

COMT val158met predicts reward responsiveness in humans

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A functional variant of the catechol-O-methyltransferase (COMT) gene [val158met (rs4680)] is frequently implicated in decision-making and higher cognitive functions. It may achieve its effects by modulating dopamine-related decision-making and reward-guided behaviour. Here we demonstrate that individuals with the met/met polymorphism have greater responsiveness to reward than carriers of the val allele and that this correlates with risk-seeking behaviour. We assessed performance on a reward responsiveness task and the Balloon analogue risk task, which measure how participants ($N=70$, western European, university and postgraduate students) respond to reward and take risks in the presence of available reward. Individuals with the met/met genotype ($n=19$) showed significantly higher reward responsiveness, $F_{2,64}=4.02$, $P=0.02$, and reward-seeking behaviour, $F(2,68)=4.52$, $P=0.01$, than did either val/met ($n=25$) or val/val ($n=26$) carriers. These results highlight a scenario in which genotype-dependent reward responsiveness shapes reward-seeking, therefore suggesting a novel framework by which COMT may modulate behaviour.

Keywords: COMT, decision-making, dopamine, genetics, individual differences, reward, risk-taking

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Although the heritability of behaviour is considerable, the search for specific mechanisms has yielded few replicated associations between genotypes and specific traits. One of the most promising candidates is a functional polymorphism (rs4680), which produces a valine (val)-methionine (met) substitution at codon 158 (val158met variant) of the catechol-O-methyltransferase (COMT) gene. Evidence shows that the val158met polymorphism, present in humans, modulates

COMT enzymatic activity (Chen *et al.* 2004), which in turn promotes the catabolism of presynaptic dopamine (Mannisto & Kaakkola 1999). In animal models, manipulation of COMT enzymatic activity alters frontal dopaminergic function (Gogos *et al.* 1998; Yavich *et al.* 2007). Researchers have therefore suggested that the COMT val158met genotype may modulate dopamine (DA) availability in prefrontal and striatal pathways in humans (Akil *et al.* 2003; Bilder *et al.* 2004; Chen *et al.* 2004; Meyer-Lindenberg *et al.* 2005; Dreher *et al.* 2009). However, the relationship between COMT and prefrontal DA function in humans remains indirect.

The COMT genotype is associated with variability in a variety of dopaminergic phenotypes, including executive function and cognition (Barnett *et al.* 2008; Mier *et al.* 2010). Indeed, researchers argue that sensitivity to reward may be a crucial factor in performance on cognitive tasks, particularly those assessing executive function (Beck *et al.* 2010; Jimura *et al.* 2010). For example, participants may experience the simple performance-based feedback inherent in tasks such as the Wisconsin Card Sorting Task as rewarding, despite the absence of explicit reward. Moreover, evidence shows that simply knowing one has answered correctly, in the absence of any feedback, activates ventral striatum, an area associated with mid-brain reward circuitry (Satterthwaite *et al.* 2012). Therefore, COMT genotype-dependent differences in cognitive performance may relate to the intrinsic reward associated with correct performance, regardless of explicit incentives.

On the basis of proposed links between dopamine, reward and cognition, recent research has sought to characterize the COMT genotype by probing the val158met variant with reinforcement-learning tasks, rather than conventional measures of cognitive/affective function. This work suggests that the COMT val158met variant may modulate task adaptation (Frank *et al.* 2007, Krugel *et al.* 2009) as well as exploratory behaviour during learning (Frank *et al.* 2009). However, the COMT variant's exact role in governing individual differences in reward responsiveness remains unknown, as much of the evidence linking the COMT genotype to reward sensitivity has been inferred from neuroimaging measures (Marco-Pallares *et al.* 2009). Interestingly, evidence based on experience sampling methods suggests a COMT-genotype by environment interaction whereby exposure to environmental rewards (pleasant events in daily life) leads to significantly greater positive affect for met homozygotes, than for val homozygotes (Wichers *et al.* 2008).

