Variation in dopamine genes influences responsivity of the human reward system

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In humans, dopamine neurotransmission is influenced by functional polymorphisms in the dopamine transporter (*DAT*1) and catechol-*O*-methyltransferase (*COMT*) genes. Here, we used event-related functional magnetic resonance imaging to directly investigate the neurofunctional effects of the Val[158]Met *COMT* and variable number of tandem repeat *DAT*1 polymorphisms on distinct components of the reward system in humans. The results revealed a main effect of *COMT* genotype in the ventral striatum and lateral prefrontal cortex during reward anticipation ($P < 0.001$, uncorrected) and in the orbitofrontal cortex at the time of reward delivery ($P < 0.005$), met/met individuals exhibiting the highest activation. The main effect of *DAT*1 genotype was seen in robust blood-oxygen-level-dependent response differences in the caudate nucleus and ventral striatum during reward anticipation ($P < 0.001$) and in the lateral prefrontal cortex and midbrain at the time of reward delivery, with carriers of the *DAT*1 9-repeat allele showing the highest activity. Moreover, an interaction between the *COMT* and *DAT*1 genes was found in the ventral striatum and lateral prefrontal cortex during reward anticipation and in the lateral prefrontal and orbitofrontal cortices as well as in the midbrain at the time of reward delivery, with carriers of the *DAT*1 9-repeat allele and *COMT* met/met allele exhibiting the highest activation, presumably reflecting functional change consequent to higher synaptic dopamine availability. Taken together, these results indicate that genetically influenced variations in dopamine transmission modulate the response of brain regions involved in anticipation and reception of rewards and suggest that these responses may contribute to individual differences in reward-seeking behavior and in predisposition to neuropsychiatric disorders.

COMT | DAT | fMRI | genetic variation

The dopamine system and its projections sites, which include the striatum and the prefrontal cortex (PFC), play crucial roles in modulating motivated behavior, emotion, and high-order cognitive functions related to reward processing. The functions of reward include approach and consummatory behavior as well as the ability to predict the outcomes of potentially rewarding situations, serving goal-directed behavior and providing an evolutionary advantage for creatures facing unpredictable environments. The integrity of the dopamine system is important for efficient processing of reward information. Dysfunction of this system is involved in a variety of disorders, including schizophrenia, Parkinson's disease, pathological gambling, and drug addiction. Although there are clear individual genetic differences regarding susceptibility to and manifestation of these neuropsychopathologies, the influence of genetic predispositions and variations on activation of the human reward system remains poorly understood. Investigating the effects of interindividual differences in dopamine signaling on the response of the reward system is thus an important research question because these differences may contribute to heritable personality traits in the general population (1, 2) and to neuropsychiatric conditions involving abnormalities in catecholamine neurotransmission, such as substance abuse (3), mood disorders (4), obsessive compulsive disorder (5), attention deficit hyperactivity disorder, and schizophrenia (6).

Two important proteins contribute to terminating the action of intrasynaptic dopamine in the brain: Catechol-*O*-methyltransferase (COMT), which catabolizes released dopamine, and the dopamine transporter (DAT), which plays a crucial role in determining the duration and amplitude of dopamine action by rapidly recapturing extracellular dopamine into presynaptic terminals after release.

In humans, the *COMT* gene contains a common and evolutionarily recent functional polymorphism that codes for the substitution of valine (val) by methionine (met) at codon 158. The COMT enzyme is involved in the metabolic degradation of catecholamines, catalyzing transfer of the methyl group from *S*-adenosyl methionine to a hydroxyl group of a catecholic substrate, thereby converting dopamine into 3-methoxytyramine and norepinephrine into normetanephrine. Because the COMT protein containing methionine is relatively thermolabile, its activity is lower at body temperatures than the COMT valine protein, which is fully active at body temperature. Hence, individuals with 2 copies of the met allele (met/met) have 25–75% reduction in COMT enzyme activity compared to individuals with 2 copies of the val allele (val/val), and therefore presumptively more baseline synaptic dopamine (7, 8).

The *DAT*1 gene (SLC6A3) includes 15 exons, with a variable number of tandem repeat (VNTR) polymorphism in the 15th exon, a region encoding the transcript's 3′ UTR (9). The 40-bp VNTR element is repeated between 3 and 13 times but occurs with greatest frequency in the 9- and 10-repeat forms. Expression of the *DAT*1 9-repeat allele is lower than the 10-repeat allele (10–12), although one study reported the opposite (13). Thus, the *DAT*1 10-repeat allele, associated with increased expression of the gene, presumably leads to relatively decreased extrasynaptic striatal dopamine levels, consistent with a human single-photon-emission computed tomography report of increased striatal DAT availability in 9-repeat carriers relative to 10-repeat carriers (ref. 14, but see ref. 12). Mice lacking the *DAT*1 gene show extensive adaptative changes in the dopaminergic system, the DAT controlling the duration of extracellular dopamine signals and regulating presynaptic dopamine homeostasis (15).

Importantly, animal studies indicate differential functional localization of the COMT and DAT proteins. The COMT enzyme plays a particular role in modulating dopamine in PFC, where *DAT*1 expression is sparse (16, 17). *COMT* is expressed more abundantly in cortical neurons than in the striatum (18), but it is unclear to what extent *COMT* modulates catecholamine function outside the cortex. Recent studies in COMT knockout mice suggest that COMT has little if any role in striatal DA levels (19). In contrast, animal research and human postmortem studies indicate

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that the *DAT*1 is expressed abundantly in midbrain, striatum, and hippocampus but sparsely in the PFC (20, 21).

