Striatal Sensitivity During Reward Processing in Attention-Deficit/Hyperactivity Disorder

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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 who were 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 with 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. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(7):722–732. **Key Words:** ADHD, reward processing, ventral striatum, caudate nucleus, *DAT1* (SLC6A3)

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: an anticipation phase, in which visual cues signal the potential to win or to avoid losing money; and (b) an outcome phase, in which 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 de-

Supplemental material cited in this article is available online.

velopment of ADHD behaviors in influential models of the disorder.[6,8] In addition, 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 to understand the nature of reward-processing deficits in children and adolescents with ADHD. Most studies report reduced activation in the ventral striatum (VS) during anticipation of monetary gains in adults with ADHD compared with controls,[4,21,22] with one exception.[23] Studies that investigated activation in the outcome phase reported increased activation in adults with ADHD (compared with 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 with 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 have 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 noninvasive 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 expressed mainly 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 nine-repeat (9R) and 10-repeat (10R) alleles being the most frequent, and a VNTR at intron-8 that contains common five-repeat (5R) and six-repeat (6R) alleles. Both polymorphisms have been associated with ADHD.[30,33] These polymorphisms have been separately linked with DAT density in the striatum, although 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 two 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 and hence were $DAT1_{10\text{-}6}$ heterozygotes.

This study, using a well-characterized clinical sample of male adolescents with ADHD combined type (ADHD-CT) and matched controls, had two primary aims. The first aim was to investigate whether 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 with controls in the VS and the caudate nucleus. The second aim was 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, suggesting 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 have shown 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 $DAT1_{10/6}$ homozy-

gosity 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 expected that, similar to the MID task, whole-brain analyses would yield a similar pattern of anticipatory activation of the reward circuitry and that activation in the VS in particular would increase with incentive magnitude.[34]

METHOD

Participants

We recruited 29 white male adolescents with a clinical diagnosis of ADHD-CT and 30 age-, gender-, and handedness-matched controls from a larger sample who had 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 before testing (Table S2, available online). Details on inclusion and exclusion criteria for the IMAGE project and handedness are provided in 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 $DAT1_{10\text{-}6}$ copies (2 copies, <2 copies; Table 1 and Table S3, available online). This stratification according to $DAT1_{10\text{-}6}$ 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 (Supplement 1, available online).

Motivated Incidental Learning Task

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 second), jittered anticipation delay (2-5 seconds), picture (1.5 seconds), requiring a fast and accurate semantic decision (living/nonliving) about unambiguous stimuli (animals or inanimate artifacts), blank screen (0.5 second), outcome notification (1.5 seconds), jittered inter-trial interval (0.5-3 seconds). An algorithm adjusted from trial to trial the upper time boundary for a valid response, maintaining a success rate of approximately 80%; the starting value was individually set based on the practice session, and the lower boundary was set to 80 milliseconds. 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 pseudorandom order) in two 13.3-minute 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 nonliving objects (Supplement 1, available online). Participants achieved a high rate (>94%) of semantically correct responses. Only successful trials (in which a semantically correct response was made within the acceptable time window) were included in the analyses reported here (Table 2 lists 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, to train them on the task, to teach them cue–reward associations, to determine the initial values for the response time window, and to 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 that 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 underwent scanning.

TABLE 1 Clinical, Experimental, and Demographic Data for the Attention-Deficit/Hyperactivity Disorder Combined Type (ADHD-CT) and Control Participants

	ADHD-CT ($DAT1_{10/6}$)		Control ($DAT1_{10/6}$)			
Mean (SD)	2 copies (n = 15)	<2 copies (n = 14)	2 copies (n = 16)	<2 copies (n = 14)	Significance Test	*p*
Age (years)	15.60 (2.35)	15.35 (2.06)	15.35 (1.4)	15.87 (2.06)	$F_{group}(1,55)=0.06$	.80
					$F_{haplotype}(1,55)=0.07$	.79
					$F_{interaction}(1,55)=0.54$	.47
IQ	109.4 (12.8)	101.07 (12.97)	111.06 (9.9)	115.5 (12.20)	$F_{group}(1,55)=6.63$	.013
					$F_{haplotype}(1,55)=0.39$	.54
					$F_{interaction}(1,55)=4.18$	.046
Conners' *DSM-IV* ADHD Inattention ratings (parent)	65.67 (10.77)	72.5 (8.23)	46.53 (4.61)	47.29 (6.35)	$F_{group}(1,54)=115.56$	<.001
					$F_{haplotype}(1,54)=3.38$	.071
					$F_{interaction}(1,54)=2.17$	.15
Conners' *DSM-IV* ADHD Hyperactivity/ Impulsivity ratings (parent)	77 (13.94)	81.07 (12.80)	47.4 (7.19)	48.14 (6.13)	$F_{group}(1,54)=126.14$	<.001
					$F_{haplotype}(1,54)=0.75$	.39
					$F_{interaction}(1,54)=0.36$	.55
Conners' *DSM-IV* ADHD Total ratings (parent)	72.6 (12.87)	79.29 (9.98)	46.53 (5.42)	47.36 (6.03)	$F_{group}(1,54)=146.16$	<.001
					$F_{haplotype}(1,54)=2.45$	.12
					$F_{interaction}(1,54)=1.49$	.23
Mean response time, Gain trials (SE)	609.24 (19.72)	631.47 (20.42)	595.01 (19.10)	571.31 (20.42)	$F_{group}(1,55)=3.49$	.067
					$F_{haplotype}(1,55)=0.00$	.97
					$F_{interaction}(1,55)=1.33$	.25
Mean response time, Loss-avoidance trials (SE)	621.31 (19.29)	638.49 (19.97)	604.33 (18.68)	580.01 (19.97)	$F_{group}(1,55)=3.75$	.058
					$F_{haplotype}(1,55)=0.03$	.86
					$F_{interaction}(1,55)=1.13$	.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)	$F_{group}(1,54)=1.50$	.23
					$F_{haplotype}(1,54)=0.04$	.84
					$F_{interaction}(1,54)=0.37$	.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)	$F_{group}(1,54)=0.01$	.90
					$F_{haplotype}(1,54)=2.12$	.15
					$F_{interaction}(1,54)=0.15$	.70
Success rate (%)	78.29 (0.48)	77.59 (0.50)	78.48 (0.47)	78.48 (0.50)	$F_{group}(1,55)=1.22$	.27
					$F_{haplotype}(1,55)=0.51$	.48
					$F_{interaction}(1,55)=0.53$	.47
Total Earned (£)	140 (3.14)	140.93 (3.25)	141.44 (3.04)	135 (3.25)	$F_{group}(1,54)=0.50$	.48
					$F_{haplotype}(1,54)=0.75$	.39
					$F_{interaction}(1,54)=1.35$	.25

