ELSEVIER

Neuropsychologia 46 (2008) 757–763

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Planning, decision-making and the COMT rs4818 polymorphism in healthy males

Panos Roussos [a], Stella G. Giakoumaki [a], Stefanos Pavlakis [a,b], Panos Bitsios [a,*]

[a] *Department of Psychiatry and Behavioral Sciences, University of Crete, Heraklion, Greece*
[b] *Royal Free and University College Medical School, Department of Clinical Sciences, University College, London, UK*

Received 2 September 2007; received in revised form 14 October 2007; accepted 16 October 2007
Available online 22 October 2007

Abstract

Recent evidence suggests that a synonymous polymorphism within the COMT gene (rs4818 C/G) accounts for a greater variation of COMT activity compared to the functional Val158Met polymorphism. This is the first study on the effects of the rs4818 C/G polymorphism on cognition. One hundred and seven healthy males were tested with the Stockings of Cambridge (SoC) and the Iowa Gambling Task (IGT) and then grouped according to their COMT rs4818 C/G status into three groups (G/G, C/G, C/C). ANOVAs showed that C/C individuals had the best performance in the SoC, G/G the worse, while C/G were intermediate. G/G individuals had strikingly better performance in the IGT compared to the other two groups and their performances in the two tasks were inversely related. These results show that the rs4818 C/G polymorphism imparts strong and differential effects on PFC functions. Low prefrontal dopamine levels are disadvantageous for planning in non-emotional problem solving but lead to optimal effects in emotionally informed decision-making. While high prefrontal dopamine levels may be advantageous for non-emotional problem solving, they lead to disadvantageous choices when decision-making depends on processing of emotional feedback.

Keywords: Synonymous polymorphism; Prefrontal cortex; Dopamine; Cognition; Emotion

1. Introduction

The catechol-*O*-methyltransferase (COMT) enzyme provides the main mechanism for degradation of released dopamine (DA) in the prefrontal cortex (PFC) (Lewis et al., 2001; Mazei, Pluto, Kirkbride, & Pehek, 2002; Moron, Brockington, Wise, Rocha, & Hope, 2002). A common functional polymorphism in codon 158 (Val158Met) of the COMT gene, leading to an amino acid substitution (valine [Val] to methionine [Met]) results in the Met/Met variant showing 40% less enzymatic activity than the Val/Val and thus, in higher PFC DA levels (Chen et al., 2004; Lotta et al., 1995; Mannisto & Kaakkola, 1999). This COMT polymorphism determines basal DA neurotransmission levels and its effect on cognition has been examined in relation to executive function tests where Met/Met perform better than Val/Val homozygotes with Val/Met individuals being intermediate (Egan et al., 2001; Goldberg et al., 2003; Malhotra et al., 2002; Mattay et al., 2003; Tunbridge, Harrison, & Weinberger, 2006). However, this is a small effect (Barnett, Jones, Robbins, & Muller, 2007) and in some studies, the observed association between cognitive performance and the Met allele (low enzyme activity) is relatively modest (Bilder, Volavka, Lachman, & Grace, 2004; Joober et al., 2002) or absent (Tsai et al., 2003; Smyrnis et al., 2007; Stefanis et al., 2004).

The COMT Val158Met polymorphism forms a haploblock with SNPs rs6269, rs4633 and rs4818, which is located in the central locus of the COMT gene (Diatchenko et al., 2005; Nackley et al., 2006). Three major haplotypes [low pain sensitivity (LPS), average pain sensitivity (APS) and high pain sensitivity (HPS)] encompassed almost 96% of the examined genotypes, with the LPS haplotype being associated with the highest, the HPS with the lowest and the APS with intermediate enzyme activity. The difference between the HPS and LPS haplotypes in expressed COMT activity is reported to be >18-fold (Nackley et al., 2006). Both the HPS and LPS haplotypes possess the allele that codes for the most stable Val variant, and therefore, the Val158Met polymorphism alone cannot account

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Faculty of Medicine, PO Box 2208, University of Crete, Heraklion 71003, Crete, Greece. Tel.: +30 2810 394610; fax: +30 2810 394617.
E-mail address: pbitsios@med.uoc.gr (P. Bitsios).

0028-3932/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2007.10.009

for the observed variation in COMT activity. On the other hand, the rs4818 C/G polymorphism seems to account for a greater variation of the COMT activity compared to the Val158Met polymorphism, since the low expressed enzyme activity haplotypes [HPS and APS] contain the C allele, while the LPS haplotype, which corresponds to highest COMT activity, contains the G allele of the rs4818 polymorphism (Diatchenko et al., 2005).

