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The mediating effect of prefrontal asymmetry on the relationship between the *COMT* Val[158]Met SNP and trait consummatory positive affect

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The Val[158]Met rs4680 polymorphism in the *COMT* gene regulates dopamine catabolism in the prefrontal cortex (PFC). Dopamine's involvement in reward experience suggests those with the methionine (Met) variant may exhibit trait-level sensitivity to reward due to more post-synaptic dopamine in the PFC. A physiological mediator of this association may be greater relative left asymmetry in the PFC, a putative biomarker for trait positive emotionality. Electroencephalograms of 120 participants were measured during a task that assesses two aspects of reward processing: pre-reward anticipation and post-reward consummatory affect. Participants provided genetics samples and completed the Temporal Experience of Pleasure Scale (TEPS), which assesses trait-level anticipatory and consummatory positive affect. Met carriers had higher TEPS-Consummatory scores. This effect was mediated by greater relative left activation in the post-reward phase of the task. No effects were observed for the pre-reward phase. Results suggest that frontal asymmetry is an endophenotype between *COMT* genotype and trait reward responsivity.

Keywords: COMT; Consummatory positive affect; EEG; Reward processing; Dopamine.

One of the major functions of dopamine is to mediate reward-related processing in the prefrontal cortex (PFC; Miller, 2000). For example, dopaminergic neurons in the ventral tegmental area of the midbrain that innervate the PFC may generate action potentials in response to unpredicted rewards (Haber & Fudge, 1997; Mirenowicz & Schultz, 1994, 1996; Williams & Goldman-Rakic, 1993). It is noteworthy that with more exposure to a particular reward, these neurons fire in response to cues that predict reward, rather than the reward itself (Schultz, 1998). The evidence for dopamine's action

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before and after receipt of reward makes it unclear if dopamine is primarily associated with anticipation of reward, consummation of reward or both processes (Wise, 2004), and there have been many shifts in the view of dopamine's role in reward processing (Berridge, 2007).

Dopamine's role in reward processing may be moderated by the amount of dopamine transmitted by neurons in the PFC. Many genes affect dopamine transmission in the brain, including the *COMT* gene. *COMT* codes for catechol-*O*-methyltranferase (COMT), an enzyme that degrades extracellular dopamine in the synapse (Männistö & Kaakkola, 1999). Most importantly, variability in this gene contributes to differential efficiency of this enzyme. One allelic variant in *COMT*, Val^{158}Met, is a single-nucleotide polymorphism (SNP) that replaces guanine with adenine, which results in an amino acid change from valine (Val) to methionine (Met) at codon 158. This change yields a more thermally unstable form of COMT, resulting in significantly lower enzymatic activity in the PFC (Chen et al., 2004; Lachman et al., 1996). Thus, individuals with the methionine allele have higher levels of synaptic dopamine in their PFC, resulting in more dopaminergic stimulation of post-synaptic neurons.

Given that the effect of this polymorphism on the amount of synaptic dopamine in the brain is fairly well understood, studies have also examined its psychological and behavioural associations. For example, there is evidence that people with the Met variant exhibit significantly higher reward responsiveness and reward-seeking behaviour during reward tasks and report higher subjective ratings of pleasure in response to positive events than those with the Val polymorphism (Lancaster, Linden, & Heerey, 2012; Wichers et al., 2007).

The positive affect associated with reward has two phases: anticipatory positive affect (APA) and consummatory positive affect (CPA). APA is experienced pre-reward and reflects motivation and/or a desire for a stimulus, whereas CPA occurs post-reward and reflects the in-the-moment experience of pleasure or the hedonic effect of a stimulus. The two affective states also parallel Berridge and Robinson's (2003) distinction between "wanting" and "liking" and have been further delineated by Klein (1974; see also Sherdell, Waugh, & Gotlib, 2012), who described the clinical impact of deficits in APA versus CPA in subtypes of depression.

