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Replication study implicates *COMT* val158met polymorphism as a modulator of probabilistic reward learning

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Previous studies suggest that a single nucleotide polymorphism in the catechol-O-methyltransferase (*COMT*) gene (val158met) may modulate reward-guided decision making in healthy individuals. The polymorphism affects dopamine catabolism and thus modulates prefrontal dopamine levels, which may lead to variation in individual responses to risk and reward. We previously showed, using tasks that index reward responsiveness (measured by responses bias towards reinforced stimuli) and risk taking (measured by the Balloon Analogue Risk Task), that *COMT* met homozygotes had increased reward responsiveness and, thus, an increased propensity to seek reward. In this study, we sought to replicate these effects in a larger, independent cohort of Caucasian UK university students and staff with similar demographic characteristics ($n = 101$; 54 females, mean age: 22.2 years). Similarly to our previous study, we observed a significant trial × *COMT* genotype interaction ($P = 0.047$; $\eta^2 = 0.052$), which was driven by a significant effect of *COMT* on the incremental acquisition of response bias [response bias at block 3 − block 1 (met/met > val/val: $P = 0.028$) and block 3 − block 2 (met/met > val/val: $P = 0.007$)], suggesting that *COMT* met homozygotes demonstrated higher levels of reward responsiveness by the end of the task. However, we failed to see main effects of *COMT* genotype on overall response bias or risk-seeking behaviour. These results provide additional evidence that prefrontal dopaminergic variation may have a role in reward responsiveness, but not risk-seeking behaviour. Our findings may have implications for neuropsychiatric disorders characterized by clinical deficits in reward processing such as anhedonia.

Keywords: Anhedonia, BART, *COMT*, dopamine, genetics, prefrontal, reward responsiveness, reward seeking, signal detection, val158met

Reward and the representation of value play important roles in cognition (Jimura *et al.* 2010; Satterthwaite *et al.* 2012). Understanding the mechanisms that underpin risk, reward and value are of fundamental importance when exploring psychopathology characterized by deficits in reward processing. Dopaminergic frontostriatal circuitry is a candidate neurobiological pathway that may link reward representation with rewarding stimuli (Aarts *et al.* 2010, 2011). Individual differences in these processes may be explained in part by common variation in genes that orchestrate dopamine catabolism [catechol-O-methyltransferase (*COMT*)], reuptake [dopamine transporter (*DAT1*)], receptor binding [dopamine receptors 2 and 4 (*DRD2* and *DRD4*)] and intracellular signal transduction [dopamine- and cAMP-regulated neuronal phosphoprotein (*DARPP32*)]. These genes harbour variants that may affect the dopaminergic tone associated with reward processing (Frank *et al.* 2007; Rogers 2011). Common genetic variants with putative effects on dopaminergic tone have been linked to differences in task adaptation (Frank *et al.* 2007; Krugel *et al.* 2009) and exploratory behaviour during learning (Frank *et al.* 2009), and it has been further suggested that they may facilitate an interaction between reward and cognition (Nymberg *et al.* 2014). The val158met polymorphism on the *COMT* gene has been widely studied as it affects the efficiency of the gene product (the *COMT* enzyme) and thus synaptic dopamine levels (Chen *et al.* 2004).

A large population study has suggested 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). We have also previously reported that the *COMT* val158met locus may be associated with reward responsiveness (Lancaster *et al.* 2012). In this study, the met homozygotes (those with putatively higher prefrontal dopamine) demonstrated increased reward responsiveness. We further showed that this association led to a beneficial increase in risky decision making on the Balloon Analogue Risk Task (BART), in which the met homozygotes were more sensitive to rewards, allowing them to benefit from the rewards available during the task to a greater degree than participants with val/met and val/val genotypes. Exaggerated risky decision making by *COMT* met homozygotes during the BART has also been reported by other researchers (Amstadter *et al.* 2012). In this study,

Table 1: Demographics for the whole sample ($n = 101$), collapsed across sample sites