This is the first study on the effects of the COMT rs4818 C/G polymorphism on cognitive function. We hypothesized that the C [lowest enzyme activity–highest PFC DA levels] and G [highest enzyme activity–lowest PFC DA levels] alleles of the rs4818, will impact on PFC-dependent cognitive tasks in a way similar to that of the Met and Val alleles of the Val158Met polymorphism, respectively. To test this hypothesis, we examined the effect of the rs4818 C/G polymorphism on two PFC-dependent tasks: (a) the Stockings of Cambridge (SoC) from the CANTAB, which is a planning and problem solving task (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Sahakian, Semple, Polkey, & Robbins, 1995) and (b) the Iowa Gambling Task (IGT), where planning depends on emotional processing and integration of incentive information for decision-making (Bechara, Damasio, Tranel, & Anderson, 1998). In agreement with evidence from Met/Met and Val/Val individuals (de Frias et al., 2005), we predicted that in the SoC, C/C individuals would perform better than the homozygotes for the G allele, with C/G heterozygotes falling in the middle. The effect of basal PFC DA levels on cognition has not been examined previously in relation to the IGT.

2. Methods

2.1. Subjects

The study was approved by the Ethics Committee of the University of Crete. All participants gave written informed consent before screening. Inclusion criteria included right-handedness, absence of personal history of head trauma, medical and neurological conditions, or use of prescribed and recreational drugs; absence of personal or family (up to second-degree relatives) history of DSM-IV axis I disorders. We restricted the study population to males only, in order to avoid the regulatory effect on the expressed activity of the COMT enzyme by the circulatory estrogens in women (Salama et al., 2006).

One hundred and seven unrelated Greek/central European descend healthy males aged 18–35 years (mean ± S.D., 26.3 ± 4.1) entered the study. All underwent IQ testing with the Raven's progressive matrices, psychiatric assessment using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and physical assessment including a urine toxicology screening. Participants were seen and assessed on a single occasion.

2.2. Genotyping

DNA was extracted from blood and analyzed for rs4818 polymorphism with polymerase chain reaction (PCR), using forward, 5′-GATCCAAGTTCCCCTCTCTC-3′ and reverse, 5′-TTTTTCCAGGTCTGACAACG-3′ followed by digestion with BclI. Details are available on request.

2.3. Cognitive assessment

The Stockings of Cambridge (SoC) is a modified, computerized version of the Tower of London (Owen et al., 1990, 1995). Subjects are asked to compare two different arrangements of "balls" in "socks" (one presented on the top half of the screen, the other on the bottom) and rearrange, in the minimum possible number of moves, the balls in the lower half of the screen such that their positions match the target arrangement in the upper half. The test presents the subject with easy 2- and 3-move and harder 4- and 5-move problems. Subjects are asked to plan the complete sequence of moves required to solve the problem prior to their first move. Initial Thinking Time (ITT) prior to execution of the first move, Subsequent Thinking Time (STT) for the execution of all subsequent moves, Mean Moves required to reach the solution and perfect solutions (problems solved correctly in the minimum possible moves) are recorded. Poor performance in this test translates into shorter ITT (less time planning), and/or longer STT (more time executing the solution) with more Mean Moves and less perfect solutions.

The Iowa Gambling Task (IGT) is a simulated gambling task administered on a computer. Participants are given €2000 in computer money and are instructed to lose as little or make as much money as possible by selecting cards (one at a time) from four decks (A–D) displayed on their screen. They are advised that each card has a different monetary value but no other information is given. However, cards in decks A and B are associated with high monetary rewards but also high penalties (monetary loses) while those in decks C and D have lower rewards but also lower penalties. Participants learn of the monetary value of each card after they have selected it. Across 100 trials, more choices from the decks C and D lead to a net gain while choosing from the other two decks results in greater loss. Scores are (a) total money won and (b) the total numbers of cards selected from advantageous decks C and D minus the total numbers of cards selected from ("risky") decks A and B (CD − AB difference), with a higher score indicating superior performance.

2.4. Statistical analysis

Subjects in the three genotype groups were compared on the demographic, SOC and IGT outcome variables using separate one-way analyses of variance (ANOVA; three levels) or the equivalent Kruskal–Wallis ANOVA in case the overall distribution of the score within the group differed from normality (Kolmogorov–Smirnov test of normality). In order to decrease skew and stabilize variances, latency data from the SoC were transformed using logarithmic transformations ($x = \log_{10} y$) in preparation for parametric analyses. Significant findings were followed-up by pairwise group comparisons using post hoc LSD tests or the Mann–Whitney test (with Bonferroni correction of the threshold of statistical significance) as appropriate. For each genotype group, Pearson's correlations were calculated for performance in the two planning tasks. Differences between correlations in the genotype groups were tested with a normal curve test based on Fisher's z-transformation.