Although APA and CPA both occur during reward processing, people vary on how much APA and CPA they experience during each phase. Gard, Gard, Kring, and John (2006) developed a self-report inventory to measure individual differences in trait-level APA, CPA and overall experiences of pleasure, the Temporal Experience of Pleasure Scale (TEPS). Studies with the TEPS suggest that the three subscales correlate with each other; but nevertheless demonstrate discriminant validity in their association with other measures of personality and in distinguishing various psychopathologies (Chan et al., 2010; Favrod, Ernst, Giuliani, & Bonsack, 2009; Gard, Kring, Gard, Horan, & Green, 2007; Gard et al., 2006; Strauss, Wilbur, Warren, August, & Gold, 2011).

Given that dopamine is a key neurotransmitter involved in reward processing, individual differences in dopamine levels in the brain might predict individual differences in APA and/or CPA. One way to investigate this question is to examine whether *COMT* genotype predicts scores on the TEPS. If people with the Met allele, who have less COMT enzymatic activity, regularly retain more dopamine in their PFC, their subjective ratings of APA and/or CPA would be hypothesised to be higher than those with the Val allele.

However, because the subjective experiences of APA and CPA occur quite downstream from the *COMT* genotype, it is important to consider physiological mediators of this relationship (Sanislow et al., 2010) or endophenotypes (Gottesman & Gould, 2003). A potential endophenotype of reward processing is asymmetric ~~EEG~~ activity in the PFC (Stewart, Bismark, Towers, Coan, & Allen, 2010). For several decades, affective scientists have theorised that asymmetric activity in the frontal brain reflects differences in affective reactivity (e.g., Davidson, 2004; Shankman & Klein, 2003). Specifically, a pattern of greater relative left activity recorded during a resting state has

repeatedly been associated with approach-related tendencies as observed in behavioural tasks (Tomarken, Davidson, & Henriques, 1990), self-report (Sutton & Davidson, 1997; Wheeler, Davidson, & Tomarken, 1993) and reward-learning tasks (Pizzagalli, Sherwood, Henriques, & Davidson, 2005). Deviation from this resting pattern of prefrontal asymmetry may also be a biological marker of an affective style that predisposes individuals to major depression (Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990).

EEG asymmetry has typically been recorded during a resting state, but recently, researchers have argued that it yields better associations with affective style if it is recorded *during* appetitive and other emotional tasks (Coan, Allen, & McKnight, 2006; Dennis & Solomon, 2010). As such, measuring prefrontal asymmetry during a reward task might also represent a psychophysiological mediator between *COMT* genotype and trait differences in APA and CPA. The present study therefore measures EEG asymmetry during a slot machine task developed by Shankman, Klein, Tenke, and Bruder (2007; Shankman et al., 2013) that separates the anticipatory and consummatory phases of reward processing (Shankman, Sarapas, & Klein, 2011).

To the authors' knowledge, only one prior study has examined the relationship between trait approach motivation, prefrontal asymmetry and *COMT* genotype (Wacker, Mueller, Pizzagalli, Hennig, & Stemmler, 2013). Wacker and colleagues found an association between greater relative left prefrontal asymmetry (as measured with resting EEG in a quasi-experimental manipulation of the emotional context—the presence of an attractive vs. non-attractive female experimenter), greater self-reported levels of trait behavioural approach and the G/G (i.e., Val/Val) allele. The present study extends this work in two important ways. First, it measures prefrontal asymmetry *during* a reward task, rather than in a subtle positively valenced context. Second, it utilises a measure specific to the phases of reward processing.

Present study

The present study examined the relationship between *COMT* genotype and individual differences in APA and CPA and whether prefrontal asymmetry during a reward task mediated this relationship. We hypothesised that individuals possessing the Met allele, known to be related to more post-synaptic dopamine in their PFC, would have higher scores on the TEPS. We expected prefrontal asymmetry recorded during a reward task (i.e., the slot machine paradigm described above) to mediate this relationship, such that possession of the Met allele would predict greater relative left activation during the task, which would in turn contribute to higher scores on the TEPS. Because we examined the anticipatory and consummatory phases separately, our results may elucidate the role of dopamine during these two phases of reward processing.

METHOD

Participants

Participants were 131 students enrolled in Introduction to Psychology at the University of Illinois at Chicago who received course credit for participation. Eleven people were excluded due to unusable EEG data (see below), which left a sample of 120 for analyses described herein. Given the associations between hemispheric asymmetry, emotional reactivity and handedness, all participants were right-handed. Participants were mean age of 19.4 (SD = 2.05) years old. The sample contained 58.8% females. The ethnic composition was quite diverse: 37.4% Caucasian, 28.2% Latino, 22.9% Asian and 11.5% African-American. As shown in Table 1, none of these variables were associated with *COMT* genotype.

