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Methylphenidate modifies reward cue responses in adults with ADHD: An fMRI study

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HIGHLIGHTS

- MPH modulates BOLD responses to reward-predicting cues in ADHD.
- MPH enhanced striatal discrimination of reward and non-reward cues in ADHD.
- MPH reduced corticostriatal connectivity during cued reward in ADHD.
- Therapeutic effects of MPH may involve altered reward processing.

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) has been associated with neural hyposensitivity to reward-predicting cues. Methylphenidate is widely used in the management of the disorder's symptoms, but its effects on reward sensitivity in ADHD are unknown. The current study used fMRI to measure striatal responses to reward-predicting cues in adults with ADHD on and off methylphenidate and a control group, during a classical conditioning task. Responses to cued reward were also explored. Larger differences in the ventral striatum activation to reward cues versus non-reward cues were observed when the ADHD participants were on methylphenidate compared to placebo. In response to cued-reward outcome, an exploratory analysis showed methylphenidate reduced the BOLD time-series correlation between the dorsal striatum and dorsal medial prefrontal cortex. Methylphenidate's therapeutic effects may be mediated by altering reward processing in individuals with ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by elevated levels of inattention, overactivity and/or impulsivity that impair daily functioning. Symptoms emerge in childhood, often continuing into adulthood (American Psychiatric Association, 2013). Altered reward sensitivity is hypothesized to contribute to the disorder's symptoms (Luman et al., 2010; Tripp and Wickens, 2008). Individuals with ADHD prefer smaller immediate over larger delayed reward (Sonuga-Barke et al., 2008), perform less well under partial vs. continuous reinforcement (Barber et al., 1996) and match their behavior less efficiently to reinforcement availability (Alsop et al., 2016). Functional magnetic resonance imaging (fMRI) studies consistently indicate reduced striatal responses to cues that predict reward in adolescents and adults with ADHD (Baroni and Castellanos, 2015; Plichta and Scheres, 2014). A small number of studies have reported hypersensitivity to reward delivery (Furukawa et al., 2014; Paloyelis et al., 2012; Ströhle et al., 2008).

Studies of reward circuitry provide clues to the pathophysiology of altered reward sensitivity in ADHD. In typically developing individuals, a previously neutral cue becomes a conditioned reinforcer after repeated pairing with a reward, which helps maintain behavior when rewards are delayed or discontinuous (Ferster, 1953; Garrud et al., 1981). Animal studies show dopamine (DA) cells initially fire in response to an unexpected reward. When a cue reliably precedes a reward, dopamine cell firing transfers to the cue. This transfer involves

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two separate processes: an increase in the DA response to the cue, together with a decrease in the DA response to reward as it becomes more predictable (Pan et al., 2005; Schultz, 1998). Reduced striatal responsiveness to reward-predicting cues, and increased responsiveness to cued reward are observed in fMRI studies (Baroni and Castellanos, 2015; Furukawa et al., 2014; Paloyelis et al., 2012; Plichta and Scheres, 2014; Ströhle et al., 2008) which suggests these processes may be disrupted in ADHD (Tripp and Wickens, 2008).

Methylphenidate (MPH) is widely prescribed for ADHD (Bolea-Alamañac et al., 2014; Spencer et al., 1995; Swanson et al., 2011). It improves attention (Solanto et al., 1997), on-task behavior (Pelham et al., 1993), inhibitory control (Aron et al., 2003) and cognitive performance (Pietrzak et al., 2006). There is also evidence that MPH reduces delay discounting (Shiels et al., 2009) and effort discounting (Wilkison et al., 1995), reduces risky betting in a gambling task (DeVito et al., 2008), and improves probabilistic reward learning (Luman et al., 2015). Changes in DA and norepinephrine (NE) availability with MPH, particularly in the ventral and dorsal striatum and prefrontal cortex, have been shown in human imaging studies (Rubia et al., 2014; Volkow et al., 2009; Zimmer, 2017). In rodents, therapeutic, low dose MPH increased DA and NE availability in the medial prefrontal cortex (mPFC) and striatum (Berridge et al., 2006; Koda et al., 2010). In monkeys, oral, low-dose MPH increased DA in the striatum (Kodama et al., 2017). Seeman and Madras (2002) and Solanto (1998) proposed that MPH has differential actions on tonic versus phasic dopamine signaling. This hypothesis recently gained experimental support (Fuller et al., 2019). By blocking the dopamine transporter, MPH reduces dopamine clearance, which causes increased tonic levels of dopamine (Butcher et al., 1991; Kuczenski and Segal, 1997). Conversely, the increased tonic dopamine has an inhibitory effect on phasic dopamine release via the action on the dopamine D2 receptors of dopamine neurons somadendrite and axon terminals, which decreases the excitability of dopamine cells (Lacey et al., 1987) and decreases release from dopamine terminals (Davis et al., 1997) At the same time, NE actions in PFC may increase attention to reward-predicting cues, in turn increasing phasic dopamine responses in the striatum on MPH (Kuczenski and Segal, 2005, 2001). Investigating the effects of MPH on neural responses to reward stimuli in individuals with ADHD is therefore an important next step.

Functional imaging studies have shown effects of MPH on response inhibition and timing estimation (Rubia et al., 2014). Some studies have assessed the effects of MPH on rewarded cognitive task performance and associated blood-oxygen-level dependent (BOLD) responses. Methylphenidate normalized increased activation in the orbitofrontal and superior temporal regions in children with ADHD, compared to controls, during a rewarded sustained attention task (Rubia et al., 2009). In another study, MPH normalized increased striatal responses during task switching when the availability of a higher magnitude of reward was signaled, but only among adults with ADHD who are carriers of the 9-repeat allele, a polymorphism in the DAT1 gene (Aarts et al., 2015). Using a gambling task, Evers et al. (2017) showed that MPH reduced striatal BOLD responses to gain and loss, while increasing expectancy-related BOLD signals based on the previous outcome, in support of differential effects of MPH on phasic vs. tonic dopamine responses.

Imaging studies have shown hyposensitivity to reward-predicting cues in ADHD, using a variant of the Monetary Incentive Delay task (Baroni and Castellanos, 2015; Knutson et al., 2001; Knutson and Heinz, 2015; Plichta and Scheres, 2014) or a classical conditioning task (Furukawa et al., 2014). Altered reward responses during these tasks were reported in studies using medication naive (Carmona et al., 2011; Edel et al., 2013; Furukawa et al., 2014), medicated, or mixed samples (Hoogman et al., 2011; Plichta et al., 2009; Scheres et al., 2007; Ströhle et al., 2008), tested off medication. Stimulant treatment history did not affect the responses (Stoy et al., 2011). However, up to now, no studies have tested the acute effects of MPH on these tasks.

