



Research report

Ventral striatal hyperconnectivity during rewarded interference control in adolescents with ADHD



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ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) is characterized by cognitive deficits (e.g., interference control) and altered reward processing. Cognitive control is influenced by incentive motivation and according to current theoretical models, ADHD is associated with abnormal interactions between incentive motivation and cognitive control. However, the neural mechanisms by which reward modulates cognitive control in individuals with ADHD are unknown.

Method: We used event-related functional resonance imaging (fMRI) to study neural responses during a rewarded Stroop color-word task in adolescents (14–17 years) with ADHD ($n = 25$; 19 boys) and healthy controls ($n = 33$; 22 boys).

Results: Adolescents with ADHD showed increased reward signaling within the superior frontal gyrus and ventral striatum (VS) relative to controls. Importantly, functional connectivity analyses revealed a hyperconnectivity between VS and motor control regions in the ADHD group, as a function of reward-cognitive control integration. Connectivity was associated with performance improvement in controls but not in the ADHD group, suggesting inefficient connectivity.

Conclusion: Adolescents with ADHD show increased neural sensitivity to rewards and its interactions with interference control in VS and motor regions, respectively. The findings support theoretical models of altered reward-cognitive control integration in individuals with ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder, characterized by inattention, heightened impulsivity, and hyperactivity (APA, 2013), and affects approximately 5% of school-aged youth (Polanczyk & Rohde, 2007). ADHD has been associated with cognitive control impairments (Barkley, 1997), such as an impaired ability to filter conflicting, irrelevant, or distracting information (interference control) (Lansbergen, Kenemans, & van Engeland, 2007; van Mourik, Oosterlaan, & Sergeant, 2005). Interference control is associated with increased signaling in the posterior medial frontal cortex (pmFC) (Bench et al., 1993; Pardo, Pardo, Janer, & Raichle, 1990; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Adults with ADHD display reduced responses in the pmFC compared with controls (Banich et al., 2009; Bush, Valera & Seidman, 2005).

Reward can modulate cognitive control (Aarts et al., 2010; Botvinick & Braver, 2015; Braver et al., 2014; Pessoa, 2009). Specifically, reward improves interference control when it is contingent on performance (Padmala & Pessoa, 2011). In other situations reward-associations can be detrimental to interference control (Aarts et al., 2014; Krebs, Boehler, & Woldorff, 2010). At the neural level, the ventral striatum (VS) plays an important role in reward processing (Knutson, Adams, Fong, & Hommer, 2001). The VS connections with the prefrontal cortex provide a mechanism by which reward information can influence cognitive processes and ultimately responding (Draganski et al., 2008; Haber, 2003; Haber & Knutson, 2010).

These processes are relevant for ADHD research as recent theories have suggested that alterations in the way motivation and cognitive control interact play a pivotal role in ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg & Casey, 2005; Sonuga-Barke, 2002; Sonuga-Barke, Bitsakou, & Thompson, 2010). In line with these theories, a number of studies have suggested that the behavioral benefit from reward is more prominent in children with ADHD than controls (Luman, Oosterlaan, & Sergeant, 2005). Children with ADHD also showed increased responses in the orbitofrontal cortex, a region strongly innervated by the VS, during rewarded sustained attention (Rubia et al., 2009, but see; Rubia, 2011). Another study suggests that resting-state connectivity in children with ADHD compared with controls is enhanced in reward-related regions, but decreased in attention networks, consistent with ADHD characteristics of impulsivity and inattention (Tomasi & Volkow, 2012).

Task-related functional connectivity in children with ADHD has only been investigated during cognitive control, irrespective of reward, and the results suggest widespread altered connectivity between cortical cognitive control regions (Arnsten & Rubia, 2012; Kelly, Margulies, & Castellanos, 2007). However, to our knowledge, no studies have been conducted that addressed task-related connectivity during rewarded cognitive control. Studies that focused on VS functioning of individuals with ADHD compared with controls, however, have shown reduced responses to reward anticipation (Plichta & Scheres, 2014), but these findings were less consistent in adolescents than in adults (Paloyelis, Mehta, Faraone, Asherson, & Kuntsi, 2012; von Rhein et al., 2015).

Importantly, studies in healthy populations suggest that developmental changes regarding the interplay between reward and cognitive control take place in adolescence (Casey,

Jones, & Hare, 2008; Crone & Dahl, 2012). Adolescent impulsivity is thought to arise from relatively matured, reward-responsive basal ganglia that interact with yet underdeveloped cortical control regions (Casey et al., 2008). Accordingly, healthy adolescents frequently show aberrant responsivity of the VS compared with adults and children (Galvan, 2010). This maturation imbalance marks adolescence as a decidedly relevant developmental stage to study the neural mechanisms of reward and its modulation of interference control. The present study, therefore, investigated both the beneficial effects of reward contingencies and detrimental effects of task-irrelevant reward associations on interference control in adolescents with ADHD. A rewarded Stroop paradigm (Krebs, Boehler, Egner, & Woldorff, 2011) was used.

We had four hypotheses. First, reward would improve behavior more in adolescents with ADHD than in controls and would be accompanied by altered VS response to reward. Second, the ADHD group would show reduced interference control and would differ in their neural response to interference control from controls within fronto-parietal regions, such as the pmFC and parietal attention-related regions. Third, adolescents with ADHD would show altered effects of reward on Stroop interference. Behaviorally, this would surface as ameliorated Stroop interference control in the ADHD group during reward, associated with aberrant task-related neural responses, as well as altered functional connectivity between the VS and cortical regions during rewarded interference control. Fourth, task-irrelevant reward-associated distracters would be more distracting and thereby detrimental to Stroop interference control, especially in adolescents with ADHD.

