Genetic Variability in the Dopamine System (Dopamine Receptor D4, Catechol-*O*-Methyltransferase) Modulates Neurophysiological Responses to Gains and Losses

Josep Marco-Pallarés, David Cucurell, Toni Cunillera, Ulrike M. Krämer, Estela Càmara, Wido Nager, Peter Bauer, Rebecca Schüle, Ludger Schöls, Thomas F. Münte, and Antoni Rodriguez-Fornells

Background: Interindividual variability in the processing of reward might be partially explained by genetic differences in the dopamine system. Here, we study whether brain responses (event-related potentials [ERPs], oscillatory activity) to monetary gains and losses in normal human subjects are modulated as a function of two dopaminergic polymorphisms (catechol-*O*-methyltransferase [COMT] valine [Val]158methionine [Met], dopamine receptor D4 [DRD4] single nucleotide polymorphism [SNP] -521).

Methods: Forty participants homozygous for the different alleles of both polymorphisms were selected from a larger population to assess the main effects and interactions. Based on the phasic/tonic dopamine hypothesis, we expected increased brain responses to losses and gains in participants homozygous for the Val/Val variant of the COMT polymorphism (related to higher enzyme activity).

Results: The medial frontal negativity (MFN) of the ERP and the increase in beta power for gains were enhanced for participants homozygous for the COMT ValVal allele when compared with homozygous MetMet participants. In contrast, no modulations in gain- and loss-related brain activity were found to be a function of the DRD4 SNP -521 polymorphism.

Conclusions: The results demonstrate the role of the COMT Val/Met polymorphism in the processing of reward, consistent with theoretical explanations that suggest the possible role of dopamine in the MFN and beta power increase generation. In addition, the present results might agree with the phasic/tonic dopamine theory that predicts higher phasic dopamine responses in ValVal participants.

Key Words: COMT Val158Met, dopamine, DRD4 SNP -521, gambling, reward

Behaviors related to reward, such as addiction or novelty seeking, present great interindividual variability that can be explained, at least in part, by genetic variability in the dopamine (DA) system (1–3), which plays a key role in reward processing (4). For example, DA turnover in frontal areas is largely dependent on catechol-*O*-methyltransferase (COMT) activity. Catechol-*O*-methyltransferase enzyme activity is substantially affected by a G to A polymorphism at codon 158, resulting in a substitution of valine (Val) to methionine (Met) (5). As a number of studies indicate, COMT plays a relatively minor role in DA catabolism in extracortical areas (6) and differences in subcortical areas such as the striatum have been interpreted as indirect feedback effects mediated by changes in the prefrontal cortex (PFC) (7–10). Bilder *et al.* (11) have specifically explained the behavioral effects of this polymorphism in terms of the tonic-phasic DA hypothesis. According to this hypothesis, the Met allele (associated with low enzyme activity) leads to increased levels of tonic DA but reduced levels of phasic DA in subcortical regions. It has been proposed that the relationship between performance and dopamine level in the prefrontal cortex follows an inverted U-shape (e.g., [12]). Carriers of ValVal have low prefrontal dopamine and, consequently, perform poorly in tasks demanding cognitive flexibility (e.g., Wisconsin Card Sorting Test) or the maintenance and manipulation of information in working memory (11,13). In contrast, MetMet carriers perform poorly on tasks demanding switching in conflictive situations (11) or in emotional processing tasks (13) (see also [14,15]). Thus, single studies suggest the marked influence of the Val158Met polymorphism on cognitive functions, while a recent meta-analysis (16) only found few effects mainly restricted to working memory tasks.

At the receptor level, the expression of the dopamine receptor D4 (DRD4) gene has received special attention because atypical antipsychotics such as clozapine show a high affinity for the D4 receptor (17). A relation between genetic variation in the DRD4 gene and the etiology of attention-deficit/hyperactivity disorder (ADHD) (18,19) and schizophrenia (20) has been proposed and is expressed in several brain regions related to planning, motivation, and reward (21–24). Although the direct involvement of the D4 receptor in reward processing has not yet been demonstrated, some studies suggest that there might be an association between the D4 receptor and risk-taking behavior, novelty seeking, and addiction (20,25–27). In a recent study (28), variations in the polymorphism DRD4 -521 C/T system that modulates the neurophysiological correlates of performance monitoring were found. Participants homozygous for the T allele showed an increase in error-related negativity, a negativity found after stop errors and more pronounced posterror slowing, which was interpreted as evidence supporting the impact of the DRD4 polymorphism on the prediction error signal in the basal ganglia. Altogether, these results suggest the possible role of DRD4 in reward processing.