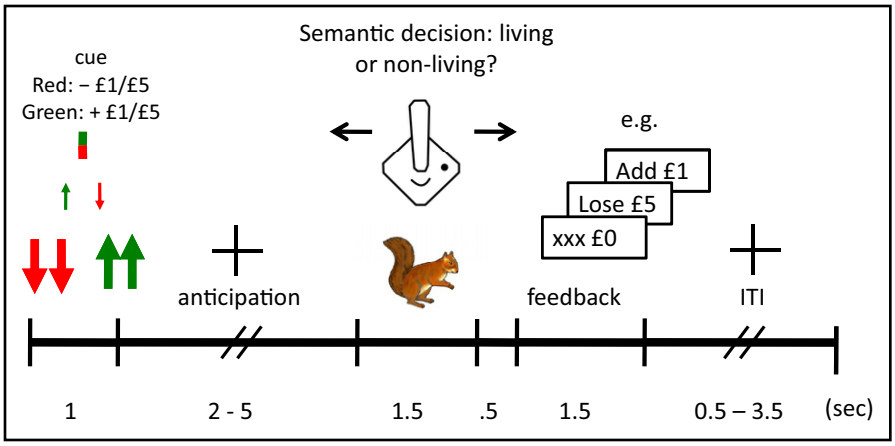
Note: DAT1 = dopamine transporter gene; IQ = intelligence quotient; SE = standard error.

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; mean = 43.2 months, SD = 9.36 months).

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) × 2 ($DAT1_{10/6}$ 2 copies, <2 copies) analysis of variance (ANOVA; Table 1). To investigate the effect of incentive mag-

FIGURE 1 Motivated incidental learning task (MILT). Note: ITI = inter-trial interval.



nitude on performance, we conducted a mixed 3 (£0, £1, £5) × 2 (ADHD-CT, control) ANOVA on response times separately for gain and loss-avoidance trials.

fMRI Data: First-Level Analysis

MRI data were acquired on a General Electric SIGNA HDx 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 (Supplement 1, available online, provides acquisition and preprocessing 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 seconds) 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 the 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, after a preliminary test showing no significant effect for brain hemisphere (or interaction with diagnostic group or $DAT1_{10/6}$). Both of 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) × 2 ($DAT1_{10/6}$ 2 copies, <2 copies) × 2 (£1, £5) ANCOVA, separately for gain and loss-avoidance anticipation and brain hemisphere, focusing on the VS (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: $\text{Anticipation}_{\pm £5}$ >

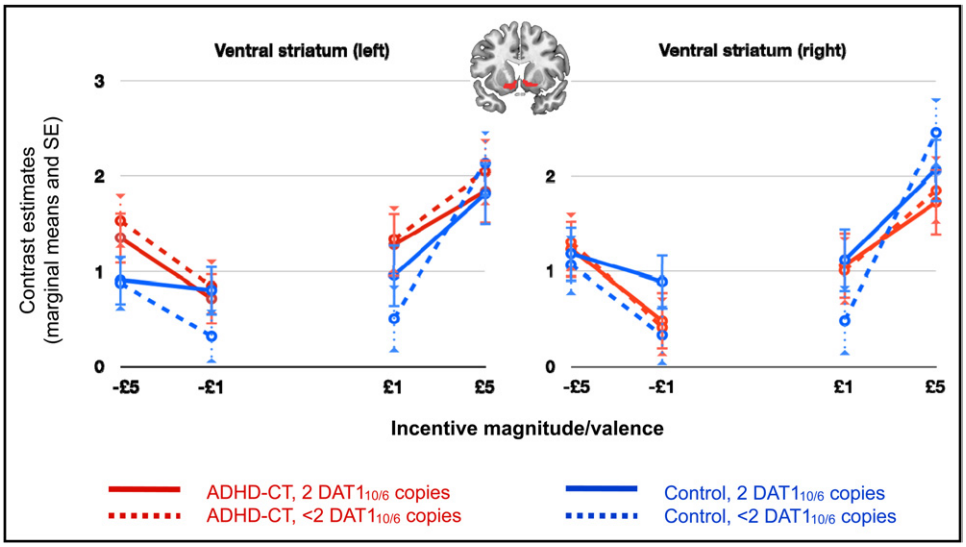
TABLE 2 Analyses of Covariance (ANCOVAs) Investigating the Effect of Clinical Group (Attention-Deficit/Hyperactivity Disorder [ADHD] Combined Type, Control), Dopamine Transporter Gene ($DAT1_{10/6}$) (2 Copies, <2 Copies), Task Phase (Anticipation, Outcome), Incentive Valence (Gain, Loss-Avoidance), and Incentive Magnitude (Small, Large) on Neural Activation in the Ventral Striatum and the Caudate Nucleus Head and Body