Electrophysiological experiments on nonhuman primates have demonstrated that midbrain dopamine cells fire both during anticipation of uncertain rewards and at the time of unexpected reward delivery (22). In parallel with these fundamental results, fMRI studies in healthy humans have documented that distinct reward anticipation- and outcome-processing phases are associated with differential patterns of specific midbrain dopaminergic postsynaptic targets (23–25). Specifically, anticipation of reward robustly activates the ventral striatum (23, 24), particularly during anticipation of rewards with maximal uncertainty (i.e., reward probability = 0.5) (25) whereas rewarded outcomes activate the lateral and orbital parts of the PFC (23, 25). Despite the direct involvement of the COMT and DAT proteins in dopamine transmission, the influences of *COMT* and *DAT*1 functional polymorphisms on distinct components of the reward system have not been as systematically explored as have been the domains of working and episodic memory (21, 26, 27). Here, we used an event-related fMRI reward paradigm to directly investigate the relationship between *COMT* and *DAT*1 functional polymorphisms and the response of the reward system during anticipation of uncertain reward and at the time of reward delivery, bridging the gap between basic molecular genetics, fundamental electrophysiological findings and functional neuroimaging in humans.

Because COMT primarily modulates dopamine in the PFC whereas the effects of *DAT*1 predominate in the striatum (16, 17, 20), our central hypotheses were that *DAT*1 and *COMT* polymorphisms would influence reward-related activity in the ventral striatum and PFC, respectively, and that there may also be gene–gene interactions. More specifically, because reward anticipation activates the ventral striatum and reward delivery involves the PFC (23–25), we tested the following hypotheses: (*i*) individuals with the 9-repeat *DAT*1 allele, associated with lower expression of the gene and relatively increased extrasynaptic striatal dopamine levels will exhibit higher ventral striatal activation during anticipation of uncertain rewards; (*ii*) compared to individuals homozygous for the *COMT* val allele, those homozygous for the met allele, who have relatively lower COMT enzyme activity and presumably higher levels of prefrontal synaptic dopamine, will exhibit stronger response in the PFC at the time of reward delivery; and (*iii*) interactive effects between *DAT*1 and *COMT* polymorphisms may be observed at both striatal and prefrontal sites.

Results

Functional Imaging Data. All participants performed at ceiling (>97% correct). No significant response time difference was observed between genotyped groups, indicating that between-group brain activation differences cannot simply be attributed to general attentional, perceptual, or cognitive phenomena. Because our a priori hypotheses concerned the roles of the PFC and the striatum, we focus on results in these brain regions. A complete list is provided in supporting information (SI) Tables S1 and S2.

Genotype Effects During Anticipation of Uncertain Rewards. First, during anticipation of uncertain rewards, we identified brain areas showing robust correlation between the number of val alleles (0, 1, or 2) and the blood-oxygen-level-dependent (BOLD) response. Met/met carriers activated the ventral striatum, the left superior prefrontal gyrus, and the dorsolateral PFC (DLPFC) more than val/val individuals, with heterozygotes showing an intermediate response (Fig. 1). That is, individuals homozygous for the met allele exhibited more activity than val/met heterozygotes, who in turn showed greater activity than val homozygotes. The opposite analysis revealed no significant findings in the PFC or striatum.

Second, we compared brain activity between 9- and 10-repeat allele carriers during anticipation of reward. Confirming our first hypothesis (see Introduction), more robust bilateral ventral striatal and caudate nuclei activities were observed in 9-repeat compared to 10-repeat *DAT1* individuals (Fig. 2). No voxel in the PFC or striatum survived the opposite comparison.

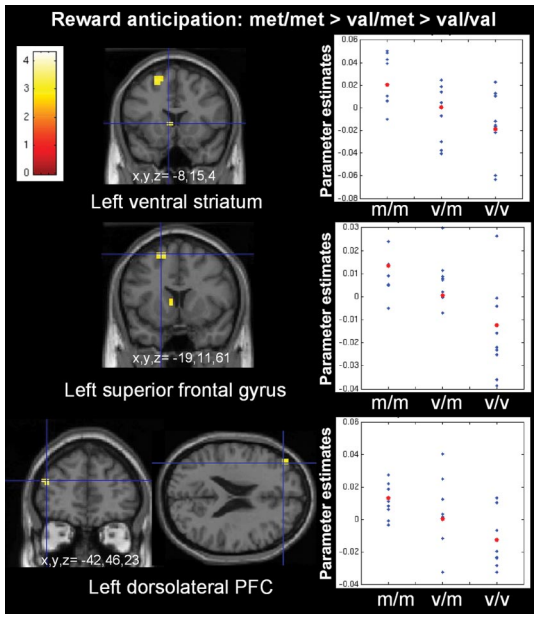

Fig. 1. Main effect of *COMT* genotype during anticipation of reward with maximal uncertainty. (*Left*) Statistical maps showing BOLD fMRI responses in the ventral striatum, left superior PFC, and dorsolateral PFC overlaid onto structural MRI coronal and axial planes. (*Right*) Negative relationship between *COMT* val allele dosage (0_met/met, 1_val/met, or 2_val/val) and BOLD response in these brain regions during anticipation of reward with maximal uncertainty.

Third, we assessed gene–gene interactions during reward anticipation by using 2 covariates: the *DAT*1 genotype [2 levels: 9-repeat (including *DAT*1 9-repeat and 9/10 repeat) and *DAT*1 10-repeat] and *COMT* genotype (3 levels: met/met, val/met, and val/val). Confirming our third hypothesis, an interaction (9-repeat > 10-repeat and met/met > val/met > val/val) was found between *COMT* and *DAT*1 in the bilateral ventral striatum, caudate nuclei, and in the left anterior lateral PFC region (Fig. 3). The opposite interaction effect (9 < 10 and met/met < val/met < val/val) was only present in the temporal cortex bilaterally.

Genotype Effects at the Time of Reward Outcome. As in the reward anticipation phase, we next identified, at the time of reward receipt, brain areas showing correlations between the number of *COMT* val alleles (0, 1, or 2) and the BOLD response. As predicted by our second hypothesis, met/met carriers activated the orbitofrontal cortex (OFC) bilaterally more than val homozygotes, with heterozygotes showing an intermediate response (Fig. 4). Regression analysis in the opposite direction revealed no significant effect in the OFC or striatum, but a small area in the left DLPFC was affected.

