Striatal Sensitivity During Reward Processing in Attention Deficit Hyperactivity Disorder (ADHD)

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Abstract

Objective—Attention-deficit/hyperactivity disorder (ADHD) has been linked to deficits in the dopaminergic reward-processing circuitry, yet existing evidence is limited and the influence of genetic variation affecting dopamine signaling remains unknown. We investigated striatal responsivity to rewards in ADHD combined type (ADHD-CT) using functional magnetic resonance imaging (fMRI), and whether it is modulated by variation in the dopamine transporter gene *(DAT1).*

Method—We tested 29 male adolescents with ADHD-CT and 30 age-, handedness-and gender-matched healthy controls, selected for $DAT1_{10/6}$ haplotype dosage. Based on previous research, we focused our analysis on the ventral striatum and the caudate nucleus.

Results—Three main findings emerged: first, male adolescents with ADHD-CT did not differ from controls in terms of blood oxygen-level dependent (BOLD) fMRI response to reward-predicting cues (gain or loss-avoidance) in the ventral striatum. Second, male adolescents with ADHD-CT showed a relative increase, compared to controls, in the striatal BOLD response to successful outcomes. Third, $DAT1_{10/6}$ dosage differentially modulated neural activation to reward-predicting cues in the caudate nucleus in the ADHD-CT and control groups.

Conclusions—The findings challenge the idea of a deficit in anticipation-related activation in the ventral striatum in male adolescents with ADHD-CT, while suggesting that the processing of reward outcomes is dysfunctional, consistent with a recent neurobiological model of the disorder.

Preliminary evidence suggests that polymorphic variations in genes affecting dopamine signaling need to be taken into consideration when investigating reward-related deficits in ADHD-CT.

Keywords

attention deficit hyperactivity disorder (ADHD); reward processing; ventral striatum; caudate nucleus; *DAT1* (SLC6A3)

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood neuropsychiatric disorder characterized by developmentally inappropriate levels of inattention, hyperactivity and impulsivity. Deficits in executive functions and the underpinning neurocircuitry have been implicated in the pathophysiology of the disorder.[1,2] Recent studies have further indicated deficits in the dopamine reward circuitry,[3–5] as predicted by developmental neurobiological models of the disorder.[6–8]

To investigate reward circuitry functionality, functional magnetic resonance imaging (fMRI) studies have often used variants of the monetary incentive delay task (MID).[9] This task involves two distinct phases: (a) an anticipation phase, where visual cues signal the potential to win or avoid losing money, and (b) an outcome phase, where participants receive feedback based on their performance. Research in non-human primates shows that rewards elicit the phasic release of dopamine from midbrain neurons to a wide network of regions, including the ventral striatum and caudate nucleus,[10] which is captured as an increase in the functional magnetic resonance imaging (BOLD) signal (or activation) in fMRI studies.[11–13] Over time, midbrain dopamine neurons respond to the predicting cues rather than the rewards themselves.[10] Atypical brain function in MID-type tasks could be used as an index of reward-related dopamine signaling deficits. Such deficits have been associated with the development of ADHD behaviors in influential models of the disorder.[6,8] Additionally, experimental data suggest an association between risky and impulsive behavior, which is characteristic of ADHD,[14–16] and dopamine release or dopamine-dependent BOLD response to rewards in the striatum.[11,17–20]

Therefore, it is important to investigate the existence and understand the nature of reward-processing deficits in children and adolescents with ADHD. In adults with ADHD most studies report reduced activation in the ventral striatum (VS) during anticipation of monetary gains compared to controls,[4,21,22] with one exception.[23] Studies that investigated activation in the outcome phase reported increased activation in adults with ADHD (compared to controls) in the caudate nucleus and the orbitofrontal cortex[4] or no differences.[23] Yet the function of the dopaminergic mechanism and the role of polymorphic variation in dopamine genes vary with age,[24,25] making extrapolation from adult studies difficult. To date, only a single study has focused on adolescents with ADHD (n=11), reporting decreased activation in the VS in the ADHD group (compared to controls) following cues predicting monetary gains, but not following cues predicting loss-avoidance, or in the outcome phase.[3]

The function of the reward circuitry can be modulated by functional genetic polymorphisms influencing dopamine neurotransmission in the striatum, directly (e.g. the dopamine transporter gene [*DAT1*]) or indirectly (e.g. the nitric oxide synthase gene [*NOS1*]).[18,22,26] Neurochemical studies have demonstrated alterations in dopaminergic signaling in the striatum and the midbrain in ADHD, and linked such alterations with inattention symptoms and motivation problems in children and adults with ADHD.[5,27–29] Such "baseline" deficits (i.e. not linked to any task) could result from genetic variations associated with the disorder,

and molecular genetic studies have indeed linked risk for ADHD with polymorphic variants of dopamine genes.[30]

The stratification of samples by genotype can be used as a non-invasive way to investigate the effect of putative differences in dopaminergic neurotransmission on reward processing. In this study we focused on a haplotype of *DAT1*. *DAT1* is mainly expressed in the striatum, with the highest density in the caudate nucleus.[31] In the striatum the dopamine transporter (DAT) constitutes the main mechanism for terminating intrasynaptic dopamine activity.[32] This haplotype consists of two polymorphic repeats that are in moderate to strong linkage disequilibrium:[33] a variable-number-tandem-repeat (VNTR) in the 3′-untranslated (3′UTR) region, with the 9-repeat (9R) and 10-repeat (10R) alleles being the most frequent, and a VNTR at intron-8 that contains common 5-repeat (5R) and 6-repeat (6R) alleles. Both polymorphisms have been associated with ADHD.[30,33] These polymorphisms have been separately linked with DAT density in the striatum, while recent evidence suggests that their joint consideration in haplotypes may provide more information than can be inferred from the analyses of single genetic markers.[25] Similar to a previous study[15], haplotype status was determined according to VNTR genotype status: homozygotes for the 10R and 6R alleles also possessed 2 copies of the $DAT1_{10\text{-}6}$ haplotype *($DAT1_{10\text{-}6}$ homozygotes)*. Carriers of at least one 9R allele would, by definition, possess <2 $DAT1_{10\text{-}6}$ copies, hence were $DAT1_{10\text{-}6}$ heterozygotes.