3. Results

Twenty-eight subjects were homozygous for C/C, 62 were heterozygous for C/G, and 17 were homozygous for G/G, a distribution consistent with Hardy-Weinberg expectations ($\chi^2 = 3.14$, d.f. = 2, $p = 0.21$). There were no differences in demographic variables between the three genotype groups (Table 1). As an additional control to rule out gross stratification effects, genotyping was also performed for the dopamine receptor D2 TaqIA restriction fragment length polymorphism on human chromosome 11q23 (rs1800497; DRD2A1), dopamine receptor D3 (rs6280; DRD3) Ser9Gly polymorphism (human chromosome 3q13), a 40-bp tandem repeat polymorphism (rs28363170; DAT1) in the 3′ region of the SLC6A3 gene on human chromosome 5p15, proline dehydrogenase T1945C (rs372055; PRODH) polymorphism on human chromosome 22q11, brain-derived neurotrophic factor (rs6265; BDNF) Val66Met polymorphism on human chromosome 11p13, and dopamine receptor D1 (rs4532; DRD1) A-48G polymorphism in the 5′ untranslated region of DRD1 gene on human chromosome 5q35. A con-

Table 1
Demographic characteristics for each genotype group (mean ± S.D.)

	C/C	C/G	G/G	F or χ^2	p
Sample size	28	62	17		
Age (years)[a]	25.1 ± 3.8	25.9 ± 3.4	25.5 ± 3.5	2.1	>0.3
Estimated IQ	115.0 ± 12.9	113.8 ± 10.4	113.2 ± 11.7	0.2	>0.9
Education (years)[a]	16.6 ± 2.0	17.1 ± 2.6	16.9 ± 2.6	0.7	>0.7
Smokers/non-smokers[b]	13/13	29/33	5/12	2.0	>0.3
Cigarettes/day[a]	7.4 ± 8.7	7.9 ± 9.5	5.0 ± 9.3	1.6	>0.4

[a] For this measure, the overall distribution of the score differed from normality, and the equivalent nonparametric Kruskal–Wallis procedure was applied.
[b] Chi square comparison.

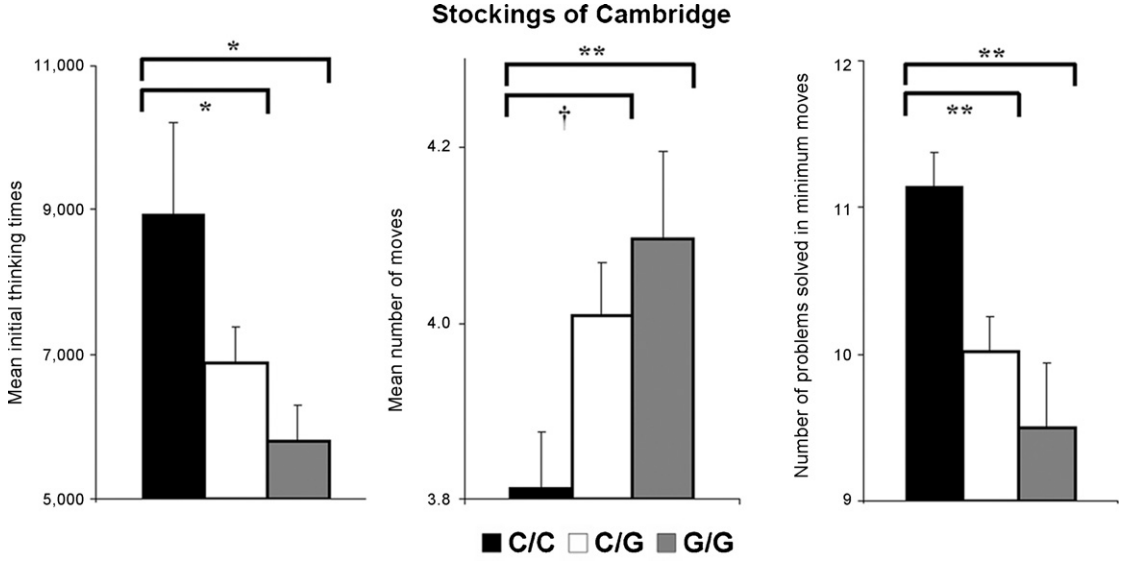

Fig. 1. Mean (trials 2–5) initial thinking times (left), mean (trials 2–5) number of moves required to reach the solution (middle) and problems solved correctly in the minimum moves (right) from the SoC test across the three genotype groups. Columns represent group means and bars represent SEM. Pairwise group comparisons for ITT were performed using the LSD; *$p < 0.05$. Pairwise group comparisons for mean moves and perfect solutions were performed using the Mann–Whitney test with significance set at $p < 0.017$; **$p < 0.01$, †trend: $0.05 > p > 0.017$.

tingency table approach (Raymond & Rousset, 1995; Yacubian et al., 2007) was used to test for differences in the allelic distributions of these additional markers for rs4818 C/C and G/G subjects. This analysis revealed no significant differences at $p < 0.05$ in allele frequencies for each locus (Table 2). This finding makes genetic inhomogeneity of the tested population unlikely.

