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ORIGINAL ARTICLE

The effects of acute fluoxetine administration on temporal discounting in youth with ADHD

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Background. Serotonin is under-researched in attention deficit hyperactivity disorder (ADHD), despite accumulating evidence for its involvement in impulsiveness and the disorder. Serotonin further modulates temporal discounting (TD), which is typically abnormal in ADHD relative to healthy subjects, underpinned by reduced fronto-striato-limbic activation. This study tested whether a single acute dose of the selective serotonin reuptake inhibitor (SSRI) fluoxetine up-regulates and normalizes reduced fronto-striato-limbic neurofunctional activation in ADHD during TD.

Method. Twelve boys with ADHD were scanned twice in a placebo-controlled randomized design under either fluoxetine (between 8 and 15 mg, titrated to weight) or placebo while performing an individually adjusted functional magnetic resonance imaging TD task. Twenty healthy controls were scanned once. Brain activation was compared in patients under either drug condition and compared to controls to test for normalization effects.

Results. Repeated-measures whole-brain analysis in patients revealed significant up-regulation with fluoxetine in a large cluster comprising right inferior frontal cortex, insula, premotor cortex and basal ganglia, which further correlated trend-wise with TD performance, which was impaired relative to controls under placebo, but normalized under fluoxetine. Fluoxetine further down-regulated default mode areas of posterior cingulate and precuneus. Comparisons between controls and patients under either drug condition revealed normalization with fluoxetine in right premotor-insular-parietal activation, which was reduced in patients under placebo.

Conclusions. The findings show that a serotonin agonist up-regulates activation in typical ADHD dysfunctional areas in right inferior frontal cortex, insula and striatum as well as down-regulating default mode network regions in the context of impulsivity and TD.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is defined as age-inappropriate inattention and/or hyperactivity/impulsiveness (APA, 2013). It is one of the most common neurodevelopmental disorders with around 5% prevalence worldwide (Polanczyk *et al.* 2014). ADHD patients have deficits in executive functions (EF) such as inhibition, attention and working memory (Willcutt *et al.* 2008), underpinned by abnormalities in fronto-striatal, fronto-temporo-parietal and fronto-cerebellar networks (Hart *et al.* 2012, 2013; Rubia *et al.* 2014*a*). Moreover, they have deficits in timing functions (Noreika *et al.* 2013) and in 'hot' EF, referring to EF involving motivation and affect such as reward-related decision-making (Kerr & Zelazo, 2004), as measured by temporal discounting (TD) and gambling tasks (Rubia *et al.* 2009; Noreika *et al.* 2013). Nonetheless, there is heterogeneity in cognitive impairments, with some patients not showing impairments or only in some cognitive domains which are likely underpinned by different pathophysiological pathways (Sonuga-Barke, 2003; Nigg *et al.* 2005; Sonuga-Barke *et al.* 2010).

TD tasks require choices between small immediate and larger delayed rewards and measure the extent to which a reward is subjectively discounted when delayed in time, i.e. the sensitivity to temporal delays measured in units of reward (Rubia *et al.* 2009). The

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ability to inhibit immediate rewards and wait for larger future rewards depends on well-developed frontal lobe-mediated motivation control and temporal foresight and is key for mature decision-making. TD matures with age (Christakou *et al.* 2011) and varies between individuals, with steeper TD, i.e. more rapidly decaying rates of reward discounting with increasing time (Richards *et al.* 1999), in more impulsive subjects (Rubia *et al.* 2009; Noreika *et al.* 2013). In individually adjusted TD paradigms (Richards *et al.* 1997; Christakou *et al.* 2011), the immediate reward is adjusted using an algorithm based on previous choices for different delays, converging towards the value of the participant's subjective equivalent of the fixed delayed reward (Richards *et al.* 1999). From this, a typically hyperbolic delay discounting function is calculated, the steepness of which indicates the individual TD rate, which is associated with impulsivity (Richards *et al.* 1999; Critchfield & Kollins, 2001).

ADHD patients are impaired in TD tasks (Noreika *et al.* 2013), with, however, some negative findings, mostly in non-individually adjusted task versions (Sonuga-Barke *et al.* 1992; Scheres *et al.* 2006, 2010). Functional magnetic resonance imaging (fMRI) studies of TD in healthy adults implicate ventromedial-fronto-limbic networks of reward-based decision-making and dorsolateral and inferior-fronto-insula-striato-parietal networks of temporal foresight (Christakou *et al.* 2011; Wesley & Bickel, 2014). Despite documented TD deficits in ADHD, few fMRI studies have investigated its neurofunctional correlates. ADHD adolescents showed underactivation relative to controls during delayed choices in an adjusted fMRI TD task in inferior frontal cortex (IFC), insula, striatal and cerebellar regions (Rubia *et al.* 2009) and significantly weaker correlations between better TD and activation during delayed choices in IFC, superior temporal lobes, insula, supplementary motor area and cerebellum (Chantiluke *et al.* 2014*d*). In adult ADHD, abnormal striato-limbic activation has been observed (Plichta *et al.* 2009).