The findings of the reduced BOLD responses to reward anticipation in ADHD were mostly in the ventral striatum (Baroni and Castellanos, 2015; Plichta and Scheres, 2014). However, MPH has been shown to affect other brain regions (Del-Ben et al., 2001; Grevet et al., 2005). Multiple pathways to ADHD symptoms (Ma et al., 2016; Sonuga-Barke et al., 2008) and network-based dysfunctions in ADHD (Petrovic and Castellanos, 2016; Plichta et al., 2013; Sonuga-Barke and Fairchild, 2012) have been proposed. Studies examining task-based functional connectivity in ADHD suggest reduced attentional network connectivity but enhanced motivational networks in the presence of reward during cognitive tasks (Rubia, 2018). Given these studies, and the studies showing a therapeutic dose of MPH altering the DA and NA availability in the striatum and mPFC (Berridge et al., 2006; Koda et al., 2010; Kodama et al., 2017), it is important to examine the effects of MPH on functional relationships between multiple brain regions in response to reward cues in ADHD.

In this study, we measured functional activations in the ventral striatum (VS) in response to reward-predicting cues, in adults with ADHD on and off MPH and a typically-developing control group. We also explored BOLD responses to cued-reward outcome, and the degree to which activation in the striatum is correlated with activation in mPFC regions. A classical conditioning task involving repeated presentation of cues and rewards was employed. This task was chosen because it is not confounded by operant behavioral responses, decision-making, complex reward probability, timing or magnitude estimation. The ADHD participants were all known MPH responders. Motivation and associative-learning were confirmed by participants' ratings and behaviors before, during and after the fMRI task. To our knowledge, this is the first fMRI study to examine the acute effects of MPH on reward-predicting cues.

Based on earlier studies, we hypothesized reduced VS activation in response to reward-predicting cues (Baroni and Castellanos, 2015; Plichta and Scheres, 2014) in those with ADHD on placebo, compared to controls. The role of VS in reward processing has been consistently indicated across a range of studies (Baroni and Castellanos, 2015; Knutson and Heinz, 2015; Plichta and Scheres, 2014; Schultz, 1998). We predicted that MPH would increase VS activation to reward-predicting cues, in adults with ADHD. We also expected increased VS activation in response to cued-reward outcome in the ADHD participants during placebo, compared to controls (Furukawa et al., 2014; Paloyelis et al., 2012; Ströhle et al., 2008). We expected a dampening of such activation in the ADHD participants in the presence of MPH.

Based on suggestions that the effects of MPH involve modulation of the corticostriatal network (Kodama et al., 2017), we also hypothesized drug effects on correlations between the striatal and cortical regions. The correlational analyses were exploratory; the dorsal striatum (DS) and medial prefrontal cortex (mPFC) regions were examined in addition to the ventral striatum. The DS receives dopaminergic inputs as strongly as the VS (Balleine et al., 2007; Everitt and Robbins, 2013; Graybiel and Grafton, 2015). Effects of low dose MPH on mPFC regions have been demonstrated in rodents (Berridge et al., 2006; Koda et al., 2010). Therapeutic effects of MPH on attention (Solanto et al., 1997) and cognitive performance (Pietrzak et al., 2006) in children with ADHD implicate the mPFC in the drug's mechanisms of action. Given the exploratory nature of the analysis, bi-directional effects were tested. We expected the inter-regional BOLD time-series correlations of ADHD participants on placebo to differ from those of controls, and that this difference would be normalized by MPH. Increased correlations would be expected from previous findings showing a heightened motivational network in the presence of reward in ADHD (Rubia, 2018). MPH enhancing DA and NE availability could either increase or decrease the corticostriatal inter-regional coupling. Increased tonic DA could reduce phasic responses to reward-predicting cues and/or cued reward in the striatum. However, with a low, therapeutic dosage of MPH, increased prefrontal NE availability might work to enhance attention to cues, which may also influence striatal DA release in response to cues. Temporal co-variation, rather than mean BOLD activity levels, might

Table 1
Participant characteristics.

	ADHD			Control		
	(n = 18)			(n = 20)		
	Mean	sd	Range	Mean	sd	Range
Age (years)	25.61	2.93	22–33	27.35	3.47	22–34
Estimated IQ	110.97	8.05	97.5–127.5	105.42	5.44	92.5–112.5
Education (years)	16.22	1.40	13–19	17.60	2.04	15–21
Socioeconomic classification (IBGE)	36.06	7.56	20–45	31.05	6.97	18–45
Males n (%)	13 (72.2%)			8 (40%)		
ADHD Inattention (ASRS Sum)	27.89	4.62	20–35	10.35	4.57	3–18
ADHD Hyperactivity/Impulsivity (ASRS Sum)	20.42	7.72	8–32	10.70	4.17	3–18
Presentation (n: Inattention/Hyperactivity/Combined)	12/0/6					
Comorbidity (n: Anxiety/Eating/OCD)	1/3/1			0/0/1		
Stimulant Medication (MPH)	Median	Mode	Range			
Current (months)	9.5	6	4–117			
First medication intake (months prior to study)	20.5	6	5–144			

thus better capture functional changes induced by MPH.

2. Methods

The study was approved by the ethics committee of the D'Or Institute for Research and Education (IDOR) in Rio de Janeiro, Brazil. All volunteer participants provided written informed consent. They were informed that they would not be paid for their participation but would be reimbursed for transportation expenses and receive a gift voucher in the amount earned in the experiment (actual earnings received varied between R$ 30 and R$ 50).

2.1. Participants

Participants were right-handed adults aged 22–34 years (Table 1). ADHD and control participants were recruited from area physicians, students attending the Federal University of Rio de Janeiro, Brazil, and through personal contacts.

All participants underwent a comprehensive assessment of past and current symptoms of ADHD and comorbidity, by a team of qualified psychiatrists at IDOR, trained and supervised by a senior psychiatrist (PM). Semi-structured interviews confirmed the presence and severity of ADHD symptoms or their absence (for controls) (Kiddie-Schedule for Affective Disorder and Schizophrenia-PL (KSADS-PL) (Grevet et al., 2005)), and evaluated comorbid conditions (Structured Clinical Interview (SCID) (Del-Ben et al., 2001)). The ADHD participants met DSM-5 criteria for ADHD before 12 years of age and demonstrated at least 5 current symptoms of inattention and/or hyperactivity/impulsivity. Control participants had fewer than 3 current or previous symptoms of inattention and hyperactivity/impulsivity. Exclusion criteria were: current non-prescription drug use, psychotic symptoms, or major depressive or bipolar disorder, and history of any neurological disorder. All ADHD participants were previously treated with MPH for at least 4 months. Most of the participants did not begin stimulant treatment until they were adolescents or adults.