In humans, electrophysiological studies have identified markers that specifically indicate negative or positive outcomes, such

From the Department of Neuropsychology (JM-P, UMK, EC, TFM), Otto von Guericke University, Magdeburg, Germany; Department of Basic Psychology (DC, TC, EC, AR-F), University of Barcelona, Barcelona, Spain; Department of Neurology (WN), Medical School Hannover, Hannover, Germany; Medical Genetics (PB) and Department of Neurology and Hertie-Institute for Clinical Brain Research (RS, LS), University of Tübingen, Tübingen, Germany; and Institució Catalana de Recerca i Estudis Avançats (ICREA) (AR-F), Barcelona, Spain.

Address reprint requests to Antoni Rodriguez-Fornells, Ph.D., Institució Catalana de Recerca i Estudis Avançats (ICREA), University of Barcelona, Vall d'Hebron 171, Barcelona, Spain; E-mail: antoni.rodriguez@icrea.es.

Received July 19, 2008; revised December 22, 2008; accepted January 6, 2009.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.01.006

as monetary losses/gains and positive/negative feedback. For negative outcomes, the feedback-related negativity (FRN; also medial frontal negativity [MFN], but see [29,30]) has been described to peak at 250 msec to 300 msec after the presentation of feedback (29,31,32) with neural sources in the anterior and the posterior cingulate cortex (33). The dynamics of the MFN have been explained by reinforcement learning (RL) theory (34,35), which proposes that actions with worse than expected consequences (i.e., an error in a selection task or a loss in a gambling task) lead to decreased mesencephalic dopaminergic activity that is transmitted to the anterior cingulate cortex (ACC). This RL signal is used to enhance the performance on the task. Although RL theory has been criticized recently ([36], see discussion), it clearly suggests that the MFN might be modulated by dopaminergic polymorphisms. With regard to positive outcomes, a power enhancement of high-frequency (20–30 Hz) oscillatory beta activity after positive feedback has been described recently that is sensitive to the magnitude (37) and probability (38) of the gains.

Using an established gambling paradigm (37), the present investigation examines the influence of polymorphisms of the dopaminergic system, COMT Val158Met and DRD4 -521 C/T, on neurophysiological correlates of the processing of monetary gains and losses. In light of the proposal that COMT Met carriers have reduced subcortical phasic dopamine responses (11), we hypothesized that there would be a smaller MFN to monetary losses and also a reduced oscillatory beta response to monetary gains in these participants compared with homozygous carriers of the Val allele. In addition, to the extent that the MFN and the error-related negativity (ERN) to performance errors represent partially overlapping cognitive and neural processes, previous results showing an increase in the ERN in participants homozygous for the T allele of the DRD4 -521 polymorphism (29) suggest that these subjects might also present a larger MFN compared with C carriers.

Methods and Materials

The local ethics committee approved all procedures and written informed consent was obtained from all participants.

Participants

A group of 658 undergraduate students (between 18 and 35 years of age) underwent genotyping of the -521 C/T DRD4 promoter polymorphism (20), as well as the COMT Val158Met polymorphism (5), as described in Supplement 1.

Of these, 48 (Caucasian, university students; mean age: 28.1 ± 3.1 years, 34 women) were selected for the electrophysiological study because they were homozygous for the two genes under investigation. Four groups of 12 participants each were created for each of the four possible combinations: C/C-MetMet, T/T-MetMet, C/C-ValVal, and T/T-ValVal. None of the subjects had a history of neuropsychiatric disorders (including alcohol abuse), as determined via a detailed health questionnaire.

Design

We used an established gambling task (37) in which the numbers 5 and 25 were presented in white on a black background in one of the possible orders, 5 25 or 25 5. Participants selected one of the numbers by pressing a spatially corresponding button with the left or right index finger. One second after the choice, one of the numbers turned green, while the other changed to red. If the number selected by the participant changed to red (green), this signaled a loss (gain) of the corresponding amount of money (in Euro cents). Two seconds later, the next trial began with the presentation of a warning signal (*; 500 msec duration) followed by a new pair of numbers. Participants were provided with an initial sum of 10€ and were encouraged to gain as much as possible and were familiarized with the task during a brief practice block.

The experiment was comprised of 17 blocks of 40 trials each, with the mean expected value of monetary outcome zero on each block, to avoid potential confounding influences of a differential probability of gains or losses. Every 10 trials, the accumulated amount of money was presented for 7 seconds, and at the end of the experiment, the participants were paid the final amount.

Electrophysiological Recording

Electroencephalogram (EEG) was recorded using tin electrodes mounted in an elastic cap in 29 standard positions (Fp1/2, Fz, F7/8, F3/4, Fc1/2 Fc5/6, Cz, C3/4, T7/8, Cp1/2, Cp5/6, Pz, P3/4, P7/P8, Po1/2, O1/2, impedance <5kOhm). Biosignals were re-referenced offline to the mean of the activity at the two mastoid processes. Vertical eye movements were monitored with an electrode at the infraorbital ridge of the right eye. The electrophysiological signals were filtered with a bandpass of .01 Hz to 70 Hz (half-amplitude cutoffs) and digitized at a rate of 250 Hz. Eight participants were removed from further analysis due to technical problems, leaving 10 participants per group (C/C-MetMet, T/T-MetMet, C/C-ValVal and T/T-ValVal).

