia, Smith, Taylor et al. 2007; Chambers et al. 2009) may have prevented patients from inhibitory impairment in the task.

Only MPX significantly normalized the right VLPFC and cerebellar underactivations in ADHD boys relative to controls that were observed under both placebo and ATX. The normalization effect was, furthermore, drug-specific relative to the effects of ATX. The findings suggest a drug-specific effect of MPX on normalizing abnormal activation in ADHD patients in key inhibition areas of the inferior frontal cortex and cerebellum. This was further confirmed by the within-subject effect, which showed that MPX upregulated right VLPFC activation relative to ATX and placebo. The upregulated right VLPFC activation cluster was, furthermore, associated with better inhibitory capacity in patients, which even exceeded that of controls under MPX. The underactivated cerebellar cluster that was normalized with MPX was also associated with inhibitory performance, albeit in controls. Together, the findings suggest that MPX had a drug-specific effect relative to ATX on key inhibitory performance-correlated regions within an established right VLPFC–striato-cerebellar network for motor response inhibition (Rubia, Smith, Taylor et al. 2007). Thus, the findings extend previous normalization and upregulation findings with MPX in these fronto-striato-cerebellar areas during inhibition tasks in children with ADHD (Vaidya et al. 1998; Epstein et al. 2007; Rubia, Halari, Cubillo et al. 2011; Rubia, Halari, Mohammad et al. 2011) by showing for

the first time that these effects are drug-specific relative to ATX.

The shared normalization findings of ATX and MPX in left VLPFC underactivation are interesting and extend, for the first time, previous findings of the upregulation of right (Chamberlain et al. 2009) and bilateral VLPFC (Graf et al. 2011) with ATX in healthy adults during motor inhibition tasks to adolescents with ADHD. Left lateralized effects may suggest stronger effects of ATX on performance monitoring (Derrfuss et al. 2005; Stevens et al. 2009) rather than inhibition per se. Alternatively, considering that ATX typically takes longer to show behavioral effects than MPX (Montoya et al. 2009), longer-term administration may have resulted in significant effect size differences relative to placebo for the below-threshold normalized right VLPFC and cerebellar underactivations, which in the cerebellum reached a trend level of significance. Future studies will have to compare long-term administration of both drugs to elucidate this question. ATX, however, in the whole-brain analysis of within-patient drug effects, enhanced activation in a cluster in the right superior temporal/inferior parietal junction, although this effect was not drug-specific, but only survived significance compared with placebo. The upregulation findings in the temporo-parietal junction with ATX in ADHD extend findings of the increase in right superior temporal lobe activation with ATX in healthy adults (Chamberlain et al. 2009). The right parieto-temporal junction is a key region for visual-spatial attention (Corbetta and Shulman 2002; Downar et al. 2002; Behrmann et al. 2004; Weissman and Woldorff 2005) and its activation may reflect task-related cognitive attention processes necessary for the detection of the relevant/salient stimuli, in this case the stop stimuli (Berridge and Waterhouse 2003; Aston-Jones and Cohen 2005). The temporo-parietal junction is commonly reported to be abnormal in ADHD children and adults during attention and inhibition tasks (Smith et al. 2006; Tamm et al. 2006; Epstein et al. 2007; Rubia, Smith, Brammer et al. 2007; Stevens et al. 2007; Rubia, Halari, Cubillo et al. 2009; Rubia et al. 2010; Rubia, Halari, Mohammad et al. 2011; Cubillo et al. 2012). Our finding of an upregulation effect of ATX in this region may thus suggest a stronger effect of ATX on attention rather than inhibition networks, which could be a reflection of an impact of ATX on right-lateralized noradrenergically mediated attention networks (Tucker and Williamson 1984).

Interestingly, MPX, in addition, showed a drug-specific upregulation effect during the executive go process of the task in key regions for response selection and motor execution in ACC/SMA, left premotor cortex, and basal ganglia (Haber

2003). Together, the findings thus suggest that MPX upregulates and normalizes right-lateralized VLPFC–cerebellar motor inhibition networks as well as medial fronto-striatal circuits of motor response execution.