The following participants were excluded from data analysis: six controls (one with childhood ADHD symptoms, two due to movement-related artifacts, three due to behavioral responses (see below)) and four ADHD participants (one not meeting the DSM-5 ADHD criteria, one with a comorbid condition set as an exclusion criteria, one did not return for the 2nd session, one due to MRI technical problems). The final sample included 18 participants in the ADHD group and 20 participants in the control group. The mean ages of the two groups were not significantly different ($t(36) = 1.66$, $p = .106$). Estimated IQ (Wechsler Abbreviated Scale of Intelligence Vocabulary and Block Design subtests (Nascimento, 2004)) was significantly higher for the ADHD than the control group ($t(36) = -2.43$, $p = .021$). The mean years of education was higher for the control than the ADHD group ($t(36) = 2.41$, $p = .021$), while the mean income classification score was higher for the ADHD group ($t(36) = -2.07$, $p = .046$). All participants belonged to middle and upper socioeconomic classes (Class C1 through A1; the Brazilian Association of Market Research Companies (http://www.abep.org/).

Control participants were scanned once, while ADHD participants were scanned twice, on and off MPH, at least 5 days and on average 15 days apart. Medication and placebo sessions were counterbalanced across participants. All fMRI sessions were conducted in the morning. Participants were asked not to eat before arrival. Breakfast (a glass of chocolate milk, a slice of white bread with a slice of cheese and ham) was offered, followed by administration of clinical interviews or questionnaires then the fMRI task.

2.2. MPH dosing

All but two ADHD participants were prescribed extended-release MPH (Concerta or Ritalin LA), average daily dose 40 mg.[1] ADHD participants were asked to withhold their usual stimulant medication for 48 h prior to each session. Compliance was confirmed on both days. After breakfast, they were given immediate-release MPH (20 mg) or placebo (capsules). Methylphenidate and placebo administration were double blind and counterbalanced. However, the final dataset included 12 ADHD participants receiving placebo, and 6 MPH, during the first session, due to participant dropout and data exclusion. Members of the research team were blind to medication order until after data collection and cleaning. Scanning began 1.5 h after MPH or placebo. After completing the fMRI task, participants rated how much they liked the medication taken on a 4 point-scale. Mean likability was slightly higher for MPH ($M = 2.50$, $SD = 1.04$) than placebo ($M = 1.94$, $SD = 0.80$), this difference was not significant ($t(17) = -1.43$, $p = .172$).

2.3. fMRI experimental paradigm

To examine the effects of reward-predicting cues and cued-reward

[1] The average daily dose was 39.6 mg for 10 participants prescribed Concerta, 43.3 mg for 3 participants prescribed Ritalin LA, 38 mg for 3 participants prescribed a mixture of Ritalin (immediate-release) and Concerta or Ritalin LA, and 45 mg for 2 participants prescribed Ritalin.

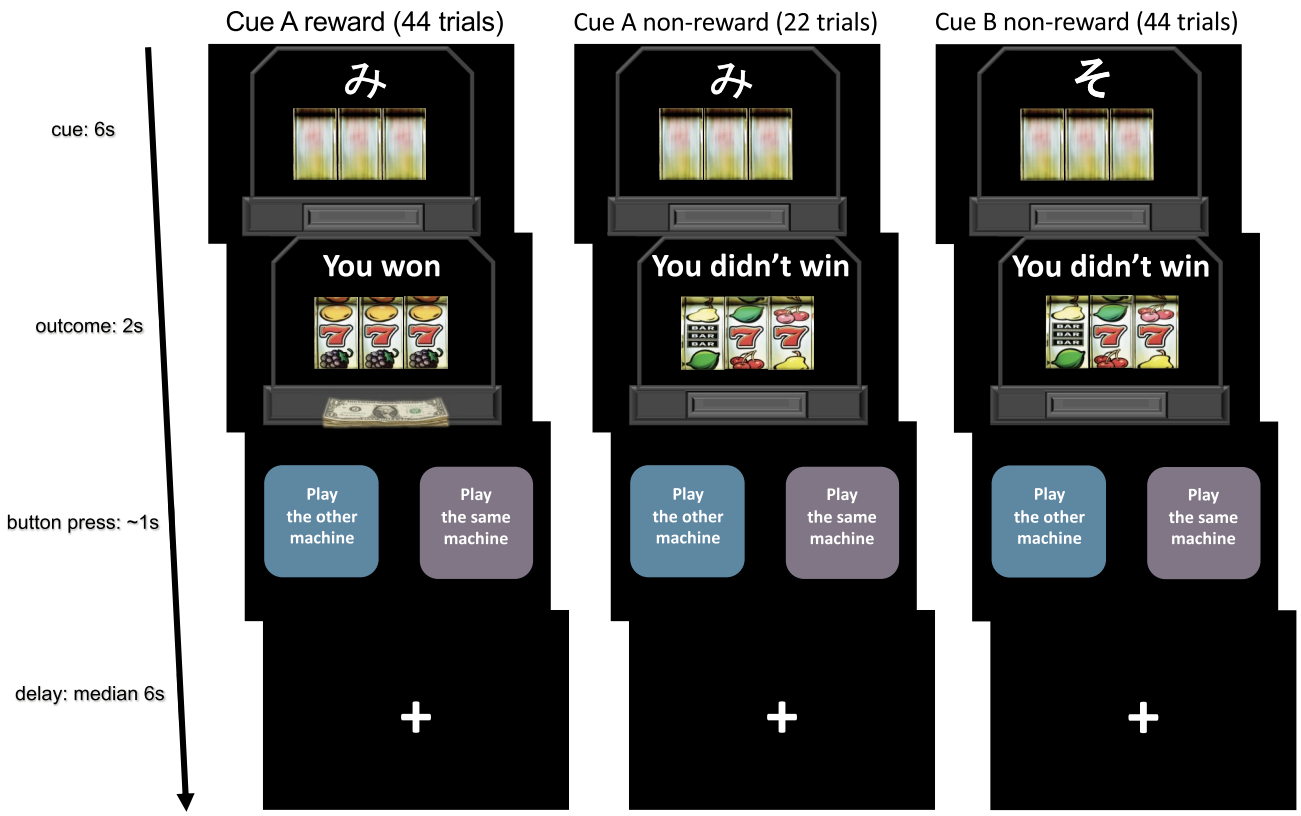

Fig. 1. Classical conditioning fMRI task. One of the two neutral stimuli (Cue A or Cue B) was followed by an outcome stimulus (reward or non-reward) after a 6-second delay. Cue A was followed by the delivery of the reward 66% of the time and non-reward 33% of the time. Cue B was always followed by non-reward.

outcomes, a classical conditioning task was used in an event-related design (Fig. 1). A picture of a slot machine was presented with one of two initially neutral stimuli (two Japanese characters deemed abstract by Brazilian participants; Cue A or Cue B). Two sets of cues were used and counterbalanced across the two sessions for ADHD participants. The slot machine spun for 6 s. The duration between a cue and outcome was kept constant to maintain the temporal predictability of outcome delivery (Furukawa et al., 2014; Metereau and Dreher, 2013). Attenuation of neural responses to reward outcome is observed only when reward can be predicted (Hollerman and Schultz, 1998)[2]. After the delay, the slot machine stopped at a win or non-win position (reward or non-reward) for 2 s. After each outcome, participants were asked to 'suggest' to the computer which machine to play next (same machine and cue or switch) by a button press (the actual presentation was pseudo-random). The response options were available for 1 s, followed by a variable inter-trial delay to reduce the temporal predictability of the next trial (Poisson distribution: min = 4 s, median = 6 s). The button press was included to maintain engagement during the classical-conditioning task and to allow checking of ongoing attention and preferences between the two slot machines.

