Genetic variation in dopamine moderates neural response during reward anticipation and delivery: Evidence from event-related potentials

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Abstract

Neuroimaging studies have found moderating effects of dopamine genes during both the anticipation and delivery of rewards, particularly the catechol-O-methyltransferase (COMT) genotype. Event-related potential studies, meanwhile, have focused on the stimulus-preceding negativity (SPN) and the feedback negativity (FN) during reward anticipation and delivery, respectively. In anticipation of uncertain outcomes, we observed an increased SPN among Met homozygotes. We also observed an increased FN among Met homozygotes in response to outcome delivery, an effect that was driven primarily by an increased response to monetary gains. The COMT genotype moderates event-related potential responses during both the anticipation and delivery of uncertain reward, suggesting that the SPN and FN are sensitive to dopaminergically mediated and reward-related neural activity.

Descriptors: EEG/ERP, Genetics, Individual differences

Animal studies have identified multiple dopamine signals involved in the processing of rewards, with widely varying time courses (Schultz, 2007a, 2007b). In particular, the anticipation of uncertain rewards is associated with a relatively slow, sustained activation of dopamine neurons, whereas reward delivery is associated with a transient burst of dopamine (Fiorillo, Tobler, & Schultz, 2003). Likewise, neuroimaging studies in humans have identified distinct patterns of activation in the prefrontal cortex and striatum during the anticipation versus delivery of rewards (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001), and recent work has focused on how this reward-related activity is moderated by genetically determined differences in dopamine availability.

Synaptic dopamine degradation is regulated in part by the enzyme catechol-O-methyltransferase (COMT), and valine to methionine allelic substitution (Val158Met) in the COMT genotype is associated with a fourfold decrease in enzymatic activity (Lachman et al., 1996). Genetic variation in COMT is thought to differentially influence cortical and subcortical dopamine regulation (Bilder, Volavka, Lachman, & Grace, 2004). Cortically, the Met allele (COMT rs4680 met158) is associated with greater extrasynaptic dopamine and an overall increase in prefrontal dopaminergic activity. Subcortically, the Met allele is associated with increased tonic dopamine levels as a result of downstream regulation from prefrontal regions, and this elevated tonic activity is thought to suppress phasic responses. The effect of COMT genotype on reward-related neural activity, therefore, appears to depend on both the brain region of interest (cortical vs. subcortical) as well as the dopamine signal that is delivered (e.g., slow activity during anticipation vs. transient activity during delivery). Several recent functional magnetic resonance imaging (fMRI) studies have shown that, during the anticipation of uncertain monetary outcomes, Met homozygotes exhibit increased prefrontal and striatal activity (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Schmack et al., 2008; Yacubian et al., 2007). On the other hand, studies of reward delivery have yielded somewhat mixed results: Dreher and colleagues (2009) found increased activity in the orbitofrontal cortex (OFC) among Met homozygotes, but no modulation of striatal activity. Two other studies, however, found decreased activity in the anterior cingulate cortex (ACC) and striatum among met homozygotes (Camara et al., 2010; Krugel, Biele, Mohr, Li, & Heekeren, 2009). Whereas the Met allele appears to be associated with increased activity throughout the mesocorticolicimbic reward circuit during reward anticipation, the effect of the Met allele during reward delivery is less clear.

In parallel to this neuroimaging research, complementary evidence on brain activity associated with reward anticipation and delivery has emerged from electrophysiological studies. In particular, event-related potential (ERP) studies have focused primarily on two components: the stimulus-preceding negativity (SPN) and the feedback negativity (FN). The SPN is a slow cortical potential that is commonly measured during time estimation tasks in which participants make a motor response and then, after a short delay, receive feedback about the accuracy of their response (Brunia, 1988; Brunia & Damen, 1988; Damen & Brunia, 1987). The SPN manifests as a sustained centroparietal negativity in the seconds leading up to the feedback, and it is thought to reflect activity in the lateral prefrontal cortex and the insula (Bocker, Brunia, & van den Berg-Lenssen, 1994; Brunia, de Jong, van den Berg-Lenssen, &
Paans, 2000; Kotani et al., 2009). Importantly, the SPN is also sensitive to manipulations of reward, such that SPN amplitude is increased during trials in which correct responses are associated with a monetary reward compared to trials in which there is no monetary incentive (Kotani, Hiraku, Suda, & Aihara, 2001; Kotani et al., 2003; Ohgami, Kotani, Hiraku, Aihara, & Ishii, 2004). SPN amplitude is also dependent on action-outcome contingencies, such that the SPN is increased on active compared to passive gambling trials (Masaki, Yamazaki, & Hackley, 2010). Reward-related modulation of the SPN is blunted among patients with Parkinson’s disease, consistent with the notion that the SPN is an index of anticipatory, dopaminergically mediated cortical activity (Mattox, Valle-Inclan, & Hackley, 2006).

