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Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis

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Background: Changes in reward processing are thought to be involved in the etiology of attention-deficit/hyperactivity disorder (ADHD), as well as other developmental disorders. In addition, different forms of therapy for ADHD rely on reinforcement principles. As such, improved understanding of reward processing in ADHD could eventually lead to more effective treatment options. However, differences in reward processing may not be specific to ADHD, but may be a trans-diagnostic feature of disorders that involve ADHD-like symptoms. **Methods:** In this event-related fMRI study, we used a child-friendly version of the monetary incentive delay task to assess performance and brain activity during reward anticipation. Also, we collected questionnaire data to assess reward sensitivity in daily life. For final analyses, data were available for 27 typically developing children, 24 children with ADHD, and 25 children with an autism spectrum disorder (ASD) and ADHD symptoms. **Results:** We found decreased activity in ventral striatum during anticipation of reward in children with ADHD symptoms, both for children with ADHD as their primary diagnosis and in children with autism spectrum disorder and ADHD symptoms. We found that higher parent-rated sensitivity to reward was associated with greater anticipatory activity in ventral striatum for children with ADHD symptoms. In contrast, there was no relationship between the degree of ADHD symptoms and activity in ventral striatum. **Conclusions:** We provide evidence of biological *and* behavioral differences in reward sensitivity in children with ADHD symptoms, regardless of their primary diagnosis. Ultimately, a dimensional brain-behavior model of reward sensitivity in children with symptoms of ADHD may be useful to refine treatment options dependent on reward processing. **Keywords:** Attention-deficit/hyperactivity disorder; fMRI; reward processing; striatum; trans-diagnostic mechanisms; reward anticipation; autism spectrum disorder.

Introduction

Changes in reward processing are suggested to be involved in the etiology of attention-deficit/hyperactivity disorder (ADHD). Indeed, various forms of therapy for ADHD are dependent on reward processing: behavior therapy and parent training programs often use reinforcement contingencies to promote desired behavior (Fabiano et al., 2009). Psychostimulants, commonly used to treat ADHD, increase dopamine availability in the synapse, thereby affecting reward processing (Frank, Santamaria, O'Reilly, & Willcutt, 2006; Pelham, Milich, & Walker, 1986; Wilkison, Kircher, McMahon, & Sloane, 1995). However, children with ADHD differ in the extent with which they respond to treatment and individual differences in reward processing may relate to differences in treatment response. Furthermore, it is an open question whether differences in reward processing are specific to ADHD or whether they are related to psychopathology in a more general, trans-diagnostic way. Changes in brain activation related to reward processing have also been reported in autism, schizophrenia, and major depressive disorder (Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Dichter et al., 2010; Juckel et al., 2006; Kohls et al., 2014; Smoski et al., 2009).

On average, children with ADHD show atypical behavioral responses to reward (Luman, Oosterlaan, & Sergeant, 2005). They tend to favor smaller, immediate rewards over larger, delayed ones (e.g., Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). Furthermore, the improvement in task performance following reward is greater for children with ADHD than for typically developing children (Luman, Tripp, & Scheres, 2010; Luman et al., 2005). As a result, some models of ADHD have focused on changes in reward processing: Sagvolden and colleagues suggested that ADHD may be associated with a general hypo-dopaminergic state, where deficits in dopamine signaling lead to a strong preference for immediate reward (Sagvolden, Johansen, Aase, & Russell, 2005). In contrast, Tripp and Wickens suggested that there may be a more specific problem with dopamine signaling in ADHD. They suggest that not the processing of a rewarding event itself is affected, but rather that the transfer of signal from rewarding events to the cues that predict them is attenuated; this would result in atypical reward learning (Tripp & Wickens, 2008, 2009). Both theories make explicit predictions about dopamine activity in anticipation of reward in ADHD. Activity in ventral striatum (VS)

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as assessed by fMRI can be used as a proxy for such dopamine activity (Knutson & Gibbs, 2007). fMRI studies of reward processing have shown VS hypoactivity during reward anticipation in adults and adolescents with ADHD (Plichta & Scheres, 2014). However, to date only limited data on younger participants exist and a first study on children with ADHD found no between-group differences (Kappel et al., 2015).