Individuals with the 9-repeat *DAT*1 allele showed a more robust BOLD response in the right DLPFC and the right anterior PFC compared to 10-repeat carriers (Fig. 5 *Top*). In the opposite comparison, 10-repeat *DAT*1 allele did not show higher BOLD response than 9-repeat carriers in the frontal lobe or the basal ganglia. In addition, because a recent episodic memory encoding study reported higher midbrain activation in 9-repeat compared to 10-repeat allele carriers (21), we searched for between-group differences in this region with a less stringent ($P < 0.01$) statistical threshold. We found higher midbrain activation in 9-repeat compared to 10-repeat carriers (Fig. 5 *Bottom*).

Finally, consistent with our third hypothesis, at the time of the rewarded outcome, an interaction between the *COMT* and *DAT*1 genes (comparison 9-repeat >10-repeat and met/met > val/

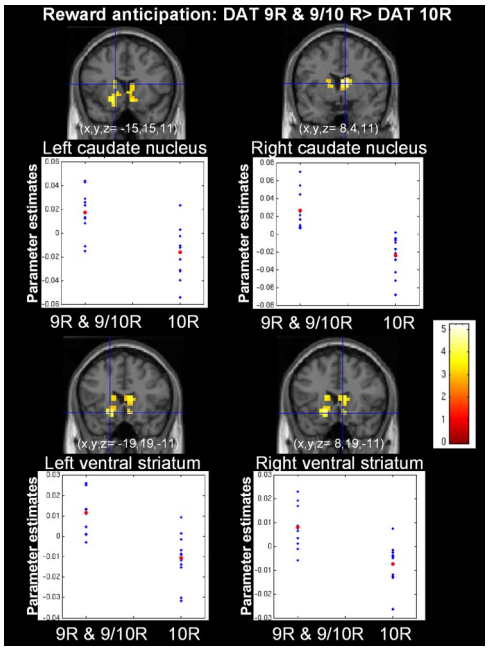

Fig. 2. Main effect of *DAT*1 genotype during anticipation of reward with maximal uncertainty. (*Top*) Statistical maps showing BOLD fMRI responses in the bilateral caudate nuclei. More robust BOLD response was observed in 9-repeat carriers (including *DAT*1 9-repeat and 9/10) compared to 10-repeat individuals during reward anticipation. (*Bottom*) Statistical maps showing BOLD fMRI responses in the bilateral ventral striatum. Again, 9-repeat carriers exhibited higher BOLD response than 10-repeat individuals.

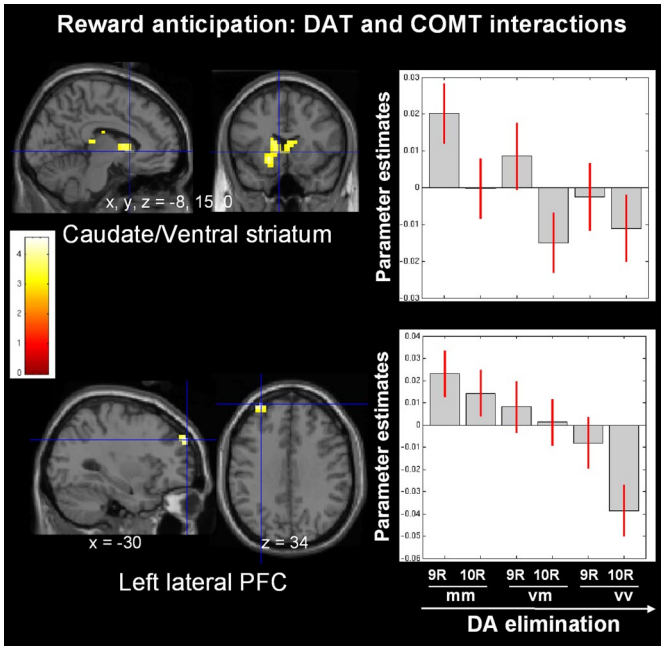

Fig. 3. Interaction between *COMT* and *DAT*1 genotypes with *COMT* Met homozygous and *DAT*1 9-repeat homozygous subjects showing augmented neural response during anticipation of reward with maximal uncertainty. (*Left*) Statistical maps of the BOLD signal interaction showing stronger engagement of ventral striatum and anterior lateral PFC. (*Right*) Interaction between the *COMT* and *DAT*1 genotypes in the prefronto-striatal system during anticipation of reward. Combined heritable variation in dopamine neurotransmission associated with the *COMT* met/met and 9-repeat and 9/10 VNTR *DAT*1 alleles produces hyperresponsivity of the reward system.

met > val/val) was observed in 2 right lateral PFC regions (Fig. 6 *Top*), near to those found with the main effect of *DAT*1 genotype. An interaction between the *COMT* and *DAT*1 genes was also observed in the midbrain and the right OFC with a less stringent ($P < 0.01$) statistical threshold (Fig. 6 *Middle* and *Bottom*). No voxel in the PFC or striatum survived the opposite interaction (9 < 10 and met/met < val/met < val/val).

Discussion

Our study identified influences of *COMT* and *DAT*1 functional polymorphisms, and interactions between them, on specific components of the reward system. A gene–gene interaction was present in ventral striatum during reward anticipation and in the PFC at the time of reward delivery, demonstrating the influence of variation in dopamine-regulating genes on two brain regions respectively involved in anticipation versus receipt of reward (23, 24).

Effects of COMT Val^{158}Met Genotype on Reward-Related Processes. First, during anticipation of rewards with maximal uncertainty, the number of met alleles positively correlated with response of the ventral striatum-lateral PFC circuit (Fig. 1), which may be due to the fact that individuals with the met/met genotype have lower COMT enzyme activity and relatively more baseline dopaminergic signaling at PFC synapses than val homozygotes. Although the action of *COMT* genotype on the PFC was hypothesized and could be predicted on the basis of the animal literature, we also observed a main effect of *COMT* genotype on the striatum during reward anticipation. That is, higher *COMT* activity conferred by the val allele and associated with reduced PFC dopamine may indirectly impact dopaminergic function in brain regions other than the PFC, likely as a manifestation of changes in *COMT* prefrontal activity leading to downstream adaptive changes (28).