Whereas the SPN relates to the anticipation of uncertain reward, the FN is a response to reward delivery. The FN is observed as a relative negativity approximately 250–300 ms following the presentation of feedback indicating monetary loss compared to gain, and it has been localized to the ACC (Gehring & Willoughby, 2002). The FN is sensitive to violations of reward prediction but is insensitive to reward magnitude (Hajcak, Moser, Holroyd, & Simons, 2006, 2007). In the context of reinforcement learning theory, it has been proposed that variation in FN amplitude is a result of phasic increases and decreases in midbrain dopamine signals when outcomes are better or worse than expected, respectively (Holroyd & Coles, 2002).

Although the FN has traditionally been thought to reflect a neural process that tracks the occurrence of unfavorable outcomes (i.e., a negativity observed on losses that is absent on gains), recent evidence suggests instead that the FN reflects reward-related neural activity (i.e., a positivity observed on gains that is absent on losses; Holroyd, Krigolson, & Lee, 2011; Holroyd, Pakzad-Vaezi, & Krigolson, 2008). Consistent with this suggestion, a recent application of temporal-spatial principal components analysis (PCA) and source localization revealed that the FN is a reward positivity that, perhaps in addition to the ACC, reflects striatal activity in response to monetary gain (Foti, Weinberg, Dien, & Hajcak, 2011). A subsequent combined ERP/fMRI study revealed that FN amplitude is correlated with reward-related BOLD signal across the mesocorticolimbic reward circuit, including the ventral striatum, caudate, medial prefrontal cortex, and OFC (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). Overall, the FN appears to reflect variation in neural activity associated with reward delivery that may span cortical and subcortical regions, thereby complementing the information provided by the SPN.

In light of this evidence that the SPN and FN reflect distinct phases of reward processing—reward anticipation and delivery, respectively—we sought to test whether these neural measures would be moderated by allelic variation in the COMT genotype. In one previous study, an effect of COMT was found on FN amplitude, such that the difference between monetary losses and gains was decreased among Met homozygotes (Marco-Pallares et al., 2009). Both outcome valence and magnitude were manipulated, however, which independently modulate the amplitudes of the FN and the P300, respectively (Hajcak et al., 2006; Sato et al., 2005; Yeung & Sanfey, 2004). Because of temporal overlap between the FN and the P300, the variation in ERP amplitude by COMT in the study by Marco-Pallares and colleagues may have been because of outcome valence, magnitude, or both. Indeed, one potential advantage of scoring the FN using a factor analytic technique such as PCA is that it is possible to effectively separate the FN from the P300 and other overlapping components (Foti & Hajcak, 2009; Foti et al., 2011).

In the current study, we focused on a relatively large sample in which the FN was recorded during a simple gambling task with reward magnitude held constant, and we scored the FN using temporal-spatial PCA to isolate the reward-related ERP response. In a prior report from this sample, we found that the FN was inversely related to symptoms of depression and stress reactivity (Foti & Hajcak, 2009). Thus, we examined whether COMT would explain additional variation in FN amplitude and whether the FN would be decreased in Met homozygotes when reward magnitude was held constant. Moreover, we addressed the novel possibility that the SPN would also be sensitive to COMT. Considering previous IMRI studies showing increased prefrontal activation during reward anticipation (Dreher et al., 2009; Schmack et al., 2008; Yacubian et al., 2007), we predicted that Met homozygotes would exhibit an increased SPN during the anticipation of uncertain rewards. Collectively then, the Met allele of the COMT genotype may be associated with increased neural activity in anticipation of rewards and reduced neural activity in receipt of them.