In this study, we set out to investigate changes in performance and brain activity during the anticipation of reward in children with ADHD symptoms, irrespective of a primary diagnosis of ADHD. In addition, we assessed reward sensitivity in daily life. We included typically developing children, children with a primary diagnosis of ADHD and children with similar levels of parent-rated ADHD symptoms but a different primary diagnosis. For this last group, we chose to include children with an autism spectrum disorder (ASD) as this is the next primary diagnosis with the highest prevalence of ADHD symptoms. We hypothesized that children with ADHD would show hypoactivity in ventral striatum during reward anticipation, similar to adults and adolescents with ADHD. We also investigated other regions in frontostriatal reward circuitry to assess the topological specificity of this hypoactivity. We further hypothesized that: this hypoactivity would not be specific to ADHD, but rather would also be found in children with ASD and ADHD symptoms; ADHD symptoms would drive this effect, where a trans-diagnostic dimensional measure of ADHD symptoms would explain additional variance in addition to any effect of diagnosis; and anticipatory activity in VS would be positively associated with reward sensitivity in daily life. The inclusion of two groups of subjects with ADHD symptoms allowed us to address the latter two hypotheses by facilitating dimensional analyses across diagnostic groups. Such analyses have been suggested to be more powerful than categorical ones, as they more closely resemble the dimensional nature of the underlying neurobiology (Robbins, Gillan, Smith, de Wit, & Ersche, 2012).

Methods and materials

Participants

A total of 108 right-handed boys, aged 8–12 years were included in the study: 33 typically developing boys and 75 boys with ADHD symptoms. The children with ADHD symptoms included 38 boys with a primary diagnosis of ADHD and 37 with a primary diagnosis of autism spectrum disorder (ASD). Typically developing children were recruited through schools in the wider Utrecht area. Children with ADHD symptoms were recruited through the outpatient clinic for developmental disorders of the University Medical Center Utrecht (UMCU) and schools for special education. Only children using no medication or short-acting psychostimulants (e.g., methylphenidate) were included; 71% of children with ADHD and 68% of children with ASD and symptoms of ADHD were using short-acting psychostimulants. All parents were instructed not to administer medication in the 24 hr prior to testing. All children completed a modified monetary incentive delay (MID) paradigm in the context of a functional MRI scan (van Hulst, de Zeeuw, Lupas, et al., 2015). After screening data quality, 27 participants were excluded on the basis of excessive head motion, three participants were excluded due to anatomical abnormalities, and two participants had to be excluded as a result of an incorrectly placed field of view (for details see Appendix S1). Data from 76 participants were available for final analyses. Notably, these 76 children did not differ from the children that were excluded from the final analyses on their level of ADHD symptoms (independent samples *t*-test per group: control: $t(31) = 0.36$, $p = .724$; ADHD: $t(33) = 0.30$, $p = .764$; ASD: $t(34) = 0.43$, $p = .674$). Participants were matched at a group level for age and IQ. Demographics are provided in Table 1.

In- and exclusion criteria

The Diagnostic Interview Schedule for Children (DISC-IV, parent version) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was administrated to parents of all participants. In addition, children participated in a four-subtest short-form of the WISC-III in order to estimate full-scale IQ. If intelligence testing using WISC-III had been performed in the past 2 years, it was not repeated and that score was used. Inclusion criteria for typically developing children were: no psychiatric diagnoses on the DISC-IV interview (except for specific phobia and enuresis) and no scores in the clinical range on any scale of the Child Behavior Checklist (CBCL), as reported by (one of) the parents. Inclusion criteria for children with ADHD symptoms included either a clinical DSM-IV diagnosis of ADHD, established by an expert clinician as part of routine clinical care and supported by the Diagnostic Interview Schedule for Children (DISC); or a DSM-IV autism spectrum diagnosis established by an expert clinician as part of routine clinical care and a score in the (sub)clinical range of the CBCL subscale of Attention Problems. For all participants, major illness, present or past neurological illness, IQ lower than 70 and the presence of interfering metal objects in or around the body were grounds for exclusion. After study procedures had been explained, all parents and adolescents (aged 12) gave full written consent, while children provided verbal assent. The study and its procedures were approved by the institutional review board of the University Medical Center Utrecht.