Neurotransmitters such as serotonin (5-HT) are implicated in ADHD (Oades, 2007, 2008), potentially via modulation of these neural circuits. Converging evidence across methodologies shows that serotonergic systems may be dysfunctional in ADHD (Oades, 2007), with evidence for chemical alterations of 5-HT systems, decreased 5-HT platelet levels (Spivak *et al.* 1999), and increased ADHD-related behaviour after 5-HT depletion in ADHD patients (Zepf *et al.* 2010). Second, there is evidence for an association between 5-HT-related polymorphisms and ADHD (Gizer *et al.* 2009; Rommelse *et al.* 2010) and methylphenidate treatment response (McGough *et al.* 2009). Moreover, the selective serotonin reuptake inhibitor (SSRI) fluoxetine has been shown to be effective in reducing ADHD-related symptoms in children (Barrickman *et al.* 1991; Quintana *et al.* 2007) and to improve the efficacy of stimulants in human and animal studies (Gammon & Brown, 1993; Findling, 1996; Gainetdinov *et al.* 1999). Further, the concurrent administration of 5-HT and dopamine amino-acid precursors can improve ADHD symptoms (Hinz *et al.* 2011). However, replication is needed as these studies are limited by comorbid samples (Quintana *et al.* 2007) and non-randomized trials in small samples (Barrickman *et al.* 1991). Last, in healthy adults, tryptophan depletion, which reduces brain 5-HT by up to 60%, down-regulates activation in key ADHD deficit areas of IFC and basal ganglia (Rubia *et al.* 2005; Lamar *et al.* 2009, 2014), which are up-regulated with 5-HT agonists (Del-Ben *et al.* 2005). 5-HT has also been implicated in reward-based decision-making in healthy adults (Cools *et al.* 2011; Rogers, 2011; Robinson *et al.* 2012), where striatal 5-HT levels have been shown to modulate choices of longer, delayed rewards (Schweighofer *et al.* 2007; Tanaka *et al.* 2007; Doya, 2008).

In conclusion, there is evidence that 5-HT is associated with ADHD, with impulsivity, in particular TD performance, and that it modulates IFC-striatal activation, a key ADHD deficit. Despite this, hardly any fMRI studies have tested the effects of 5-HT agonists on brain function in ADHD. We have previously shown that in ADHD children, the SSRI fluoxetine *v.* placebo up-regulated and normalized IFC-striatal and parietal underactivation during inhibition (Chantiluke *et al.* 2014*a*, *c*), and enhanced the deactivation in default mode network (DMN) regions during working memory (Chantiluke *et al.* 2014*b*).

This study therefore aimed to investigate the effect of a single dose of fluoxetine relative to placebo on brain activation in ADHD adolescents during a TD task. Further, to test for potential normalization effects of fluoxetine on abnormal brain activation in ADHD patients under placebo, we also compared brain activation during both drug conditions to that of healthy adolescents.

Based on previous findings, we hypothesized that ADHD adolescents under placebo would show steeper TD rates (Noreika *et al.* 2013) and reduced IFC-insular-striatal activation during TD (Plichta *et al.* 2009; Rubia *et al.* 2009; Chantiluke *et al.* 2014*d*). Further, based on our fMRI studies showing up-regulation and normalization with fluoxetine in task-relevant regions during related tasks of cognitive control in ADHD (Chantiluke *et al.* 2014*a*–*c*), and evidence for 5-HT modulation of IFC-striatal regions in healthy adults (Rubia *et al.* 2005; Lamar *et al.* 2009), we hypothesized that fluoxetine would up-regulate IFC-insula-striato-parietal activation in patients and normalize regional underactivation relative to controls.

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Method

Participants

Thirty-two right-handed (Oldfield, 1971) boys with ($N = 12$) and without ADHD ($N = 20$) were recruited from local clinics and support groups, aged 11–17 years, with IQ⩾70 measured by the Wechsler Abbreviated Scale of Intelligence – Revised (WASI-R) short form (Wechsler, 1999). ADHD boys had a clinical DSM-IV diagnosis of non-comorbid ADHD, inattentive/hyperactive-impulsive combined subtype, assessed using the standardized Maudsley diagnostic interview (Goldberg & Murray, 2006). Patients scored above clinical threshold for ADHD symptoms on the Strengths and Difficulties Questionnaire (SDQ; Goodman & Scott, 1999) and Conner's Parent Rating Scale – Revised (CPRS-R; Conners *et al.* 1998). They also scored below clinical threshold for autistic spectrum disorders on the Social Communication Questionnaire (SCQ; Rutter *et al.* 2003). Nine ADHD boys were on psychostimulants but withheld medication for 48 h prior to scanning.

Patients were scanned twice in a randomized, double-blind, placebo-controlled design. Due to the half-life of fluoxetine (1–3 days) and its metabolite norfluoxetine (5–16 days) (Wong *et al.* 1995), scans were conducted 3–4 weeks apart. To ensure the fluoxetine dose had reached peak plasma levels (after 5–8 h; Wong *et al.* 1995), patients were scanned 5 h post-administration. Liquid fluoxetine was titrated to age and weight: boys 10–13 years and <30 kg received 8 mg, those >30 kg received 10 mg. Boys 14–17 years and <30 kg received 10 mg, and those >30 kg received 15 mg. Placebo was equivalent volumes of peppermint water, similar in taste and appearance to fluoxetine.

Twenty healthy age and handedness-matched control boys were recruited locally by advertisement and scanned once. Controls scored below clinical threshold on the SDQ, SCQ and CPRS-R and did not have any psychiatric condition.

Exclusion criteria for all participants were neurological disorders, drug/alcohol dependency and MRI contraindications.

