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DAT1 and COMT Effects on Delay Discounting and Trait Impulsivity in Male Adolescents with Attention Deficit/Hyperactivity Disorder and Healthy Controls

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Choice impulsivity has been linked to dopamine function and is consistently observed in attention deficit/hyperactivity disorder (ADHD) as a preference for smaller-immediate over larger-delayed rewards using choice-delay paradigms. More sophisticated delay discounting paradigms have yielded inconsistent results. Context and sample characteristics may have contributed to these variations. In this study we examine the effect of type (real *vs* hypothetical) and magnitude of reward as well as of variation in dopamine genes on choice impulsivity. We selected 36 male adolescents with ADHD-combined subtype (ADHD-CT) and 32 controls (mean age = 15.42, SD = 2.05) to form four roughly equally sized subgroups on the basis of $DAT1_{10/6}$ haplotype dosage (2 copies and <2 copies). Participants, who were also genotyped for the $COMT_{val158met}$ and $DRD4_{48bp-VNTR}$ polymorphisms, performed a hypothetical and a real-time discounting task and provided self-ratings of trait impulsivity. The ADHD-CT group discounted rewards more steeply than controls only in the hypothetical task, with delay, but not reward magnitude, influencing choices. They also rated themselves as more impulsive compared with controls. $DAT1_{10/6}$ dosage and the $COMT_{Val158Met}$ genotype predicted trait impulsivity and discounting rates in the hypothetical task, but not in the real-time task. Our results directly link variation in genes putatively influencing dopamine signaling in the prefrontal cortex ($COMT_{Val158Met}$) and the striatum ($DAT1_{10/6}$) with discounting rates in a hypothetical task (but not a real-time task) and self-ratings of trait impulsivity in ADHD-CT and healthy controls. The lack of magnitude effects in the hypothetical task suggests that discounting in this task may be influenced by different processes in ADHD-CT than in healthy controls.
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INTRODUCTION

Impulsive behavior is a key characteristic of several psychiatric conditions, including attention deficit/hyperactivity disorder (ADHD) (Moeller *et al*, 2001). One aspect of impulsivity is the preference for immediate gratification, even when waiting longer might lead to higher absolute gains (Evenden, 1999). The decrease in the subjective value of a reinforcer with time is called delay discounting and is observed in many species (Ainslie, 1975; Rachlin and Green, 1972). In humans, delay discounting is usually assessed through choices between hypothetical gains that systematically vary in magnitude or in the delay one needs to wait to receive them (Richards *et al*, 1999). The pattern of responses, determined by the rate at which an individual discounts potential gains as a function of time, is mathematically best described by a hyperbolic-like curve (Green and Myerson, 2004; Reynolds, 2006b). A steeper curve indicates a higher discounting rate, reflecting greater impulsivity or reduced self-control (Logue, 1988). Populations with impulse control problems consistently demonstrate higher discounting rates compared with healthy controls (see Green and Myerson, 2004; Reynolds, 2006b for reviews), and prospective studies suggest that high discounting rates may indicate vulnerability for the development of such problems across species (eg, substance abuse/dependence; Anker *et al*, 2009; Audrain-McGovern *et al*, 2009; Dandy and Gatch, 2009; Diergaarde *et al*, 2008; Perry *et al*, 2005; Perry *et al*, 2008; Poulos *et al*, 1995; Wilhelm and Mitchell, 2009).

Different lines of evidence have linked delay discounting to dopamine and the function of dopamine-modulated frontostriatal circuits (Adriani *et al*, 2009; Cardinal *et al*, 2001; Kable and Glimcher, 2009; Kobayashi and Schultz, 2008;

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Lee *et al*, 2009; Pothuizen *et al*, 2005). Dysfunctions in the neurobiological systems involved, from the cellular to the network level, are also postulated to give rise to changes in reinforcement sensitivity in ADHD (see, eg, Frank *et al*, 2007; Sagvolden *et al*, 2005; Tripp and Wickens, 2008; and see Luman *et al*, 2010 for a review). Pharmacological, genetic, and neuroimaging studies converge on the idea that ADHD is associated with deficiencies in dopamine signaling and abnormalities in dopamine-modulated frontostriatal circuits (Bush, 2010; Gizer *et al*, 2009; Krause *et al*, 2000; Paloyelis *et al*, 2007; Spencer *et al*, 2007; Volkow *et al*, 2009; Volkow *et al*, 2007).

As predicted by most of these neurobiological models (Luman *et al*, 2010), ADHD patients consistently prefer smaller-immediate over larger-delayed rewards using the choice-delay paradigm (Willcutt *et al*, 2008; see Paloyelis *et al*, 2009 for a review). In the choice-delay paradigm, participants make repeated choices between two *standard* amounts available at *fixed* delays. This paradigm is, however, faced with certain methodological issues: reduced sensitivity to detect individual differences in impulsivity, the confounding of time on task with choice preference, and concerns over the validity of using tertiary reinforcers to elicit impulsive behavior (Kuntsi *et al*, 2006b; Paloyelis *et al*, 2009).

Delay discounting paradigms overcome many of these problems, but have been used in few studies with ADHD patients, yielding somewhat inconsistent findings. In a study using a hypothetical discounting task, adolescents with ADHD and comorbid oppositional-defiant disorder made more impulsive choices than controls when the maximum hypothetical gain per trial was \$100, but not when it was \$1000 (Barkley *et al*, 2001). Using tasks presenting choices between real rewards and delays, Scheres *et al* (2006) did not find any differences, but in a later study where they examined ADHD subtypes separately they found that the ADHD-combined subtype (ADHD-CT) group, but not the inattentive subtype group, discounted rewards more steeply than controls (Scheres *et al*, 2010).

Experimentally measured discounting rates using hypothetical tasks show good temporal stability (Audrain-McGovern *et al*, 2009; Beck and Triplett, 2009; Kirby, 2009; Ohmura *et al*, 2006), similar to personality traits (Costa and McCrae, 1992), suggesting that they reflect a relatively stable individual difference. Real-time tasks, where participants experience the rewards and delays associated with each decision they make, are thought to be sensitive to state changes in impulsivity (McDonald *et al*, 2003; Reynolds *et al*, 2006; Reynolds and Schiffbauer, 2004). Evidence from acute pharmacological interventions with psychomotor stimulants and suppressants supports the greater sensitivity of real-time tasks to manipulations likely to induce changes in state impulsivity: discounting rates are affected when real-time task are used, but not in hypothetical tasks (Acheson and de Wit, 2008; Acheson *et al*, 2006; De Wit, 2009; McDonald *et al*, 2003; Richards *et al*, 1999). For example, methylphenidate reduced discounting rates in a real-time task but not in a hypothetical discounting task in ADHD patients (Shiels *et al*, 2009).