This study, using a well-characterized clinical sample of male adolescents with combined type ADHD (ADHD-CT) and matched controls, has two primary aims: First, to investigate if the BOLD response to incentive-predicting cues (for monetary gain *or* loss-avoidance), and the response to successful outcomes, differ in adolescents with ADHD-CT compared to controls in the VS and the caudate nucleus. Second, to provide an initial test of the hypothesis that genetic variation of *DAT1* modulates striatal responsivity to incentive-predicting cues (which elicit phasic firing of midbrain dopamine neurons) in a diagnosis-specific manner. This hypothesis is based on two lines of evidence. First, there is a positive association between trait impulsivity or reward-related impulsivity and neural activation in the striatum following reward-predicting cues[19,20,22] in healthy adult samples, and suggestion that the genetic variant that predicts increased reward-related activation in the striatum also predicts increased reward-related impulsivity.[22] Second, previous data from the same sample showed that $DAT1_{10/6}$ homozygosity predicted reduced reward-related impulsivity in the ADHD-CT group, but increased impulsivity in the control group.[15] Considering this evidence together, we hypothesized here that $DAT1_{10/6}$ homozygosity would be associated with decreased striatal responsivity to anticipated incentives in the ADHD-CT group and increased responsivity in the control group.

In this study, we measured neural activation to incentive-predicting cues and successful outcomes using the Motivated Incidental Learning Task (MILT)—a variant of the MID paradigm,[34,35]. Given that this exact variant has not been used before, a secondary but essential aim of this study was to confirm the validity of MILT as a measure of incentive cue-elicited activation. To this effect, we expect that, similar to the MID task, a whole brain analyses will yield a similar pattern of anticipatory activation of the reward circuitry and that activation in the VS in particular will increase with incentive magnitude.

Method

Participants

We recruited 29 Caucasian male adolescents with a clinical diagnosis of ADHD-CT and 30 age-, gender- and handedness-matched controls from a larger sample that participated in a previous study.[36] The ADHD-CT group was part of the London subset of the International

Multi-Centre ADHD Genetics (IMAGE) project.[37] No co-morbid disorder was associated with either subgroup formed by the stratification of the ADHD sample by $DAT1_{10/6}$ dosage (2 copies, <2 copies; supplement 1 and Table S1, available online). Stimulant treatment (received by 72% of the ADHD-CT group) was discontinued at least 48 hours prior to testing (Table S2, available online). For details on inclusion and exclusion criteria for the IMAGE project and handedness, see supplement 1 (available online). The South London and Maudsley NHS Trust Research Ethics Committee approved the study and all participants, along with a parent/guardian provided written, informed consent.

Genetic analyses

Participants were selected to form four similar sized groups according to diagnostic status and the number of $DAT1_{10-6}$ copies (2 copies, <2 copies; Tables 1 and S3, available online). This stratification according to $DAT1_{10-6}$ dosage overlaps with and allows comparisons with the stratification according to either constituent genotype (namely, 10R homozygotes versus 9R carriers, which is most commonly used, or 6R homozygotes versus 5R carriers), while providing more information as it takes into account the joint information provided by both genotypes.[25] Standard genotyping procedures were used to determine $DAT1_{10/6}$ status (see supplement 1, available online).

Motivated Incidental Learning Task (MILT)

In this task (Figure 1), one small or two large arrows represented incentives (£1/£5 respectively), with color denoting valence (green: win; red: avoid losing). A red/green rectangle represented trials involving no money (neutral). Trial set-up was as follows: incentive cue (1 sec), jittered anticipation delay (2–5 sec), picture (1.5 sec), requiring a fast and accurate semantic decision (living/non-living) about unambiguous stimuli (animals or inanimate artefacts), blank screen (0.5 sec), outcome notification (1.5 sec), jittered inter-trial interval (0.5–3 sec). An algorithm adjusted from trial to trial the upper time boundary for a valid response, maintaining a success rate of about 80%; the starting value was individually set based on the practice session, and the lower boundary was set to 80 msec. A separate aim was to investigate the effects of reinforcement context on episodic memory formation for target pictures (not reported here). Participants completed 160 trials (in pseudo-random order) in two 13.3 min sessions. There were 32 trials for each incentive valence and magnitude combination (±£1/£5, £0). All participants saw the same 160 colored pictures of living (50%) and non-living objects (see supplement 1, available online). Participants achieved a high rate (> 94%) of semantically correct responses. Only successful trials (where a semantically correct response was made within the acceptable time window) were included in the analyses reported here (see Table 2 for success rates by subgroup).

MRI scanning was preceded by a rewarded 40-trial practice session in a mock scanner to familiarize participants with the scanning environment, train them on the task, teach them cue-reward associations, determine the initial values for the response time window and increase the salience of rewards. Participants were shown a box containing real money that they could earn and were informed that they would earn money in proportion to the amount they had accumulated playing the task (although all participants received £2.75 for the practice session and £7.50 for the main task). At the end of the scanning session, participants completed two visual-analog scales to indicate how exciting they found each incentive condition ("not exciting at all" to "extremely exciting") or how much effort they exerted to get a fast and accurate response ("didn't bother much" to "tried very hard"). For technical reasons, visual analog scale data were only available for monetary gain trials.