COMT rs4680	met/met	val/met	val/val	*P*
Hardy–Weinberg equilibrium	25	56	20	0.321*
Age	21.28 ± 3.84	22.37 ± 5.68	23.00 ± 4.49	0.502†
Gender (M/F)	10/15	26/30	11/9	0.606‡

*Denotes HWE (Hardy–Weinberg equilibrium).
†Group differences tested with one-way ANOVA.
‡Group differences tested with χ^2 test.

we sought to replicate our findings in a larger, independent cohort. We anticipated that the *COMT* met homozygotes would have a higher propensity to respond to rewarding stimuli. In line with our previous observations, we further hypothesized that the *COMT* genotype would modulate the association between reward responsiveness and individual differences in risk taking.

Materials and methods

Participants

We recruited 68 participants from Bangor University and 33 participants from Cardiff University (all participants where staff and students with +15 years education). All participants were Caucasian and of western European descent. Table 1 describes the demographic data for the combined sample ($n = 101$), stratified by *COMT* val158met genotype group. The mean age and gender distributions of the sample are comparable to our previous study (Lancaster *et al.* 2012). No participants had a history of psychiatric or neurological illness. All participants gave informed consent to the study protocol that was approved by the ethics panels of Bangor University and Cardiff University.

Genotyping

Bangor site

Genomic DNA was obtained from saliva using Oragene OG-500 saliva kits (DNA Genotek Inc, Ontario, Canada) for 68 participants. Genotyping of rs4680 (*COMT* val158met) was performed using the Illumina GoldenGate assay (Illumina, Inc., San Diego, CA, USA) using the BeadXpress platform, which allows high-throughput multiplex genotyping of SNPs. Assays were designed for the experiment using Illumina's Assay Design Tool (http://support.illumina.com/array/array_software/assay_design_tool.ilmn). Nucleic acid concentration was evaluated using PicoGreen assay (Life Technologies, Carlsbad, CA, USA). Golden Gate genotyping was performed according to the manufacturer's protocols. Genotype calling and annotation were performed using GenomeStudio (Illumina, Inc.).

Cardiff site

Genomic DNA was obtained from saliva using Oragene OG-500 saliva kits for 37 participants. *COMT* val158met (rs4680) was genotyped using custom SNP genotyping arrays from Illumina (Illumina, Inc.). Quality control was implemented in PLINK (Purcell *et al.* 2007), to ensure genotypes did not display ambiguous sex, cryptic relatedness up to third-degree relatives by identity of descent, genotyping completeness < 97% and non-European ethnicity admixture detected as outliers in iterative EIGENSTRAT analyses of an LD-pruned dataset (Price *et al.* 2006). *COMT* val158met was above 98% call rate. After quality control, 33 of the 37 individuals included in the sample had genotype data available for *COMT* val158met (rs4680).

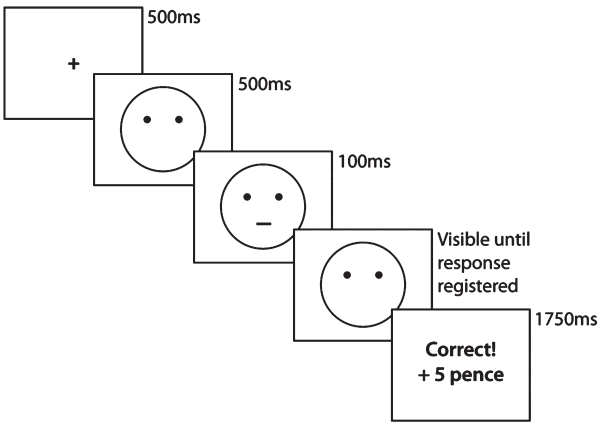

Figure 1: Trial timeline for a 'feedback trial' in the reward responsiveness paradigm.

