ORIGINAL INVESTIGATION

Age modulates the effect of COMT genotype on delay discounting behavior

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Abstract

Rationale and objective A form of impulsivity, the tendency to choose immediate over delayed rewards (delay-discounting) has been associated with a single nucleotide polymorphism (SNP) in the catechol-*O*-methyltransferase (COMT) gene (*COMTval*^{158}*met; rs4680*). However, the existing data regarding the nature of this association are in conflict. We have previously reported that adults homozygous for valine (val) at the *COMTval*^{158}*met* SNP demonstrate greater delay-discounting than do methionine (met) allele carriers (Boettiger et al., *J Neurosci* 27:14383–14391, 2007). In contrast, a recent study of adolescent males found that those with the met/met genotype demonstrate greater delay-discounting than do val-allele carriers (Paloyelis et al., *Neuropsychopharmacology* 35:2414–2426, 2010). Based on reported age-related changes in frontal dopamine function and COMT expression, we hypothesized that the association of COMT genotype with delay-discounting behavior is modulated by age from late adolescence to young adulthood.
Methods To test this hypothesis, we genotyped late adolescents (18–21 years; $n=72$) and adults (22–40 years; $n=70$) for the *COMTval*^{158}*met* polymorphism, measured their delay-discounting behavior, and tested for an interaction between age group and COMT genotype.

Results This cross-sectional study found that age modulates *COMTval*^{158}*met* genotype effects on delay-discounting behavior. Among met-carriers, delay-discounting was negatively correlated with age from late adolescence to adulthood, while among val/val individuals delay-discounting was positively correlated with age across this range.
Conclusions These results confirm our previous finding of enhanced delay-discounting among val/val adults relative to met-allele carriers, and help reconcile existing literature. We propose a single U-shaped model of the relationship between frontal DA levels and impulsive choice that accounts for both adolescent and adult data.

Keywords Adolescence · Decision-making · Delay discounting · Development · Dopamine · Impulsivity

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Introduction

Humans and other animals tend to discount the value of delayed, relative to immediate, rewards a phenomenon known as delay-discounting (Ainslie 1975; Frederick et al. 2002; Green and Myerson 2004; Mazur 1987). Delay-discounting is heightened among individuals with a history of substance use disorders (Bickel and Marsch 2001; Reynolds 2006), as well as other impulse control disorders, such as attention deficit/hyperactivity disorder (ADHD; Paloyelis et al. 2009; Sagvolden and Sergeant 1998; Winstanley et al. 2006). Such immediate reward bias represents one facet of the multi-dimensional construct of impulsivity (Evenden 1999). A variety of evidence links delay-discounting to dopamine (DA) and DA-modulated frontostriatal circuits (Adriani et al. 2009; Altamirano et al. 2011; Boettiger et al. 2007; Doya 2008; Kobayashi and Schultz 2008; Lee et al. 2009; Mitchell et al. 2007; Paloyelis et al.

2010; Pine et al. 2010). Such evidence includes data showing that variation in the gene encoding catechol-*O*-methyltransferase (COMT) is associated with differences in the tendency to choose immediate over delayed rewards (Boettiger et al. 2007; Paloyelis et al. 2010). COMT is an enzyme that regulates DA levels in the prefrontal cortex (Gogos et al. 1998; Kaenmaki et al. 2010; Tunbridge et al. 2004; Yavich et al. 2007), where it is the primary regulator of DA levels (Kaenmaki et al. 2010; Karoum et al. 1994). A polymorphism in the COMT gene (*COMTval*^{158}*met*; *rs4680*) causing a valine (val)-to-methionine (met) substitution at codon 158 results in a four-fold reduction of COMT enzymatic activity (Lachman et al. 1996), which is presumed to result in reduced cortical DA in val/val homozygotes relative to the met/met genotype (Chen et al. 2004).