3.1. SoC test

There were significant group differences in the number of perfect solutions (Kruskal–Wallis $\chi^2 = 10.29$, d.f. = 2, $p = 0.006$), mean number of moves (Kruskal–Wallis $\chi^2 = 7.2$, d.f. = 2, $p = 0.027$) and initial thinking time ($F[2,104] = 3.3$, $p = 0.042$). Pairwise group comparisons revealed that the G homozygotes group had significantly fewer perfect solutions, significantly greater number of mean moves and shorter initial thinking times compared to the other two groups (Fig. 1). The subsequent thinking times (mean ± S.D.) were (untransformed): 575.9 ± 138.7 for the C/C, 895.6 ± 165.7 for the C/G and 613.4 ± 104.4 for the G/G group and they did not differ significantly between groups ($F[2,104] = 1.5$, $p > 0.2$).

Table 2
Test for significant group differences in allele frequencies for each locus when dividing samples by COMT rs4818 C/G

Locus	χ^2 (d.f. = 1)	p
DRD2A1	0.72	0.39
DRD3	0.4	0.53
DAT1	1.31	0.25
PRODH	0.04	0.84
BDNF	1.06	0.30
DRD1	1.65	0.20

3.2. IGT test

There were significant group differences in the total numbers of cards selected from advantageous decks C and D minus the total numbers of cards selected from ("risky") decks A and B (CD − AB difference scores) ($F[2,103] = 9.77$, $p < 0.001$). Pairwise group comparisons revealed that the G homozygotes group selected fewer cards from the "risky" decks A and B compared to the other two groups (Fig. 2, right panel). There were also significant group differences in the total money won ($F[2,103] = 3.99$, $p < 0.02$) and pairwise group comparisons revealed that the G

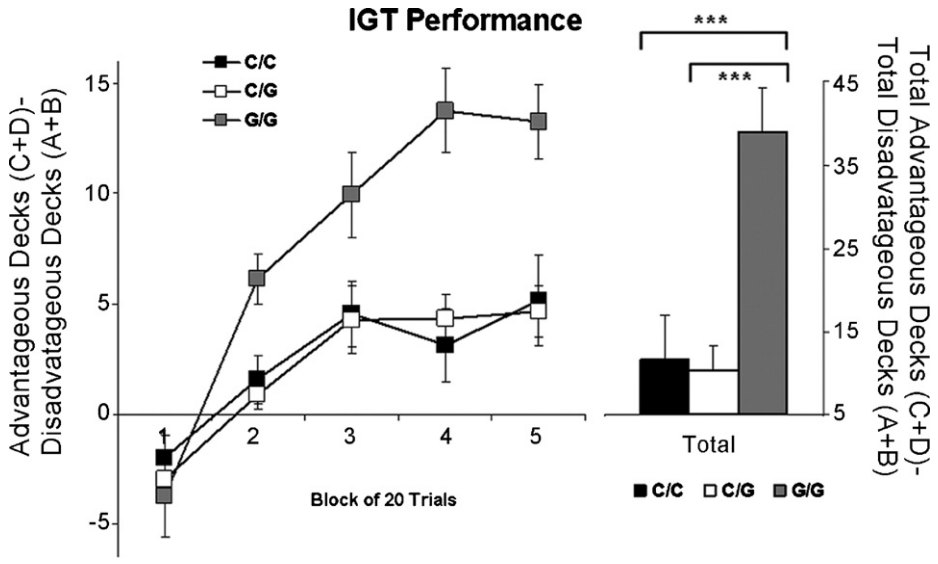

Fig. 2. Total numbers of cards selected from advantageous decks C and D minus the total numbers of cards selected from the "risky" decks A and B (CD − AB) of the IGT test, across the three genotype groups. Squares represent group means and bars represent S.E.M. (Left panel) CD − AB difference per block of 20 trials. (Right panel) CD − AB difference collapsed across the five blocks (100 trials in total). Pairwise group comparisons of the collapsed data were performed using post hoc LSD tests. ***$p < 0.001$.

homozygotes group won significantly more money compared to the other two groups.