A primary role for *COMT* genotype in PFC functions is supported by a wealth of findings, such as the fact that *COMT* is expressed more abundantly in cortical neurons than in the striatum (17, 18) and accounts for more than 60% of dopamine degradation in rodent PFC, but less than 15% in the striatum (16), likely because of the scarcity of cortical dopamine transporters relative to the striatum (20). Recently, a real-time study of evoked dopamine overflow showed that removal of dopamine was twofold slower in the PFC of mice lacking *COMT* than in wild-type mice, whereas dopamine overflow/decline in the dorsal striatum was not affected (19), thus demonstrating the significant contribution of COMT in modulating dopamine dynamics in rodent PFC.

Confirming our second hypothesis at the time of the rewarded outcome the presence of val alleles was associated with less activation in the OFC (Fig. 4). Because this region is normally implicated in rewarded versus nonrewarded outcomes and in discriminating the relative value of rewards (23), the reduced excitability of the OFC to rewarded outcome in val/val carriers may reflect lower extrasynaptic dopamine levels and lower saliency of reward value in that group, which mirrors their lower ventral striatal activation during anticipation of uncertain rewards.

Relationship to Previous COMT Findings. A number of recent studies indicate that whether the val allele is beneficial or detrimental for prefrontal functions depends on a variety of factors, such as the nature of the task undertaken and the current dopaminergic state of the PFC (29). For example, whereas the met allele is beneficial for performance of working memory and PFC function (30), it is also associated with greater activity of limbic regions in response to unpleasant visual stimuli (28, 31), as well as with abnormal affective responses such as OCD in men (32), increased anxiety in women (2), and panic disorder (33) or negative states such as pain sensitivity (34). The present results extend this body of work to reward processing. The differences between findings in working memory versus processing of emotional and rewarding stimuli may reflect the importance of dopamine for intrinsic signal-to-noise

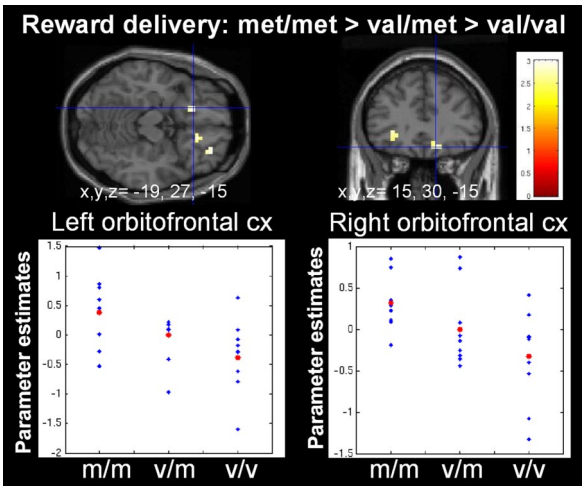

Fig. 4. Main effect of *COMT* genotype at the time of reward delivery (Outcome$_{\$20_All\ potentially\ rewarded\ slots}$ > Outcome$_{\$0_Slot_D}$ where slot_D denotes the slot machine with sure knowledge to get no reward). (*Upper*) Statistical maps showing BOLD fMRI responses in the OFC. (*Lower*) Negative relationship between *COMT* val allele dosage and OFC activation at the time of reward delivery.

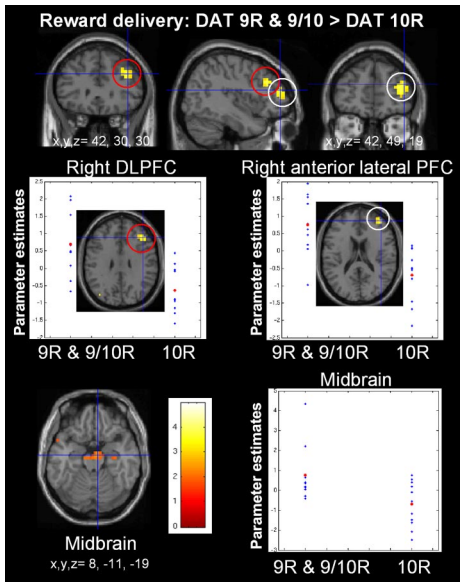

Fig. 5. Main effect of *DAT*1 genotype at the time of reward delivery. (*Top*) Statistical maps showing BOLD fMRI responses in the lateral prefrontal cortex. The graphs below show higher prefrontal BOLD signal in *DAT*1 9-repeat allele dosage compared to 10-repeat carriers at the time of reward delivery. (*Bottom Left*) Statistical map showing BOLD fMRI responses in the midbrain. (*Bottom Right*) Graph showing higher midbrain BOLD response in 9-repeat carriers as compared to 10-repeat individuals at the time of reward delivery.

regulation in PFC for the former versus the primacy of subcortical dopamine in the latter. The impact of *COMT* genotype on PFC, thus, depends on the cognitive domain, the neural circuit recruited by the task as well as the role of the PFC in processing specific components of the task.

Our findings concerning the effect of *COMT* genotype on the reward system have important clinical implications. Indeed, the *COMT* Val^{158}Met polymorphism has been associated with substance abuse and neuropsychiatric conditions involving abnormalities in catecholamine neurotransmission, such as mood disorders (35), OCD (5), attention deficit hyperactivity disorder, and schizophrenia (6), long believed to involve a dysfunction of the dopaminergic system. Interestingly, smokers with genes associated with low resting dopamine tone (such as val/val individuals) have greater smoking-induced dopamine release than those with alternative genotypes (36). This finding suggests that polymorphisms of dopamine-regulating genes explain a significant proportion of the interindividual variability in smoking-induced dopamine release (37) and may confer genetic predisposition to smoking. Moreover, at the behavioral level, the *COMT* polymorphism may be associated with specific individual differences in personality traits, val/val carriers being more likely to have higher novelty-seeking and risk-seeking scores (1, 2) than met/met individuals. In contrast, in women, who are more prone to anxiety disorders than men, met/met individuals tend to have more anticipatory worry and fear of uncertainty (2). These personality differences, although not always found, may reflect relative differences in levels of synaptic dopamine, which modulates emotion and motivation.