To our knowledge, no studies to date have examined the effects of variation in genes involved in dopamine signaling on impulsive decision making in adolescents, whereas a single study has examined the effects of $COMT_{Val158Met}$ in an adult sample of abstinent alcoholics and healthy participants (Boettiger *et al*, 2007). The present study was therefore designed to address these issues, focusing on the following three aims:

(1) To compare impulsive decision-making paradigms using a hypothetical and a real-time discounting task. We predicted that the ADHD-CT group would show higher discounting rates on both tasks and higher trait impulsivity scores on a self-report measure.
(2) To test if the impact of reward magnitude on the rate of discounting of hypothetical rewards differs depending on diagnosis. If delay exerts a greater influence in guiding impulsive choice in ADHD-CT compared with controls, as some theories would predict (Sonuga-Barke, 2005), we would expect that the effect of reward magnitude on discounting rates in the hypothetical task would be attenuated in the ADHD-CT group compared with controls (expecting a significant interaction between diagnosis and reward magnitude).
(3) To investigate whether common variants of the genes for the dopamine transporter ($DAT1_{10/6}$ haplotype) (Asherson *et al*, 2007; Brookes *et al*, 2006b) and the catechol-*O*-methyl transferase ($COMT_{Val158Met}$) enzyme (Lachman *et al*, 1996), which are responsible for the bulk of dopamine degradation in the striatum and the prefrontal cortex, respectively (Akil *et al*, 2003; Chen *et al*, 2004; Lewis *et al*, 2001; Mazei *et al*, 2002; Morón *et al*, 2002), and a common variant of the dopamine D_4-receptor gene ($DRD4_{48bp-VNTR}$) (Asghari *et al*, 1995) that has consistently been associated with ADHD (Brookes *et al*, 2006a; Gizer *et al*, 2009), can predict performance in measures of different aspects of impulsivity.

MATERIALS AND METHODS

Sample

In all, 68 boys of Caucasian origin (ADHD-CT = 36; control = 32) aged 11–20 years (M = 15.42, SD = 2.05) were recruited from a sample that had taken part in a previous study (Andreou *et al*, 2007; Kuntsi *et al*, in press; Wood *et al*, 2009) (see Table 1 for clinical and demographic data). The clinical group was part of the London branch of the International Multi-Centre ADHD Genetics (IMAGE) project (Chen *et al*, 2008; Kuntsi *et al*, 2006a; see Supplementary Material for details). Participants were selected based on $DAT1_{10/6}$ haplotype dosage (2 copies and <2 copies) (Asherson *et al*, 2007; Brookes *et al*, 2006b), forming four roughly equally sized subgroups. Participants receiving stimulant treatment for ADHD (72%) discontinued their medication for at least 48 h before testing (see Supplementary Material, Table S1 for details on medication history). Parents completed the long form of the revised Conners' Rating Scale (Conners *et al*, 1998) at the time of testing. In all, 30 participants (83%) had current total DSM-IV ADHD T-scores in the diagnostic range (with 67% scoring in the diagnostic range on both the inattention and

Table 1 Clinical, Experimental, and Demographic Data for the ADHD-CT and Control Participants, Presented by $DAT1_{10/6}$ Haplotype

	Mean (SD)				Significance test	*p*
	ADHD-CT $DAT1_{10/6}$ (2 copies) ($n=20$)	**ADHD-CT $DAT1_{10/6}$ (<2 copies) ($n=16$)**	**Control $DAT1_{10/6}$ (2 copies) ($n=16$)**	**Control $DAT1_{10/6}$ (<2 copies) ($n=16$)**		
Age (years)	15.05 (2.35)	15.65 (2.33)	15.35 (1.4)	15.76 (2.02)	$F_{group}(1,64)=0.16$	0.69
					$F_{haplotype}(1,64)=0.97$	0.32
					$F_{interaction}(1,64)=0.03$	0.85
IQ	107.8 (13.68)	102.38 (12.97)	111.06 (9.9)	114.12 (12.19)	$F_{group}(1,64)=6.21$	0.015
					$F_{haplotype}(1,64)=0.15$	0.70
					$F_{interaction}(1,64)=1.98$	0.16
Parents' SES	41.42 (10.74)	38.07 (15.53)	47.16 (11.62)	48.06 (12.68)	$F_{group}(1,60)=6.18$	0.016
					$F_{haplotype}(1,60)=0.15$	0.70
					$F_{interaction}(1,60)=0.45$	0.50
Conners' DSM-IV ADHD inattention ratings (parent)	67.05 (9.89)	72.25 (7.72)	46.53 (4.61)	47.75 (6.43)	$F_{group}(1,63)=144.00$	0.000
					$F_{haplotype}(1,63)=2.93$	0.092
					$F_{interaction}(1,63)=1.13$	0.29
Conners' DSM-IV ADHD hyperactivity/impulsivity ratings (parent)	78.1 (13.6)	81.94 (12.17)	47.4 (7.19)	47.81 (5.84)	$F_{group}(1,63)=157.20$	0.000
					$F_{haplotype}(1,63)=0.68$	0.41
					$F_{interaction}(1,63)=0.44$	0.51
Conners' DSM-IV ADHD total ratings (parent)	73.95 (12.07)	79.44 (9.35)	46.53 (5.42)	47.56 (5.93)	$F_{group}(1,63)=182.61$	0.000
					$F_{haplotype}(1,63)=2.21$	0.14
					$F_{interaction}(1,63)=1.03$	0.31
Barratt's Impulsiveness Scale, version 11, adolescents	72.7 (9.56)	84.19 (10.66)	66.12 (10.16)	68.94 (8.02)	(see Tables 3 and 4)	
Hypothetical delay discounting task (AUC)	0.5 (0.27)	0.36 (0.21)	0.48 (0.23)	0.72 (0.28)	(see Tables 3 and 4)	
Real-time delay discounting task (AUC)	0.73 (0.25)	0.74 (0.23)	0.81 (0.19)	0.79 (0.13)	(see Tables 3 and 4)	

Abbreviations: ADHD-CT, attention deficit/hyperactivity disorder-combined subtype; SES, socioeconomic status; AUC, area under the curve.

hyperactivity/impulsivity subscales). Of the six participants with current total parent T-scores of <63 (the clinical cutoff in IMAGE; Marco *et al*, 2009), three were still receiving stimulant treatment. To include as many participants with ADHD as possible, we did not exclude participants with current parent ratings below the diagnostic range, but we repeated analyses excluding them. No comorbid disorder was associated with any of the three dopamine gene variants (see Supplementary Material, Tables S2–S4). Current levels of substance use were assessed using a self-report questionnaire (see Supplementary Material, Table S5). Analyses were repeated excluding four ADHD-CT participants with frequent or occasional use of drugs and/or heavy cigarette smoking (>5 cigarettes per day).

