Association between the COMT gene and rumination in a Hungarian sample

Dorottya Pap[1], Gabriella Juhasz[1,2] and Gyorgy Bagdy[1]

[1] *Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary*
[2] *Neuroscience and Psychiatry Unit, School of Community Based Medicine, Faculty of Medical and Human Sciences, The University of Manchester, UK and Manchester Academic Health Sciences Centre, Manchester, UK*

Introduction: Rumination is a multidimensional trait which is a proven risk factor in the vulnerability to depression. The aim to identify the main risk genes for depression in addition to the gene-environment interactions pointed to the importance of intermediate phenotypes, like rumination, to improve our understanding of the biological mechanisms of depression. Catechol-O-Methyltransferase (COMT) gene is extensively investigated in depression with contradictory results but its association with rumination, as an intermediate phenotype in depression, has not been investigated yet. **Methods:** In our study, four tagging SNPs in the COMT gene (rs933271, rs740603, rs4680, rs4646316) were genotyped in a nonclinical Hungarian sample (n=939). We investigated the association between the COMT gene and rumination scores measured by the Ruminative Response Scale using haplotype trend regression. **Results:** We found a significant association between COMT haplotypes and rumination scores (p=0.013) but no significant association was apparent between the functional Val[158]Met polymorphism (rs4680) and rumination in any genetic model. **Discussion:** Variations in the COMT gene exert complex effects on susceptibility to depression involving intermediate phenotypes, such as rumination and also impulsivity, as we previously demonstrated. Both rumination and impulsivity represent maladaptive cognitive styles that can lead to depressive state by influencing the response to negative life events and life stressors. In conclusion, our findings provide evidence that in addition to other genes, COMT also has a significant role in the development of depression, and demonstrate that analysing the complex phenotype associations of genes by haplotype tagging is a powerful method.
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Rumination is a cognitive style characterised by "repetitively and passively focusing on symptoms of distress and on the possible causes and consequences of these symptoms" (Nolen-Hoeksema et al. 2008). According to Nolen-Hoeksema's theory, people have different response styles during negative emotional states. Ruminators exhibit "attentional inflexibility" and these deficits of executive functions can lead to depression (Nolen-Hoeksema 2000). The three major components of executive processes are inhibition, set switching, and updating of working memory (Miyake et al. 2000) and a study found that rumination in healthy people was associated with set switching difficulties (Whitmer and Gotlib 2012). The role of prefrontal cortex is significant for the appropriate executive function (Teffer and Semendeferi 2012). Poor executive function is associated with dysfunction in the frontosubcortical network, including the prefrontal cortex (PFC) (Biringer et al. 2005; Clark et al. 2009). PFC is the area of the brain which is activated by changes in the affective relevance of stimuli, and the increased activity in this area among ruminators suggests that they chronically recruit brain regions associated with updating the affective salience of stimuli, even when not instructed to regulate their affect (Ray et al. 2005). In a previous study we found evidence for an indirect relationship between the COMT gene and depression, mediated by impulsivity and executive function (Pap et al. 2012), which further suggest the importance of altered reactivity in prefrontal areas, and thus rumination, in the development of depression.

COMT is very important in the PFC, because this enzyme eliminates dopamine from the synaptic cleft due to the low density of dopamine transporter in this region (Chen et al. 2004). Furthermore, COMT is a key metabolic enzyme also for noradrenaline and adrenaline, neurotransmitters which have a role in related functions. The most studied and common functional polymorphism in the COMT gene is the valine to methionine substitution in the position158. This substitution affects the activity of COMT enzyme and thus, the intrasynaptic dopamine level. Chen et al. found that the enzyme activity of COMT-Val is 40% higher than COMT-Met allele in human dlPFC, leading to more efficient elimination of dopamine from the synaptic cleft, hence the Val/Val genotype causes lower levels of synaptic dopamine in the PFC (Chen et al. 2004; Meyer-Lindenberg et al. 2005), and this dopamine decrease results in more active striatal dopamine neurotransmission (Bilder et al. 2004; Meyer-Lindenberg et al. 2005; Tunbridge et al. 2006).

The relationship between the Val/Met substitution and its effect on cognition and executive function is more complex, thus we can find controversial results in the literature. These controversies can be explained by the complexity of the COMT gene, therefore it is necessary to investigate not just the known functional variants, but more SNPs throughout the gene. In case of the COMT gene, a growing body of evidence supports that individual alleles have non-linear effects on enzyme activity that are dependent on several other genetic variants and environmental components (Akil et al. 2003; Bray et al. 2003; Chen et al. 2004; Craddock et al. 2006; Meyer-Lindenberg et al. 2006; Meyer-Lindenberg and Weinberger 2006; Ursini et al. 2011). For example, the promoter 2 region controls the transcription of the membrane-bound, brain-dominant form of COMT, and variations in this region together with other synonymous and non-synonymous polymorphisms throughout the gene affect the enzyme activity (Chen et al. 2004; Nackley et al. 2006).

