Catechol-*O*-methyltransferase val^{158}met genotype modulates sustained attention in both the drug-free state and in response to amphetamine

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Objective **Variation in the catechol-*O*-methyltransferase (COMT) val^{158}met polymorphism has been associated with executive cognition and working memory, presumably mediated by the prefrontal cortex. Here, we extend these observations by examining two measures of cognitive function, lapses in attention and visuo-spatial-motor speed of processing, in both the drug-free state and after administration of *d*-amphetamine.**

Methods **Healthy Caucasian male and female participants ($n=161$) participated in a double-blind, crossover design study where they received placebo or *d*-amphetamine (10 and 20 mg). The outcome measures included self-reported mood states, a simple reaction time task, and a task measuring visuo-spatial-motor speed of processing. We first evaluated whether the genotypic groups differed on any of the measures in the absence of drug administration, including a measure of personality. We then determined whether the genotypic groups differed in their responses to acute doses of *d*-amphetamine (10 or 20 mg).**

Results **We found that without drug, val/val and val/met carriers showed greater lapses in attention on the reaction time task than met/met carriers, but the genotypic groups did not differ on the visuo-spatial-motor speed of processing task. Val/val carriers scored higher on a personality measure of extraversion than val/met and met/met carriers. Compared with placebo, the lower dose of *d*-amphetamine (10 mg) improved lapses in attention and visuo-spatial-motor speed of processing in val/val carriers, and decreased lapses in attention in val/met carriers. The highest dose of *d*-amphetamine (20 mg) improved performance on lapses in attention and visuo-spatial-motor speed of processing tasks in both val/val and val/met carriers, but not in met/met carriers. None of the genotypic groups differed on mood states, either with or without drug administration.**

Conclusion **The results of this study extend earlier findings with the COMT genotypes to additional measures of cognition, and suggest that the presence of the val allele is associated with poorer performance and greater improvement with a stimulant drug. The results further suggest that this polymorphism does not affect the mood-altering effects of *d*-amphetamine, consistent with the preferential influence of COMT in cortical regions.** ***Psychiatr Genet*** **20:85–92 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Catechol-*O*-methyltransferase (COMT) is an enzyme that metabolizes catecholamines and catechol-estrogens in both the central nervous system and periphery. The discovery of a common functional genetic variant at codon 158 (val^{158}met) (Lotta *et al.*, 1995; Lachman *et al.*, 1996) led to the observation that individuals who were homozygous for the val allele performed more poorly than other genotypic groups on tasks of executive function (Egan *et al.*, 2001). The differences in performance have been attributed to localized function of COMT in the prefrontal system. Furthermore, these differences seem to contribute to individual differences in responses to stimulant drugs, such as *d*-amphetamine (Mattay *et al.*, 2003). However, given the complex modulation and functional heterogeneity of frontal lobe systems, further evaluation of *COMT* val^{158}met-related phenotypes is needed. Here, we examined additional measures of cognition, including lapses in attention and general measures of visuo-spatial-motor speed of processing, as well as self-reports of mood, both without a drug and in response to acute administration of *d*-amphetamine.

Dopamine (DA) is removed from the synapse in most parts of the brain by the DA transporter, but in the frontal cortex the DA is cleared mainly by the catabolic enzyme COMT (Karoum *et al.*, 1994). The substitution of methionine (met) for valine (val) at codon 158 in the COMT gene (*COMT*) leads to a lower enzymatic activity so that met/met carriers have higher synaptic levels of DA in the frontal cortex, which seems to improve their performance on measures of executive function and working memory (Egan *et al.*, 2001; Mattay *et al.*, 2003; Tunbridge *et al.*, 2006). Both environmental factors and pharmacologic manipulations modify the effects of *COMT*