This study aimed to bridge the gap between COMT genotype and reward responsiveness by providing behavioural evidence of genotype-dependent differences in reward responsiveness and in the degree to which behaviour depends on the presence or possibility of gaining rewards

(reward-seeking). We hypothesized that relative to val/val participants, met/met participants would show increased responsiveness to rewards by developing greater bias towards a more frequently reinforced target in a signal detection task (Pizzagalli et al., 2005) and by attempting to obtain more rewards in a risky reward-guided decision-making task (LeJuez et al. 2002). On the basis of the finding that the COMT met allele appears to enhance the degree to which individuals experience rewards as rewarding (Wichers et al. 2008), we also predict that the met allele should enhance the degree to which reward responsiveness motivates reward-seeking. Thus, we anticipate the presence of a differential relationship between reward responsiveness and reward-seeking across the genotype groups.

Methods

Participants

Two hundred and forty-four volunteers were recruited to a participant panel genotyped for the COMT val158met variant (rs4680). Participants in this panel were recruited by advertisement from among the University community (e.g. students, employees) based on the following criteria: western European descent; no experience of psychiatric/neurological symptoms or diagnoses in either themselves or first-degree relatives; no illegal (or recreational) substance use/dependence (excluding nicotine) and no alcohol abuse/dependence. Genotype frequencies in this larger sample did not deviate from Hardy–Weinberg Equilibrium ($\chi^2 = 0.005$, $P > 0.9$; Table 1). For this study, 70 undergraduate and postgraduate student participants were recruited from this panel on an opportunistic schedule based on genotype and availability. This process, which has been used in previous behavioural/imaging genetics studies (Marco-Pallares et al. 2009; Camara et al. 2010), allowed us to increase study power by recruiting larger met/met and val/val groups than would be expected in a random sample. All participants provided written informed consent prior to gDNA extraction and to participation in this study. The University's Ethics Committee approved all study procedures. Researchers were blind to participants' COMT genotype status during data collection. The COMT genotype groups did not differ in age or male:female ratio (Table 1).

Genotyping

Participants provided gDNA samples via buccal swabs (Isohelix, Cell Project Ltd, Kent, UK). All 70 participants were successfully genotyped for the COMT val158met (rs4680) single nucleotide polymorphism (SNP). Source Biosciences (Life-Sciences Division, Nottingham, UK) provided genomic services. SNP genotyping was performed using a MATRIX PlateMatePlus (Matrix Technologies Corp, Cheshire, UK). Polymerase chain reaction was performed

using KBiosystems Super Duncan thermal cycler (KBiosystems Ltd, Essex, UK). An ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) was used to visualize allelic discrimination at the rs4680 loci with a fluorogenic 5' nuclease TaqMan[®] SNP assay (Applied Biosystems, Foster City, CA, USA).

Procedure

Reward responsiveness task

To measure reward responsiveness, we used a line discrimination task with asymmetric reinforcement, closely modelled after that described in Pizzagalli et al. (2005), Heerey et al. (2008). Asymmetric reinforcement, in which responses to one stimulus receive more frequent rewards than responses to another, leads to the development of response bias by increasing participants' likelihood of reporting the more frequently reinforced stimulus (Macmillan & Creelman 2005). Individuals who develop greater levels of response bias are more responsive to rewards (Pizzagalli et al. 2008a, 2008b).

Trials began with a fixation cross (500 milliseconds), followed by the presentation of a cartoon face with no mouth. After 500 milliseconds, either a short (22 mm) or long (24 mm) mouth appeared on the face. It was visible for 100 milliseconds before disappearing. The face remained on screen until the participant responded with a button press indicating the presence of either the short or long mouth. Following the response, participants saw a screen that either displayed feedback ('Correct! +5 pence') or remained blank (no-feedback trials) for 1750 milliseconds (Fig. 1). Participants completed three blocks of 100 trials. Both versions of the mouth appeared equally often in pseudo-random order such that there were no more than four successive trials of the same mouth.

Participants received reward feedback on 40 correct responses per block. To induce a reward-related response bias in the task, we distributed the rewards asymmetrically across the mouths.