Effects of *DAT*1 VNTR Genotype on Reward-Related Processes. Confirming our first hypothesis, during reward anticipation, *DAT*1 9-repeat carriers activated the ventral striatum more than 10-repeat individuals (Fig. 2), likely reflecting lower extrasynaptic striatal dopamine levels in 10-repeat carriers in whom *DAT*1 gene expression is greater both in vitro and in vivo (10, 11, 14), although see ref. 12 for opposite results. It should additionally be noted that uptake by the DAT is the most effective mechanism for terminating the synaptic action of dopamine in the striatum, and the role of COMT in dopamine elimination is minimal in this brain region (38).

Our finding of higher lateral PFC activation in 9-repeat carriers at the time of rewarded outcome (Fig. 5), while not hypothesized, nevertheless extends to the reward domain a recent working memory report (27) of prefrontal modulation by *DAT*1 genotype and a report of higher reactivity of an episodic-memory network in 9-repeat carries (21). Thus, it seems that 9-repeat carriers, irrespective of the investigated domain, show hyperresponsivity of specific brain networks. *DAT*1 genotype influence on lateral PFC activity at the time of reward delivery may reflect: (*i*) local volume transmission of dopamine in PFC circuits; (*ii*) indirect influence of striatal *DAT*1 genotype on prefrontal activity via striato-cortical loops and/or (*iii*) direct influence via dopamine neurons, projecting to the PFC. The last is in part supported by our data because we found higher midbrain activity in carriers of the 9-repeat allele of the *DAT*1 VNTR when compared with 10-repeat homozygotes, extending a recent result obtained in the midbrain/substantia nigra during episodic memory encoding (21). That study, as ours, also observed no comparable effect in the midbrain for the *COMT* Val^{158}Met polymorphism, suggesting that the *DAT*1 polymorphism more reliably influences BOLD activity in this brain region.

Our findings regarding the effect of the *DAT*1 polymorphism on reward functions may shed light on the neural correlates of a number of neuropsychiatric disorders because the 10-repeat allele has been associated with attention deficit hyperactivity disorder and because the DAT is a target for psychoactive drugs and a gateway for several neurotoxins that destroy dopaminergic neurons.

Although the 3′ VNTR polymorphism of the DAT gene is not associated with an amino acid variation and there is uncertainty about its functional effects, the observation of genotype-dependent differences in reward-related brain activity and in the availability of dopamine transporters implicates an effect of this polymorphism, or of a functional polymorphism to which it is linked, on the molecular mechanisms that account for availability of the DAT protein.

Interaction Between the *COMT* and *DAT*1 Genes. One important insight provided by our data is a clear demonstration of interaction between the *DAT*1 and *COMT* genes that controls a complex phenotype (activation of the reward system). This interaction likely reflects differences in dopamine level because of the combined effect of the *COMT* val/val and *DAT*1 10/10 genotypes on dopamine

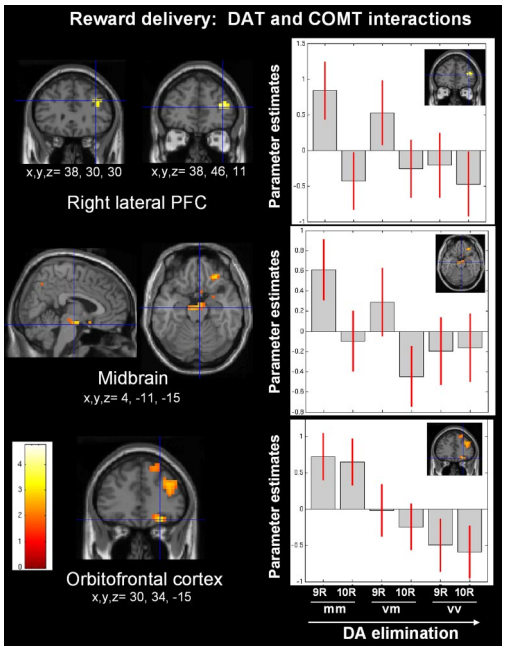

Fig. 6. Interaction between the *COMT* and *DAT*1 genotypes in the lateral PFC, midbrain, and OFC at the time of reward delivery. (*Left*: *Top*, *Middle*, *Bottom*) Statistical maps showing BOLD fMRI responses in the right lateral prefrontal cortex, midbrain, and right OFC. (*Right*: *Top*, *Middle*, *Bottom*) Effect of the interaction between *COMT* and *DAT*1 genotype on BOLD response in these brain regions at the time of reward delivery.

elimination in the fronto-striatal system. Interestingly, the effects of this presumed low dopamine level in val/val and 10-repeat carriers differ both according to brain regions and task phases (Figs. 3 and 6). Although an interaction between the *COMT* and *DAT*1 genes was found in the ventral striatum and left lateral PFC during reward anticipation, it was present in the right lateral and orbital PFC and in the midbrain at the time of reward delivery, carriers of the *DAT*1 9-repeat allele and *COMT* met/met allele exhibiting the highest activation, presumably reflecting functional change consequent to higher synaptic dopamine availability.

Dopaminergic innervation to the striatum plays an important role in drug-seeking behavior and both the Val^{158}Met genotype and the *DAT*1 VNTR polymorphisms (3) show association with drug abuse. Because gambling, with its intrinsic reward uncertainty characteristics, may share common reinforcing neural mechanisms with addictive drugs, the highest functional reactivity of the ventral striatum and OFC observed in met/met and 9-repeat carriers may boost susceptibility to drug addiction. At the behavioral level, the robust striatal and PFC (lateral and orbital parts) activations observed with the number of *COMT* met and *DAT*1 9-repeat alleles may be associated with greater motivation during reward anticipation and higher hedonic response at the time of reward delivery. Thus, our data demonstrate that variation in genes coding for enzymes crucial for dopamine transmission interactively modulate response of distinct components of the reward system.