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val^{158}met genotype on cognition. For example, years of education – one possible marker of socioeconomic status – interacts with the *COMT* val^{158}met genotype such that met/met carriers' cognitive scores improve markedly with increasing years of education, whereas the scores of val/val individuals are only marginally influenced by years of education (Enoch *et al.*, 2009). Interestingly, in one study (Mattay *et al.*, 2003) the psychostimulant *d*-amphetamine, which increases synaptic DA levels, worsened executive function and working memory of met/met carriers, whereas it improved performance among val/val carriers. This was explained as an inverted 'U' functional response curve so that performance is improved by modest increases in synaptic DA levels, but impaired when levels exceed a certain optimal level. The goal of this study was to further characterize the function of *COMT* val^{158}met by analyzing; (i) whether genotypic groups differ in the drug-free condition on measures of motor processing and attention, and (ii) whether genotypic groups differ in their responses to these measures after administration of *d*-amphetamine. We used two measures of cognition: the Digit Symbol Substitution Test (DSST; Wechsler, 1958), which provides a non-specific measure of visuo-spatial and motor speed-of-processing, and Deviation from the Mode (DevMod), a new measure of lapses in attention (de Wit, 2009), derived from a simple reaction time task. We used a task measuring lapses in attention to obtain important information about moment-to-moment fluctuations in task performance. In addition to these measures of cognitive function, we also evaluated mood states with Profile of Mood States (McNair *et al.*, 1971) and personality, using the Multidimensional Personality Questionnaire (MPQ, Tellegen, 1982).

We hypothesized that the val/val carriers would perform more poorly than met/met carriers on lapses in attention and visuo-spatial-motor speed of processing tasks in the absence of pharmacologic manipulation, consistent with what has been reported on other measures of cognition. In addition, we hypothesized that val/val carriers would exhibit a greater improvement in performance after *d*-amphetamine than met/met carriers. We did not expect that these genotypic groups would differ in the mood-altering effects of *d*-amphetamine because these effects are not believed to be mediated in brain regions where COMT plays a major role (Volkow *et al.*, 1997). Studies of this kind, investigating the relationships between genotype and responses to drugs, will help to explain inter-individual variability in responses to drugs, including drugs such as stimulants that are used in clinical settings. These studies will also help to identify the separate brain processes that mediate the cognitive and mood-altering effects of drugs.

Methods

Participants

Healthy Caucasian male and female participants (n = 161), aged 18–35 years, were recruited by posters, advertisements and word-of-mouth referrals. To reduce variability related to tolerance or withdrawal from nicotine or caffeine, we excluded participants who smoked more than 10 cigarettes per week or consumed more than three cups of coffee per day. All participants completed a psychiatric screening interview on the basis of *Diagnostic and Statistical Manual of Mental Disorders*-IV criteria (American Psychiatric Association, 1994), a psychiatric symptom checklist (SLC-90; Derogatis, 1983), the Michigan Alcoholism Screening Test (Selzer, 1971), and a health questionnaire with a detailed section on current and lifetime drug use. Participants currently taking prescription medication, or who had an Axis I psychiatric disorder, a history of treatment for substance use disorder or a history of personal or legal problems related to drug use, or any current or past medical condition considered to be a contraindication to *d*-amphetamine (such as abnormal Electrocardiogram or hypertension) were excluded from the study. Candidates had to speak English and have at least high school education. Body mass index (BMI) limitations were 19–26 kg/m^2. As women show a dampened response to *d*-amphetamine during the luteal phase of the menstrual cycle (White *et al.*, 2002) they were scheduled to participate during the follicular phase only. Women who were pregnant or lactating, or planning to become pregnant during the study were excluded.

Design

This within-subject design study consisted of three sessions separated by at least 48 h. Participants received capsules containing placebo, *d*-amphetamine 10 mg and *d*-amphetamine 20 mg in counterbalanced order under double-blind conditions. A smaller subset of participants also received a 5 mg dose, but these data are not reported here to maximize power to detect genotypic differences. The *d*-amphetamine (Mallinkrodt, Missouri, USA) was placed in size 00 capsules with dextrose filler. Placebo capsules contained dextrose only. The study was approved by The University of Chicago Institutional Review Board and was performed in accordance with the Helsinki Declaration of 1975.

Participants first completed an orientation session in which the study procedures were explained. They signed the consent form and then provided a blood sample for genotyping purposes. They completed self-questionnaires and practiced computerized tests used in the study. Participants were instructed to abstain from taking drugs, including alcohol, 24 h before each session and to fast from midnight the night before the sessions. In addition, they were instructed not to consume more nicotine or caffeine than usual 24 h before and 12 h after the start of each session.

