Cerebral Cortex August 2010;20:1985–1996
doi:10.1093/cercor/bhp263
Advance Access publication December 27, 2009

The Effects of COMT (Val108/158Met) and DRD4 (SNP −521) Dopamine Genotypes on Brain Activations Related to Valence and Magnitude of Rewards

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People's sensitivity to reinforcing stimuli such as monetary gains and losses shows a wide interindividual variation that might in part be determined by genetic differences. Because of the established role of the dopaminergic system in the neural encoding of rewards and negative events, we investigated young healthy volunteers being homozygous for either the Valine or Methionine variant of the catechol-*O*-methyltransferase (COMT) codon 158 polymorphism as well as homozygous for the C or T variant of the SNP −521 polymorphism of the dopamine D4 receptor. Participants took part in a gambling paradigm featuring unexpectedly high monetary gains and losses in addition to standard gains/losses of expected magnitude while undergoing functional magnetic resonance imaging at 3 T. Valence-related brain activations were seen in the ventral striatum, the anterior cingulate cortex, and the inferior parietal cortex. These activations were modulated by the COMT polymorphism with greater effects for valine/valine participants but not by the D4 receptor polymorphism. By contrast, magnitude-related effects in the anterior insula and the cingulate cortex were modulated by the D4 receptor polymorphism with larger responses for the CC variant. These findings emphasize the differential contribution of genetic variants in the dopaminergic system to various aspects of reward processing.

Keywords: dopamine, fMRI, polymorphism, reward, ventral striatum

Introduction

Much of human behavior as well as that of other species is driven by the desire to increase rewards and to minimize negative, punishing events. The association of an event with a reward or a loss therefore constitutes a powerful learning signal. Interestingly, humans show a great interindividual variation in their sensitivity to rewards on the one hand and susceptibility to punishments (or losses) on the other hand (Gray 1987; Carver and White 1994; Depue and Collins 1999; Torrubia et al. 2001). Moreover, work in experimental economics (Camerer et al. 2005; Glimcher et al. 2005) and decision science (Schall 2005) suggests that there are also interindividual differences with regard to the way we deal with rewards and losses of different magnitude.

A considerable portion of interindividual differences in the processing of reward valence and magnitude might be attributed to genetic factors. The present experiment was conducted with the aim to provide further evidence for a link between genetic variability and reward processing. Of particular relevance for the processing of rewards is the dopaminergic system encompassing several midbrain structures (e.g., ventral tegmental area and substantia nigra) and projecting to the ventral striatum (including the Ncl accumbens, NAcc) and the prefrontal cortex among other structures (Apicella et al. 1991; Hikosaka and Watanabe 2000; Wise 2002), which is the main reason to focus on the genetic variations in the dopaminergic system for the current study. For example, Schultz (1998) recorded phasic activity of midbrain dopamine (DA) neurons from primates and showed that their firing rate changed according to the delivery of and expectation for salient and rewarding events. Specifically, increases of DA cell firing were associated to positive outcomes, whereas choices that did not lead to a reward evoked dips in the firing rate that were below baseline (Schultz 2002).

Functional magnetic resonance imaging (fMRI) studies have firmly established a role of the ventral striatum/NAcc in reward processing (Delgado et al. 2000, 2003; Breiter et al. 2001; Knutson et al. 2001, 2003; McClure et al. 2004; Yacubian et al. 2006; Tom et al. 2007; Riba et al. 2008) with the activity varying as a function of reward magnitude and probability. Moreover, the interactions of the medial prefrontal cortex (anterior cingulate cortex [ACC]) and the ventral striatum, both structures receiving DA input from the midbrain, in the adjustment of behavior have been recently highlighted.

The key role of DA in the processing of rewards has fuelled research on the possible contribution of genetic variability in the DA system to interindividual differences in reward processing (Cohen et al. 2005; Frank et al. 2007; Yacubian et al. 2007; Marco-Pallarés et al. 2009) and related functions such as error monitoring (Klein et al. 2007; Krämer et al. 2007). The present study following these earlier observations examines the influence on reward processing of polymorphisms in 2 genes, the catechol-*O*-methyltransferase (COMT) and the DA D4 receptor (DRD4), and by focusing on the effects of reward magnitude in addition to valence.

COMT is an enzyme involved in DA degradation, mostly present in the prefrontal cortex (Chen et al. 2004). A common polymorphism at codon 158/108 (valine → methionine exchange) is associated with a 3- to 4-fold variation in the

enzymatic activity. Thus, persons homozygous for the Val/Val allele should have a 4-fold higher COMT activity in the prefrontal cortex compared with Met/Met carriers. This should lead to lower tonic DA levels and therefore an inhibition of prefrontal functioning. More importantly, several authors have pointed out that different levels of prefrontal DA lead (via glutamatergic projections to the striatum and midbrain) to effects in phasic DA release in the striatum (Bilder et al. 2004; Meyer-Lindenberg and Weinberger 2006). We therefore predicted that the differential levels in prefrontal DA in the ValVal and MetMet groups should, via prefrontal–striatal interactions, lead to a differential modulation of reward and loss-related activity in the ventral striatum.

In addition to COMT, the present study also focuses on a polymorphism (C/T substitution at position −521) in the DRD4 gene. The −521 C/T single nucleotide polymorphism (SNP) belongs to a series of polymorphisms identified in the promoter region of the DRD4 gene including a 120-bp duplication and other SNPs (−616 G/C, −615 A/G, and −1217 G insertion/deletion). The T-allele has been associated with 40% inferior transcriptional efficiency relative to the C-allele (Okuyama et al. 1999; but see for different results Kereszturi et al. 2006). The D4 receptor, which is a D2-like receptor (Strange 1993), is expressed in several brain regions related to planning, motivation, and reward (Meador-Woodruff et al. 1994; Matsumoto et al. 1996; Mrzljak et al. 1996; Ariano et al. 1997; Sanyal and Van Tol 1997). The association between the DRD4 −521 polymorphism and novelty seeking (Okuyama et al. 2000; Ronai et al. 2001; Schinka et al. 2002; Golimbet et al. 2007) or addiction (Geijer et al. 1997; Rubinstein et al. 1997) is well established, but no information is available with regard to the processing of rewards.

To evaluate the influence of COMT and DRD4 SNP −521 polymorphisms on the processing of reward valence and magnitude, selected volunteers, homozygous for each of the 2 polymorphisms, participated in a gambling task (modified from Gehring and Willoughby 2002; see Marco-Pallares et al. 2007). The gambling task was modified from these earlier studies such that in addition to standard gain and loss trials of either 5 or 25 Euro cent unexpected, larger monetary gains and losses (125 Euro cent) were presented in 10% of the trials. Motivated by animal experiments demonstrating dopaminergic activity in the midbrain to be highest for unexpected rewards, such boost trials (restricted to gains, however) have been introduced by Riba et al. (2008) in a slow event-related fMRI design. Indeed, unexpected and large wins led to an increase of activation in the ventral striatum. We therefore included such unexpected trials in the current study and expected to observe genetic effects in particular for these trials as they engage the dopaminergic system to a higher degree than standard trials.

Materials and Methods

Participants

All procedures reported in this investigation were approved by the local ethical Institutional Review Board (IRB00003099) at the University of Barcelona.