3.3. Correlations

ITT from the SoC was negatively correlated with performance in the IGT in the G/G group only ($r = -0.61$, d.f. = 17; $p < 0.01$) (Fig. 3). There were no other significant correlations between performance measures from the two tests in any of the groups. We compared the correlations between ITT and total CD − AB in the three genotype groups with a normal curve test based on Fisher's z-transform. Data are presented in Table 3. There was a significant difference between the G/G and the other two groups in the correlations between performance in the IGT and the SoC.

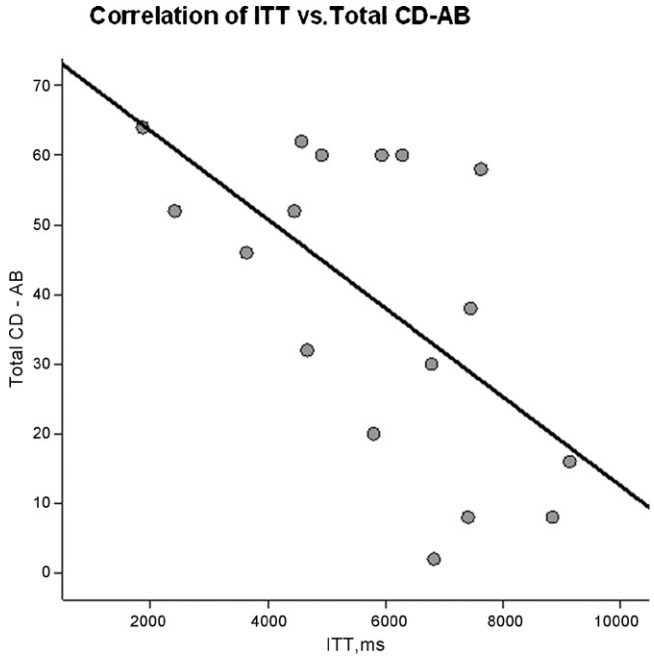

Fig. 3. Correlation of ITT from the SoC vs. total CD − AB from the IGT, for G/G_ individuals. ITT, Initial Thinking Time; SoC, Stockings of Cambridge; Total CD − AB, total advantageous decks (C + D) minus total disadvantageous decks (A + B); IGT, Iowa Gambling Task. Lower ITT indicates poorer performance in the SoC. Lower Total CD − AB indicates poorer performance in the IGT.

Table 3
Pearsons's correlations between ITT measure from the SoC and total CD − AB measure from the IGT, in the three genotype groups

	Pearsons's r	z	p (two-tailed)
GG ($n = 17$)	−0.61	GG vs. CG: 2.86	0.004
CG ($n = 62$)	0.14	GG vs. CC: 1.94	0.052
CC ($n = 28$)	−0.06	CG vs. CC: 0.84	0.4

Normal curve test of the difference is based on Fisher's z-transform. Abbreviations as in Fig. 3.

4. Discussion

The COMT rs4818 polymorphism is part of a haploblock located in the central locus of the COMT gene that affects the expressed enzyme activity over an 18-fold difference, by modifications in the secondary structure of mRNA, which results in alterations in mRNA stability (Nackley et al., 2006). While the effects of the functional Val158Met polymorphism on cognition have been extensively studied, this is the first demonstration in humans on the effects of the synonymous rs4818 polymorphism on cognitive performance.

We found that in healthy males COMT rs4818 (C/G) polymorphism is differentially associated with performance in two prefrontal tasks. More specifically, we found that in the SoC test, G allele load was associated with shorter initial thinking times,

more moves to reach the solution and fewer perfect solutions. No association was found with subsequent thinking time. These findings suggest that participants with the G allele had a difficulty in planning ahead the solutions and a tendency to act before a plan was fully formed (Owen et al., 1990). Consequently, these subjects may need to reassess and even plan new solutions during execution of the task, resulting in increased number of moves and fewer perfect solutions. Fig. 1 shows that C/C individuals had the best performance in the SoC, G/G the worse, while C/G were intermediate. Although the C/C individuals were significantly better than both the other two groups, the differences between the C/G and the G/G groups did not reach statistical significance, probably due to reduced power. Our findings suggest that the G allele load is associated with less efficient planning and problem solving ability. However, in the IGT, subjects homozygous for the G allele had (a) the lowest picks from the risky A and B decks, compared to the C allele loading individuals and (b) as a result of more advantageous choices, these subjects won more money compared to the other two genotype groups. The influence of genotype grouping on the relationship between SoC and IGT performance was significant. For subjects homozygous for the G allele, better performance in the IGT was associated with less time spent planning ahead and worse performance in the SoC as a result. G allele homozygotes differed significantly in this respect from the other two genotypes. This suggests that the inverse relationship between planning and decision-making is mediated by a G allele-related mechanism, probably the low PFC DA levels associated with G allele homozygocity. Importantly, our findings were obtained in a homogeneous cohort of healthy male subjects and cannot be attributed to differences in demographic characteristics or genetic inhomogeneity, since the genotype groups did not differ in that respect (Tables 1 and 2).