Control participants were aged matched to the clinical group. To exclude potential undiagnosed ADHD cases, participants with initial parent or teacher Conners' T-scores of >63 on any DSM-IV subscale were excluded. The $DRD4_{48bp-VNTR}$ genotype could not be determined for one control participant, who was not included in some of the analyses.

Genotyping

Standard genotyping procedures were used (described in the Supplementary Material). $DAT1_{10/6}$ status (2 copies and <2 copies) was determined on the basis of zygosity for the constituent DAT1 polymorphisms (see Supplementary Material, Table S6). Frequencies for the $DRD4_{48bp-VNTR}$ at exon 3 and the $COMT_{Val158Met}$ polymorphisms are presented in Supplementary Material (Table S7); no significant associations were observed with disease status. For statistical analyses we created binary groups for each genotype ($COMT_{Val158Met}$: methionine homozygotes *vs* valine carriers; $DRD4_{48bp-VNTR}$: 7R-carriers *vs* rest).

Behavioral Measures of Impulsivity

Hypothetical delay discounting task. A computerized, adjusting-amount algorithm asked participants to make successive choices between a standard monetary amount available after a delay and a smaller adjusting amount available immediately (see Richards *et al*, 1999 for details on the adjusting-amount procedure). The subjective value at which a participant was indifferent between the larger-delayed and the smaller-immediate reward (*indifference point*) was estimated for eight delay intervals (1, 2, 7, 14, 30, 60, 120, and 180 days) using three standard amounts (£5, £15, and £30). Discounting curves were plotted for each participant and for each monetary magnitude using normalized indifference points (proportions of the standard amount) and delays

(proportions of the maximum delay). Questions were presented in a random order. To increase motivation and accuracy, participants were told at the end of the task that the choice from one question, selected at random by themselves, would be honored. To keep the general level of compensation at acceptable levels for adolescents, we followed a credible procedure ensuring that the 'randomly' selected question always came from the £5 category.

Real-time delay discounting task. We used the UK version of the experiential discounting task (for a detailed description, see Supplementary Material) (Reynolds *et al*, 2006; Reynolds and Schiffbauer, 2004), in which participants experience the delays and receive the rewards associated with each decision they make. An indifference point was calculated for each of four choice blocks where participants made successive choices between a certain and immediate adjusting amount (initially £0.10) and a probabilistic (35%) £0.20 available at different delays (1, 7, 14, or 28 s depending on choice block). Because of the probabilistic nature of the larger amount (consistent across choice blocks), indifference points for each choice block were divided by the indifference point for the no-delay (1 s) choice block to control for individual differences in responses to probabilistic outcomes (Reynolds and Schiffbauer, 2004). The indifference points for the remaining blocks now reflected the relative change in discounting for each choice block compared with the no-delay block. This data adjustment and the systematic manipulation of delays render this task a measure of delay discounting, rather than risk discounting (Reynolds *et al*, 2006). Individual discounting curves were plotted after normalizing indifference points and delays (see description above). The four choice blocks were administered in random order after the participant had completed a practice session with the 7-s choice block.

Estimating discounting rates. In both tasks, discounting rates were assessed using the widely used (Scheres *et al*, 2010; Shiels *et al*, 2009) area-under-the-curve (AUC) method, which presents theoretical and practical advantages over alternatives (Beck and Triplett, 2009; Myerson *et al*, 2001). AUC values range from 0 to 1, with lower values indicating a higher rate of discounting and higher levels of impulsivity.

Self-Report Measures of Trait Impulsivity

Barratt's Impulsiveness Scale for Adolescents, version 11 (BIS-11A). Adapted from the adult version (Patton *et al*, 1995; Stanford *et al*, 2009), it has been increasingly used with younger samples in many languages (Cosi *et al*, 2008; Fossati *et al*, 2002; Leshem and Glicksohn, 2007; von Diemen *et al*, 2007). With adult samples BIS-11 can differentiate between non-planning, attentional, and motor aspects of impulsivity (Patton *et al*, 1995; Stanford *et al*, 2009), yet a consistent factor structure is not reproduced with younger groups (Cosi *et al*, 2008; Fossati *et al*, 2002; Leshem and Glicksohn, 2007; von Diemen *et al*, 2007). Thus, the total scale score (ranging from 30 to 120) has been recommended (Fossati *et al*, 2002) and used (Melanko *et al*, 2009) as the most appropriate measure of trait impulsivity with adolescents. Higher scores reflect higher trait impulsivity levels.

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 (Conners *et al*, 1998).

General intelligence. The vocabulary, similarities, picture completion, and block design subtests of the Wechsler Intelligence scale for children III (Wechsler, 1991) or the Wechsler Intelligence Scale for Adults (Wechsler, 1997) were used to obtain an estimate of the child's IQ at the time of the initial assessment.

Socioeconomic status (SES). The SES status of participants' families was estimated based on information about both parents' educational and occupational background using the Barratt Simplified Measure of Social Status (Barratt, 2006), which updated Hollingshead's Four-Factor Index of Social Status (Hollingshead, 1975) with a current occupation list (Baldwin and Dadds, 2007). Higher scores indicate higher socioeconomic levels.

Procedure

The discounting tasks (in counterbalanced order) and the BIS-11A questionnaire were administered under laboratory conditions in the afternoon session during a day-long visit to our research center as part of a larger study. Parent ratings were obtained during the same visit. Any cash earned during the tasks was exchanged for vouchers of equivalent value for the participant's preferred store. Ethics approval was obtained from the South London and Maudsley NHS Foundation Trust and informed consent was obtained from all participants.