Measures

Anticipatory and CPA

The 18-item TEPS was used to measure anticipatory and consummatory positive affective tendencies (Gard et al., 2006). Participants rated each

Table 1. *Sample characteristics and relationship to* COMT *genotype*

	COMT *genotype*		
Variable	*G/G*	*A-carrier*	*Relation to* COMT *genotype*
Gender (n)			
Female	26	51	χ^2_{female} = 0.44, ns
Male	16	27	χ^2_{male} = 0.046, ns
Race (n)			
Caucasian	11	33	χ^2 = 0.00, ns
Latino	12	22	χ^2 = 0.027, ns
Asian	14	14	χ^2 = 0.14, ns
African-American	5	9	χ^2 = 0.03, ns
Hemispheric asymmetry (M)			
Pre-goal	.001	−.004	$t(118)$ = −0.037, ns
Post-goal	−.013	.024	$t(118)$ = 1.83, p = .07

item from 1 (very false for me) to 6 (very true for me); from their responses, TEPS-Anticipatory and TEPS-Consummatory scores were determined. Consistent with previous research (Gard et al., 2006), this scale had acceptable reliability (TEPS-Ant: α = .69, TEPS-Con: α = .69, TEPS-Total: α = .81).

Handedness

Although participants were pre-screened for handedness during recruitment, the Edinburgh Handedness Scale (Oldfield, 1971) was used to confirm laterality (range of laterality quotient +30 to +100).

Procedure

Slot machine task

Each participant played a computerised slot machine game (Shankman et al., 2007, 2013) that consisted of three reels that displayed fruit and numbers. The reels spun simultaneously for 11 s (anticipatory phase) and displayed the results for 11 s (consummatory phase; see Table 2). The game consisted of 72 spins, which were divided into three different pay-off situations: reward (R, 30 trials), during which participants won money if the reels landed on three pieces of fruit; no incentive (NI, 30 trials), in which participants were ineligible to win money regardless of outcome; and loss (L, 12 trials), in which participants lost money when the reels landed on three pieces of fruit. Although only the R and NI conditions are necessary to examine online reward processing, results from pilot testing revealed that a win in the R condition was more exciting if there were L trials in the game (Shankman et al., 2013). Thus, the L condition was included to keep the participant engaged in the task. The amount of money won or lost for each trial varied from $0.50 to $3.00. The game was divided into 3 blocks of 24 spins, and participants had a short break in between blocks during which they rated their emotions (see Table 2).

Participants were told that the trial order was random to generate authentic anticipatory and CPA; however, unbeknownst to the participant, the trials were fixed, in that half of the spins landed on three pieces of fruit. They received their winnings (~$12.00) in cash after completing all 72 trials.

Data processing

EEG recording and processing

EEG data were recorded from Ag/AgCl electrodes in a 64-channel stretch-lycra electrode cap (Compumedics Neuroscan 4.4, Charlotte, NC). The ground electrode was at the frontal pole (AFZ) and the online reference was near the

Table 2. *Design of slot machine paradigm*

Condition	*Number of trials*	*Time in trial*	*Result and outcome*	*Number of trials*	*Time in trial*
Reward	30	11 s	Win– win $	15	11 s
			Lose– no win $ 5 2	15	11 s
No incentive	30	11 s	Win– no win $	15	11 s
			Lose– no lose $ 6	15	11 s
Loss	12	11 s	Lose– lose $	6	11 s
			Nolose – no lose $ 2	6	11 s
Totals	72	792 s in "pre-goal phase"		72	792 s in "post-goal phase"

Adapted from Shankman et al. (2007, 2013).

vertex (between CZ and CPZ). Electrodes placed at the right supra- and infra-orbital sites were used to monitor vertical eye movements (VEOG) and electrodes placed at the right and left outer canthi were used to monitor horizontal eye movements (HEOG). Electrode impedances were under 5000 ohms, and homologous sites (e.g., F3/F4) were within 1500 ohms of each other. Data were recorded through a Neuroscan Synamp2 data acquisition system at a gain of 10 K (5 K for eye channels) with a bandpass of DC-200 Hz. Data were acquired and digitised continuously at a rate of 1000 Hz.