Data Analysis

Feedback-locked event-related potentials (ERPs) were averaged for epochs of 1100 msec, starting 100 msec prior to the feedback (baseline). Epochs exceeding ±50 μV in electrooculogram (EOG) or EEG were removed from further analysis.

To study the time-frequency behavior of the electrical activity elicited by the feedback, 4-sec epochs were generated (2000 msec before and after the feedback stimulus). Single-trial data were convoluted using a complex Morlet wavelet:

$$w(t,f_0) = \left(2\pi\sigma_t^2\right)^{-1/2} e^{\frac{-t^2}{2\sigma_t^2}} e^{2i\pi f_0 t}$$

with the relation f_0/σ_f (where $\sigma_f = 1/(2\pi\sigma_t)$) set to 6.7 (39). Changes in the time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (from 1 Hz to 40 Hz; linear increase) with respect to baseline were computed for each trial and averaged for each subject before performing a grand average.

Time windows for analyses were derived from an earlier study using different subjects (38). Analyses of variance (ANOVAs) with condition and electrode location (Fz, Cz, Pz) as within-subject factors and COMT (ValVal, MetMet) and DRD4 (CC, TT) as between-subject factors were performed using the Greenhouse-Geisser epsilon correction as appropriate.

Results

Behavioral Results

Participants selected "5" in 45.5 ± 10% and "25" in 55.5 ± 10% of trials. On average, participants lost .5 ± 4.0 €. There were no significant differences in the genetic subgroups with regard to the selection (5 or 25) or the amount of money gained over the course of the experiment [$F(1,36) < 2$, ns; see Table 1]. No differences were seen among groups in high selection (25 instead of 5) after maximum loss [$F(1,36) < .5$, ns] or after

Table 1. Demographic and Behavioral Parameters Associated with Each Genetic Subgroup (mean ± SD)

	CC/MetMet	CC/ValVal	TT/MetMet	TT/ValVal
Sex (F/M)	7/3	8/2	7/3	8/2
Age (mean years)	20.3 ± 2.0	20.8 ± 1.4	24.7 ± 5.0	21.9 ± 2.4
Reaction Time (msec)	627 ± 179	580 ± 242	764 ± 348	642 ± 288
Percentage of High Value Choices (%)	55 ± 8	52 ± 6	53 ± 11	53 ± 12
Percentage of High Value Choices After Maximum Loss (%)	55 ± 10	53 ± 10	51 ± 15	54 ± 16
Percentage of High Value Choices After Maximum Gain (%)	58 ± 16	47 ± 10	55 ± 15	55 ± 16

F, female; M, male; Met, methionine; Val, valine.

maximum gain [$F(1,36) < 1.7$, ns; Table 1]. There were also no reaction time effects among groups [$F(1,36) < 1.3$, ns; Table 1].

Event-Related Potentials

A frontocentral MFN that peaked between 250 msec and 300 msec was observed for losses (Figure 1). An ANOVA on the mean amplitude (250 msec to 300 msec) with valence (gain vs. loss, averaged across maximum and minimum conditions) and electrode site (midline locations: Fz, Cz, Pz) as factors revealed a main effect of valence [$F(1,36) = 104.8$, $p < .001$; losses 8.0 ± 1.0 μV; gains 12.6 ± 1.3 μV; note that absolute values are positive because the MFN is superimposed on a slow positive deflection]. This effect was larger at Fz and Cz [electrode × valence $F(2,72) = 15.9$, $p < .001$].

All groups showed an MFN (Figure 2). A significant valence by COMT interaction was found [$F(1,36) = 9.4$; $p < .005$, reflecting the larger difference between gain and loss conditions in the ValVal group (Figure 2B)]. Clearly, the amplitude of the MFN in the difference waveform gain minus loss was larger in the ValVal than the MetMet group. In contrast, the effect of valence was neither modulated by the DRD4 polymorphism nor by a DRD4 × COMT interaction [$F(1,36) < 1$, ns for valence × DRD4 and for valence × DRD4 × COMT interaction). Also, we observed no genetic modulation of the gain minus loss waveform peak latency [TT MetMet 280 ± 26 msec; CC MetMet 286 ± 20 msec; TT ValVal 279 ± 18 msec; TT MetMet 298 ± 22 msec; COMT $F(1,36) = .6$, ns; DRD4 $F(1,36) = 3.1$, ns; COMT × DRD4 $F(1,36) = .9$, ns).