Participants completed a brief training run on a computer before entering the MRI scanner, exposing them to the cue and outcome stimuli and familiarizing them with the button press response. Training consisted of 4 trials of Cue A (CS+) followed by a reward, 2 trials of Cue A followed by non-reward, and 4 trials of Cue B (CS-) followed by non-reward, in a pseudo-random order. Participants were asked to indicate which symbol (cue) they preferred. Within the MRI scanner, Cue A was followed by reward 66% of the time (44 trials) and non-reward 33% of the time (22 trials). Cue B was always followed by non-reward (44 trials). Participants were told that they could earn up to R$ 50 during the experiment.

2.4. Ratings and behavioral measures before, during and after the fMRI task

Several self-report and behavioral measures were used to assess motivation, attention to the task, classical-conditioning effects and awareness of the cue-outcome association. At the beginning of the experiment, participants were asked to rate their motivation to earn money in the experiment. Motivation ratings were not significantly different for the ADHD placebo (M = 2.83, SD = 0.71), ADHD MPH (M = 2.89, SD = 0.68), and control (M = 2.85, SD = 0.75) participants ($F(2, 55) = 0.03$, $p = .971$).

During the fMRI task, the participants' button-press responses were recorded. Participants sometimes missed the response window (1 s). The percentage of missed responses ranged from 0 to 22%, except for one control participant (60%). Participants' suggestions to stay with the same machine after Cue A trials (regardless of the outcome) or to switch machines after Cue B trials indicated a preference for CS+. All but one control participant showed a consistent preference for the reward-predicting cue.

Participants' explicit awareness of the cue types was checked by asking them to indicate which of the two symbols (cues) they preferred after the training session and after completing the classical conditioning task in the scanner. All but four control participants indicated they preferred CS+ over CS- after training, three of them indicating a preference for CS+ after completing the fMRI task. One ADHD participant did not indicate such a preference after training or completing the first session (placebo), but did show a preference for CS+ in the second

[2] It has been shown that when rewards are delivered a half second before the expected timing of the reward, dopamine neurons fire at the time of the reward delivery. When rewards are delayed, dopamine neurons show an undershoot of activity at the time of the expected, undelivered reward, and fire when the reward is eventually delivered later (Hollerman and Schultz, 1998).

session (MPH). Two control participants, one who missed the button-press responses 60% of the time, and another who did not show a behavioral preference for the CS+ in the scanner *and* did not indicate an explicit preference for the CS+ after training, were excluded from data analysis.

Conditioning effects were also evaluated using a Pavlovian-to-instrumental transfer (PIT) procedure (da Costa et al., 2019) (Supplemental Fig. 1). Before the fMRI classical conditioning task, participants completed an independent operant procedure, which required them to apply force to a hand dynamometer repeatedly to obtain monetary rewards. After the fMRI task, participants were asked to complete the same operant procedure again, but this time with Cue A and Cue B present, and outcomes hidden (transfer phase). Invigoration of behavioral responses during the transfer phase demonstrated that classical conditioning of Cue A to reward was effective for ADHD participants on and off MPH and control participants. Frequency of responses and grip force applied in the presence of the reward cue were greater than the non-reward cue for the ADHD placebo (frequency $t(17) = 11.47$, $p < .001$; force $t(17) = 5.69$, $p < .001$), ADHD MPH (frequency $t(17) = 10.45$, $p < .001$; force $t(17) = 7.82$, $p < .001$), and control (frequency $t(19) = 7.12$, $p < .001$; force $t(19) = 5.29$, $p < .001$) participants.

2.5. fMRI image acquisition

Functional images were acquired with a 3T Philips Achieva scanner, using an 8-channel SENSE head coil, LCD display with a mirror, shingle-shot T2*-weighted fast-field echo, echo-planar imaging sequence (TR = 2000 ms, TE = 22 ms, Matrix = 80 x 80, FOV = 240 mm, flip angle = 90, isotropic voxel size 3 mm, 37 slices in ascending order with no gap), a SENSE factor of 2, dynamic stabilization, and paddings and straps over the forehead and under the chin. Reference anatomical images were acquired using a T1-weighted SD magnetization-prepared, rapidly acquired gradient echo sequence (TR/TE = 7.2/3.4 s, Matrix/FOV = 240/240 mm, flip angle = 8°, 1 mm isotropic voxel size, 170 sagittal slices). Each scanning session comprised 3 runs, 285 vol each, total functional scanning time 28.5 min. The trial number, sequence and time were uniform across all the participants, and two sessions for the ADHD group.

2.6. fMRI analysis

2.6.1. Preprocessing

The functional images were analyzed using Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Preprocessing used realignment, slice-time correction (referencing slice 19), co-registration, and normalization to the standard echo planar imaging template (MNI: Montreal Neurological Institute) resulting in the reconstructed functional images with voxel dimensions of 3 mm. Images were spatially smoothed (6 mm Gaussian kernel). Boxcar functions at stimulus onset for specified events were convolved with the hemodynamic response function with autocorrelation correction (AR(1)) and high-pass filtering (128 s) for each participant.

Seven condition-specific regressors (Cue A, Cue B, Cue A reward, Cue A non-reward, Cue B non-reward, button press and ITI Fixation) were entered together with six movement parameters. The variance inflation factors (VIF) of all regressors of interest (Cue A, Cue B, Cue A reward, Cue A non-reward, Cue B non-reward) were under 1.5 (https://github.com/canlab/CanlabCore/blob/master/CanlabCore/diagnostics/scn_spm_design_check.m), indicating a low level of collinearity in the task design (Mumford et al., 2015). Based on the SPM collinearity test, the cue and outcome conditions were orthogonal (ranged from 0.00 to 0.05 for all participants). The Finite Impulse Response (FIR) model was applied with event duration of 0s. The effect of CS+ (Cue A vs. Cue B) was the main contrast of interest. Secondarily, the effect of cued-reward outcome (Cue A reward vs. Cue B non-reward) was explored. While the outcome was probabilistic and the regressors of interest showed acceptable levels of collinearity, it is well known that the hemodynamic nature of BOLD effects is sluggish, taking around 6 s to return to baseline. For this reason, observed BOLD responses associated with the reward delivery may reflect a compound effect of cue and outcome.