A recent study used a guessing task to investigate how individual variation in *COMT* and *DAT*1 genes influences reward processing (39). In accordance with our results, that study reported that, during reward anticipation, lateral PFC and ventral striatum activities were *COMT* genotype-dependent: met homozygotes showed larger response in these brain regions than val homozygotes. This effect was observed when averaging all probabilities and magnitudes against baseline, but no main effect of *COMT* genotype was observed on ventral striatal sensitivity to reward uncertainty and no main effect of *DAT*1 genotype on striatal activity during reward anticipation was reported despite the well-established abundancy of DAT in the striatum. A gene–gene interaction between *COMT* and *DAT*1 was observed in the ventral striatum when sorting genotypes from met/met *DAT*1 10-repeat allele to val/val 9-repeat allele, interpreted as consistent with the notion that basal dopaminergic tone, regulated by *COMT*, interacts with phasic dopamine release, regulated by the *DAT* (40). It is difficult to directly compare our findings to these previous results because *COMT* and *DAT*1 genotypes may both directly influence distinct components of the human reward system (COMT modulating the DLPFC and DAT, the striatum) and differentially affect their neurofunctional balance in a task-dependent manner. Finally, because this previous study did not report results at the time of reward delivery, it remains unclear whether distinct phases of this guessing task induce differential brain activity dependent on *COMT* and *DAT*1 polymorphisms.

Patterns of genetic interactions among unlinked loci that produce impaired synaptic function or impaired development of homeostatic response may account for the epistatic component of genetic risk for neuropsychiatric disorders. One interesting possibility inferred from our finding of interaction of met/met and 9-repeat alleles is that *COMT* may have a general homeostatic role in regulating several genes, such as *DAT*1, to enhance dopaminergic signaling. This hypothesis extends recent transcriptional profiling and pharmacological manipulations identifying a transcriptional and behavioral interaction between the proline dehydrogenase (*Prodh*) and *COMT* genes, which may represent a homeostatic response to enhanced dopaminergic signaling in the frontal cortex (41).

Possible Future Directions. Our work may have implications for potential genotype-based targeted pharmacological treatments aimed at modifying activity of the reward system in neuropathogical disorders, such as drug addiction, depression, schizophrenia, and Parkinson's disease. For example, whereas no applications related to reward have yet been attempted, treatment with tolcapone, a specific *COMT* inhibitor, affected measures of verbal episodic memory in a *COMT* genotype-specific manner, such that individuals with val/val genotypes improved, whereas individuals with met/met genotypes worsened (5). A similar gene-based pharmacological intervention on reward-related neural activity would extend the current results.

Conclusion

It should be noted that our study cannot establish the neurophysiological mechanisms underlying the relationship between dopamine release and BOLD signal increase. However, the present work directly links genotype-dependent synaptic dopamine availability with BOLD signal change in humans and suggests more activity at prefronto-striatal sites, conferred by specific genotypes, is associated with greater dopamine synaptic availability (i.e., less dopamine elimination), in agreement with recent studies observing: (*i*) that in young adults there is a tight coupling between increased midbrain dopamine synthesis and reward-related increase BOLD signal in the PFC both during reward anticipation and at the time of reward delivery (42); and (*ii*) that in animals, injection of dopamine-releasing agents increases BOLD signal in mesolimbic regions (frontal cortex, striatum, cingulate cortex) with a time course that parallels changes observed by microdialysis measurements of striatal dopamine release (43).

Taken together, our fMRI results indicate that responsivity of a prefronto-striatal reward-related network is directly influenced by heritable variation in dopamine neurotransmission associated with the *COMT* and *DAT*1 polymorphisms. The increased BOLD responses observed in met/met and 9-repeat individuals at sites receiving dopaminergic projections may correspond to greater synaptic dopamine availability. Such genetically driven variations in dopamine function and consequent reactivity of the reward system have important implications for clinical manifestations of diseases

that involve disordered catecholamine regulation and that may clarify biological mechanisms underlying individual differences.

Interestingly, both the val/met and the *DAT*1 VNTR polymorphisms may be evolutionarily recent, as a VNTR homologue has been observed in humans, chimpanzees, and cynomologous macaques, but not in lower mammals, including the rat and mouse. Because no equivalent polymorphism of the human *COMT* gene has been found in any other species examined to date (44), the met variant appears to be specific to humans. As previously discussed, the met allele is associated not only with beneficial effects in the cognitive domain, but also with detrimental phenotypes, such as impaired emotional processing and OCD (28, 31). Thus, these multiple and complex associations may explain the persistence in the human population of the val and met alleles as well as their synergistic action with the *DAT*1 VNTR polymorphisms.

Materials and Methods

Subjects. Twenty-seven right-handed young subjects (mean age = 27.3 ± [SD] 5.7, 16 males) with known *COMT* genotype provided written informed consent following procedures approved by the National Institute of Mental Health Institutional Review Board. Twenty-two had available *DAT*1 genotype. Because many factors other than genetic polymorphisms contribute to variance in the fMRI data and must be minimized to identify genetic effects, the three *COMT* genotype groups on one hand, and the two *DAT1* groups on the other hand, were matched for age, sex, handedness, and educational background. All subjects (except one) were of European ancestry. The final *COMT* sample consisted of 9 val/val subjects (age = 25.5 ± 3.8 years; years of education = 16.8 ± 2.9; 4 women), 9 val/met carriers (age = 28.6 ± 6; years of education = 15.8 ± 2; 3 women) and 9 met/met individuals (age = 27.8 ± 3.8; years of education = 16.6 ± 1.7; 4 women). The *DAT*1 sample was composed of 11 10/10 subjects (age = 26.2 ± 5.5 years; 5 women) and 11 9-repeat allele carriers (age = 29.5 ± 4.7; 4 women, 3 of these 11 subjects had 9/9 *DAT*1 genotype and 8 were 9/10 *DAT*1 carriers). All subjects were free of neurologic, psychiatric, and substance abuse problems. They had no history of gambling and no medical problems or medical treatment that could affect cerebral metabolism and blood flow. Smokers were also excluded. Subjects were paid for participating and earned extra money for performing the task described below. They were told that they would earn only a percentage of each of the cash values presented on the screen.