	Ventral striatum					Caudate Nucleus Body					Caudate Nucleus Head				
Effect	**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	0.01	NS	0.97	1,54	NS	0.02	NS	1.18	1,54	NS	0.02	NS
$DAT1_{10/6}$	0.87	1,54	NS	0.02	NS	0.44	1,54	NS	0.01	NS	0.04	1,54	NS	0.00	NS
Group × $DAT1_{10/6}$	0.47	1,54	NS	0.01	NS	0.18	1,54	NS	0.00	NS	0.37	1,54	NS	0.01	NS
Phase[a]	39.95	1,54	<.001	0.43	<.001	18.41	1,54	<.001	0.25	<.001	23.87	1,54	<.001	0.31	<.001
× Group[a]	0.03	1,54	NS	0.00	NS	1.53	1,54	NS	0.03	NS	0.29	1,54	NS	0.01	NS
× $DAT1_{10/6}$[a]	0.55	1,54	NS	0.01	NS	0.27	1,54	NS	0.01	NS	0.03	1,54	NS	0.00	NS
× Group × $DAT1_{10/6}$[a]	1.67	1,54	NS	0.03	NS	8.63	1,54	.005	0.14	.011	3.36	1,54	.072	0.06	NS
Valence[a]	13.60	1,54	.001	0.20	<.001	2.09	1,54	NS	0.04	NS	5.05	1,54	.029	0.09	.027
× Group[a]	0.10	1,54	NS	0.00	NS	3.51	1,54	NS	0.04	NS	0.31	1,54	NS	0.01	NS
× $DAT1_{10/6}$[a]	0.19	1,54	NS	0.00	NS	0.22	1,54	NS	0.00	NS	0.04	1,54	NS	0.00	NS
× Group × $DAT1_{10/6}$[a]	0.19	1,54	NS	0.00	NS	0.00	1,54	NS	0.00	NS	0.01	1,54	NS	0.00	NS
Magnitude[a]	12.84	1,54	.001	0.19	.001	7.22	1,54	.010	0.12	.010	7.85	1,54	.007	0.13	.007
× Group[a]	4.07	1,54	.049	0.07	.058	2.05	1,54	NS	0.04	NS	2.68	1,54	NS	0.05	.077
× $DAT1_{10/6}$[a]	0.20	1,54	NS	0.00	NS	0.16	1,54	NS	0.00	NS	0.03	1,54	NS	0.00	NS
× Group × $DAT1_{10/6}$[a]	0.03	1,54	NS	0.00	NS	0.04	1,54	NS	0.00	NS	0.02	1,54	NS	0.00	NS
Phase × Valence[a]	2.70	1,54	NS	0.05	NS	3.46	1,54	.069	0.06	.069	1.91	1,54	NS	0.03	NS
× Group[a]	0.88	1,54	NS	0.02	NS	0.40	1,54	NS	0.01	NS	1.41	1,54	NS	0.03	NS
× $DAT1_{10/6}$[a]	1.12	1,54	NS	0.02	NS	0.30	1,54	NS	0.02	NS	0.60	1,54	NS	0.01	NS
× Group × $DAT1_{10/6}$[a]	0.00	1,54	NS	0.00	NS	0.39	1,54	NS	0.01	NS	0.00	1,54	NS	0.00	NS
Phase × Magnitude[a]	15.64	1,54	<.001	0.23	<.001	8.13	1,54	.006	0.01	.006	9.03	1,54	.004	0.14	.004
× Group[a]	5.61	1,54	.021	0.09	.026	2.87	1,54	.096	0.05	NS	6.38	1,54	.015	0.11	.022
× $DAT1_{10/6}$[a]	1.70	1,54	NS	0.03	NS	0.00	1,54	NS	0.00	NS	0.54	1,54	NS	0.01	NS
× Group × $DAT1_{10/6}$[a]	1.29	1,54	NS	0.02	NS	0.78	1,54	NS	0.01	NS	1.42	1,54	NS	0.03	NS
Phase × Valence Magnitude[a]	0.08	1,54	NS	0.00	NS	1.65	1,54	NS	0.03	NS	0.41	1,54	NS	0.01	NS
× Group[a]	0.19	1,54	NS	0.01	NS	0.00	1,54	NS	0.00	NS	0.36	1,54	NS	0.01	NS
× $DAT1_{10/6}$[a]	0.44	1,54	NS	0.00	NS	0.50	1,54	NS	0.01	NS	0.46	1,54	NS	0.01	NS
× Group × $DAT1_{10/6}$[a]	0.64	1,54	NS	0.01	NS	0.08	1,54	NS	0.00	NS	0.14	1,54	NS	0.00	NS

Note: p *Values .10 are shown; NS = nonsignificant.*
[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]).*

$Anticipation_{£0,}$ Inferences were conducted at the cluster-level using family-wise error correction ($\alpha = 0.05$); a voxel was considered for cluster-level analysis if p was <.001 (Supplement 2, available online, provides group comparisons). Finally, we present correlations between neural activation and ADHD symptom ratings in supplemental material (Supplement 2; Tables S4 and S5, available online).

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.



RESULTS

Does Neural Activation to Incentive-Predicting Cues and Successful Outcomes Differ Between Adolescents With ADHD-CT and Controls?

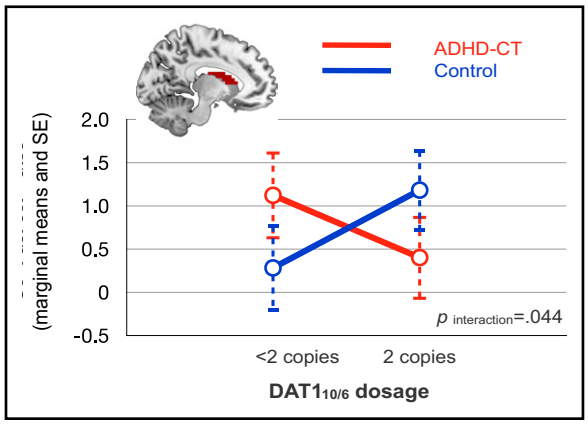
Although there were no significant main effects for diagnostic group, or interactions between diagnostic group, task phase, and incentive valence, we observed significant interactions between diagnostic group, task phase, and incentive magnitude in the VS and the caudate nucleus head (Table 2). We explored 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 ($F_{1,54} = 6.91$, $p = .011$, $\eta^2_p = 0.11$; $p_{IQ} = .012$) and the VS ($F_{1,54} = 12.65$, $p < .001$, $\eta^2_p = 0.13$; $p_{IQ} = .004$), but not during the incentive anticipation phase ($F < 1.90$, NS). Further post-hoc simple effects analyses to explore the interaction between diagnostic group and incentive magnitude showed that neural activation in the VS ($F_{1,54} = 4.85$, $p = .032$, $\eta^2_p = 0.08$; $p_{IQ} = 0.014$) and the caudate nucleus head ($F_{1,54} = 6.58$, $p = .013$, $\eta^2_p = 0.11$; $p_{IQ} = .002$) was higher in the ADHD-CT group compared with controls for large (£5), but not small (£1; $F < 1.00$, 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) × 2 ($DAT1_{10/6}$ 2 copies, <2 copies) × 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; $F < 1.00$, 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 among 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 ($F_{(1,54)} = 4.25$, $p = .044$, $\eta^2_p = 0.06$; $p_{IQ} = 0.031$), 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