Ethical statement

The study was conducted according to the latest version of the Declaration of Helsinki. Ethical approval was obtained from the local Research Ethics Committee. Study details were explained to both child and guardian, and written informed consent was obtained for all participants.

Temporal discounting fMRI paradigm

Prior to the first scan, subjects practised the 12-min task once in a 'mock' scanner. Subjects made a choice, by pressing a left or right button, between receiving a small amount of money immediately (£0–£100) or £100 in 1 week, month or year. Delay choices (20 trials of each delay length) were randomized, but the delayed option was consistently displayed on the right side, and the variable immediate choices on the left side of the screen to minimize potential sensorimotor mapping effects. Choices were displayed for 4 s, followed by a blank screen of at least 8 s (inter-trial interval: 12 s). The amount of immediate reward was adjusted through an algorithm based on previous choices which was calculated separately for each of the three delays. This narrows the range of values, converging into an indifference point where the immediate reward is considered by the subject to be equivalent to the delayed amount for the given delay (Rubia *et al.* 2009; Christakou *et al.* 2011). This algorithm ensures equal numbers of immediate and delayed choices to be contrasted in the fMRI analysis.

Analysis of performance data

To estimate the steepness of TD for each subject, the indifference value between the immediate amount and the delayed £100 for each delay was calculated, equivalent to the subject's subjective value of £100 after each delay, and defined as the midpoint between the lowest immediate reward chosen by the subject and the next lowest immediate reward available (i.e. the value of the immediate reward offered at which point the subject began to instead consistently choose the delayed reward) (Rubia *et al.* 2009; Christakou *et al.* 2011).

Reward is typically discounted as a hyperbolic decay function depending on amount, delay and a free impulsiveness indicator k, calculated by fitting a hyperbolic function to the indifference values for each delay (see Supplementary material).

However, the limitations of the fMRI task adaption, i.e. relatively few trials and only three delay points, limit the goodness-of-fit of the data to a nonlinear curve function. In addition, the distribution of k values was not normal, skewed by low-frequency and high-value outliers. Thus, TD was measured using the area under the curve (AUC) which is more appropriate for investigations with quantitative, inferential statistics (Myerson *et al.* 2001). The normalized subjective values of the delayed £100 for each delay were plotted against the normalized delays and AUC of these plots were calculated for each participant, using this obtained value as the main dependent variable. AUC correlated inversely with k values ($r = -0.898$, $p < 0.001$), where smaller AUC values denote steeper discounting rates, indicating increased choice impulsivity.

A repeated-measures within-group analysis of variance (ANOVA) was conducted with patients with

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medication condition (placebo, fluoxetine) as a within-subjects variable to test for medication effects on TD. Two ANOVAs were conducted with group as independent variable and AUC as dependent measure to test for differences in TD performance between controls and ADHD patients on either placebo or fluoxetine. To test for potential main effects of drug administration order and of an interaction between order and drug condition, order was included as a between-subjects factor in the repeated-measures ANOVA.

fMRI image acquisition

Gradient-echo echo-planar MR imaging (EPI) data were acquired at King's College London, Institute of Psychiatry's Centre for Neuroimaging Sciences on a 3-T General Electric Signa HDx MRI scanner (GE Healthcare, UK). For details of scan acquisition, see Supplementary material.

fMRI image analysis

Event-related activation data were acquired in randomized trial presentation and analysed using the non-parametric XBAM software package developed at the Institute of Psychiatry, King's College London (www.brainmap.co.uk; Brammer *et al.* 1997). The individual- and group-level analyses methods are described in detail elsewhere (Brammer *et al.* 1997; Bullmore *et al.* 1999*a*, *b*, 2001; Cubillo *et al.* 2014*b*) and in the Supplementary material.

ANCOVA of within-patient medication effects

To investigate medication effects on brain activation in the ADHD group, a within-group repeated-measures analysis of covariance (ANCOVA) with motion as covariate and medication condition as within-subjects factor was conducted using randomization-based testing for voxel- or cluster-wise differences, as described previously (Bullmore *et al.* 1999*b*, 2001) and in the Supplementary material. Voxel- and cluster-level statistical thresholds were set so as to obtain less than one false positive 3D cluster per map ($p < 0.05$ was used for voxel and $p < 0.005$ for cluster comparisons). The standardized blood oxygen level dependent (BOLD) response values for each participant were extracted for each of the significant clusters of the ANCOVA analyses and plotted to determine the direction of effects. Repeated-measures ANOVAs on the extracted BOLD response measures were conducted in patients to test for potential effects of scan-order and interactions between scan order and drug condition.

ANCOVA of between-group effects

One-way ANCOVAs with group as main factor and motion as covariate were conducted using randomization-based testing to test for case-control differences under placebo or fluoxetine (Bullmore *et al.* 1999*b*, 2001). For these comparisons, $p < 0.05$ (voxel-level) and $p < 0.05$ (cluster-level) were used. Standardized BOLD responses were then extracted from significant clusters for each participant and plotted to determine direction of effects.

Correlations with behaviour and IQ

To examine whether clusters which showed group effects in case-control comparisons were related to IQ or TD, the BOLD response in these clusters was extracted for each participant and Pearson correlations were performed with IQ and AUC in each group (ADHD placebo, ADHD fluoxetine, controls).