The three experimental sessions were conducted from 09:00 a.m. to 1:00 p.m. and were separated by at least 48 h. Before the start of every session, participants gave urine and breath samples to verify their abstinence from

alcohol and other drugs. They received a light breakfast and at 9:00 a.m. their baseline cognitive (DSST – see below) and mood (Profile of Mood States – see below) states were assessed. Participants were tested individually, and remained in a comfortably furnished room with television and reading material for the 4-hour session. They could watch emotionally neutral movies and read during the sessions when measurements were not being taken, but they were not allowed to study. At 09:30 a.m., participants ingested a capsule containing *d*-amphetamine (10 or 20 mg) or placebo with a glass of water. For blinding purposes, they were informed that the capsule might contain a stimulant, sedative, or placebo. Self-reported drug effect questionnaires and DSST (see below) were obtained 30, 60, 90, 150, and 180 min after ingestion of the capsule. Participants completed a simple reaction time task once (DevMod – see below), 90 min after capsule administration, when *d*-amphetamine is expected to have the highest concentration in the blood. At 1:00 p.m. participants left the laboratory. After completing all three sessions participants were debriefed and paid.

Dependent measures

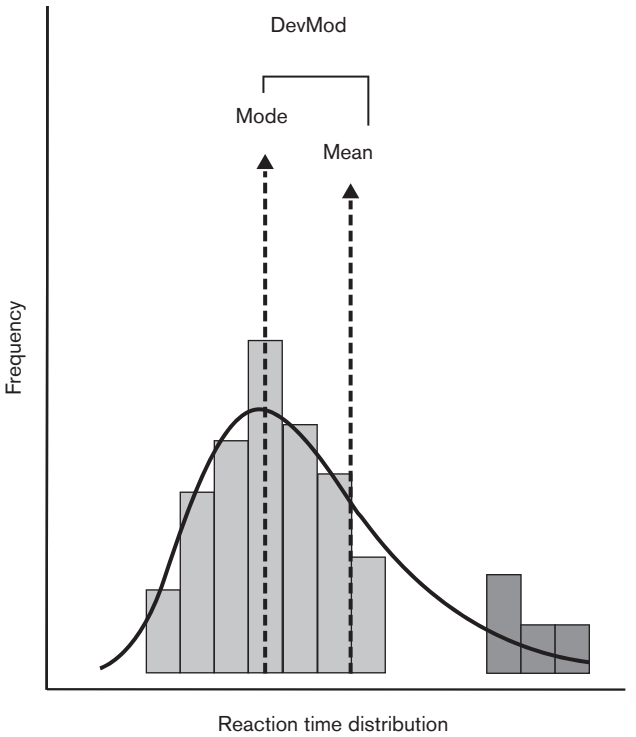
The Profile of Mood States (POMS) (McNair *et al.*, 1971) is an adjective checklist that is sensitive to the effects of psychoactive drugs. We used a version of the POMS consisting of 72 adjectives commonly used to describe momentary mood states. Participants indicate how they feel at the moment in relation to each of the 72 adjectives on a 5-point scale from not at all (0) to extremely (4). Eight clusters (scales) of items are separated empirically using factor analysis (anxiety, depression, anger, vigor, fatigue, confusion, friendliness, elation). The value of each scale is determined by averaging the scores for the adjectives in that cluster. Two additional (non-validated) scales are derived from the other scales as follows: arousal = (anxiety + vigor) – (fatigue + confusion); positive mood = elation – depression.

DSST (Wechsler, 1958) is a pencil and paper test in which participants are required to substitute a series of numbers and symbols within 90 s. The number of correct responses within 90 s is reported. One point is given for each correctly drawn symbol. DSST is a test of visuo-spatial and motor speed-of-processing and has a considerable executive function component. It is frequently used as a sensitive measure of frontal lobe executive functions (Vilkki and Holst, 1991; Parkin and Java, 1999). We used eight versions of this task, in mixed order, to reduce practice effects.

DevMod (Leth-Steensen *et al.*, 2000; de Wit, 2009; Spencer *et al.*, 2009) is a measure of lapses in attention determined from the distribution of reaction times of a simple visual reaction time task (see Fig. 1). A simple stimulus (a star) is presented in brief on the computer screen and the participant is required to press a mouse button as quickly as possible each time the stimulus appears. This is repeated 100 times. On average, the task takes 2–3 min to complete. Three summary measures are derived from the distribution of each individual's reaction times: the mean, the mode, and the median. The measure of lapses of attention corresponds to the mean DevMod, or the mean of the difference between each RT and the mode (see Fig. 1 for details). It provides a measure of skew, or unusually long RTs, because the mean is more sensitive to the outliers (i.e. lapses in attention) than the mode, which is generally unaffected by outliers. The mean DevMod is equivalent to the difference between the mean and the mode of a reaction time distribution. The larger the DevMod, the greater the proportion of long reaction times. The task has been validated in earlier studies under both physiologic and pharmacologic challenge conditions (Acheson *et al.*, 2007; Acheson and de Wit, 2008; Childs and de Wit, 2008; Spencer *et al.*, 2009).

