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# The flexible mind is associated with the catechol-O-methyltransferase (COMT) Val$^{158}$Met polymorphism: Evidence for a role of dopamine in the control of task-switching

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ABSTRACT

Genetic variability related to the catechol-O-methyltransferase (COMT) gene (Val$^{158}$Met polymorphism) has received increasing attention as a possible modulator of cognitive control functions. Recent evidence suggests that the Val$^{158}$Met genotype may differentially affect cognitive stability and flexibility, in such a way that Val/Val homozygous individuals (who possess low prefrontal dopamine levels) may show more pronounced cognitive flexibility than Met/-carriers (who possess high prefrontal dopamine levels). To test this, healthy humans ($n = 87$), genotyped for the Val$^{158}$Met polymorphism at the COMT gene, performed a task-switching paradigm, which provides a relatively diagnostic index of cognitive flexibility. As predicted, Met/-carriers showed larger switching costs (i.e., less cognitive flexibility), $F(1,85) = 4.28$, $p < 0.05$, than Val/Val homozygous individuals. Our findings support the idea that low prefrontal dopamine levels promote cognitive flexibility.



## 1. Introduction

Dopamine (DA) plays a key role in the regulation of executive functions in the prefrontal cortex (PFC). The supply of DA, in turn, is assumed to be affected by a number of genetic factors, such as the predisposition regarding catechol-O-methyltransferase (COMT), an enzyme responsible for the degradation of dopamine. A single nucleotide polymorphism (SNP), leading to a valine (Val) to methionine (Met) substitution (Val$^{158}$Met), in the coding region of the *COMT* gene has been shown to influence the activity of the enzyme at body temperature (Lachman et al., 1996). The low-activity Met allele results in slower inactivation of extracellular DA within the brain, being associated with higher DA in the PFC for the Met/-carriers than for Val/Val homozygous individuals (Chen et al., 2004).

Interestingly, recent reports have suggested that the Val$^{158}$Met genotype may differentially affect cognitive stability (defined as the maintenance of task-relevant representations) and flexibility (defined as the ability to adapt, update, and shift between informational states)—two major functions of cognitive control (Miyake et al., 2000). In particular, Met/-carriers might be comparatively high in cognitive stability but comparatively low in cognitive flexibility (see Cools, 2006, for a review). Bilder, Volavka, Lachman, and Grace (2004) discussed the effects of the *COMT* polymorphism on DA transmission in terms of a distinction between tonic and phasic DA processes. Of most relevance to the current study, Val/Val homozygous individuals are assumed to be associated with low tonic DA levels in PFC, whereas Met/-carriers are assumed to be associated with high tonic DA levels in PFC.

According to Cools (2006), the same high DA levels in the PFC (as in the case of the Met/-carriers) that are beneficial for the stability of representations may reduce the ability to flexibly alter cognitive representations. On the other hand, the low DA levels in the PFC (as in the case of Val/Val homozygous) may be beneficial for the flexible alteration of cognitive representations, but at the same time may impair the ability to maintain representations in the face of intervening distractors.

Further evidence for such an interplay has been reported by Nolan, Bilder, Lachman, and Volavka (2004). They have shown that, in a reversal learning task, Val/Val homozygous individuals show worse performance than Met/Met homozygous individuals at the acquisition stage but outperform them at the reversal stage, suggesting that their genetic predisposition impairs cognitive stability but enhances cognitive flexibility. Moreover, de Frias et al. (2010) recently found that Met carriers displayed a greater transient medial temporal lobe response in the updating phase of working memory, whereas Val carriers showed a greater sus-

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tained PFC activation in the maintenance phase. Consistent with this picture, in animals, PFC DA depletion improved performance on an attentional set-shifting task, requiring the ability to alter behavior according to changes in dimensional relevance of multidimensional stimuli while increasing distractibility (Roberts et al., 1994), whereas DA depletion in the striatum reduced distractibility (Crofts et al., 2001).