Given the proven role of prefrontal dopamine levels in the prefrontally mediated cognitive functions (Goldman-Rakic et al. 2004), it is likely that COMT gene plays a role in cognitive flexibility, stability (Nolan et al. 2004), working memory, and executive functions (Sawaguchi 2000; Tunbridge et al. 2006). Regarding the neurocognitive background of rumination and its relationship to the function of the PFC, we can assume that rumination is associated with the COMT gene, making it a possible candidate to explore the genetic risk factors for rumination.

In this study, our aim was to investigate the association between rumination scores and the COMT gene in a non-clinical population. We hypothesised that the less active COMT haplotype would increase rumination.

METHODS

Subjects

939 unrelated volunteers, 669 women and 270 men were included in the study. All subjects were Hungarian and of Caucasian origin.

From the present study, we excluded those reporting manic or hypomanic episodes, psychotic symptoms, obsessive-compulsive disorder and those of non-Caucasian origin, but we did not exclude those with a self-reported history of depression or any other anxiety disorder, or substance misuse (based on Background questionnaire).

The studies were approved by the local Ethics Committees and were carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent before entering the study.

Questionnaires and tasks

The Background questionnaire included questions covering age, ethnicity, family and environmental circumstances, personal and family psychiatric history. This questionnaire is developed by our lab and accepted in many scientific papers (Juhasz et al. 2011; Pap et al. 2012).

Rumination was measured by the Ruminative Response Scale (RRS) of the Response Style Questionnaire (Nolen-Hoeksema, 1991). We used the Brooding and Reflection items of the original RRS and the analyses were performed on the weighted mean scores (sum of scores divided with the number of items completed).

Genotyping

Buccal mucosa cells were collected using a cytology brush (Cytobrush plus C0012, Durbin PLC) and 15-mL plastic tube containing 2.0 ml of collection buffer. Genomic DNA was extracted according to a published protocol (Freeman et al. 2003). The HaploView software package (http://www.broad.mit.edu/personal/jcbarret/haploview/) was employed to identify haplotype tag SNPs (htSNP), according to Gabriel et al's method (Barrett 2002; Gabriel et al. 2002), based

on the CEPH population data of the International HapMap Project (http://www.hapmap.org, Phase I. June 2005). The chosen SNPs were genotyped using the Sequenom ® MassARRAY technology (Sequenom ®, San Diego). The Iplex™ assay was followed according to manufacturer's instructions (http://www.sequenom.com) using 25ng of DNA. Genotyping was blinded with regard to phenotype. All laboratory work was performed under the ISO 9001:2000 quality management requirements.

Statistical Analysis

HelixTreeTM 6.4.3 (Golden Helix, USA) software was used to analyse genetic data (Hardy-Weinberg Equilibrium, linkage disequilibrium, and haplotypic association). For haplotypic association analysis we used haplotype trend regression. Only haplotypes with a frequency greater than 5% were used in the analysis. In all cases, data were adjusted for age and sex. We used a linear regression model in HelixTree to identify variance in the dependent variable explained by age and sex (the "reduced model"). We then used a variance ratio F-test to determine whether adding haplotype frequencies to the model (the "full model") explained significantly more variance than the reduced model. To remove the influence of multiple testing we used a permutation test, randomly grouping the sample 1000 times. PLINK v1.06 (http://pngu.mgh.harvard.edu/purcell/plink/) was used for testing association of different genetic models (additive, dominant, recessive). Age and sex were covariates in all analyses. Other statistical analyses were performed with SPSS 15.0 for Windows. All statistical testing used two-tailed $p<0.05$ threshold.

RESULTS

Detailed description of the study populations are shown in Table 1.

The selected four haplotype tagging SNPs (rs933271, rs740603, rs4680 and rs4646316, Figure 1) correspond to the haplotype structure of the European population comprising the promoter 1 and 2 regions, the coding region and the 3' end (Mukherjee et al. 2008) together with the most investigated functional variant of the COMT gene, the Val^{158}Met polymorphism (rs4680). All SNPs are in modest LD and in Hardy-Weinberg equilibrium.