An initial pool of 655 students from the University of Barcelona (491 women; age range from 18 to 39, mean = 21.7, standard deviation = 3.5) was genotyped by preparing DNA using standard techniques from 2 independent ethylenediaminetetraacetic acid blood samples of each participant. Genotyping of the −521 C/T polymorphism in the DA D4 receptor gene (DRD4) promoter (Okuyama et al. 1999) as well as the COMT G to A polymorphism at codon 108/158 (short/long isoform) resulting in valine to methionine substitution (Lachman et al. 1996) was carried out using real-time fluorescence resonance energy transfer polymerase chain reaction (PCR). The region spanning the SNP was amplified with the primers DRD4for (5′ CTG AGG GCC AGA GGC TG 3′)/DRD4rev (5′ GAG GAT CAA CTG TGC AAC GG 3′) and COMTfor (5′ GGG CCT ACT GTG GCT ACT CA 3′)/COMTrev (5′ TTC AGT GAA CGT GGT GTG AAC A 3′), respectively. The polymorphic nucleotide is covered by the fluorescein-labeled donor probe (DRD4sensor 5′ CGG GCG TGG AGG GCG CG-Fl 3′; COMTsensor 5′ ATT TCG CTG GCA TGA AGG ACA A-Fl 3′). The adjacent acceptor probe (DRD4anchor 5′ LCRed610-GAC TCG CCT CGA CC–TCG T 3′; COMT anchor 5′ LCRed610- GTG TGC ATG CCT GAC CCG TTG TCA-ph 3′) was labeled with LCRed640). Melting curve analysis of the matrix-probe duplex is allele dependent and allows discrimination of the 2 SNP alleles. Primers and probes were designed and synthesized by Tib Molbiol, Germany. Amplification and melting analysis were carried out on a LightCycler480 instrument (Roche Diagnostics, Germany). For PCR amplification, the LightCycler480 genotyping master (Roche Diagnostics) was used in a 384-well format with 10-μL reaction volumes. Cycling conditions with touchdown annealing temperatures from 65 to 55 °C over the first 10 cycles were as following: 10 min 95 °C, 45 cycles with 20-s annealing temperature, 20 s 72 °C and 20 s 95 °C followed by a high-resolution melting curve from 50 to 85 °C with continuous fluorescence acquisition. We also examined additional polymorphisms of the dopaminergic system in the whole population of 655 participants: DRD4 exon III variable number randem repeat (VNTR), DRD4 120-bp tandem duplication upstream of the start codon, DAT1 40-bp repeat (VNTR) polymorphism in the 3 untranslated region, and MAOA 30-bp repeat in promoter. We restricted our imaging study to participants being homozygous for either the ValVal or MetMet variant of the COMT polymorphism and in addition being homozygous for the either the CC or TT variant of the DRD4 −521 polymorphism for reasons of feasibility and based on our earlier study on action monitoring (Krämer et al. 2007).

In the entire population, 128 participants (= 20.3%) were homozygous MetMet for COMT, 328 (50.8%) were heterozygous ValMet, and 182 (28.9%) were homozygous ValVal (data from 25 participants were lost due to technical reasons). With regard to the DRD4 −521 polymorphism, we observed 197 (31.2%) participants homozygous for TT, 275 (43.5%) heterozygous CT, and 160 (25.2%) homozygous for CC (data from 25 participants were lost). Hardy–Weinberg equilibrium data were tested by chi-square analysis for both genotypes ($\chi^2 = 0.81$, $P > 0.05$; $\chi^2 = 10.15$, $P < 0.005$, COMT and DRD4, respectively). As we only wanted to include persons homozygous for these 2 polymorphisms, the following participants qualified for examination: TT-MetMet $n = 43$; CC-MetMet $n = 34$; TT-ValVal $n = 61$; and CC-ValVal $n = 31$. These qualifying participants were contacted via phone or e-mail about 1 year after the first phase of the study and had to be willing to engage in several sessions of neuropsychology, imaging, and electrophysiology and to go to Magdeburg, Germany, for functional imaging.

Fifty-three participants (36 women; age range: 18–34 years, mean = 21.2) were selected for the fMRI experiment based on their DRD4 −521 and COMT alleles. We included only homozygous participants for both polymorphisms, yielding a 2-by-2 factorial design with the 4 groups TT-ValVal, TT-MetMet, CC-ValVal, and CC-MetMet. Data of 4 participants (2 TT-ValVal, 2 CC-MetMet) were lost because of technical problems during their scanner session (response device problems). Two participants had to be excluded due to a genotyping error (TC-MetMet instead of TT-MetMet and TC-ValVal instead of TT-ValVal), whereas in 1 case, the DNA replication was not possible. In another case (one TT-MetMet) participant, the participant was excluded because of a large morphological abnormality of the brain. Two more participants had to be excluded because of movements during the scanning (2 CC-ValVal), and one subject (TT-MetMet) did not follow the instructions (always responded to 25, 100% of the times). Finally, one participant presented data artifacts (distortion at the orbitofrontal side), and 2 subjects could not be scanned due to metallic dental alloys (2 CC-MetMet and 1 TT-ValVal). One subject did not finish the scanning session (CC-MetMet). This left 9 participants for the TT-ValVal group and the TT-MetMet group. Ten participants remained in the CC-ValVal and in the CC-MetMet group. The number of participants in the CC-ValVal and in the CC-MetMet group was reduced to 9 as well (by excluding 2 participants

from the analysis based on movement parameters) in order to have an equal number of participants in each group. Therefore, the final sample comprised 36 right-handed Spanish students (n = 9 per group; 24 women) of European ancestry. All participants were paid for their participation and gave written informed consent.

Genotypes of participants selected for the neuroimaging study were controlled in an independent second DNA sample by direct sequencing using the ABI PRISM BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA). Sequencing products were resolved on an ABI 3100 automated sequencer (Applied Biosystems) and analyzed using the Staden Package (Bonfield et al. 1995).

Experimental Design

Several important modifications were made to a monetary gambling task designed by (Gehring and Willoughby 2002; Marco-Pallares et al. 2008). Each trial began with a warning signal ("*"; 500-ms duration) followed by the presentation of 2 numbers (5 and 25) displayed in white against a black background in the 2 possible combinations [5 25] or [25 5]. Participants had to select 1 of the 2 numbers by pressing a spatially corresponding button with the left or right index finger (see Fig. 1). One second after the choice, one of the numbers turned into green, whereas the other turned red. If the number selected by the participant changed to red, the participant incurred a loss of the corresponding amount of money in Euro cent. In contrast, if the number turned into green, this indicated a gain.

In addition to the standard trials described above (80%), 2 additional conditions were (see Fig. 1). In 10% of the trials ("boost unexpected trials"), an unexpected large gain or loss occurred: In these trials, the number "125" appeared in either red or green signaling the loss or gain of the corresponding sum in Euro cent (see Fig. 1). This change in magnitude occurred equally often for "5" and "25" trial bets in order to avoid positive or negative biases in choosing "25" items. These "boost" trials were included, because animal studies have shown repeatedly that unexpected gains give rise to particularly high dopaminergic activity. To control for the fact that boost trials were both, large and unexpected, in an additional 10% of the trials ("similar unexpected") the chosen number turned to either 7 (instead of 5) or 27 (instead of 25). Although these trials were unexpected, the magnitude of the gain or loss was virtually unchanged. The inclusion of these similar unexpected trials allowed us to assess effects of magnitude unconfounded by probability effects (see sections on magnitude effects in Results and Discussion parts of this paper). Additionally, each run included 12 randomized fixation trials that lasted 20 s.