1. Methods

1.1. Participants

Fifty-nine adolescents (14–17 years) were screened. To ensure that all participants were post-puberty onset and to avoid large sample heterogeneity, we recruited participants of 14 years and older (Galvan, 2010). Exclusion criteria were: MRI contraindications, neurological conditions, current psychotropic medication other than methylphenidate, severe dyslexia, and an IQ below 70 based on the vocabulary and block design of the Dutch Wechsler intelligence scale for children (WISC) (Kort et al., 2002). Individuals with ADHD who were using methylphenidate ($n = 15$) discontinued their medication 24 h prior to the day of testing (Greenhill, 1998). Participants with ADHD were recruited via the child and adolescent psychiatry department of the university medical centre. Controls were recruited via local advertisements and schools.

Inclusion criteria for the ADHD group were: a clinical diagnosis of ADHD according to the DSM-IV-TR (APA, 2000), as previously assessed by a clinician. In addition, the “behavioral disorders” and “whole life” modules of the diagnostic interview schedule for children (DISC-IV, parent version) were used to confirm the current validity of the diagnosis. Participants with ADHD were excluded if they met psychiatric disorder criteria other than ADHD on the DISC-IV, and/or scored

within clinical range on the child behavior checklist (CBCL) (Achenbach & Edelbrock, 1991) and/or the behaviour disorder rating scale (DBDRS) (Oosterlaan, Scheres, Antrop, Roeyers, & Sergeant, 2000; Pelham, Gnagy, Greenslade, & Milich, 1992). We included participants with comorbid oppositional defiant disorder (ODD) because of high comorbidity with ADHD (Biederman, Newcorn, & Sprich, 1991). Controls were also screened for psychiatric disorders on the DISC-IV, CBCL, and DBDRS and were excluded if they scored within clinical range on any of these instruments.

Five participants were excluded from the final analyses. One control participant was excluded because of hyperactivity symptoms. Two participants with ADHD were excluded due to excessive head motion, and two felt uncomfortable in the scanner. The final sample included 25 adolescents with ADHD and 33 controls matched for gender ($\chi^2 = 1.02, p = .40$) and age (Table 1).

1.2. Procedure

This study was approved by the local medical ethics committee (CMO 2012/288) consistent with the Helsinki Declaration. Written informed consent was obtained from participants and their parents. The study consisted of two test sessions: in the first session parents completed the DISC-IV, while participants were prepared for the scan session in a mock scanner. Participants also completed the WISC vocabulary and block pattern to assess IQ (Kort et al., 2002). In the second session participants performed the motivational Stroop task in the MRI scanner. Money earned during the task was added to their €20 participation fee.

1.3. Rewarded Stroop task

The task was programmed in Presentation software (Neurobehavioral Systems, Inc. <https://www.neurobs.com>). Similar to the classic Stroop color-word paradigm (Stroop, 1935), participants responded to the ink color of a written word

(presented for 600 msec) by pressing one of four corresponding keys with their right/left index or middle finger, while ignoring its semantic meaning (Fig. 1). Participants were informed that two ink colors resulted in a monetary reward of 5 ct per trial if the response was fast and correct, or a 5 ct penalty if the response was too slow or incorrect (rewarded trials). The other two ink colors yielded no monetary gain or penalty (unrewarded trials). The irrelevant dimension (semantic meaning) was either congruent (e.g., “red” in red ink) or incongruent (e.g., “red” in green ink). The stimuli occurred in four different font colors (red, yellow, green, blue) and were presented in an event-related design. There were two types of incongruent irrelevant dimensions (words); one where the irrelevant dimension referred to an unrewarded color (neutral distracter) and one where the irrelevant dimension referred to a rewarded color (reward-associated distracter). Both neutral and reward-associated distracters appeared in colors that were rewarded and unrewarded. Additionally, congruent trials for both rewarded and unrewarded colors were included, yielding a total of six conditions (Fig. 1):

Unrewarded:

1. congruent
2. reward-associated distracter
3. neutral distracter

Rewarded:

4. congruent
5. reward-associated distracter
6. neutral distracter

Each condition consisted of 80 trials. Trials were followed by an inter-stimulus interval of 1.5–6 sec and were presented in a pseudo-randomized sequence (trial types were not repeated more than 3 times in a row). To enhance task engagement, the earnings were displayed every 40 trials, followed by a short, self-paced break during which a picture of

Table 1 – Participant characteristics.

Variable	Controls	ADHD ($n = 25$;	Group difference
	($n = 33$; 22 boys)	19 boys)	
	Mean, SD	Mean, SD	
Age	15.30 ± 1.05	15.36 ± 1.08	$p = .84$
Estimated IQ	108.94 ± 12.81	98.28 ± 16.26	$p = .01$
DBDRS (parents) ^a			
Inattention	10.48 ± .85	14.41 ± 2.13	$p < .001$
Hyperactivity/Impulsivity	10.23 ± .67	14.45 ± 2.18	$p < .001$
ODD	10.46 ± .96	12.95 ± 2.06	$p < .001$
CD	10.57 ± 2.87	10.08 ± 5.39	$p = .68$
CBCL DSM scales (T-scores) ^b			
ADHD	51.40 ± 2.22	65.17 ± 7.88	$p < .001$
ODD	51.33 ± 2.43	57.17 ± 6.53	$p < .001$
CD	51.13 ± 2.69	55.33 ± 5.80	$p = .003$

ODD = oppositional defiant disorder; CD = conduct disorder.