The MPQ (Tellegen, 1982) is a self-report personality instrument designed to assess three broad traits: Positive Emotionality (Extraversion), Negative Emotionality (Neuroticism) and Constraint (Constraint-Impulsivity). In this analysis we had an a priori hypothesis that COMT

Fig. 1



Schematic of Deviation from the Mode (DevMod) measuring lapses of attention. This figure shows the separation of the mode and the mean when there are long reaction times or 'lapses in attention'. It shows that long reaction times change the mean while leaving the mode relatively unaffected. The difference between the mean and the mode provides a measure of the skew, and DevMod is considered a measure of inattention. Text and figure printed with permission from de Wit (2009).

genotypic groups would differ on Extraversion scale (Positive Emotionality) of MPQ owing to a finding by Stein *et al.* (2005) that individuals who are homozygous for the met allele are more likely to score low on extraversion than individuals with the val allele. Analysis of the MPQ in twins suggests that scores on all three higher-order scales are influenced by moderate-to-strong genetic factors (Tellegen, 1988).

Genotyping

Genotyping was performed using the Addictions Array (Hodgkinson *et al.*, 2008) based on the Illumina GoldenGate platform. Arrays were imaged using an Illumina Beadstation GX500 and the data were analyzed using GenCall v6.2.0.4 and GTS Reports software v5.1.2.0 (Illumina). Criteria for sample exclusion and classification as genotyping failure have been described earlier (Hodgkinson *et al.*, 2008).

Population stratification

To examine potential population stratification, we genotyped all participants taking part in the study for 186 ancestry markers (AIMs) that were included on an Illumina array (Hodgkinson *et al.*, 2008). We then ran STRUCTURE (Pritchard *et al.*, 2000), which identifies subpopulations of individuals who are genetically similar through a Markov chain Monte Carlo sampling procedure using markers selected across the genome.

Statistical analysis

Participants were categorized into three *COMT* val^{158}met groups: met/met carriers, met/val carriers or val/val carriers. The three genotypic groups were compared on demographic and personality measures assessed in this study including sex, BMI, education in years, age, current and lifetime substance use, and personality, using analysis of variance (ANOVA) for continuous measures or χ^2 tests for categorical measures. If we found that possible confounding variables of demographic factors were associated with outcome measures in this analysis their effect was removed by including them as covariates in further statistical analyses.

Comparison of genotypic groups on measures obtained during experimental sessions, without drug

We calculated the mean baseline mood and DSST score for individual genotypic group by averaging precapsule scores for each session (i.e. placebo, *d*-amphetamine 10 mg and *d*-amphetamine 20 mg). As DevMod was assessed only once during each session (at 90 min after *d*-amphetamine administration), genotypic groups were compared using the data from the placebo session. The three genotypic groups were compared using one-way ANOVA. Post hoc analyses were conducted using *t*-tests and the *P* value was set at $P \leq 0.05$ (two-tailed) for all analyses.

Comparison of genotypic groups, in response to d*-amphetamine*

Responses to *d*-amphetamine in the three genotypic groups were compared by calculating the area under the curve (AUC) for the placebo and 10 and 20 mg *d*-amphetamine sessions, using two-way ANOVAs or analysis of covariances (if we found a significant effect of covariates). AUC was calculated by multiplying the average of each pair of consecutive observations by the corresponding time interval and then summing all such values, starting with the first time point and ending with the last, as described in Matthews *et al.* (1990).

When significant gene–drug interactions were obtained, post hoc analyses were conducted using *t*-tests to determine which groups differed, at which drug doses. The *P* value was set at $P \leq 0.05$ (two-tailed) for all analyses.

Relationship between DSST and DevMod

To investigate how brief lapses in attention relate to more general measures of cognitive performance according to the genotype, we examined correlations between DSST and DevMod (i) in the drug-free condition (i.e. placebo condition) and (ii) in response to *d*-amphetamine (10 and 20 mg).