2.6.2. Region-of-interest (ROI) analyses

Mean parameter estimates from the 5 mm sphere around the bilateral ventral striatum MNI coordinates were extracted for each condition of interest (Cue A, Cue B, Cue A reward, Cue B non-reward) using the rfxplot toolbox (http://rfxplot.sourceforge.net/). The coordinates (12/-12, 10, −6 for rVS/lVS [nucleus accumbens]) were the same meta-analytical coordinates (Liu et al., 2011) used in our previous study (Furukawa et al., 2014) examining striatal responses to reward-predicting cue and cued-reward outcome in ADHD. Extracted mean parameter estimates were analyzed in SPSS 23 (https://www.ibm.com/analytics/spss-statistics-software). Two-way repeated-measures ANOVAs, using SPSS GLM, examined the within-subject effects of condition (Cue A vs. Cue B; Cue A reward vs. Cue B non-reward) and medication status (MPH vs. placebo) on BOLD responses (parameter estimates extracted for each condition), controlling for medication order (0, 1), in participants with ADHD. Separately, two-way mixed ANOVAs, using SPSS GLM, examined the within-subject effects of condition (Cue A vs. Cue B; Cue A reward vs. Cue B non-reward) and the between-subject effects of group (control vs. ADHD placebo; control vs. ADHD MPH) on BOLD responses. Bonferroni family-wise error (FWE) corrections were applied for the two striatal regions and FWE corrected p values (i.e., p multiplied by two) are presented.

2.6.3. Exploratory correlational analyses

To examine the degree to which BOLD responses in the striatum was correlated with responses in the mPFC, the images were further processed and evaluated in CONN17, www.conn-toolbox.org/(Whitfield-Gabrieli and Nieto-Castanon, 2012). White matter and cerebrospinal fluid BOLD-time series were modeled as voxel-specific noise effects, together with movement covariates (Whitfield-Gabrieli and Nieto-Castanon, 2012). In addition to the ventral striatum (rVS/lVS), dorsal striatum (rDS/lDS) and three mPFC regions (medial prefrontal/orbitofrontal cortex [mPFC/OFC], dorsal portion of the medial prefrontal cortex [dmPFC], and anterior cingulate cortex [ACC]) were included in the exploratory correlational analyses. The bilateral ventral striatum were defined in CONN using the same coordinates and 5 mm sphere as the ROI analyses. The 5 mm spheres were drawn for the other regions using the following coordinates based on previous literature: 20/-20, 4, 18 for rDS/lDS (Liu et al., 2011); 0, 54, −8 for mPFC/OFC (Moll et al., 2012), 0, 62, 19 for dmPFC (Moll et al., 2012); −2, 40, −4 for aCC (Clithero and Rangel, 2014). The average BOLD time series was calculated across voxels within each region, and a correlation coefficient was computed for each pair of regions. The same conditions of interest and no-interest as the ROI analyses were applied. An initial examination of bivariate correlation coefficients showed moderate to high correlations for some participants. Thus, semi-partial correlation coefficients were estimated to examine uniquely shared variance by each striatal seed region with each cortical region.

GLM examined within-subject medication effects (MPH vs. placebo) and between-subject group effects (control vs. ADHD placebo, control vs. ADHD MPH) on the Fisher r-to-z transformed semi-partial correlation coefficients of the reward cue contrast (Cue A vs. Cue B) and cued reward contrast (Cue A reward vs. Cue B non-reward). For each striatal seed, an omnibus F-test evaluated multivariate effects across six target regions (i.e., a seed-level difference according to medication status or group membership for the cue or reward contrast). The models for further inspection were selected based on this seed-level threshold ($p < .05$, uncorrected). For the selected models, paired or independent t-tests, respectively, examined the differences in the strength of

correlations between a seed and each target region, two-tailed, FWE corrected for the six pairs per seed. Bonferroni FWE corrected p values (i.e., p multiplied by six) are presented.

2.6.4. Further examination of relationship between BOLD responses in two regions

To understand the nature of a significant difference in correlation strengths, post-hoc analyses were conducted in SPSS with correlation coefficients extracted from CONN. In addition, to visualize the relationship between BOLD responses in the two regions, eigenvariate values for the same region spheres were extracted from SPM for the control and ADHD group participants (during the placebo and MPH for the ADHD group) and were displayed in a scatter plot.

3. Results

3.1. Region-of-interest analyses

3.1.1. Medication effects on the ventral striatum responses to reward-predicting cue

Medication (MPH vs. Placebo) and condition (Cue A vs. Cue B) within-subject effects were examined for the bilateral striatal regions. For the rVS responses, a significant medication*condition interaction effect ($F(1, 16) = 6.87$, $p = .038$, FWE), together with a main effect of condition ($F(1, 16) = 6.48$, $p = .044$, FWE), were observed. There was no significant main effect of medication ($F(1, 16) = 0.44$, $p = 1.03$, FWE). For the lVS responses, a significant medication*condition interaction effect was also observed ($F(1, 16) = 6.60$, $p = .042$, FWE), while there was no significant main effect of medication ($F(1, 16) = 1.02$, $p = .656$, FWE) or condition ($F(1, 16) = 3.78$, $p = .140$, FWE). Greater differences in BOLD responses to Cue A vs. Cue B were observed when the ADHD group participants were on MPH, compared to placebo, for the bilateral ventral striatum.

3.1.2. Group differences in the ventral striatum responses to reward-predicting cue

Group (control vs. ADHD Placebo) between-subject and condition (Cue A vs. Cue B) within-subject effects were examined. A main effect of condition was observed in the rVS ($F(1, 36) = 7.57$, $p = .018$, FWE). There was no significant effect of group ($F(1, 36) = 0.70$, $p = .816$, FWE) or group*condition interaction ($F(1, 36) = 0.02$, $p = 1.79$, FWE). For the responses in the lVS, no significant effect was observed for condition ($F(1, 36) = 3.87$, $p = .011$, FWE), group ($F(1, 36) = 0.38$, $p = 1.09$, FWE), or group*condition interaction ($F(1, 36) = 0.08$, $p = 1.56$, FWE).

Group (control vs. ADHD MPH) between-subject and condition (Cue A vs. Cue B) within-subject effects were also examined. Main effects of condition were observed in the rVS ($F(1, 36) = 15.43$, $p < .001$, FWE) and lVS ($F(1, 36) = 8.07$, $p = .014$, FWE). No significant effect of group was observed for the rVS ($F(1, 36) = 1.61$, $p = .426$, FWE) or lVS ($F(1, 36) = 0.29$, $p = 1.19$, FWE). There was no group*condition interaction effect for the rVS ($F(1, 36) = 1.10$, $p = .600$, FWE) or lVS ($F(1, 36) = 1.42$, $p = .484$, FWE).

BOLD responses to the reward predicting cue were greater than responses to the non-reward predicting cue across groups in the bilateral striatum (Fig. 2a).