Participants were provided with an initial sum of 10 Euro and were encouraged to gain as much as possible. They were informed about the potential occurrence of unexpected trials. The experiment comprised 4 blocks, each one comprising 140 trials. The 4 possible outcomes for the standard trials ([*25* **5**] [*5* **25**] [**5** *25*] [**25** *5*]; italics = red = loss, bold = green = gain), for the unexpected similar trials ([*25* **7**] [*5* **27**] [**7** *25*] [**27** *5*]), and for the unexpected boost trials ([*25* **125**] [*5* **125**] [**125** *25*] [**125** *5*]) were presented in random order. These combinations were counterbalanced by condition, making the statistically expected outcome zero on each trial in order to avoid confounds of differential probability of gains or losses. At the end of each run, participants were informed about their accumulated amount of money at this point. At the end of the experiment, the participants were paid the final amount obtained (bank transfer).

MRI Scanning Methods

fMRI data were collected using a 3-T whole-body MRI scanner (Siemens Magnetom Trio, Erlangen, Germany). Visual images were backprojected onto a screen using an light-emitting diode projector and participants viewed the images through a mirror on the head coil. Magnet-compatible response buttons were used. Conventional high-resolution structural images (magnetization-prepared, rapid-acquired gradient echoes sequence, 192 slice sagittal, time repetition [TR] = 2500 ms, time echo [TE] = 4.77 ms, time to inversion = 1100 ms, flip angle = 7°, 1-mm thickness [isotropic voxels]) were followed by functional images sensitive to blood oxygenation level–dependent (BOLD) contrast (echo planar T2*-weighted gradient echo sequence, TR = 2000 ms, TE = 30 ms, and flip = 80°). Each functional run consisted of 336 sequential whole-brain volumes comprising 32 axial slices aligned to the plane intersecting the anterior and posterior commissures, 3.5-mm in-plane resolution, 4-mm thickness, no gap, positioned to cover all but the most superior region of the brain and the cerebellum.

Preprocessing

Data were analyzed using standard procedures implemented in the Statistical Parameter Mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm). The preprocessing included slice timing, realignment,

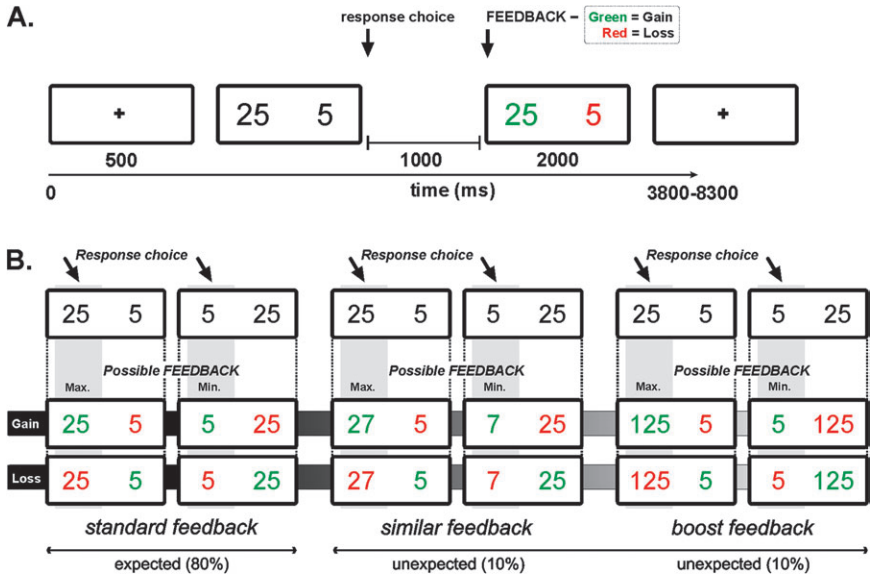

Figure 1. (*A*) Sequence of stimulus and response events in the gambling task. After a warning signal, a pair or numbers ([5 25] or [25 5]) was presented, and participants were forced to select 1 of the 2 numbers by pressing the corresponding button at left or right hand (response choice). One second after the choice, one of the numbers turned red and the other green (feedback) indicating a gain (green) or loss (red) of the corresponding amount of money in Euro cent. (*B*) In the frequent "standard feedback," trial participants gained or lost the same amount of money they betted. By contrast, in the unexpected boost feedback condition, the magnitude of the reward was much larger than the expected one (10% probability). In the "similar feedback" condition, the magnitude was changed only slightly. This allowed us to dissociate the effects of reward magnitude and reward probability.

normalization, and smoothing. First, functional volumes were phase shifted in time with reference to the first slice to minimize purely acquisition-dependent signal variations across slices. Head-movement artifacts were corrected based on an affine rigid body transformation, where the reference volume was the first image of the first run (e.g., Friston et al. 1996). Functional data were then averaged, and the mean functional image was normalized to a standard stereotactic space using the echo planar imaging (EPI)-derived Montreal Neurological Institute (MNI) template (ICBM 152, MNI) provided by SPM2. After an initial 12-parameter affine transformation, an iterative nonlinear normalization was applied using discrete cosine basis functions by which brain warps are expanded in SPM2 (Ashburner and Friston 1999). Resulting normalization parameters derived for the mean image were applied to the whole functional set. Finally, functional EPI volumes were resampled into 4-mm cubic voxels and then spatially smoothed with an 8-mm full-width half-maximum isotropic Gaussian Kernel to minimize effects of intersubject anatomical differences.

Data Analysis

The statistical evaluation was based on a least-square estimation using the general linear model by modeling the different conditions with a regressor waveform convolved with a canonical hemodynamic response function (Friston et al. 1998). Thus, an event-related design matrix was created including the conditions of interest: Gain 5, Gain 25, Gain 7/27, Gain 125, Loss 5, Loss 25, Loss 7/27, Loss 125, and fixation.

The data were high-pass filtered (to a maximum of 1/90 Hz), and serial autocorrelations were estimated using an autoregressive model (AR(1) model). Resulting estimates were used for nonsphericity correction during the model estimation. Confounding effects in global mean were removed by proportional scaling, and signal-correlated motion effects were minimized by including the estimated movement parameters. The individual contrast images were entered into a second-level analysis using a one-sample *t*-test employing a random effects analysis within the general linear model.

Main Contrasts of Interest

First, in order to reveal brain regions responding selectively to gains and losses, we created 2 contrasts: in standard trials, the comparison Gain (25 + 5) versus Loss (25 + 5) (and vice versa) reflected the effect of valence, whereas for the unexpected boost trials, the corresponding contrast was Gain (125) versus Loss (125) (and vice versa).

Second, to investigate whether differences in the previous contrasts could be explained in terms of reward magnitude (both contrasts differ with regard to magnitude and probability), magnitude-related effects were assessed by contrasting maximum versus minimum feedback for standard (25 [Gain + Loss] vs. 5 [Gain + Loss]) and unexpected trials (125 [Gain + Loss] vs. 7/27 [Gain + Loss]) conditions separately. Notice that the last contrast is not confounded by probability as 125 and 7/27 trials appeared with equal (low) probability. Finally, potential interactions between valence and magnitude were tested for both standard and unexpected boost trials.

The previous general contrasts were investigated in the entire sample (36 subjects) and were thresholded at $P < 0.05$, corrected for multiple comparisons at the whole-brain level by using a familywise error (FWE) rate. The maxima of suprathreshold regions were localized by rendering them onto the mean volunteers′ normalized T1 structural images on the MNI reference brain. Maxima and all coordinates are reported in MNI coordinates, as used by SPM and labeled in line with the Talairach atlas. The specific contrasts performed in order to investigate the influence of COMT, DRD4, and their interaction on valence and magnitude are detailed in the following sections:

In order to study the interaction between genetic groups and valence-magnitude factors, we reconstructed the BOLD event-related responses from the trial-specific evoked response depicted as a function of peristimulus time for the main regions of interest derived from the previous group level analysis (NAcc, right insular cortex, inferior parietal lobe [IPL] and rostral ACC [rACC]). First, peristimulus–time histograms were computed for each participant and voxel of interest within each session and then averaged over sessions and subjects. Finally, the corresponding parameter estimates (β values) for each condition and individual were extracted and entered as dependent variables into a mixed-model repeated measures analysis of variance (ANOVAs), using Valence or Magnitude as within-subjects factors and Genetic Groups (COMT and DRD4) as a between-subjects factors. When necessary, the corresponding interactions were decomposed using pairwise *t*-test comparisons.