We have previously reported that *COMTval*^{158}*met* genotype predicts variation in delay-discounting behavior in adult humans, including those with a history of alcoholism; specifically, those with the val/val genotype demonstrate greater delay discounting than do met-allele carriers (Boettiger et al. 2007). In contrast, a recent study of male adolescents with and without ADHD found that those with the met/met genotype demonstrate greater delay-discounting than do val-allele carriers (Paloyelis et al. 2010). The sample size in our 2007 study was rather small; thus, in the present study, we sought to confirm our earlier finding in a larger sample. In addition, we sought to determine whether the relationship between COMT genotype and impulsive choice changes from late adolescence to adulthood. Several measures of frontal DA neurotransmission decrease from adolescence to adulthood (see Wahlstrom et al. (2010) for recent review). Moreover, COMT expression increases with age in humans (Tunbridge et al. 2007), which should contribute to reduced frontal DA signaling from adolescence to adulthood. Behaviors that depend on frontal DA commonly operate within a range of optimal functioning, with both excessive and deficient levels of DA impairing behavioral performance (Goldman-Rakic 1998). Thus, an increase in COMT with age could mean that the low activity COMT genotype yields an "overdose" of DA in adolescence, but a more optimal level in adulthood, whereas the high activity COMT genotype may compensate for other aspects of enhanced DA signaling in adolescence, but produce a DA deficit in adulthood, as DA signaling declines. Specifically, we hypothesized that the effects of genetically determined variation in COMT function on delay-discounting behavior are oppositely modulated by age from late adolescence to young adulthood. To test this hypothesis, we genotyped late adolescent and adult participants for the *COMTval*^{158}*met* polymorphism, measured their delay-discounting behavior, and tested for interacting effects of age group and COMT genotype on discounting behavior. As cognitive studies commonly consider participants 18 and over to be adults,

we were particularly interested in testing this hypothesis in late adolescents that are frequently assumed to be adults (ages 18–21 years).

Methods

Subjects

Participants (n=142) were recruited from the University of North Carolina, Chapel Hill (UNC) and surrounding community. Participants were healthy individuals 18–40 years old with no known past or present neurological or psychiatric diagnoses, no history of substance use disorders, and no current use of psychoactive medications or other psychoactive substances aside from moderate caffeine, nicotine or alcohol. All subjects were native English speakers, had at least a high-school education, and reported having consumed alcohol at least once in their lifetime. Participants were recruited into one of two age groups: late adolescents (18–21 years; n=72) or adults (22–40 years; n=70). These age group criteria were based on preliminary results from other studies in our lab indicating behavioral differences in our task between these two age groups. This age cutoff is supported by a recent large scale investigation of functional brain maturation that indicated that brain maturation asymptotes at approximately age 22 (Dosenbach et al. 2010). Information regarding participants' personal and parental occupation and education was collected via a questionnaire and quantified as Hollingshead socioeconomic status SES scores (Hollingshead 1975). Participants gave written informed consent, as approved by the UNC Office of Human Research Ethics. Subjects received monetary compensation for participating.

Delay discounting task

The paradigm was based on a previously described task (Altamirano et al. 2011; Boettiger et al. 2007; Mitchell et al. 2005; Mitchell et al. 2007). Briefly, in each session, subjects completed a short (~4 min) practice block and then 8 full blocks of approximately 42 or 43 trials each (~7 min). There were four trial types: WANT (W), DON'T WANT (DW), SOONER, and LARGER. Trial types were randomly ordered and weighted such that 50% were W condition trials and the remaining trials were evenly divided between the other conditions. Trials began with an instruction cue, followed by two options, each of which was a monetary value and a time. Subjects were asked to evaluate the options as if they would actually receive the specified amounts at the corresponding times. The options consisted of one of five "full" amounts ($2, $5, $10, $20, or $100) at one of five future delays (1 week, 2 weeks, 1 month, 3 months, or 6 months) and

a discounted amount (70%, 85%, 90%, or 95% of the "full" amount) offered at no delay ("TODAY").