**Methods**

**Participants and Measures**

Eighty-eight undergraduate students participated in the current study; this was the same sample from a prior report on the effect of depressive symptoms on the FN (Foti & Hajcak, 2009). Three participants were excluded from analysis because of poor quality electroencephalogram (EEG) recordings, 1 was excluded for having missing genetic data, and 1 was excluded for failing to yield a genotype assignment (call rate = 98.81%). For the latter subject, the genotyping process was performed twice to be sure that the data were not usable. This resulted in a final sample of 83 participants (38 female, 45 male). All participants received course credit for their participation, as well as $5.00 as their winnings from the gambling task. Written informed consent was obtained from all participants, and this research was formally approved by the Stony Brook University Institutional Review Board.

Self-reported levels of psychological distress over the past week were assessed using the short-form version of the Depression Anxiety Stress Scale (Lovibond & Lovibond, 1995). Of interest were the depression and stress reactivity subscales, both of which were previously shown to predict blunted FN amplitude in the current sample (Foti & Hajcak, 2009).

**Genotype Analysis**

Buccal cells were collected from each participant using a cheek swab, and genomic DNA was extracted from these samples using the QuickExtract DNA Extraction Solution (Epigen Technologies, Madison, WI). Of interest for the genotyping process was a single nucleotide polymorphism (SNP) in the coding region of the COMT gene (rs4680) that results in a G to A substitution at codon 158, subsequently changing the amino acid valine to methionine (Val<sup>158Met</sup>).<sup>1</sup> Genotype analysis was

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<sup>1</sup> In addition to COMT, we assessed participants for two additional genotypes shown to influence striatal reactivity in a prior report (Forbes et al., 2009): the insertion/deletion polymorphism of the dopamine receptor D2 gene (DRD2–141C Ins/Del; rs1799732) and the 48-base pair variable number tandem repeat of the dopamine receptor DR gene (DRD4 7-repeat allele). Neither yielded a significant effect on FN or SPN amplitude (all *p* > .25), and the effects of COMT remained significant after adding DRD2 and DRD4 as additional predictors.
performed with high-resolution melt analysis. Polymerase chain reaction was carried out in a 10 ml volume with forward (5'-ACCCAGCGATGTTGATT-T3') and reverse (5'-ATGCCCTCCTGGCCACAG-3') primers. Each amplification was overlaid with 25 μl of mineral oil and contained 2 μl of extracted buccal DNA, 0.25 μM of each primer, and 1× LightScanner Master Mix (Idaho Technology, Inc., Salt Lake City, UT). Reaction conditions began with a denaturation at 94°C for 2 min, followed by 40 cycles of 94°C for 30 s, 68.1°C for 30 s, and 72°C for 30 s. Melt analysis was performed between 75° and 95°C (0.1°C/s) with a LightScanner (Idaho Technology, Inc.), and SNP status was determined using the Small Amplicon Module. Samples from 3 participants identified through the melt analysis as the expected genotypes (Met/Met, Val/Met, and Val/Val) were confirmed by DNA sequencing, and these were then included for comparison on every polymerase chain reaction plate.

The genotyping procedure described above was performed on a broader sample of 421 total individuals, not all of which completed the gambling task. In total, 124 individuals were identified as Val homozygotes, 97 as Met homozygotes, and 200 as heterozygotes, frequencies that are consistent with the Hardy-Weinberg equilibrium, \( \chi^2(1) = 8.89, p = .35 \). Of those 83 participants who completed the gambling task, 32 were identified as Val homozygotes, 22 as Met homozygotes, and 28 as heterozygotes. These frequencies indicated a statistically significant deviation from the Hardy-Weinberg homozygotes, and 28 as heterozygotes. These frequencies that were consistent with the Hardy-Weinberg equilibrium, and 97 as Met homozygotes, and 200 as heterozygotes, frequencies that are consistent with the Hardy-Weinberg equilibrium, \( \chi^2(1) = 8.14, p < .01 \), although, given that the full sample did not violate the Hardy-Weinberg equilibrium, it is likely that the deviation observed in the current subsample was a result of chance rather than an error in the genotyping procedure.