Continuous EEG during the pre- and post-goal phases were segmented into consecutive 1.024 s epochs every 0.512 s (50% overlap). After re-referencing to a digitally derived "linked mastoid" reference offline and then applying a baseline correction, epochs contaminated by blinks, eye movements and movement-related artefacts were excluded from analyses manually, by direct visual inspection of the data. The EEG was tapered over the entire 1.024s epoch by a Hanning window to suppress spectral side lobes. After removal of contaminated epochs, the average activity in the alpha power band for each electrode in each condition of the task was calculated and log transformed to normalise the skewed and kurtotic distributions. Consistent with previous studies (e.g., Bruder et al., 1997), the alpha band was defined as an activity between 8 and –13 Hz and was used as an inverse measure of brain activation at a particular site.

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Hemispheric asymmetry

To examine hemispheric asymmetry as a mediator, we first subtracted alpha power on the left from alpha power in the homologous right electrode (e.g., F4–F3) for each condition. Higher values on these asymmetry scores reflect greater activity in the left relative to right prefrontal regions and this measure controls for individual differences in overall alpha power and scalp thickness (Allen, Coan, & Nazarian, 2004). Similar to prior studies with this sample (Sarapas et al., 2013; see also Shankman et al., 2013 for other studies with the task), to examine the change in asymmetry between the experimental (R) and control (NI) conditions, we subtracted the asymmetry scores in the NI condition from asymmetry scores in the R condition for each phase of the task. Thus, the variable that remains is the relative difference in asymmetry between the R and NI condition (i.e., "reward potentiated asymmetry").

Genotyping

Each participant provided a saliva sample for genotype analyses using Oragene collection kits (DNA Genotek, Kanata, ON, Canada). Genomic DNA was isolated according to the manufacturer's specification. A sequence validated TaqMan (Applied Biosystems) assay was utilised for genotyping which was done blind to behavioural data. We compared G/G homozygotes (i.e., individuals homozygous for the Val allele) to A/A homozygotes and A/G heterozygotes (i.e., carriers of the

Met allele). Examining genotype as a three-level variable indicated that A/A homozygotes and heterozygotes displayed nearly identical patterns of results for both TEPS-Consummatory scores and asymmetry, and both groups differed from the G/G homozygotes at a trend level. Therefore, we collapsed across A-carriers and A/A homozygotes to increase statistical power.

Data analysis

All statistical analyses were conducted using SPSS 20.0. To examine the relationship between *COMT* genotype and personality (i.e., *c* path of the mediation model), we conducted a one-way analysis of variance (ANOVA) for comparing GG homozygotes to A-carriers on TEPS-Anticipatory and TEPS-Consummatory scores. We performed another one-way ANOVA to look at the relationship between *COMT* genotype and prefrontal asymmetry during each phase of the task (i.e., *a* path of the mediation model). We conducted linear regression analyses to examine whether prefrontal asymmetry in each phase of the task predicted TEPS-Anticipatory and TEPS-Consummatory scores, respectively (i.e., *b* path of the mediation model).

We took two approaches to determining the effect of ethnicity on *COMT* genotype. First, we employed a chi-square analysis to examine allelic distributions within each ethnicity. Second, we used hierarchical linear regression to look at the effects of specific ethnicities and genotype-by-ethnicity interactions on TEPS-Consummatory scores (see Table 3). Three dummy codes for ethnicity were created to reflect membership in African-American, Latino and Asian ethnic groups, with Caucasian serving as the reference group. Any significant main effects of ethnicity or genotype-by-ethnicity interactions would be included as covariates in the primary analyses. To examine whether hemispheric asymmetry mediated the relationship between genotype and trait differences in anticipatory and CPA, we used Hayes and Preacher's (2013) *MEDIATE* macro for SPSS in two mediation models. In each model, dichotomous *COMT* genotype was the independent variable. In the APA model, TEPS-Anticipatory score was the dependent variable, and asymmetry during the pre-goal phase was the mediator. In the CPA model, TEPS-Consummatory score was the dependent variable, and asymmetry during the post-goal phase was the mediator. For all analyses, age and gender were also included as covariates. Effects of ethnicity (a critical variable in genetics studies) were examined thoroughly and are described below.