3.1.3. Medication effects on the ventral striatum responses to cued-reward outcome

Medication (MPH vs. Placebo) and condition (Cue A reward vs. Cue B non-reward) within-subject effects were explored for the bilateral striatal regions. A condition main effect was observed in the rVS ($F(1, 16) = 6.68$, $p = .040$, FWE). There was no significant effect of medication ($F(1, 16) = 2.60$, $p = .254$, FWE) or medication*condition interaction ($F(1, 16) = 1.07$, $p = .632$, FWE). During MPH and placebo, increased BOLD responses were observed to cued reward, compared to cued non-reward, in the right ventral striatum. No significant effect of medication ($F(1, 16) = 5.46$, $p = .066$, FWE), condition ($F(1, 16) = 4.98$, $p = .080$, FWE), or medication*condition interaction ($F(1, 16) = 1.34$, $p = .528$, FWE) was observed for the lVS responses.

3.1.4. Group differences in the ventral striatum responses to cued-reward outcome

Group (control vs. ADHD Placebo) between-subject and condition (Cue A reward vs. Cue B non-reward) within-subject effects were examined. Main effects of condition were observed in the rVS ($F(1, 36) = 8.17$, $p = .014$, FWE) and lVS ($F(1, 36) = 13.41$, $p = .002$, FWE). There was no main effect of group for the rVS ($F(1, 36) = 0.03$, $p = 1.74$, FWE) or lVS ($F(1, 36) = 0.60$, $p = .892$, FWE). No significant group*condition interaction effect was observed for the rVS ($F(1, 36) = 0.00$, $p = 1.98$, FWE) or lVS ($F(1, 36) = 0.00$, $p = 1.94$, FWE).

Group (control vs. ADHD MPH) between-subject and condition (Cue A reward vs. Cue B non-reward) within-subject effects were also examined. Main effects of condition were observed in the rVS ($F(1, 36) = 9.34$, $p = .008$, FWE) and lVS ($F(1, 36) = 9.53$, $p = .008$, FWE). There was no main effect of group for the rVS ($F(1, 36) = 1.37$, $p = .498$, FWE) or lVS ($F(1, 36) = 0.17$, $p = 1.37$, FWE). No significant group*condition interaction effect was observed for the rVS ($F(1, 36) = 0.18$, $p = 1.34$, FWE) or lVS ($F(1, 36) = 1.78$, $p = .380$, FWE).

BOLD responses to cued reward were greater than responses to cued non-reward across groups (Fig. 2b).

3.2. Exploratory correlational analyses

In response to reward-predicting cues (Cue A vs. Cue B), omnibus F-tests were not significant for the bilateral ventral and dorsal striatum seeds for the effects of medication (placebo vs. MPH) or group (control vs. ADHD placebo; control vs. ADHD MPH).

In response to cued-reward outcome (Cue A reward vs. Cue B non-reward), omnibus F-tests were significant for the rVS ($F(4, 14) = 6.31$, $p = .004$) and rDS ($F(4, 14) = 3.78$, $p = .028$) seeds for the medication effects (placebo vs. MPH). Paired t-tests indicated a significant difference between the correlation of the rVS and mPFC/OFC BOLD time series during MPH compared to placebo ($t(17) = 3.40$ $p = .020$, FWE). The correlation strength was increased during MPH. Paired t-tests also indicated a significant difference between the correlation between the rDS and dmPFC BOLD time series during MPH compared to placebo ($t(17) = -4.27$ $p = .003$, FWE). The correlation strength was lower during MPH.

For the ADHD placebo vs. control group comparison, an omnibus F-test showed a trend effect for the rDS seed ($F(6, 31) = 2.37$, $p = .053$). Independent t-tests indicated that the correlation between the rDS and dmPFC BOLD time series was larger for the ADHD placebo than for the control group ($t(36) = 3.13$ $p = .016$, FWE). None of the F-tests approached significance for the ADHD MPH vs. control group comparison.

Semi-partial correlation coefficients for each group are presented, and significant and non-significant comparisons are noted, in Supplemental Table 2.

3.3. Post-hoc examination of rVS-mPFC/OFC and rDS-dmPFC correlations

Due to the differential correlations between rVS and mPFC/OFC, and rDS and dmPFC regions observed during cued-reward outcome, post-hoc analyses were conducted in SPSS, using the Fisher-transformed r-to-z values computed in CONN. Two-way mixed ANOVAs, using SPSS GLM, examined the effects of the condition (Cue A reward and Cue B non-reward) and group (ADHD placebo, ADHD MPH, and control).

No significant effect of condition ($F(1, 53) = 2.12$, $p = .151$), group ($F(2, 53) = 0.06$, $p = .938$) or a group*condition interaction ($F(2, 53) = 0.08$, $p = .926$) was observed on the correlation strength between rVS and mPFC/OFC.

No significant main effect of condition ($F(1, 53) = 2.69$, $p = .107$)