^a Behaviour disorder rating scale. Standardized scores. 10 ± 3: average, 15: subclinical, ≥16: clinical.

^b Child behaviour checklist.

Word (irrelevant)	Color (relevant)	
	Congruent	Incongruent
	Neutral	Reward-associated
Unrewarded	RED YELLOW	YELLOW RED GREEN BLUE
Rewarded	GREEN BLUE	RED YELLOW RED YELLOW BLUE GREEN

Fig. 1 – Task conditions (adapted from Krebs et al., 2011). The irrelevant dimension (words) is depicted on the horizontal axis. Top row depicts unrewarded colors, bottom row rewarded colors. Incongruent neutral = neutral distracter. Incongruent reward-associated = reward associated distracter.

the color-finger mapping was displayed as a reminder. Halfway through the task, participants had a 15-min break outside the scanner. Color-finger mapping and reward colors were counterbalanced. A tracking algorithm adjusted the response deadline to approximately 70% correct responses in the rewarded conditions. The initial response deadline was based on the average reaction times (RTs) during the final practice block (below).

1.4. Rewarded Stroop task practice sessions

Before scanning, participants completed three practice sessions of the task. In Practice Session 1 (120 trials), participants learned the stimulus response (color-finger) mappings. They had to respond as quickly as possible to the color of four crosses (XXXX) presented on screen in the colors used in the task after which feedback (“correct”/“incorrect”) was given. In Practice Session 2 (120 trials), the stimuli were words (color names) instead of crosses, identical to the actual task. Participants were asked to respond to the color of the ink and ignore the words. They were also informed for which colors a correct and sufficiently fast response was rewarded. Feedback was given for each trial to make sure that participants understood the task. For neutral trials, feedback was “correct” or “incorrect.” For rewarded trials, it was “correct +5 ct” or “incorrect –5 ct.” In Practice Session 3, feedback was omitted to increase the speed of responding and reduce total task length, identical to the actual task.

2. Analyses

2.1. Behavioral analyses

RTs (averaged for each condition) and error rates (square root transformed) were submitted to a 2 (Group: ADHD vs Control) \times 2 (Reward: Rewarded vs Unrewarded) \times 3 (Congruence: Congruent vs Incongruent Reward-associated vs Incongruent Neutral) analysis of variance (ANOVA) with reward and congruence as repeated-measures factors. Because we hypothesized a priori that the reward-associated distracter would cause more interference than the neutral distracter, we also directly compared both unrewarded incongruent conditions in a repeated-measures ANOVA with ADHD as between-subject factor.

2.2. Functional resonance imaging (fMRI) acquisition and preprocessing

Participants were scanned using a 1.5T Siemens Magnetom Avanto scanner using a 32-channel head coil. Multi-echo GRAPPA EPI scan sequence was used [echo times – TE: 9.2 msec, 20.9 msec, 33 msec, 44 msec and 56 msec]. Each scan consisted of 32 slices, 3 mm thickness with a text revision (TR) of 2010 msec using an ascending scan order (field of view (FOV) = 224 mm, voxel size = 3.5 \times 3.5 \times 3.0 mm and flip angle = 90°). For coregistration and normalization purposes, a whole-brain T1-weighted anatomical scan was collected (176 slices, voxel size = 1 \times 1 \times 1 mm, FOV = 256 mm, TR = 2250 msec, TE = 2.95 msec, flip angle = 15°).

fMRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK) and MATLAB 2013 (The MathWorks Inc., Natick, MA, 2013). Prior to preprocessing, the five TE readouts were combined and realigned using the multi-echo sequence via standard procedures (Poser, Versluis, Hoogduin, & Norris, 2006). Functional images were first realigned using rigid body transformation and resliced. Slice timing correction was applied using the middle slice as reference image. The anatomical T1 images were segmented into gray and white matter. Structural and functional data were coregistered and normalized (voxel size resampling 2 \times 2 \times 2 mm) to a standard anatomical space (Montreal Neurological Institute, MNI) using a unified segmentation procedure (Ashburner & Friston, 2005). Finally, functional images were smoothed using a full-width at half maximum 5 mm Gaussian kernel.

2.3. Task-related whole-brain neural responsivity

The preprocessed images were analyzed, modeling the stimulus onsets of correct trials for each condition and each run. The general linear model (GLM) included 12 task regressors (6 conditions \times 2 runs) and 32 regressors of no interest: 2 regressors for incorrect trials, 12 temporal derivatives of task regressors, and 18 motion parameters (3 translation and 3 rotation parameters, their quadratic effects and first order derivatives). A high-pass filter of 128 Hz was applied before model estimation.

All of the above described regressors were specified at the first-level for each subject. Next, four contrasts were defined: 1. For the main effect of interference control, congruent trials were contrasted with incongruent trials (congruent < incongruent), 2. To examine the main effect of reward, rewarded trials were contrasted with unrewarded trials (rewarded > unrewarded), 3. The effects of reward on interference control were assessed by contrasting rewarded congruent < incongruent trials with unrewarded congruent < incongruent trials, 4. The effect of reward-associated distracters was assessed by contrasting reward-associated distracters with neutral distracters (limited to unrewarded trials) (Krebs et al., 2011).