Statistical Analyses

Age was covaried in all analyses; *p*-values after covarying IQ and SES are reported separately. A three-step approach was utilized to address the goals of this study.

First, separate MANCOVA/ANCOVA tests were conducted for each measure of impulsivity to test for an ADHD-CT deficit independently from genetic effects (obtaining results directly comparable to previous studies). The MANCOVA was used for the hypothetical discounting task, with the AUC measures for each reward magnitude used as the dependent variables and diagnosis (ADHC-CT *vs* control) as the between-subjects factor. Given the high correlations (Pearson's r from 0.80 to 0.94) in the discounting rates across magnitudes in the hypothetical task, we estimated a single overall AUC measure by averaging the three indifference points at each delay interval for each participant. This measure was used in an ANCOVA to estimate the effect size for the diagnosis effect and in subsequent genetic analyses.

Second, to test whether reward magnitude differentially affected the rate of discounting (AUC; reflecting the decrease in the subjective value of a reward with delay) of hypothetical rewards for the ADHD-CT and control groups, we used a mixed ANCOVA, with reward magnitude as the within-subjects factor (£5, £15, and £30) and diagnosis as the between-subjects factor.

Table 2 Pearson's Correlation Coefficients Between Impulsivity Measures and ADHD Symptom Ratings

	Control group			ADHD-CT group			Pooled within-group correlations		
	BIS-11A	**HDT**	**EDT**	**BIS-11A**	**HDT**	**EDT**	**BIS-11A**	**HDT**	**EDT**
Hypothetical discounting task (HDT)	−0.24			−0.29			−0.26*		
Real-time discounting task (EDT)	−0.20	−0.12		0.27	−0.13		0.11	−0.12	
DSM-IV ADHD inattention ratings[a]	0.42*	−0.23	−0.34	0.32	−0.19	−0.22	0.35**	−0.20	−0.25*
DSM-IV ADHD hyperactivity impulsivity ratings[a]	0.44*	−0.08	−0.26	0.27	−0.21	−0.24	0.31*	−0.16	−0.24
DSM-IV ADHD total ratings[a]	0.51**	−0.20	−0.39*	0.36*	−0.20	−0.24	0.39***	−0.19	−0.27*

Abbreviations: ADHD, attention deficit/hyperactivity disorder; BIS-11A, Barratt's Impulsiveness Scale (version 11, adolescents).
[a]Parent ratings on the revised version of the Conners' Rating Scales.
*$p<0.05$; **$p<0.01$; ***$p<0.001$.
See Supplementary Material for details on the calculation of pooled within-group correlations.

Third, we tested for the main effects of $DAT1_{10/6}$, $COMT_{val158met}$, and the $DRD4_{48bp-VNTR}$, and their interactions with diagnosis, using separate ANCOVAs for each measure of impulsivity. Family-wise error rate was contained at the $\alpha = 0.05$ level using a Bonferroni adjustment of the critical p-value for each ANCOVA to $\alpha = 0.05/3 = 0.017$. Similarly, a critical p-value of $\alpha = 0.017/4 = 0.004$ was used when simple effects analyses for significant or trend-level (<0.10) interactions were conducted. Owing to the relatively small sample and cell sizes, p-values obtained from parametric tests were confirmed using nonparametric procedures. We performed 10 000 random permutations on the age-regressed residuals for each measure and estimated p-values and 95% confidence intervals on the basis of Monte Carlo simulations.

All analyses were repeated without including the six ADHD participants with current T-scores of <63 on the parent Conners' total ADHD scale. In all cases, p-values and effect sizes either improved or remained approximately the same (see Supplementary Material). Similarly, excluding the four ADHD participants with frequent or occasional current use of cannabis (including two with frequent/occasional use of cocaine and all heavy smokers (>5 cigarettes per day)) did not change the observed pattern of results (see Supplementary Material). Pearson's correlation coefficients among ADHD ratings and the impulsivity measures are provided in Table 2.

RESULTS

Adolescents with ADHD-CT Displayed Higher Levels of Impulsivity

The ADHD-CT group displayed significantly steeper discounting rates (AUC) compared with controls in the hypothetical but not the real-time discounting task (see Table 3 and Figure 1). They also reported significantly higher levels of trait impulsivity. These effects remained significant after covarying IQ and SES.

Delay but not Reward Magnitude Affected Discounting Rates (AUC) in the Hypothetical Discounting Task in the ADHD-CT Group

Discounting rates in the hypothetical task were submitted to a mixed ANCOVA with monetary magnitude (£5, £15, and £30) as the repeated factor and diagnosis as the between-subjects factor. The rate of discounting decreased as the magnitude of the monetary amount increased (magnitude effect: $F_{(2,132)} = 7.62$, $p = 0.001$; covarying IQ/SES: $p<0.001$), but only in the control group (magnitude × diagnosis: $F_{(2,132)} = 5.39$, $p = 0.009$; covarying IQ/SES: $p = 0.022$; Figure 2; p-values were adjusted using the Greenhouse–Geisser epsilon).

$DAT1_{10/6}$ and $COMT_{Val158Met}$ Polymorphisms Predicted Discounting Rates (AUC) in the Hypothetical Task and Trait Impulsivity Ratings

Hypothetical discounting task. $DAT1_{10/6}$ status interacted with diagnosis (Table 4 and Figure 3a); this effect remained significant after covarying trait impulsivity scores ($p_{\text{corrected}}<0.05$; $p_{\text{uncorrected}}=0.005$; $R^2=0.086$). Adolescents with ADHD-CT showed higher discounting rates than controls only among carriers of <2 copies of $DAT1_{10/6}$ ($p_{\text{corrected}}<0.05$; $p_{\text{uncorrected}}<0.001$); there was no group difference for $DAT1_{10/6}$ homozygotes ($p_{\text{uncorrected}}=0.61$). Furthermore, $DAT1_{10/6}$ homozygotes showed significantly higher discounting rates compared with those with <2 copies ($p_{\text{corrected}}<0.05$; $p_{\text{uncorrected}}=0.002$) among control participants. Numerically, the effect was in the opposite direction for the ADHD-CT group, but was not significant ($p_{\text{uncorrected}}=0.12$).

The $COMT_{val158met}$ polymorphism predicted discounting rates independent of diagnosis; covarying trait impulsivity ratings had no impact ($p_{\text{corrected}}<0.05$; $p_{\text{uncorrected}}=0.013$; $R^2=0.068$). Met-allele homozygotes showed higher discounting rates than Val-allele carriers ($p_{\text{corrected}}<0.05$; $p_{\text{uncorrected}}=0.014$).