Results

Participant characteristics

Univariate ANOVA revealed no significant group differences in age, but IQ, which was lower in ADHD (Table 1). However, since low IQ is associated with ADHD (Bridgett & Walker, 2006), IQ was not covaried as covarying for differences between groups that were not randomly selected violates ANCOVA assumptions (Miller & Chapman, 2001). Nonetheless, to assess potential effects of IQ on case-control comparisons, BOLD responses were correlated with IQ and analyses were repeated covarying for IQ. As expected, patients had significantly lower CPRS-R *t* scores, SDQ and SCQ scores than controls (Table 1).

Performance data

For repeated-measures ANOVA in patients, no significant drug effects were found on AUC ($F_{1,11} = 0.08$, $p =$ N.S.), reaction time (RT) ($F_{1,11} = 0.01$, $p =$ N.S.) or omission errors (OM) ($F_{1,11} = 0.16$, $p =$ N.S.) (see Table 1). Case-control ANOVAs showed no differences in RT or OM, but controls had larger AUC than patients under placebo ($F_{1,30} = 4$, $p < 0.05$) but no longer differed from patients under fluoxetine ($F_{1,30} = 2$, $p =$ N.S.), suggesting that fluoxetine normalized case-control performance differences (see Table 1).

Drug administration order had no main effect on the primary behavioural outcome of AUC in the ADHD group ($F_{1,10} = .07$, $p =$ N.S.) and there was no interaction between scan order and drug condition ($F_{1,10} = 1.31$, $p =$ N.S.).

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Table 1. *Participants' characteristics*

Variables	Controls ($N = 20$) Mean (S.D.)	ADHD ($N = 12$) Mean (S.D.)	F test (df)	p value
Demographic data				
Age (years)	15.29 (1.78)	14.86 (1.71)	0.43 (1,30)	0.52
Handedness	88.4 (16.37)	92.92 (11.48)	0.70 (1,30)	0.41
IQ	118.9 (11.91)	94.5 (7.35)	40.71 (1,30)	<0.001
CPRS-R total T score[a]	48.63 (8.82)	82.83 (7.79)	113.79 (1,26)	<0.001
SCQ total score[b]	2.24 (2.51)	6.58 (3.29)	16.32 (1,27)	<0.001
SDQ total score[c]	4.89 (3.69)	20.75 (4.31)	116.32 (1,28)	<0.001
Performance data		Placebo/fluoxetine		
AUC	0.557 (0.13)	0.440 (0.20)/0.458 (0.23)	–	–
Reaction time (ms)	2141 (591.47)	2354 (578.6)/2306 (381.5)	–	–
Omissions	0.75 (1.83)	1.92 (2.4)/1.58 (2.0)	–	–

S.D., Standard deviations; df, degrees of freedom; CPRS-R, Conner's Parent Rating Scale – Revised; SCQ, Social Communication Questionnaire; SDQ, Strengths and Difficulties Questionnaire; AUC, area under the curve.

[a] CPRS-R total T score could not be obtained for four control participants.

[b] SCQ scores could not be obtained from three control participants.

[c] SDQ scores could not be obtained from two control participants.

fMRI data

Motion

No differences were found for largest head displacement in 3-dimensional space in the ADHD group under each drug condition ($F_{2,10} = 0.51$, $p =$ N.S.). Moreover, no group×displacement interaction was found between controls and ADHD under placebo ($F_{2,29} = 2.63$, $p =$ N.S.) or fluoxetine ($F_{2,29} = 2.54$, $p =$ N.S.). Nevertheless, to exclude potential effects of non-significant motion, motion parameters in 3D Euclidian space were included as covariates in the fMRI analyses.

Group brain activation maps for delayed minus immediate choices

For the contrast of delayed minus immediate choices, controls showed activation in dorsomedial PFC (dmPFC) and anterior cingulate cortex (ACC), insula, pre- and post-central gyri and parieto-occipital and cerebellar regions. ADHD patients on placebo showed activation in ACC, pre- and post-central gyrus, posterior cingulate (PCC), and occipito-cerebellar regions, while under fluoxetine they showed activation in right dorsolateral and inferior PFC (dlPFC/IFC)/insula extending into basal ganglia (BG), ACC, temporo-parietal and occipital cortices and cerebellum (see Supplementary material and Fig. S1).

Within-group differences between ADHD patients on placebo v. *fluoxetine*

Repeated-measures ANCOVA revealed a significant drug effect in a large cluster comprising right IFC, insula, precentral gyrus and superior temporal cortices extending into BG, which was enhanced under fluoxetine relative to placebo (Fig. 1, Table 2). *Post-hoc* calculations in SPSS version 21 (IBM Corp., USA) indicated an observed power of 89% (partial $\eta^2 = 0.53$). Activation in IFC was significantly negatively correlated in the placebo group with AUC ($r = -0.676$, $p < 0.016$). Under fluoxetine, however, the correlation was at a trend-level positive ($r = 0.563$, $p = 0.057$).

Under placebo relative to fluoxetine, patients had enhanced activation during delayed minus immediate choices in two clusters, one comprising bilateral cerebellar hemispheres and vermis, PCC, precuneus and occipital lobe, and the other in left pre- and post-central gyrus, extending into middle frontal gyrus and inferior parietal lobe (IPL) (Fig. 1, Table 2). Further, activation in the cerebellum/PCC/precuneus cluster was negatively correlated with the IFC cluster that was up-regulated under fluoxetine ($r = -0.859$, $p < 0.001$).