For second-level analyses, two-sample t-tests were used to assess group differences and were calculated on the amplitude haemodynamic response function (HRF) parameter in a random-effects analysis (whole-brain corrected, $p = .05$). Specifying contrasts at the first-level and running two-sample t-tests at the second-level to assess group differences within these contrasts is generally recommended to correctly use the partitioned error variance.

2.4. VS and pMFC analyses

Because of strong a priori predictions of aberrant responses in the pMFC and VS in participants with ADHD compared to controls, we applied small volume corrections (SVC) to these regions of interest. In order to ensure statistical independence, we followed the recommended procedure by Kriegeskorte, Simmons, Bellgowan, and Baker (2009), basing the volumes of interest (VOI) on independent data. To this

end, we derived the coordinates from studies using similar task designs as the current study. Specifically, we extracted the peak coordinates from the study by Krebs et al. (2011) in the VS for the rewarded > unrewarded contrast. The incongruent > congruent contrast was not conducted by Krebs et al. (2011). Therefore, the pMFC coordinates in the incongruent > congruent contrast were derived from Leung, Skudlarski, Gatenby, Peterson, and Gore (2000), who used a standard event-related Stroop color-word task. SVCs were then applied on an 8 mm radius sphere around these coordinates (Guitart-Masip et al., 2011). Both SVC clusters were considered significant at a threshold of FWE-corrected $p < .05$, and applied to: VS ($x, y, z = -10, 10, -2$) and pMFC ($x, y, z = 6, 22, 42$).

2.5. Generalized psychophysiological interaction (gPPI) analysis

Changes in functional connectivity between the VS and the rest of the brain as a function of the interaction between reward and interference control were assessed using a generalized psychophysiological interaction (gPPI, <https://www.nitrc.org/projects/gppi>) (McLaren, Ries, Xu, & Johnson, 2012) analysis. We predefined the VS activation cluster that showed the highest signal peak (across groups) in the rewarded > unrewarded contrast as seed region ($x, y, z = -8, 10, -4, k = 147$). For each subject, the mean time series within the VS cluster was used as physiological regressor. The BOLD signal from this seed region was deconvolved (Gitelman, Penny, Ashburner, & Friston, 2003). As psychological regressor, we included our 12 task regressors and 2 regressors for incorrect trials in the gPPI analysis. These task regressors were multiplied with the physiological regressor and the result was convolved with a canonical HRF.

In the first-level model, the PPI regressors, the psychological regressors and the physiological regressor were analyzed using a GLM in SPM8. To assess whether functional connectivity between the VS and the rest of the brain was altered in individuals with ADHD compared to controls as a function of reward \times interference control, an independent-samples t-test was conducted on this interaction [(rewarded congruent < rewarded incongruent) > (unrewarded congruent < unrewarded incongruent)].

Finally, we investigated the relationship between functional connectivity and the behavioral benefit of reward on interference control. For this purpose, beta weights from the regions that showed functional connectivity with the VS were extracted using Marsbar (Brett, Anton, Valabregue, & Poline, 2002). Next, correlations were computed between the beta weights and the differences in RT between the rewarded and unrewarded Stroop trials.

3. Results

3.1. Behavioral results

Participants showed a Stroop effect, both in RT, [$F(1.64, 91.83) = 98.53, p < .001, \eta_p^2 = .64$] and error rates, [$F(1.79, 100.29) = 21.22, p < .001, \eta_p^2 = .28$]. They were faster and more

accurate on congruent trials than for neutral and reward-associated distracters (Table S1, available online). The neutral distracter and reward-associated distracter conditions did not differ from each other across groups [RT: $F(1, 56) = 1.15, p = .29, \eta_p^2 = .02$; error rates: $F(1, 56) = .67, p = .42, \eta_p^2 = .01$], or between groups [RT: $F(1, 56) = .48, p = .49, \eta_p^2 = .008$; error rates: $F(1, 56) = 1.94, p = .66, \eta_p^2 = .003$].

Participants were also faster and more accurate on rewarded than unrewarded trials [RT: $F(1, 56) = 95.74, p < .001, \eta_p^2 = .63$; error rates: $F(1, 56) = 42.97, p < .001, \eta_p^2 = .43$]. However, reward did not influence the Stroop effect (no significant reward \times congruency interaction) [RT: $F(1.69, 93.73) = 2.79, p = .08, \eta_p^2 = .05$; error rates: $F(2, 112) = 2.61, p = .08, \eta_p^2 = .05$].

The ADHD group was overall slower and less accurate than controls [RT: $F(1, 56) = 7.92, p = .007, \eta_p^2 = .12$; error rates: $F(1, 56) = 5.11, p = .03, \eta_p^2 = .08$], but there were no group differences in terms of the Stroop effect [RT: $F(1.64, 91.83) = 2.22, p = .12, \eta_p^2 = .04$; error rates: $F(1.71, 100.29) = 1.02, p = .37, \eta_p^2 = .02$], or on the effect of reward as a function of congruency (reward \times congruency \times group) [RT: $F(1.69, 94.73) = .13, p = .85, \eta_p^2 = .003$; error rates: $F(2, 112) = .15, p = .86, \eta_p^2 = .003$].¹

3.2. fMRI results

3.2.1. Reward effects

Participants showed increased neural signaling in response to reward in the bilateral VS (Fig. 2A), the inferior parietal lobe (extending into the supramarginal gyrus) and the right anterior cingulate (Table 2). The ADHD group exhibited increased neural responses to reward compared with controls in two clusters of the superior frontal gyrus (Fig. 2B and Table 2), and in the left VS after SVC was applied ($x, y, z = -6, 8, -8; t = 4.56, p_{svc} = .04, k = 3$, Fig. 2C).