Table 3. *Effects of ethnicity and genotype-by-ethnicity interaction on TEPS-Consummatory scores.*

Variables entered	β	p
Model 1		
African-American	−.181	.048*
COMT genotype	−.172	.058+
African-American × *COMT*	−.255	.356
Model 2		
Latino	−.535	.052+
COMT genotype	−.261	.017*
Latino × *COMT*	.442	.117
Model 3		
Asian	.131	.654
COMT genotype	−.180	.054+
Asian × *COMT*	−.097	.750

RESULTS

Genetic distribution

Genotype counts for *COMT* Val^{158}Met were 22 A/A, 56 A/G and 42 G/G. Genotypes did not deviate from Hardy-Weinberg Equilibrium in the entire sample or by ethnic group (all *p*s > .25).

EEG descriptives

A mean of 1530 (SD = 513) epochs was kept and used for analyses. Bivariate correlations revealed that the total number of accepted epochs were not systematically related to post-goal asymmetry or TEPS scores (all *p*s > .18), and results from one-way ANOVAs showed that the total number of accepted epochs did not differ across *COMT* genotype or by condition (all *p*s > .29).

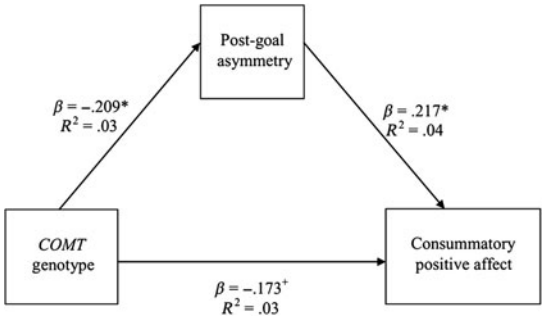

Figure 1. *Mediation model between* COMT *genotype, asymmetry in the post-goal phase of slot machine task, and self-reported CPA with statistical significance and effect sizes for each path.*

CPA model

Three pathways were examined in the CPA mediation model (see Figure 1). First, we examined the relationship between *COMT* genotype and TEPS-Consummatory scores (i.e., the *c* path). Although A-carriers had higher TEPS-Consummatory scores than GG-homozygotes, this result only approached significance, $F(1, 117) = 3.68$, $p = .058$. *COMT* genotype did predict differences in prefrontal asymmetry[1] during the consummatory phase of the task (i.e., the *a* path), such that A-carriers exhibited greater reward-potentiated asymmetry than GG-homozygotes, $F(1, 117) = 4.41$, $p < .05$. Finally, prefrontal asymmetry during the consummatory phase of the task predicted TEPS-Consummatory scores (i.e., the *b* path), with greater reward-potentiated asymmetry during the consummatory phase of the task scored higher on the TEPS-Consummatory scale ($\beta = .217$, $p < .05$).

Most importantly, mediational analyses indicated that *COMT* genotype exerted a significant indirect effect on TEPS-Consummatory scores, as the *c* path between *COMT* and TEPS-Consummatory was mediated by asymmetry in the post-goal phase of the task [$B = -0.73$, 95% confidence interval (CI): -1.82 to $-.05$]. [2] To see if either the R or NI condition was driving the mediation effect, we also conducted separate mediation analyses with asymmetry in the R and NI conditions as the mediator, and neither was significant (CIs contained 0). Rather, it was reward-potentiated asymmetry (i.e., the relative difference in asymmetry between the R and NI conditions) driving the mediation effect. Because these data are cross-sectional, we also examined whether TEPS-Consummatory scores mediated the relationship between *COMT* genotype and prefrontal asymmetry. However, the model did not reach significance (CI contained 0). As indicated above, gender and age were included as covariates in all regression analyses and contributed no unique variance to the dependent variable (all ps > .17).