More converging evidence has been provided by studies investigating patients with Parkinson's disease (PD), a neurodegenerative disorder characterized by severe DA depletion in the striatum vis-à-vis relatively intact PFC DA levels, at least in the early stages of the disease (Sawamoto et al., 2008). Cools (2006) suggests that high DA levels in the striatum may be beneficial for the flexible alteration of cognitive representations, it is not surprising that Cools et al. (2010) found enhanced distractor resistance in PD patients OFF medication compared to controls.

Recently, Cools and D'Esposito (2009) have suggested that the balance between cognitive flexibility and stability depends on the adjustment of dopaminergic processing in the circuits connecting the PFC with the striatum. DA in the striatum supposedly promotes flexibility by allowing the updating of novel relevant representations, whereas DA in the PFC is proposed to support stability by increasing distractor resistance. These two processes seem to interact with each other: too much flexibility may be associated with distractibility, while too much stability may be related to inflexibility—one of the major control dilemmas discussed by Goschke (2000).

So far, most studies on the relationship between *COMT* and executive functions have made use of the Wisconsin Card Sort Test (WCST) to assess executive control (see Barnett, Jones, Robbins, & Müller, 2007 for a review). Egan et al. (2001) and Caldu, Vendrell, and Bartres-Faz (2007), who used the WCST as an index of working memory, showed that the high-activity Val allele is associated with a reduction in performance of the WCST compared with the Met allele and that Val allele load is related to reduced "efficiency" of the physiologic response in the dorsolateral PFC during performance of working memory. The authors suggested that the *COMT* Val allele may reduce signal-to-noise ratio in prefrontal neurons, presumably by compromising the postsynaptic impact of the evoked dopamine response. However as pointed out by Barnett et al. (2007), the WCST is a complex task involving multiple cognitive functions which may limit its ability to discriminate between cognitive stability and cognitive flexibility.

The goal of the present study was to examine the association between the *COMT* polymorphism and control with a more well-established diagnostic index of cognitive flexibility. A reliable indicator of cognitive flexibility is task-switching performance (Miyake et al., 2000; Monsell, 2003). The amount of the time needed to switch between two different tasks can be taken to indicate the efficiency in adapting and restructuring cognitive representations, so that smaller switching costs would reflect a higher level of cognitive flexibility. In this kind of paradigm, the sequence of tasks is often regular and predictable (e.g., AABBAABB. . .). Accordingly, participants know when to prepare for a task switch, so that the interval between the previous response and the upcoming stimulus (the response–stimulus interval or RSI Fig. 1) represents a preparation interval. In switch trials participants can use this preparation interval to reconfigure their cognitive task set. The shorter the interval the less likely this reconfiguration will be completed before the stimulus is presented, which fits with the observation that switching costs (i.e., the increase of reaction time in task-switching trials relative to task repetition trials) are more pronounced with short than with long RSIs (Monsell, 1996).

Based on the considerations of Bilder et al. (2004) and Cools (2006), we predicted that switching performance in a task-switching design is determined by *COMT* variability. In particular,

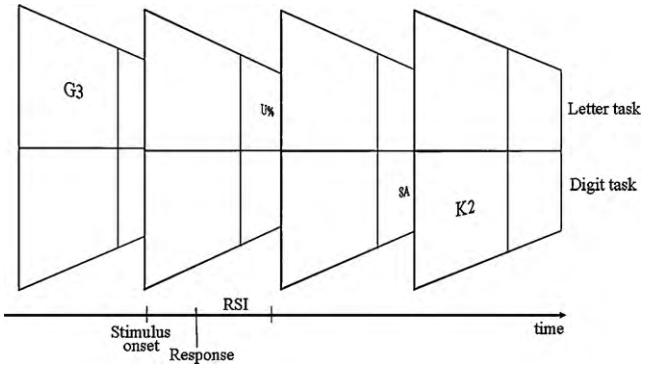


**Fig. 1.** Illustration of the sequence of events. A stimulus is comprised of two characters, as described in the text. On consecutive trials, stimuli appear in adjacent quadrants rotating clockwise in the four quadrants of the square. One pair of adjacent quadrants is assigned to the letter task (the upper two, in the example) and the other pair to the digit task. As a consequence, the task changes predictably every second trial. The response–stimulus interval (RSI) was either 150 or 2000 ms.