Subjects were instructed to make a choice in each trial, according to the trial type: preferred option on W trials, non-preferred option on DW trials, and the side with the sooner time or larger amount of money for SOONER and LARGER trials, respectively. These latter two conditions are considered together as control ("CON") trials. The order of trial types was the same for all subjects; however, the delayed amount, delay time, and discount were pseudorandomly ordered.

The length of the task (~56 min) could raise the concern that choice behavior is affected by fatigue or other temporally dependent effects. This could be a particular concern if such effects varied with age or genotype. These concerns can be dismissed on the basis of the following analyses. First, a repeated measures ANOVA found no significant effect of block number on impulsive choice ratio (ICR, see "Data Analysis"; $F_{(4.94, 647.49)}=0.49$, $p=0.78$), nor any significant ICR by block interaction with age ($F_{(4.94, 647.49)}=0.31$, $p=0.91$) or genotype ($F_{(9.89, 647.49)}=0.22$, $p=0.99$). Second, when we calculated the split-half ICR for odd and even blocks, the correlation across all subjects was $r=0.98$ ($p<0.001$). Similarly, the correlation between first half ICR and second half ICR was $r=0.96$ ($p<0.001$). Furthermore, for the sample as a whole, Cronbach's $\alpha=0.99$. Finally, Cronbach's α was also 0.99 when calculated separately for each age group and each genotype. We note that these reliability measures are well above the standard criterion for adequate reliability of 0.70 (Kline 2000).

Genotyping

$COMTval^{158}met$ (*rs4680*) genotyping was performed on DNA extracted from saliva samples (DNA Genotek, Kanata, Ontario, Canada) using TaqMan technology (Applied Biosystems, Foster City, CA), as described previously (Boettiger et al. 2007). Genotyping was performed by the UNC Mammalian Genotyping Core and/or the Duke Center for Human Genetics. Genotyping was performed in duplicate for $n=42$ samples and compared to ensure validity of the data. The genotype concordance rate was 100% both within ($n=42$) and across ($n=32$) genotyping facilities. Allele frequencies in this sample did not deviate from Hardy–Weinberg equilibrium ($\chi^2=0.098$, $df=2$, $p=0.95$).

Data analysis

Our index of temporal discounting was the proportion of "TODAY" choices in W trials, which we have termed the impulsive choice ratio (ICR). Although this value was calculated separately according to delay time and delayed amount, here we focus on the ratio collapsed across all W trials.

To test the significance of across group comparisons, we used unpaired two-tailed t tests for continuous measures and χ^2 tests for categorical measures. For multi-factorial comparisons, we used regular or mixed repeated measures ANOVA in SPSS (SPSS Inc., Chicago, IL), with age group and genotype as between subjects factors. When necessary, a Greenhouse–Geisser non-sphericity correction was applied. Post hoc paired comparisons were performed where indicated using two-tailed t tests. When data were not normally distributed, appropriate arcsine-root transformations were applied in Excel (Microsoft Corp., Redmond, WA) prior to making statistical comparisons to ensure the validity of parametric statistical tests. Simple regression analyses were performed in SPSS.

Results

Demographic and psychometric data

To test whether $COMTval^{158}met$ genotype differentially predicts ICR among late adolescents versus adults, we genotyped two groups of subjects: late adolescents (18–21 years; $n=72$) and adults (22–40 years; $n=70$). There were no significant differences between the two groups in terms of gender, ethnicity, or parental socio-economic status (SES; see Table 1). As expected, the late adolescent group was significantly younger than the adult group, and also reported lower personal SES levels (driven primarily by a lower level of education), and slightly greater alcohol use (AUDIT score) than did the adult group (Table 1).