Questionnaires

Aside from the CBCL, parents completed two questionnaires: the first was the Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) questionnaire (Lakes, Swanson, & Riggs, 2012). We chose this questionnaire as it assesses symptoms listed in the DSM-IV definition of ADHD across the complete spectrum of functioning (both attention problems and attention skills relative to their peers). The second was the Sensitivity to Punishment and Sensitivity to Reward Questionnaire for children (SPSRQ-c) (Luman, van Meel, Oosterlaan, & Geurts, 2012), a questionnaire designed to assess sensitivity to reinforcement in children. To provide some examples, questions include: 'Your child has a lot of difficulty ending a fun activity', 'Your child engages in risky behavior to obtain a reward,' and 'Your child does a lot of things for approval'. We computed Crohnbach's α to test the internal consistency of the different questionnaire subscales in the present sample.

Monetary incentive delay paradigm

We used a child-friendly version of the monetary incentive delay task (De Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; van Hulst, de Zeeuw, Lupas, et al., 2015) to

Table 1 Demographics and questionnaire data per clinical group

	Control (*SD*)	ADHD (*SD*)	ASD (*SD*)	*F*-value	*p*-value
N (76)	27	24	25		
Age	10.5 (1.0)	11.2 (1.0)	10.8 (1.4)	(2,73) 2.59	.082
IQ	116.9 (18.3)	108.2 (16.0)	107.4 (19.1)	(2,73) 2.27	.110
SWAN-hyp	0.42 (0.73)	−1.09 (0.65)[a]	−0.90 (0.70)[a]	(2,70) 34.84	<.001
SWAN-att	0.39 (0.62)	−1.34 (0.65)[a]	−1.46 (0.46)[a]	(2,70) 81.27	<.001
SPSRQ-C	2.70 (0.39)	3.26 (0.33)[a,b]	2.97 (0.63)[a,b]	(2,70) 8.53	<.001

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; *SD*, standard deviation; SWAN-hyp, hyperactivity/impulsivity subscale of the Strengths and Weaknesses of ADHD and Normal Behavior Rating Scale; SWAN-att, inattention subscale of the Strengths and Weaknesses of ADHD and Normal Behavior Rating Scale; SPSRQ-C, reward sensitivity subscale of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire for Children.
[a]Significant post hoc group difference from typically developing children. [b]Significant post hoc group difference between children with ADHD and children with ASD and symptoms of ADHD.

assess brain activity during reward anticipation. Children were instructed that they could win real money during the task and were paid afterwards using gift certificates. The trial sequence was as follows: first, a picture of a wallet with 0, 5, or 15 cents was shown (2,000 ms), indicating the amount of money that could be won on the upcoming trial. Next, pictures of two cartoon figures (SpongeBob and Patrick Star from the SpongeBob TV-series) were shown (750 ms) and participants were asked to guess which cartoon figure was hiding the wallet by pressing the left or right response button as fast as possible. Then, a black screen was shown (500 ms) and finally, a thumbs-up or a thumbs-down picture, indicating a correct or incorrect choice, was shown (750 ms) along with the total amount of money won so far. However, the task was rigged in such a way that trial outcome was fixed; the choices made did not affect reward outcome. Two hundred and forty Trials (80 trials per cue type) were divided evenly into four blocks. Each block had a fixed reward frequency of either 20% (low reward) or 80% (high reward). Participants were randomly presented with one out of two counterbalanced reward sequences ('high-low-high-low' or 'low-high-low-high'), so that average reward frequency was 50% for the full task. The task design is described elsewhere (De Zeeuw et al., 2012). The primary neuropsychological outcome measure was the speeding-up of response times in reaction to the anticipation of reward (cue of filled wallet); as compared to response times when no monetary reward was anticipated (cue with empty wallet). This was quantified using linear regression of the rank ordered response times to high rewarded trials (15 cents) on the rank ordered response times to unrewarded trials (0 cents), as described previously (De Zeeuw et al., 2012). We chose this measure as it is minimally influenced by differences in response-time variability, as intraindividual variability in response times is greater in ADHD than in typical development (Klein, Wendling, Huettner, Ruder, & Peper, 2006). A regression coefficient smaller than one indicates faster responses on rewarded than on unrewarded trials.