We also tested for magnitude effects in the loss conditions (maximum loss vs. minimum loss) and found a higher amplitude for maximum [8.9 ± 1.1 μV; minimum 7.2 ± .9 μV; $F(1,36) = 19.0$; $p < .001$] losses. This effect was also significantly modulated by the COMT polymorphism [magnitude × COMT, $F(1,36) = 5.54$; $p < .05$] with ValVal carriers presenting a greater difference between maximum and minimum loss. As was the case with valence, no effect of DRD4 on the magnitude effect of the MFN was found [magnitude × DRD4, $F(1,36) = .5$, ns]. Since MFN differences may partly be due to the overlap of a large positive component (40), we performed the same analysis on the difference waves as suggested by Holroyd and Krigolson (41). Thus, we compared maximum loss minus maximum gain with minimum loss minus minimum gain, which revealed a significant effect [$F(1,36) = 7.1$; $p < .05$] but no genetic modulation [$F(1,36) < 2$, ns]. Therefore, the MFN magnitude effects found in previous analyses may partially be due to a modulation of a larger effect of the P3 component.

Time-Frequency Analysis

Time-frequency analysis revealed greater activity in the beta range for gains than for losses (see Figure 1 in Supplement 1 and Figure 3; 20–30 Hz, 250–400 msec as in [37]), valence effect [$F(1,36) = 14.2$; $p < .001$]. This effect was greatest at Fz [valence × electrode interaction $F(2,72) = 4.5$; $p < .05$; Fz: $t(39) = 4.4$; $p < .001$; Cz: $t(39) = 3.9$; $p < .001$; Pz: $t(39) = 2.8$; $p < .01$].

Figure 4 shows the difference between gain and loss trials for all groups at the Fz electrode. A significant valence × COMT interaction was found [$F(1,36) = 6.3$; $p < .02$], showing a greater difference in the beta range for the ValVal than the MetMet group. No significant effect of DRD4 [valence × DRD4 $F(1,36) < 1$; ns] was found on the modulation of beta activity by valence.

Given that beta activity is sensitive to gains (Figure 4C), we tested for the possible effect of magnitude in gain trials. No significant main effect of magnitude was found for the beta

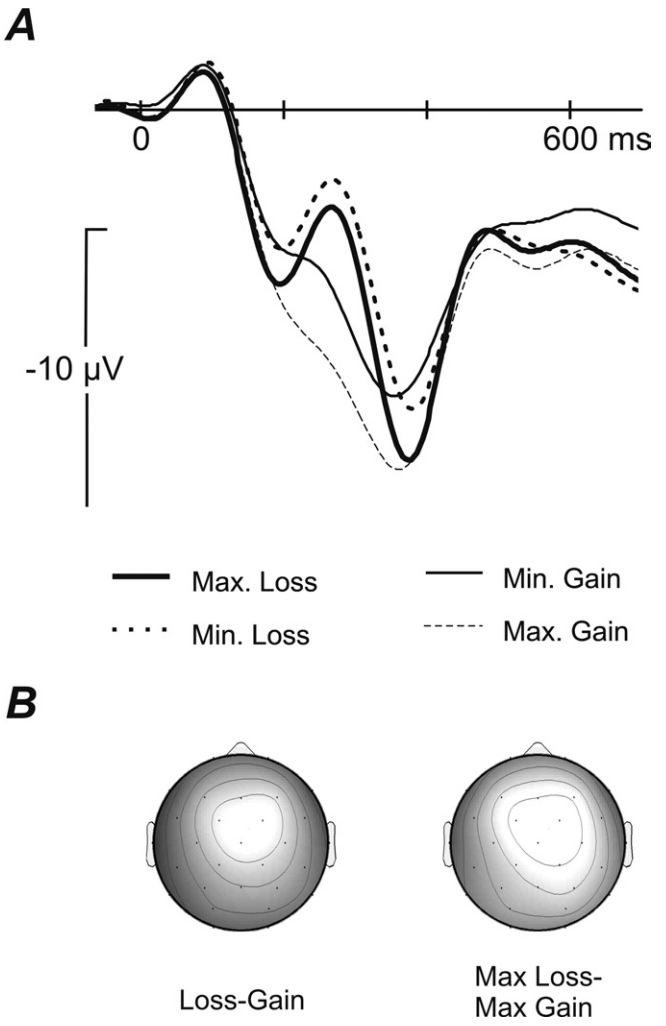

Figure 1. (A) Grand average waveforms at Fz for all the participants. A large increase in the MFN is observed in response to monetary losses (either 5, minimum loss, or 25, maximum loss). **(B)** Scalp distribution of the MFN component derived from difference waveforms (spherical spline-interpolated isovoltage maps; 40 msec interval centered on the peak amplitude value). MFN, medial frontal negativity.