Real-time discounting task. No significant genetic effects were observed (Table 4).

Self-reported trait impulsivity ratings. $DAT1_{10/6}$ status predicted trait impulsivity ratings independent of diagnosis (Table 4 and Figure 3b). $DAT1_{10/6}$ homozygotes reported lower impulsivity levels than carriers of <2 copies, an effect that remained highly significant after covarying discounting rates in the hypothetical task ($p_{\text{corrected}}<0.05$; $p_{\text{uncorrected}}=0.004$; $R^2=0.095$). A trend for a diagnosis × $DAT1_{10/6}$ ($p_{\text{uncorrected}}<0.10$) suggested that this effect might be significant only in the ADHD-CT group ($p_{\text{corrected}}$

Table 3 (M)ANCOVAs Examining the Effect of Diagnosis on Measures of Impulsivity (Age Is Covaried)

Measure	Statistical test	Pillai's trace	F	df	*p*	R^2	η_p^2	Covarying IQ	Covarying IQ/SES
Hypothetical delay discounting task	MANCOVA	0.20	5.21	3, 63	0.003	—	—	0.011	0.024
	ANCOVA	—	6.24	1, 65	0.015	0.081	0.088	—	—
Barratt's Impulsiveness Scale (version 11)	ANCOVA	—	16.05	1, 65	<0.001	0.198	0.198	0.001	0.003
Real-time delay discounting task	ANCOVA	—	1.69	1, 65	>0.10	0.025	0.025	>0.10	>0.10

Diagnosis: attention deficit/hyperactivity disorder-combined subtype and controls.

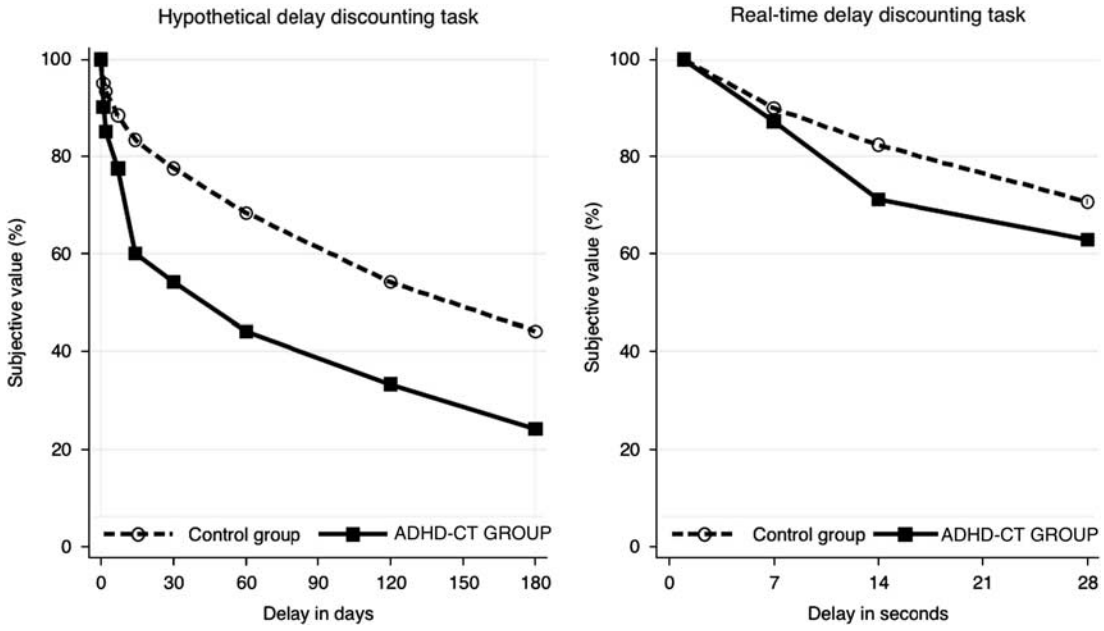

Figure 1 Discounting curves for the hypothetical (overall discounting rate, group median) and real-time (group mean) delay discounting tasks for the attention deficit/hyperactivity disorder-combined subtype (ADHD-CT) and control groups. The graphs plot group indifference points—the subjective value (percentage of larger-delayed amount) at which participants were indifferent between the larger-delayed and the smaller-immediate reward—against delay intervals. In the real-time task, indifference points are adjusted for individual differences in response to probabilistic outcomes.

<0.05; $p_{\text{uncorrected}} = 0.002$; control group: $p_{\text{uncorrected}} > 0.10$). It further indicated that adolescents with ADHD-CT reported higher levels of impulsivity compared with controls if they carried <2 $DAT1_{10/6}$ copies ($p_{\text{corrected}} < 0.05$; $p_{\text{uncorrected}} < 0.001$) but not among $DAT1_{10/6}$ homozygotes ($p_{\text{uncorrected}} = 0.13$).

There were no effects for the $DRD4_{48bp-VNTR}$ polymorphism on any on the impulsivity measures (see Table 4).

DISCUSSION

This study used a relatively homogeneous sample of male adolescents with ADHD-CT and typically developing controls, and reports three novel findings. First, when comparing performance on a hypothetical and a real-time discounting task, we found that the ADHD-CT group showed steeper discounting rates (smaller AUC, denoting higher levels of impulsivity) in the hypothetical task, but not when rewards/delays were real. The ADHD-CT group also reported higher trait impulsivity self-ratings than controls. Second, discounting rates in the hypothetical task were influenced by delay but not reward magnitude for the ADHD-CT group. Third, $DAT1_{10/6}$ haplotype dosage and the $COMT_{Val158Met}$ genotype predicted discounting rates in the hypothetical discounting task (but not the real-time task) and trait impulsivity ratings.