**Gambling Task**

The task was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) to control the presentation and timing of all stimuli. On each trial, participants were shown a graphic displaying two doors horizontally adjacent (occupying 6° of the visual field vertically and 8° horizontally) and chose which door they wanted to open using the left or right mouse button. Following each choice, a feedback stimulus appeared on the screen informing participants of the outcome, with a green ↑ indicating a correct guess and a gain of $.20, and a red ↓ indicating an incorrect guess and a loss of $.10. The magnitude of gains was double that of losses in order to approximately equate subjective value, as indicated by research on loss aversion (Tversky & Kahneman, 1992). Prior to each trial, a white 0, 1, or 2 cue was presented to inform participants how many doors would contain a prize on that trial, thereby indicating a reward probability of 0, .5, or 1, respectively. ERP responses on the zero- and two-cue trials of a subsample have been previously reported (Dunning & Hajcak, 2007). All cues and feedback were presented against a black background and occupied approximately 3° of the visual field vertically and 1° horizontally. The order and timing of all stimuli were as follows: (i) cues were presented for 2000 s, (ii) a fixation mark was presented for 500 ms, (iii) the two doors were presented until a response was made, (iv) a fixation mark was presented for 1000 ms, (v) feedback was presented for 2000 ms, (vi) a fixation mark was presented for 1500 ms, and (vii) the instruction “Click for next round” was presented until a response was made. To familiarize participants with the task, they first completed a practice block containing five trials. The actual experiment consisted of 100 trials (25 zero-cue, 50 one-cue, and 25 two-cue trials). Positive feedback was presented on exactly 50% of the one-cue trials (i.e., 25 gains and 25 losses), 100% of the two-cue trials, and 0% of the zero-cue trials, such that all participants earned a total of $5.00. The order of feedback and trial type was randomized across participants. Every 20 trials, a running total of money earned was presented on the screen.

**Psychophysiological Recording, Data Reduction, and Analysis**

The continuous EEG was recorded using a custom cap (Cortech Solutions, Wilmington, NC) and the ActiveTwo Biosemi system (BioSemi, Amsterdam, Netherlands). The signal was preamplified at the electrode with a gain of one, and the EEG was digitized at 24-bit resolution with an LSB value of 31.25 nV and a sampling rate of 512 Hz, using a low-pass fifth-order sinc filter with a ~3 db cutoff of 102.4 Hz. Recordings were taken from 64 scalp electrodes based on the 10/20 system as well as two electrodes placed on the left and right mastoids. The electrooculogram was recorded from two electrodes 1 cm above and below the left eye, one 1 cm to the left of the left eye, and one 1 cm to the right of the right eye. Each electrode was measured online with respect to a common mode sense electrode that formed a monopolar channel. Off-line analysis was performed using Brain Vision Analyzer software (Brain Products, Munich, Germany). All data were re-referenced to the average of the two mastoid electrodes and band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented for each trial as follows: For the FN, epochs began 200 ms before feedback onset and continued for 800 ms; for the SPN, epochs began 200 ms before motor response and continued for 1000 ms (i.e., until the feedback was presented). Each trial was corrected for blinks and eye movements using the method developed by Gratton, Coles, and Donchin (1983). Specific channels in each trial were rejected using a semi-automated procedure, with physiological artifacts identified by the following criteria: a step of more than 50 μV between sample points, a difference of 75 μV within a trial, and a maximum difference of less than 0.5 μV within 100-ms intervals.

For the SPN, response-locked ERPs were averaged separately for zero-, one-, and two-cue trials. The SPN was scored as the mean level of activity from 800 to 1000 ms relative to the response (i.e., the 200-ms window immediately prior to feedback onset) at two bilateral poolings of centrotemporal sites (C3/4, C5/6, T7/8), where the difference between certain and uncertain trials was maximal across the entire sample (see Figure 1); the 200-ms window before the behavioral response served as the baseline. For the FN, stimulus-locked ERPs were averaged separately for uncertain gains and losses (one-cue trials only); certain outcomes were not considered. The FN was scored as the mean level of activity from 275 to 325 ms relative to feedback onset at a pooling of frontocentral sites (FCz/1/2, Cz/1/2), where the difference between losses and gains was maximal across the entire sample (see Figure 3, below); the activity in the 200-ms window before feedback onset served as the baseline.