Other measures

ADHD rating scales—ADHD symptoms were assessed using the 18 *DSM-IV* items from the long form of the revised Conners' Parent Rating Scales,[38] obtained on the day that participants were scanned.

General intelligence—The vocabulary, similarities, picture completion and block design subtests of the Wechsler Intelligence scales for children [39] and adults [40] were used to estimate IQ at the time of the initial assessment (18–60 months before the current study; M=43.2, SD=9.36).

Sample and performance data analysis

We examined the effects of diagnosis and $DAT1_{10/6}$ dosage on a range of sample or task performance variables using a 2 (ADHD-CT, control) $\times$ 2 *($DAT1_{10/6}$ 2 copies, <2 copies)* analysis of variance (ANOVA; see Table 1). To investigate the effect of incentive magnitude on performance, we conducted a mixed 3 (£0, £1, £5) $\times$ 2 (ADHD-CT, control)

fMRI data: first-level analysis

MRI data were acquired on a General Electric SIGNA HD$\times$ 3.0T MR scanner (General Electric Medical Systems, Milwaukee, WI) and analyzed in SPM8 (www.fil.ion.ucl.ac.uk/spm) using the general linear model (see supplement 1, available online, for acquisition and pre-processing details). Event-specific regressors were convolved with the canonical hemodynamic response function to model the BOLD signal. We used 10 regressors marking events of interest: phase (anticipation or outcome onset), incentive magnitude (£0, £1 or £5) and valence (gain or loss-avoidance) in successful trials. Regressors for events of no interest were: unsuccessful/error trials and the first and second order movement parameters from the realignment procedure. A high-pass filter (128 sec) was applied to the data and first-order temporal autocorrelation was modeled. Weighted contrasts were used to test the effect of cue-elicited changes on BOLD signal (henceforth referred to as activation) during gain or loss-avoidance anticipation or outcome notification for each individual. For second level (group) analyses, the contrast images from the first-level analysis were used to calculate mean activation for each region of interest (ROI) using MarsBar (http://marsbar.sourceforge.net/),[41] or to conduct whole brain analyses.

fMRI data: group analyses

In line with previous studies,[3,4,21–23] our primary ROI was the VS. We further included separate ROIs for caudate nucleus head and body. The caudate nucleus is a core region of the dopamine reward-circuit,[42] implicated in ADHD-control differences,[4] and genetic variation in *DAT1* is reported to affect its function and structure [26,43] (supplement 1, available online, describes anatomical ROI definition).

We calculated mean brain activation in each ROI, using neutral trials as the baseline, across task phase, incentive valence and magnitude. Data were averaged over left and right hemispheres, following a preliminary test showing no significant effect for brain hemisphere (or interaction with diagnostic group or $DAT1_{10/6}$). Both our primary aims were tested within an omnibus analysis of covariance (ANCOVA) model (fitted separately for each ROI), with clinical diagnosis (ADHD, control) and $DAT1_{10/6}$ dosage (2 copies, <2 copies) as the between-subjects factors, and task phase (anticipation, outcome), incentive valence (gain, loss-avoidance) and incentive magnitude (£1, £5) as the within-subjects factors (Table 2 presents the main effects, and the interactions of interest). Age was included as a covariate,[42,44] and analyses were repeated covarying IQ (p-values reported separately). Significant interactions were followed-up using simple effects analyses. Complementary

whole-brain analyses were conducted and are reported in supplemental material (available online).

To directly replicate and facilitate comparison with previous research in relation to our first aim,[3] we ran a 2 (ADHD, control) $\times$ 2 *(DAT1$_{10/6}$* 2 copies, <2 copies) $\times$ 2 (£1, £5) ANCOVA, separately for gain and loss-avoidance anticipation and brain hemisphere, focusing on the VS (see Figure 2). This test was further used to confirm that anticipatory activation in the VS increased with incentive magnitude.[34] The validity of the task was also confirmed by testing the BOLD response to incentive-predicting cues using whole-brain analyses and conducting one sample *T*-tests on the following contrast for each incentive valence: Anticipation$_{\pm £5}$ > Anticipation$_{£0}$. Inferences were conducted at the cluster-level using family-wise error correction (α=0.05); a voxel was considered for cluster-level analysis if *p*<.001 (see supplement 2, available online, for group comparisons). Finally, we present correlations between neural activation and ADHD symptom ratings in supplemental material (supplement 2; Tables S4 and S5, available online).

Results

Does neural activation to incentive-predicting cues and successful outcomes differ between adolescents with ADHD-CT and controls?

While there were no significant main effects for diagnostic group, or interactions between diagnostic group, task phase and incentive valence, we observed significant interactions between diagnostic group, task phase and incentive magnitude in the VS and the caudate nucleus head (Table 2). We explored these interactions post-hoc using simple effects analyses. The interaction between diagnostic group and incentive magnitude was significant during the outcome presentation phase in the caudate nucleus head ($F_{(1,54)}$=6.91, *p*=.011, η^2_p=.11; *p*$_{IQ}$=.012) and the VS ($F_{(1,54)}$=12.65, *p*<.001, η^2_p=.13; *p*$_{IQ}$=.004), but not during the incentive anticipation phase (*F*s<1.90, ns). Further post-hoc simple effects analyses to explore the interaction between diagnostic group and incentive magnitude showed that neural activation in the VS ($F_{(1,54)}$=4.85, *p*=.032, η^2_p=.08; *p*$_{IQ}$=.014) and the caudate nucleus head ($F_{(1,54)}$=6.58, *p*=.013, η^2_p=.11; *p*$_{IQ}$=.002) was higher in the ADHD-CT group, compared to controls, for large (£5), but not small (£1; *F*s<1.00, ns) outcomes.