Table 1 Demographic data by age group

	Late adolescent (ages 18–21; $n=72$)	Adult (ages 22–40; $n=70$)	$t_{(140)}$	p value
Age (yrs)	20±1	27±5	11.53	<0.001
Education (yrs)	14±1	17±2	11.90	<0.001
Subject Hollingshead SES	40±3	47±7	7.49	<0.001
Parent Hollingshead SES	54±9	54±11	0.13	ns
Sex (% female)	53	54		ns[a]
Ethnicity (% white)	62	66		ns[a]
Black (%)	13	19		ns[a]
Hispanic (%)	4	4		ns[a]
Asian (%)	14	7		ns[a]
Other/mixed (%)	7	4		ns[a]
AUDIT score	8.9±6.3	7.2±4.1	1.99	0.049

Values are reported as mean±standard deviation. Reported p values reflect the results of unpaired two-tailed comparisons between groups. Exact p values reported unless $p<0.001$

AUDIT alcohol use disorders identification test, *SES* socioeconomic status

[a] p-value represents results of χ^2 test

Interaction between age and COMT genotype on frequency of impulsive choices

On the basis of $COMTval^{158}met$ genotype, participants were subdivided into met-homozygotes (met/met; $n=33$), heterozygotes (val/met; $n=69$), and val/val homozygote individuals ($n=40$). COMT genotype groups did not differ significantly in terms of demographic features (education, age, sex, ethnicity, SES, and alcohol use), or task performance (reaction times and control trial accuracy; Table 2). On the basis of our a priori hypothesis for an age×genotype interaction in delay-discounting behavior, we conducted a factorial ANOVA with age group and $COMTval^{158}met$ genotype as between-subjects factors, taking an index of delay-discounting, the ICR (see the "Methods" section), as the dependent measure. Although our groups were matched for sex (Tables 1 and 2), we included sex as a factor in our analyses as a means of detecting sexually dimorphic effects of COMT on delay discounting, as sex-dependent effects on COMT enzyme activity have been reported (Chen et al. 2004). We included SES and alcohol use (AUDIT score) as covariates due to the fact that we observed significant differences in SES and AUDIT scores between our age groups (Table 1).

In a 2×2×3 ANOVA (age group×sex×COMT genotype), we did not detect significant main effects of age group

Table 2 COMT genotype groups: demographics and task performance

	V/V ($n=40$)	V/M ($n=69$)	M/M ($n=33$)	$F_{(2,139)}$	p value
Demographics					
Age (years)	24±5	23±6	23±5	0.57	ns
Education (years)	16±2	15±2	15±2	1.85	ns
Subject Hollingshead SES	44±7	43±6	45±7	0.35	ns
Sex (% female)	45	54	64		ns[a]
Ethnicity (% white)	50	68	73		ns[a]
Black (%)	25	15	6		ns[a]
Hispanic (%)	7.5	1	6		ns[a]
Asian (%)	12.5	10	9		ns[a]
Other/mixed (%)	5	6	6		ns[a]
AUDIT score	8.5±5.0	7.5±5.0	8.6±6.6	0.67	ns
Task performance					
CON Trial Acc	96.6±3.9	97.6±2.5	97.1±2.7	1.60	ns
CON Trial RT	1289±317	1308±288	1338±318	0.24	ns
WANT Trial RT	1550±333	1678±337	1688±323	2.24	ns

Values are reported as mean±standard deviation. Reported p values reflect the results of unpaired two-tailed comparisons between groups. Exact p values reported unless $p<0.001$

Acc accuracy, *AUDIT* alcohol use disorders identification test, *COMT* catechol-*O*-methyltransferase, *CON* control, *M/M* methionine/methionine, *RT* reaction time, *SES* socioeconomic status, *V/M* valine/methionine, *V/V* valine/valine