3.2.2. Stroop interference

There was a main effect of congruency in the bilateral inferior frontal gyrus (IFG) (Table 2). The right cluster extended to the middle frontal gyrus and precentral gyrus, whereas the left cluster extended into the pMFC. Furthermore, significant clusters were detected in the superior parietal lobule, post-central gyrus, insula, cuneus, and lingual gyrus. There were no significant group differences for Stroop interference at the whole brain level. SVC in the pMFC also did not yield a significant group difference.

3.2.3. Reward effects on Stroop interference

We assessed the effect of relevant reward on Stroop-related neural signaling by contrasting the neural signal during Stroop interference (incongruent > congruent) on rewarded

¹ In order to examine group differences in interference control, we additionally computed ratio scores between RTs of the incongruent and congruent conditions, thereby controlling for potential group differences in baseline color naming speed (Lansbergen et al., 2007). Using ratio scores instead of difference scores did not change the non-significant group findings. Adding IQ as covariate also did not change the results. Moreover, there were 6 participants ($n = \text{ADHD}$) who reported regular use of nicotine or recent (within 2 weeks prior to testing) use of marijuana or MDMA. These were not outliers and the behavioral and fMRI results did not change when excluding these 6 individuals.

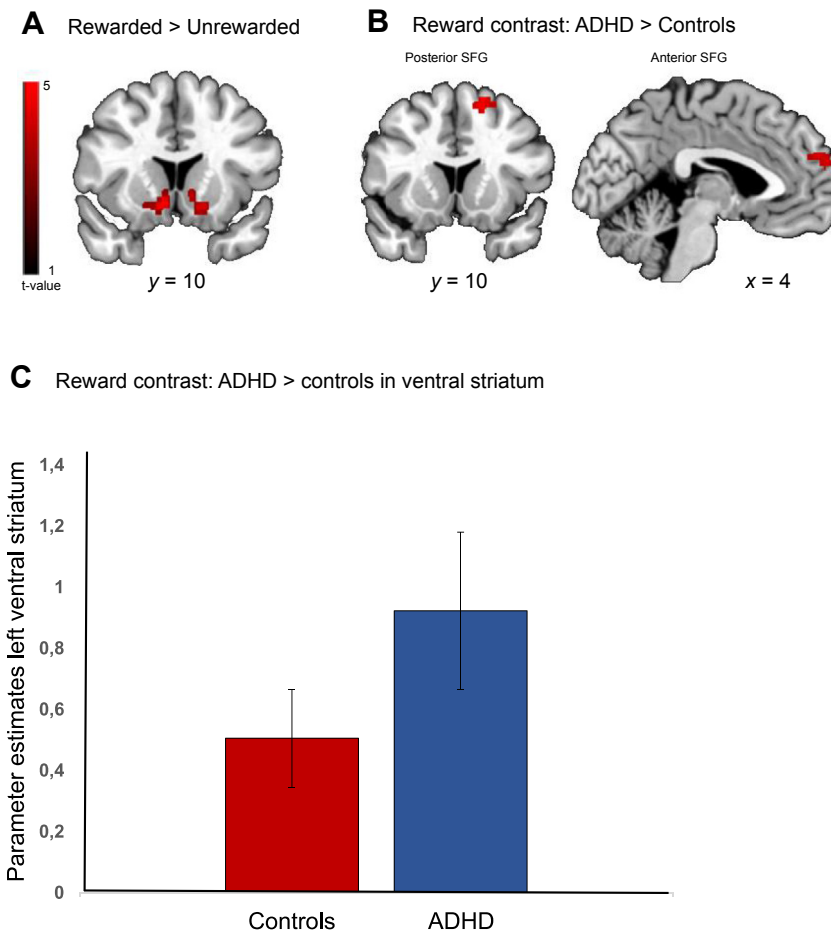


Fig. 2 – A. Bilateral ventral striatum (VS) response to reward. B. Superior frontal gyrus (SFG) response in ADHD compared to controls $p_{(FWE\ cluster)} < .05$. C. Small volume corrected left VS response in ADHD compared to controls.

trials with unrewarded trials. There was an increase in neural signaling in several visual areas, specifically in the middle occipital gyrus and calcarine sulcus (Table 2). However, there were no group differences in the effect of reward on Stroop interference.

3.2.4. Reward-associated distracters versus neutral distracters

Contrasting reward-associated with neutral distracters, increased activity was observed in the calcarine sulcus, extending to a large portion of the visual cortex (Table 2). Contrary to what we predicted, there were no group differences in the effects of reward-associated distracters on neural signaling.

3.2.5. Corticostriatal functional connectivity

We observed increased functional connectivity during rewarded Stroop interference in the ADHD group than in controls between the VS and the motor cortex [right precentral gyrus; $x, y, z = 52, -12, 38$, $p_{(FWE\ cluster)} = .004$, $t = 4.35$, $k = 102$] and a marginal effect in the left precentral gyrus [$x, y, z = -60, -6, 30$, $p_{(FWE\ cluster)} = .06$, $t = 4.06$, $k = 60$, Fig. 3]. Interestingly, controls showed negative connectivity, whereas the ADHD group showed positive connectivity between the VS and precentral gyrus during rewarded Stroop interference,

suggesting that the VS in adolescents with ADHD is hyper-connected with the precentral gyrus in rewarded versus unrewarded Stroop interference control.