In addition to these area measures, the SPN and FN were also scored with two-step PCA using the ERP PCA Toolkit, version 1.3 (Dien, 2010a). This approach parses the ERP waveform into a set of unique responses, maximizing the separation between components. This is particularly important for the FN, which overlaps in time with both the P200 and the P300; we have previously demonstrated how PCA may be useful to isolate the FN from these other ERP components (Foti et al., 2011). Following published guidelines for applying PCA to ERP data (Dien, 2010b), we conducted the temporal PCA first using Promax rotation (i.e., a separate
temporal PCA for the SPN and FN). This step considered all time points from each participant’s averaged ERP as variables, and it considered participants, trial types, and recording sites as observations. Based on the resulting Scree plots (Cattell, 1966), 10 temporal factors were retained for the SPN, and eight factors were retained for the FN. For each temporal factor, this analysis yielded factor scores for each combination of recording site, participant, and trial type, representing the amount of activity in the original data captured by that factor. The spatial distributions of these factor scores were then analyzed using spatial PCA and Infomax rotation. This step considered all participants, trial types, and temporal factor scores as observations. A separate spatial PCA was performed for each temporal factor. Based on the averaged Scree plot for the 10 SPN temporal factors, three spatial factors were retained, yielding 30 unique factor combinations. Temporal Factor 1/Spatial Factor 1 was most consistent with the morphology of the SPN based on the temporal and spatial loadings of the uncertain minus certain difference, and scores for this factor were submitted to statistical analysis. Likewise, based on the averaged Scree plot for the eight FN temporal factors, three spatial factors were retained, yielding 24 factor combinations. Temporal Factor 3/Spatial Factor 1 was most consistent with the morphology of the FN, and scores from this factor were submitted to statistical analysis.

Effects of interest on the SPN and FN were first examined using repeated measures analysis of variance (ANOVA) with Greenhouse–Geisser correction to confirm ERP differences across trial type (SPN: uncertain outcome vs. certain gain vs. certain loss; FN: uncertain loss vs. uncertain gain). Effects of COMT allele status were then analyzed using analyses of covariance (ANCOVAs) to adjust for group differences in demographic variables and psychological distress. Between subjects factors were COMT allele status (Met/Met, Val/Met, Val/Val), gender, and ethnicity (Caucasian, other). Depression and stress scores from the DASS-21 were included as continuous covariates. All statistical analysis was performed using PASW Statistics (18.0; SPSS, Inc., Chicago, IL).

Results

Demographic Characteristics

The frequencies of gender and ethnicity for the three groups are presented in Table 1. Ethnicity significantly varied as a function of COMT allele status, with non-Caucasian participants more likely to be in the Val/Val group compared to either the Val/Met or Met/Met groups. No significant effect was observed for gender. Both gender and ethnicity were included as covariates in all further analysis of COMT on ERP variables.

Reward Anticipation

Area measure. The SPN was evident as a relative negativity in the ERP waveform for uncertain compared to certain trials, with the effect of uncertainty maximal immediately prior to feedback deliv-
ery (Figure 1, left). This impression was confirmed in a repeated measures ANOVA, which yielded a main effect of trial type, $F(2,164) = 28.70, p < .001$; partial $\eta^2 = .26$. Follow-up contrasts indicated that the SPN was increased for uncertain trials compared to either certain loss, $t(82) = 5.86, p < .001$, or certain gain, $t(82) = 7.48, p < .001$; there was no difference between certain loss and certain gain ($p = .97$). Taking the difference between uncertain (one-cue) and certain (zero- and two-cue) trials and adjusting for all covariates, an effect of COMT allele status was observed on SPN amplitude, $F(2,76) = 3.12, p < .05$, partial $\eta^2 = .08$, indicating that the increase in SPN amplitude on uncertain trials significantly varied across the three groups. Confirming the impression in Figure 2, the Met/Met group exhibited a significantly larger SPN (i.e., uncertain minus certain) compared to the average of the Val/ Val and Val/Met groups, $t(76) = 2.35, p < .05$; the Val/Val and Val/ Met groups did not differ from one another ($p = .43$). Considering uncertain and certain trials separately, the SPN in anticipation of uncertain outcomes was significantly modulated by COMT allele status, $F(2,76) = 3.07, p = .05$, partial $\eta^2 = .08$, with the Met/Met group having a larger response compared to the other groups, $t(76) = 2.18, p < .05$, which did not differ from one another ($p = .26$). No effect of COMT allele status was observed for certain trials ($p = .86$, partial $\eta^2 = .01$).