[a] p value represents results of χ^2 test

($F_{(1, 128)}=0.68$, $p=0.411$, $\eta^2=0.005$), $COMTval^{158}met$ genotype ($F_{(2, 128)}=0.08$, $p=0.921$, $\eta^2=0.001$) or sex ($F_{(1, 128)}=1.33$, $p=0.252$, $\eta^2=0.009$) on ICR. Moreover, we observed no significant interaction between sex and COMT genotype ($F_{(2, 128)}=0.86$, $p=0.424$, $\eta^2=0.012$), or three-way interaction between sex, COMT genotype, and age group ($F_{(2, 128)}=0.42$, $p=0.658$, $\eta^2=0.006$). In contrast, consistent with our hypothesis, there was a significant age-by-$COMTval^{158}met$ interaction effect on delay-discounting behavior. ($F_{(2, 128)}=5.15$, $p=0.007$, $\eta^2=0.069$; Fig. 1). We also detected a smaller interactive effect between sex and age-group ($F_{(1, 128)}=4.08$, $p=0.046$, $\eta^2=0.027$). Given our somewhat ethnically mixed sample (see Tables 1 and 2) and the reported racial differences in $COMTval^{158}met$ allele frequencies (e.g., McLeod et al. 1994, 1998), it is worth noting that the age-by-$COMTval^{158}met$ interaction was also seen in our white participants, the largest ethnic group included ($F_{(2, 83)}=12.51$, $p<0.001$, $\eta^2=0.216$). Among non-white participants, we observed a similar, albeit non-significant, trend ($F_{(2, 43)}=1.68$, $p=0.198$, $\eta^2=0.066$), likely due to the heterogeneity within this smaller group. This interaction effect reflects a significant age-related increase in delay-discounting among val-homozygotes ($t_{(38)}=2.48$, $p=0.018$) and a significant age-related decline in delay-discounting among both met-homozygotes ($t_{(31)}=2.20$, $p=0.036$) and $COMTval^{158}met$ heterozygotes ($t_{(67)}=2.01$, $p=0.048$). Considering age as a continuous variable, we observed a negative correlation between age and ICR among met-allele carriers ($r=-0.31$, $p=0.001$). In contrast, among val/val individuals we observed a significant positive correlation between age and ICR ($r=0.32$, $p=0.047$).
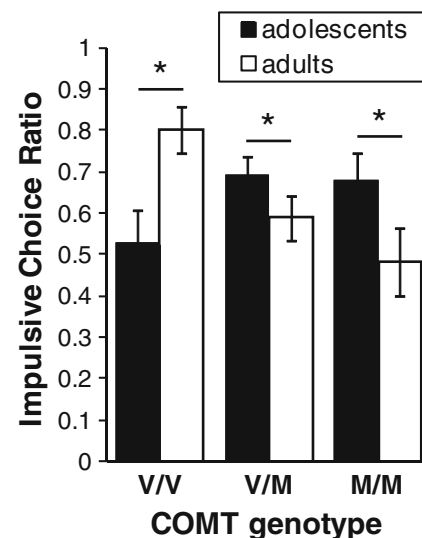

Fig. 1 Age interacts with COMT genotype to influence impulsive decision-making. **a** Plot of impulsive choice ratio (ICR) as a function of COMT genotype, showing a significant age by genotype interaction ($F_{(2,134)}=7.13$, $p=0.001$). This effect reflects significant age-related changes in ICR for all three genotypes. *M/M* methionine/methionine, *V/M* valine/methionine, *V/V* valine/valine. *$p<0.05$

While we have previously reported that choice behavior in this task does not correlate with education or SES (Mitchell et al. 2005, 2007), the present study included a somewhat younger demographic. Thus, we carried out bivariate correlations to assess whether demographic factors predicted decision-making behavior in this cohort of participants. We found that the tendency to choose a smaller immediate reward did not correlate with years of education ($r=-0.09$, $t=-1.04$, $p=0.299$). Similarly, SES was not significantly correlated with ICR ($r=-0.14$, $t=-1.66$, $p=0.1$). We also observed no correlation between age and ICR ($r=-0.14$, $t=-1.62$, $p=0.107$), which is not unexpected based on the opposing age effects for met-carriers and val homozygotes.