Results

Behavioral Data

Overall, participants chose 25 more often than 5 (54.3 ± 11.8% vs. 45.3 ± 11.7, $t(35) = -2.31$, $P < 0.05$). No differences were observed in choice (25 or 5) between the different genetic groups (main effects of COMT and DRD4, $F(1,32) < 1$ and COMT × DRD4, $F(1,32) = 1.7$, $P > 0.2$, Fig. 2). On average, participants lost 0.5 ± 3.0 Euro.

Risk-taking behavior of participants was quantified by assessing the percentage of risky (25) decisions after unexpected boost trials. A significant interaction was encountered between DRD4 × condition (previous trial loss 125 vs. gain 125) ($F(1,32) = 4.5$, $P < 0.05$). After losses, no group differences in choosing 25 were seen (CC: 55.3% vs. TT: 55.6, $t(34) < 1$), whereas the CC group had a greater preference for 25 after boost wins (CC: 59% vs. TT: 46.3, $t(34) = -4.0$, $P < 0.001$). This pattern of increased risk taking after boost wins by CC participants differs from other studies, in which risk-aversive behavior has been demonstrated after large wins (Gehring and Willoughby 2002; Riba et al. 2008). No differences in risk taking were observed for COMT.

Main Effects of Valence and Magnitude in Standard and Boost Trials

Main effects of Valence and Magnitude were assessed using the multiple comparison correction approach ($P < 0.05$; see Table 1).

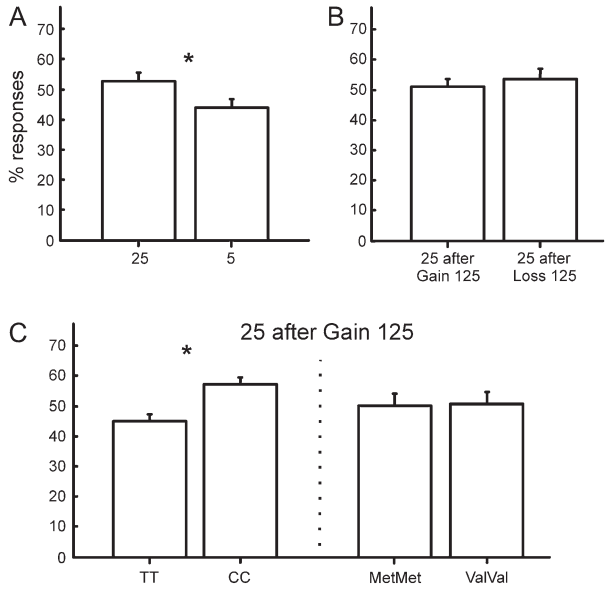

Figure 2. Main behavioral effects. (*A*) Overall, participants chose significantly 25 more often than 5 ($t(35) = -2.31$, $P < 0.05$). Risk-taking behavior of participants was quantified by assessing the percentage of risky (25) decisions after unexpected boost trials. (*B*) Overall, no differences were observed across participants in choosing 25 neither after boost losses nor boost wins. (*C*) In contrast, when genetic groups were investigated a greater preference for 25 after boost wins in the CC group ($t(34) = -4.0$, $P < 0.001$) was obtained. No differences in risk taking were observed for the COMT genotype.

Table 1
Main effects observed for valence and magnitude in standard and boost trials

Brain region	~BA	n. voxels	Stereotactic coordinates				
			X	*Y*	*Z*	*T* peak	*P* value
A. Valence standard trials: gain (5 + 25) versus loss (5 + 25)							
L ventral striatum		59	−24	4	−12	6.52	<0.0001
			−12	8	−12	6.13	<0.0001
R ventral striatum			28	−8	−4	6.22	<0.0001
B. Valence boost trials: Gain (125) versus Loss (125)							
L ventral striatum		79	−8	4	−8	6.68	<0.0001
R ventral striatum			16	8	−4	6.32	<0.0001
R cuneus	BA18	56	12	−88	16	6.81	<0.0001
C. Magnitude in boost trials: 125 (Gain + Loss) versus 7/27 (Gain + Loss)							
R cuneus	BA18	43	20	−95	0	7.62	<0.0001
R INS		25	24	20	−16	7.01	<0.0001
rACC	BA32	80	8	40	24	6.65	<0.0001
R IPL	BA40	26	44	−48	48	6.02	<0.0001

Note: MNI coordinates and *T* value for the peak location in a particular identified anatomical cluster. $P < 0.05$; 20 voxels spatial extent corrected for multiple comparisons at the whole-brain level by using an FWE rate. Reported also is the *P* value for the peak of activation at cluster level corrected for multiple comparisons and the number of voxels in each cluster (n. voxels). BA = approximate Brodman's area; L = left hemisphere; R = right hemisphere; INS = insular cortex; ACC = anterior cingulate cortex; and IPL = inferior parietal lobe.

The contrast gain (5 + 25) versus loss (5 + 25) led to activation in the ventral striatum (NAcc) bilaterally, with the activity extending to the amygdala (see Table 1*a* and Fig. 3*a*). No significant differences were found for the inverse contrast (loss vs. gain trials). With regard to the main effect of magnitude (i.e., 25 [Gain + Loss] vs. 5 [Gain + Loss]), there were no significantly activated brain regions at the specified threshold. Similarly, the assessment of the interaction between Valence and Magnitude did not reveal activated brain regions.

The valence effect for the analogous analysis on the boost trials (gain [125] vs. loss [125]) activated roughly the same region in the ventral striatum as the analysis for the standard trials (see Table 1*b* and Fig. 3*b*). No effect was seen for the inverse comparison. In contrast to the standard trials, magnitude-related activations were found for the unexpected trials (i.e., 125 [Gain + Loss] vs. 7/27 [Gain + Loss]) located in the right insular cortex, the right IPL, the rACC, and right cuneus (see Fig. 4*a* and Table 1*c*). No significant regions were observed for the interaction between Valence and Magnitude for the boost trials.