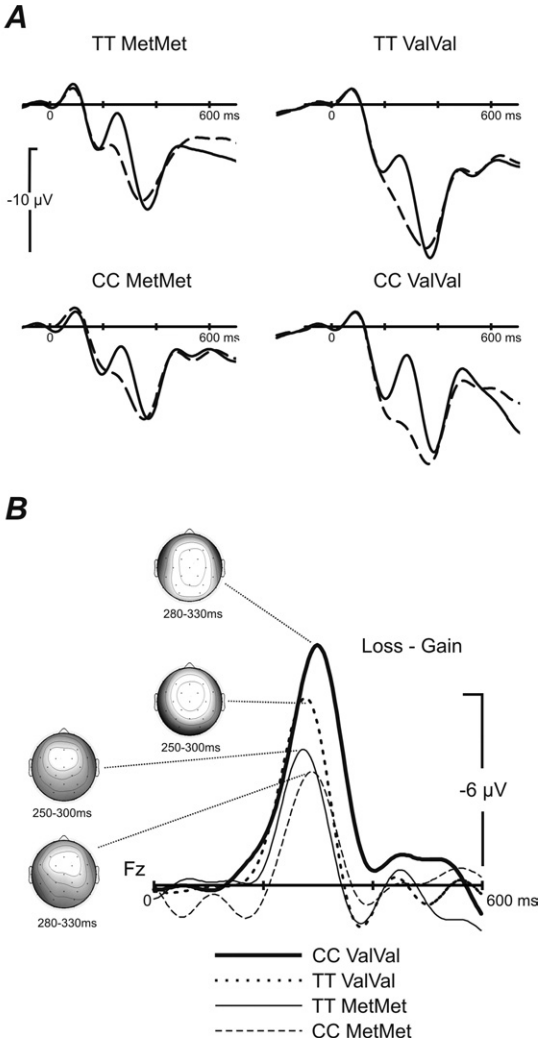

Figure 2. (A) Grand average waveforms for the gain and loss conditions at Fz for the four groups studied: TT MetMet (left top), TT ValVal (right top), CC MetMet (bottom left), and C ValVal (bottom right). Notice that all the groups show a clear MFN deflection. **(B)** Difference waveforms (loss minus gain) at a frontal location (Fz) for all groups. ValVal groups presented significantly greater difference than MetMet groups. Scalp distributions of the MFN component derived from the difference waveforms for each group are also depicted (spherical spline-interpolated isovoltage maps; 40 msec interval centered on the peak amplitude value). Met, methionine; MFN, medial frontal negativity; Val, valine.

activity [$F(1,36) = 2.5$; ns]. However, the ValVal group exhibited greater beta activity in the gain trials than the MetMet group [COMT main effect $F(1,36) = 4.1$; $p < .05$]. No other effects were found on the beta magnitude of gain trials.

Discussion

We used a simple gambling paradigm to investigate how the processing of gains and losses is moderated by interindividual differences in DRD4 and COMT genes. With regard to the COMT polymorphism, participants homozygous for the Val allele presented a larger MFN amplitude than participants homozygous for the Met allele. In addition, the high-frequency beta response to gains was much smaller in MetMet participants. By contrast, no differential effects were observed for the DRD4 -521 polymorphism for either the MFN or the beta oscillatory response.

This result raises questions as to the locus of the COMT modulation. Where COMT directly influences cortical DA levels, remote effects on striatal activations (42,43) and on midbrain dopamine synthesis (10) have been reported. Bilder *et al.* (11) and Meyer-Lindenberg and Weinberger (44) make specific suggestions regarding cortical-subcortical interactions. Reinforcement learning theory (34) may explain the pattern for the COMT polymorphism by a greater phasic DA response in subcortical regions in carriers of Val alleles. According to RL theory, this would translate into a greater amplitude of the modulatory dopaminergic signal transmitted from the mesencephalic dopamine system to the anterior cingulate cortex and, hence, to a greater amplitude of the medial frontal negativity to losses in the MFN ERP. However, where an increase in dopaminergic activity for ValVal carriers might be explained by proposed cortico-subcortical interaction schemes (11,44), it is more difficult to mechanistically explain phasic decreases of DA for losses. The ACC is the target of three main pathways related to emotional and motivational states (45). Animal studies have demonstrated midbrain-cingulate connections that could underlie the negative deflection in the anterior cingulate cortex produced by a mesencephalic dopaminergic activity decrease (45). A second important pathway to the ACC comes from the limbic system, mainly from the amygdala and ventral striatum (45,46). Using invasive recordings in awake humans (47), we have shown that error-related modulations, similar to the scalp ERN, are produced locally in the nucleus accumbens. Moreover, nucleus accumbens activity preceded the scalp ERN by 40 msec. To the extent that ERN and MFN are supported by similar RL processes (34), this suggests that the nucleus accumbens might be involved in the MFN generation. Finally, striatal activity could also impact the production of MFN by an indirect thalamic route, given that the ACC is the target of afferents from the thalamus, specifically from the mediodorsal, anterior, and midline thalamic nuclei.