Experimental Paradigm. Experimental trials were divided into 2 phases: Reward anticipation and outcome. During reward anticipation, a slot machine was presented on the screen and the words: ''Chance to win $ XX'' (where XX stood for $0, $10, or $20) remained visible on top of each slot machine with a pie chart indicating the probability of winning the indicated amount of money. There were four slot machines (see *SI Methods*) and subjects indicated which slot machine was presented by pressing a specific response button on a diamond-shaped four-response button device at the time of slot presentation and again at the time of the outcome (regardless of winning or not).

Image Analysis. See *SI Methods* for details. We used a threshold of $P < 0.005$, uncorrected in the PFC and striatum (random effects model) in all comparisons because of our strong a priori hypotheses concerning these reward-related brain regions. Findings outside these hypotheses-driven brain regions are reported if they met a statistical threshold of $P < 0.001$, uncorrected.

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Supporting Information

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SI Methods

Experimental Paradigm. Using Presentation software, stimuli representing "slot machines" were projected on a screen positioned at the foot of the subject. Experimental trials were divided into 2 phases: Reward anticipation and outcome. During reward anticipation, a slot machine was presented on the screen and the words: "Chance to win $XX" (where XX stood for $0, $10, or $20) remained visible on top of each slot machine with a pie chart, indicating in red the probability of winning the indicated amount of money and in white the probability of receiving nothing.

There were 4 slot machines (A, B, C ,or D) designed to vary reward probability, magnitude, and expected reward value (reward probability*magnitude): Slot A: $P = 1{:}4$, \$20, $P = 3{:}4$, \$0; Slot B: $P = 1{:}2$, \$20, $P = 1{:}2$, \$0; Slot C: $P = 1{:}2$, \$10, $P = 1{:}2$, \$0; Slot D: $P = 1$, \$0 (sure to get no reward). During the delay phase, each of 3 spinners of the slot machine rotated successively before stopping on a fixed image that was shown until the end of the trial. The delay duration was fixed (15 s). In the outcome phase, "$0", or pictures of "$10" and "$20" bills were projected for 2 s, the latter two surrounded, respectively, by a small and a large stack of gold pieces to produce visual experience of distinct reward magnitudes and reinforce the pleasantness of winning money. To equalize visual similarity between stimuli, the "$0" outcome was presented in a gray rectangle having the same dimensions as the bills. The inter-trial interval between slot machines varied between 4 s and 16.5 s with a geometric distribution of mean = 6.8 s.

Subjects indicated which slot machine was presented by pressing a specific response button on a diamond-shaped four-response button device at the time of slot presentation and again at the time of the outcome (regardless of winning or not). The association between each slot machine and a specific response button was learned during a training session before scanning. These motor responses ensured that subjects were attending to the specific types of slot machines as well as their outcomes and enabled us to keep the motor component equal between slot presentation and outcome. Importantly, the stimuli presentations were not contingent on the subject's response. There were a total of 6 runs, each consisting of 16 trials (4 trials for each type of slot machine). Each of the 4 possible slot machines occurred pseudorandomly during each run. The order of the runs was randomized between subjects.

Genetic Analysis. DNA was extracted by standard methods. *COMT Val*^{158}*Met* genotype was determined by 5′ exonuclease allelic discrimination TaqMan assay that uses the 5′ nuclease activity of TaqDNA polymerase to detect a fluorescent reporter signal generated after PCRs. Genotyping of the *DAT1* 40-bp repeat (VNTR) polymorphism in the 3′ untranslated region was determined by using forward 5′-TGTGGTGTAGGGAACG-GCCTGAG-3′ and reverse 5′- CTTCCTGGAGGTCACG-GCTCAAGGTCA-3′ primers. DNA amplification by PCR of the 40-base pair repeat alleles was performed as described elsewhere (1). PCR products were separated by 4% agarose gel electrophoresis, visualized by UV transillumination and fragment sized by comparison with Invitrogen 100-bp DNA ladder.

FMRI Data Acquisition. Imaging was conducted on a GE 3-Tesla scanner with a real-time functional imaging upgrade. Functional imaging involved a series of 29 contiguous 3.3-mm axial slices per volume collected over 6 runs, plus 8 "dummy" volumes at the start of each session. These functional scans used an echo-planar single shot real-time gradient echo T2* weighting (EPIRT sequence, RT = 2300 ms, TE = 23 ms, FOV = 24 cm, 64 × 64 matrix, voxel size = 3.75*3.75*3.3, flip angle = 90°). Signal dropout in orbitofrontal cortex from susceptibility artifact was reduced with local high-order *z*-shimming performed in the axial direction and by tilting subjects' heads 30° relative to the AC–PC line. High-resolution T1-weighted structural scans were acquired by using a MP-RAGE sequence (180 sagittal slices of 1 mm; FOV = 256 mm, NEX = 1, TR = 11.4 ms, TE = 4.4 ms; matrix = 256 × 256; TI = 300 ms).

Image Analysis. Data were analyzed by using Statistical Parametric Mapping (SPM99, http://www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, United Kingdom). Preprocessing included slice timing and motion correction, coregistration to a standard template, alignment to the first volume for each subject and spatial normalization to the Montreal Neurological Institute (MNI) T1-weighted template image. The data were then smoothed with a 10-mm FWHM Gaussian kernel. Within-subject time series modeling accounted for the following 11 regressors: 4 regressors for each slot cue-type during the delay period and 7 regressors at the time of the outcome (3 rewarded and 4 nonrewarded). The fMRI response was modeled as a ramping mode of increasing activity during the delay period (Fixed Impulse Response model: FIR) and as a delta function at the outcome (2 s) and convolved with a canonical hemodynamic response function (HRF). The model defined during the delay period used a FIR basis function with a bin width of 3.75 s, modeling a total of 4 bins from 0 to 15 s poststimulus, resulting in 4 delay regressors for each slot machine (the parameter estimates reflect the average response at each point in peristimulus time). This FIR model was used to capture brain regions responding with a progressive increase of activity because during the delay period between the cue and the outcome, dopamine neurons display a ramping mode of increasing activity which is greatest with reward probability = 0.5 (2). The SPM default high-pass filter was applied to the time series. Condition-specific estimates of neural activity (betas) were computed independently at each voxel for each subject, by using the general linear model.