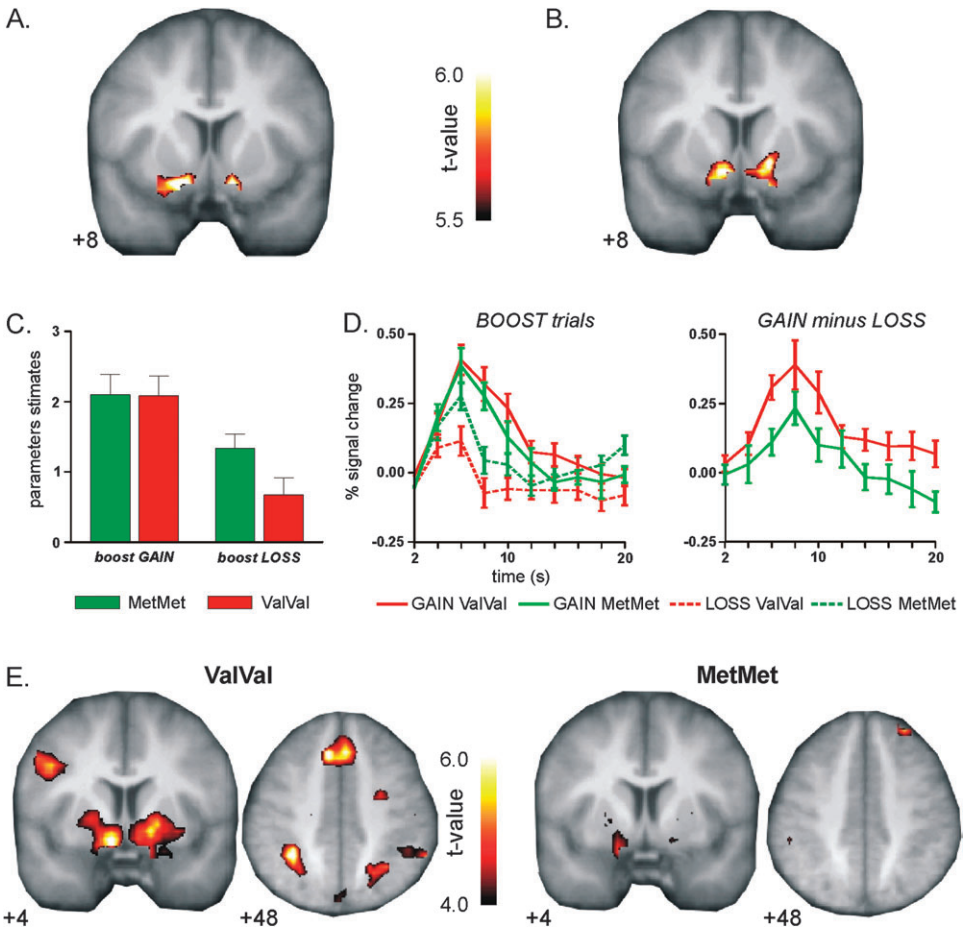

Figure 3. Valence effects. Coronal views of the group average Gain versus Loss contrast superimposed on a group-averaged structural MRI image in standard stereotactic space (*t*-score overlays after multiple comparisons correction at the whole-brain level, $P < 0.05$). Both the standard trials (*A*) (peak *x*, *y*, *z*: −24, 4,−12 mm) and the boost trials (*B*) (peak, −8, 4, −8 mm), showed increased activity in the left and right ventral striatum. (*C*) Reward-related activations for each boost condition (Gains and losses) and each COMT group. Notice the reduced activation in the boost loss condition for the ValVal group. (*D*) BOLD time-course BOLD at the activation peak in the NAcc plotted separately for the COMT groups (left side). The difference between gain and loss boost conditions in each COMT group is shown on the right. (*E*) Gain versus Loss contrast for each COMT group (*t*-score overlays, $P < 0.001$ uncorrected). Notice the activation in this contrast in the NAcc, ACC, and IPL in the ValVal, which is largely missing in the MetMet group.

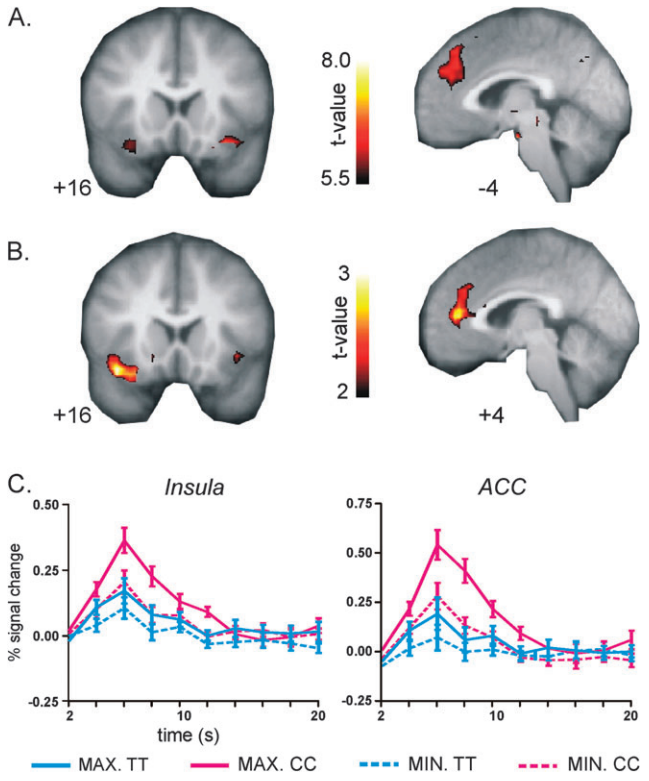

Figure 4. (*A*) Magnitude effects, reward sensitivity contrast (boost trials, maximum vs. minimum values) (*t*-score overlays after multiple comparisons correction at the whole-brain level $P < 0.05$). Main magnitude effects were observed in the right insula (*x*, *y*, *z*: 24, 20, −16 mm) and the ACC (8, 40, 24 mm). (*B*) DRD4 difference (CC vs. TT) in the Max (Gain + Loss) versus Min (Gain + Loss) boost contrast at the whole-brain level (*t*-score overlays, $P < 0.01$, uncorrected). (*C*) Left, time-course peak activation of the reconstructed hemodynamic response in the right insula (24, 20, −16 mm) in gain trials only. A larger amplitude of the response was observed in the CC group for maximum gains. A similar pattern was seen for the rACC region (8, 40, 24 mm, right).

COMT and DRD4 Effects in Standard and Boost Trials

At the locations of the peak activities observed in the contrasts mentioned above (valence effects: right and left ventral striatum [NAcc]; magnitude effects only in boost trials: right insular cortex, IPL, rACC; see table 1), we reconstructed the BOLD event-related responses as outlined in the Materials and Methods. For these regions, a repeated-measures ANOVA analysis was performed introducing Valence and Magnitude as within-factors and COMT and DRD4 as between-subject factors.

In the "standard trials," the corresponding ANOVA for the left NAcc showed no differential recruitment of the NAcc as a function of genetic group (main effect of Valence, $F(1,32) = 42.7$, $P < 0.001$; Valence × COMT, $F < 1$; Valence × DRD4, $F < 1$). The other main effects and interactions were not significant.

For "boost trials," the corresponding ANOVA showed a significant Valence × COMT interaction ($F(1,32) = 4.4$, $P < 0.05$). The interaction reflected the fact that the ValVal group showed a larger activation difference between gain and loss trials than the MetMet group (see Fig. 3*b*). Further pairwise *t*-tests showed significant differences between COMT groups in loss ($t(34) = 2.1$, $P < 0.04$) but not in gain trials ($t < 1$). Indeed, Figure 3*d* shows a clear reduction in the BOLD response for the ValVal group in loss trials (left) resulting in an enhanced BOLD difference between gains and losses in this group (right). The remaining interactions or main effects, in particular those involving DRD4, were not significant.