These results (Table 2) suggest the ADHD-CT and control groups did not differ in terms of neural activation to incentive-predicting cues in any ROI. To directly replicate and facilitate comparison with a previous publication[3], we ran a 2 (ADHD, control) $\times$ 2 *(DAT1$_{10/6}$* 2 copies, <2 copies) $\times$ 2 (£1, £5) ANCOVA, separately for gain and loss-avoidance anticipation and brain hemisphere, focusing on the VS. We confirmed that the ADHD-CT and control groups did not differ in terms of neural activation to incentive cues in the VS, for either incentive valence or brain hemisphere, irrespective of incentive magnitude (or *DAT1$_{10/6}$* haplotype; *F*s<1.00, ns; Figure 2).

Does genetic variation in DAT1$_{10/6}$ modulate neural activation in response to incentive-predicting cues?

We observed a significant three-way interaction between diagnostic group, *DAT1$_{10/6}$* and task phase. This interaction was explored post-hoc with separate ANCOVAs for each task phase using simple effects analysis. There was a significant two-way interaction between diagnosis and *DAT1$_{10/6}$* in the incentive anticipation phase ($F_{(1,54)}$=4.25, *p*=.044, η^2_p=.06; *p*$_{IQ}$=.031), but not in the (successful) outcome presentation phase ($F_{(1,54)}$=1.92, *p*=.17). Figure 3 shows that the interaction of diagnosis and *DAT1$_{10/6}$* during incentive anticipation followed a crossover pattern, indicating that the effect of *DAT1$_{10/6}$* dosage on neural activation to incentive-predicting cues differs between the two groups: in the ADHD-CT

group, activation tended to decrease as $DAT1_{10/6}$ dosage increased, but in the control group the reverse was found.

The MILT task: behavior, reward-network activation and motivational effects

In both the ADHD-CT and control groups, the incentive-predicting cues activated the predicted network, as previously identified (see supplement 2, available online, for more details and group comparisons; Tables S6-S8 and Figure S1, available online). Consistent with previous reports,[34] cue-elicited activation in the VS increased with the magnitude of the anticipated incentive (gain trials: $F_{(1,55)}=17.48$, $p<.001$, $\eta^2_p=.24$; loss-avoidance: $F_{(1,55)}=8.17$, $p<.006$, $\eta^2_p=.13$), irrespective of diagnosis or $DAT1_{10/6}$ dosage ($Fs<1.81$, ns; Figure 2). The increase in incentive magnitude also resulted in a linear decrease in response times for each incentive valence across groups ($F_{\text{Gain}(1,57)}=138.52$, $P<.001$; $F_{\text{Loss-avoidance}(1,57)}=57.37$, $p<.001$), $Fs_{\text{Diagnosis} \times \text{magnitude}} <1$, ns). The lack of significant group differences on indices of task performance indicated that all groups experienced similar outcomes and contributed a similar number of trials (Table 1).

Discussion

Three main findings emerged in this study of 29 male adolescents with ADHD-CT and 30 healthy controls. First, adolescents with ADHD-CT did not differ from controls in terms of cue-elicited (gain or loss-avoidance) neural activation in the VS. Second, adolescents with ADHD-CT showed a relative increase in the striatal BOLD response, compared to controls, following confirmation of a successful outcome. Third, $DAT1_{10/6}$ dosage modulated incentive cue-elicited activation in the caudate nucleus body differently in the ADHD-CT and control groups.

The lack of a deficit in cue-elicited activation in the VS for the ADHD-CT group (compared to the control group) cannot be explained by a general lack of task engagement. Both groups showed similar increases in anticipatory activation and decreases in response times with incentive magnitude, irrespective of incentive valence. The groups did not differ either in task performance measures. These effects confirm the validity of MILT as a measure of incentive cue-elicited neural activation, suggest that the motivational manipulation was effective and that the interpretation of potential group differences in brain activation is not confounded by performance differences.

To date, a single previous study has compared adolescents with ADHD to healthy controls using an MID paradigm[3]. Our findings, while in agreement with the reported lack of significant group differences in neural activation to loss-avoidance anticipation, apparently contradict the demonstration of reduced activation in the VS during gain anticipation.[3] Yet the relatively small sample size in that study (n=11)[3] and the inclusion of both genders and mixed ADHD subtypes (factors that have been associated with reward-related activation and impulsivity[16,45]) make direct comparisons difficult.

A further difference from previous studies regards the task itself. MILT differed from MID-type paradigms used in earlier ADHD research in two ways: first, the conditioned cues predicted successful outcomes with greater certainty (~80%, compared to ~66%[3,4]). The strength of the association between cue and outcome was matched between groups, as all groups demonstrated similar success rates. Research in non-human primates, confirmed in humans, indicates that differences the probability with which a cue predicts a reward produce a quantitative change in the engagement of dopaminergic systems.[46,47] Thus, the increased certainty may even have sharpened the degree to which cues elicited anticipatory activity, while we would not expect that it makes a qualitative difference with regard to incentive-elicited activation. Nonetheless we cannot fully preclude different sensitivities to

reward in ADHD and comparison groups between tasks using different reward rates based on the literature to date. Clearly, future studies should examine more explicitly the integration of absolute reward value and probability in ADHD. The second way in which MILT differed from previous applications in ADHD research (but see[35] for a similar variant in cognitive neuroscience) was that, due to its nature as an incidental learning task (an aspect that is not discussed in this paper), the targets comprised drawings of living and non-living objects and required a semantic judgment (living or nonliving). Previous MID-variants have used targets requiring an element of cognitive processing,[35] which is controlled for by using non-incentive trials that are matched on semantic processing as the comparison condition. Participants were pre-trained on this aspect of the task and achieved an extremely high (>94%) percentage of correct semantic decisions. Importantly, semantic decisions followed the anticipation phase. Moreover, the focus on ROIs directly relevant to reward processing reduces the possibility that our findings are biased by this aspect of the task.

