

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 (*DAT1*) and catechol-*O*-methyltransferase (*COMT*) genes. Here, we used event-related functional magnetic resonance imaging to directly investigate the neurofunctional effects of the Val¹⁵⁸Met *COMT* and variable number of tandem repeat *DAT1* 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 *DAT1* 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 *DAT1* 9-repeat allele showing the highest activity. Moreover, an interaction between the *COMT* and *DAT1* 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 *DAT1* 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 *DAT1* 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 *DAT1* 9-repeat allele is lower than the 10-repeat allele (10–12), although one study reported the opposite (13). Thus, the *DAT1* 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 *DAT1* gene show extensive adaptive 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 *DAT1* 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 *DAT1* 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 *DAT1* 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 *DAT1* 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 *DAT1* predominate in the striatum (16, 17, 20), our central hypotheses were that *DAT1* 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 *DAT1* 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 *DAT1* 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

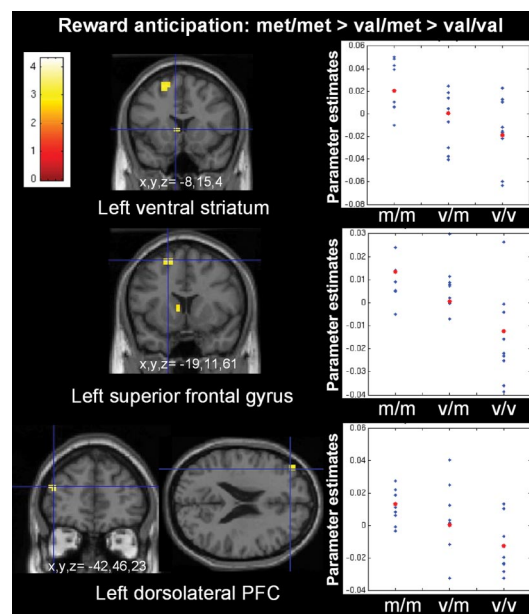


Fig. 1. Main effect of *COMT* genotype during anticipation of reward with maximal uncertainty. (Left) Statistical maps showing BOLD fMRI responses in the ventral striatum, left superior PFC, and dorsolateral PFC overlaid onto structural MRI coronal and axial planes. (Right) Negative relationship between *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.

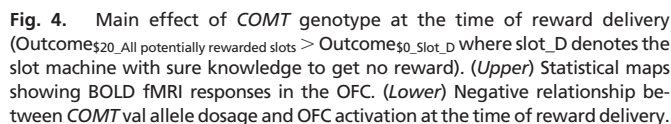
and caudate nuclei activities were observed in 9-repeat compared to 10-repeat *DAT1* individuals (Fig. 2). No voxel in the PFC or striatum survived the opposite comparison.

Third, we assessed gene–gene interactions during reward anticipation by using 2 covariates: the *DAT1* genotype [2 levels: 9-repeat (including *DAT1* 9-repeat and 9/10 repeat) and *DAT1* 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 *DAT1* 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.

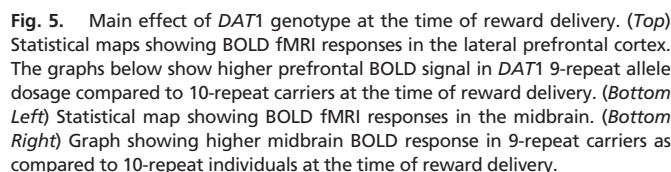
Individuals with the 9-repeat *DAT1* allele showed a more robust BOLD response in the right DLPFC and the right anterior PFC compared to 10-repeat carriers (Fig. 5 Top). In the opposite comparison, 10-repeat *DAT1* allele did not show higher BOLD response than 9-repeat carriers in the frontal lobe or 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 *DAT1* genes (comparison 9-repeat > 10-repeat and met/met > val/



Our findings concerning the effect of *COMT* genotype on the reward system have important clinical implications. Indeed, the *COMT* Val¹⁵⁸Met 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.

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



Our findings regarding the effect of the *DAT1* 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 *DAT1* Genes. One important insight provided by our data is a clear demonstration of interaction between the *DAT1* 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 *DAT1* 10/10 genotypes on dopamine

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

Interestingly, both the val/met and the *DAT1* VNTR polymorphisms may be evolutionarily recent, as a VNTR homologue has been observed in humans, chimpanzees, and cynomolgous 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 *DAT1* VNTR polymorphisms.

Materials and Methods

Subjects. Twenty-seven right-handed young subjects (mean age = $27.3 \pm [SD] 5.7$, 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 *DAT1* 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 *DAT1* 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 *DAT1* genotype and 8 were 9/10 *DAT1* 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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