Drug administration order had no effect on within-group differences in BOLD response (right IFC: $F_{1,10} = 2.8$, $p =$ N.S.; cerebellum/occipital: $F_{1,10} = 0.40$, $p =$ N.S.; left pre-/post-central gyrus: $F_{1,10} = 0.88$, $p =$ N.S.), and there was no interaction between drug administration order and condition (IFC: $F_{1,10} = 0.07$, $p =$ N.S.; cerebellum/occipital: $F_{1,10} = 0.15$, $p =$ N.S.; left pre-/post-central gyrus: $F_{1,10} = 0.75$, $p =$ N.S.).

Between-group differences

Controls v. *ADHD patients on placebo*

Between-group ANCOVA showed significantly increased activation in controls relative to ADHD under placebo for delayed minus immediate choices

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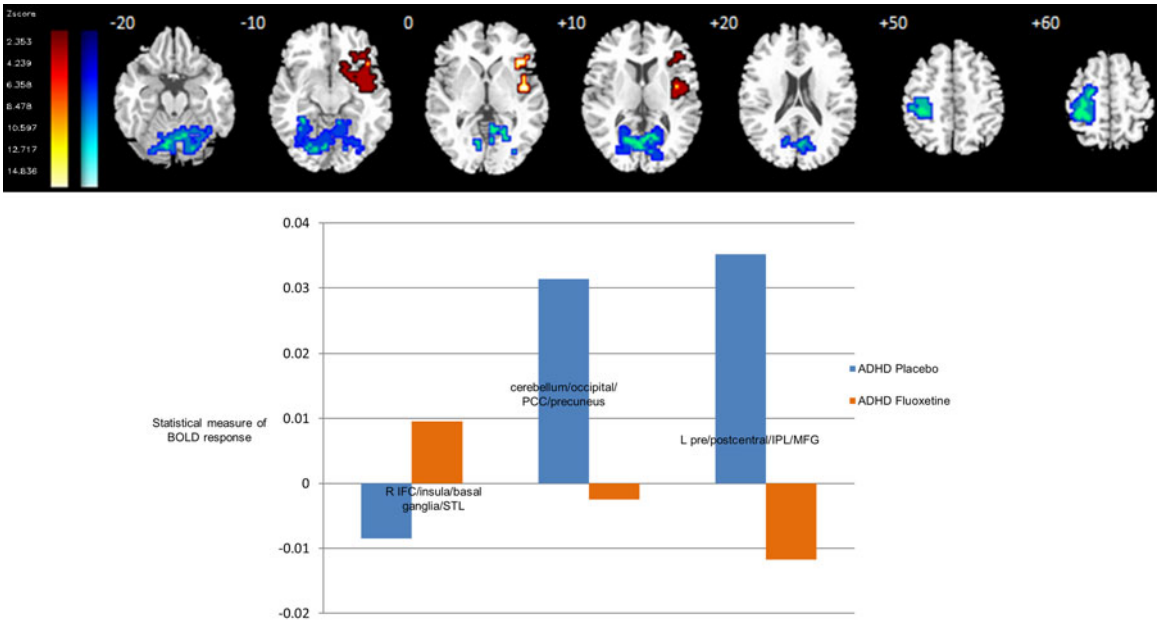

Fig. 1. Within-patient comparisons. Axial sections show medication effects in the ADHD group. Red = fluoxetine > placebo; blue = placebo > fluoxetine. Also shown are the statistical measures of the blood oxygen level-dependent (BOLD) response for each of the brain regions that showed a significant effect of medication in patients. R, Right; L, left; IFC, inferior frontal cortex; STL, superior temporal lobe; PCC, posterior cingulate cortex; IPL, inferior parietal lobe; MFG, middle frontal gyrus. 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 2. *Within-patient comparisons of activation differences for delayed minus immediate choices*

Brain regions of activation difference	Brodmann area (BA)	MNI coordinates (x, y, z)	Voxels	Cluster *p* value	η^2_P
(*a*) ADHD fluoxetine > ADHD placebo					
R IFC/dlPFC/insula/precentral gyrus/STL/putamen/ caudate/globus pallidus	47/10/46/45/6/22	52, 0, −20	107	0.003	0.53
(*b*) ADHD placebo > ADHD fluoxetine					
L + R lateral cerebellum and vermis/occipital lobe/ PCC/precuneus	30/31/23/19/18	−11, −75, −12	384	0.0002	0.38
L post-/pre-central gyri/IPL/middle frontal gyrus	2/3/1/6/40/5	−30, −22, 48	116	0.0007	0.38

MNI, Montreal Neurological Institute; R, right; L, left; IFC, inferior frontal cortex; dlPFC, dorsolateral prefrontal cortex; STL, superior temporal lobe; PCC, posterior cingulate cortex; IPL, inferior parietal lobe. η^2_P refers to the effect size of the differences in activation between groups.

in three right-hemispheric clusters comprising right pre- and post-central gyri, extending into IPL and insula. Patients on placebo showed increased activation relative to controls in left anterior cerebellum/occipital lobe (Table 3, Fig. 2*a*). No significant correlations were observed between extracted BOLD response from these clusters and IQ. Further, ANCOVA with IQ as covariate showed that all significant clusters remained with the exception of right insula. No correlations were observed between AUC and extracted BOLD response in any clusters.