The frequency of the G allele is over 40% in population of central European descend. Our findings suggest that the G allele homozygotes (low PFC DA levels) compensate for their relatively inefficient abstract problem solving abilities, by better integration of emotional stimuli for decision-making. This resonates with the notion that Val homozygotes, who presumably have low PFC DA levels, present with emotional resilience against anxiety and dysphoric mood (Enoch, Xu, Ferro, Harris, & Goldman, 2003). It has been recently shown that Met homozygotes, who presumably have higher PFC DA levels, are less efficient in processing faces displaying negative emotion (Drabant et al., 2006; Smolka et al., 2005; Weiss et al., 2007). This led to the assumption of a possible inflexible processing of affective stimuli, resulting in reduced resilience against negative mood states. The poorer IGT performance of the C allele-loading individuals in the present study, supports this assumption and shows that inefficiency in processing of emotionally arousing stimuli extends to processing of emotional feedback, thus affecting emotionally informed decision-making. Such disadvantageous decision-making does not necessarily result in dysfunctional behavior since all our subjects were normal healthy volunteers, with no history or presence of psychiatric illness. However, such implicit disadvantageous decision-making in the context of critical or chronically stressful real-life situations may lead to a vicious cycle of stress, disadvantageous decisions and adverse outcome. This may be at least one route to affective disorders and indeed, susceptibility for negative mood and affective disorders has been established for Met/Met individuals (Mynett-Johnson, Murphy, Claffey, Shields, & McKeon, 1998; Ohara, Nagai, Suzuki, & Ohara, 1998; Papolos, Veit, Faedda, Saito, & Lachman, 1998). It has been shown that the COMT gene alone (Jabbi, Kema et al., 2007) or in combination with polymorphic variations in genes coding for serotonin transporter and monoamine oxidase A influence the regulation of hypothalamic–pituitary–adrenal axis response to stress (Jabbi, Korf et al., 2007) with the Met-allele conferring a reduced resilience to psychological stress. Thus, disadvantageous decision-making could be exacerbated by reduced tolerance to stress due to gene–gene interactions.

It is interesting that the COMT rs4818 (C/G) polymorphism differentiates between two tests of planning ability, one of which involves planning based on emotional processing of incentive information for decision-making. It is possible that this is because the prefrontal neural systems underlying these two tests may be different. Indeed, functional neuroimaging studies have shown that the SoC depends more on the DLPFC (Baker et al., 1996; Morris, Ahmed, Syed, & Toone, 1993; Newman, Carpenter, Varma, & Just, 2003; Owen et al., 1990; Owen, Doyon, Petrides, & Evans, 1996; Rowe, Owen, Johnsrude, & Passingham, 2001) while the IGT depends more on the ventrolateral PFC (VLPFC) and orbitofrontal cortex (OFC) (Bechara et al., 1998; Collette et al., 2001; Ernst et al., 2002; Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). Interestingly, the VLPFC was also implicated in studies on affective processing of aversive stimuli interacting with COMT genotype (Drabant et al., 2006; Smolka et al., 2005). In the light of the present findings, it would be interesting for future fMRI studies to test subjects characterized for their COMT rs4818 (C/G) status for their performance in DLPFC- and VLPFC-based tasks.

To our knowledge, this is the first study to show that a synonymous polymorphism within the COMT gene, that does not alter the structure of the COMT protein but impacts on its expressed activity instead, imparts strong and differential effects on PFC functions. In summary, high PFC DA resulting from low COMT expressed activity in C allele-loading individuals is advantageous for non-emotional problem solving but leads to disadvantageous choices when decision-making depends on processing of emotional feedback. Future studies with patient populations are required to determine the role of such C allele-driven decision-making to risk for affective disorders. Since synonymous SNPs within haplotypes can have functional consequences drastically different from those of each isolated mutation, it is important to study haplotypes over SNPs for analysis of genetic variations.

Conflict of interest

None.

Acknowledgments

This project was supported by University of Crete Research Funds Account (E.L.K.E. 1348). P. Roussos holds a "Manasaki" scholarship and S.G. Giakoumaki was supported by a "Propondis Foundation" post-doctorate fellowship.

References

Baker, S. C., Rogers, R. D., Owen, A. M., Frith, C. D., Dolan, R. J., Robbins, T. W., et al. (1996). Neural systems engaged by planning: A PET study of the Tower of London task. *Neuropsychologia*, *34*, 515–526.

Barnett, J. H., Jones, P. B., Robbins, T. W., & Muller, U. (2007). Effects of the catechol-*O*-methyltransferase Val158Met polymorphism on executive function: A meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular Psychiatry*, *12*, 502–509.

Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience*, *18*, 428–437.

Bilder, R. M., Volavka, J., Lachman, H. M., & Grace, A. A. (2004). The catechol-*O*-methyltransferase polymorphism: Relations to the tonic–phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*, *29*, 1943–1961.

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., et al. (2004). Functional analysis of genetic variation in catechol-*O*-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics*, *75*, 807–821.

Collette, F., Van der Linden, M., Delfiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2001). The functional anatomy of inhibition processes investigated with the Hayling task. *Neuroimage*, *14*, 258–267.

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2005). Catechol-*O*-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. *Journal of Cognitive Neuroscience*, *17*, 1018–1025.

Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Maixner, W., et al. (2005). Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetics*, *14*, 135–143.

Drabant, E. M., Hariri, A. R., Meyer-Lindenberg, A., Munoz, K. E., Mattay, V. S., Weinberger, D. R., et al. (2006). Catechol-*O*-methyltransferase val158met genotype and neural mechanisms related to affective arousal and regulation. *Archives of General Psychiatry*, *63*, 1396–1406.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Weinberger, D. R., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of United States of America*, *98*, 6917–6922.

Enoch, M. A., Xu, K., Ferro, E., Harris, C. R., & Goldman, D. (2003). Genetic origins of anxiety in women: A role for a functional catechol-*O*-methyltransferase polymorphism. *Psychiatric Genetics*, *13*, 33–41.

Ernst, M., Bolla, K., Mouratidis, M., Contoreggi, C., Matochik, J. A., London, E. D., et al. (2002). Decision-making in a Risk-taking Task: A PET study. *Neuropsychopharmacology*, *26*, 682–691.

Fukui, H., Murai, T., Fukuyama, H., Hayashi, T., & Hanakawa, T. (2005). Functional activity related to risk anticipation during performance of the Iowa gambling task. *NeuroImage*, *24*, 253–259.

Goldberg, T. E., Egan, M. F., Gscheidle, T., Coppola, R., Weickert, T., Weinberger, D. R., et al. (2003). Executive subprocesses in working memory: Relationship to catechol-*O*-methyltransferase Val158Met genotype and schizophrenia. *Archives of General Psychiatry*, *60*, 889–896.

Horn, N. R., Dolan, M., Elliott, R., Deakin, J. F., & Woodruff, P. W. (2003). Response inhibition and impulsivity: An fMRI study. *Neuropsychologia*, *41*, 1959–1966.

Jabbi, M., Kema, I. P., van der Pompe, G., te Meerman, G. J., Ormel, J., & den Boer, J. A. (2007). Catechol-*O*-methyltransferase polymorphism and susceptibility to major depressive disorder modulates psychological stress response. *Psychiatric Genetics*, *17*, 183–193.

Jabbi, M., Korf, J., Kema, I. P., Hartman, C., van der Pompe, G., Minderaa, R. B., Ormel, J., & den Boer, J. A. (2007). Convergent genetic modulation of the endocrine stress response involves polymorphic variations of 5-HTT, COMT and MAOA. *Molecular Psychiatry*, *12*, 483–490.

Joober, R., Gauthier, J., Lal, S., Bloom, D., Lalonde, P., Rouleau, G., et al. (2002). Catechol-*O*-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Archives of General Psychiatry*, *59*, 662–663.

Lewis, D. A., Melchitzky, D. S., Sesack, S. R., Whitehead, R. E., Auh, S., & Sampson, A. (2001). Dopamine transporter immunoreactivity in monkey cerebral cortex: Regional, laminar, and ultrastructural localization. *Journal of Comparative Neurology*, *432*, 119–136.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Taskinen, J., et al. (1995). Kinetics of human soluble and membrane-bound catechol *O*-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry*, *34*, 4202–4210.

Malhotra, A. K., Kestler, L. J., Mazzanti, C., Bates, J. A., Goldberg, T., & Goldman, D. (2002). A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *American Journal of Psychiatry*, *159*, 652–654.

Mannisto, P. T., & Kaakkola, S. (1999). Catechol-*O*-methyltransferase (COMT): Biochemistry, molecular biology, pharmacology and clinical efficacy of the new selective COMT inhibitors. *Pharmacolical Reviews*, *51*, 593–628.

Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., & Egan, M. F. (2003). Catechol *O*-methyltranspherase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences of United States of America*, *100*, 6186–6191.

Mazei, M. S., Pluto, C. P., Kirkbride, B., & Pehek, E. A. (2002). Effects of catecholamine uptake blockers in the caudate-putamen and subregions of the medial prefrontal cortex of the rat. *Brain Research*, *936*, 58–67.