A recent study has proposed a modification to RL theory in which the MFN might be a specific instance of a more common component, the N200, and that the response to positive feedback

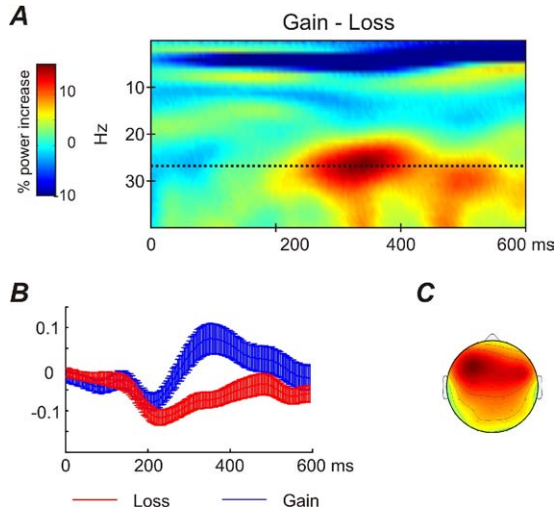

Figure 3. (A) Differences in change in power with respect to baseline (100 msec period prior to feedback stimulus) between the gain and loss conditions at Fz. **(B)** Time course of beta activity at 27 Hz (dotted lines in **[A]**) plotted for gain and loss conditions with the corresponding standard error of the mean. **(C)** Scalp distribution of power (gain minus loss) scalp maps for beta response (20 Hz to 30 Hz) at the 250 msec to 400 msec time range.