The contrast between discounting rates in the hypothetical and real-time tasks in terms of diagnostic group and gene effects is novel. It cannot be attributed to validity issues with the real-time task, as both groups showed discounting in this study, supporting evidence from earlier studies (Fields *et al*, 2009; Krishnan-Sarin *et al*, 2007; Melanko *et al*, 2009). These data therefore suggest that discounting rates in hypothetical and real-time tasks may reflect different aspects of impulsivity. As discussed in the Introduction, one possible distinction is that performance in the hypothetical task putatively reflects a relatively stable individual difference (an aspect of trait impulsivity), whereas performance in the real-time task may be more sensitive to the transient effects of factors affecting state impulsivity, such as acute pharmacological interventions

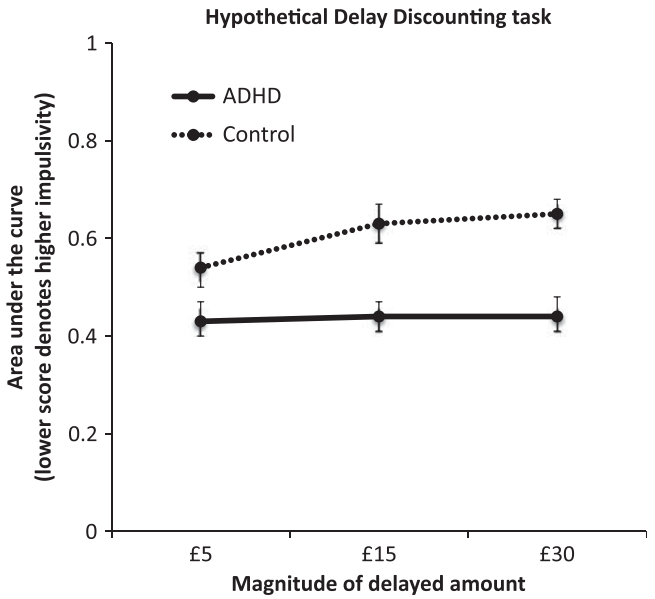

Figure 2 Effect of monetary magnitude of the delayed amount on discounting rates (measured using the area under the curve) for adolescents with attention deficit/hyperactivity disorder-combined subtype (ADHD-CT) and control participants in the hypothetical delay discounting task.

(Shiels *et al*, 2009) or task characteristics. Further support for this distinction is provided by the lack of significant correlations between discounting rates in the real-time task and trait impulsivity scores, or discounting rates in the hypothetical task, which is consistent with the literature (Fields *et al*, 2009; Krishnan-Sarin *et al*, 2007; Melanko *et al*, 2009; Reynolds *et al*, 2008; Reynolds *et al*, 2006) with few exceptions (Meda *et al*, 2009; Reynolds, 2006a).

Although impulsive decision making in discounting paradigms is consistent with the pattern of neurobiological deficits observed in ADHD and predicted by most neurobiological models of the disorder (see Luman *et al*, 2010 for a review), such models do not distinguish between performance in real-time and hypothetical paradigms, as most of them imply context-invariant deficits. One possible explanation for the lack of case–control differences in the real-time discounting task could be that decision making in this task (where participants experience the delays and rewards associated with each choice they make) impacts on an individual's current state of arousal considerably more than in the hypothetical task, which consequently might induce changes in state impulsivity (to which real-time tasks are assumed to be more sensitive). As shown using reaction time performance paradigms, the performance of ADHD patients tends to approach or equal control levels under task conditions that increase stimulation/arousal levels (Andreou *et al*, 2007; Johnson *et al*, 2007a; Johnson *et al*, 2007b; Konrad *et al*, 2000; Kuntsi *et al*, 2009; McInerney and Kerns, 2003; O'Connell *et al*, 2008; Slusarek *et al*, 2001; Uebel *et al*, 2010). Therefore, it is possible that discrepancies among studies using real-time tasks (eg, this study and Scheres *et al*, 2010) might be explained by altered arousal-regulation processes in ADHD. This could occur if case–control differences in measures of state impulsivity depend on the extent to which specific task characteristics alter arousal levels, because of differences in factors such as the monotony of the task, salience of the reward, and length and expectancy of the delay. This explanatory framework leads to specific predictions that can be investigated by examining the relationship between indices of arousal-regulation deficits and performance in a range of real-time discounting paradigms.

Another novel finding in this study was the lack of reward magnitude effects in the hypothetical task for the ADHD-CT group, suggesting that their choices were influenced only by delay. Discounting rates in the control group were inversely related to reward magnitude, consistent with the literature (Chapman and Winquist, 1998; Kirby and Marakovi, 1996; Myerson and Green, 1995; Smith and Hantula, 2008). This discrepancy indicates that different processes might drive discounting in ADHD-CT and controls. One possible explanation could be that ADHD-CT participants were particularly sensitive to delays, as would be predicted by delay aversion theory (Sonuga-Barke, 2005), thus overriding the effect of reward magnitude, at least when choices do not affect current state and with the range of values used in this study.

The predictive value of variants for the *DAT1* and *COMT* genes was restricted to measures of relatively stable aspects of impulsivity. Previous studies have linked the *DAT1* 9-repeat allele (one of the two polymorphisms constituting the haplotype studied here) with increased ventral striatal reactivity during reward anticipation (Forbes *et al*, 2009), which in turn had been linked with steeper hypothetical discounting rates (Hariri *et al*, 2006). In this study we extend this work, showing that $DAT1_{10/6}$ dosage directly predicted hypothetical discounting rates and trait impulsivity in ADHD-CT and controls. Previous studies had failed to show a reliable effect of *DAT1* genotype on executive functions/response inhibition (Rommelse *et al*, 2008), although a study focusing on the same $DAT1_{10/6}$ haplotype (Bellgrove *et al*, 2009) reported a significant interaction of diagnosis with spatial attention measures explaining 4.9–5.8% of the variance. In our study, $DAT1_{10/6}$ interacted with diagnosis in the hypothetical task, explaining 11.7% of the variance. Although the $DAT1_{10/6}$ interaction with diagnosis was only a trend for trait impulsivity ratings, it accounted for 4.7% of the variance, which is comparable to the effect sizes observed with the same haplotype in the study by Bellgrove *et al* (2009).

Post hoc analyses of the interaction effect (controlling for multiple testing) revealed remarkably similar effects of $DAT1_{10/6}$ dosage across measures, providing a within-sample replication of the effect. The differential effects of $DAT1_{10/6}$ dosage depending on diagnostic status (and the reverse) are not entirely surprising. Dopamine effects on neurocognitive functions have been shown to reflect an inverted-U shape (Goldman-Rakic *et al*, 2000). Therefore, assuming that there is some optimal level of dopamine modulating the function of frontal-striatal circuits underlying impulsive behavior, any factor disturbing this balance in either direction would be likely to impair behavior (Egan *et al*, 2001; Goldberg *et al*, 2003; Williams-Gray *et al*, 2007).