The lack of a deficit in anticipatory activation was accompanied by increased neural activation in the striatum following confirmation of successful outcomes for the ADHD-CT group. Although in agreement with previous evidence from adults with ADHD,[4] the single previous study that examined outcome-related activation in adolescents with ADHD had focused solely on the VS and did not find group differences.[3] Yet, given that successful trials in MILT are more common (~80%) compared to previous paradigms (~66%), it is more difficult to directly compare findings across studies. The phasic firing of midbrain dopamine neurons is expected to transfer to reward-predicting cues,[6,10] and therefore the higher the expected success rate the more complete this transfer would be expected to be. This is consistent with the lack of significant activation in response to successful outcomes in the control group in our study (see whole brain analyses in supplement 1, available online). Our finding of increased caudate nucleus activity in the ADHD-CT group is also consistent with a dysfunctional transfer of phasic dopamine release from the actual reward to its predicting stimulus. This may result in impaired appraisal of motivational outcomes and subsequent adaptation of behavior.[6]

Polymorphic variation in the *DAT1* gene was found to modulate neural activation in response to incentive-predicting cues in the striatum in a diagnosis-specific manner. Specifically, $DAT1_{10/6}$ homozygosity was associated with decreased striatal responsivity to anticipated incentives in the ADHD-CT group and increased responsivity in the control group. The specificity of this finding for the caudate nucleus could be due to the relatively lower levels of the dopamine transporter in the ventral portion of the striatum.[48] Moreover, apart from the VS, dorsal regions of the caudate also receive efferent phasic input from midbrain dopamine neurons in response to reward predicting cues. This finding confirms previous evidence from healthy volunteers that genetic variation in *DAT1* modulates striatal reward-related activation.[26,49,50] Furthermore, when our data here are considered together with our previous report using a hypothetical delay discounting task with the same participants,[15] a pattern emerges, consistent with findings from other genes indirectly involved in dopamine signaling (*NOS1*), that the genetic variant that predicted increased reward-related activation in the striatum also predicted increased reward-related impulsivity.[22] This pattern suggests a putative neural mechanism linking genetic variation in *DAT1*, striatal responsivity to rewards and behavioral impulsivity *across* diagnostic categories and indicates that the established inverted U-shape model of prefrontal cortical dopamine levels and function (and consequently neurocognitive performance), might also operate in the striatum.[51-53]

One limitation of our study is the modest sample size for genetic analyses. Our genetic findings should therefore be treated as preliminary and be interpreted with caution until further replication studies have been completed. While the use of an ADHD-CT sample that

had a current or previous history of stimulant treatment is also a potential limitation, recent evidence showed that ventral striatal activation does not differ between medicated and medication-naïve adults with ADHD.[22] The presence of possible comorbid oppositional-defiant disorder and conduct disorder in some patients may also limit the interpretation of our findings as reflecting ADHD-specific abnormalities in reward processing. While the effect sizes for those with and without comorbidities are similar, further research in larger groups assessed quantitatively against symptoms is clearly warranted.