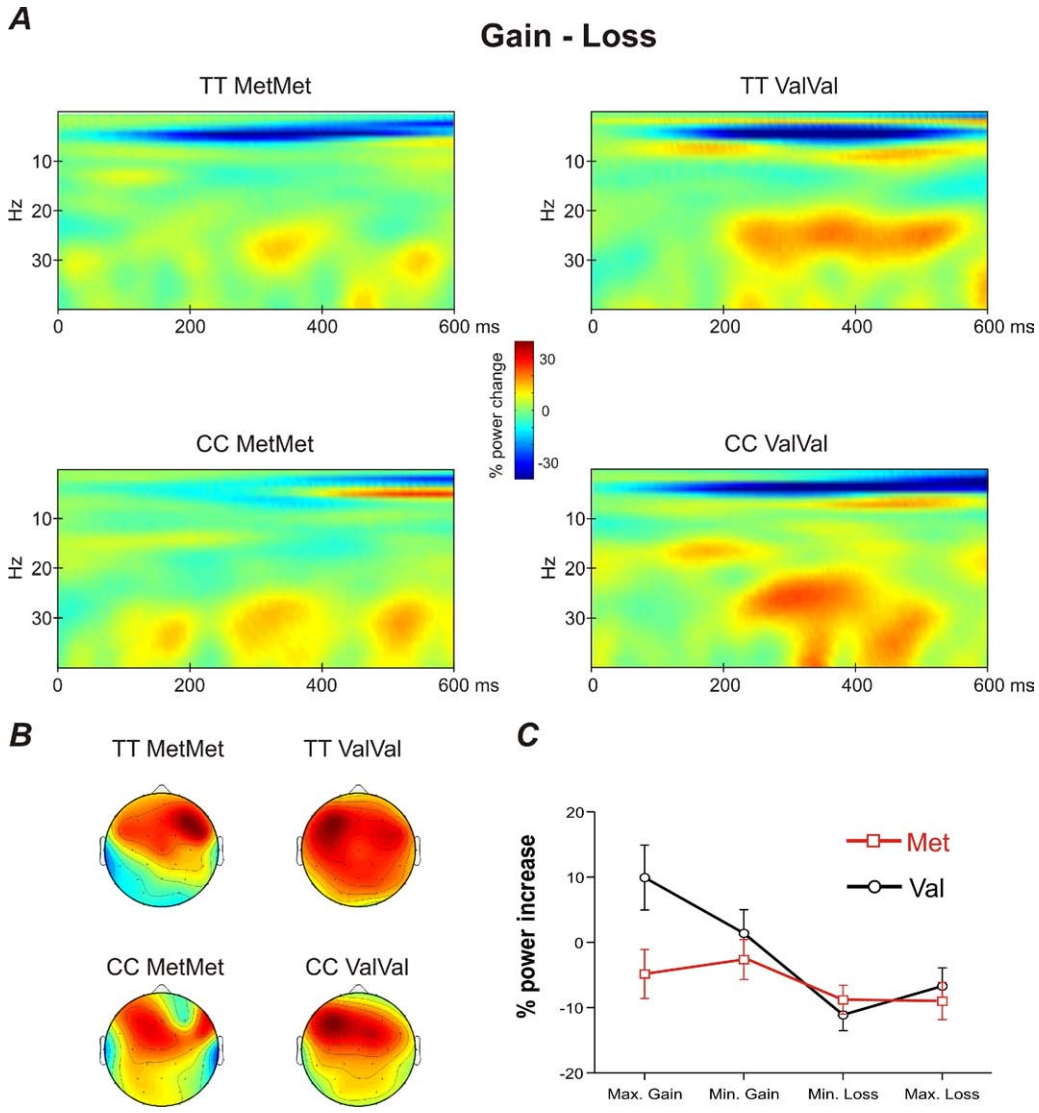

Figure 4. (A) Differences in change in power with respect to baseline (100 msec period prior to feedback stimulus) between the gain and loss conditions at Fz location for the four studied groups: TT MetMet (left top), TT ValVal (right top), CC MetMet (bottom left), and CC ValVal (bottom right). Note the increase of beta activity with respect to baseline in the gain compared with loss condition in the ValVal group and the lack of beta power increase in the MetMet group. **(B)** Scalp maps at beta band (20 Hz to 30 Hz, 250 msec to 400 msec time interval) for the four groups. **(C)** Changes in power with respect to baseline (100 msec period prior to feedback stimulus) at Fz in the beta band in the ValVal and MetMet groups. Note the increase of power of beta band in the gain conditions in the ValVal group. Met, methionine; Val, valine.

is characterized by a reduction of this component (48). In other words, negative feedback would give rise to the default N200, whereas positive feedback would elicit a component (the feedback correct-related positivity) that adds a frontocentral, positive-going deflection that cancels the N200 modulation. If this was the case, the differences between gain and loss ERPs in the current study should be interpreted as produced by the gain instead of the loss trials, paralleling results found with the reward-related beta activity (see below).

Although RL theory of the MFN has received a lot of support in recent years and seems to fit well with the present data, some authors have noted that a decrease of midbrain dopaminergic activity in the ventral tegmental area may not be fast enough to drive the MFN component in the ACC (36). Therefore, they propose that the decrease in midbrain dopaminergic activity after a worse than expected outcome is produced by top-down modulation coming from frontal areas, especially from the ACC, rather than the other way around. The present results do not clearly support the different accounts, but obviously there is a need to reconsider RL theory in light of these and other results.

The increase in high-frequency beta oscillatory activity to monetary gains in carriers of the Val allele compared with the Met allele could also be attributed to a higher amplitude in the phasic modulatory dopamine signal. This oscillatory beta response replicates recent observations in our laboratory (37). In parallel, Cohen *et al.* (38) also describe a high-frequency oscillatory component that is correlated to the probability of the gain. While the nature of this component has not been fully explored, it has been proposed that it might be a candidate for a neural marker of reward associated with monetary gains. Interestingly, an increase in beta activity has been found in the striatum of macaque monkeys after receiving a reward in a simple motor

task (49). Also, an increase in cortical EEG beta power after reward delivery has been observed in humans (50). Given the role of high-frequency oscillations in the communication of distant neural assemblies (51), we have suggested in previous works that beta oscillations might be involved in the synchronization of neural populations (e.g., within frontostriatal circuits) involved in the processing of reward and emotion (37). The increased beta power in ValVal carriers compared with the MetMet group could, in the light of the Bilder *et al.* (11) model, be due to increased phasic dopaminergic activity in the striatum, which in turn is due to a reduction in the tonic prefrontal dopaminergic activity. However, since in the present sample we did not have a heterozygote group, it is not possible to know to what degree the increase observed in beta for the ValVal group is driven by the Val allele inducing greater beta power or the Met alleles eliciting less beta power (or a combination of both effects).