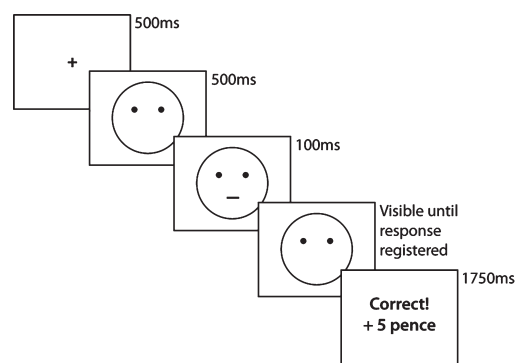


Figure 1: Trial timeline for a feedback trial in the reward sensitivity task.

Table 1: Descriptive Statistics for COMT rs4680 Groups

COMT rs4680	Met/Met	Val/Met	Val/Val	<i>P</i>
Genotype*	27% (<i>n</i> = 66)	41% (<i>n</i> = 101)	32% (<i>n</i> = 77)	>0.5
Sample Genotype [†]	27.1% (<i>n</i> = 19)	35.7% (<i>n</i> = 25)	37.1% (<i>n</i> = 26)	n/a
Age [‡]	22.9 (3.8)	21.6 (2.4)	23.7 (6.4)	>0.5
Sex [§]	M (<i>n</i> = 9); F (<i>n</i> = 10)	M (<i>n</i> = 10); F (<i>n</i> = 15)	M (<i>n</i> = 8) F (<i>n</i> = 18)	>0.5

Table shows means (except where noted; standard deviations appear in parentheses).

** Group differences tested for Hardy–Weinberg Equilibrium (larger genetics panel).

†† COMT genotype cell sizes in present sample.

‡‡ Group differences tested with one-way ANOVA.

§§ Group differences tested with chi-square.

The more frequently reinforced mouth received 30 rewards per block and the remaining 10 rewards occurred after responses to the other mouth. We used a pseudo-random reward schedule such that no more than three correct trials in a row received reinforcements. Participants never received feedback on incorrect trials. Reinforcements scheduled for incorrect trials were delayed until a later unreinforced correct trial of the same type occurred. The length (short or long) of the more frequently reinforced mouth was counterbalanced across participants. We excluded four participants from analysis for confusing the response keys (3 val/val individuals and 1 val/met individual). A post-task debriefing interview confirmed that no participants were aware of the reinforcement asymmetry. We used a standard signal detection analysis to calculate d' , a measure of discrimination accuracy [$d' = z(H) - z(F)$] and 'criterion,' the degree to which participants showed a bias towards the more frequently reinforced mouth ($c = -1/2[z(H) = z(F)]$; Heerey *et al.* 2008; Macmillan & Creelman 2005).

Balloon analogue risk task (BART)

Participants completed the BART (LeJuez *et al.* 2002) as a measure of risk-taking/reward-seeking behaviour. On each trial of the task, participants saw a coloured balloon that they could inflate by clicking a button labelled 'pump' with a mouse. For each mouse click, participants earned 5 pence, which accumulated during the trial in a temporary 'bank.' They could click as often as they liked until either the balloon burst or they chose to end the trial by clicking a button labelled 'stop'. On trials in which the balloons burst, participants forfeited all the money in the temporary bank. If participants stopped a trial before bursting the balloon, the money they earned in the trial transferred to a permanent bank for safekeeping. Participants received these earnings as a monetary bonus at the end of the task.

Balloons in the task had three strengths or thresholds for bursting (weak: 1–8 pumps; medium: 1–32 pumps; strong: 1–128 pumps), each shown in a different colour (blue, magenta and yellow). Participants received no explicit information about the different thresholds for bursting the balloons and balloon colours were randomly assigned to balloon strengths across participants.

The task consisted of four blocks: one block of 30 trials in which 10 balloons of each type appeared in random order; and three learning blocks (20 trials each) in which all the balloons were the same colour (colour blocks occurred in random order).

Results

There were no differences between men and women on any of the dependent variables, either within or across allele groups ($P > 0.23$). Results are therefore collapsed across participant gender. Correlations between age and performance were also non-significant, within and across groups ($P > 0.35$).