APA model

Results from analogous analyses in the anticipatory phase of the task did not yield significant results for any path involved in the mediation model. Specifically, the *c* path for the effect of *COMT* genotype on TEPS-Anticipatory scores was not significant, $F(1, 117) = 0.00$, ns. The component parts (i.e., the *a* and *b* paths) of the mediation model were not significant either. That is, *COMT* genotype did not predict prefrontal asymmetry during the anticipatory phase of the task, $F(1, 117) = 0.14$, ns, and prefrontal asymmetry did not

[1] We also examined the relationship between *COMT* genotype, TEPS-Consummatory scores and hemispheric asymmetry in the post-goal phase in posterior electrodes, focusing on the parietal region. We did not find an association between posterior asymmetry in the post-goal phase and TEPS-Consummatory scores (all p > .52). Additionally, there was no significant association between *COMT* genotype and posterior asymmetry (all p > .65).

[2] When TEPS-Anticipatory score was included as a covariate in the CPA mediation model, the model became insignificant (i.e., the CI contained 0). This is likely due to the high correlation between the TEPS-Anticipatory and Consummatory scores ($r = .60$), which impedes finding statistical specificity when both variables are included in the model. That being said, when TEPS-Anticipatory score was included as a covariate in the univariate ANOVA testing the *c* path (i.e., *COMT* genotype predicting TEPS-Consummatory score) and regression testing the *b* path (i.e., prefrontal asymmetry in the post-goal phase predicting TEPS-Consummatory score) the effects remained significant.

predict TEPS-Anticipatory scores (β = −.02, ns). Because none of the proposed paths of the mediation model were significant, test of mediation was not performed.

Effect of ethnicity on TEPS scores

We took several approaches to examining whether the observed phenotypic differences associated with *COMT* did not merely reflect different ethnic groups' genetic distributions.

First, we examined the allelic distributions that were associated with each ethnic group. A chi-square analysis comparing the allelic ratios across ethnic groups indicated that the ratios of A/A, A/G and G/G did not differ by ethnic group, χ^2 = 4.71, ns. Results from the regression analyses indicated significant main effects of Latino and African-American group membership on TEPS-Consummatory scores but no significant genotype-by-ethnicity interactions. Additionally, when Latino and African-American group membership were included as covariates, *COMT* still predicted TEPS-Consummatory scores (*c*-path coefficient: β = −0.243, $p < .05$), and the mediation effect was still observed (i.e., the CI did not contain 0).

DISCUSSION

Results from this study indicate that prefrontal hemispheric asymmetry mediated the relationship between *COMT* genotype and trait differences in positive affectivity. Specifically, the Met variant was associated with higher TEPS-Consummatory scores, and that effect was mediated by greater relative activation in the left hemisphere of the PFC after receipt of a reward.

These results support previous findings of positive associations between the Met polymorphism and reward responsiveness (Lancaster et al., 2012; Wichers et al., 2007) and may have important implications for the development of psychopathology. Reward responsivity is one of the transdiagnostic domains outlined in NIMH's Research Domain Criteria (Insel et al., 2010; Sanislow et al., 2010). Indeed, associations between *COMT* genotype and psychiatric disorders characterised by deficits in reward responsiveness, such as major depressive disorder (MDD) and substance use disorders (SUDs), have been examined. For example, the reward deficiency hypothesis (Blum, Cull, Braverman, & Comings, 1996) posits that individuals who experience less pleasure in response to natural rewards (e.g., food, sex and social interaction) are more likely to seek sensations of pleasure from unnatural rewards (i.e., addictive substances), thereby incurring greater risk for developing SUDs. Genetic studies that have tested this theory have implicated genes involved in dopamine synthesis, degradation and transport, such as *COMT* and *DRD4* (Comings & Blum, 2000), and indeed reported links between the Val allele and nicotine dependence (Beuten, Payne, Ma, & Li, 2006), methamphetamine abuse (Li et al., 2004) and polysubstance abuse (Vandenbergh, Rodriguez, Miller, Uhl, & Lachman, 1997). Thus, the increased consummatory pleasure associated with the *COMT* Met allele may be protective against development of SUDs. However, several studies have also found the Met allele to be associated with risk-taking (Heitland et al., 2012; Lancaster et al., 2012) or higher levels of sensation seeking (at least in females: Amstadter et al., 2012; Lang, Bajbouj, Sander, & Gallinat, 2007) and impulsivity (Soeiro-De-Souza, Stanford, Bio, Machado-Vieira, & Moreno, 2013), which may contribute to risk for development of SUDs. Studies have also differed on the contribution of *COMT* genotype to the development of MDD (Funke et al., 2005; Henderson et al., 2000; Smolka et al., 2005). As such, more research is necessary to elucidate the likely complex relationship between *COMT* genotype and development of psychopathology.