To follow up the "magnitude effect" reported in boost trials, we performed separate ANOVAs for right cuneus, right insula, rACC, and rIPL (see Table 1*c*). A significant DRD4 × Valence × Magnitude interaction was revealed in the right insular cortex (coordinates 24, 20, –16; $F(1,32) = 7.1$, $P < 0.012$) and the rACC (8, 40, 24 mm; $F(1,32) = 5.02$, $P < 0.032$; see Fig. 4*b*). The decomposition of this interaction showed that the DRD4 × Magnitude effects were restricted to gains (gains, DRD4 × Magnitude, right insular cortex, $F(1,34) = 12.26$, $P < 0.001$; rACC, $F(1,34) = 13.02$, $P < 0.001$; loss trials, DRD4 × Magnitude, $F < 1$, in both regions). For the insular cortex, further pairwise *t*-tests showed a significant difference between boost and similar gains in the CC genotype ($t(17) = 6.15$, $P < 0.0001$) but not in the TT group ($t(17) = 1.526$, $P > 0.1$). Also, CC and the TT groups differed for the boost gains condition ($t(34) = -2.9$, $P < 0.007$) but not for the similar gains trials ($t(34) < 1$) (see Fig. 4*c*). In the rACC, a significant difference between boost and similar gains was also observed in both the CC genotype ($t(17) = 7.36$, $P > 0.0001$) and the TT group ($t(17) = 3.94$, $P < 0.0001$). In this region, CC and the TT groups differed in the boost condition ($t(34) = -2.8$, $P < 0.008$) but not in the similar gains ($t(34) = 1.3$) (see Fig. 4*c*). Moreover, for the insular cortex a significant DRD4 main effect was observed ($F(1,32) = 4.3$, $P < 0.05$) reflecting greater overall activity in the CC group (see Fig. 4*c*).

Finally, because the reliability of the results is crucial particularly in small samples, we included in the analysis 2 new participants (TT-ValVal and CC-MetMet). Data were reanalyzed at the locations of the previous peaks without including the last 2 participants. Main genetic differences in the NAcc (Valence × COMT, $F(1,34) = 4.25$, $P < 0.05$), and the insular cortex (Valence × Magnitude × DRD4 $F(1,34) = 4.99$, $P < 0.032$) continued significant in the new analysis in the boost trials. The effect at the rACC remained marginal (Valence × Magnitude × DRD4, $F(1,34) = 3.79$, $P < 0.06$). However, the decomposition of this last interaction into its corresponding pairwise comparisons showed the same effects as in the previous analysis for the rACC (Boost gain trials, DRD4 × Magnitude, $F(1,34)=5.2$ $P < 0.029$; Gains (TT group), Boost versus similar trials, $T(17) = 3.94$, $P < 0.001$; Gains (CC group), Boost versus similar, $T(19) = 5.01$, $P < 0.0001$; Gains Boost trials (CC vs. TT), $T(36) = -2.38$ $P < 0.023$; Loss, DRD4 × Magnitude, $F > 1$).

Interestingly, in order to test whether the D4-sensitive magnitude effects were predictive of risk taking in the subsequent trial, the differential magnitude effect in the rACC (125 [Gain + Loss] vs. 7/27 [Gain + Loss]; peak 8, 40, 24 mm) was correlated to the 2 risk-taking behavioral measures, the percentage of choosing 25 after an unexpected win and loss boost trial. A significant correlation was obtained after unexpected wins ($r = 0.33$, $P < 0.02$, one-tailed) but not after unexpected losses ($r = -0.02$, $P < 0.45$, one-tailed).

Exploratory Analysis: COMT Modulations in the ACC and IPL

The use of a very conservative threshold revealed only one significant region for the Valence contrast, that is, the NAcc. In light of previous studies (e.g., Riba et al. 2008), which have also found activity in medial prefrontal cortex and because of

theoretical accounts predicting a coupling between the ventral striatum (NAcc) and medial prefrontal cortex (ACC; Holroyd and Coles 2002), we evaluated the SPM interaction contrast between COMT by Valence in boost trials (gain 125 > loss 125) at the whole-brain level. A less conservative threshold was applied for this analysis ($P < 0.001$ uncorrected, 20 voxels spatial extent; corrected for multiple comparisons at the cluster level, $P < 0.01$), which revealed 2 regions showing a COMT by Valence interaction (boost trials): the posterior medial prefrontal cortex (ACC) and the inferior parietal lobe (rIPL) (see Table 2*a* and Fig. 5*a*/*b*).

We reconstructed the corresponding BOLD event-related responses for both regions and carried out the corresponding repeated measures ANOVAs introducing Valence, Magnitude, and the 2 group factors (COMT/DRD4). As expected, the ValVal group showed a greater difference between gains and losses (see difference BOLD response, Fig. 6, right panel). For the ACC, the corresponding ANOVA showed a significant interaction between Valence and COMT ($F(1,32) = 22.3$; $P < 0.001$; Valence main effect, $F(1,32) = 10.3$; $P < 0.003$). Further pairwise group comparisons showed that although there were no differences in the MetMet group between gains and losses in this region ($t(17) < 1$), this difference was highly significant in the ValVal group ($t(17) = 6.2$, $P < 0.001$). Figure 3*e* illustrates

Table 2
Interactions between COMT and valence effects in the corresponding boost trial contrasts

Brain region	~BA	n. voxels	Stereotactic coordinates				
			X	*Y*	*Z*	*T* peak	*P* value
A. COMT × Valence (Gain (125) vs. Loss (125))							
Posterior media PFC (ACC)	BA8/BA32	27	4	24	48	4.77	<0.01
R IPL	BA40	55	44	-48	40	3.84	<0.001

Note: MNI coordinates and *T* value for the peak location in a particular identified anatomical cluster. $P < 0.001$; 20 voxels spatial extent uncorrected for multiple comparisons at the whole-brain level. Reported also the *P* value for the peak of activation at cluster level the number of voxels in each cluster (n. voxels).

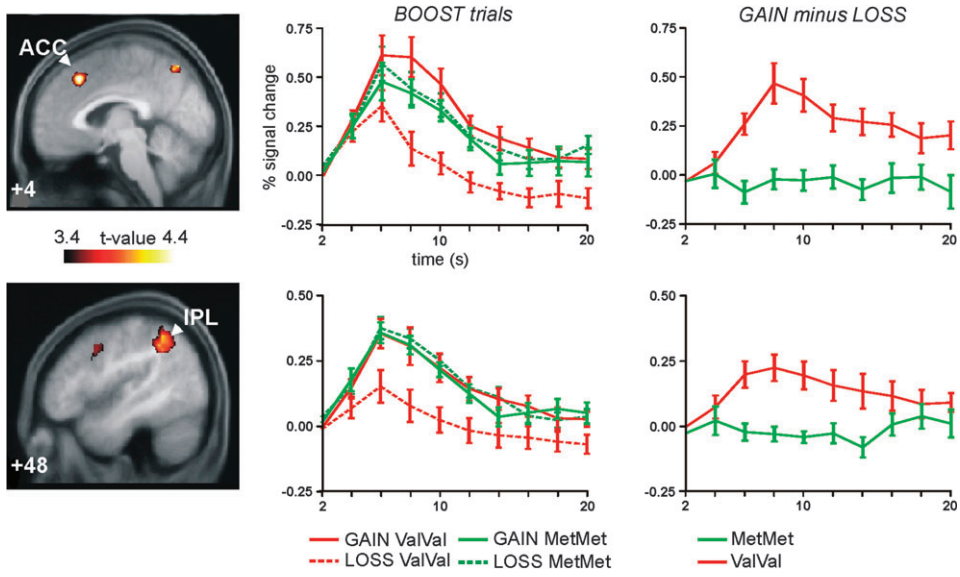

Figure 5. Sagittal views of the COMT difference (ValVal vs. MetMet) in the Gain versus Loss contrast (boost trials) showing the main significant difference for the COMT alleles in the ACC (peak *x*, *y*, *z*: 4, 24, 48 mm) and left IPL (peak *x*, *y*, *z*: 44, −48, 40 mm) (*t*-score overlays, $P < 0.001$, uncorrected). The middle panel shows the BOLD time course for boost reward conditions separately for each COMT genotype in the 2 regions. On the right, the corresponding gain minus loss difference waves are shown. A larger difference was present in the ValVal group in both regions.