**PCA measure.** Two-step PCA isolated the SPN as Temporal Factor 1/Spatial Factor 1, a negativity to uncertain outcomes peaking at 839 ms after the behavioral response (Figure 1, right). Both the area and PCA measures were maximal at centroparietal sites, with the area measure having a somewhat more lateral distribution. Statistical analysis of the factor scores yielded a pattern of results identical to the area measure: The SPN factor varied by trial type, $F(2,164) = 18.36, p < .001$, partial $\eta^2 = .18$, with a significantly increased amplitude for uncertain outcomes relative to certain loss, $t(82) = 4.46, p < .001$, or certain gain, $t(82) = 6.01, p < .001$; certain loss and certain gain did not differ from one another ($p = .63$). Taking the uncertain minus certain difference and adjusting for all covariates, a trend of COMT allele status was observed, $F(2,76) = 2.97, p = .06$, partial $\eta^2 = .07$; the SPN was larger in the Met/Met group compared to the average of the Val/Met and Val/Val groups, $t(76) = 2.57, p < .05$, which did not differ from one another ($p = .54$). Considering uncertain and certain trials

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### Table 1. Demographic Characteristics

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$\chi^2(2)$

**p < .01

**p < .001

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Figure 2. Stimulus-Preceding Negativity during the anticipation of uncertain and certain outcomes, presented for the three COMT groups. Head maps show the spatial distribution of the uncertain minus certain outcomes from 800 to 1000 ms.
separately, an effect of COMT allele status was observed for uncertain trials, $F(2,76) = 3.49$, $p < .05$, partial $\eta^2 = .08$, with the Met/Met group exhibiting a larger SPN compared to the other groups, $t(76) = 2.40$, $p < .05$, which did not differ from one another ($p = .29$). No effect was observed for certain trials ($p = .71$, partial $\eta^2 = .01$).

**Reward Delivery**

**Area measure.** The FN was evident as a relative positivity in the ERP waveform for gain trials and a relative negativity for loss trials, with the difference between gains and losses peaking at approximately 300 ms after feedback onset (Figure 3, left). A repeated measures ANOVA confirmed that the FN significantly varied by outcome, $F(1,82) = 109.324$, $p < .001$, partial $\eta^2 = .57$. Taking the loss minus gain difference and adjusting for all covariates, a significant effect of COMT allele status was observed, $F(2,76) = 3.84$, $p < .05$, partial $\eta^2 = .09$, indicating that FN amplitude varied across the three groups (Figure 4). As with the SPN, the FN was larger in the Met/Met group compared to the average of the Val/Met and Val/Val groups, $t(76) = 2.31$, $p < .05$, which did not differ from one another ($p = .37$). Considering gains and losses separately, the FN in response to gains was significantly modulated by COMT allele status, $F(2,76) = 5.69$, $p < .01$, partial $\eta^2 = .13$, with the Met/Met group again having a larger response compared to the other groups, $t(76) = 3.12$, $p < .01$, which did not differ from one another ($p = .19$). No effect of COMT allele status was observed for losses ($p = .34$, partial $\eta^2 = .03$).

**PCA measure.** Two-step PCA isolated the FN as Temporal Factor 3/Spatial Factor 1, an increased positivity to gains peaking at 298 ms after feedback onset (Figure 3, right). Both the area and PCA measures were maximal at frontocentral sites. Statistical analysis of the factor scores yielded a pattern of results identical to the area measure: A repeated measures ANOVA confirmed that FN amplitude varied by outcome type, $F(1,82) = 75.52$, $p < .001$, partial $\eta^2 = .48$. Taking the loss minus gain difference and adjusting for all covariates, a significant effect of COMT allele status was observed, $F(2,76) = 4.57$, $p < .05$, partial $\eta^2 = .11$. The Met/Met group exhibited an increased FN compared to the average of the Val/Met and Val/Val groups, $t(76) = 2.68$, $p < .01$, which did not differ from one another ($p = .44$). Considering gain and loss trials separately, a robust effect of COMT allele status was observed for gains, $F(2,76) = 5.98$, $p < .01$, partial $\eta^2 = .14$. The Met/Met group exhibited an increased response to gains compared to the other groups, $t(76) = 3.18$, $p < .01$, which did not differ from one another ($p = .28$). No effect of COMT allele status was found for loss trials ($p = .56$, partial $\eta^2 = .01$).