The current findings are further supported by evidence for the localisation of COMT to activity in the PFC. Both the animal and the human literature have demonstrated that COMT moderates dopamine neurotransmission in the PFC (Karoum, Chrapusta, & Egan, 1994), and that *COMT* is expressed more in neurons found in the PFC (Matsumoto et al., 2003). For example, an imaging genetics study found that the Met variant

of the *COMT* genotype was associated with greater activation in the orbitofrontal cortex upon receipt of reward (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009). Taken together, this evidence corroborates the present study's demonstrated link between *COMT* genotype, prefrontal asymmetry in the post-goal phase and self-reported CPA.

Our findings indicate that *COMT* genotype is associated specifically with the consummatory phase of reward processing—seen both in its relationship with prefrontal asymmetry during the post-goal phase of the slot machine task and trait differences in CPA reported on the TEPS-Consummatory scale. Other psychophysiological examinations of dopamine and reward have also suggested dopamine's association with consummatory processes. For example, studies of non-human primates have demonstrated that dopaminergic neurons in the midbrain fire both during anticipation *and* upon receipt of reward (Fiorillo, Tobler, & Schultz, 2003). Similarly, fMRI studies in humans have shown activation of the PFC in response to receipt of a reward (Dreher, Kohn, & Berman, 2006; Knutson, Fong, Bennett, Adams, & Hommer, 2003), whereas dopaminergic neurons in the ventral striatum are more responsive to anticipation of reward (Knutson et al., 2003; O'Doherty, Deichmann, Critchley, & Dolan, 2002). Although others have postulated that dopamine may be specifically involved in anticipatory processes (see Berridge, 2007 for review), the positive associations between dopamine functioning and consummatory processes observed in the current study could be explained by the fact that we were examining prefrontal asymmetry in the context of reward processing, where COMT has been implicated.

One possible mechanism to explain the relationship between *COMT* genotype, prefrontal asymmetry in the post-goal phase of reward processing, and trait CPA is the opioid system. μ-opioids have been linked to hedonic experience, or "liking" (Barbano & Cador, 2007; Berridge, 2003), and *COMT* genotype has been linked to the μ-opioid receptor system. For example, post-mortem studies of the human brain have demonstrated that the Met variant of *COMT* is linked to increased numbers of μ-opioid receptor binding sites (Berthele et al., 2005; Kowarik et al., 2012). Most of the studies examining the effect of *COMT* genotype on the μ-opioid receptor system have focused on pain and have found the Met allele to be associated with increased experience of pain (e.g., Zubieta et al., 2003). Given the overlapping neurobiology of pleasure and pain (Leknes & Tracey, 2008), it is possible that individuals with the Met allele of the *COMT* are more sensitive and reactive to environmental stimuli, which may help explain why they are more responsive to reward and more sensitive to pain.

Several prior studies have failed to link dopamine neurotransmission and prefrontal asymmetry (e.g., Schmidt, Fox, Perez-Edgar, & Hamer, 2009; Wacker & Stemmler, 2006). These studies, however, measured prefrontal asymmetry during a resting condition. Interestingly, recent evidence suggests that relationships between the two variables may be more observable during an experimental context that manipulates approach motivation, similar to other capability models postulated by affective scientists (Coan et al., 2006; Dennis & Solomon, 2010). For example, as previously discussed, one study found that the associations between prefrontal asymmetry, behavioural approach tendencies and *COMT* genotype depended on the situational context in which the resting EEG was recorded—specifically, the attractiveness of the experimenter (Wacker et al., 2013).