While there were no performance differences between patients under placebo and healthy controls, boys with ADHD were significantly better in their inhibitory capacity relative to controls when under MPX. Although acute MPH administration reduced the SSRT slightly within patients, this did not reach significance. The finding of no significant effects of MPH on the SSRT is in line with previous fMRI studies using the stop task in ADHD patients (Rubia, Halari, Mohammad et al. 2011) and healthy adults (Pauls et al. forthcoming 2012), or in healthy adults during the go/no-go task (Costa et al. forthcoming 2012). fMRI stop task designs, however, lose behavioral sensitivity over neuropsychological task versions. This is due to the fact that stop stimuli are more predictable, given that they need to be separated by at least 3 trials, and cannot be consecutive, to allow for the separation of hemodynamic response curves. Furthermore, while fMRI studies in 20 subjects for each group are sufficiently powered for fMRI analysis (Thirion et al. 2007), they are underpowered for behavioral analyses. In fact in larger numbered neuropsychological studies, single doses of MPX have shown to improve inhibitory performance in children with ADHD (Tannock et al. 1989; Bedard et al. 2003; Scheres et al. 2003; Konrad et al. 2004; Lijffijt et al. 2006; DeVito et al. 2009) and in healthy adults (Nandam et al. 2011). Although restrictions in fMRI task design may have contributed to the lack of significant effects of the drugs on performance within patients, MPX nevertheless significantly improved inhibitory performance in children with ADHD relative to that of the healthy control group, suggesting it did have a positive impact on the SSRT. The stronger effects of MPH on inhibitory brain function than inhibitory performance is in line with prior evidence, showing that brain activation is more sensitive to the effects of stimulant medication than behavior during inhibitory and related cognitive tasks (Shafritz et al. 2004; Konrad et al. 2007; Peterson et al. 2009; Rubia, Halari, Christakou et al. 2009; Rubia, Halari, Cubillo et al. 2009; Rubia, Halari, Cubillo et al. 2011; Rubia, Halari, Mohammad et al. 2011). Thus, the normalization effects on key inhibitory activation areas after a single dose of MPX may have accounted for their relative improvement on inhibitory performance compared with healthy controls. This is further reinforced by the finding that activation in the right VLPFC was negatively correlated with the SSRT only when patients were under MPX.

A strength of this study is the double-blind, placebo-controlled crossover design in exclusively medication-naive boys with combined-type ADHD, thus testing a homogeneous sample and avoiding the potential confound of previous stimulant medication history, known to confound brain structure and function deficits (Konrad et al. 2007; Nakao et al. 2011; Frodl and Skokauskas 2012). A limitation is that ADHD boys performed the task 3 times, while, for financial and ethical reasons, controls were scanned only once. However, the lack of practice effects within patients suggests that these unlikely confounded the between-groups analyses. Another limitation is the single-dose administration. While MPX has immediate effects on behavior (Greenhill et al. 2001), ATX reaches its maximum behavioral efficacy at about 12 weeks (Montoya et al. 2009). Consequently, a single-dose

comparison may have favored MPX. The investigation of acute mechanisms of action, however, is a first step toward improving our understanding of drug-specific effects on brain activation and cognition, and has the advantage of avoiding potential confounds of long-term treatment such as symptomatic improvement, side effects, or chronic effects on brain activation. Nevertheless, future studies should compare long-term effects of both drugs on brain activation after reaching maximum clinical efficacy. Lastly, the findings are only generalizable to right-handed male adolescents with combined-type ADHD and may not apply to other ADHD subtypes, female or left-handed patients.

To summarize, the findings show shared effects of both drugs in normalizing left VLPFC activation deficits in ADHD patients, presumably mediating performance monitoring. MPX, however, had drug-specific upregulation and normalization effects in the right VLPFC, which, furthermore, was associated with improved inhibitory performance in ADHD patients relative to controls, as well as of normalizing cerebellum dysfunction. In addition, MPX not only upregulated fronto-cerebellar areas of inhibitory control, but also fronto-striatal regions mediating the executive go process of the task. While the findings need to be replicated in longer-term administration of both drugs, they point toward potentially superior effects of MPX on alleviating abnormalities in inhibitory neural networks in ADHD.

Supplementary Material

Supplementary material can be found at: http://www.cercor. oxfordjournals.org/.

Notes

Conflict of Interest: K.R. has received speaker's honoraria from Shire, Novartis, and Medice and Lilly.

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