Reward responsiveness

To measure reward responsiveness, we used a line discrimination task with asymmetric reinforcement, closely modelled after those previously described (Heerey *et al.* 2008; Lancaster *et al.* 2012; Pizzagalli *et al.* 2005). 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 an individual's propensity to choose the stimulus that is more frequently reinforced (Macmillan & Creelman 2005). Individuals who develop greater levels of standard deviation (SD) have higher levels of reward responsiveness. 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. Participants then responded with a left or right button press on a keyboard to indicate which mouth they had seen. Following the response, participants saw a screen that either displayed feedback (Correct! + 5 pence) or remained blank (no-feedback trials) for 1750 milliseconds (see 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. 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. 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 response bias (criterion), the degree to which participants showed a bias towards the more frequently reinforced mouth [$c = -1/2[z\ (H) = z\ (F)]$], as previously described (Heerey *et al.* 2008; Lancaster *et al.* 2012)]. During quality control, we excluded two participants with a mean discrimination accuracy that fell ±3 SD outside the mean [$n = 1$ (met/met), $n = 1$ (val/met)] and one participant for whom mean response bias (criterion) fell ±3 SD outside the mean [$n = 1$ (val/met)]. Including these three participants into the statistical analysis did not significantly affect any of the genetic results.

Balloon Analogue Risk Task

Participants completed the BART (Lejuez *et al.* 2002) as a measure of risk-taking 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). There were no outliers in adjusted pumps, average number of burst balloons or earnings.

Statistical analyses

To account for potential demographics effects, we first tested associations between demographics and behavioural parameters, and entered these as covariates into the *COMT* genotype analysis where appropriate. As *COMT* val158met effects on *COMT* enzyme activity may be sexually dimorphic and affected by age (Chen *et al.* 2004; Tunbridge *et al.* 2007), we included age and sex as covariates in mixed-model analysis of covariance (ANCOVA) that investigated *COMT* genotype effects on discriminability and response bias. *COMT* effects on individual BART measures were computed using one-way ANCOVA (controlling for age and gender). On the basis of our prior work (Lancaster *et al.* 2012), we anticipated to see genotype differences driven specifically by the *COMT* met homozygotes, so we employed both an additive (all three groups explored separately: met/met > val/met > val/val) and a recessive (comparing the met homozygotes to individuals with at least one val allele: met/met > val/met and val/val) genetic models to explore *COMT* effects on reward responsiveness and the BART. Statistical analyses were performed in R (version 3.0.2; http://cran.r-project.org/). Power calculations were performed in the 'pwr' package (version 1.1-2) (Champely 2012). We carried forward the effect sizes (Cohen's d) from our previous study (comparing met homozygotes to val homozygotes) for reward responsiveness (mean response bias: $d = 0.50$, block 3 response bias: $d = 0.75$) and for the BART (adjusted pumps: $d = 0.76$, burst balloons: $d = 0.73$ and total earnings: $d = 0.51$). When we compared the homozygote groups (met/met > val/val) in this study, we had between 37% and 69% power to detect an effect on our measures ($\alpha = 0.05$). When we employed a recessive genetic model (met/met > val/met and val/val) we had between 59% and 90% power to detect an effect on our measures ($\alpha = 0.05$).

Results

Demographic effects on reward responsiveness

There was a sample site difference in mean discrimination accuracy ($F_{1,96} = 4.001$, $P = 0.048$), so sample site was entered as a covariate into a mixed-model ANCOVA to explore *COMT* val158met genotype differences in discrimination accuracy. There were no sample site differences in mean response bias ($F_{1,96} = 0.339$, $P = 0.561$) so samples were combined to investigate *COMT* genotype effects. There were no associations between age and mean discrimination accuracy ($t_{96} = 1.660$, $P = 0.100$) or mean response bias ($t_{96} = 0.063$, $P = 0.525$). There were no gender differences in mean discrimination accuracy ($F_{1,96} = 0.130$, $P = 0.718$) or mean response bias ($F_{1,96} = 0.240$, $P = 0.624$).