In conclusion, our findings challenge the idea of a deficit in neural activation to incentive-predicting cues in the VS in male adolescents with ADHD-CT, while suggesting that the processing of reward outcomes is dysfunctional, which may impair learning and adaptive behavior.[6] Furthermore, the results suggest that polymorphic variations in genes affecting dopamine signaling play a key role in regulating in neural activation to incentive-predicting cues and need to be taken into consideration when investigating deficits in disorders that may be characterized by genetically driven changes in the baseline function of the dopamine system. Future research needs to investigate the integrity of the different aspects of the reward-processing mechanism in ADHD and illuminate possible interactions with other genes affecting dopaminergic neurotransmission directly or indirectly (e.g. serotonergic) in the shaping of clinically relevant behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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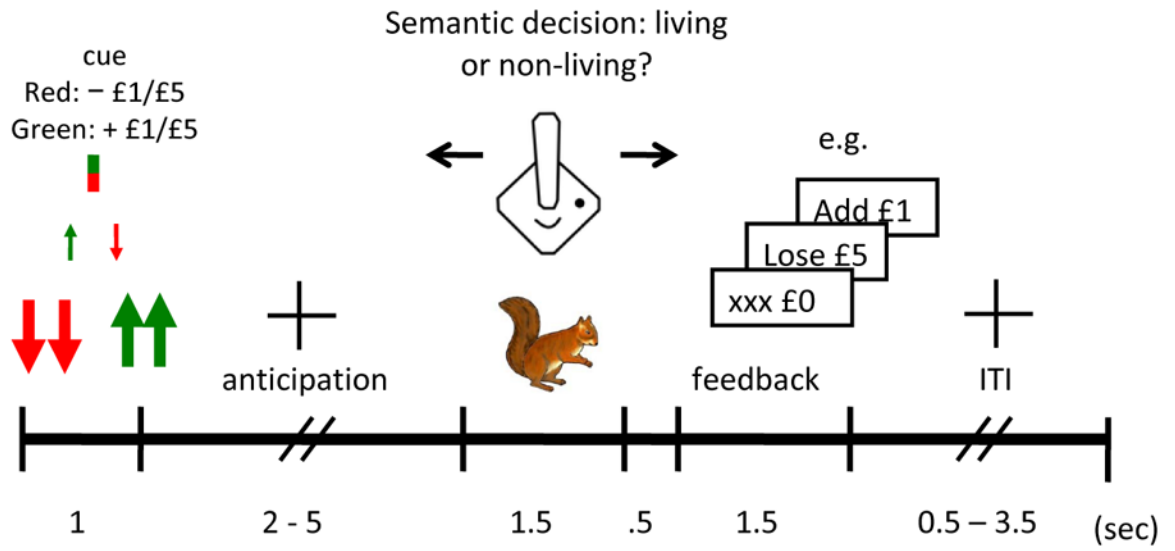
Figure 1.
Motivated incidental learning task (MILT). Note: ITI = inter-trial interval.
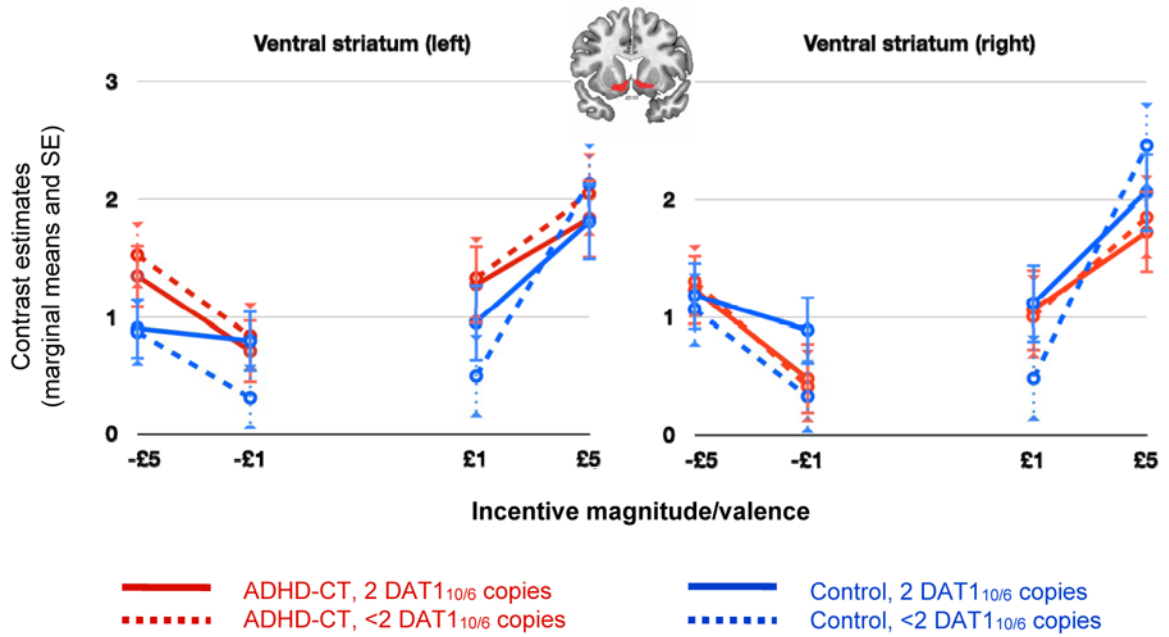
Figure 2.
Ventral striatum (VS): response to incentive-predicting cues. Note: Cue-induced activation in the VS increased with incentive magnitude in gain ($p < .001$) and loss-avoidance ($p = .006$) trials. Main effects for diagnosis, dopamine transporter gene ($DAT1_{10/6}$) dosage or their interaction were not significant. ADHD-CT = attention deficit hyperactivity disorder combined type; DAT1 = dopamine transporter gene; SE = standard error.

Figure 3.
Caudate nucleus body: Blood oxygen level dependent (BOLD) response to incentive-predicting cues. Note: BOLD response to incentive-predicting cues in the caudate nucleus body, averaged over task valence (gain or loss-avoidance), incentive magnitude (£1 or £5) and brain hemisphere. ADHD-CT = attention deficit hyperactivity disorder combined type; DAT1 = dopamine transporter gene; SE = standard error.