Beta weights from the connectivity between VS and right precentral gyrus correlated with the behavioral benefit of reward on Stroop interference control in controls ($r = .38$, $p = .03$), but not in adolescents with ADHD ($r = .21$, $p = .33$; Fig. 3C).

4. Discussion

The neural correlates of reward modulation on interference control in adolescents with and without ADHD were investigated. We examined task-related neural correlates and VS functional connectivity of rewarded interference control. Behaviorally, reward improved general task performance in both groups, confirming that the reward manipulation was effective. Task-related activation revealed that adolescents with ADHD exhibited neural hyperresponsivity to reward anticipation within VS and SFG. Despite this group difference in neural functional connectivity, behavior or task-related activation in the reward-cognition interactions was not altered. However, our connectivity results demonstrated that adolescents with ADHD show corticostriatal

Table 2 – Cluster regions and coordinates in each fMRI contrast.

Contrast	Regions	Side	k	MNI coordinates			t-Value
				x	y	z	
Stroop: Incongruent > Congruent	Inferior frontal gyrus	R	392	46	4	34	6.42
	Frontal inferior operculum			48	12	30	4.80
	Frontal inferior operculum			36	10	32	4.48
	Inferior parietal lobule	L	691	–28	–54	48	6.16
	Superior parietal lobule			–30	–60	56	4.83
	Precuneus			–24	–66	36	4.79
	Medial frontal gyrus	L	1799	–10	–2	54	5.87
	Supplementary motor area			–4	18	44	5.86
	Inferior frontal gyrus	L		–44	6	32	5.65
	Postcentral gyrus	R	139	46	–32	50	5.70
	Postcentral gyrus			38	–36	48	4.01
	Postcentral gyrus			36	–36	56	3.76
	Superior parietal lobule	R	437	20	–56	60	5.69
	Angular gyrus			32	–56	46	4.79
	Precuneus			18	–66	50	4.56
	Inferior parietal lobule	L	294	–48	–32	44	5.62
	Inferior parietal lobule			–32	34	44	5.62
	Postcentral gyrus	L		–40	–36	48	4.87
	Lingual gyrus			–12	–68	0	5.04
	Calcarine	L	143	16	–84	2	4.95
	Cuneus			8	–82	2	4.85
	Cuneus			18	–92	4	4.60
	Medial frontal gyrus	R	150	20	2	56	4.84
	Middle frontal gyrus			30	–2	56	4.19
	Insula	R	95	34	22	8	4.25
	Insula			34	26	0	3.85
Reward: Rewarded > Unrewarded	Caudate head	L	147	–8	10	–4	6.50
	Putamen	R	131	18	8	–6	4.92
	Caudate			12	12	0	3.33
	Caudate			8	6	–8	3.65
	Inferior parietal lobule	R	71	56	–36	48	4.63
	Supramarginal gyrus			60	–36	38	3.76
	Anterior cingulate	R	79	10	42	26	4.41
	Anterior cingulate			8	42	16	3.99
	Anterior cingulate			2	36	12	3.67
	Superior frontal gyrus	R	71	18	10	60	4.72
Reward contrast: ADHD > Controls	Superior frontal gyrus	R	148	4	58	26	4.31
	Superior frontal gyrus	R		14	56	30	4.29
	Anterior cingulate			10	46	22	3.64
	Calcarine	R	236	0	–90	6	5.24
Rewarded Stroop > Unrewarded Stroop	Cuneus			10	–90	8	5.06
	Cuneus			12	–98	8	4.66
	Middle occipital gyrus	L	132	–38	–80	–4	4.69
	Middle occipital gyrus			–42	–88	0	4.37
	Middle occipital gyrus			–34	–90	8	4.18
Reward-associated distracters > Neutral associated distracters	Calcarine	L	236	0	–90	6	5.24

Side: Left/right hemisphere.

k = number of voxels in cluster.

T = t-value; threshold all reported statistics $p_{(FWE\ cluster)} < .05$.

hyperconnectivity during rewarded interference control. In contrast to controls, the ADHD group showed no association between corticostriatal connectivity and behavioral improvement as the result of reward.

The hyperresponsivity of the SFG and VS in response to reward in adolescents with ADHD supports theories that imply disruptive reward pathways in individuals with ADHD (Castellanos et al., 2006; Haenlein & Caul, 1987; Nigg & Casey, 2005). Although, our finding differed from the frequently

reported VS hyporesponsivity to reward anticipation in adults with ADHD (Plichta & Scheres, 2014), it is in line with recent studies demonstrating VS hyperresponsivity in individuals with ADHD during reward receipt (Furukawa et al., 2014; von Rhein et al., 2015). The divergent results may be explained by differences in the reward processing phase: anticipation, target, or receipt (Tripp & Wickens, 2009). Alternatively, it is possible that ADHD-control differences in VS reactivity vary as a function of neurodevelopment. For example, Kappel et al.

