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# Catechol-*O*-methyltransferase val$^{158}$met genotype influences neural processing of reward anticipation

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ABSTRACT

Reward processing depends critically on dopaminergic neurotransmission in the ventral striatum. The common polymorphism val$^{158}$met of catechol-*O*-methyltransferase (COMT) accounts for significant interindividual variations in dopamine (DA) degradation, although the direct effect of COMT on striatal DA might be limited. Using fMRI we assessed the influence of COMT val$^{158}$met genotype on brain activations elicited by the anticipation of monetary gains and losses in forty-four healthy volunteers. We found that the met$^{158}$ allele, which is presumably linked to higher synaptic DA levels, was associated with higher responses in ventral striatum to loss incentives. There was a linear relationship between the number of met$^{158}$ alleles and ventral striatal activity. Furthermore, we observed a similar gene-dose effect in the anterior temporal cortex, a region that has been linked to the coupling of sensory information with emotional contents. Temporal cortex also showed enhanced connectivity to the ventral striatum during the processing of incentive stimuli. Increased ventral striatal reactivity to loss incentives related to the met$^{158}$ allele might contribute to the observed association of the met$^{158}$ allele to higher loss aversion behaviour. Current evidence and our results are compatible with an interpretation that construes this effect of COMT genotype on striatal reactivity as a result of a cortico-striatal interaction.



## Introduction

The ability to detect and predict rewards is crucial for motivation and motivated behaviour. Dopamine (DA) is critically involved in reward anticipation and is thought to mediate the attribution of incentive salience to a reward-related stimulus (Berridge and Robinson, 1998; Kalivas and Volkow, 2005). The neural correlate of this reward component can be assigned to midbrain neurons that fire in response to a cue that precedes a pleasant event (Schultz, 1998). They project to the ventral striatum, including the nucleus accumbens. A considerable number of imaging studies show that the ventral striatum is reliably activated by the anticipation of reward of various modalities (for review see Knutson and Cooper, 2005). Consistent with these observations, abnormalities in dopaminergic neurotransmission that are found in a broad range in psychiatric disorders might contribute to associated motivational disturbances (Heinz, 2002). Thus, elucidating the biological mechanisms of inter-individual differences in reward sensitivity can confer to a better comprehension of both normal and pathological variability in motivated behaviour.

This issue can be addressed by investigating genetic polymorphisms that influence dopaminergic neurotransmission. One polymorphism whose molecular functional implications are well understood is val$^{158}$ met polymorphism of catechol-*O*-methyltransferase (COMT). COMT catabolizes catecholamines including dopamine (DA). The common single nucleotide polymorphism (SNP) val$^{158}$met has been identified as the molecular basis of interindividual differences in COMT function (Lachman et al., 1996). The met$^{158}$ allele translates into a less thermostable variant of the enzyme which is linked to a reduced activity, and is therefore thought to lead to higher extrasynaptic DA levels. Reflecting codominant expression met homozygotes exhibit 35–50% lower brain COMT activity than val$^{158}$ homozygotes, while heterozygotes show an intermediate enzyme function (Chen et al., 2004).

A recent study showed an influence of val$^{158}$met polymorphism on fMRI activations in a guessing task (Yacubian et al., 2007). During an active choice that was linked to the expectation of monetary outcome val$^{158}$ homozygotes exhibited lower activations than met$^{158}$ homozygotes in striatal

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and prefrontal regions with heterozygotes in between. However, differential effects of COMT genotype on specific processing of gain and loss anticipation were not investigated. In our present study, we addressed the question whether COMT val$^{158}$met polymorphism affects the processing of reward information in the ventral striatum. We used a simple conditioning paradigm that included a non-rewarding control condition in order to discern specific reward activations and non-specific signals linked to cognition and motor responses. Moreover our experimental paradigm allowed us to differentiate between the anticipation of monetary gain and loss, as reward and punishment have been suggested to be mediated by different neurotransmitter signals (Daw et al., 2002; Schultz, 2007).

Striatal DA is thought to be regulated by COMT via top-down modulation from prefrontal and other cortical regions (Smiley et al., 1992; Sesack et al., 1998; Ciliax et al., 1999). We therefore asked whether any of these cortical regions would also show a COMT genotype effect and investigated their functional role by analyzing their connectivity during incentive processing.

## Materials and methods

### *Subjects*

Forty-four right-handed healthy volunteers participated in the study (mean age 38.7 ± 10.0 years; nine female). Exclusion criteria were axes I and II psychiatric disorders (SCID interview), neurologic disorders, family history of psychiatric disorders and current or past drug abuse. Written informed consent was obtained from all subjects after the procedures had been fully explained. The study was approved by the Ethics Committee of the Charité University Medicine Berlin.