Table 1

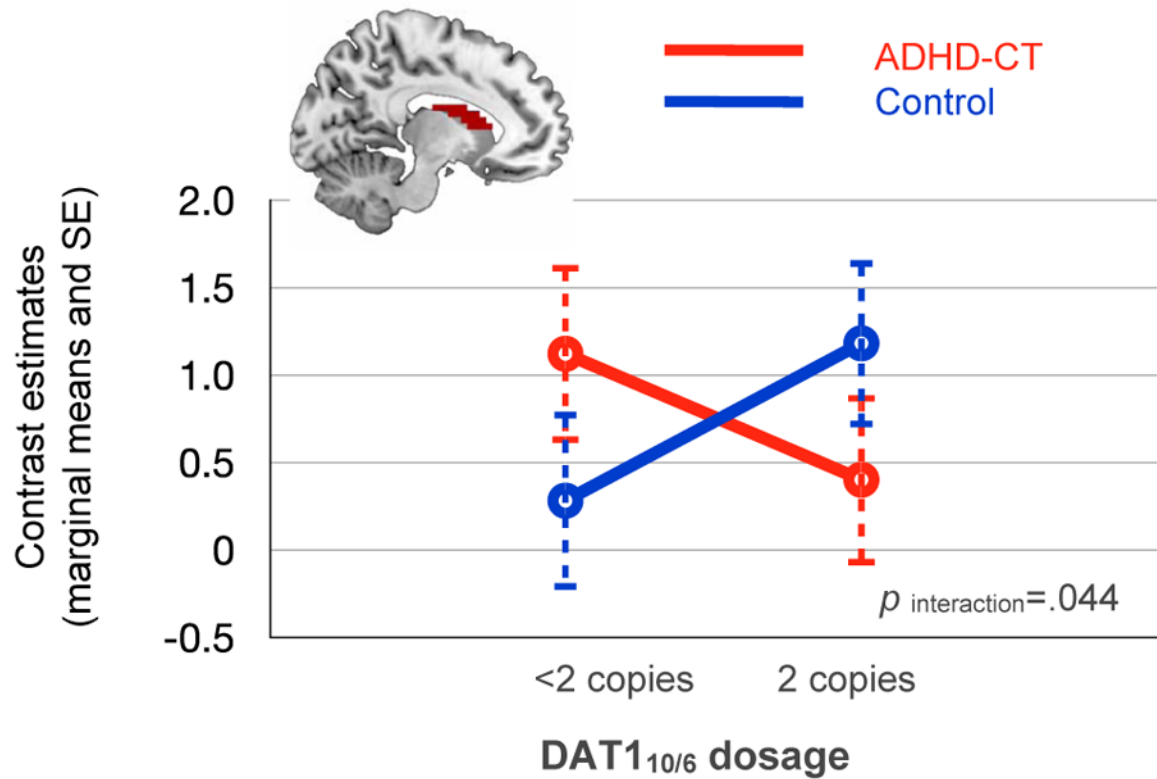Clinical, experimental and demographic data for the attention-deficit/hyperactivity disorder combined type (ADHD-CT) and control participants.

Mean (SD)	ADHD-CT ($DATI_{10/6}$)		Control ($DATI_{10/6}$)		Significance Test	p
	2 copies (n=15)	<2 copies (n=14)	2 copies (n=16)	<2 copies (n=14)		
Age (years)	15.60 (2.35)	15.35 (2.06)	15.35 (1.4)	15.87 (2.06)	$F_{group}(1, 55)=0.06$ $F_{haplotype}(1, 55)=0.07$ $F_{interaction}(1, 55)=0.54$	.80 .79 .47
IQ	109.4 (12.8)	101.07 (12.97)	111.06 (9.9)	115.5 (12.20)	$F_{group}(1, 55)=6.63$ $F_{haplotype}(1, 55)=0.39$ $F_{interaction}(1, 55)=4.18$	.013 .54 .046
Conners' *DSM-IV* ADHD Inattention ratings (parent)	65.67 (10.77)	72.5 (8.23)	46.53 (4.61)	47.29 (6.35)	$F_{group}(1, 54)=115.56$ $F_{haplotype}(1, 54)=3.38$ $F_{interaction}(1, 54)=2.17$	<.001 .071 .15
Conners' *DSM-IV* ADHD Hyperactivity/Impulsivity ratings (parent)	77 (13.94)	81.07 (12.80)	47.4 (7.19)	48.14 (6.13)	$F_{group}(1, 54)=126.14$ $F_{haplotype}(1, 54)=0.75$ $F_{interaction}(1, 54)=0.36$	<.001 .39 .55
Conners' *DSM-IV* ADHD Total ratings (parent)	72.6 (12.87)	79.29 (9.98)	46.53 (5.42)	47.36 (6.03)	$F_{group}(1, 54)=146.16$ $F_{haplotype}(1, 54)=2.45$ $F_{interaction}(1, 54)=1.49$	<.001 .12 .23
Mean response time, Gain trials (SE)	609.24 (19.72)	631.47 (20.42)	595.01 (19.10)	571.31 (20.42)	$F_{group}(1, 55)=3.49$ $F_{haplotype}(1, 55)=0.00$ $F_{interaction}(1, 55)=1.33$	.067 .97 .25
Mean response time, Loss-avoidance trials (SE)	621.31 (19.29)	638.49 (19.97)	604.33 (18.68)	580.01 (19.97)	$F_{group}(1, 55)=3.75$ $F_{haplotype}(1, 55)=0.03$ $F_{interaction}(1, 55)=1.13$	.058 .86 .29
Subjective ratings of excitement induced by gain-anticipation (£5 vs. £0)	41.73 (17.06)	39.54 (25.08)	45.13 (22.76)	49.57 (13.38)	$F_{group}(1, 54)=1.50$ $F_{haplotype}(1, 54)=0.04$ $F_{interaction}(1, 54)=0.37$	.23 .84 .55
Subjective ratings of effort invested in large incentive trials (£5 vs. £0)	40.47 (23.46)	33.46 (29.28)	42.20 (23.85)	30.14 (17.51)	$F_{group}(1, 54)=0.01$ $F_{haplotype}(1, 54)=2.12$ $F_{interaction}(1, 54)=0.15$	.90 .15 .70
Success rate (%)	78.29 (0.48)	77.59 (0.50)	78.48 (0.47)	78.48 (0.50)	$F_{group}(1, 55)=1.22$ $F_{haplotype}(1, 55)=0.51$ $F_{interaction}(1, 55)=0.53$	.27 .48 .47
Total Earned (£)	140 (3.14)	140.93 (3.25)	141.44 (3.04)	135 (3.25)	$F_{group}(1, 54)=0.50$ $F_{haplotype}(1, 54)=0.75$ $F_{interaction}(1, 54)=1.35$	.48 .39 .25

Note: DAT1 = dopamine transporter gene; IQ = intelligence quotient; SE = standard error.