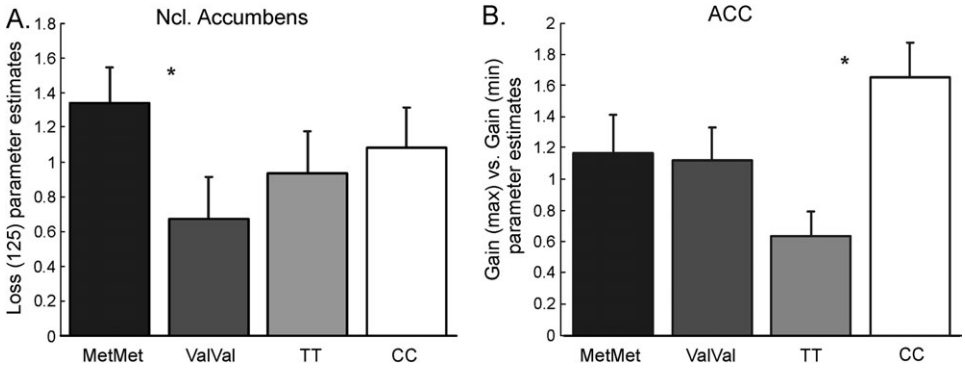

Figure 6. Functional valence-magnitude dissociation between the COMT and DRD4 genotypes. (*A*) In the left ventral striatum (peak, −8, 4, −8 mm; Valence boost trials: Gain (125) vs. Loss (125)), a reduced significant activation in the boost loss condition for the ValVal group is obtained when comparing with the MetMet group. No significant effects were observed for the DRD4 genotype in this region. (*B*) In the rACC (peak 8, 40, 24 mm; Magnitude boost trials: 125 [Gain + Loss] vs. 7/27 [Gain + Loss]), a larger amplitude of the response was shown in the CC group for maximum gains compared with TT. No significant effects were observed for the COMT genotype in this region.

the contrast between unexpected gain and loss boost trials for ValVal and MetMet groups separately. The MetMet group did not show differential activation (see also time course of the BOLD difference).

The pattern of activation observed in the rIPL was unpredicted but very reliable (see Fig. 5*b*). The ANOVA showed a significant interaction in this region for Valence and COMT, $F(1,32) = 15.3$, $P < 0.001$; Valence main effect, $F(1,32) = 9.9$, $P < 0.003$. Further pairwise comparisons showed that the COMT groups differed for the loss trials only ($t(34) = 2.6$, $P < 0.012$; gains: $t < 1$; see Fig. 5*b*). As was the case for the ACC, no differential activation was seen in the MetMet group (see also Fig. 5*a*).

Discussion

In this reward task with monetary gains and losses, we observed reliable activations in the ventral striatum for gains compared to losses that were modulated by genetic differences of dopaminergic genes. Obviously, fMRI can only reveal indirect evidence for changes in dopaminergic activity in the ventral striatum but the assumption that the observed activation changes are related to DA (and thus differences between genetically defined groups to differences in dopaminergic functioning) is supported by at least 3 different points of evidence: First, evidence from pharmacological fMRI in small animals reviewed by Knutson and Gibbs (2007) suggests that DA release in the Nucleus accumbens activates postsynaptic D1 receptors, which in turn changes postsynaptic membrane potential and eventually increases local BOLD signal. Moreover, in humans, striatal activations in reward tasks have been shown to be modulated by dopaminergic medication (Riba et al. 2008). Finally, a recent combined ^{11}C-Raclopride positron emission tomography/fMRI study demonstrated that mesolimbic fMRI activations during reward anticipation correlated with reward-related DA release in the ventral striatum (Schott et al. 2008).

Specifically, we encountered a larger differential increase in the NAcc activity for ValVal homozygous participants after the delivery of large and unexpected monetary gains (boost trials) when compared with the MetMet group (Fig. 3*c,d* and 6*a*). A similar pattern was also seen in the posterior medial prefrontal cortex (ACC) and the right IPL (Fig. 5*a*/*b*). This pattern was observed in the boost but not in the standard trials. This result is compatible with the idea that subtle genetic differences might manifest themselves only in extreme or demanding conditions and thus corroborates previous work on COMT and working memory in which genetic effects were found only in the most taxing conditions (Egan et al. 2001; Bertolino et al. 2006). Although the DRD4 polymorphism did not show an effect of valence, it modulated the brain's sensitivity to the magnitude of the feedback stimulus, that is, the CC group showed a larger activation in the boost (gain + loss) versus unexpected similar (gain + loss) contrast in 2 reward-related regions, the rACC, and the right insular cortex (Fig. 4 and 6*b*).

COMT Effects on Valence

Although monetary gains and losses activated a similar fronto-striatal network for standard and boost trials, monetary gains elicited greater activation, which replicates previous studies (van Veen et al. 2004; Nieuwenhuis et al. 2005; Marco-Pallares et al. 2007). Additionally, BOLD activations were more sustained for gains, again replicating earlier studies (Delgado et al. 2000, 2003; May et al. 2004).

No modulation of valence effects by the DRD4 polymorphism was seen. In contrast, a profound effect of COMT genetic differences was observed, in that a greater gain/loss difference was seen for the boost trials in the ValVal group (Fig. 6*a*). To reiterate, the phasic-tonic hypothesis advanced with respect to the differential effects of Met and Val alleles of the COMT polymorphism (Bilder et al. 2004) proposes that low prefrontal tonic levels of DA (associated to the Val allele) would lead an amplification of the phasic DA response in the NAcc.

Critically, our conclusions are based on the significant interaction between condition (gain vs. loss) and COMT (MetMet vs. ValVal) in the NAcc and ACC. As demonstrated by the post hoc comparisons (see Results), this interaction reflects mostly a decrease in activity to the loss trials for ValVal participants (see Figs. 3*d* and 5*a*/*b*). Thus, in light of the prefrontal/striatal dopaminergic interactions that guided our hypotheses (Bilder et al. 2004; Meyer-Lindenberg and Weinberger 2006), it is important to ask whether this smaller response to losses in the ValVal group reflects diminished presynaptic input from the midbrain dopaminergic neurons. In a recent study, Tom et al. (2007) showed that the activation in the ventral striatum decreased as the size of a potential loss increased. Thus, the degree of suppression of the BOLD response to losses appears to be related to the impact of the loss. This also is consistent with primate electrophysiological recordings showing decreased midbrain DA neural firing for negative events (Mirenowicz and Schultz 1996). As the ventral striatum is one of the target regions of dopaminergic midbrain neurons, less dopaminergic input to the ventral striatum is expected after losses. This reduction of input to the NAcc could lead to a reduced or even negative BOLD signal.

Although prefrontal–striatal interactions in the regulation of striatal DA as explained above have been invoked to explain the impact of the COMT polymorphism on striatal functioning by many researchers (e.g., Grace 2000; Sesack et al. 2003; Bilder et al. 2004; Meyer-Lindenberg and Weinberger 2006; Yacubian et al. 2007), it has been pointed out that COMT may also have a local effect in the striatum (Bilder et al. 2004). Future research must address the question, whether such local effects might explain, at least in part, the current pattern of results. Finally, in light of the known effect of the COMT polymorphism on working memory (e.g., Goldberg et al. 2003; Tan et al. 2007; Diaz-Asper et al. 2008), an indirect way in which this polymorphism might impact reward processing in the striatum is by a differential representation of reward history in working memory. ValVal individuals have been found to perform considerably worse than MetMet carriers in *n*-back tasks (Goldberg et al. 2003). In ValVal individuals, unexpected gains might therefore have had a weaker working memory representation, and the resulting greater unexpectedness might have led to an increased response to unexpected gains in these subjects.