The mean overall ICR values (shown in Fig. 1), including SD, were as follows for the Late Adolescent group: val/val, 0.56 ± 0.39; val/met, 0.70 ± 0.24; and met/met, 0.70 ± 0.28. Corresponding values for the Adult group were: val/val, 0.79 ± 0.21; val/met, 0.57 ± 0.31; and met/met, 0.45 ± 0.32. We have previously reported that discounting in this task is modulated by reward magnitude (Mitchell et al. 2005, 2007), such that participants show greater discounting for smaller rewards. This finding was replicated in the present study (Fig. 2) as shown by a three-way ANOVA (delayed reward amount × age group × genotype), which found a significant main effect of delayed reward amount ($F_{(2.15, 292.96)}=146.24$, $p<0.001$, $\eta^2=0.512$). We did not observe significant interactions between delayed reward amount and either age group ($F_{(2.15, 292.96)}=0.79$, $p=0.465$, $\eta^2=0.003$) or genotype ($F_{(4.31, 292.96)}=0.67$, $p=0.624$, $\eta^2=0.005$). Likewise, we observed no significant three-way interaction ($F_{(4.31, 292.96)}=0.66$, $p=0.632$, $\eta^2=0.005$). Thus the genotype × age group interaction that we observed does not appear to be specific to certain magnitudes of reward.
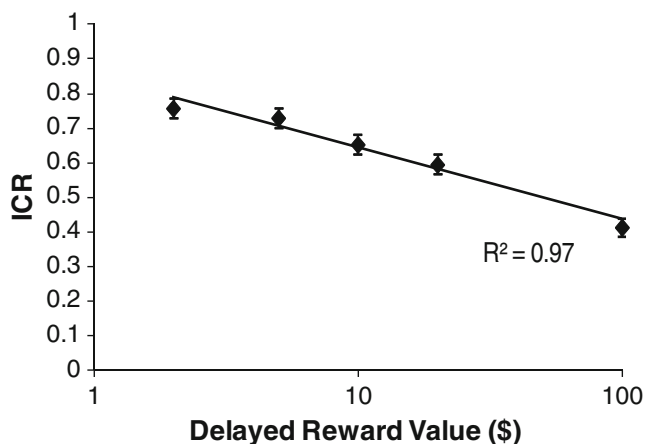

Fig. 2 Reward magnitude discounting function. Semi-log plot of impulsive choice ratio (ICR) as a function of the delayed reward amount. Data reflect mean±SEM. *Curve* represents logarithmic fit of the group averaged data

Discussion

The present results confirm our previous finding of enhanced delay-discounting among COMTval[158]met val/val adults relative to met-allele carriers (Boettiger et al. 2007). Moreover, these results help account for the discrepancy between our earlier findings and the results of Paloyelis et al. (2010) showing enhanced delay-discounting among COMTval[158]met met/met adolescent males. Furthermore, as our study included females and found no main effect of sex, nor any interaction of sex with our genotype by age effect, these data extend the previous finding in adolescent males of Paloyelis et al. (2010) to late adolescent females.

Relationship between alcohol use and delay-discounting

We previously found a significant positive relationship between ICR and alcohol use in studies including both control subjects and those with a history of alcoholism (Boettiger et al. 2007; Mitchell et al. 2005, 2007). We have also reported a positive correlation between ICR and the dependence and harm subscales of the AUDIT (Mitchell et al. 2005). However, consistent with the present data, we have not found a significant relationship between ICR and AUDIT scores in studies restricted to those with no history of alcoholism (Altamirano et al. 2011). This discrepancy may reflect inadequate power to detect an effect due to insufficient variance in AUDIT dependence and harm scores in samples excluding people with alcohol use disorders. For example, the median AUDIT dependence and harm score here was 2 (interquartile range, 1–4.75). In contrast, the median in Mitchell et al. (2005) was the same, but the interquartile range was >3× larger (0.75–16). Alternatively, the relationship between ICR and AUDIT may be weak.