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.



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.

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 (Supplement 2, available online, provides additional 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: $F_{(1,55)} = 17.48$, $p < .001$, $\eta^2_p = 0.24$; loss-avoidance: $F_{(1,55)} = 8.17$, $p < .006$, $\eta^2_p = 0.13$), irrespective of diagnosis or $DAT1_{10/6}$ dosage ($F < 1.81$, NS; Figure 2). The increase in incentive magnitude also resulted in a linear decrease in response times for each incentive valence across groups ($F_{Gain(1,57)} = 138.52$, $p < .001$; $F_{Loss\text{-}avoidance(1,57)} = 57.37$, $p < .001$), $F_{Diagnosis \times magnitude} < 1$, 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 with controls, following confirmation of a successful outcome. Third, $DAT_{10/6}$ 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 with 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 with healthy controls using an MID paradigm.[3] Our findings, albeit 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 with ~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 nonhuman 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, although we would not expect that it would make 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 (a similar variant in cognitive neuroscience was reported by Wittmann *et al.*[35]) was that, because of its nature as an incidental learning task (an aspect that is not discussed in this article), the targets comprised drawings of living and nonliving 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 nonincentive trials that were matched on semantic processing as the comparison condition. Participants were pretrained 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 after 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 with 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 (Supplement 1, available online, summarizes whole-brain analyses). 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.[48] 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-shaped 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 should be interpreted with caution until further replication studies have been completed. Although 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-naive 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. Although 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 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 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. &

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SUPPLEMENT 1

METHOD

Sample

There were no differences among the groups in the mean handedness laterality quotient: $F_{1,55} = 2.57$, $p = .11$; ADHD-CT: mean (SD) = 63.45 (6.31); control: mean (SD) = 77.61(6.21)).[1]

As part of the International Multi-Centre Attention Deficit Hyperactivity Disorder Genetics (IMAGE) project,[2,3] all participants were of European white descent. Exclusion criteria were an intelligence quotient (IQ) <70, autism, epilepsy, general learning difficulties, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic attention-deficit/hyperactivity disorder (ADHD). At the time of initial assessment (18–60 months before the current study; mean = 43.2, SD = 9.36), clinical participants had a clinical diagnosis of *DSM-IV* ADHD-combined subtype (ADHD-CT) confirmed through a semi-structured clinical interview using the Parental Account of Children's Symptoms (PACS)[4] and parent and teacher ratings on the Conners' *DSM-IV* ADHD subscales in the diagnostic range (T-score >63).[5,6] Parents completed the long form of the revised Conners' Rating Scale[5] at the time of testing. Twenty-four participants (83%) had current total DSM-IV *ADHD* T-scores in the diagnostic range. Of the five participants with current total parent T-scores <63 (the clinical cut-off in IMAGE)[7], two participants were still receiving stimulant treatment, and the remaining three were older than 18 years and had stopped receiving medication 2 to 3 years before testing. We repeated the analyses excluding those five participants with current total parent T-scores <63: results were similar.

Experimental Paradigm and Procedure

Trials, reflecting combinations of different valences (gain, loss-avoidance or no-incentive), magnitudes (£1 or £5), and pictures (living or nonliving) were randomly presented, subject to the rule that each of the 10 trial types occurred once every 10 trials (to avoid freak clustering). The images had been derived from a pool of 240 pictures containing an additional 80 distractors that would be used in subsequent memory tests. The pictorial dataset included stimuli provided by Rossion and Pourtois[9] and additional images of similar visual qualities (processed in Adobe Photoshop 8.0) obtained from online clip art libraries (picture set available from the first author). All pictures (197 × 281 pixels) contained low-resolution images of objects (72 dots per inch [DPI]) on a white background.

Magnetic Resonance Imaging Acquisition

A General Electric SIGNA HDx 3.0T magnetic resonance (MR) scanner (General Electric Medical Systems, Milwaukee, WI) with an eight-channel head coil was used to acquire gradient-echo, echo-planar images (EPI-RT) with repetition time (TR) = 2000 milliseconds, echo time (TE) = 30 milliseconds, flip angle = 75°, field of view (FOV) = 24 cm, in-plane resolution = 3.75^2 mm^2, and matrix size = 64^2. A total of 39 axial slices aligned parallel to the anterior commissure–posterior commissure (AC-PC) line were obtained with a thickness of 3.0 mm (0.3 mm gap). For each of the two runs of the Motivated Incidental Learning Task (MILT), 400 T2*-weighted image volumes were acquired over 13.3 minutes, preceded by four dummy scans that allowed for T1 equilibration. A T1-weighted high-resolution MR image was also acquired using single-shot EPI with TR = 2000 milliseconds, TE = 30 milliseconds, flip angle = 90°, FOV = 24 cm, slice thickness = 3.0 mm with 0.3-mm gap, matrix = 128^2 and 43 slices, for estimation of normalization parameters to a standard space. Stimuli were projected onto a screen at the foot of the scanner bed using a liquid crystal display (LCD) projector. Participants viewed the projector through a mirror and made responses using a joystick.