Results

Participants

Table 1 summarizes participant demographics and self-reported personality for the overall sample. On average, participants were in their early twenties, with either some college education or a college degree. They consumed moderate amounts of caffeine and alcohol, and their lifetime illicit drug use was typical for individuals of college age. Despite similarities on these measures, the val/val carriers were younger than either val/met or met/met carriers. Age was included as a covariate in all the analyses. Caucasian ancestry was confirmed in all participants. *COMT* val^{158}met differed on Positive Emotionality scale (Extraversion) [$F_{(2,147)} = 4.2$, $P \leq 0.05$]. Post hoc comparisons revealed that val/val carriers scored higher than met/met carriers and val/met carriers ($P \leq 0.01$ for both; Table 1).

Genotype frequencies

This sample of participants consisted of 36 val/val carriers, 72 val/met carriers and 53 met/met carriers. This genotype frequency is in Hardy–Weinberg equilibrium.

Profile of mood states

COMT val^{158}met genotypic groups did not differ in their rating of mood in the drug-free condition on either of the POMS composite scales [Arousal: $F_{(2,153)} = 2.61$, NS; Positive Mood $F_{(2,153)} = 2.41$, NS]. Furthermore, although *d*-amphetamine produced typical effects on mood in the group as a whole [Arousal: $F_{(2,300)} = 56.1$, $P < 0.001$; Positive Mood $F_{(2,300)} = 38.1$, $P < 0.001$], the genotypic

Table 1 Demographics for participants in the three *COMT* val^{158}met genotype groups

N	val/val 36	val/met 72	met/met 53
Demographics			
Age (mean years ± SEM)[a]	21.6 ± 0.4	23.2 ± 0.4	23.3 ± 0.6
Sex			
Male/female	26/27	46/26	17/19
BMI (mean ± SEM)	22.3 ± 0.3	22.8 ± 0.3	22.8 ± 0.3
Education			
High school or some college (*N*)	23	27	20
College degree (*N*)	24	34	12
Advanced (*N*)	6	11	4
Multidimensional Personality Questionnaire			
Positive emotionality (extraversion)[b]	73.8 ± 1.7	66.5 ± 1.6	65.8 ± 2.3
Negative emotionality (neuroticism)	23.9 ± 1.5	24.9 ± 1.1	26.5 ± 1.6
Constraint (constraint-impulsivity)	63.6 ± 2.6	67.4 ± 1.8	66.6 ± 2.0
Current substance use			
Alcohol (drinks per week)	3.5 ± 0.5	4.5 ± 0.4	5.3 ± 0.6
Cigarettes (per week)	0.3 ± 0.1	0.7 ± 0.2	1.0 ± 0.3
Marijuana (occasions per month)	0.3 ± 0.1	0.8 ± 0.3	1.3 ± 0.4
Caffeine (cups per week)	6.4 ± 1.0	7.0 ± 0.8	8.4 ± 1.1
Lifetime illicit substance use			
Opiates (% never used)	90.3	82.8	77.1
Hallucinogen (% never used)	71	68.8	75
Tranquilizers (% never used)	90.3	95.3	89.6
Inhalants (% never used)	90.3	89.1	87.5
Stimulants (% used)	83.9	76.6	75

Genotype groups were compared by one-way analysis of variance for continuous data and χ^2 for frequency data.
COMT, catechol-*O*-methyltransferase.
[a]Difference between the val/val group and both val/met and met/met groups at $P<0.05$.
[b]Difference between the val/val group and both val/met and met/met groups at $P<0.01$.

groups did not differ on these responses [Arousal × COMT genotype interaction $F_{(4,296)} = 0.15$, $P =$ NS; Positive Mood × COMT genotype interaction $F_{(4,296)} = 0.96$, $P =$ NS].

Digit symbol substitution test

One participant's DSST data were lost and three participants' data were outliers. Their AUC values on the placebo session and their genotypes were 445-met/met, 461.5-val/met and −366.5-met/met. After their removal the data were normally distributed. Important demographic factors such as age, sex, and BMI did not influence performance on DSST either in a drug-free state or in response to *d*-amphetamine. Table 2 lists mean (SD) for all the timepoints across all three sessions. Genotypic groups did not differ on DSST in the drug-free state [$F_{(2,146)} = 0.589$, NS]. However, there was an interaction between genotype and *d*-amphetamine on DSST [$F_{(4,290)} = 3.2$; $P \leq 0.05$], as shown in Fig. 2. The interaction reflects a significant improvement in performance after *d*-amphetamine administration in the val/val and val/met carriers, but no similar improvement in the met/met group.