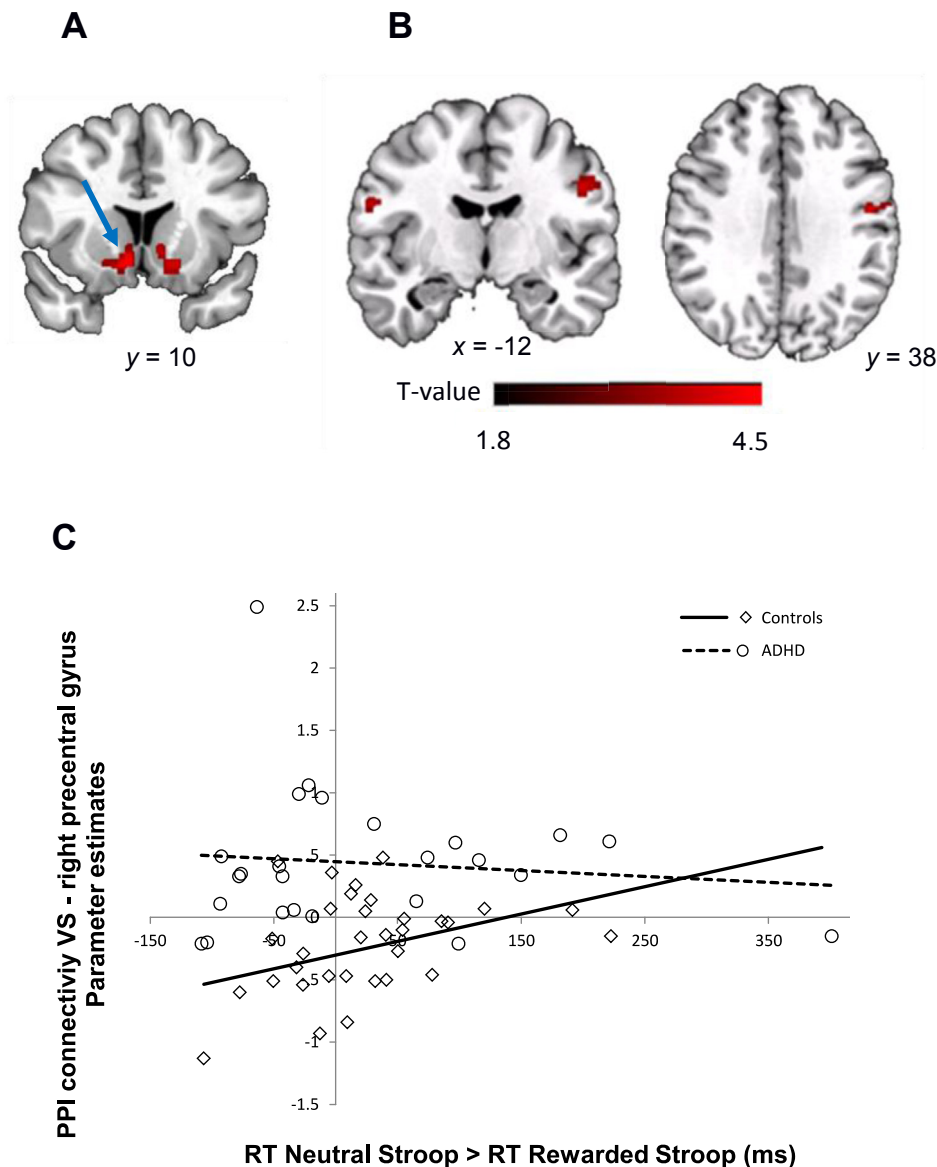


Fig. 3 – A. Left VS seed region. B. Functional connectivity group difference of the left VS in the contrast: rewarded Stroop > neutral Stroop [$p_{(FWE\ cluster)} < .05$]. C. Correlations between precentral gyrus parameter estimates from the psychophysiological interaction (PPI) analysis and the beneficial effect of reward on Stroop interference control reaction times.

(2014) found hypo-activation during reward anticipation in adults but not in children with ADHD (von Rhein et al., 2015). Interestingly, findings regarding VS reactivity to reward in healthy adolescents are inconsistent as well, with some studies reporting hyperresponsivity in adolescents (Galvan et al., 2006; Van Leijenhorst et al., 2010) and others reporting hypo-activation (Bjork et al., 2004). Results may also depend on the level of task engagement, with more engaging tasks resulting in VS hyper-reactivity and more boring tasks in hypo-activation (Galvan, 2010), which may be especially relevant for ADHD research.

In addition to VS hyperresponsivity, the ADHD group showed SFG hyperresponsivity to reward compared with controls. The SFG is mainly associated with working memory functions (du Boisgueheneuc et al., 2006; Owen, 2000; Petrides,

2000). Therefore, its activation in the ADHD group might reflect compensatory recruitment as a function of reward. Consistent with typical patterns of reward anticipation signaling, both groups showed additional responses within the anterior cingulate cortex, putamen and caudate during reward trials (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Kunishio & Haber, 1994; Schultz, 2000; Shidara & Richmond, 2002; Williams, Bush, Rauch, Cosgrove, & Eskandar, 2004).

Our data also confirmed the expected Stroop interference effect across groups: participants were faster and more accurate on congruent trials than on incongruent trials. This interference effect was associated with increased response in the fronto-parietal network replicating numerous Stroop fMRI studies in adults (Pardo et al., 1990; Peterson et al., 1999) and

adolescents (Adleman et al., 2002). Consistent with our behavioral findings there were no group differences in the neural responses to interference control. In general, however, the ADHD group performed worse than controls, as expected (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). Specific neuropsychological deficits are heterogeneous in ADHD groups and, therefore, complex to pinpoint at the group level (e.g., Coghill, Seth, & Matthews, 2014). Our data supported this notion and suggest that hampered general task performance characterized our sample better than specific interference control deficits.