Reward responsiveness

We used mixed-model ANOVAs to compare d' and criterion across task blocks (1–3) using the three allele-combinations [met/met ($n = 19$), val/met ($n = 23$) and val/val ($n = 24$)] as the between-subjects variable. Participants performed the line-discrimination equally well regardless of genotype group, $F_{2,65} = 0.70$, $P = 0.40$, $\eta_p^2 = 0.01$ (Fig. 2a). Critically, results showed genotype-dependent reward-responsiveness differences, such that the met homozygotes developed greater response bias than the other allele groups, $F_{2,64} = 4.02$, $P = 0.02$, $\eta_p^2 = 0.11$ (Fig. 2b). There was also a Genotype \times Block interaction suggesting that bias towards reinforced stimuli increased over blocks, $F_{2,63} = 2.43$, $P = 0.05$, $\eta_p^2 = 0.07$, particularly at block 3, in which met homozygotes showed significantly greater response bias than the other allele groups, $F_{2,64} = 6.37$, $P = 0.003$, $\eta_p^2 = 0.17$. To illustrate this point, we determined the proportion of people in each genotype group who developed a bias towards the more frequently reinforced stimulus (coded as 'present' if there was greater bias towards the more frequently reinforced stimulus in block 3 than in block 1 and 'absent' if not). There was a linear increase in the proportion of participants developing a response bias across the allelic combinations (val/val: 29%; val/met: 47%; met/met: 63%). Together, these results show that whereas genotype does not affect perceptual sensitivity in the task as indexed by line discrimination performance, it does influence responsiveness to environmental rewards. We therefore suggest that met homozygotes' increased reward responsiveness should lead them to make riskier decisions in the pursuit of reward.

Balloon analogue risk task (BART)

Number of burst balloons, number of pumps adjusted for burst balloons and task earnings served as the dependent measures. The met homozygotes showed a riskier strategy by bursting more balloons, $F_{2,68} = 6.59$, $P = 0.002$, $\eta_p^2 = 0.16$ (Fig. 3a), but they also pumped un-burst balloons more, $F_{2,68} = 7.46$, $P = 0.001$, $\eta_p^2 = 0.18$ (Fig. 3b), and therefore earned more on each trial, $F_{2,68} = 3.21$, $P = 0.05$, $\eta_p^2 = 0.09$ (Fig. 3c). Because participants attempt to increase their payoffs with each pump, this response pattern is indicative of greater reward-seeking despite the risks involved with each successive pump of a balloon. Although

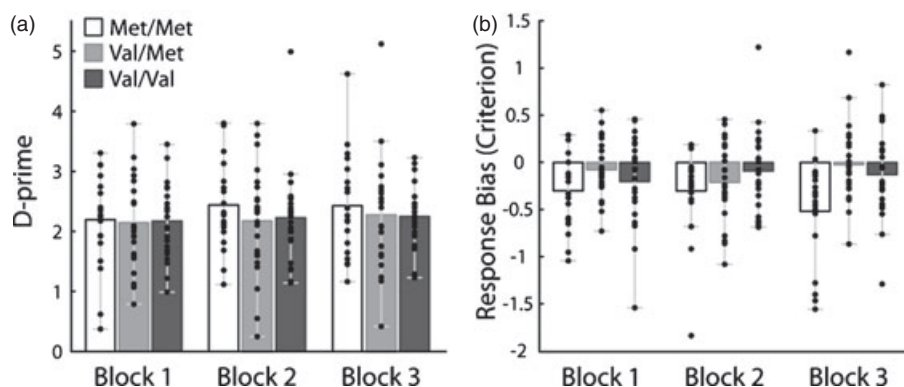


Figure 2: Reward sensitivity results. Data from 66 healthy participants (18–52 years, mean 21.6, SD ± 4.3 ; met/met $n = 19$, val/met = 23, val/val = 24). (a) There were no genotype differences in d' across task blocks. (b) Met/met participants showed significantly greater response bias than val/met or val/val groups. Error bars span $3 \times$ IQR (interquartile range).