Controls vs. ADHD patients on fluoxetine

Controls relative to ADHD patients on fluoxetine showed enhanced activation in left pre- and post-central gyri reaching into IPL. No clusters were increased in ADHD relative to controls (Table 3,

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Table 3. *Case-control comparisons of activation differences for delayed minus immediate choices*

Subject contrast	Brain regions of activation difference	Brodmann area (BA)	MNI coordinates (x, y, z)	Voxels	Cluster *p* value	η^2_P
(*a*) Controls *v.* ADHD placebo						
C > ADHD	R pre-/post-central gyrus/insula	6/4/3/2	56, −5, 5	14	0.04	0.10
	R pre-/post-central gyrus	6/4/3/2/1/40	41, −11, 37	25	0.04	0.19
	R post-central gyrus/IPL	4/1/2/40	34, −22, 45	14	0.04	0.24
	L post-central gyrus/IPL	2/3/40	−33, −28, 45	4	0.03	0.08
ADHD > C	L cerebellum (anterior)/occipital lobe/PCC	19/30	−14, −71, −12	16	0.02	0.12
(*b*) Controls *v.* ADHD fluoxetine						
C > ADHD	L pre-/post-central gyri/IPL	6/4/3/2/1/40	−34, −22, 45	77	0.001	0.27
ADHD > C	No observed clusters	–	–	–	–	–

MNI, Montreal Neurological Institute; R, right; L, left; IPL, inferior parietal lobe. η^2_P refers to the effect size of differences in activation between groups.

Fig. 2*b*). Thus, the right hemispheric clusters which were enhanced in activation in controls relative to ADHD under placebo were no longer observed, suggesting that fluoxetine normalized these activation differences. No significant correlations were observed between extracted BOLD response and IQ. ANCOVA with IQ as covariate showed that all significant clusters remained. No correlations were found between AUC and extracted BOLD response in significant clusters.

Discussion

Behaviourally, an acute dose of fluoxetine normalized TD abnormalities in ADHD relative to controls. At the brain level, in patients, fluoxetine relative to placebo significantly up-regulated activation in a large right-hemispheric IFC-premotor-insular-striatal cluster, which correlated trend-wise with better TD. Fluoxetine additionally down-regulated activation in presumably default mode network activations in PCC/precuneus and in pre- and post-central gyrus/IPL as well as cerebellum. Relative to controls, patients on placebo showed underactivation in right insula, pre-/post-central gyrus and IPL but enhanced activation in left anterior cerebellum/PCC. Fluoxetine normalized all case-control differences, due to up-regulation/down-regulation of these regions in patients, but lead to underactivation in left-hemispheric pre-/post-central gyrus/IPL in ADHD relative to controls, due to down-regulation of this activation in patients.

Fluoxetine relative to placebo up-regulated a large right-lateralized cluster in ADHD comprising IFC, premotor cortex, insula and BG, which was associated trend-wise with better TD. This right IFC-insular-striatal network comprises key regions for TD important for integrating external information with internal value representations to support goal-directed EF (Wittmann *et al.* 2007; Christakou *et al.* 2009, 2013*a*; Rubia *et al.* 2009; Wesley & Bickel, 2014). Right IFC is a key cognitive control hub region, crucial for inhibiting immediate reward choices as well as for inter-temporal bridging and future reward representation (Wiener *et al.* 2010; Radua *et al.* 2014). The BG are linked to a reward-valuation network that mediates reinforcement learning, reward-processing and inter-temporal bridging (Wittmann *et al.* 2007; Koch *et al.* 2009; Peters & Büchel, 2011) while the insula plays a role in future reward-value representation as well as timing functions including temporal foresight (Carter *et al.* 2010; Wiener *et al.* 2010; Radua *et al.* 2014; Wesley & Bickel, 2014). In particular right hemispheric IFC, insula and BG have been shown to be consistently hypoactivated in ADHD in meta-analyses of EF tasks (Cortese *et al.* 2012; Hart *et al.* 2013), including TD (Rubia *et al.* 2009; Chantiluke *et al.* 2014*d*). Right IFC underactivation has further been shown to be disorder-specific relative to other childhood disorders such as conduct and obsessive-compulsive disorder (Rubia, 2011; Rubia *et al.* 2014*a*; Norman *et al.* 2015). In this study, we only observed underactivation in ADHD relative to healthy adolescents in insula and premotor regions, rather than in IFC and basal ganglia, presumably due to low power.

Given that our recent meta-analysis findings of a consistent up-regulation with stimulants of right IFC, insula and BG activation in ADHD (Rubia *et al.* 2014*b*), the findings suggest that 5-HT agonists may have comparable up-regulatory effects to stimulants. In fact, the up-regulated region in ventrolateral PFC