Functional MRI Data Preprocessing

Neuroimaging data were preprocessed and analyzed in Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm) running in MATLAB 7.8 (Mathworks, Natick, MA) on an Apple Mac computer running OSX 10.5. Images were initially realigned to the first scan (and then the mean image) from the time series. Parameters from normalization into standard space defined by the EPI template in SPM were determined from the high-resolution EPI image and applied to the co-registered time series of functional images. Data were spatially smoothed using an 8-mm full-width at half maximum (FWHM) Gaussian kernel.

Correlations With ADHD Symptoms

We examined the association between activation in the ventral striatum (mean extracted signal from region of interest [ROI]) and Conners' *DSM-IV* ADHD symptom ratings using Pearson's product–moment correlation coefficient. In addition, we examined the association between the ADHD symptom dimensions and blood oxygen level–dependent (BOLD) response in the caudate nucleus body and head ROIs that showed significant effects of diagnosis and/or dopamine transporter gene (*DAT1*) in the anticipation and outcome phases, respectively. Statistical analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL) and Stata (StataCorp, College Station, TX).

ROI Analysis

The anatomical boundaries of the ventral striatum were manually defined on the single-subject T1-

weighted brain in SPM using FSLview (http://www.fmrib.ox.ac.uk/fsl/) based on previous definitions.[9,10] The boundaries for the remaining regions were taken from the automated anatomic labeling (AAL) atlas using the Wake Forest University (WFU) Pickatlas program.[11] The boundaries for the caudate head were modified to avoid overlap with the definition of the ventral striatum.

Whole-Brain Analyses

We tested our hypotheses on the following two contrast for each incentive valence: $\text{Anticipation}_{\pm £5} > \text{Anticipation}_{£0}$; and $\text{Outcome}_{\pm £5} > \text{Outcome}_{£0\ \text{(neutral trials)}}$. The statistical inference was performed at the cluster level ($p < .05$), using family-wise error (FWE) correction for multiple comparisons across the brain (voxel-level threshold: $p = .001$). We used a 2 (diagnosis: control, ADHD-CT) × 2 ($DAT1_{10/6}$ dosage: 2 copies, >2 copies) analysis of covariance (ANCOVA), with age included as a covariate[12,13]; analyses were repeated controlling for IQ.

Genotyping

DNA was extracted directly from blood samples or using a mouth swab sampling technique. Standard polymerase chain reaction (PCR) methods were used to genotype the variable number tandem repeat (VNTR) markers according to previous optimized protocols.[14]

SLC6A3/DAT1 Gene. VNTR elements in DAT1 3′untranslated region (3′UTR) and DAT1 Intron 8 were genotyped in-house using the following protocols:

DAT1 3′UTR VNTR. PCR amplifications were performed in 9.5-μL reactions containing 50 ng of genomic DNA, 10 mmol/L dNTPs, 5 pmol of both forward and reverse primers, 25mmol/L $MgCl_2$, 10X NH4 reaction buffer, and 1 Unit of Taq polymerase. The primers used had sequences: 5- TGTGGTGTAGGGAACGGCCTGAG-3′ (forward) and 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′ (reverse). Using a PTC-225 thermocycler, DNA was denatured at 95°C for 5 minutes followed by 30 cycles of 95°C (1 min), 60°C (1 min), and 72°C (1 min), followed by a final extension step of 72°C for 10 minutes. Final PCR products were electrophoresed in ethidium bromide–stained agarose gel (2%) for 1.5 hours at 220 V. Genotypes were scored based on the size of the repeat allele, i.e., 6, 9, 10, or 11.

DAT1 Intron 8 VNTR. PCR amplifications were performed in 9.5-μL reactions containing 50 ng of genomic DNA, 10 mmol/L dNTPs, 5 pmol of both forward and reverse primers, 25 mmol/L $MgCl_2$, 10X NH4 reaction buffer, and 1 Unit of Taq polymerase. The primers used had sequences: 5′- GCTTGGGGAAGGAAGGG-3′ (forward) and 5′-TGTGTGCGTGCATGTGG-3′ (reverse). Using a PTC-225 thermocycler, DNA was denatured at 95°C for 5 minutes followed by 30 cycles of 95°C (1 min), 65°C (1 min), and 72°C (1 min), followed by a final extension step of 72°C for 10 minutes. Final PCR products were electrophoresed in ethidium bromide–stained agarose gel (2%) for 1.5 hours at 220 V. Genotypes were scored based on the size of the repeat allele, i.e., 5, 6, or 9.

Given that our sample was selected on the basis of $DAT1_{10/6}$ haplotype copies, Hardy–Weinberg equilibrium (for contributing DAT1 polymorphisms) or comparability to population haplotype/genotype frequencies would not be expected and were not estimated.

SUPPLEMENT 2

RESULTS

Whole Brain Analyses

Motivated Incidental Learning Task (MILT): Successful Outcome-Related Activation. Successful outcome notification phase. In the control group, the notification of successful outcomes did not increase activation in any region; activation was attenuated (compared with neutral trials) over an extensive network of regions. In the attention-deficit/hyperactivity disorder combined type (ADHD-CT) group, the notification of monetary gains increased activation at the right anterior cingulate cortex and the left occipital gyrus; no changes in brain activation followed the notification of successful loss-avoidance outcomes (Tables S6 and S7 and Figure S1).

Main Effects of Diagnosis. Anticipation phase. No significant diagnosis effect was observed.

Notification of successful outcomes. The ADHD-CT group showed higher activation, compared with controls, in a cluster extending over the left anterior insula, middle orbital and inferior frontal gyri in gain trials, and the superior parietal lobe, the precuneus, the lingual gyrus, and the cerebellum in loss-avoidance trials (Table S8).

All clusters remained significant after controlling for intelligence quotient (IQ). The control group did not show higher activation than the ADHD-CT group in any contrast.