Moron, J. A., Brockington, A., Wise, R. A., Rocha, B. A., & Hope, B. T. (2002). Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: Evidence from knock-out mouse lines. *Journal of Neuroscience*, *22*, 389–395.

Morris, R. G., Ahmed, S., Syed, G. M., & Toone, B. K. (1993). Neural correlates of planning ability: Frontal lobe activation during the Tower of London test. *Neuropsychologia*, *31*, 1367–1378.

Mynett-Johnson, L. A., Murphy, V. E., Claffey, E., Shields, D. C., & McKeon, P. (1998). Preliminary evidence of an association between bipolar disorder in females and the catechol-*O*-methyltransferase gene. *Psychiatry Genetics*, *8*, 221–225.

Nackley, A. G., Shabalina, S. A., Tchivileva, I. E., Satterfield, K., Korchynskyi, O., Diatchenko, L., et al. (2006). Human catechol-*O*-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science*, *314*, 1930–1933.

Newman, S. D., Carpenter, P. A., Varma, S., & Just, M. A. (2003). Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. *Neuropsychologia*, *41*, 1668–1682.

Ohara, K., Nagai, M., Suzuki, Y., & Ohara, K. (1998). Low activity allele of catechol-*O*-methyltransferase gene and Japanese unipolar depression. *NeuroReport*, *9*, 1305–1308.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory deficits following frontal lobe lesions in man. *Neuropsychologia*, *28*, 1021–1034.

Owen, A. M., Doyon, J., Petrides, M., & Evans, A. C. (1996). Planning and spatial working memory: A positron emission tomography study in humans. *European Journal of Neuroscience*, *8*, 353–364.

Owen, A. M., Sahakian, B. J., Semple, J. M., Polkey, C. E., & Robbins, T. W. (1995). Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalohippocampectomy in man. *Neuropsychologia*, *13*, 1–24.

Papolos, D. F., Veit, S., Faedda, G. L., Saito, T., & Lachman, H. M. (1998). Ultra–ultra rapid cycling bipolar disorder is associated with the low activity catecholamine-*O*-methyltransferase allele. *Molecular Psychiatry*, *3*, 346–349.

Raymond, M., & Rousset, F. (1995). An exact test for population differentiation. *Evolution*, *49*, 1280–1283.

Rowe, J. B., Owen, A. M., Johnsrude, I. S., & Passingham, R. E. (2001). Imaging the mental components of a planning task. *Neuropsychologia*, *39*, 315–327.

Salama, S. A., Ho, S. L., Wang, H. Q., Tenhunen, J., Tilgmann, C., & Al-Hendy, A. (2006). Hormonal regulation of catechol-*O*-methyl transferase activity in women with uterine leiomyomas. *Fertility and Sterility*, *86*, 259–262.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., & Weiller, E. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clinical Psychiatry*, *59*, 22–33.

Smolka, M. N., Schumann, G., Wrase, J., Grusser, S. M., Flor, H., Heinz, A., et al. (2005). Catechol-*O*-methyltransferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *Journal of Neuroscience*, *25*, 836–842.

Smyrnis, N., Avramopoulos, D., Evdokimidis, I., Stefanis, C. N., Tsekou, H., & Stefanis, N. C. (2007). Effect of schizotypy on cognitive performance and its tuning by COMT val158 met genotype variations in a large population of young men. *Biological Psychiatry*, *61*, 845–853.

Stefanis, N. C., Van Os, J., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Stefanis, C. N., et al. (2004). Variation in catechol-*O*-methyltransferase val158 met genotype associated with schizotypy but not cognition: A population study in 543 young men. *Biological Psychiatry*, *56*, 510–515.

Tsai, S. J., Yu, Y. W., Chen, T. J., Chen, J. Y., Liou, Y. J., Hong, C. J., et al. (2003). Association study of a functional catechol-*O*-methyltransferase gene polymorphism and cognitive function in healthy females. *Neuroscience Letters*, *338*, 123–126.

Tunbridge, E. M., Harrison, P. J., & Weinberger, D. R. (2006). Catechol-*O*-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biological Psychiatry*, *60*, 141–151.

Weiss, E. M., Stadelmann, E., Kohler, C. G., Brensinger, C. M., Nolan, K. A., Marksteiner, J., et al. (2007). Differential effect of catechol-*O*-methyltransferase Val158Met genotype on emotional recognition abilities in healthy men and women. *Journal of the International Neuropsychological Society*, *18*, 1–7.

Yacubian, J., Sommer, T., Schroeder, K., Glascher, J., Kalisch, R., Buchel, C., et al. (2007). Gene–gene interaction associated with neural reward sensitivity. *Proceedings of the National Academy of Sciences of United States of America*, *104*, 8125–8130.