Two haplotype tagging SNPs showed significant association with rumination in the recessive model (rs740603, p=0.032; rs4646316, p=0.028) but association between rumination and Val^{158}Met polymorphism was not significant in any model (p_{add}=0.907, p_{dom}=0.667, p_{rec}=0.808). Haplotype trend regression was significant for rumination (p_{perm}=0.020, Table 2). COMT haplotypes explained 1.44% variance in rumination, with T,A,A$^{(M)}$,C and T,G,G$^{(V)}$,C as significant risk haplotypes (p=0.028 and p=0.015 respectively; Table 3), while the T,G,G$^{(V)}$,T showed a trend toward a preventive effect (p=0.088; Table 3).

Figure 2 demonstrates the direction of haplotype effects on rumination.

Table 1 Details of the investigated population

DESCRIPTIVE DATA	
number	939
female	71%
male	29%
age (mean +/- SEM)	31 +/- 10,4
rumination (mean +/- SEM)	1.93 +/- 0.46 [a]
REPORTED LIFETIME PSYCHIATRIC DISORDER	
depression	19%
recurrent depression	13%
suicide attempt	4%
anxiety	18%
drug or alcohol problem	2%

(a) measured by RRS (Rumination Response Scale, Nolan-Hoeksema, 1991).
SEM: standard error of mean

DISCUSSION

The main finding of this study is that haplotypic variants in the COMT gene are also associated with rumination, measured by the Ruminative Response Style Questionnaire, in a large healthy population from Budapest, Hungary. This significance survived correction for multiple testing.

Several genes have been associated with rumination in earlier studies. These included complex interactions, like the CREB1-BDNF-NTRK2 pathway and the CREB1-GIRK gene-gene interaction (Juhasz et al. 2011; Lazary et al. 2011), but to our knowledge this is the first study to investigate the association between rumination and COMT gene. As we mentioned in the introduction, COMT is required in the PFC to elimi-

Table 2 Global haplotypic association with rumination

Full vs. Reduced model				
	F	**df**	**p**	**p(perm)**
rumination	2.888	7. 2	0.013	0.02

Age and sex were covariates. Linear haplotype trend regression analysis as implemented in HelixTreeTM 6.4.3 (Golden Helix, USA) software was used to calculate associations.

Table 3 Specific haplotype effects in the haplotypic association with rumination

Haplotype Regression				
Regressor	**Frequency**	**B**	**t**	**p**
T,A,A$^{(M)}$,C	31.91%	0.136	2.199	0.028
T,G,G$^{(V)}$,C	16.53%	0.229	2.445	0.015
T,G,G$^{(V)}$,T	11.86%	-0.172	-1.708	0.088
C,G,A$^{(M)}$,C	10.32%	-0.035	-0.281	0.779
T,A,G$^{(V)}$,T	5.64%	0.166	0.922	0.356
rare	23.74%			
	p(full vs. reduced model):			0.013
	p(permutated):			0.020

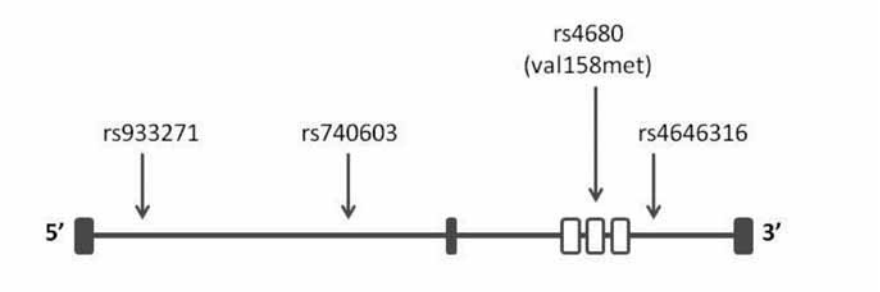
Age and sex were covariates in all calculations and the order of the htSNPs in the haplotypes corresponds to the SNP order in Figure 1.

nate dopamine (DA) from the synaptic cleft, playing an important role in adjusting DA levels (Chen et al. 2004). The level of DA in the PFC determines the top-down controlling effect of the frontal cortex on subcortical regions like the amygdala, striatum, hippocampus, and the state of these structures in a feedback mode alter the activity of the PFC. According to the tonic-phasic DA hypothesis, the DA level in the PFC have a dual action on executive functions in the following way: tonic DA is a constant, low-level, 'background' DA that maintains stability of cognition by preventing uncontrolled, spontaneous switches. It increases the signal-to-noise ratio supporting better cognition. The phasic DA level is a transient DA, it helps updating, resetting, gating the relevant new information (D2 receptors activating GABAergic neurons) via decreased signal-to-noise ratio. However, when the rate shifts towards noise (high phasic DA) this may disturb cognitive processes by providing excessive non-relevant information leading to impulsive cognitive style. In contrast, if tonic DA level is higher in the PFC, switches between thoughts will decrease and cognitive processes show less flexibility, become rigid, which is a feature of the ruminative cognitive style.