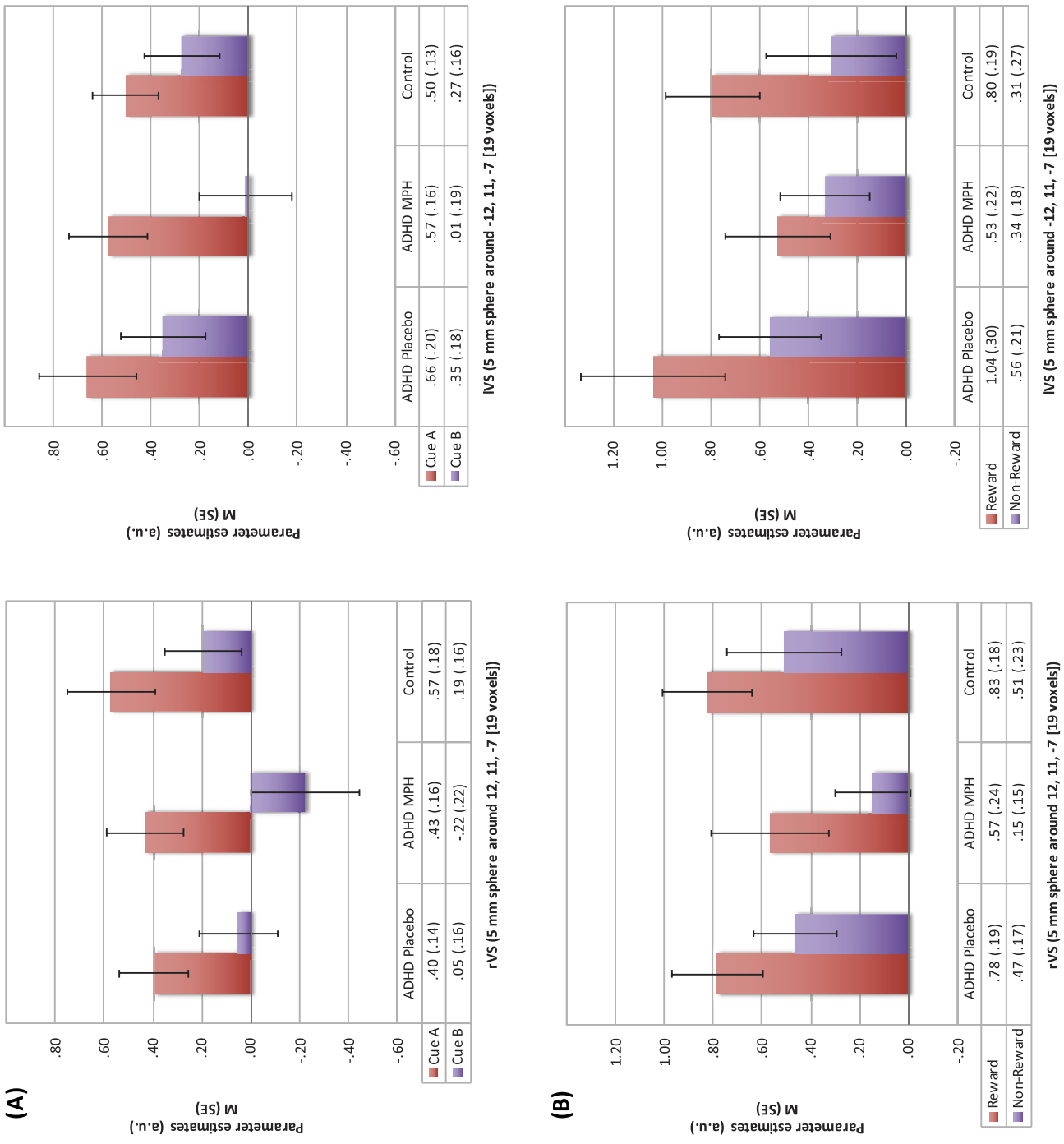

Fig. 2. ROI (bilateral ventral striatum, 5 mm sphere) mean responses to (A) reward-predicting cue and (B) cued-reward outcome.

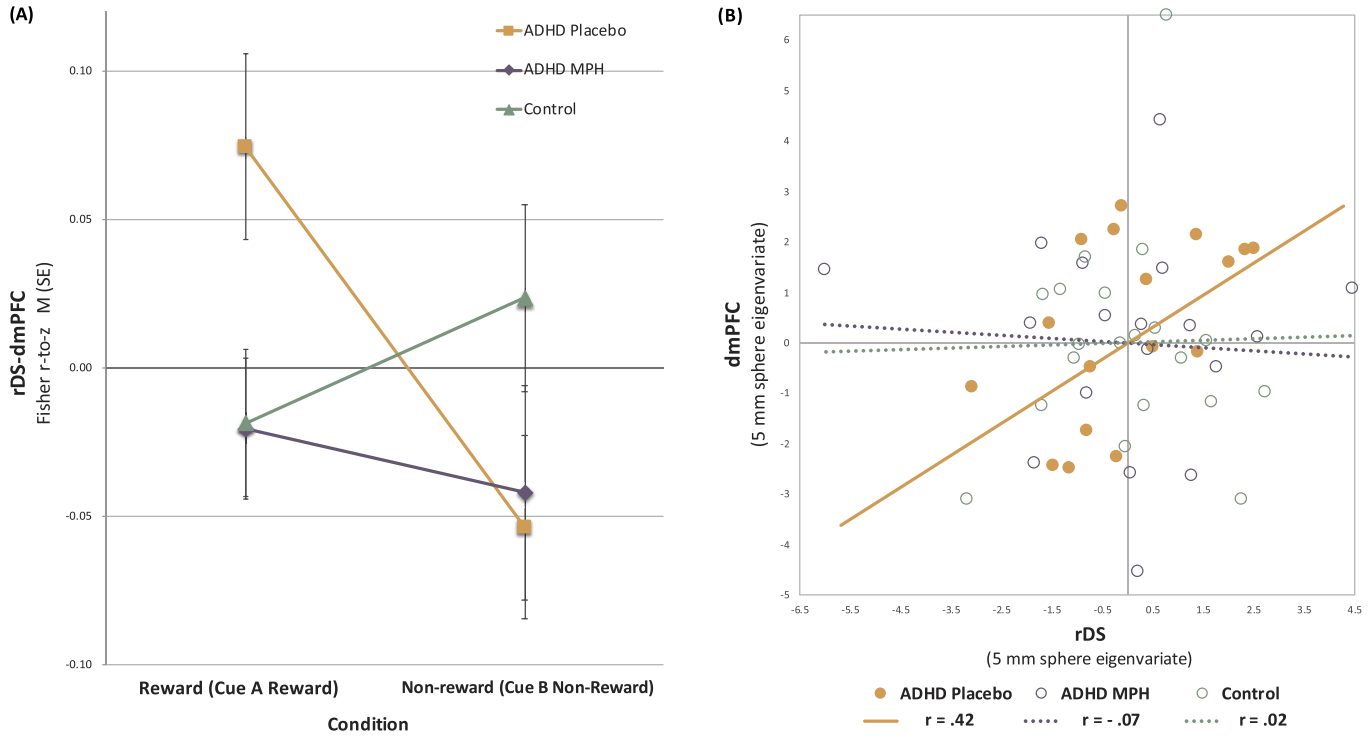

Fig. 3. (A) Means and standard errors of Fisher r-to-z converted rDS-dmPFC correlations during cued-reward and non-reward outcome, and (B) correlations between rDS and dmPFC 5 mm sphere eigenvariate values during cued reward (Cue A reward vs. Cue B non-reward).

or group ($F(2, 53) = 0.88$, $p = .420$) was observed on the correlation strength between rDS and dmPFC either. However, there was a significant group*condition interaction effect ($F(2, 53) = 5.23$, $p = .008$, Fig. 3a). During cued reward (Cue A reward), the ADHD placebo group's rDS-dmPFC correlation was different from the other two groups ($F(2, 53) = 4.04$, $p = .023$) in a one-way ANOVA, and significantly greater than zero ($t(17) = 3.12$, $p = .006$) in a one-sample *t*-test.

3.4. Visualization of rDS-dmPFC correlations for the control and ADHD participants

To visualize and understand the nature of the rDS-dmPFC correlation during cued reward, eigenvariate values from the same 5 mm rDS and dmPFC spheres (Cue A reward vs. Cue B non-reward contrast) were extracted in SPM and plotted for the control and ADHD participants (during the placebo and MPH for the ADHD group) (Fig. 3b). The data are consistent with the results of the CONN analysis.

4. Discussion

The current study showed methylphenidate modulates striatal responses to reward-predicting cues in young adults with ADHD using a classical conditioning paradigm. Larger differences in BOLD responses to reward cues versus non-reward cues were observed when ADHD participants were on MPH, compared to placebo. The cue contrast showed significant effects in bilateral ventral striatum for ADHD participants on MPH. MPH did not necessarily increase the magnitude of their striatal responses to reward-predicting cues. Rather, MPH appeared to improve discriminability between the reward and non-reward cues, i.e., elevated striatal activity was seen only to the reward cues, but not to the non-reward cues. During placebo, the magnitude of striatal responses to reward cues and non-reward cues were similar.