Functional connectivity analyses revealed that adolescents with ADHD showed hyperconnectivity between the VS and precentral gyrus during rewarded Stroop interference control. The precentral gyrus is a motor region implicated in inhibition or interference control tasks (Liddle, Kiehl, & Smith, 2001; Menon, Adleman, White, Glover, & Reiss, 2001). Controls and participants with ADHD showed opposite directions of their connectivity patterns. In controls, the negative connectivity between VS and motor regions was associated with slower rewarded Stroop performance. In the ADHD group, no relation was found between positive connectivity and behavior. This suggests that adolescents with ADHD show an inefficient hyperconnectivity between VS and motor regions during rewarded interference control. The result concurs with our hypothesis and theoretical models in which reward is proposed to modulate cognitive control differentially in individuals with ADHD via altered corticostriatal connectivity (Castellanos et al., 2006).

When interpreting these results in the context of ADHD, it is important to note the potential neurochemical underpinnings of the effects. Dopamine is expected to play a role, given its well-established involvement in reward-related processing (Schultz, 1998), motor control (Graybiel, Aosaki, Flaherty, & Kimura, 1994), and ADHD (Volkow et al., 2009). However, recently evidence has accumulated for a role for serotonin in reward processing (Nakamura et al., 2008; see for review Rogers, 2011), and to some extent for serotonin dysfunction in ADHD (e.g., Faraone et al., 2005; Oades, 2008). In fact, contemporary views propose that rather than being independent systems, the dopaminergic and serotonergic systems interact and together modulate behavioral activation and inhibition (for review see Cools et al., 2011). For example, in healthy adults serotonin depletion induced deficits in inhibitory control, although these may be restricted to conditions in which participants anticipate punishment (Crockett et al., 2009; Helmsbold et al., 2015, but see Gaber et al., 2015). Thus far, our understanding of the role of serotonin in reinforced cognitive control and ADHD remains limited. In the current study, we cannot disentangle the effects of reward and punishment anticipation, and we did not manipulate or measure the dopaminergic and/or serotonergic systems directly. Future psychopharmacological studies are required to disentangle the role of both neuromodulators in reinforcement and cognitive control interactions in ADHD.

Increased neural responses in visual processing regions were found across groups when examining the interaction of reward with interference control. Visual attention is modulated by salience, such as reward (Padmala & Pessoa, 2011; Serences, 2008; Small et al., 2005). In the Stroop task

specifically, enhanced visual processing of the task-relevant aspect (color) and suppression of the task-irrelevant aspect (word) has been demonstrated (Polk, Drake, Jonides, Smith, & Smith, 2008). Our result of increased response in visual regions during rewarded Stroop interference control therefore may suggest enhanced attention to incongruent rewarded stimuli across groups. However, responses in cortical cognitive control regions were additionally expected (Engelmann, Damaraju, Padmala, & Pessoa, 2009; Kastner & Ungerleider, 2000; Padmala & Pessoa, 2011). The lack of group differences in rewarded Stroop interference control in both our neural and behavioral results show that in the ADHD sample interference control was not ameliorated by reward. We are, however, cautious to suggest that reward does not ameliorate interference control in adolescents with ADHD, as interference control itself was unimpaired in the current ADHD sample.

We observed no detrimental behavioral effects of reward-associated distracters. This may have been caused by the practice procedure, which deviated from the original task. Our participants did demonstrate a main effect of reward, suggesting sufficient explicit reward learning. Krebs et al. (2011) suggested that the reward-associated distracter effect may be attributed to non-conscious saliency, automatically triggering visual processing and subsequent response selection in the pre-SMA as slower responses on these trials correlated with increased pre-SMA signaling. Although we also found enhanced visual processing for reward-associated distracters, suggesting low-level saliency processing, this was not accompanied by increased pre-SMA signaling. These findings may suggest that these response selection pathways were not triggered in our adolescent sample, and consequently, no conflict occurred at the response level.

The results may have implications for treatment by offering insight into the mechanism by which reward-interference control interactions are processed differently in adolescents with ADHD versus controls. Reinforcement (e.g., tangible rewards and/or verbal praise) is typically recommended as a component of behavioral modification programs in youth with ADHD (Fabiano et al., 2009). Behavioral studies have demonstrated that during reinforcement, youth with ADHD are able to normalize partly in interference control (Geurts, Luman & Van Meel, 2008) and inhibition (for meta-analysis see: Ma, van Duijvenvoorde, & Scheres, 2016). So far, neuroimaging studies on this topic primarily investigated indirect measurements, such as reward and cognitive control processes in isolation (e.g., Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Plichta & Scheres, 2014) or resting state functional connectivity (e.g., Tomasi & Volkow, 2012). Our results uncover the potential mechanism underlying these effects more directly. Future studies can elucidate this further by using more behaviorally sensitive paradigms.

Two limitations should be addressed. First, the design may not have been optimal to detect behavioral effects of reward on Stroop interference control, as reward enhanced performance on both congruent and incongruent trials. However, using a task with rewarding incongruent trials only would have created a bias in favor of incongruent trials. Second, reward and loss avoidance were combined to maximize motivation but their separate effects could not be distinguished in this task. Previous work, however, has indicated

that VS responses to loss avoidance do not differ between adolescents with ADHD and controls (Scheres, Milham, Knutson, & Castellanos, 2007), making it less plausible that the neural differences can be explained by loss avoidance.

In conclusion, adolescents with ADHD appear to show inefficient hyperconnectivity between the VS and motor regions during rewarded interference control. Adolescents with ADHD furthermore demonstrated hyperresponsivity in the VS and SFG in response to potential reward. These findings concur with theoretical models proposing altered reward sensitivity and deficient reward modulations of cognitive control in individuals with ADHD.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cortex.2016.05.021>.

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