Steeper discounting rates in the hypothetical task were also associated with homozygosity for the $COMT_{Val158Met}$ Met-allele (which substantially reduces dopamine catabo-

Table 4 ANCOVAs Examining the Role of $DAT1_{10/6}$ haplotype, $COMT_{Val158Met}$, and $DRD4_{48bp-VNTR}$ Status on Measures of Impulsivity

Measure	Effect	Parametric tests						Permutation tests[a]		Covarying IQ	Covarying IQ/SES
		F	df	$p_{corr.}$	$p_{uncorr.}$	R^2	η_p^2	*p*	CI 95%	*P*	*p*
Hypothetical delay discounting task	$DAT1_{10/6}$	1.34	1,58	NS	>0.10	0.014	0.023	>0.10	—	>0.10	>0.10
	Diagnosis × $DAT1_{10/6}$	10.98	1,58	<0.05	0.002	0.117	0.159	0.002	0.001, 0.003	0.002	0.004
	$COMT_{Val158Met}$	6.45	1,58	<0.05	0.014	0.069	0.100	0.014	0.011, 0.016	0.043	0.031
	Diagnosis × COMT	0.17	1,58	NS	>0.10	0.002	0.003	>0.10	—	>0.10	>0.10
	$DRD4_{48bp-VNTR}$	0.15	1,58	NS	>0.10	0.002	0.005	>0.10	—	>0.10	>0.10
	Diagnosis × $DRD4_{48bp-VNTR}$	0.51	1,58	NS	>0.10	0.005	0.009	>0.10	—	>0.10	>0.10
Barratt's Impulsiveness Scale (version 11)	$DAT1_{10/6}$	7.16	1,58	<0.05	0.010	0.108	0.110	0.008	0.007, 0.010	0.010	0.052
	Diagnosis × $DAT1_{10/6}$	2.83	1,58	NS	0.098	0.032	0.047	0.093	0.089, 0.099	>0.10	>0.10
	$COMT_{Val158Met}$	0.00	1,58	NS	>0.10	0.000	0.000	>0.10	—	>0.10	>0.10
	Diagnosis × COMT	0.05	1,58	NS	>0.10	0.000	0.000	>0.10	—	>0.10	>0.10
	$DRD4_{48bp-VNTR}$	0.08	1,58	NS	>0.10	0.000	0.000	>0.10	—	>0.10	>0.10
	Diagnosis × $DRD4_{48bp-VNTR}$	0.73	1,58	NS	>0.10	0.000	0.000	>0.10	—	>0.10	>0.10
Real-time delay discounting task	$DAT1_{10/6}$	0.00	1,58	NS	>0.10	0.001	0.001	>0.10	—	>0.10	>0.10
	Diagnosis × $DAT1_{10/6}$	0.01	1,58	NS	>0.10	0.003	0.004	>0.10	—	>0.10	>0.10
	$COMT_{Val158Met}$	0.02	1,58	NS	>0.10	0.006	0.006	>0.10	—	>0.10	>0.10
	Diagnosis × COMT	0.00	1,58	NS	>0.10	0.000	0.000	>0.10	—	>0.10	>0.10
	$DRD4_{48bp-VNTR}$	0.03	1,58	NS	>0.10	0.011	0.011	>0.10	—	>0.10	>0.10
	Diagnosis × $DRD4_{48bp-VNTR}$	0.01	1,58	NS	>0.10	0.002	0.002	>0.10	—	>0.10	>0.10

[a]In all, 10 000 random permutations on the age-regressed residuals for each measure were performed and *p*-values and 95% confidence intervals (95% CIs) were estimated on the basis of Monte Carlo simulations.
Diagnosis: attention deficit/hyperactivity disorder-combined subtype and controls.

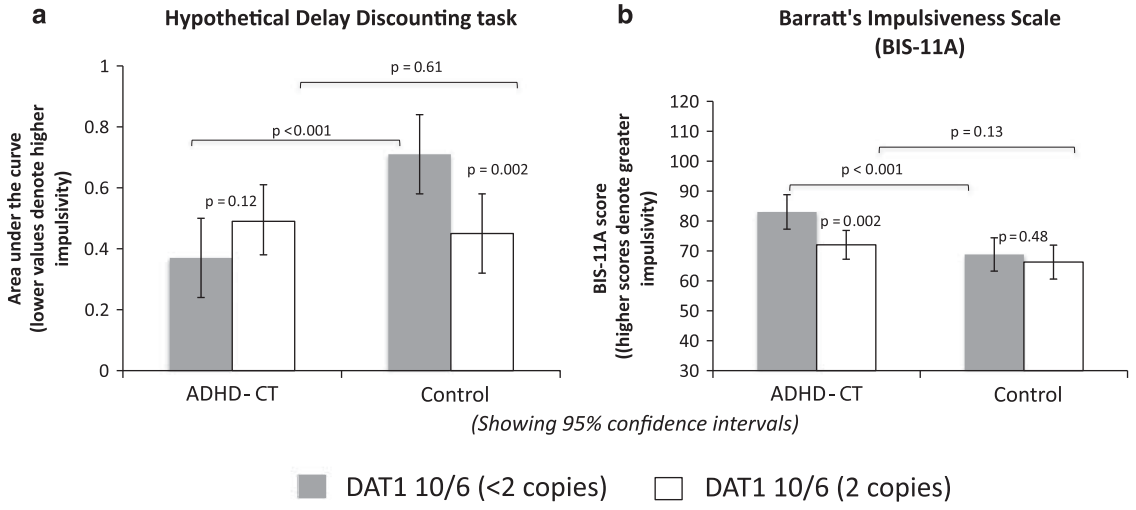

Figure 3 (a) Mean overall discounting rates (measured using the area under the curve (AUC)) in the hypothetical discounting task as a function of diagnosis (attention deficit/hyperactivity disorder-combined subtype (ADHD-CT) and controls) and $DAT1_{10/6}$ haplotype status (2 copies and <2 copies). Significance values from simple effects analyses are shown. (b) Self-reported scores on Barratt's Impulsiveness Scale (BIS-11A) as a function of diagnosis (ADHD-CT and controls) and $DAT1_{10/6}$ status (2 copies and <2 copies). Significance values from simple effects analyses are shown.