fMRI data acquisition

The study was run on a 3.0 T Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) using an eight-channel, sensitivity-encoding (SENSE), parallel imaging head coil. For anatomical reference, a whole-brain, three-dimensional fast field echo T1-weighted scan (200 slices; repetition time = 10 ms; echo time = 4.6 ms; flip angle = 8°; field of view, 240 × 240 × 160 mm; voxel size: 0.75 × 0.8 × 0.75 mm isotropic) was acquired. Whole-brain T2*-weighted echo planar images (EPI) with blood oxygen level-dependent (BOLD) contrast (4 sessions; 122 volumes per session; 36 slices per volume; interleaved acquisition; TR = 2.02 s; TE = 35 ms; field of view = 232 × 123 × 256 mm; flip angle = 70°; voxel size = 2.67 × 2.67 × 3.43 mm) oriented in a transverse plane were acquired. Six dummy scans were acquired to allow for T1 equilibration effects.

Preprocessing of fMRI data

FMRI data were analyzed using SPM8 (r4290) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) as implemented in Matlab 7.12 (Mathworks Inc., Natick, MA). To correct for between-scan head motion, all images were realigned to the first volume using rigid body transformations. Next, the anatomical image was coregistered to the first fMRI image using the mutual information criteria method and subsequently normalized to Montreal Neurological Institute (MNI) space using unified segmentation. The image was then resliced at a voxel size of 1.0 × 1.0 × 1.0 mm. Functional images were normalized using the normalization parameters generated in this step, the images were resliced at a voxel size of 3.0 × 3.0 × 3.0 mm. Finally, the fMRI images were spatially smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm. In addition, scan-to-scan movement was assessed using ArtRepair (Mazaika, Hoeft, Glover, & Reiss, 2009). Scans with more than a 1.0-mm scan-to-scan movement or where the average signal deviated more than 1.5% from the average global signal over scans, were replaced using a linear interpolation of the values of neighboring scans (i.e., the scan before and after the discarded scan). Participants with more than 30% replaced scans were excluded from further analyses (for details, see Appendix S1).

Statistical analyses – task performance

We tested for an effect of diagnosis (i.e., categorically) and ADHD symptoms (i.e., dimensionally) on three performance measures: baseline (no reward condition) mean response times (MRT), baseline standard deviation of response times (SDRT), and the shift in response time distribution between high reward and no reward ($B_{0vs.15}$). After testing for normality (Shapiro–Wilk test) and homogeneity of variances (Levene's test), analysis of covariance (ANCOVA) was conducted with diagnosis as a factor. If age or IQ covaried with a measure of task performance, analyses were run both with and without the covariate. If not, the covariates were left out of the final model. If between-group differences were found, we performed post hoc testing using Fisher's least significant difference (LSD) to compare the three groups. We followed up with trans-diagnostic, dimensional analyses: here, we tested for an effect of ADHD symptoms [i.e., SWAN-inattention and SWAN-hyperactivity/impulsivity subscores (Lakes et al., 2012)] and parent-rated reward sensitivity [i.e., SPSRQ-c reward subscores (Luman et al., 2012)] on the three different performance measures, within the combined clinical group and the control group separately. If there were no between-group differences,

we ran correlational analyses on the entire sample. Results were corrected for multiple comparisons using False Discovery Rate (FDR) correction on the separate ANCOVA results (per performance measure) using the Benjamini–Hochberg method (Benjamini & Hochberg, 1995).