These observed effects of COMT allele status were independent of the previously reported effects of depression and stress on variation in the FN. Estimated marginal means for both the SPN and FN (area measures) after adjusting for gender, ethnicity, depression, and stress are presented in Figure 5. Across the full sample, the SPN (uncertain minus certain) and FN (loss minus gain) were also related to one another, with a larger FN on average ($r = .27$, $p < .05$). As shown previously (Foti & Hajcak, 2009), the P300 was isolated as Temporal Factor...
1/Spatial Factor 1, a distinct factor from the FN, characterized as a centroparietal positivity peaking at 468 ms (data not shown). This factor was increased for losses compared to gains, \(F(1,82) = 39.59, p < .001\), partial \(\eta^2 = .33\); adjusting for covariates, the loss minus gain difference in P300 amplitude was unaffected by COMT allele status (\(p = .51\), partial \(\eta^2 = .02\)).

Discussion

The current results demonstrate for the first time that ERP responses during the anticipation and delivery of uncertain reward are moderated by the COMT genotype, with homozygosity for the Met allele associated with increased neural activity during both phases of reward processing. Consistent with previous research, we observed an increase in SPN amplitude on trials in which the monetary outcome was uncertain (Kotani et al., 2001, 2003; Ohgami et al., 2004); however, the effect of uncertainty was enhanced among Met homozygotes compared to Val homozygotes and heterozygotes. This moderation of SPN amplitude by COMT allele status converges with two recent fMRI studies showing increased activation in lateral prefrontal areas, a likely generator of the SPN, among Met homozygotes during anticipation of uncertain reward (Dreher et al., 2009; Yacubian et al., 2007).

Using PCA, the FN was isolated as an increased positivity to rewards, and the effect of COMT allele status on FN amplitude was specific to gains and not losses. Contrary to one previous ERP study (Marco-Pallares et al., 2009), however, FN amplitude was increased among Met homozygotes. This divergent finding may be because of important differences in the gambling paradigms used.

In the current study, outcome magnitude was fixed for gain and loss trials, whereas Marco-Pallares and colleagues incorporated high- and low-magnitude outcomes for both gains and losses. Although they found an increased FN among Val homozygotes for the overall gain versus loss comparison (i.e., collapsing across magnitude), they also found a Valence \(\times\) Magnitude interaction such that Val homozygotes exhibited a greater difference between large and small losses (gains were not analyzed separately). In other words, the modulation of the ERP response by outcome magnitude was increased among Val homozygotes compared to Met homozygotes.

In light of consistent evidence that outcome magnitude primarily influences the P300 and not the FN (Hajcak et al., 2006; Sato et al., 2005; Yeung & Sanfey, 2004), it is possible that the group differences observed by Marco-Pallares and colleagues were because of modulation of the P300 by allele status, which could have also influenced FN amplitude because of temporal overlap between the P300 and FN. Consistent with this possibility, a recent fMRI study from the same group again found increased neural responses among Val homozygotes—in the striatum and the ACC—but only on unexpected large magnitude trials; no group differences were found on small magnitude trials (Camara et al., 2010). Overall, this pattern of results across studies suggests that neural responses to outcome valence and magnitude may be differentially influenced by COMT genotype, such that valence effects—as indexed by the FN—are increased among Met homozygotes, whereas magnitude effects—as indexed by the P300—are increased among Val homozygotes, a possibility that warrants further investigation.

The influence of COMT genotype on reward-related neural activity may also depend on whether the experimental paradigm...
emphasizes cognitive stability or flexibility. The Met allele is thought to convey an advantage on tasks that require stability, such as working memory maintenance and the execution of prepotent responses, whereas the Val allele is thought to convey an advantage on tasks that require flexibility, such as updating action outcome contingencies (Bilder et al., 2004), and experimental evidence supports this distinction (Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010). In one reward-learning study requiring participants to adapt to shifting outcome contingencies, thereby emphasizing cognitive flexibility, striatal reactivity was increased among Val homozygotes (Krugel et al., 2009). On the other hand, in another study in which outcomes were fully random and no learning was possible, thereby emphasizing cognitive stability, OFC reactivity was increased among Met homozygotes, and no COMT effects were observed on the striatum (Dreher et al., 2009). The latter example is more consistent with the paradigm used here, in which outcomes were random and no true learning was possible. This emphasis on cognitive stability over flexibility could also account for the increased FN amplitude found in Met homozygotes in the current study.