Methylphenidate is the first line pharmacological treatment for ADHD, and its positive effects on behavioral symptoms and cognitive performance are well documented (Bolea-Alamañac et al., 2014; Spencer et al., 1995; Swanson et al., 2011). Methylphenidate increases postsynaptic DA and NE availability (Rubia et al., 2014; Volkow et al., 2009; Zimmer, 2017), which are strongly implicated in the brain's reward mechanisms. Previous behavioral and imaging research has consistently indicated altered reward processing in ADHD, leading to suggestions that MPH might act by modulating responses to reward stimuli. The current study provides the first direct evidence that MPH has acute effects on hemodynamic responses to reward-predicting cues in the ventral striatum. Questions remain, however, regarding whether such effects are unique to individuals with ADHD. No significant group difference was observed between the controls and ADHD participants during placebo in the mean activation levels in the ventral striatum. Control participants were not scanned on MPH.

Exploratory analyses were carried out to examine how striatal responses may relate to BOLD responses in mPFC. The finding of significant MPH effects on the correlation of ventral striatum and medial prefrontal/orbitofrontal cortex, and of dorsal striatum and dorsal medial prefrontal cortex, during cued-reward outcome is consistent with network-based dysfunction in ADHD (Petrovic and Castellanos, 2016; Plichta et al., 2013; Sonuga-Barke and Fairchild, 2012). For those with ADHD, the responses to cued reward in rDS and dmPFC shared a larger variance than the control group, suggesting greater synchrony of the two regions during placebo. A significant decrease in the strength of the correlation was observed in the presence of MPH. These results are consistent with hypersensitivity to reward in ADHD and suggest that this is mediated by the PFC-striatum network. MPH may reduce hypersensitivity by decoupling the rDS and dmPFC. The correlation between rVS and mPFC/OFC was greater on MPH, compared to placebo. However, there was no ADHD placebo vs. control group difference. Variability in the effect of MPH on corticostriatal connectivity may reflect known anatomical and functional differences in DA innervation

in these regions (Saunders et al., 2018).

The ventral striatum regions were evaluated *a-priori*; the reduced responsiveness to reward-predicting cues in individuals with ADHD have been consistently documented (Baroni and Castellanos, 2015; Plichta and Scheres, 2014). The examination of BOLD correlations in the dorsal striatum and medial prefrontal cortex were exploratory; the results are consistent with the existing literature. The dorsal striatum exhibits neural activity in relation to the learned association of sensory cues with movements, and receives strong dopaminergic inputs (Balleine et al., 2007; Everitt and Robbins, 2013; Graybiel and Grafton, 2015). Dopamine action on the dorsal striatal neurons during preparation for the button-press required after an outcome might underlie the observed hemodynamic effects (Wickens et al., 2003). Dorsal striatum is also thought to play a greater role in the later stages of associative learning (Everitt and Robbins, 2013). The medial prefrontal cortex receives a wide range of limbic and sensory inputs, while projecting to the striatum and motor cortex (Euston et al., 2012; Ishikawa et al., 2008). The dorsal mPFC is thought to provide a context (e.g., reward availability) for action (Euston et al., 2012).

In terms of mechanisms of action, we speculate that at therapeutic doses, MPH's effects on striatal dopamine signals in ADHD may be exerted through increased norepinephrine availability in the medial prefrontal cortex (Kuczenski and Segal, 2005, 2001). Effects of norepinephrine include improved attention, which could secondarily affect dopamine release in response to conditioned cues in the striatum. Methylphenidate has also been shown to increase tonic levels of dopamine, while reducing phasic dopamine release (Fuller et al., 2019; Seeman and Madras, 2002; Solanto, 1998). This may be reflected in decreased sensitivity to cued-reward outcomes. The results of the current study provide some support for these possible mechanisms of action.

In the current experiment, care was taken to ensure that group differences were not due to differences in the participants' ability to 'learn' the cue-reward association. All participants completed a brief training session before image acquisition in the scanner. The participants learned the association quickly. Both control and ADHD participants showed similar preference for the reward-predicting cue over the non-reward-predicting cue.

Study participants were carefully selected, increasing our confidence that observed effects are due to group membership and drug condition. Lifetime symptoms of ADHD and functional impairments were verified by structured clinical interview. No participants demonstrated cognitive impairment or reported a history of substance use disorder. Comorbidity rates in the ADHD group were low. All ADHD participants were stimulant-responders. None were prescribed medication in childhood or had more than three years exposure to stimulant treatment with one exception.[3]

Our study has some important caveats and limitations that need mention. All ADHD participants reported significant childhood symptoms of ADHD but did not begin pharmacotherapy until young adulthood. All were willing to suspend medication use during the working week, suggesting a high functioning subpopulation of ADHD. Given the on and off medication design, individuals with ADHD were scanned twice, whereas controls participated only once. Control participants were not tested on medication, and the control group data was used twice for the group comparison analyses. Due to randomization and exclusions, only six participants with ADHD were scanned on MPH in the first session. For these participants, prior exposure to the paradigm, albeit with a different set of cues, may have enhanced the conditioning effect off medication in the second session, reducing any on-off medication differences. Other possible order effects cannot be excluded. A placebo effect may have operated for the ADHD participants (Zubieta and Stohler, 2009). However, likeability ratings for MPH and placebo were not significantly different. The effects of MPH may not have been optimized, as doses were not individually titrated against participants' prescription or body weight (Huss et al., 2017). On the physiological side, BOLD responses are indirect measures of neural responses and possess limited temporal resolution. The temporal predictability required for examining responses to a classically-conditioned cue and to predicted reward may not have been optimal in separating these two phases. However, the model estimate showed an adequate level of non-collinearity among the conditions of interest, likely resulting from the probabilistic reward design. Finally, functional heterogeneity of striatal neurons poses challenges when examining spatially-smoothed voxel or region level data in fMRI. Thus, our study design and sample characteristics may have reduced observed group differences.

[3] Taking out this participant, who started medication at age 12, did not change the direction of the results.

5. Conclusions

The current study demonstrated that MPH influences sensitivity to reward-predicting cues in adults with ADHD. Acute dosing with MPH appeared to "rescue" the striatal responses to reward cues, enhancing discrimination between reward cues and non-reward cues. Methylphenidate was accompanied by changes in cortico-striatal communication in response to cued reward. The effects of MPH on sensitivity to reward-predicting cues and cued-reward outcomes raise the intriguing possibility that it facilitates an excitatory process for increasing dopamine responses to cues, and an inhibitory process in the circuitry for reducing responses to predicted reward. These may be due to the interplay of tonic DA and NE levels in the striatum and prefrontal cortex, and phasic DA responses in the striatum. Complementary effects of actions of multiple neurotransmitters in different brain regions are likely involved. Present knowledge of the neural mechanisms is insufficient to draw conclusions and further research is needed to address these questions.

Data statement

Data will be made available on request and will be deposited to OpenNeuro (https://openneuro.org/).

Declaration of competing interest

Dr. Paulo Mattos was on the speakers' bureau, received travel awards and/or acted as consultant for Shire in the last five years.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropharm.2019.107833.

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