Does Genetic Variation in the Dopamine Transporter Gene ($DAT1_{10/6}$) Modulate Striatal Responsivity to Rewards? Anticipation phase. There were no significant main or interaction effects for $DAT1_{10/6}$ dosage during gain-anticipation in the whole-brain analyses.

Successful outcome notification phase. There were no significant main or interaction effects for $DAT1_{10/6}$ dosage in the whole-brain analyses.

Correlations With ADHD Symptom Ratings. We did not find evidence for a significant association between Conners' *DSM-IV* parent ratings of either inattention or hyperactivity-impulsivity symptoms and anticipatory or outcome-related brain activation in any region of interest (ROI) for either diagnostic group (Tables S4 and S5).

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TABLE S1 Possible Psychiatric Comorbidities for the Attention-Deficit/Hyperactivity Disorder Combined Type (ADHD-CT) Group (by Dopamine Transporter Gene [$DAT1_{10/6}$] Haplotype Dosage) Based on the Parental Account of Children's Symptoms (PACS) Interview[4] at the Time of Initial Assessment

Disorder	ADHD-CT $DAT1_{10/6}$ (2 Copies), n = 15	ADHD-CT $DAT1_{10/6}$ (<2 Copies), n = 14	ADHD-CT (All) (Frequencies), N = 29	Association Test	
				$\chi^2(1)$	*p*
Mood disorder	3	2	5 (17%)	0.10	.75
Bipolar affective disorder	0	0	0	—	—
Anxiety disorder	9	5	14 (48%)	1.29	.26
Tourette syndrome	0	0	0	—	—
Substance abuse disorder	0	0	0	—	—
Obsessive-compulsive disorder	1	0	1 (3%)	0.90	.34
Reactive attachment disorder	0	0	0	—	—
Psychosis	0	0	0	—	—
Oppositional-defiant disorder	11	11	22 (76%)	0.53	.47
Conduct disorder	5	6	11 (38%)	0.48	.49

TABLE S2 Medication History for the Attention-Deficit/Hyperactivity Disorder Combined Type (ADHD-CT) Group

Type of Medication	No. of Adolescents With ADHD-CT (N = 29)	Medication Dose Range (mg)
Methyphenidate HCl (SR)	14	18–90
Methyphenidate HCl (IR)	1	20
Methyphenidate HCl (SR and IR)	2	18–40 and 5–10
Methyphenidate HCl (unspecified)	2	30–40
Methyphenidate HCl (SR) and Risperidone	1	81 and 1
Unspecified	1	—
Previously but not currently medicated		—
Methyphenidate HCl (SR)	2	—
Methylphenidate HCl (IR)	4	—
Never medicated	2	—

Note: HCl = hydrochloride; IR = immediate release; SR = slow release.

2

TABLE S3 Dopamine Transporter Gene (*DAT1*$_{10/6}$) Haplotype Assignment on the Basis of Zygosity for the *DAT1 3′UTR* and *Intron 8 Variable Number Tandem Repeats (VNTRs)*

DAT1 VNTRs			Diagnostic group (frequencies)		
3′UTR		*Intron 8*	ADHD-CT Group	Control Group	*DAT1*$_{10/6}$ Haplotype Status
10/10	AND	6/6	15	16	2 copies
9/10	AND	5/5	0	5	<2 copies
9/10	AND	5/6	7	4	<2 copies
9/10	AND	6/6	5	0	<2 copies
9/9	AND	5/5	1	2	<2 copies
9/9	AND	5/6	1	3	<2 copies

Note: ADHD-CT = attention-deficit/hyperactivity disorder combined subtype; UTR: untranslated region.

TABLE S4 Pearson Correlation Coefficients Between Brain Activation and Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Ratings

$DAT1_{10/6}$	Conners' *DSM-IV* ADHD Inattention ratings (parent)				Conners' *DSM-IV* ADHD Hyperactivity-impulsivity ratings (parent)			
	< 2 Copies		2 Copies		< 2 Copies		2 Copies	
	CONTROL	ADHD-CT	CONTROL	ADHD-CT	CONTROL	ADHD-CT	CONTROL	ADHD-CT
Ventral striatum: anticipation								
Gain	−.15	.28	.11	−.24	−.24	−.16	.21	−.22
Loss-avoidance	−.41	−.14	.22	−.13	−.38	−.46§	.06	−.23
Ventral striatum: outcome								
Gain	.23	.09	.09	.36	.29	.23	.00	.45§
Loss-avoidance	.13	−.12	.27	.41	.06	−.20	.27	.44

Note: All p-values >.10, except where marked with §. ADHD-CT = attention-deficit/hyperactivity disorder combined type.
§.05<p≤.10.

TABLE S5 Pearson Correlation Coefficients Between Brain Activation and Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Ratings in the Regions of Interest (ROI) Showing Significant Diagnosis and/or Dopamine Transporter Gene (*DAT1*) Effects

	Conners' *DSM-IV* ADHD Inattention Ratings (Parent)		Conners' *DSM-IV* ADHD Hyperactivity-Impulsivity Ratings (Parent)	
$DAT1_{10/6}$	<2 Copies	2 Copies	<2 Copies	2 Copies
Caudate nucleus body (anticipation phase)				
Control	−0.43	0.05	−0.09	−0.05
ADHD-CT	−0.02	0.09	−0.43	−0.11
Caudate nucleus head (outcome phase)				
Control	0.17	−0.09	0.22	0.08
ADHD-CT	−0.24	0.32	−0.07	0.25

Note: All p values > .10. ADHD-CT = attention-deficit/hyperactivity disorder combined type.