Demographic effects on BART

There were no sample site differences in adjusted pumps ($F_{1,96} = 2.648$, $P = 0.107$), average number of burst balloons ($F_{1,96} = 0.045$, $P = 0.831$) or earnings across the trial ($F_{1,96} = 0.159$, $P = 0.692$) and where therefore combined. There were no associations between age and adjusted pumps ($t_{96} = -0.75$, $P = 0.123$), average number of burst balloons ($t_{96} = -1.821$, $P = 0.071$) or earnings across the trial ($t_{96} = 0.241$, $P = 0.809$). There were no gender differences in adjusted pumps ($F_{1,96} = 0.599$, $P = 0.440$), average number of burst balloons ($F_{1,96} = 0.141$, $P = 0.522$) or earnings across the trial ($F_{1,96} = 0.095$, $P = 0.757$).

Reward responsiveness and COMT *val158met*

Mixed-model ANCOVAs (controlling for sample site, age and gender) suggested that discrimination accuracy did not change across trial blocks ($F_{2,184} = 0.862$, $P = 0.424$). There was no main effect of *COMT* val158met (rs4680) on mean discrimination accuracy in the additive ($F_{2,94} = 0.937$, $P = 0.395$) or recessive ($F_{1,95} = 0.525$, $P = 0.471$) genetic models. There were also no significant interactions between trial block and *COMT* val158met genotype (additive: $F_{4,190} = 1.569$, $P = 0.184$; recessive: $F_{2,192} = 0.392$, $P = 0.676$) (see Fig. 2a). We observed a main effect of response bias, where participants' propensity to choose reinforced rewards increased over the task ($F_{2,194} = 4.164$, $P = 0.021$), which was driven by an incremental increase in response bias from block 1 to block 3 ($P = 0.015$) and from block 2 to block 3 ($P = 0.041$), replicating previous work (Heerey *et al.* 2008; Pizzagalli *et al.* 2005). Mixed-model ANCOVAs (both controlling for age and gender) were then used to determine *COMT* effects on response bias. Unlike in our previous study, we found no main effect of *COMT* val158met on mean response bias in either the additive or recessive genetic model (additive: $F_{2,94} = 0.591$, $P = 0.556$; recessive: $F_{1,95} = 0.176$, $P = 0.675$). Critically however, as in our previous study, we found significant task block × *COMT* val158met genotype interaction in both genetic models (additive: $F_{4,190} = 2.507$, $P = 0.047$, $\eta^2 = 0.052$, see Fig. 2b and recessive: $F_{2,192} = 3.511$, $P = 0.037$, $\eta^2 = 0.036$). *Post hoc* pairwise comparisons showed that this interaction was driven by increased reward responsiveness in met homozygotes compared to val homozygotes in the third block of the task (met/met > val/val:

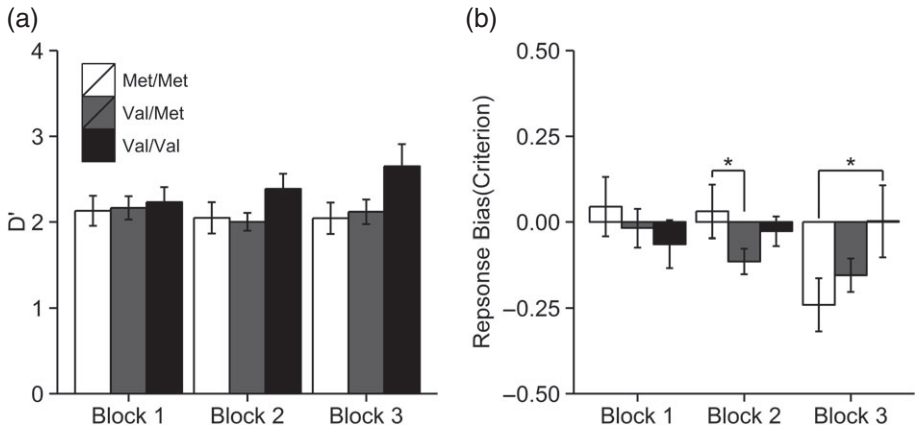

Figure 2: Bar plots represent mean ± SEM. (a) Discrimination accuracy (D') and (b) response bias (criterion) stratified by *COMT* val158met genotype across the three trial blocks. There were no significant differences in D' between *COMT* val158met genotype groups across any of the trial blocks ($P > 0.05$ in all cases). There was a significant interaction between *COMT* val158met genotype and trial block, where met homozygotes showed a significant in response bias towards the last block of the trial (*$P < 0.05$). Smaller values for criterion represent an increase in response bias.