### *Genotyping*

Peripheral venous blood was drawn from all participants and deoxyribonucleic acid (DNA) was extracted from the white blood cells according to standard procedures. The COMT coding polymorphism c.675G>A (dbSNP: rs4680, p.Val158Met) was genotyped in a 384-well microtiter plate format using a TaqMan 5′-exonuclease assay (Livak, 1999). TaqMan probes and primers were obtained from the assortment of TaqMan® Drug Metabolism Genotyping Assays provided by Applied Biosystems (Assay ID: C 25746809 50; Applied Biosystems, Foster City, CA, USA). Briefly, 10 ng of genomic DNA was amplified in a total volume of 5 µl containing both allele probes labeled with 5′-VIC or 5′-FAM fluorophore and 2.5 µl of TaqMan universal PCR master mix. Amplification reaction conditions were 10 min at 95 °C, followed by 50 cycles of 95 °C for 15 s and 60 °C for 1.5 min. Allelic discrimination analysis was performed on the Prism 7900HT Fast Real-Time PCR system using the software SDSv2.2.2 (Applied Biosystems, Foster City, CA, USA).

### *Monetary incentive delay task*

To reliably activate reward-related brain areas we used the previously established "Monetary Incentive Delay" task as described by Knutson et al. (2001). Each trial started with one of seven different cues that indicated potential gain and loss of different amounts of money (€ 0.10, € 0.60 or € 3.00) or a neutral trial. This was followed by an interactive task, in which participants had to press a button in response to a visual target. Effective gain or loss avoidance depended on their performance in this simple reaction task. In the neutral condition performance had no monetary consequence (no outcome condition). After the target presentation feedback appeared, informing participants that they had won or lost money and indicating their cumulative total. The time window for a valid response, e.g. responses followed by monetary gain or avoidance of monetary loss, was adapted to the participants' performance. This way it was ensured that all participants succeeded on an average of 67% and gained a comparable amount of money in the end. The mean trial duration was approximately 7.69 s, and the mean inter-trial interval was 3.53 s. Trial structure and trial timing are depicted in Fig. 1.

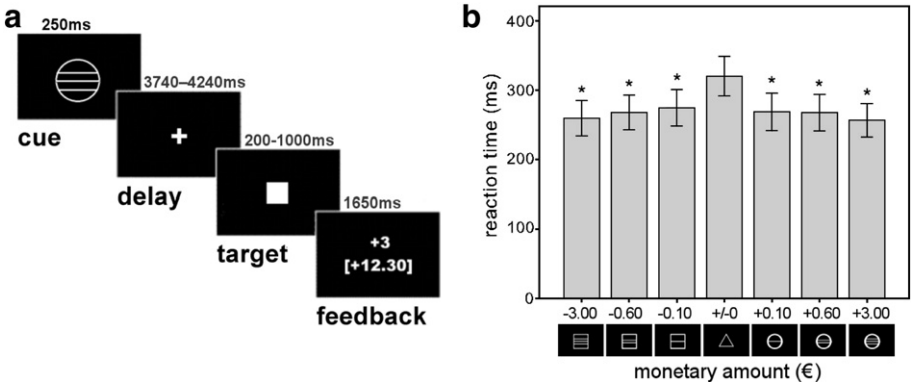


**Fig. 1.** (a) Task structure for a representative trial. During each trial, volunteers saw one of seven shapes ("cue" 250 ms), which indicated that they would, in a few moments, be able to respond and either win or avoid losing different amounts of money (€ 3.00, € 0.60 or € 0.10), or that they should respond for no monetary outcome. After the cue, volunteers waited a variable interval ("delay" 3740–4240 ms) and then responded to a white target square that appeared for a variable length of time ("target" 200–1000 ms) by pressing a button. To succeed in a given trial, volunteers had to press the button while the target was visible. During incentive trials, volunteers could win or avoid losing money by pressing the button during target presentation. The target duration was continuously adapted to the participants' performance, so that the overall chance of winning was 67%. Immediately after target presentation, feedback appeared ("feedback" 1650 ms), notifying volunteers that they had won or lost money and indicating their cumulative total at that point. The inter-trial interval was between 3280 and 3780 ms. Trial types were randomly ordered within each session. (b) Reaction times in ms as a function of trial type. The seven different cues are shown at the bottom. Cues signaling potential gain were denoted by circles, potential loss was denoted by squares, and no monetary outcome was denoted by triangles; the possible amount of money that volunteers were able to win was indicated by one horizontal line for €0.10, two horizontal lines for €0.60 and three horizontal lines for €3.00. Similarly, loss cues signaled the possibility of losing the same amounts of money. Asterisks denote significant paired comparisons between incentive versus no outcome trials ($p < 0.05$, Bonferroni-corrected).