Considering the multiphasic nature of dopamine action in the brain (Schultz, 2007a, 2007b), the SPN and the FN may relate to qualitatively different dopamine signals that have unique behavioral and psychological sequelae. Drawing from Berridge and Robinson’s (2003) tripartite model of reward, the sustained increase of the SPN prior to uncertain outcomes may be the most relevant to motivational components of reward processing, such as wanting and incentive salience. Indeed, there is evidence that the SPN is increased on trials preceded by a large monetary reward, compared to either a small reward or a loss (Masaki, Takeuchi, Gehring, Takasawa, & Yamazaki, 2006). The FN, on the other hand, may be most relevant to reinforcement learning, with FN amplitude being sensitive to violations of outcome expectation and reflecting reward prediction error signals (Hajcak et al., 2007; Holroyd & Krigolson, 2007).

Integrating information from these two components allows for a more comprehensive assessment of dopaminergic neural activity involved in reward processing, which will be useful for studying individual differences in reward sensitivity. For example, it has been proposed that quantifying anhedonia—a pervasive lack of reactivity to rewards—in terms of dopaminergic dysfunction and other objective biological outcomes may help us to better understand core deficits associated with the etiology and course of major depressive disorder (Forbes, 2009; Nestler & Carlezon, 2006). To date, blunted neural responses in depression have been observed during both reward anticipation (Robinson, Klein, Tenke, & Bruder, 2007; Smoski et al., 2009) and delivery (Foti & Hajcak, 2009; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; McCabe, Cowen, & Harmer, 2009; Pizzagalli et al., 2009). In building on this research, it will be informative to examine whether there are co-occurring deficits in SPN and FN amplitudes in depressed individuals as well as the extent to which the SPN and FN may uniquely relate to self-reported anticipatory anhedonia and abnormal reward learning, respectively.

The modulation of the SPN by outcome uncertainty observed here maps closely onto a previous study of in vivo dopamine recordings showing sustained, anticipatory activation varying with reward probability, with the largest response for 50% reward likelihood (i.e., maximum uncertainty) and a decreasing response for more predictable outcomes (Fiorillo et al., 2003). Uncertainty is thought to be an aversive state (Luhmann, Ishida, & Hajcak, 2011), and uncertain reward outcomes are rated as more unpleasant (Tobler, O’Doherty, Dolan, & Schultz, 2007). Broadly, the augmentation of the SPN among Met carriers during the anticipation of uncertain outcome may reflect increased reactivity to aversive states. In line with this perspective, Met carriers have been shown to exhibit potentiated startle (Montag et al., 2008), increased visual ERPs (Herrmann et al., 2009), and increased amygdala and prefrontal activation (Smolka et al., 2005) while viewing unpleasant images. Insofar as the SPN has also been shown to be increased in anticipation of unpleasant images (Poli, Sarlo, Bortoletto, Buodo, & Palomba, 2007), it may be of interest to see whether this emotional modulation of the SPN is also influenced by COMT allele status.

The current results build on the existing literature demonstrating a moderating effect of COMT allele status on neural activity associated with reward processing. Converging with prior fMRI work (Dreher et al., 2009; Yacubian et al., 2007), the SPN elicited by uncertain monetary outcome appears to be enhanced among Met homozygotes. The FN in response to reward delivery also appears to be enhanced among Met homozygotes when outcome magnitude is fixed, although future work will be necessary to clarify possible differential influences of reward valence and magnitude. It is noteworthy that the effects of COMT genotype on both SPN and FN amplitudes represent independent effects: The

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**Figure 5.** Estimated marginal means of the Stimulus-Preceding Negativity (top) and Feedback Negativity (bottom) area measures, adjusting for gender, ethnicity, depression, and stress. Error bars represent the standard error of the mean.
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SPN was examined comparing uncertain and certain trials, whereas the FN was examined comparing subsequent monetary gain and loss outcomes on uncertain trials only. Both measures, therefore, appear to provide unique information about dopaminergically mediated neural activity related to reward processing.

In future work, considering the SPN and FN in conjunction as two distinct indices of reward processing will aid in developing a more complete understanding of how neural activity involved in reward processing is shaped by genotypic differences in dopamine activity.

References


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