Table 2

Analyses of Covariance (ANCOVAs) investigating the effect of clinical group (attention-deficit/hyperactivity disorder [ADHD] combined type, control), dopamine transporter gene ($DAT1_{10/6}$) (2 copies, <2 copies), task phase (anticipation, outcome), incentive valence (gain, loss-avoidance) and incentive magnitude (small, large) on neural activation in the ventral striatum and the caudate nucleus head and body.

Effect	Ventral striatum					Caudate nucleus body					Caudate nucleus head				
	F	df	p^b	η^2_p	p_{IQ}^c	F	df	p^b	η^2_p	p_{IQ}^3	F	df	p^b	η^2_p	p_{IQ}^c
Clinical group	0.52	1,54	ns	.01	ns	0.97	1,54	ns	.02	ns	1.18	1,54	ns	.02	ns
$DAT1_{10/6}$	0.87	1,54	ns	.02	ns	0.44	1,54	ns	.01	ns	0.04	1,54	ns	.00	ns
Group × DAT110/6	0.47	1,54	ns	.01	ns	0.18	1,54	ns	.00	ns	0.37	1,54	ns	.01	ns
Phase[a]	39.95	1,54	<.001	.43	<.001	18.41	1,54	<.001	.25	<.001	23.87	1,54	<.001	.31	<.001
× Group[a]	0.03	1,54	ns	.00	ns	1.53	1,54	ns	.03	ns	0.29	1,54	ns	.01	ns
× $DAT1_{10/6}$[a]	0.55	1,54	ns	.01	ns	0.27	1,54	ns	.01	ns	0.03	1,54	ns	.00	ns
× Group × $DAT1_{10/6}$[a]	1.67	1,54	ns	.03	ns	8.63	1,54	.005	.14	.011	3.36	1,54	.072	.06	ns
Valence[a]	13.60	1,54	.001	.20	<.001	2.09	1,54	ns	.04	ns	5.05	1,54	.029	.09	.027
× Group[a]	0.10	1,54	ns	.00	ns	3.51	1,54	ns	.04	ns	0.31	1,54	ns	.01	ns
× $DAT1_{10/6}$[a]	0.19	1,54	ns	.00	ns	0.22	1,54	ns	.00	ns	0.04	1,54	ns	.00	ns
× Group × $DAT1_{10/6}$[a]	0.19	1,54	ns	.00	ns	0.00	1,54	ns	.00	ns	0.01	1,54	ns	.00	ns
Magnitude[a]	12.84	1,54	.001	.19	.001	7.22	1,54	.010	.12	.010	7.85	1,54	.007	.13	.007
× Group[a]	4.07	1,54	.049	.07	.058	2.05	1,54	ns	.04	ns	2.68	1,54	ns	.05	.077
× $DAT1_{10/6}$[a]	0.20	1,54	ns	.00	ns	0.16	1,54	ns	.00	ns	0.03	1,54	ns	.00	ns
× Group × $DAT1_{10/6}$[a]	0.03	1,54	ns	.00	ns	0.04	1,54	ns	.00	ns	0.02	1,54	ns	.00	ns
Phase × Valence[a]	2.70	1,54	ns	.05	ns	3.46	1,54	.069	.06	.069	1.91	1,54	ns	.03	ns
× Group[a]	0.88	1,54	ns	.02	ns	0.40	1,54	ns	.01	ns	1.41	1,54	ns	.03	ns
× $DAT1_{10/6}$[a]	1.12	1,54	ns	.02	ns	0.30	1,54	ns	.02	ns	0.60	1,54	ns	.01	ns
× Group × $DAT1_{10/6}$[a]	0.00	1,54	ns	.00	ns	0.39	1,54	ns	.01	ns	0.00	1,54	ns	.00	ns
Phase × Magnitude[a]	15.64	1,54	<.001	.23	<.001	8.13	1,54	.006	.01	.006	9.03	1,54	.004	.14	.004

Effect	Ventral striatum					Caudate nucleus body					Caudate nucleus head				
	F	df	p^b	η^2_p	p IQ^c	F	df	p^b	η^2_p	p IQ^3	F	df	p^b	η^2_p	p IQ^c
× Group^a	5.61	1,54	.021	.09	.026	2.87	1,54	.096	.05	ns	6.38	1,54	.015	.11	.022
× DAT1$_{10/6}$^{a}	1.70	1,54	ns	.03	ns	0.00	1,54	ns	.00	ns	0.54	1,54	ns	.01	ns
× Group × DAT1$_{10/6}$^{a}	1.29	1,54	ns	.02	ns	0.78	1,54	ns	.01	ns	1.42	1,54	ns	.03	ns
Phase × Valence ×	.08	1,54	ns	.00	ns	1.65	1,54	ns	.03	ns	0.41	1,54	ns	.01	ns
Magnitude^a															
× Group^a	0.19	1,54	ns	.01	ns	0.00	1,54	ns	.00	ns	0.36	1,54	ns	.01	ns
× DAT1$_{10/6}$^{a}	0.44	1,54	ns	.00	ns	0.50	1,54	ns	.01	ns	0.46	1,54	ns	.01	ns
× Group × DAT1$_{10/6}$^{a}	0.64	1,54	ns	.01	ns	0.08	1,54	ns	.00	ns	0.14	1,54	ns	.00	ns

Note: ns = non-significant.

[a] With Greenhouse-Geisser correction.

[b] p-values from ANCOVA, with age as a covariate.

[c] p-values from ANCOVA, with age and intelligence quotient (IQ) as covariates (df=[1,53]). p-values <.10 are shown. p-values <.05 are displayed in bold.