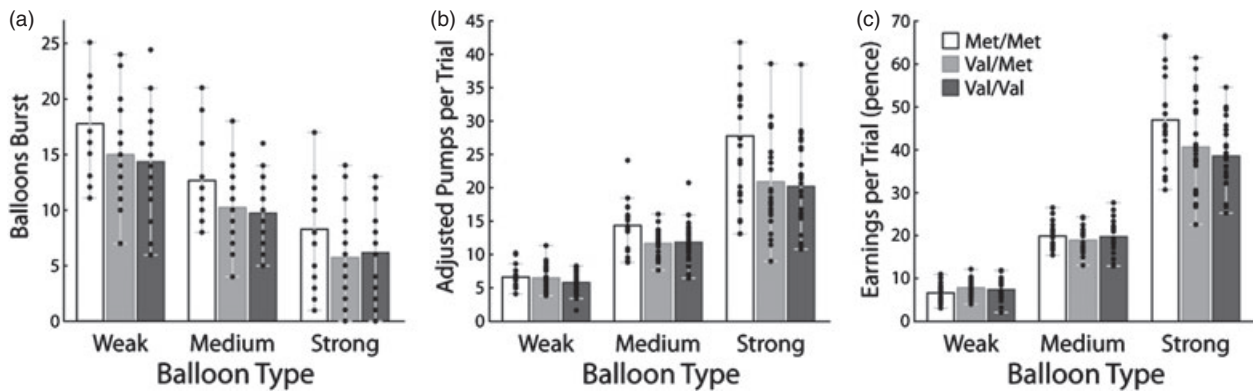


Figure 3: The BART results. (a) The met/met group burst more balloons but (b) pumped un-burst balloons more successfully, leading to (c) greater earnings. Results include 70 participants; error bars span $3 \times$ IQR (interquartile range).

the met/met participants' behaviour appeared riskier, it was advantageous, particularly as balloon strength increased. In support of this idea, there was a Genotype \times Balloon strength interaction, $F_{2,67} = 4.36$, $P = 0.002$, $\eta_p^2 = 0.12$, driven by met/met participants' higher earnings on the strongest balloons, $F_{2,68} = 4.52$, $P = 0.01$, $\eta_p^2 = 0.12$.

Cross-task correlations

We have argued that the met allele enhances the degree to which reward responsiveness motivates reward-seeking behaviour. Thus, the reward-responsiveness/reward-seeking relationship should be stronger in the met/met group than in the val/val group. To test for the presence of this predicted interaction, we performed a hierarchical regression analysis with reward-seeking as the dependent variable. Step 1 of the model included reward responsiveness and COMT genotype as the predictors and step 2 included the reward-responsiveness \times COMT genotype interaction. Results showed that over and above the main effects, the genotype \times reward-responsiveness interaction was statistically significant ($\Delta R^2 = 0.08$, $b_{\text{unstandardized}} = 6.45$, $t(62) = 2.59$, $P = 0.01$), suggesting differences in the relationship between reward-responsiveness and reward-seeking across genotype groups. To ensure that the indirect effects of reward-responsiveness on the relationship between genotype and reward-seeking did not account for this interaction, we examined a mediational model in which genotype served as the predictor variable, reward-seeking as the outcome variable and reward-responsiveness as the mediator. We used Preacher and Hayes (2004) bootstrap method for SPSS (version 19) to estimate the strength of the indirect effect. Results showed that reward-responsiveness was not a significant mediator of the relationship between genotype and reward-seeking (indirect effect = -0.76 ; $SE = 0.53$; $CI_{95\%} = -1.79$ to 0.28 ; $z = -1.43$; $P = 0.15$). (We thank an anonymous reviewer for suggesting this analysis).

To examine these differences more closely, we computed the correlation between reward responsiveness and reward-seeking within genotype groups, transformed these to z-scores using Fisher's r to z transformation, and examined

differences in the strength of the relationship between the met/met and val/val groups. For ease of interpretation, we reversed the direction of the bias effect so that participants who showed greater bias towards the more frequently reinforced stimulus had positive scores (rather than the negative scores originally calculated) by multiplying participants' block-3 response bias scores by -1 . Reward-sensitivity significantly predicted reward-seeking in the met/met group (Burst-Balloons: $r = 0.54$, $P = 0.02$; Adjusted-Pumps: $r = 0.47$, $P = 0.04$; Fig. 4), but not in either of the other groups (Val/Met: Burst-Balloons, $r = 0.17$, $P = 0.43$; Adjusted-Pumps, $r = 0.30$, $P = 0.16$; Val/Val: Burst-Balloons, $r = -0.16$, $P = 0.48$; Adjusted-Pumps, $r = -0.02$, $P = 0.92$). However, as anticipated, we found significant differences between the met/met and val/val groups in the strength of the relationship between reward responsiveness and reward-seeking (Burst-Balloons: $z = 2.31$, $P_{\text{one-tailed}} = 0.01$; Adjusted-Pumps: $z = 1.60$, $P_{\text{one-tailed}} = 0.05$), suggesting that reward responsiveness motivates reward-seeking more strongly among met/met than among val/val participants.