Statistical analyses – fMRI

Statistical analyses of fMRI data were performed in a two-level procedure within the framework of the general linear model. First, for each subject, we modeled the blood oxygenation level-dependent (BOLD) activation invoked by task cues as conditions of interest, and realignment parameters as potential confounders (condition of no interest). Three cues were modeled as conditions of interest: anticipation of respectively 0, 5, and 15 cents reward. Regressors were created by convolving delta functions coding for cue onset with a canonical hemodynamic response function (as implemented in SPM8) for each cueing category separately. The estimated regression coefficients for the different cues were then contrasted resulting in first-level contrast images for each subject. The contrast between 0 and 15 cent was used for the main analyses. If effects were found, post hoc analyses were conducted on the two underlying contrasts (0 vs. 5 cents and 5 vs. 15 cents) in order to dissociate reward valence and reward magnitude. Our task was only designed to detect differences in anticipatory activity, and as a consequence of collinearity we could not analyze reward outcome separately. Data were high-pass filtered using discrete cosine basis functions with a 128-s cut-off. At the group level, the analysis focused on average activity in a priori-specified regions of interests (ROIs). Our main hypotheses focused on the bilateral ventral striatum. However, we included a number of additional regions in the ventral fronto-striatal loop to assess whether any results were specific to the ventral striatum or a more widespread feature of neural reward circuitry. ROIs were created using different atlases provided in the FSL software package (the Harvard-Oxford cortical and subcortical structural atlases and the Oxford thalamic connectivity atlas). Four fronto-striatal regions putatively involved in reward anticipation were selected per hemisphere: ventral striatum (VS), anterior cingulate, pallidum (combined internal and external segment), and thalamus, resulting in a total of eight ROIs. We chose not to include orbitofrontal regions in our analyses, as our fMRI sequence was designed for optimal signal-to-noise in the midbrain, as this was our primary region-of-interest. As a result, our scans were vulnerable to artifacts and signal loss in prefrontal regions (mostly caused by distortion from the air pockets of the frontal sinuses). Average activity per ROI was operationalized as average β-values of the contrast image and extracted using Marsbar (http://marsbar.sourceforge.net/). Main effects of reward anticipation on brain activity were analyzed in typically developing children using a single-factor analysis of variance (ANOVA). To test for group differences in brain activity, we conducted an ANCOVA with diagnosis as factor. If age and IQ covaried with activity in an ROI, analyses were run both with and without the covariate. If not, the covariates were left out of the final model.

If there were between-group differences, we performed a series of follow-up analyses. First, we conducted post hoc testing using Fisher's least significant difference (LSD) to compare the three groups. Also, we included the shift in response time distribution between rewarded and unrewarded trials as an additional performance-related covariate. Next, we performed trans-diagnostic, dimensional analyses: Using ANCOVA, we tested for an effect of ADHD symptoms (i.e., scores on two separate SWAN subscales), parent-rated reward sensitivity (i.e., scores on the SPSRQ-C reward subscale), and response time speeding (i.e., $B_{0\ vs.\ 15}$) on anticipatory brain activity, within the combined clinical group and control group separately. If there were no between-group differences, we ran correlational analyses on the entire sample. Results were corrected for multiple comparisons using False Discovery Rate (FDR) correction on the separate ANCOVA results (per ROI) using the Benjamini–Hochberg method (Benjamini & Hochberg, 1995).

Results

Questionnaires

All questionnaire subscales showed good or excellent internal consistency (SWAN-att α = .91, SWAN-hyp α = .94 and SPSRQ-C α = .82). ANOVA showed between-group differences on the reward sensitivity scale of the SPSRQ-c, the inattention scale of the SWAN and the hyperactivity/impulsivity scale of the SWAN (see Table 1). Post hoc testing indicated that both groups of children with ADHD symptoms had lower scores (i.e., more symptoms of ADHD) on the two SWAN subscales than typically developing children. SPSRQ-c scores differed between all three groups, with parents reporting lowest reward sensitivity for typically developing children, highest reward sensitivity for children with ADHD, and intermediate scores for children with ASD and ADHD symptoms.

Task performance

AN(C)OVA showed group differences in the standard deviation of response times on baseline trials (SDRT) (see Table 2). There was no effect of age or IQ. Post hoc testing showed that children with ADHD had higher SDRT than typically developing children and children with ASD and ADHD symptoms. There were no other group differences or associations with dimensional measures.

Brain activity

In typically developing children, there was a main effect of reward anticipation on brain activity in all ROIs (see Table S1). Furthermore, there was a between-group difference in anticipatory activity in right ventral striatum (VS) ($F(2,73) = 6.38$, $p = .003$), but not in any of the other seven ROIs (see Table 3). Age and IQ were left out of the model, as we found no associations between brain activity and age or IQ. Both clinical groups (ADHD: $M = 0.26$, $SD = 0.42$; ASD: $M = 0.12$, $SD = 0.42$) showed less anticipatory activity in right ventral striatum than typically developing children ($M = 0.52$, $SD = 0.45$). Task performance (i.e., $B_{0\ vs.\ 15}$) covaried with activity in bilateral ventral striatum. Specifically, increased speeding of response times when reward was at stake was associated with increased activity of ventral striatum. When we added task performance as a covariate to the model, we found between-group differences in ventral striatum activity bilaterally (for detailed results, see Table 4). Reward sensitivity as reported by parents (SPSRQ-c) was positively associated with anticipatory activity in the right VS for