lism in the prefrontal cortex) (Chen *et al*, 2004; Lachman *et al*, 1996; Lotta *et al*, 1995), independent of diagnosis ($R^2 = 6.9\%$). This finding is consistent with evidence showing that the dopamine-modulated prefrontal cortex has a key role in choice impulsivity (Kable and Glimcher, 2007; Kable and Glimcher, 2009; Kheramin *et al*, 2004; McClure *et al*, 2007; McClure *et al*, 2004; Winstanley *et al*, 2006). The role of $COMT_{Val158Met}$ in impulsivity has received

scant attention to date, with the Met-allele being associated with reduced immediate-reward bias (Boettiger *et al*, 2007) and increased novelty seeking (Golimbet *et al*, 2007). Variants of $COMT_{Val158Met}$ and *MAOA* (which perform most of the catecholamine catabolism in the prefrontal cortex) (Chen *et al*, 2004; Gogos *et al*, 1998; Huotari *et al*, 2002; Matsumoto *et al*, 2003; Tunbridge *et al*, 2004; Volavka *et al*, 2004) with reduced enzymatic activity have been associated with aggressive impulsivity and suicide (Contini *et al*, 2006; Huang *et al*, 2004; Volavka *et al*, 2004). Meta-analytic evidence has not associated ADHD with $COMT_{Val158Met}$ (Gizer *et al*, 2009), although some evidence suggests that gender could be a moderating factor with Met being the risk allele in boys (Biederman *et al*, 2008; Qian *et al*, 2003). This is consistent with evidence that $COMT_{Val158Met}$ is differentially expressed across genders (Dempster *et al*, 2006; Gogos *et al*, 1998). A recent study confirmed the association of the Met-allele with increased risk for ADHD in children in a predominantly male (84%) sample, and also reported that Met was associated with increased symptom severity (Pálmason *et al*, 2010). Moreover, Met has been associated with ADHD inattention and hyperactivity impulsivity symptoms in adult community samples (Ettinger *et al*, 2006; Gothelf *et al*, 2007; Michaelovsky *et al*, 2008; Reuter *et al*, 2006). The $DRD4_{48bp-VNTR}$ was not associated with any impulsivity measure, in line with a recent meta-analytic review (which suggested that another marker on the gene might be related to impulsivity; Munafò *et al*, 2008).

Although our data confirmed our hypotheses that variation in $DAT1_{10/6}$ and $COMT_{Val158Met}$ predicts behavioral impulsivity, the precise mechanisms mediating these effects, in terms of dopamine signaling or the neural processes involved, remain unknown. One reason is the lack of sufficient evidence regarding the precise functional effects of these genetic variants. For example, although the $DAT1_{3'UTR}$ 48 base-pair VNTR polymorphism (part of the $DAT1_{10/6}$ haplotype) has been associated with alterations in gene expression, evidence regarding the impact of specific variants is inconsistent (for a review, see van de Giessen *et al*, 2009). Second, even when the effects of genetic variation in terms of gene expression and dopamine catabolism are better understood (eg, $COMT_{Val158Met}$), predicting the precise role of a variant on behavioral impulsivity may still be elusive, given that it is likely to depend on the dynamic interaction among many factors and reflect the outcome of long-term adaptation processes. For example, the *DAT1* 10-repeat allele is considered to increase risk for ADHD in children and adolescents, yet in adults (and thus, by definition, in persisting forms of the disorder) ADHD has been associated with the 9-repeat allele (Franke *et al*, 2008; Franke *et al*, 2010). Our study, alongside recent work (Bellgrove *et al*, 2009), has documented that variation in $DAT1_{10/6}$ modulates behavioral outcomes, highlighting the need for a better understanding of the impact of this haplotype on gene expression, dopamine signaling, and neural mechanisms involved. Some promising initial evidence has indicated that the $DAT1_{3'UTR}$ polymorphism may be modulating the responsivity of the striatum during a response inhibition and a reward-processing paradigm (Durston *et al*, 2008; Forbes *et al*, 2009).

Our genetic findings finally suggest that the rate of experimental discounting and trait impulsivity ratings reflect distinct aspects of impulsivity. Covarying trait impulsivity ratings or discounting rates when examining the genetic effects on either measure left effect sizes virtually unchanged and results remained significant. This finding provides no support for the mediation of gene effects on discounting by impulsive behavior (or the reverse), but rather that the two measures of relatively stable impulsivity predispositions (hypothetical discounting and self-report rating scale) represent pleiotropic effects (multiple outcomes) of the genetic influences.

In summary, the pattern of findings in this study distinguishes between aspects of impulsivity by demonstrating specific effects of diagnosis and variation in dopamine genes ($DAT1_{10/6}$ and $COMT_{Val158Met}$) on behavioral and laboratory measures assumed to reflect relatively stable aspects of impulsivity (discounting in the hypothetical task and trait impulsivity self-ratings) but not on discounting rates in a real-time task, which may be more sensitive to factors impacting on state impulsivity levels. However, our study was not designed to distinguish between trait and state aspects of impulsivity, or test the various models predicting impulsive behavior in ADHD; these goals should be addressed in future research. Our data suggest that existing ADHD models need to distinguish between trait and state aspects of impulsivity, and that arousal regulation should be further investigated as one potential mechanism contributing to real-time impulsive decision making in ADHD. Future studies should also employ a wider range of real-time paradigms. The sample size is a limitation of this study; the genetic findings should be considered as preliminary until confirmed within a larger sample, which should also examine gene-by-gene interactions and assess the impact of potential confounds pertaining to the ADHD-CT group, such as possible gene interactions with the effects of long-term stimulant treatment.

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DISCLOSURE

PA has given sponsored talks and/or been an advisor for Shire, Janssen-Cilag, Eli-Lilly, Flynn Pharma, and Pfizer, regarding the diagnosis and treatment of ADHD; all funds have been donated to the University Research Fund for studies of ADHD. MAM receives research funding from Eli Lilly and is a scientific advisor to Cambridge Cognition. SVF has, in the past year, received consulting fees and has been on Advisory Boards for Eli Lilly, Ortho-McNeil, and Shire

Development and has received research support from Eli Lilly, Pfizer, Shire, and the National Institutes of Health. In previous years, SVF has received consulting fees or has been on Advisory Boards or has been a speaker for the following sources: Shire, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. In previous years, he has received research support from Eli Lilly, Shire, Pfizer, and the National Institutes of Health. JK has received a speaker's fee from Eli Lilly that has been used for educational and research activities.

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