With regard to reward processing, Yacubian *et al.* (43) recently reported functional magnetic resonance imaging (fMRI) data from a reward prediction task in participants differing in polymorphisms of the COMT and dopamine transporter (DAT) genes. Prefrontal and striatal areas showed an increase in activity for participants homozygous for Met alleles during reward anticipation relative to Val allele homozygotes. At first glance, our results would seem at odds with those of Yacubian *et al.* (43). It has to be kept in mind, however, that the current study investigated neural activity at the time of delivery of gains and losses, while Yacubian *et al.* (43) studied anticipation of uncertain rewards. Previous studies have shown that the brain network associated with expected monetary gains is different from the one associated with the experience of monetary gains (52). In addition, two networks covarying with different reward information signals have been delineated. The response properties of these networks have been related to transient (prefrontal cortex) and sustained (ventral striatum) dopaminergic activities (53). Also, Schultz (54,55) has recently pointed out that at the postsynaptic neuronal level, a distinction between uncertainty and reward signals could be made according to the differential stimulation of dopamine receptors. While the uncertainty signal, investigated in the Yacubian *et al.* (43) experiment, evokes low dopamine concentrations appropriate for stimulating high-affinity dopamine D2 receptors, the reward signals studied in the present investigation induce much higher dopamine concentrations appropriate for stimulating low-affinity dopamine D1 receptors (see also [56]). We thus propose that the apparent contradiction between Yacubian *et al.* (43) and the present results are related to the differential role of tonic (Yacubian *et al.* [43]) and phasic (current experiment) dopamine signals and their orthogonal relationship to COMT activity. Where the Yacubian *et al.* (43) study, as well as fMRI data from our own group (E. Camara *et al.*, unpublished data, 2008), demonstrated the influence of the COMT polymorphism on ventral striatum activations, a recent fMRI study by Forbes *et al.* (57) on the role of four dopamine-associated genes (dopamine transporter 1 [DAT1] variable number tandem repeat [VNTR], DRD4 thin exon 48 base pair [bp] VNTR, dopamine receptor D2 [DRD2] -142 insertion/deletion variant [Ins/Del], and COMT Val158Met) in reward processing and impulsivity failed to find an effect of the COMT polymorphism on ventral striatal reactivity. Since at least two studies have demonstrated COMT modulation of reward-related activity in the ventral striatum (43; E. Camara *et al.*, unpublished data, 2008), we suggest specific design aspects as an alternative explanation for the missing effect found by Forbes *et al.* (57). Specifically, a blocked design was used in Forbes *et al.* (57) and possible outcome effects (i.e., E. Camara *et al.*, unpublished data, 2008, and the present study) might be obscured by increases in striatal activation in reward anticipation in the MetMet group (43). However, the interpretation entertained by Forbes *et al.* (57) may serve as a reminder that the origin of the impact of the COMT Val158Met polymorphism on the electrophysiological correlates of reward processing in the current study needs further specification.

Interestingly, we found no relationship between the C and T alleles of the DRD4 -521 polymorphism and the MFN or beta increase after positive feedback. Polymorphisms in the DRD4 gene have been shown to be related to addiction (58,59) and novelty seeking (27), which can be considered to be reward-related. In addition, DRD4 knockout mice have been shown to have an increased sensitivity to ethanol (26), cocaine, and methamphetamine. In spite of these indications that the DRD4 might be involved in reward processing, the current results do not show a relationship of the DRD4 -521 polymorphism to the processing of gains and losses. The current pattern is different from recent findings from our laboratory (28) in a flanker task designed to investigate action-monitoring processes. In this study, participants homozygous for the DRD4 T allele showed an increased error-related negativity following choice errors and failed inhibitions compared with participants homozygous for the C allele. This was associated with more pronounced compensatory behavior reflected in higher posterror slowing. A slightly enhanced ERN amplitude was also found for carriers of the Val allele compared with Met allele carriers. Therefore, this differential modulation of the MFN and ERN by the DRD4 -521 single nucleotide polymorphism (SNP) might suggest that the two electrophysiological phenomena might be distinct (29,33) or might, in contrast, reflect a differential modulation of the DRD4 -521 SNP on the input to the MFN system (i.e., [60]) rather than the MFN/ERN itself. However, a lack of statistical power might also explain the failure to find a DRD4 effect.

Another interesting aspect of the current set of results is that the MFN has been studied recently in the context of learning (33,34,61,62) using either probabilistic or associative learning tasks. In such tasks, the ERN and MFN amplitudes are inversely related, suggesting that the MFN is related to the information transmitted by the negative feedback signal (see also [63]). Thus, the current results may suggest differences in learning from negative feedback for the different COMT alleles. In fact, there is initial behavioral evidence in this direction (64) that needs to be followed up with electrophysiological studies.

In conclusion, the results of this investigation show that brain electric activity to monetary gains and losses is modulated by COMT activity, which is modulated by the Val158Met polymorphism but not by the DRD4 -521 promoter polymorphism. More specifically, our results show larger MFN to monetary losses and increased medial frontal beta oscillations for Val allele carriers in the COMT gene, which we take to reflect a lower tonic prefrontal dopaminergic activity and a higher striatal phasic activity compared with Met allele carriers as previously suggested (11,14,15).

This study was supported by a grant from the Volkswagen-Foundation awarded to TFM, AR-F, and LS. JM-P was supported by the Alexander von Humboldt Foundation and is a fellow of the Ramon y Cajal program from the Spanish Ministry of Education and Science.

We thank Andrea Seibel for excellent technical assistance in sequencing and genotyping procedures and Jürn Möller and Anna Mestres-Missé for help in behavioral testing.

All authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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