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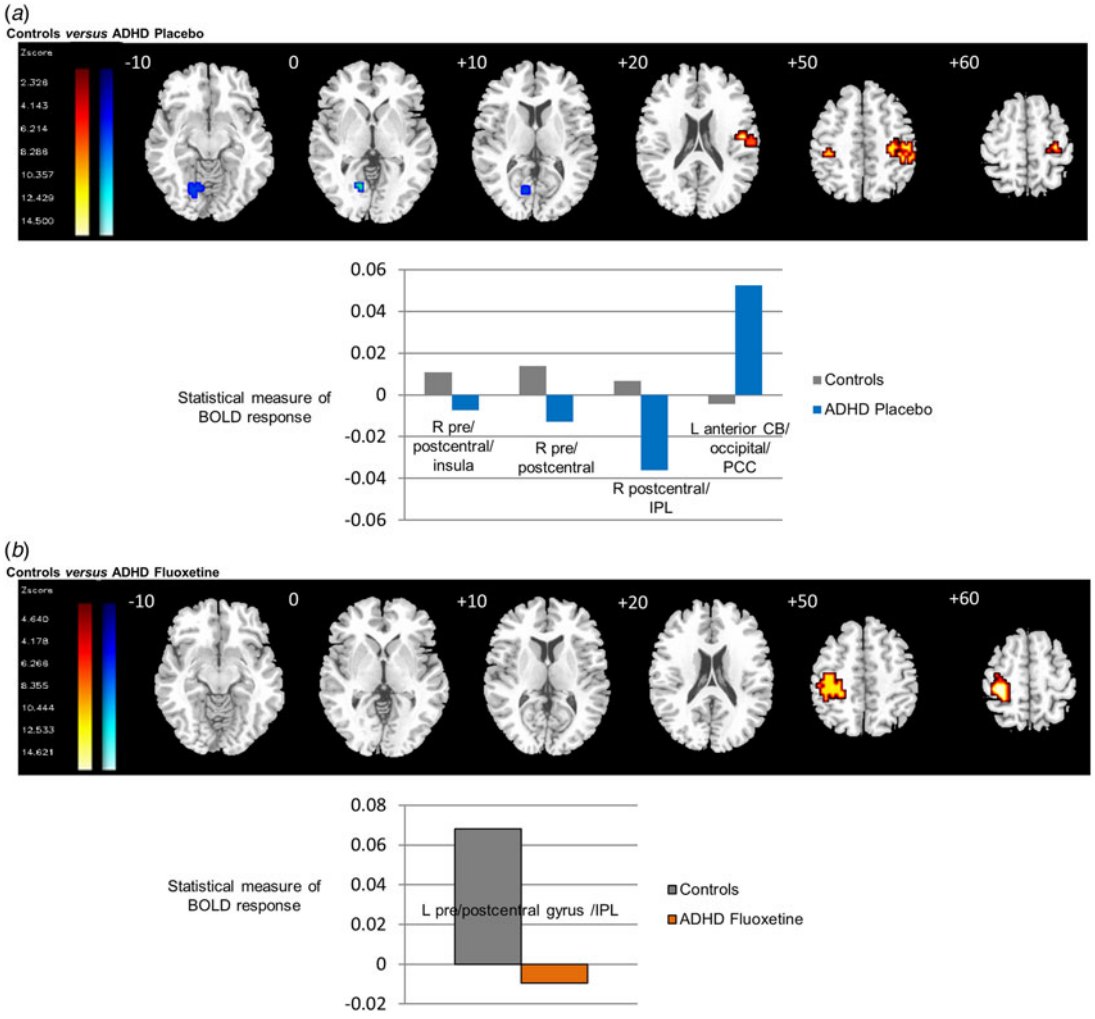

Fig. 2. Case-control comparisons. Axial sections show the between-group ANCOVA findings between controls and patients under (*a*) placebo and (*b*) fluoxetine. Red = controls > ADHD; blue = ADHD > controls. Also shown are the statistical measures of the blood oxygen level-dependent (BOLD) response for each of the brain regions that showed a significant group effect. R, Right; L, left; IPL, inferior parietal lobe; CB, 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.

reaching into anterior insula, putamen and superior temporal lobe is in a very similar location to the cluster observed in our meta-analysis of methylphenidate effects on ADHD brain function (Talairach coordinates: 42, 20, −12), with a sizable effect size of 1 relative to the meta-analytical effect size of 1.5 (Rubia *et al.* 2014*b*). Further, it is markedly similar to the up-regulated IFC location in our fMRI studies of methylphenidate effects on inhibition and timing, with effect sizes of 0.7 and 0.2, respectively (Smith *et al.* 2013; Cubillo *et al.* 2014*b*; Rubia *et al.* 2014*b*). The finding of right IFC-striatal up-regulation together with normalization of behavioural TD deficits extends previous evidence for modulation of behavioural TD rates with 5-HT (Schweighofer *et al.* 2007, 2008) and of IFC-striatal activation with 5-HT modulators such as tryptophan depletion and SSRIs in healthy adults (Del-Ben *et al.* 2005; Rubia *et al.* 2005; Lamar *et al.* 2009) in the ADHD population. It also extends our previous findings in ADHD that fluoxetine enhances and normalizes frontal activation during other impulsiveness-related functions such as IFC-striatal regions during inhibition (Chantiluke *et al.* 2014*c*) and dlPFC during working memory (Chantiluke *et al.* 2014*b*). The findings of right IFC modulation suggest that indoleamine agonists have similar effects to catecholamine agonists on ADHD brain function, given that not only methylphenidate but also atomoxetine up-regulated right IFC activation during inhibition and timing (Smith *et al.* 2013; Cubillo *et al.* 2014*a*, *b*).