TABLE S6 Clusters Showing Significant Activation in Response to Incentive Predicting Cues in the Control Group

	Cluster size (voxels)	P (FWE-corrected)	Zmax	Peak Voxels (x,y,z MNI)
$Anticipation_{£5}>Anticipation_{£0}$				
B ventral striatum, B caudate, B putamen, B globus pallidus, midbrain (SN/VTA), B anterior insula, B pre-motor cortex/SMA (BA 6), L primary somatosensory cortex (BA 1/2), R MFG/SFG (rostrolateral), R dorsal ACC	3984	<.001	5.13	[12,16,−7] [23,49, −7] [−29, −18,65]
B visual cortex (BA 17/18), B occipital gyrus, B cerebellum (lobule VIIa crus I/lobule VI)	1186	<.001	5.76	[16, −97, 9] [16, −93, 4] [−10, −101, 13]
B superior parietal lobule, B precuneus (BA 7)	151	.016	3.83	[8, −82, 49] [−7, −78, 36] [12, −74, 52]
$Anticipation_{£5}<Anticipation_{£0}$				
	—	—	—	—
$Anticipation_{£5}>Anticipation_{£0}$				
B ventral striatum, B caudate, B ventral pallidum, R thalamus	152	.011	5.05	[12 −101 9] [16 −93 1]
R visual cortex (BA 17/18)/occipital gyrus	259	.001	4.85	[8 8 −1] [−10 4 −10]
L visual cortex (BA 17/18)/occipital gyrus	116	.026	4.56	[−10 −97 −1] [−14 −101 13] [−26 −97 6]
$Anticipation_{£5}<Anticipation_{£0}$				
	—	—	—	—
$Outcome_{Gain(£5)}>Outcome_{£0}$				
	—	—	—	—
$Outcome_{Gain(£5)}<Outcome_{£0}$				
L lateral SFG/MFG/OFG/IFG, B insula, R STG, B precuneus, B SPL, B supramarginal gyrus, L POTZ, L TOTZ, R posterior MTG, R lingual gyrus/occipital gyrus, B caudate, L pallidum, L thalamus, R amygdala, B SN/VTA	5780	<.001	5.43	[8 −52 62] [4 −44 65] [61 −26 23]
R thalamus, R pallidum	118	.022	4.04	[16 −22 −1] [20 −3 6]
$Outcome_{Loss\text{-}avoidance(£5)}>Outcome_{£0}$				
	—	—	—	—
$Outcome_{Loss\text{-}avoidance(£5)}<Outcome_{£0}$				
B SMA, B precuneus, B SPL, L MCG, B occipital gyrus/POTZ/TOTZ/lingual gyrus, R insula, B STG, R ventral striatum, R caudate, R putamen, R pallidum, R thalamus, R amygdala	5825	<.001	6.01	[38 −74 9] [−3 −56 62] [−10 −86 46]
L SFG/MFG/OFG/IFG, L insula, L medial SFG, L mPFC, L MTG,	1167	<.001	5.34	[−22 57 9] [−33 46 23] [−33 49 6]
L putamen, L ventral striatum, L caudate, L pallidum	136	.004	3.89	[−14 8 −7] [−14 12 13] [−14 23 −7]

Note: All reported clusters were significant at p = .05 *using familywise error correction (FWE) (voxel-level threshold:* p = .001*).*
ACC = anterior cingulate cortex; B = bilateral; BA = Brodmann area; IFG = inferior frontal gyrus; L =left; MCG = middle cingulate gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; OFG = orbital frontal gyrus; POTZ = parieto-occipital transition zone; R = right; SFG = superior frontal gyrus; SMA = supplementary motor area; SN/VTA = sunbstantia nigra/ventral tegmental area; SPL = superior parietal lobule; STG = superior temporal gyrus; TOTZ = temporo-occipital transition zone.

FIGURE S1 (a) Statistical parametric maps of the regions activated following incentive-predicting cues and successful outcome presentation in the control and attention-deficit/hyperactivity disorder combined subtype (ADHD-CT) groups. (b) Statistical parametric maps showing regions activated significantly higher in the ADHD-CT group compared with controls during outcome presentation, when comparing the presentation of successful outcomes to no-incentive trials. All clusters significant at $\alpha = 0.05$ (family-wise error corrected), voxel-level threshold. ***$p = .001$.

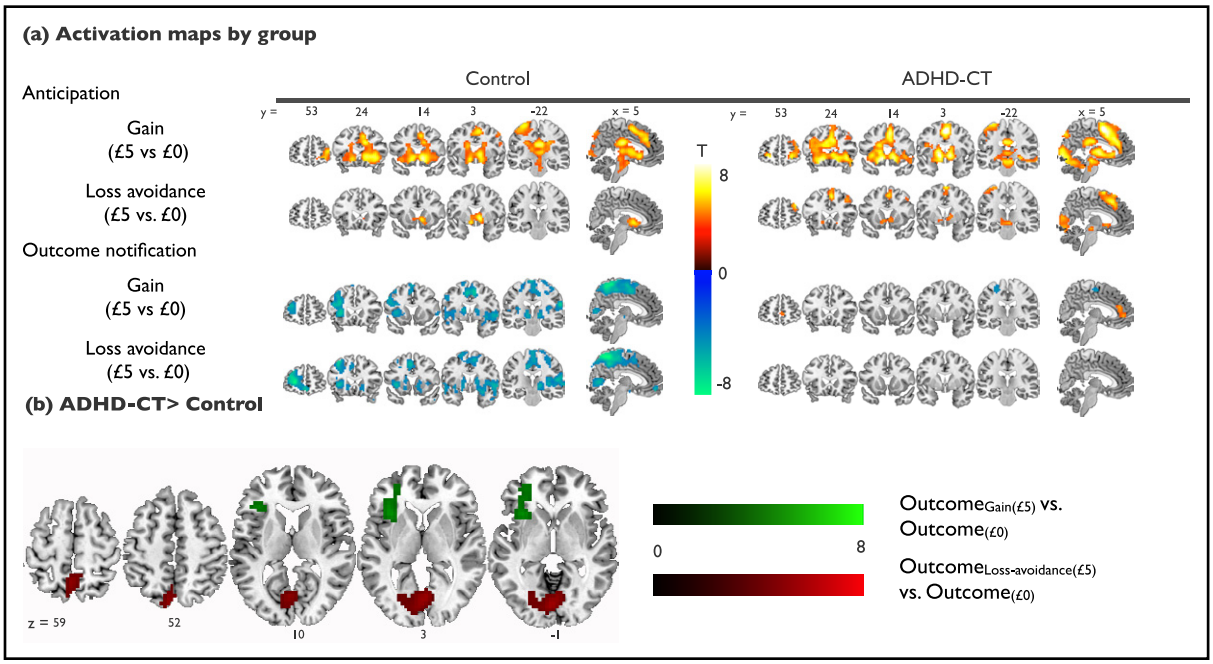

TABLE S7 Clusters Showing Significant Activation in Response to Incentive Predicting Cues in the Attention-Deficit/Hyperactivity Disorder Combined Type (ADHD-CT) Group