Deviation from the mode

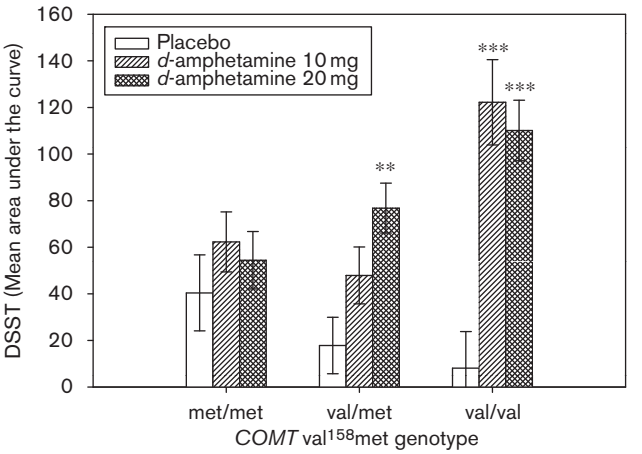
This group of participants consisted of a smaller sample size including 22 val/val carriers, 49 val/met carriers and

Table 2 Digit symbol substitution test scores

Timepoint	Placebo	*d*-amphetamine 10 mg	*d*-amphetamine 20 mg
Baseline	79.3 ± 12.7	79.3 ± 12.8	80.0 ± 11.9
30	79.8 ± 11.3	79.8 ± 12.0	81.2 ± 10.9
60	80.4 ± 11.4	83.0 ± 13.1	84.3 ± 11.4
90	80.4 ± 11.8	83.9 ± 11.4	85.0 ± 11.1
150	81.4 ± 11.9	85.2 ± 11.9	85.9 ± 11.5
180	82.4 ± 12.2	85.0 ± 12.2	86.4 ± 11.7

All values represent (mean ± SD).

Fig. 2



Mean area under the curve ± SEM of participants' performance on the Digit Symbol Substitution Test according to catechol-*O*-methyltransferase (*COMT*) val^{158}met genotype. The groups did not differ significantly on the placebo session, but *d*-amphetamine 10 mg (***$P \leq 0.001$) and *d*-amphetamine 20 mg (***$P \leq 0.001$) improved performance in the val/val carriers ($N=36$). *D*-amphetamine (20 mg) improved performance in the val/met ($N=72$) carriers (**$P \leq 0.01$), whereas the drug did not change performance in the met/met carriers ($N=53$). DSST, Digit Symbol Substitution Test.

28 met/met carriers owing to the fact that DevMod was only tested in a subset of the participants. Allele frequencies were in Hardy–Weinberg equilibrium for this subset of the sample as well. One participant's score was excluded for being an extreme outlier in the *d*-amphetamine 20 mg session (z score = 7.4). The groups were similar on all demographic measures except that the val/val carriers were slightly younger (mean age = 21.2, SEM = 0.5) than the val/met carriers (mean age = 23.5, SEM = 0.5). We included age as a covariate in analyses of DevMod. Of all the demographic variables studied, only caffeine use was associated with DevMod; therefore caffeine use was included as a covariate. Table 3 provides mean (SD) reaction times for each genotype in each of the three conditions. We first evaluated the performance of each genotypic group in the drug-free state (i.e. placebo condition). The genotypic groups differed in their performance on DevMod [$F_{(2,94)} = 3.21$; $P \leq 0.05$]. Post hoc comparisons indicate that, compared with met/met carriers, val/met carriers and val/val carriers had

higher DevMod in the placebo condition ($P \leq 0.05$ for both). We detected an interaction between amphetamine dose and genotype [$F_{(4,188)} = 2.83$; $P \leq 0.05$]. Post hoc comparisons showed that both doses of *d*-amphetamine improved performance in val/met carriers (10 mg $P \leq 0.05$; 20 mg $P \leq 0.01$) and val/val carriers (10 mg $P \leq 0.001$; 20 mg $P \leq 0.05$), but neither dose of *d*-amphetamine improved performance for the met/met carriers.

Thus, like the DSST, we observed an improvement in performance in the val/val and val/met but not in the met/met groups after administration of *d*-amphetamine (Fig. 3).