Cortical dopamine regulation of delay-discounting

Consistent with our hypothesis, we found that age modulates COMTval[158]met genotype effects on delay-discounting behavior. Adult met-allele carriers showed significantly less delay-discounting relative to late adolescent met-carriers, while val/val adults showed significantly more delay-discounting relative to late adolescent val/val individuals. To account for both the adolescent and adult data we report, we propose a single U-shaped model of the relationship between frontal DA levels and impulsive choice (Fig. 3). Such a model is supported by evidence that dopaminergic modulation of frontal functions often follows a U-shaped curve, where deficient or excess DA can impair frontal functioning (Arnsten 1997; Goldman-Rakic et al. 2000; Williams and Castner 2006; Zahrt et al. 1997). Our model posits that reduced frontal DA signaling in adulthood relative to late adolescence results in opposing effects on
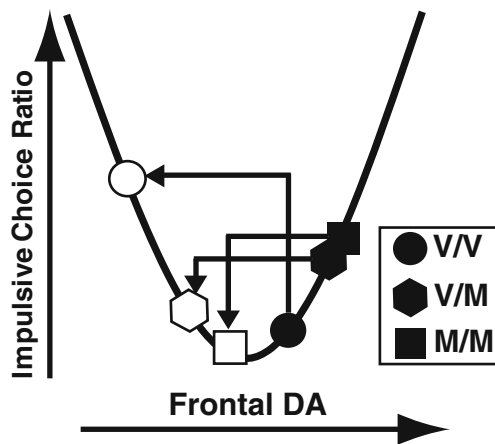
Fig. 3 Model depicting hypothetical regulation of impulsive choice by frontal dopamine. *Closed symbols* represent adolescents, while *open symbols* represent adults. *Arrows* indicate the effects of a developmental decline in frontal dopamine function for each genotype. Model posits that reduced frontal DA signaling in adulthood relative to late adolescence results in opposing effects on impulsive choice that vary with COMT genotype, based on an underlying U-shaped relationship. An age-dependent drop in frontal DA signaling in val/val individuals is predicted to yield greater ICR in adults relative to adolescents. In contrast, an equivalent age-dependent drop in frontal DA signaling is predicted to result in reduced ICR in met-carrier adults relative to adolescents. For simplicity, equivalent declines in frontal DA signaling are proposed for all COMT genotypes, although differential changes may occur. *COMT* catechol-*O*-methyltransferase, *DA* dopamine, *M/M* methionine/methionine, *V/M* valine/methionine, *V/V* valine/valine

impulsive choice in different COMT genotypes, based on this U-shaped relationship. Specifically, an age-dependent drop in frontal DA signaling in val/val individuals yields greater ICR in adults relative to adolescents. In contrast, an equivalent age-dependent drop in frontal DA signaling results in reduced delay-discounting in met-carrier adults relative to adolescents. For simplicity, we have proposed equivalent declines in frontal DA signaling across COMT genotypes; however, developmental declines in frontal DA signaling may vary by COMT genotype. Support for this possibility comes from recent data showing *COMTval[158]met* genotype-dependent methylation resulting in reduced val allele expression (Ursini et al. 2011). Developmental regulation of methylation is one mechanism by which declines in frontal DA signaling could vary by COMT genotype. An important prediction of this model is that within typical "healthy young adult" samples (ages 18–40), the admixture of late adolescents and young adults would tend to obscure COMT genotype effects. While this model is currently hypothetical, future PET studies may test the validity of this U-shape model of the effects of age-dependent differences in frontal DA signaling on impulsive choice.

One remaining important question is whether age-dependent differences in COMT genotype effects on decision-making behavior differ among different ethnic groups. While the present data conclusively find an age by COMT genotype interaction among white participants, they lack sufficient power to draw this same conclusion for other ethnic groups. Heterogeneity within the non-white sample may contribute to this lack of power. Moreover, the relationship between age and discounting behavior could vary with ethnicity, introducing another source of variance. Larger explicit studies of the effects of ethnicity may resolve this question.