	Cluster size (voxels)	*p* (FWE-corrected)	Zmax	Peak voxels (x,y,z MNI)
$Anticipation_{£5}>Anticipation_{£0}$				
L MFG/superior OFG, B dorsal ACC/MCG/SMA, B IFG, B insula, B ventral striatum/caudate/putamen, B thalamus, B pallidum, B SN/VTA, midbrain, L precentral gyrus, L postcentral gyrus, L hippocampus, L SPL, L IPL, PCC, B precuneus, R lingual gyrus/cuneus (BA 17), R superior occipital gyrus (BA 18), left superior orbital gyrus, B cerebellum (lobule VI & VIIa)	6743	<.001	6.04	[−44 −41 62] [1 0 56] [−48 −37 56]
R MFG/superior OFG	277	<.001	4.5	[27 49 −4] [34 49 29] [38 46 19]
R angular gyrus/IPL	100	.022	4.04	[38 −63 42] [53 −60 39]
$Anticipation_{£5}<Anticipation_{£0}$				
	—	—	—	—
$Anticipation_{£5}>Anticipation_{£0}$				
B lingual gyrus/cuneus/occipital gyrus (BA 17/18), L fusiform gyrus, B cerebellum (lobule VI)	1044	<.001	5.12	[12 −82 −14] [16 −97 13] [−22 −74 −17]
B SMA, R medial SFG	248	.002	4.62	[4 23 49] [4 8 69] [4 30 62]
R MFG	162	.009	4.34	[34 53 29] [46 38 29] [31 57 23]
R angular gyrus/IPL	115	.028	3.98	[34 −67 52] [50 −52 42]
L precentral/postcentral gyri, L SPL, L IPL, L precuneus	221	.003	3.96	[−29 −18 65] [−33 −44 69] [−29 −33 65]
L amygdala, B ventral striatum, R caudate, L pallidum, L thalamus, L hippocampus, midbrain	232	.002	3.93	[−26 −14 −10] [4 −22 −10] [−7 −26 −10]
$Anticipation_{£5}<Anticipation_{£0}$				
	—	—	—	—
$Outcome_{Gain(£5)}>Outcome_{£0}$				
L occipital gyrus	79	.043	4	[−29 −78 −14] [−22 −90 −10] [−14 −86 −14]
R ACC	84	.036	3.97	[8 38 19] [4 49 3]
$Outcome_{Gain(£5)}<Outcome_{£0}$				
B precentral gyrus	157	.004	3.85	[−22 −14 62] [−7 −14 59] [16 −11 69]

TABLE S7 Continued.

	Cluster size (voxels)	*p* (FWE-corrected)	Zmax	Peak voxels (x,y,z MNI)
$Outcome_{Loss\text{-}avoidance(£5)} > Outcome_{£0}$				
	—	—	—	—
$Outcome_{Loss\text{-}avoidance(£5)} < Outcome_{£0}$				
	—	—	—	—

Note: All reported clusters were significant at p=.05 *using familywise error correction (FWE) (voxel-level threshold:* p=.001).
ACC = anterior cingulate cortex; B = bilateral; BA = Broadmann's area; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; L = left; MCG = middle cingulate gyrus; MFG = middle frontal gyrus; MNI = Montreal Neurological Institute; MTG = middle temporal gyrus; OFG = orbital frontal gyrus; PCC = posterior cingulate cortex; POTZ = parieto-occipital transition zone; R = right; SFG = superior frontal gyrus; SMA = supplementary motor area; SN/VTA = sunbstantia nigra/ventral tegmental area; SPL = superior parietal lobule; STG = superior temporal gyrus; TOTZ = temporo-occipital transition zone.

TABLE S8 Main and Interaction Effects for Dopamine Transporter Gene ($DAT1_{10/6}$) and Diagnosis on Neural Activation in Response to Incentive Predicting Cues

	Cluster Size (voxels)	*p* (FWE-corrected)	Zmax	Peak voxels (x,y,z MNI)
Main effects: less than 2 copies > 2 copies				
	—	—	—	—
Main effects: less than 2 copies < 2 copies				
	—	—	—	—
Main effects: ADHD-CT>controls				
$Outcome_{Gain(£5)}$ vs. $Outcome_{£0}$				
L anterior insula/middle orbital gyrus/inferior frontal gyrus (pars orbitalis)	161	0.007	4.1	[−33 19 3] [−33 46 −7] [−33 38 −4]
$Outcome_{Loss\text{-}avoidance(£5)}$ vs. $Outcome_{£0}$				
B lingual gyrus (BA 17/18, hOC3v/hOC4v), B cerebellum (lobule VI)	395	<.001	4.47	[−3 −78 −4] [−14 −78 −10] [12 −86 −10]
B superior parietal lobule (BA 5), L precuneus/superior parietal lobule (BA 7)	179	0.004	4.13	[−3 −56 59] [−7 −74 52] [8 −52 65]
Main effects: ADHD-CT<controls				
	—	—	—	—
$DAT1_{10/6}$ by diagnosis interaction				
	—	—	—	—

Note: All reported clusters were significant at p = .05 *using familywise error correction (FWE) (voxel-level threshold:* p = .001).
ADHD-CT=attention deficit-hyperactivity disorder, combined subtype; B=bilateral; BA=Brodmann's area; L=left; MNI = Montreal Neurological Institute; R=right.