Rumination can be characterised by extreme inflexibility and rigidity in cognition and executive functions. Thus less active COMT gene variants are hypothesised to increase PFC DA level and enhance rumination, while most active variants should decrease PFC DA level and improve executive function allowing switches (Nolan et al. 2010; Rosa et al. 2010).

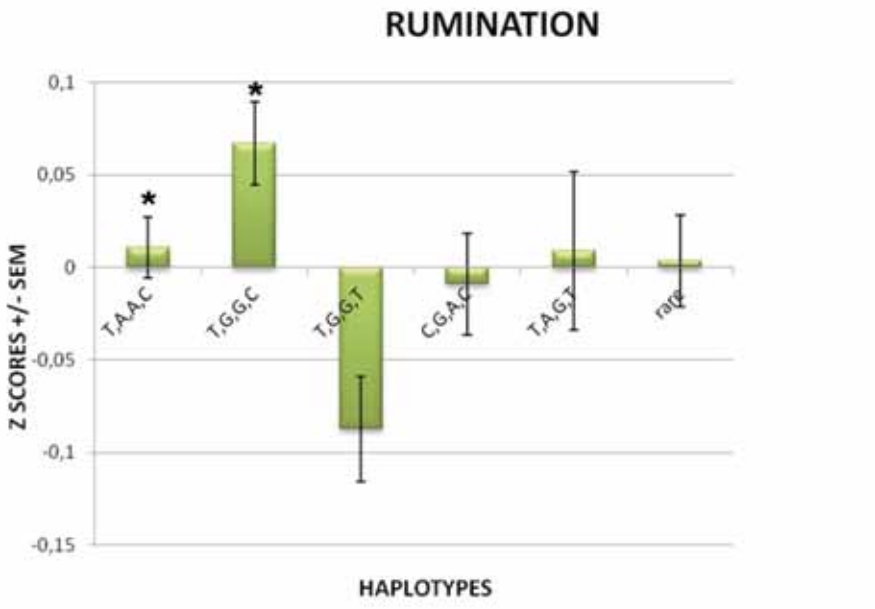
Our significant association between haplotypes and rumination scores is consistent with the above

Figure 1 Schematic figure of the COMT gene and the genotyped SNPs based on USC Genome Browser (University of California at Santa Cruz Browser, http://genome.ucsc.edu/)



Grey line: introns; white boxes: exons; grey boxes: promoters and 3′ end.

Figure 2 Haplotypic effect of COMT gene on rumination



For demonstration purposes, haplotypes have been assigned to participants where the expectation maximisation (EM) was greater than 70% (n=640). Next z-scores +/- standard error of mean (SEM) were calculated for each haplotype group. Age and sex were covariate in all calculations. The order of the htSNPs in the haplotypes corresponds to the SNP order in Figure 1.

discussed tonic-phasic hypothesis. However, we found that both T,A,$A^{(M)}$,C and T,G,$G^{(V)}$,C haplotype carriers scored higher on rumination scale, despite having different alleles at the $Val^{158}Met$ polymorphism. These results are a good evidence of the importance of investigating haplotypes and not SNPs alone, because the COMT gene is too complex (Mukherjee et al. 2008) and haplotypes of the COMT gene has stronger effect on the effectiveness of the enzyme than the functional polymorphism alone, possibly because the haplotypes influence enzyme synthesis via other mechanisms, such as mRNA stability (Nackley et al. 2006).