Table 2 Task performance per clinical group

	Control (*SD*)	ADHD (*SD*)	ASD (*SD*)	*F*-value	*p*-value
MRT	422.18 (65.74)	465.49 (60.54)	444.80 (80.75)	(2,73) 2.47	.091
SDRT	137.75 (33.79)	170.81 (43.88)[a,b]	144.31 (42.24)[b]	(2,73) 4.77	.011
$B_{0\ vs.\ 15}$	0.85 (0.25)	0.76 (0.26)	0.83 (0.30)	(2,73) 0.82	.447

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; *SD*, standard deviation; MRT, mean response time in no reward condition; SDRT, standard deviation of response times in no reward condition; $B_{0\ vs.\ 15}$, shift in response time distribution between high reward and no reward.
[a]Significant post hoc group difference from typically developing children. [b]Significant post hoc group difference between children with ADHD and children with ASD and symptoms of ADHD.

Table 3 Activity per region of interest – group differences

	Control (*SD*)	ADHD (*SD*)	ASD (*SD*)	*F*-value (2,73)	*p*-value
L-tha	0.29 (0.23)	0.22 (0.32)	0.14 (0.29)	1.99	.145
R-tha	0.30 (0.26)	0.23 (0.34)	0.15 (0.32)	1.66	.197
L-vs	0.44 (0.38)	0.28 (0.39)	0.14 (0.47)	3.35	.041
R-vs	0.53 (0.42)	0.26 (0.42)[a]	0.12 (0.42)[a]	6.38	.003[b]
L-pal	0.18 (0.21)	0.28 (0.22)	0.07 (0.24)	1.56	.217
R-pal	0.17 (0.23)	0.10 (0.25)	0.06 (0.25)	1.18	.312
L-acg	0.21 (0.32)	−0.04 (0.33)	0.02 (0.47)	3.13	.050
R-acg	0.23 (0.32)	−0.01 (0.34)	0.00 (0.47)	3.49	.036

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; *SD*, standard deviation; L, left; R, right; tha, thalamus; vs, ventral striatum; pal, pallidum; acg, anterior cingulate. [a]Significant post hoc group difference from typically developing children. [b]Significant group difference ($p < .05$, corrected for multiple comparisons using the False Discovery Rate method).

the combined clinical group ($F(1,44) = 5.98$, $p = .019$) (see Figure 1): This indicates that more parent-rated reward sensitivity was associated with more VS activity during reward anticipation. Furthermore, response time speeding (i.e., a decrease in $B_{0\ vs.\ 15}$) was positively associated with anticipatory activity in right VS for the combined clinical group ($F(1,47) = 13.29$, $p = .001$). We found no association between activity in VS and any of the SWAN subscales, within either (clinical or control) group. Post hoc testing indicated that VS activity did not differ between groups for either the 0 versus 5 or the 5 versus 15 cents contrasts (see Table S2).

Post hoc analysis

Within the combined clinical group, we performed a post hoc two-way ANOVA to test for an effect of medication status, or a group by medication status interaction, on activity in right ventral striatum during the anticipation of reward. We found that children who were currently using psychostimulant medication had more activity in ventral striatum ($M = 0.29$) than children not using short-acting psychostimulant medication ($M = -0.02$) ($F(3,45) = 5.76$,

Table 4 Differences in activity in ventral striatum with task performance as covariate

	Factor	β	*F*-value	*p*-value
Left	$B_{0\ vs.\ 15}$	−.47	9.25	.003[a]
	Group		5.40	.006[b]
Right	$B_{0\ vs.\ 15}$	−.48	9.29	.003[a]
	Group		9.82	<.001[b]

$B_{0\ vs.\ 15}$, shift in response time distribution between high reward and no reward.
[a]Significant covariate.
[b]Significant group difference.