$P = 0.036$, Cohen's $d = 0.57$), suggesting that the met homozygotes group showed an increased propensity to adjust behaviour based on prior rewarding contingencies.

This observation was supported by independent sample *t*-test that showed incremental reward bias (Δresponse bias: block 3 response bias − block 1 response bias) was significantly higher in met homozygotes compared to the val homozygotes (met/met > val/val: $P = 0.015$, Cohen's $d = 0.76$, see Fig. 3a). We validated this critical finding using Bayesian estimation (BEST; Kruschke 2013) and observed significant mean credible differences in response bias between met homozygotes compared to val/val homozygotes (mean difference: −0.299; 95% highest density interval, HDI [−0.594|−0.014]) but no credible mean differences between met/met and val/met (mean difference: −0.158; 95% HDI [−0.337|0.032]) or between val/met heterozygotes and val homozygotes (mean difference: −0.025; 95% HDI [−0.231|0.180]). Mean credible differences occur when the 95% HDI (highest density interval) does not cross zero. Furthermore, change in response bias (block 3 response bias − block 2 response bias) was significantly higher in met homozygotes compared to both val/met heterozygotes ($P = 0.011$) and val homozygotes ($P = 0.007$) (see Fig. 3b). Descriptive statistics for the discrimination accuracy and criterion means between *COMT* val158met genotype groups is provided in Table 2.

COMT val158met and BART

Unlike in our previous study, the present data did not show an effect of *COMT* val158met on risky decision-making parameters including number of adjusted pumps ($F_{2,95} = 1.822$, $P = 0.167$), popped balloons ($F_{2,95} = 0.961$, $P = 0.386$) or total earnings throughout the task ($F_{2,95} = 0.165$, $P = 0.848$), all controlling for age and gender. Descriptive statistics for all BART-derived measures between *COMT* val158met genotype groups is provided in Table 3.

COMT genotype and cross-task correlations

As we did not see any effects of the *COMT* genotype on risk-seeking behaviour, we did not anticipate seeing genotype-specific associations between reward responsiveness and risk-seeking behaviour. We found no difference in the associations between reward responsiveness (response bias at accumulated block 3: see Lancaster *et al.* 2012) and risk-seeking behaviour between the *COMT* val158met genotype groups (adjusted pumps: $t = 0.419$, $P = 0.676$; burst balloons: $t = 0.520$, $P = 0.604$).

Discussion

We did not see a main effect of *COMT* val158met on response bias (criterion) or risk taking on the BART. However, we replicated one of our previous findings suggesting that *COMT* met homozygotes show an increased propensity to accrue response bias during asymmetric reinforcement compared to val homozygotes. This finding suggests that the *COMT* val158met variant may be associated with a neurobiological mechanism responsible for reward processing. Response bias in the probabilistic reward task may reflect both (1) reward responsiveness and (2) learning rate (Huys *et al.* 2013), so the *COMT* val158met-related incremental differences in response bias could potentially reflect influences of genotype on either or both of these constructs. Preliminary evidence suggests that reward responsiveness is moderately heritable (Bogdan & Pizzagalli 2009) and is disrupted during stress and in neuropsychiatric disorders such as bipolar disorder and major depression (Berghorst *et al.* 2013; Bogdan *et al.* 2013; Pechtel *et al.* 2013; Pizzagalli *et al.* 2005, 2007, 2008a,b; Vrieze *et al.* 2013b). Accumulating evidence also suggests that reward responsiveness has a dopaminergic basis (Lancaster *et al.* 2012; Vrieze *et al.* 2013a). Replication studies such as the present investigation are essential for the understanding of individual differences