we predicted that Met/-carriers (assumed to be equipped with relatively high DA levels in PFC) showed larger costs in switching between tasks than Val/Val homozygous participants (assumed to be equipped with low DA levels in the PFC). However, even though it is clear that a less beneficial genetic predisposition should affect the efficiency and, thus, the speed of the task-switching process, this does not mean that the less efficient individuals would be unable to execute the same control functions at all. Accordingly, the impact of genetic differences should be more visible in, and probably even restricted to, the condition in which speed and efficiency really matters: the short RSI. With a long RSI, however, time to prepare for a task switch may have been sufficient even for less efficient individuals, so that the genetic effect would be smaller or even absent. We thus predicted a three-way interaction between *COMT* polymorphism, task switch and RSI, resulting in larger switching costs in Met/-carriers than in Val/Val homozygous individuals, in particular at the short RSI.

## 2. Methods

### 2.1. Participants

One hundred young healthy adults (47 male/53 female), with a mean age of 22.6 years (SD = 2.3, range 18–30) and 115.9 IQ (SD = 3.0, range 100–130); served as participants for partial fulfilment of course credit or a financial reward. The sample was drawn from adults in the Leiden and Rotterdam metropolitan area (The Netherlands), who volunteered to participate in studies of behavioral genetics. Exclusion criteria were any major medical illness that could affect brain function, current substance abuse, neurological conditions, a history of head injury, and a personal history of psychiatric medical treatment. Written informed consent was obtained from all participants after the nature of the study was explained to them; the protocol was approved by the Ethical Committee of the Leiden University Institute for Psychological Research.

### 2.2. Apparatus, stimuli and task

The experiment was controlled by a PC attached to a 17 in. monitor with a refresh rate of 100 Hz. The task was modeled after Nieuwenhuis and Monsell (2002). Throughout each block, a 10 $cm^2$ divided into four quadrants was displayed on the computer screen. On each trial, a character pair was presented in a white uppercase Triplex font in the center of one quadrant. Each pair subtended a visual angle of 1.4° both horizontally and vertically. The next stimulus was displayed clockwise in the next quadrant. One pair of adjacent display positions was assigned to the letter task and the other pair to the digit task, so that the display location served as a task cue, and the task changed predictably every second trial. Depending on the task, the relevant character was either a letter or a digit. The second and irrelevant character was either a member of the other category, so that the response afforded by this character was either congruent or incongruent with the task-relevant response, or was drawn from a set of neutral characters.

Consonants were sampled randomly from the set [G, K, M, R] vowels from the set [A, E, I, U], even digits from the set [2, 4, 6, 8], odd digits from the set [3, 5, 7, 9] and neutral characters from the set [#, ?, *, %] with the restriction that a character

**Table 1**
Mean response latencies (in ms), error rates (in percent) and switching costs (alternation –repetition) for Met/-carriers and Val/Val homozygous individuals. Standard errors in parentheses.

| Variables (SE) | Met/-carriers ($n = 45$) | | Val/Val homozygous ($n = 42$) | |
|---|---|---|---|---|
| SOA | 150 | 1200 | 150 | 1200 |
| Repetition | | | | |
| Reaction times (ms) | 815 (21) | 832 (24) | 781 (22) | 812 (25) |
| Error rates (%) | 1.6 (0.3) | 2.1 (0.3) | 1.3 (0.3) | 1.7 (0.3) |
| Alternation | | | | |
| Reaction times (ms) | 1350 (38) | 1194 (41) | 1218 (39) | 1146 (42) |
| Error rates (%) | 4.6 (0.6) | 4.3 (0.5) | 3.9 (0.6) | 4.7 (0.5) |
| Switch costs | | | | |
| Reaction times (ms) | 535* | 362 | 437* | 334 |
| Error rates (%) | 3.0 | 2.2 | 2.6 | 3.0 |

* $p < 0.05$, significant group difference.

could not be repeated on successive trials. The position of the task-relevant character within a pair was randomly determined on each trial. The participants responded with their left index finger (on the "C" key) to indicate "even" or "consonant" and their right index finger (on the "M" key) to indicate "odd" or "vowel."