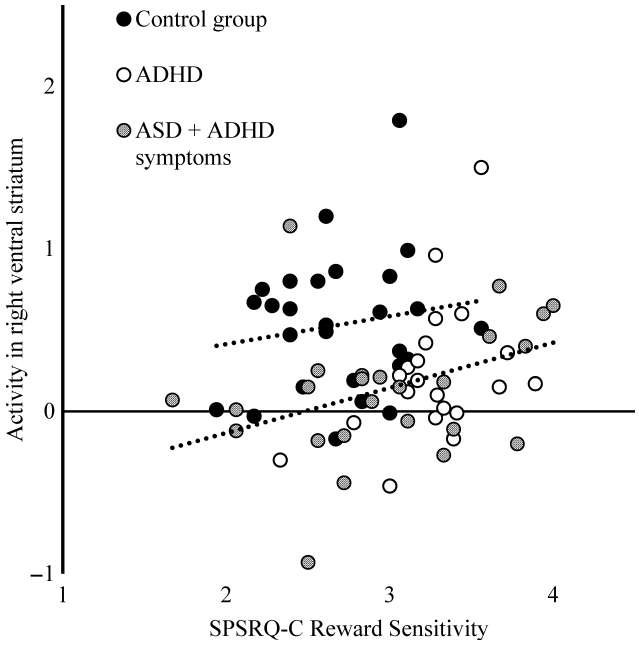

Figure 1 Ventral striatal activity and parent-rated reward sensitivity. Figure shows the relationship between activity in right ventral striatum during reward anticipation and reward sensitivity in daily life (as assessed by one of the parents using the SPSRQ-C questionnaire). For the group of children with ADHD symptoms and for the group as a whole there was a positive correlation between the two

p = .021). All participants did not take their medication 24 hr prior to testing.

Discussion

We studied reward processing in children with ADHD symptoms, as this neuropsychological domain holds strong relevance for clinical practice (Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016). We found that children with ADHD symptoms had decreased activity in ventral striatum during the anticipation of reward, and increased sensitivity to reward, as rated by their parents. This was apparent for children with ADHD, as well as for children with a primary diagnosis of ASD and ADHD symptoms. In addition, we found that for children with ADHD symptoms, parent-rated reward sensitivity was positively correlated with anticipatory activity in ventral striatum.

We found reduced activity in ventral striatum during the anticipation of reward in childhood ADHD, confirming our first hypothesis. Previous studies have reported anticipatory hypoactivity in adolescent or adult ADHD populations (Plichta & Scheres, 2014), but a first study on children with ADHD (Kappel et al., 2015) found no group differences. Accordingly, the authors suggested that this hypo-activation might be an epiphenomenon of ADHD that emerges at a later developmental stage. In contrast, we found evidence for anticipatory hypoactivity as early as 8 years of age. Our finding is in line with theories of reward processing in ADHD that suggest changes in mesolimbic reward processing are a core etiological factor in the development of the behavioral symptoms (Sagvolden et al., 2005; Tripp & Wickens, 2008). Differences in sample characteristics might account for the contrasting result. The study by Kappel and colleagues included only children with ADHD with the combined presentation, whereas we included all ADHD presentations. Moreover, our study had a larger sample size and the previous null finding might have been a result of insufficient statistical power.

Our second hypothesis was that anticipatory hypoactivity in ventral striatum would be found in children with ADHD symptoms irrespective of whether their primary diagnosis was ADHD. In order to test this we included a third group of children with similar levels of parent-rated ADHD symptoms, but a different primary diagnosis (ASD). Both groups showed comparable hypoactivity in the ventral striatum, in line with our hypothesis as well as with previous findings on reward processing in ASD (Dichter et al., 2010, 2012; Kohls et al., 2014). One could argue that if these children with a primary diagnosis of ASD, indeed have similar symptom levels of ADHD, they also fulfill criteria for ADHD. We argue that as these children have a different primary diagnosis and are treated as a qualitatively different group in clinical practice, these studies stress the importance of the movement away from strict diagnostic reasoning. However, to extend this line of reasoning, future studies could include diagnoses where the symptoms are even more qualitatively different from those of ADHD. An example would be to investigate a group of adolescents with major depressive disorder and similar levels of attention problems and to compare them to adolescents with ADHD.