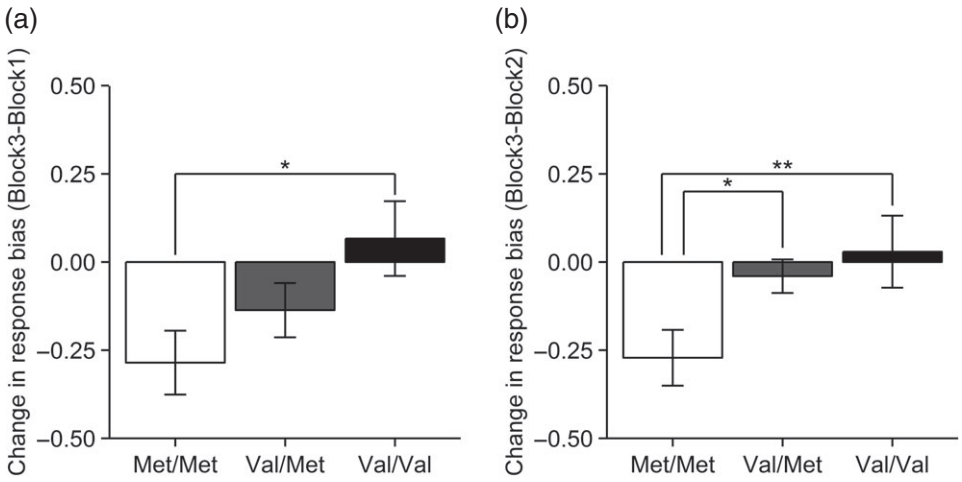

Figure 3: Bar plots represent mean ± SEM. *COMT* val158met genotype differences in propensity for change in response bias (change in response bias: block 3 criterion − block 1 criterion). *COMT* met homozygotes show a significant adjustment in response bias from (a) block 1 to block 3 of the trial compared to val/val genotype group and from (b) block 2 to block 3 of the trial compared to both val/met and val/val genotype groups ($*P < 0.05$, $**P < 0.01$). Smaller values for criterion represent an increase in response bias.

Table 2: Descriptive statistics for all individuals ($n = 98$) who completed the reward responsiveness task

COMT	Block 1	Block 2	Block 3
Discrimination accuracy (D')			
met/met	2.130 ± 0.861	2.048 ± 0.893	2.043 ± 0.897
val/met	2.164 ± 1.000	2.002 ± 0.764	2.119 ± 1.055
val/val	2.232 ± 0.783	2.386 ± 0.787	2.651 ± 1.152
Response bias (criterion)			
met/met	0.0447 ± 0.4253	0.0310 ± 0.3817	−0.2406 ± 0.3804
val/met	−0.0177 ± 0.4091	−0.1141 ± 0.2741	−0.1542 ± 0.3590
val/val	−0.0640 ± 0.3104	−0.0267 ± 0.1903	0.0025 ± 0.4668

COMT val158met genotype group mean ± SD for each task block for (1) discrimination accuracy (D') and (2) response bias (criterion). For response bias, negative numbers reflect a greater propensity to choose the stimuli that were reinforced more often during the task.

Table 3: Descriptive statistics for all individuals ($n = 98$) who completed the Balloon Analogue Risk Task (BART)

COMT	Adjusted pumps	Burst balloons	Earnings
met/met	14.515 ± 2.899	11.236 ± 2.555	4013.958 ± 602.881
val/met	14.902 ± 3.209	11.346 ± 3.300	4046.574 ± 608.823
val/val	16.526 ± 6.043	12.433 ± 4.857	3951.250 ± 867.909

COMT val158met genotype group mean ± SD for each of (1) the average number of successful balloon pumps per trial (adjusted pumps), (2) the number of burst balloons across all trials (burst balloons) and (3) the grand total of points accumulated across the whole task (earnings).

in reward processing that may contribute to neuropsychiatric symptomatology.