Discussion

Here, we show that a common genetic variant (val158met, rs4680), hypothesized to alter cortico-striatal dopamine dynamics (Bilder *et al.* 2004; Meyer-Lindenberg *et al.* 2005), predicts reward responsiveness during asymmetric reinforcement and sequential risk-taking. This complements previous pharmacological and radioligand imaging evidence suggesting that modulation of dopamine influences response to reward (Pizzagalli *et al.* 2008a; Santesso *et al.* 2009; Vrieze *et al.* 2011) and hints at a link between the COMT genotype and dopamine function in humans. In the BART, met/met participants were more willing to take calculated risks when rewards were attainable. The degree to which they did so related to the development of response bias under an asymmetric reinforcement schedule. This was not the case for val/met or val/val groups. The genotype \times reward-responsiveness interaction in our data suggests that available rewards may motivate reward-seeking more

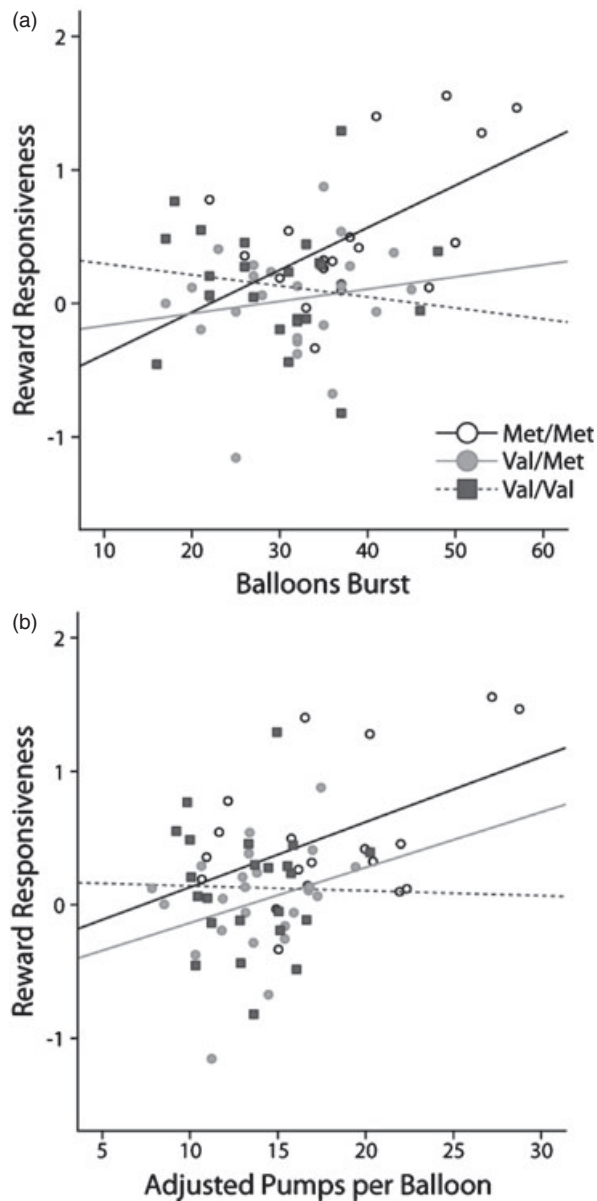


Figure 4: Correlations between reward responsiveness and reward-seeking across genotype groups. (a) Total burst balloons; (b) average adjusted pumps per balloon.

strongly for met/met than for other participants, perhaps because met/met individuals experience rewards as more pleasant (Wichers *et al.* 2008).