The participants received a practice set of 9 switch blocks, each with 16 trials, before entering the experimental phase. This consisted of two sets of 15 blocks, one set for each RSI, each block consisting of 16 trials. The RSI was 150 or 1200 ms, and remained constant for a given set. The order of the RSIs was counterbalanced across participants. The stimulus was displayed until a response was registered.

### 2.3. DNA laboratory analysis

Genomic DNA was extracted from saliva samples using the Oragene™ DNA self-collection kit following the manufacturer's instructions (DNA Genotek Inc, 2006). The SNP Val[158]Met of the *COMT* gene was genotyped using Applied Biosystems (AB) TaqMan technology. Primers *COMT*-F 5′-TCA CCA TCG AGA TCA ACC CC-3′ and *COMT*-R 5′-GAA CGT GGT GTG AAC ACC TG-3′ were used to amplify the 176 bp polymorphic *COMT* fragment (Barr et al., 1999). The amplification was done in 50 μl reactions containing ~125 ng genomic DNA, 200 μM deoxynucleoside triphosphates (dNTPs), 10 pmol/l of each primer, 10× HotStarTaq® buffer (QIAGEN) and 1 U HotStarTaq® DNA polymerase (QIAGEN). Polymerase chain reaction (PCR) conditions consisted of an initial denaturation step at 95 °C for 15 min followed by 30 cycles on a thermocycler (denaturation at 94 °C for 30 s, annealing at 52 °C for 30 s, and extension at 72 °C for 30 s) and finished with a final extension at 72 °C for 10 min. All genotypes were scored by two independent readers by comparison to sequence-verified standards. For *COMT* Val[158]Met three genotype groups were established: Val/Val homozygotes, Val/Met heterozygotes and Met/Met homozygotes. *COMT* genotype was unavailable in 8 participants.

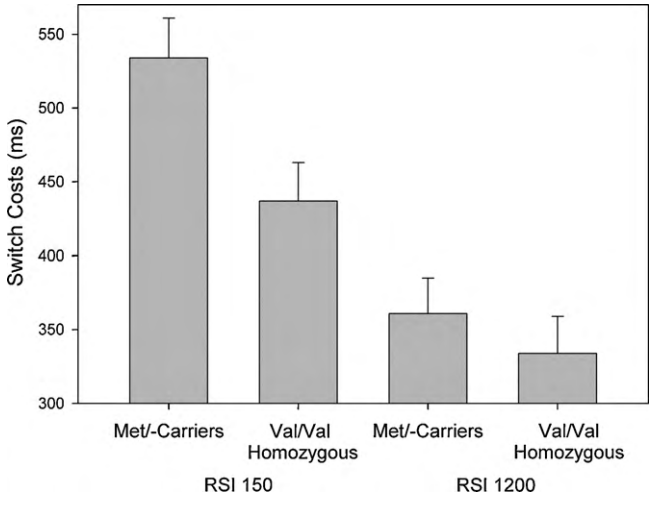


**Fig. 2.** Mean switch costs (calculated as the RT difference between Task Repetition and alternation) as a function of *COMT* polymorphism (Val/Val homozygous vs. Met/-carriers) and the response–stimulus interval (RSI) (150–1200). Standard errors of the difference between Task Repetition and alternation trials are represented by the error bars.

### 2.4. Procedure and design

All participants were tested individually. Individual IQs were determined by means of a 30 min reasoning-based intelligence test: the Raven Standard Progressive Matrices (SPM). The SPM assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely-used test to measure Spearman's g factor and of fluid intelligence in particular (Raven, Court, & Raven, 1988). Participants completed the SPM and subsequently performed on the behavioral task measuring cognitive flexibility which took about 30 min. Participants were allowed to take a short break (maximal 10 min) between task blocks. In practice, however, participants decided to go on with the next block immediately.