Limitations

We acknowledge that the sample size is modest for a genetic study, a caveat that may increase incidence of false positives and artificially inflate effect sizes in behavioural genetic studies (Barnett *et al.* 2007; Wardle *et al.* 2013). We also acknowledge that our study was under-powered to detect all the effects we anticipated, although we had adequate power to detect the effect of *COMT* genotype on response bias at block 3 (68–89%, $\alpha = 0.05$). The variance explained (η^2) by the *COMT* genotype × trial block interaction was similar between our initial and present study (7% and 5% variance explained, respectively), although effect sizes may reduce in larger samples (Button *et al.* 2013). In light of the negative findings and limited power, we suggest that these results are still treated with caution until replicated in larger population studies. However, we would suggest that there is accumulating evidence to support the claim that *COMT* val158met variant influences reward processing. Several studies have documented pleiotropic effects of *COMT* genotype on brain function (Mier *et al.* 2010), specifically on reward- and learning-related parameters (Farrell *et al.* 2012; Katz *et al.* 2015; Wichers *et al.* 2008). We also note that Goetz *et al.* (2013) did not find

an effect of *COMT* val158met on reward responsiveness in a sample of 59 participants, although the raw data (mean ± SD) from this study (see Goetz *et al.* 2013; Table 2) suggests that met homozygotes group had higher response bias [met/met ($n = 14$) = 0.16 ± 0.18] compared to val/met [($n = 28$) = 0.11 ± 0.14] and val/val [($n = 17$) = 0.11 ± 0.15] groups [met/met > val: Cohen's $d = 0.32$ (95% CI = −0.277 to 0.928)], which points in the same direction as our findings. We did not replicate any of the associations between BART measures of risk seeking and *COMT* val158met from our previous study. However, findings similar to our previous study (Lancaster *et al.* 2012) have been observed in larger, independent samples (Amstadter *et al.* 2012). Similar to our initial study, Amstadter *et al.* showed that propensity for *COMT* met homozygotes to complete more successful balloon pumps (although this was exclusively observed in females, in a younger sample). We therefore suggest that future studies should examine interactions between *COMT* val158met genotype groups, the reward response and other sample characteristics that may mediate such effects. It is also worth noting that most studies converge to show effects of the *COMT* genotype on one or several aspects of reward processing, and that, for phenotypes downstream from the molecular effect (the altered dopamine levels), replication may not always entail modification of identical behavioural parameters.

Conclusions and future directions

The neurobiological pathways that link dopaminergic genetic variation to reward responsiveness are beginning to emerge. For instance, several studies now suggest that genetic variation in *COMT* may affect an individual's propensity to discount larger, future rewards (Gianotti *et al.* 2012; Kelm & Boettiger 2013; Paloyelis *et al.* 2010; Smith & Boettiger 2012). Understanding how dopaminergic genetic variation contributes to risk, reward responsiveness and value representation may help in the understanding of psychopathological traits characterized by deficits in reward processing. Recent developments in translational research may also allow us to model mechanisms of reward responsiveness using animal models (Der-Avakian *et al.* 2013). We also suggest that pharmacological intervention using *COMT* inhibitors may also help to elucidate the mechanisms by which variation in prefrontal dopamine may affect reward responsiveness, as previously seen for other reward or learning parameters (Farrell *et al.* 2012; Kayser *et al.* 2014). Understanding the genetic mechanisms that underpin reward responsiveness will also help to understand susceptibility for neuropsychiatric illness. We suggest that genetic risk variants that confer risk to disorders such as bipolar disorder may also have a role in modulating reward responsiveness in healthy individuals (Lancaster *et al.* 2014), and thus, understanding the genetic architecture that supports reward responsiveness may shed light on the neurobiological mechanisms of clinical symptoms such as anhedonia. Although *COMT* val158met may not be formally identified as a risk variant for these disorders, it could be associated with clinical traits mechanistically linked to the disorders (Docherty & Sponheim 2008; Paloyelis *et al.* 2010).

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