These findings suggest that enhanced reward responsiveness may be a unifying mechanism underlying previously documented val158met differences in reinforcement learning (Frank *et al.* 2007), motivated decision-making (Frank *et al.* 2009) and neural responses to reinforcement (Dreher *et al.* 2009; Marco-Pallares *et al.* 2009). Specifically, the met/met participants' increased reward responsiveness may have heightened their motivation to seek to available rewards,

as their decisions, although riskier (Amstadter *et al.* 2012), also proved more financially rewarding. Thus, we argue the met/met group displayed 'functional impulsivity' (Dickman 1990), in the extent to which they adjusted task performance to optimize their rewards. The association between reward responsiveness and advantageous reward-seeking in the met/met group suggests that the magnitude of reward representation may modulate the degree to which people learn to maximize environmental rewards (Sapra *et al.* 2012). Indeed, research suggests that met/met individuals adapt to task contingencies more flexibly (Frank *et al.* 2007), a finding that resonates with the present study's results.

Together, these results suggest that enhancing reward-responsiveness is one way in which the COMT genotype exerts its effect on a broad range of tasks with inherent feedback, motivation and reward components. We therefore hypothesize that increased ability to adjust behaviour based on trial outcomes is the missing link between COMT and its general cognitive performance effects. A number of the behavioural assays that demonstrate COMT genotype differences are executive function tasks in which performance feedback serves as a motivational incentive, even in the absence of explicit reward (Barnett *et al.* 2007; Barnett *et al.* 2008; Jimura *et al.* 2010; Aarts *et al.* 2011). Individuals with the met/met variant may outperform those with other variants simply because they are more motivated to maximize intrinsic and extrinsic rewards.

Insofar as the COMT genotype modulates the tonic-phasic dopamine balance as researchers suggest (Bilder *et al.* 2004), it may increase incentive-driven 'proactive control' over rewarded stimuli (Jimura *et al.* 2010). Our data support this theory by demonstrating that the COMT genotype does not influence basic perceptual sensitivity but does influence reward responsiveness. If dopamine does indeed modulate cognition/motivation dynamics as research suggests (Aarts *et al.* 2011; Rogers 2011), our results imply that COMT may modulate the link between cognition and motivation. The stability of the reward-related behaviour for the met/met individuals across both tasks, along with the consistency and directional effects of the COMT variant suggest that the val158met polymorphism may modulate a neurobiological platform by which individuals interpret and respond to rewarding stimuli.

Finally, we note that recent work (Barnett *et al.* 2008; Chabris *et al.* 2011) has highlighted concerns about false positive associations in behavioural genetics studies. We have minimized such risks by testing only pre-defined genetic hypotheses (COMT's effect on reward responsiveness and reward-seeking). In addition, we demonstrate consistent performance across both tasks and carefully embed our findings in an extensive context of previous neurobiological and behavioural work. Although our sample size is small (particularly in the met/met group), given the strength and stability of our findings and the degree to which they follow from previous literature, we suggest that our results are reliable. Nonetheless, these results do require independent replication.

There are two additional limitations to the study. First, although our participants were screened for illegal substance use, we did not assess their nicotine use, which relates

to risk-taking behaviour on the BART (LeJuez *et al.* 2003). However, based on their ages and education levels, we do not have reason to suspect that our groups differed in smoking behaviour (Office for National Statistics, Great Britain, 2010), meaning that it is unlikely that smoking explains the genotype differences. Second, although we did not explicitly control IQ across the groups, participants were all intermediate or advanced university students, suggesting that they possess average or better intelligence. Intelligence quotient (IQ), however, has not been shown to correlate with performance on the BART (LeJuez *et al.* 2002), or other measures of reward responsiveness (Luman *et al.* 2005). Therefore, it is unlikely that IQ discrepancies caused the genotype-dependent differences in this study.

In sum, this study validates several hypothesized associations between the COMT val158met genotype and dopamine-related reward responding. Specifically, results demonstrate robust and specific COMT genotype-dependent reward focus in laboratory tasks and potentially in the broader environment. Indeed, understanding the association between the COMT locus and reward responsiveness/reward-seeking may also help explain COMT's involvement in neuropsychiatric disorders characterized by decision-making deficits (Docherty & Sponheim 2008; Langley *et al.* 2010; Paloyelis *et al.* 2010) as well as the genetic contributions towards heritable symptoms states associated with these disorders (Anokhin *et al.* 2009; Bogdan & Pizzagalli 2009).

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