Relationship between DSST and DevMod

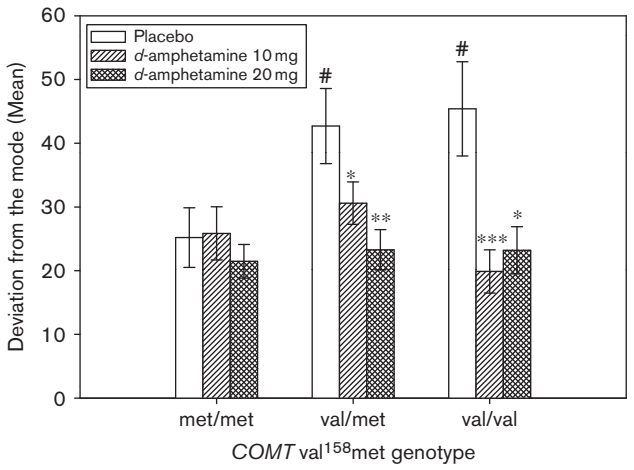
In most comparisons DSST and DevMod were not related. However, in the val/met genotype group, DSST and DevMod scores were negatively correlated in the drug-free condition ($r^2 = -0.323$, $P = 0.025$).

Table 3 Simple reaction times after administration of *d*-amphetamine for three *COMT* val^{158}met genotype groups

	d-amphetamine dose		
Genotype	Placebo	*d*-amphetamine 10 mg	*d*-amphetamine 20 mg
met/met ($n=28$)	324.4 ± 56.9	304.4 ± 44.0	294.6 ± 40.3
val/met ($n=49$)	350.8 ± 64.8	302.6 ± 43.0	300.7 ± 43.2
val/val ($n=22$)	332.3 ± 52.2	295.8 ± 37.5	287.8 ± 30.0

All values represent (mean ± SD).
COMT, catechol-*O*-methyltransferase.

Fig. 3



Mean ± SEM of participants' performance on the Deviation from the Mode (DevMod) according to catechol-*O*-methyltransferase (*COMT*) val^{158}met genotype. In the absence of any drug, val/met carriers and val/val carriers had higher DevMod than met/met carriers ($^{\#}P \leq 0.05$ for both). *D*-amphetamine (10 and 20 mg) decreased lapses in attention in the val/val carriers ($N=22$; $^{***}P \leq 0.001$ and $^{*}P \leq 0.05$ respectively). *D*-amphetamine (10 and 20 mg) also decreased lapses in attention for val/met carriers ($N=49$) $^{*}P \leq 0.05$ and $^{**}P<0.01$ respectively). The drug did not change DevMod performance in the met/met carriers ($Ns=28$).

Conclusion

In summary, we found that val/val and val/met carriers of *COMT* val^{158}met polymorphism showed more lapses in attention in a drug-free state and a greater improvement in general cognition after administration of *d*-amphetamine. We also found that val/val carriers scored higher on the personality trait of extraversion than val/met and met/met carriers. The groups did not differ in mood states, either in a drug-free state or after administration of *d*-amphetamine.

Our finding that homozygotes for the met allele of the *COMT* val^{158}met genotypic performed better in the drug-free condition on the measure of attention (i.e. lapses in attention) is consistent with earlier research. Mattay *et al.* (2003) reported that healthy participants with the met/met alleles performed better on measures of working memory and executive function, and Egan *et al.* (2001) reported that schizophrenic met/met patients had better executive function. In our study met/met carriers of *COMT* val^{158}met had fewer lapses in attention on DevMod than val/val and val/met carriers. However, the three genotypic groups did not perform differently on a general measure of cognition (DSST) despite earlier reports that working memory and executive function, also dependent on prefrontal cortex functioning, are mediated by the *COMT* val^{158}met genotype. This suggests that the DSST may not be sensitive to the deficits related to COMT function, but also that the impairments in individuals with the val allele may be relatively modest.

Most cognitive tasks involve more than a single underlying process, and brief lapses in attention, such as those measured here, might contribute to more general measures of cognitive performance. For example, it has been proposed that momentary lapses in attention can disrupt goal-oriented behavior (Czeisler *et al.*, 2005) in both healthy individuals (Dockree *et al.*, 2006) and clinical syndromes such as Attention Deficit Hyperactivity Disorder (Castellanos *et al.*, 2005; Reimer *et al.*, 2005). Our results provide some support for this idea. Although the DevMod was not related to DSST performance in most participants, the two measures were inversely correlated in the val/met group. In that group, individuals who exhibited more lapses in attention performed worse on our measure of general psychomotor performance, supporting the idea that attention can affect general cognitive function. Further studies are needed to provide more information about how lapses in attention relate to more general measures of cognition.