In our previous study we demonstrated an association between the COMT gene, impulsivity and depression (Pap et al. 2012). In this study we found that COMT haplotypes showed association with impulsivity and the pattern was opposite as we found in this study. We can compare impulsivity and rumination regarding the role of cognitive flexibility and rigidity in the two apparently distant phenotypes. Impulsivity can be characterized by too high cognitive flexibility, therefore subjects behave without considering the consequences, while in rumination the cognition is too rigid and switching becomes difficult. All of the two phenotypes have heritable components, but in case of rumination only a few studies investigated its relationship with the dopaminergic system (Vakalopoulos 2007; Whitmer and Gotlib 2012), while impulsivity is more investigated from this point of view (Pap et al. 2012). The COMT gene's effect on cognitive effectiveness, thereby association with rumination and impulsivity can be explained by the inverted-U shape theory (Goldman-Rakic et al. 2000). This model suggests that both sub- and super-optimal PFC DA levels can impair the appropriate PFC functions, such as the balance between cognitive flexibility and rigidity, making difficult to identify the effect of individual SNPs causing conflicting results in the literature (Goldman-Rakic et al. 2000; Meyer-Lindenberg et al. 2006; Tunbridge et al. 2006). The balance between cognitive flexibility and rigidity can aid the appropriate decision when PFC DA level is near the optimum, but as soon as the optimal DA level shifts to sub- or superoptimal levels, the effectiveness of cognition deteriorates because of the too rigid, or too flexible cognitive style. The impaired cognitive function, represented by excessive rumination or increased impulsivity, could be especially disadvantageous during negative and stressful life events leading to depression or other psychiatric disorders.

There are some limitations of our study such as the low number of the used polymorphisms and variants to cover the COMT gene. Although it would be desirable to use as much polymorphisms as we can, recent studies demonstrated that with these variants we can capture safely the most prevalent and possibly functional haplotype blocks in the Caucasian population (Mukherjee et al. 2008).

In summary, our findings further emphasise that the COMT gene has pleiotropic effect on different intermediate phenotypes that can convey increased risk to depression. Both impulsivity (in our previous study) and rumination (in this paper) showed association with COMT haplotypes and, as it was expected, the effect on these phenotypes indicated opposite direction. These observations might explain why studies using end diagnosis can provide controversial results. Further studies are needed to investigate the genetic background of risk cognitive factors in the development of depression.

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Corresponding author: Dorottya Pap, Department of Pharmacodynamics, Semmelweis University, 1089 Budapest, Nagyvárad tér 4., Hungary. Tel./fax: +36 1 210 4411.
e-mail: papdorka1@gmail.com

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A rumináció és a COMT gén közötti összefüggés vizsgálata magyar mintán

Célkitűzés: A rumináció összetett személyiségvonás, mely bizonyítottan rizikófaktorként működik a depresszióra való hajlam kialakításában. A depresszió génjeinek megtalálására irányuló kutatások nyilvánvalóvá tették, hogy a gén-környezet kölcsönhatásokkal együtt az átmeneti fenotípusok (pl. rumináció) segítségével jobban megközelíthetőek a betegség kialakulásában részt vevő biológiai folyamatok. A katekol-o-metiltranszferáz (COMT) gén depresszióval való összefüggését vizsgálva sok egymásnak ellentmondó eredmény született, míg a ruminációval való összefüggését eddig nem vizsgálták. **Módszer:** Vizsgálatunkban 939 magyar önkéntes résztvevő személy genotípusát határoztuk meg négy, a katekol-o-metiltranszferáz génben elhelyezkedő tag SNP-re (rs933271, rs740603, rs4680, rs4646316), míg ruminációra való hajlamukat a Ruminációs Válaszkészség Skálával (Ruminative Response Scale) mértük. A COMT haplotípusok és a rumináció pontszámok közötti összefüggést haplotípus trend regresszió segítségével vizsgáltuk. **Eredmények:** Szignifikáns összefüggést mutattunk ki a COMT haplotípusok és a ruminációs pontszámok között (p=0.013), míg a funkcionális Val^{158}Met polimorfizmus (rs4680) nem mutatott szignifikáns asszociációt egyik genetikai modellben sem. **Következtetés:** A COMT génen belüli variációk összetett módon fejtik ki hatásukat a depresszióra, melyben a rumináció és korábbi vizsgálataink szerint az impulzivitás kulcsszerepet játszik. Mind a rumináció, mind pedig az impulzivitás maladaptív kognitív stílusok, melyek a negatív és stresszt okozó élethelyzetekre adott válaszainkat befolyásolva depresszióhoz vezethetnek. Eredményeink tehát a korábban már azonosított gének mellett a COMT szerepére mutatnak és igazolják, hogy a jól megválasztott köztes fenotípusok igen jól használhatóak a depresszió genetikai rizikófaktorainak kutatásában. Ezen kívül vizsgálatunk alátámasztotta, hogy a teljes gént lefedő haplotípusok releváns SNP kombinációinak elemzése hatékony a komplex betegségek genetikai kutatásában, mivel a haplotípusok hosszabb, feltehetőleg funkcionális variánsokat is hordozó, genetikai régiókat reprezentálnak.

Kulcsszavak: COMT, rumináció, kérődzés, genetika, depresszió