The fact that fluoxetine normalized both underactivation in right pre-/post-central gyri, insula and IPL *and* behavioural TD deficits in ADHD is in line with

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the role of lateral fronto-insular-striato-parietal circuitry in intertemporal choice (McClure *et al.* 2004; Bickel *et al.* 2009; Xu *et al.* 2009) and for the modulation of these regions by 5-HT (Long *et al.* 2009; Cools *et al.* 2011; Rogers, 2011; Robinson *et al.* 2012). Apart from fronto-insular-striatal regions, IPL are also consistently underactivated in ADHD during EF (Cortese *et al.* 2012; Hart *et al.* 2012, 2013). We have found left IPL underactivation to be normalized in ADHD with fluoxetine during inhibition (Chantiluke *et al.* 2014*c*). The up-regulation and normalization with fluoxetine of insula, pre-/post-central and IPL deficits in ADHD thus provides promising novel evidence for modulatory effects of 5-HT agonists on typically dysfunctional fronto-insular-parietal systems in ADHD.

The down-regulation of PCC/precuneus under fluoxetine *v.* placebo likely reflects deactivation of the default mode network (DMN), comprised of ACC, precuneus and PCC, thought to represent mind-wandering, and which is typically anti-correlated with task-positive regions as it needs to be switched off during cognitive effort (Northoff *et al.* 2010). This is reinforced by the negative correlation under placebo of this cluster with the IFC activation. There is accumulating evidence that the DMN is insufficiently deactivated and anticorrelated with task-positive activation in ADHD (Christakou *et al.* 2013*b*), leading to enhanced mind-wandering, poor attention, EF and timing functions. We have found a similar effect of fluoxetine enhancing the deactivation of PCC during working memory in ADHD patients (Chantiluke *et al.* 2014*b*), which we also observed with methylphenidate and atomoxetine (Cubillo *et al.* 2014*a*). The finding suggests that fluoxetine, like catecholamine agonists (Rubia *et al.* 2014*b*), can strengthen the weak deactivation of the DMN in ADHD, presumably improving mind-wandering. Given that the key functional deficits in ADHD are both reduced activation in key fronto-striato-parietal networks mediating EF as well as a reduced deactivation of the DMN (Rubia *et al.* 2014*a*), the findings suggest that a 5-HT agonist positively modulates both 'task-positive' as well as 'task-negative' activation deficits of not switching off the DMN.

5-HT is relatively ubiquitous in the brain. However, 5-HT modulates specifically ADHD-relevant impulsivity-related functions mediated by ventrolateral-prefrontal regions which are dependent on 5-HT input such as inhibitory control and reward-related decision-making (Dalley & Roiser, 2012). The up-regulation with a 5-HT agonist of key right-hemispheric IFC-striatal activation that is typically abnormal in ADHD suggests that abnormal 5-HT may be underlying abnormal activation in these networks and not just catecholamine systems, in line with accumulating evidence of a role of 5-HT in ADHD (Barrickman *et al.* 1991; Spivak *et al.* 1999; Quintana *et al.* 2007; Oades, 2008; Gizer *et al.* 2009; McGough *et al.* 2009; Rommelse *et al.* 2010; Zepf *et al.* 2010; Hinz *et al.* 2011). However, it cannot be ruled out that fluoxetine had no indirect effects on other neurotransmitter systems which are known to be influenced by 5-HT such as dopamine, acetylcholine and other monoamines (Mongeau *et al.* 1997; Bymaster *et al.* 2002; Oades, 2008). All three main monoamine systems are likely to interact in a concerted manner to mediate impulsiveness-relevant functions (Dalley & Roiser, 2012).

The strength of this study is a carefully selected non-co-morbid ADHD group. Limitations are a relatively small patient sample size and the fact that for ethical and financial considerations, the control group was scanned only once while patients were scanned twice. However, the randomization accounted for potential training effects, and order did not affect the results. The significantly lower IQ in the ADHD group, typical for the population, is a limitation, in particular because IQ impacts upon decision-making (Toplak *et al.* 2010).However, covariance and correlation findings did not suggest that IQ confounded group differences. Finally, long-term stimulant use affects brain function and structure, so deficit findings may have been mitigated by the majority of patients taking stimulant medication (Hart *et al.* 2012; Rubia *et al.* 2014*a*).

Conclusions

A single fluoxetine dose in ADHD up-regulated activation in key right IFC-premotor-insular-striatal circuitry that mediates TD and which correlated trend-wise with better TD, and enhanced the deactivation of posterior DMN regions. Moreover, fluoxetine, via up-regulation of these right hemispheric regions, normalized underactivation in ADHD under placebo relative to controls in right premotor-insular-parietal areas and behavioural TD abnormalities. The findings show for the first time that a 5-HT agonist can modulate right IFC-insular-striato-parietal neural mechanisms underlying poor temporal foresight in ADHD. While the study aim was to clarify the mechanism of action of an acute dose of fluoxetine, which has the advantage of revealing true drug effects not confounded by indirect symptom improvements after chronic administration, future studies need to assess longer-term effects, as clinical behavioural changes are typically observed after weeks of administration. Longer-term SSRI administration has been shown to lead to down-regulation of 5-HT_{1A} receptors and 5-HT transporters (Lesch *et al.* 1991) and may well have different effects on brain function than acute doses, which are clinically more informative.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715002731.

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Declaration of Interest

K.R. has received funding from Lilly for another project and consultancy fees from Lilly, Shire, and Novartis. M.B. is a consultant for P1 Vital Ltd, Oxford, UK. The other authors have no conflict of interests to declare.

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