Consistent with earlier studies, we found that *d*-amphetamine improved performance on the DSST and the DevMod measures only in the val/val and val/met individuals. Mattay *et al.* (2003) also showed that amphetamine preferentially improved working memory and executive function in val/val carriers. However, in the Mattay *et al.* (2003) study, amphetamine did not improve performance in the heterozygotes (val/met), whereas in

our study amphetamine reduced lapses in attention and improved performance on DSST in val/met carriers. In addition, met/met carriers in the Mattay *et al.* (2003) study exhibited decrements in performance after administration of amphetamine, whereas amphetamine did not affect either DSST or DevMod in met/met carriers in our study. It may be that the larger sample size (27 vs. 161) in our study accounts for these differences.

It is notable that the genotypic groups in our study differed on measures of cognition but not on mood-altering effects of *d*-amphetamine. Earlier studies have not focused on the *COMT* val^{158}met genotype in relation to subjective ratings of mood, either in the drug-free condition or after stimulant administration. However, the dissociation between cognitive and mood effects of the drug, in relation to COMT, suggests that these effects might be mediated by different brain areas. COMT might be expected to have a greater impact on cognition, which is dependent on cortical function, but not mood, which is thought to depend more on the actions of DA in the striatum. Consistent with this, we have earlier reported the genotypic differences in subjective ratings of amphetamine in relation to polymorphism in function of the DA transporter (Lott *et al*., 2005) and norepinephrine transporter (Dlugos *et al*., 2007), which are thought to have greater influence on dopaminergic function in striatal, relative to prefrontal, brain regions.

We found that the *COMT* val^{158}met genotype is associated with extraversion, but not neuroticism or constraint-impulsivity. In our analysis we used the Multidimensional Personality Questionnaire – a self-reported measure of personality known to be influenced by moderate-to-strong genetic factors (Tellegen, 1988). Our results showed that val/val carriers scored higher on a measure of extraversion than the met/met and val/met carriers. This is consistent with the study by Stein *et al.* (2005), who found that among female college students, met/met carriers scored lower on extraversion than val/met or val/val carriers. Although we did not observe sex differences in our sample, the direction of the genotypic-personality association was the same as that in the Stein *et al.* (2005) study.

Although we seem to have had enough power to detect significant effects of *COMT* val^{158}met, the sample may not have been powerful enough to detect more subtle differences between the groups. For example, earlier research indicates that val/val carriers perform more poorly than other genotypes on tasks measuring executive function and working memory in a drug-free state (for a review see Tunbridge *et al.*, 2006), whereas we failed to observe group differences on the DSST, a task of general cognition (Vilkki and Holst, 1991; Parkin and Java, 1999). It is possible that we would have detected an effect of genotype with a larger number of participants. Similarly, insufficient power might have prevented us from observing previously reported sex differences in extraversion or emotionality (Stein *et al.*, 2005; Hettema *et al.*, 2008). In our analyses we failed to observe sex differences, either in the relationship between the MPQ and genotype or mood changes in response to drug and genotype. Finally, the sensitivity of the DSST task may have been influenced by practice effects from administering the task repeatedly. Although there was some evidence of improvement across administrations of the task within the placebo session, performance was stable across the three sessions.

The results of this study extend our knowledge of how the *COMT* val^{158}met polymorphism affects behavior, both in the drug-free state and after administration of amphetamine. Although earlier research focused on measures of cognition, including working memory and executive function, this is the first study, to our knowledge, that shows that inattention, or lapses in attention, is dependent on *COMT* val^{158}met genotype in both the drug-free state and in response to amphetamine. In addition, our results show beneficial effects of amphetamine on sustained attention and visuo-spatial-motor speed of processing for val/val and val/met carriers, but do not support the idea that the stimulant has detrimental effects on met/met carriers. Finally, the results indicate that the cognitive effects of *d*-amphetamine may involve different brain mechanisms than the mood-altering effects of the drug, as we failed to detect associations between *COMT* genotype and amphetamine-induced mood states. Our results extend our understanding of the mechanisms involved in individual differences in sustained attention in the absence of any drug. They also add to our understanding of individual differences in responses to a stimulant drug that is used clinically to inhibit inappropriate behavior.

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