Broader implications of age-dependent differences in COMT genotype effects

In addition to playing a role in modulating impulsive choice, the val/val genotype is also associated with poorer performance on executive tasks and greater frontal activation relative to met-carriers (Blasi et al. 2005; Egan et al. 2001; Minzenberg et al. 2006; Tan et al. 2007; Winterer et al. 2006a, b), which is thought to reflect frontal processing inefficiency, particularly during tasks requiring maintenance of stable representations (Bilder et al. 2004; Nolan et al. 2004; Tunbridge et al. 2006). However, published data regarding the role of the *COMTval[158]met* genotype in cognition are mixed (Barnett et al. 2008; Dennis et al. 2010). Thus, in addition to reconciling the literature regarding the effect of *COMTval[158]met* genotype on delay-discounting behavior, these data also suggest an explanation for discrepancies in the literature regarding COMT genotype effects on executive function.

We note that the present study was cross-sectional in nature; a prospective study is required to determine whether the age modulation of COMT genotype effects on delay-discounting reflects developmental processes. Such processes may specifically affect delay-discounting behavior or may also impact linked behaviors, such as working memory (Shamosh and Gray 2008; Shamosh et al. 2008). Specificity of underlying neural circuits may result in task-dependent sensitivity to frontal DA levels, whereby the optimal level for certain tasks is sub-optimal for other tasks (Cools and Robbins 2004; Nolan et al. 2004). Moreover, frontal circuit maturation remains incomplete until the early-to-mid twenties (Sowell et al. 1999; Casey et al. 2000; Sowell et al. 2001; Giedd 2004; Gogtay et al. 2004; Lenroot and Giedd 2006), and components of this circuitry critical for particular tasks may mature at different rates.

Implications for effects of manipulating DA signaling

As noted earlier, several measures of frontal DA signaling decrease from adolescence to adulthood (see Wahlstrom et al. (2010) for recent review). COMT expression increases across the lifespan in humans (Tunbridge et al. 2007), which should result in an age-dependent decrement in frontal DA. An important implication of the age-dependent differences in COMT genotype effects on delay-discounting is that

accounting for both age and COMT genotype may be required to accurately predict the effects of medications that alter frontal DA. Relevant clinical disorders are those associated with impaired frontal DA function, such as schizophrenia, addiction, and ADHD. As these disorders frequently onset in late adolescence (or sooner, in the case of ADHD), understanding how age may impact medication response could help to optimize clinical outcomes for these conditions.

Study limitations

A limitation of the present study is that it cannot completely reconcile the differences between the findings of Paloyelis et al. (2010) and Boettiger et al. (2007), since the adolescent group in the present study did not include participants younger than 18, as did that of Paloyelis and colleagues. Another limitation is the lack of investigation of other genetic variations that may impact delay-discounting behavior, a substantially heritable trait (Anokhin et al. 2011; Mitchell 2011). For example, the DA D_4 receptor (DRD4) and D_2 receptor (DRD2) genes have been linked to variation in delay-discounting behavior (Eisenberg et al. 2007), although these findings are not unequivocal (Paloyelis et al. 2010; White et al. 2009, 2008). As such it is important to consider these results primarily as further evidence that proxy indicators of frontal DA signaling can predict some of the individual differences in delay-discounting. In addition, our results highlight the importance of considering age as a possible confounding factor in future studies evaluating genetic contributions to delay-discounting behavior. Future studies designed to test for interactions between COMT and other polymorphisms in adults may help to clarify the interacting roles for frontal and striatal DA signaling in regulating delay discounting behavior; such studies will also require larger sample sizes than that reported here. Beyond age, we did not find additional environmental variables that accounted for substantial variance in discounting behavior within our sample. However, future larger-scale studies that explicitly test for effects of alcohol use, gender, as well as related cognitive phenotypes may allow for a more complete understanding of the neurobiology of discounting behavior. In particular, measures of working memory, reward sensitivity, and response inhibition may each be regulated by separate DA-regulated networks, which in turn make differing contributions to delay-discounting behavior.

Conflict of interest The authors declare no conflict of interest.

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