The present results complement a recent paper investigating the effects of COMT and DA transporter (DAT) polymorphisms on reward anticipation (Yacubian et al. 2007). In this study, the ventral striatum showed activation that scaled as a function of both, reward probability and magnitude. MetMet participants showed larger responses in the ventral striatum and the prefrontal cortex compared with ValVal carriers, that is, an effect that is seemingly opposite to the one found in the current study. The pattern of results in the Yacubian et al.

(2007) study was considerably more complicated, however. Overall, an increase in striatal activity was seen when anticipation of high probability large rewards was compared with low probability small rewards. When genotypes for both genes were examined in isolation, no effect was seen on the slope of this striatal activation increase. However, when MetMet homozygous participants were considered that were also carrying the 9R variant of DAT an increase of striatal activity was seen from low probability small to high probability large rewards, whereas ValVal/9R participants showed an opposite tendency. Interestingly, MetMet participants also carrying the 10R variant showed higher striatal activity for low-probability small rewards than high-probability large rewards, whereas, again, carriers of the ValVal/10R combination showed an opposite effect. It is important to point out that Yacubian et al. (2007) studied reward "anticipation," whereas the present study focused on the "delivery" of unexpectedly high reward outcomes and participants were not able to predict when boost trials would appear. The differences between both studies might thus be related to differences in the neural mechanisms involved in anticipation and processing of reward outcomes. For example, reward anticipation has been shown to rely more on tonic dopaminergic activity (Fiorillo et al. 2003), whereas the processing of unexpected rewards is thought to be related to phasic dopaminergic activity (Schultz 2002). As MetMet participants are thought to have higher tonic but blunted phasic dopaminergic response, this could explain their smaller response in the current study but greater response in the Yacubian et al. (2007) study.

The greater ACC activation for boost gains in the ValVal group (Fig. 2*e*) is consistent with previous observations showing that this region is modulated by the valence of performance feedback (larger for positive than negative, Nieuwenhuis et al. 2005). This region has also been found to be activated in several reward studies (Elliott et al. 1998; Knutson et al. 2000; Delgado et al. 2003; Rogers et al. 2004; Taylor et al. 2006), and a number of recent investigations highlighted the interactions of the ACC and the ventral striatum (Lee et al. 2007; Walton et al. 2007; Rushworth and Behrens 2008). The larger differential activation observed in the ValVal group in conjunction with the greater effect in this group for the NAcc suggests that the reinforcement learning system functions at a higher gain in this group.

The more pronounced activation in the right IPL for the ValVal group could be related to an increased salience of positive versus negative outcomes in this group in boost trials, as this region has been shown to reflect allocation of attention resources (Corbetta et al. 2000). Also, the posterior parietal, as well as the cingulate cortex, has been associated with the desirability of an action in oculomotor tasks (Platt and Glimcher 1999; Glimcher 2003; Dorris and Glimcher 2004; Sugrue et al. 2004, 2005; McCoy and Platt 2005).

DRD4 Effects in the Insular Cortex and rACC Related to Magnitude

Previous behavioral research in experimental economics has demonstrated that besides valence, the magnitude of the gains/losses involved in a transaction exerts an independent effect. For example, studies of delay discounting of real (Kirby and Marakovic 1995; Kirby 1997) or hypothetical rewards (e.g., Benzion et al. 1989; Green et al. 1994) have shown a magnitude effect on discount rates. Also, electrophysiological studies have suggested an independent neural coding of reward magnitude and valence (Yeung and Sanfey 2004). This motivated us to assess the general effects of magnitude in the present experiment and their modulation by genetic factors.

Two regions showed increased activity in the DRD4/CC homozygous participants relative to the TT group as a function of reward magnitude: the rACC and the anterior insular cortex. Magnitude-related activations in the insular cortex have been previously reported (Elliott et al. 2000; Knutson et al. 2000; Breiter et al. 2001; Delgado et al. 2003). The magnitude effect in the rACC may be related to the role of this area in emotional processing (Devinsky et al. 1995; Bush et al. 2000). Interestingly, lesions in rats in the ACC impair the choice of a high-cost/high-reward option, without affecting the choice of a less-demanding and less-rewarding option (Walton et al. 2003).

The modulation of magnitude-related activity by the DRD4 polymorphism in both regions suggests a role of the D4 receptor in the assessment of the magnitude or impact of outcomes. This may go hand in hand with the reported associations between this polymorphism and novelty seeking (Okuyama et al. 2000; Ronai et al. 2001; Schinka et al. 2002; Golimbet et al. 2007). This interpretation should be regarded as tentative at this point due to the lack of knowledge about the transcriptional effects of this polymorphism (Ogawa et al. 1990; Kereszturi et al. 2006). For example, Kereszturi et al. (2006) did not confirm previous data showing different transcriptional activities of the –521 C/T alleles on DRD4 promoter activity in any of the neuronal cell lines evaluated. The importance of genetic differences of D2-type receptors, to which the D4 receptor belongs, has been underscored by previous functional investigations, however. For example, Fan et al. (2003) studied the insertion/deletion of a guanosine residue at the upstream position –1217 of the DRD4 gene and found greater conflict-related brain activity in the ACC in participants carrying the insertion variant of the polymorphism. Focusing on the presence/absence of the A1 allele on the DA D2 receptor gene, Cohen et al. (2005) showed that this polymorphism predicted a significant amount of intersubject variability in the magnitudes of reward related, but not anticipation-related, activations. Moreover, Klein et al. (2007) demonstrated that presence of the A1-allele, known to lead to a reduced receptor density, is associated to a reduced BOLD response to negative feedback in the medial prefrontal cortex.

Finally, although the present study attempted to dissociate the effects of COMT and DA receptor D4 genotypes on brain activations related to valence and magnitude of rewards, the missing interactions between the 2 polymorphisms studied might be due to the comparatively small sample and thus should be interpreted with caution. Although there is no question about the functional effects of the COMT (Val108/158Met) variant (Chen et al. 2004), some concerns have been raised by Kereszturi et al. (2006) regarding the functional role of the –521 variant on promoter function. However, even if the –521 C/T SNP might not be functional, it may be in linkage disequilibrium (LD) with other variants that are responsible for the observed effects. By the design of this study, it is impossible to determine such linked factors as a full coverage of the gene and its coding regions by LD mapping would require hundreds of SNPs. Clearly, further analyses on functionally relevant variants in DRD4 and its promoter region are needed.

Conclusions

In the present study, we have shown the impact of 2 dopaminergic polymorphisms on reward processing: The COMT Val(108/158)Met polymorphism modulated valence-related responses in the ventral striatum and the ACC for unexpectedly large gains/losses, whereas the C/T polymorphism at position −521 of the DA receptor D4 gene was associated with differential activity as a function of reward magnitude.

Funding

Volkswagen-Foundation grant awarded to T.F.M., A.R.F., and L.S; Alexander von Humboldt Foundation to J.M.P. and DFG SFB779/A5 to T.F.M.

Notes

We thank Andrea Seibel for excellent technical assistance in sequencing and genotyping procedures, Jürn Möller for help in behavioral testing, Lluis Fuentemilla and Ruth de Diego for their comments through the elaboration of the manuscript, and I. Clemente for providing access to laboratory facilities. *Conflict of Interest*: None declared.

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