### 2.5. Statistical analysis

Repeated-measures ANOVAs were performed for analysis of age, sex, IQ differences between Val/Val homozygotes, Val/Met heterozygotes and Met/Met homozygotes. In order to obtain two equally sized subsamples to investigate the effect of *COMT* genotype on cognitive flexibility we collapsed Val/Met heterozygotes and Met/Met homozygotes in the subsample Met/-carriers. The effect of *COMT* genotype on cognitive flexibility was assessed by means of $2 \times 2 \times 2$-ANOVAs with *COMT* (Val/Val homozygous vs. Met/-carriers) as between-subject factor and with Task Repetition (i.e., repetition vs. alternation of task) and RSI (150 vs. 1200) as within-subject factors.[1] We adopted a significance level of $p < .05$ for all statistical tests.

## 3. Results

Genotype distribution of the Val[158]Met polymorphism in our Dutch healthy population was 42 Val/Val homozygous subjects (45.6%), 40 Val/Met heterozygous subjects (43.4%) and 10 Met/Met homozygous subjects (11.0%). The genotype frequency from our cohort of participants did not deviate from Hardy–Weinberg equilibrium ($p < .10$). No significant differences were found among genotype frequencies with respect to age, sex and IQ, $F < 1$.

Due to technical failure the data of five participants (one Met/Met homozygous and four Val/Met heterozygous subjects) were excluded from the analysis. Table 1 provides an overview of the outcomes for reaction times (RTs) and proportion errors (PEs). RTs revealed a significant main effect of Task Repetition, $F(1,85) = 681.37$, $p < 0.00001$, MSE = 22131.83, $\eta^2 p = 0.89$ and of RSI, $F(1,85) = 5.31$, $p < 0.05$, MSE = 33063.83, $\eta^2 p = 0.06$. These two main effects were involved in two-way interaction, $F(1,85) = 67.49$, $p < 0.0001$, MSE = 6141.72, $\eta^2 p = 0.44$ and in a three-way interaction involving *COMT*, $F(1,85) = 4.28$, $p < 0.05$, MSE = 6141.72, $\eta^2 p = 0.05$.

[1] We also examined effects of cross-talk (i.e., whether the currently irrelevant, unattended symbol of the two-symbol stimulus compound was related to the task or neutral) and congruency (i.e., whether the currently irrelevant, unattended symbol of the two-symbol stimulus compound was signaling the same response as the relevant symbol or not). However, neither factor was involved in any interaction involving the *COMT* genotype, $F < 1$, so that they were not considered further.

Both Val/Val homozygous and Met/-carriers exhibited a significant main effect of Task Repetition, $F(1,44) = 397.61$, $p < .0001$, MSE = 22676.476, $\eta^2 p = 0.90$; $F(1,41) = 289.73$, $p < .0001$, MSE = 21547.338, $\eta^2 p = 0.88$; respectively. *t*-tests for the obtained switch costs effect revealed that there was a significant difference between Met/-carriers and Val/Val homozygous, $t(85) = 2.58$, $p = .012$ at the short RSI (150 ms), but not at the long RSI (1200 ms), $t(85) = .79$, $p = .432$. As expected, Met/-carriers showed more pronounced task-switching costs than Val/Val homozygous individuals, but only at the short RSI (see Fig. 2).

In the error analysis, Task Repetition revealed a main effect, $F(1,85) = 122.023$, $p < 0.0001$, MSE = 513.00, $\eta^2 p = 0.59$, due to fewer errors when the task was repeated than alternated. *COMT* was not involved in any significant effect.

## 4. Conclusions

Our findings show that the *COMT* Val$^{158}$Met polymorphism, a gene coding the enzyme responsible for the degradation of DA in PFC, modulates cognitive flexibility as measured by a task-switching paradigm. Met/-carriers showed larger switch costs than Val/Val homozygous individuals when the preparation interval to switch was short, but not when it was long. This implies that both groups of participants were comparable with respect to the intended results of the control operations (the reconfiguration of the task set) but Val/Val homozygous individuals were more efficient and faster to produce this result under time pressure. Given that no significant differences were found among genotype frequencies by age, sex, or estimated IQ, we can rule out an account of our results in these terms. Particularly important was the matching of the age range and intelligence: cognitive flexibility is known to be related to general/fluid intelligence (Colzato, van Wouwe, Lavender, & Hommel, 2006) and to decline with increasing age (Kray, Li, & Lindenberger, 2002).