Our third hypothesis was that ADHD symptoms would drive this anticipatory hypoactivity. Notably, we found no association between ADHD symptoms and anticipatory brain activity within the combined clinical group or within the group of typically developing children. Consequently, the hypoactivity in ventral striatum in children with ADHD symptoms may be related to distinct traits in both groups, as was suggested by a recent paper by Van Dongen and colleagues (van Dongen et al., 2015). Another explanation is that the linear relationship does not hold for the extreme ends of the distribution, as represented by both clinical groups and as might be represented by the sample of (hyper) control children. Environmental and neurobiological factors might have a differential effect on the expression of symptoms across the ADHD continuum A third explanation could be neurobiological heterogeneity (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2002), where only a subgroup of participants might show this effect, making it hard to detect in the group as a whole. Techniques to model and quantify this heterogeneity are needed to allow for differential relationship within one clinical group (e.g., Fair, Bathula, Nikolas, & Nigg, 2012; van Hulst, de Zeeuw, & Durston, 2015).

Reward sensitivity in children was assessed at three different levels: behavior in daily life (SPSRQ-C reward subscale), neuropsychological task performance ($B_{0\ \mathrm{vs.}\ 15}$), and activity in ventral striatum. Higher anticipatory activity was related to better task performance (i.e., increased response time speeding when anticipating reward), replicating our previous finding (van Hulst, de Zeeuw, Lupas, et al., 2015) and challenging the assumption of performance independent brain activity during an MID task (Knutson, Adams, Fong, & Hommer, 2001). In addition, within the combined group of children with ADHD symptoms, anticipatory ventral striatal activity was positively correlated with parent-rated reward sensitivity. This is a counterintuitive yet insightful result, as the combined clinical group showed higher parent-rated reward sensitivity and lower ventral striatum activity than typically developing children. One interpretation of this finding is that children actually exhibit ADHD-related behavior as an auto-regulatory mechanism to compensate for a lack of arousal (Geissler, Romanos, Hegerl, & Hensch, 2014; Zentall & Zentall, 1983). Potentially, these children may show behavior focused on short-term reward as a mechanism to normalize

dopaminergic neurotransmission in striatum. If the characteristic inattentive, hyperactive, and impulsive behavior can be interpreted as a compensatory mechanism for an understimulated midbrain, arousal levels may be considered a direct target for treatment (for an example see: Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010).

We found that as a group, children with ADHD symptoms had decreased brain activity during reward processing and increased reward sensitivity in daily life. However, within the group of children with ADHD symptoms, these measures of neurobiology and behavior were positively related to each other. The delineation of such a trans-diagnostic deficit in reward processing, both at a behavioral and a biological level, is a promising step toward a dimensional brain-behavior model of reward sensitivity in children with symptoms of ADHD. Ultimately, such a model might be used to refine treatment options that are dependent on reward processing.

Limitations

First, we had to exclude 30% of our participants, primarily due to head motion. In our experience, this is not an unusual percentage for children in this age range. When hyperactivity is part of the phenotype, exclusion on the basis of head motion conveys the risk of confounding results. However, the children we excluded did not differ from children included in the analyses in terms of the level of their ADHD symptoms. Second, we chose to include only boys in this study, to preserve statistical power. As a result, any inferences taken from it only apply to boys with (symptoms of) ADHD. Third, our reward task was designed to detect differences in anticipatory activity rather than reward processing, and as a result of collinearity we could not analyze the brain activity related to the latter separately. Studies combining reward anticipation and reward receipt are needed to discriminate between models on dopamine signaling in ADHD (e.g., Furukawa et al., 2014). Fourth, our fMRI sequence was designed for optimal signal-to-noise in the midbrain. As a result, our scans were vulnerable to artifacts and signal loss in prefrontal regions and we chose not to include orbitofrontal regions in our analyses. Finally, in this study, children receiving psychostimulant medication had more anticipatory activity in ventral striatum, despite being off medication 24 hr prior to scanning. However, considering the direction of this effect, it seems that the current results are more likely to represent an underestimation rather than an overestimation of the between-group effect.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Screening of data quality.

Table S1. Activity per region of interest – main effects for controls.

Table S2. Right ventral striatum activity per individual contrast – where there were no significant group differences when correcting for multiple comparisons.

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Key points

- We report hypoactivity in ventral striatum during reward anticipation in children (aged 8–12) with ADHD, similar to that previously reported in adolescents and adults with ADHD.
- Decreased activity in ventral striatum during the anticipation of reward was also found in children with autism spectrum disorder diagnoses and elevated ADHD symptoms.
- However, within the combined clinical group, anticipatory activity was not associated with symptoms of ADHD.
- Among children with symptoms of ADHD, ventral striatal activity was positively related to parent-rated reward sensitivity.

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