The present study contained important methodological distinctions from ~~the~~ Wacker and colleagues' (2013) investigation that point to specific aspects of dopaminergic functioning in the context of reward. First, instead of quasi-experimentally manipulating the affective context of the EEG recording situation (i.e., asking participants to retrospectively rate the attractiveness of the experimenter one year after testing and using that rating as measure of experimental context), we measured EEG asymmetry *during* a reward task. This allowed us to examine not only the prefrontal asymmetry associated with reward but also the separate patterns of asymmetry that

occur during the anticipatory and consummatory phases of reward processing. Furthermore, rather than broadly measuring positive affectivity or behavioural approach (e.g., positive emotionality scale of the General Temperament Survey, Clark & Watson, 1990; or the BIS/BAS Scale, Carver & White, 1994), the present study used the TEPS which closely aligns with the two phases of the reward task. The present results also diverge from those of Wacker et al. (2013), who found that the G/G variant of *COMT* Val^{158}Met was associated with greater prefrontal asymmetry, whereas we found that the A-carrier variants predicted greater prefrontal asymmetry. Given the relative infancy of the work linking genetics, psychophysiological endophenotypes and personality phenotypes associated with reward processing, more research is needed to clarify the relationship between these variables.

Although the *a* and *b* paths of the CPA model, as well as the full mediational model, were significant, the overall *c* path (i.e., the direct effect of COMT genotype on TEPS-Consummatory scores) only approached significance. This may be due to the fact that CPA, based on responses to the self-report TEPS-Consummatory scale, occurs quite "downstream" from the effects of *COMT* genotype. In other words, all of the intermediate steps between genotype and self-reported personality phenotype (e.g., genotype, proteins, cellular activity, brain structures, brain systems, behaviours and cognition, personality) may reduce the power of a direct effect from being observed. Therefore, it is important to investigate intermediate phenotypes, such as prefrontal hemispheric asymmetry, whose intermediate effects can elucidate these complex pathways (Kendler & Neale, 2010; Rasetti & Weinberger, 2011; Sanislow et al., 2010).

Contemporary views of statistical mediation can also help explain why a significant effect of *COMT* genotype on TEPS-Consummatory scores was not observed. Modern conceptualisations of mediation do not require the *c* path to reach significance to proceed with tests of mediation (Hayes, 2009; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Shrout & Bolger, 2002). In some cases, such as instances of partial mediation, there may be other (i.e., unmeasured) mediators exercising the opposite effect of the observed mediator, essentially "canceling out" the direct effect.

Strengths and limitations

This study contained several strengths. First, the sample was relatively large for a psychophysiological study and had a broad range of positive affective responses, thereby allowing us to use the task to examine individual differences in personality. Second, the within-subjects design of the slot machine game afforded greater power to look at hemispheric asymmetry and its relationship to *COMT* genotype and personality variables. Third, this study examined reward responsiveness at three levels of analysis—genotype, psychophysiology and personality—and found a significant meditational effect for psychophysiology, highlighting a potential endophenotype for CPA. Finally, this study provided psychophysiological validation for the TEPS-Consummatory scale (Gard et al., 2007). Since its inception, the scale has been widely used in assessing anticipatory and consummatory pleasure in clinical populations, particularly individuals with schizophrenia (Gard et al., 2007; Horan, Kring, & Blanchard, 2006) and major depression (Liu et al., 2011~~; Pizzagalli et al., 2009).~~ This study demonstrates that this scale is useful for the study of personality in non-clinical samples, and that the scale maps onto genetic and psychophysiological correlates of reward processing.

Despite these strengths, this study contained limitations as well. The sample size and ethnic diversity of the sample were not ideal for genetic analyses, although we still found effects consistent with our hypothesis. A second limitation is that the mediation analysis was cross-sectional which eliminates concluding causality of the model (MacKinnon, Fairchild, & Fritz, 2007). A third limitation is that the sample was obtained from an undergraduate Introduction to Psychology course, which may call into question the generalisability of the results.

CONCLUSION

This study demonstrated important links between *COMT* genotype, prefrontal asymmetry during the consummatory phase of reward processing and self-reported trait-level CPA. The present findings provide psychophysiological validation of the TEPS and may help explain how *COMT* genotype contributes to risk for psychopathology, specifically major depression and SUDs. Finally, the results described here highlight the role of dopamine in consummatory processes in the PFC.

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