The observation that the *COMT* polymorphism predicts performance on a relatively well-established diagnostic index of cognitive flexibility (Miyake et al., 2000; Monsell, 2003) provides considerable support for the idea of a crucial role of dopaminergic pathways in cognitive flexibility in general, and for Bilder et al.'s (2004) and Cools's (2006) theoretical considerations in particular. As hypothesized by these authors, cognitive flexibility might benefit from relatively low DA levels in PFC (as in Val/Val homozygous individuals) but suffer from relatively high DA levels in PFC (as in Met/-carriers). With regard to the wider picture, our observations are also in line with the hypothesis by Cools and D'Esposito (2009) that low DA level in PFC promote flexibility by facilitating the update of information in working memory (such as the current task set).

Our results are consistent with the pattern of results reported by animal and patient studies and other studies investigating the genetic variability associated with the *COMT* gene. In animals PFC DA depletion can improve set-shifting (Roberts et al., 1994) while increasing distractibility, whereas DA depletion in the striatum prevents the interference from distractors. Moreover, patients with mild PD, who suffer from severe DA depletion in the striatum (Sawamoto et al., 2008), exhibit enhanced switch costs while showing abnormally reduced distractor costs (Cools, Miyakawa, Sheridan, & D'Esposito, 2009). Along the same lines, Nolan et al. (2004) found Val/Val homozygous individuals to perform worse than Met/Met homozygous individuals at the acquisition stage but outperform them at the reversal stage in a reversal learning task, suggesting that their genetic predisposition impairs cognitive stability but enhances cognitive flexibility.

One may have expected that depleted DA levels in PFC would promote flexibility while increasing distractibility. However, in our results there is only evidence for increased flexibility (i.e., reduced switch cost), but no evidence for increased distractibility (i.e., no COMT interaction with cross-talk/congruency). This discrepancy may be explained by the fact that while switch cost are considered a reliable index of cognitive flexibility, in the literature, there is still no consensus about the meaning of congruency. It is currently under debate whether such response congruency effects are mediated by the activation of an abstract representation of the irrelevant task in working memory or by "direct" associations between specific stimuli and responses. Recently, Kiesel, Wendt, and Peters (2007) found converging evidence for the direct associations hypothesis suggesting that congruency effect may not be taken as reliable index of distractibility.

Our results are inconsistent with some studies using that have shown a reduction of performance in the WCST for the high-activity Val allele (Egan et al., 2001; Caldu et al., 2007). However, the WCST is a complex task involving multiple cognitive functions, which is likely to limit its ability to discriminate between cognitive stability and cognitive flexibility. Our results are also not consistent with a developmental study that has found an advantage of cognitive flexibility in Met/Met homozygotes children in a task in which the subjects performed, in a randomly intermixed way, two different tasks (Diamond, Briand, Fossella, & Gehlbach, 2004). However, Diamond et al. (2004) failed to control for IQ and tested a small sample ($n = 39$) for a genetic association study, so that it cannot be excluded that other factors contributed to the obtained behavioral pattern. An alternative explanation of the discrepant results between the two studies may be that in children the genotype modulates the phenotype differently than adults.

Interestingly, a recent longitudinal genetic study in older adults using the same task-switching paradigm as we did, found no effect of *COMT* gene for either the switch condition or the repeat condition (Erickson et al., 2008). These results were used as evidence that *COMT* polymorphism did not affect the trajectory of age-related executive control decline. However, Erickson et al. (2008) did not vary the preparation interval to switch and used only a single long interval, so that the older adults were not tested under real time pressure. In contrast, we found reliable *COMT* effects when only little time was available for preparation. This suggests that the beneficial genetic predisposition effect on cognitive control is rather subtle and restricted to conditions where speed and efficiency really matter. Taken together, the current observations provide converging evidence for the idea that the Val$^{158}$Met genotype may differentially affect cognitive stability and flexibility, and that low DA levels in PFC may be beneficial for cognitive flexibility.

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