To detect association between *COMT* genotype and fMRI activation on a voxel-by-voxel basis, the subjects *COMT* genotypes were included in a second level regression analysis of the contrast images. To model the assumed *COMT* gene-dose effect, *COMT* genotype was coded as a covariate by the number of val alleles (0, 1, or 2). The analysis of the genotype*task interaction investigated which brain areas showed robust genotype-dependent activation related to: (*i*) the reward anticipation period with maximal uncertainty as defined by the comparison, $\text{Delay}_{\text{slot\_B}} > \text{Delay}_{\text{Slot\_A}}$ and (*ii*) the reward delivery at the time of the outcome as defined by $\text{Outcome}_{\$20\_\text{All potentially rewarded slots}} > \text{Outcome}_{\$0\_\text{Slot\_D}}$. For the main effect of *DAT*1 genotype, we performed an ANOVA by using the same comparisons as for the *COMT* genotype during reward anticipation and at the time of the outcome, contrasting images of 9-repeat carriers (including *DAT*1 9-repeat and 9/10) with those of 10-repeat subjects.

We also searched for interactions between *COMT* and *DAT*1 by using two separate multiple regression analyses (one during reward anticipation and the other at the time of the outcome) with two covariates: (*i*) *DAT*1 genotype [with 2 levels: 9-repeat

(including *DAT* 9-repeat and 9/10) and 10-repeat]; and (*ii*) *COMT* genotype (with 3 levels: met/met, val/met, and val/val).

Additionally, for purposes of plotting and displaying the parameter estimates for each subgroup of subjects (Figs. 3 and 6), we performed two separate ANOVAs (F-tests), again one during reward anticipation and the other at the time of the outcome, each having 6 subgroups as factors. For these ANOVAs, single-subject contrasts were entered with number of val- and 10-repeat alleles as predictors (coded as follows: met/met 9/9 and 9/10 = 0; met/met 10-repeat = 1; val/met 9/9 and 9/10 = 2; val/met 10-repeat = 3; val/val 9/9 and 9/10 = 4; val/val 10-repeat = 5). We chose this order for displaying the group data because both the *DAT*1 10-repeat allele, associated with increased expression of the gene, and the *COMT* val/val genotype, associated with increased dopamine catabolism, presumably lead to relatively decreased intrasynaptic dopamine levels (i.e., higher DA elimination), whereas both the *DAT*1 9/9 and 9/10-repeat allele and the met/met genotype are associated with increased intrasynaptic dopamine. *COMT* genotype was used as the major grouping factor for displaying the data based on a previous fMRI study proposing a greater effect of *COMT* versus that of *DAT*1 on cortical signal-to-noise (3), and the *COMT* group order was chosen because of human postmortem data showing that COMT protein abundance and enzyme activity in heterozygotes are intermediate between the higher levels in val/val homozygotes and the lower levels in met/met homozygotes (4).

We used a threshold of $P < 0.005$, uncorrected in the prefrontal cortex and striatum (random effects model) in all comparisons because of our strong a priori hypotheses concerning these reward-related brain regions. Findings outside these hypotheses-driven brain regions are reported if they met a statistical threshold of $P < 0.001$, uncorrected.

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Table S1. Foci of activations during anticipation of rewards with maximal uncertainty ($P = 0.5$ \$20 > $P = 0.25$ \$20)

Anatomical structure (Brodmann's area)	COMT main effect (mm > vm > vv)				DAT main effect (9/9 & 9/10 > 10/10)				Epistatic interaction between COMT and DAT			
	Peak MNI coordinates				Peak MNI coordinates				Peak MNI coordinates			
	x	*y*	*z*	Z-value	*x*	*y*	*z*	Z-value	*x*	*y*	*z*	Z-value
Left superior frontal gyrus	−19	11	61	3.20*								
Left anterior lateral PFC	–42	46	23	2.89					−30	57	34	3.58*
Left motor cortex (BA 4)	–38	−27	38	3.67*								
Right motor cortex (BA 4)									57	−30	49	3.16*
Right thalamus	15	−15	8	3.54*					11	−11	19	3.61*
Left thalamus									−19	−19	11	3.09*
Left inferior parietal cortex	–61	−27	30	3.51*								
Left intra-parietal cortex	–27	−49	38	3.10*								
Visual cortex	–8	−87	15	3.12*								
Right caudate nucleus					8	4	11	4.06*	8	4	11	3.67*
Left caudate nucleus					−15	15	11	3.09	−11	8	8	3.21*
Right ventral striatum					8	19	−11	3.30*	8	19	−11	2.87
Left ventral striatum	–8	15	4	3.11*	−19	19	−11	3.62*	−8	15	0	3.37*

All areas are reported with a threshold of $P < 0.005$, uncorrected. Exception areas (designated with *) are reported with a threshold of $P < 0.001$, uncorrected.

Table S2. Foci of activations at the time of reward delivery *versus* no reward delivery

Anatomical structure (Brodmann's area)	COMT main effect (mm > vm > vv)				DAT main effect 9/9 & 9/10 > 10/10				Epistatic interaction between COMT and DAT			
	Peak MNI coordinates				Peak MNI coordinates				Peak MNI coordinates			
	x	*y*	*z*	Z-value	*x*	*y*	*z*	Z-value	*x*	*y*	*z*	Z-value
Left orbitofrontal cortex	−19	27	−15	2.74								
Right orbitofrontal cortex	15	30	15	2.75								
Right dorsolateral PFC					42	30	30	3.26*	38	30	30	2.86
Right anterior PFC					42	49	19	3.38*	38	46	11	3.36*
Right orbitofrontal cortex									30	34	−15	2.56†
Right intraparietal cortex					27	−61	42	3.92*	27	−65	42	3.77*
Left intraparietal cortex					−42	−72	46	3.28*				
Midbrain					8	−11	−19	2.36†	4	−11	−15	2.54†

Prefrontal and striatal areas were significant at $P < 0.005$, uncorrected (random effects model).
*Areas activated with a threshold at $P < 0.001$, uncorrected.
†Areas activated with a threshold at $P < 0.01$, uncorrected.