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Original scientific paper

Association Study of a Functional Catechol-O-Methyltransferase Polymorphism and Cognitive Function in Patients with Dementia

Gordana Nedić[1], Fran Borovečki[2,3], Nataša Klepac[2], Zdenko Mubrin[2], Sanja Hajnšek[2], Matea Nikolac[1], Dorotea Muck-Seler[1] and Nela Pivac[1]

[1] »Rudjer Bošković« Institute, Division of Molecular Medicine, Zagreb, Croatia
[2] University of Zagreb, Zagreb University Hospital Center, Department of Neurology, Zagreb, Croatia
[3] University of Zagreb, School of Medicine, Center for Functional Genomics, Zagreb, Croatia

A B S T R A C T

A functional catechol-o-methyltransferase (COMT Val158/108Met) polymorphism, a valine (Val) to methionine (Met) substitution, has been associated with cognitive processing in the normal brain, older age, mild cognitive impairment and in various dementias. COMT is involved in the breakdown of dopamine and other catecholamines, especially in the frontal cortex; hence the carriers of Met allele, with the lower enzymatic activity, are expected to perform better on particular neuro-cognitive tests. The study included 46 patients with dementia and 65 healthy older subjects. The neurological status was assessed, using the Mini Mental Status Examination (MMSE), and the batery of different neurological tests. In DNA samples COMT polymorphism was genotyped. Patients with dementia exhibited significant genotype-induced differences in scores for MMSE, Visual Association Test (VAT) duration of numbers test, VAT time of response to numbers test, VAT average response to numbers test and WPLCR/PPLR unanswered. Carriers of Met/Met genotype had significantly lower scores of MMSE, significantly longer time to respond to VAT duration of numbers test, VAT time of response to numbers test and VAT average response to numbers test, and significantly greater number of unanswered questions to WPLCR/PPLR when compared to Met/Val or Val/Val genotypes. Our preliminary data showed significantly impaired performance in several neuro-cognitive tests in carriers of Met/Met genotype in patients with dementia compared to either Met/Val or Val/Val genotype carriers. Although Met/Met genotype with more dopamine available in the frontal cortex should be associated with better neuro-cognitive test results than Met/Val or Val/Val genotype, our data on patients with dementia did not confirm this hypothesis. Further study on larger sample of patients is needed to clarify the role of COMT polymorphism in cognitive functions.

Key words: *COMT polymorphism, cognitive function, dementia*

Introduction

Catechol-o-methyl-transferase (COMT) is an enzyme that degrades catecholamines dopamine, noradrenaline and adrenaline. Besides catecholamines, COMT inactivates catecholestrogens[1]. COMT is widely distributed in the human brain[2], but its neurobiological effects are especially important in the prefrontal cortex where COMT degrades dopamine, and thus regulates dopamine availability since dopamine transporters are expressed in low abundance in the frontal cortex[3,4]. Prefrontal cortex has a major role in various aspects of higher-order information processing, and dopamine signaling is implicated in cognitive functioning and in fine tuning of these neuronal and circuit responses during executive processes[5]. COMT has been proposed to represent a risk factor for various psychiatric disorders[6,7], such as attention deficit hyperactivity disorder (ADHD), schizophrenia, substance use disorders, bipolar disorder and neurodegenerative disorders such as Alzheimer's disease[8] and other dementias, and for a possible susceptibility to psychosis in Alzheimer's disease[9].

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COMT gene is located on chromosome 22q11. Activity of COMT is modulated by a common functional SNP in exon 4: Val(158/108)Met, with G to A transition at codon 158, that results in an amino-acid substitution of valine (Val) with methionine (Met). Homozygosity for Val allele results in a 3 to 4 fold higher COMT activity compared to Met homozygotes, while heterozygotes have intermediate COMT activity[10]. The Met allele is referred as the low-activity (L allele), whereas Val allele is more stable, referred as a high-activity variant (H allele), associated with greater enzymatic activity and hence greater dopamine degradation than the Met allele. The functional Val(158/108)Met polymorphism has been studied in relation to cognitive disorders in healthy subjects[11–15], different psychiatric diseases[6,7], and in AD[8,16], with both positive and negative results[5,17]. The COMT variants have been proposed to be related to cognitive functions such as executive functioning, working memory, attentional control, and episodic memory, cognitive and emotional information[5], and carriers of Met allele, with the lower enzymatic activity, are expected to perform better on particular neurocognitive tests[5].

The goal of this study was to examine the association of cognitive processes and their deficits (working memory, executive function, memory or basic attentional processes), with COMT genetic variants.

Methods

Patients

The study included 22 male and 24 female patients with dementia, as well as 34 male and 31 female healthy older subjects. The participants were unrelated, medication-free Caucasian subjects of Croatian origin, who were recruited from 2007 to 2009 at Department for Cognitive Neurology, Zagreb University Hospital Centre, Zagreb, Croatia. Male and female healthy subjects were 60.03±2.10 and 51.81±6.03 while male and female patients with dementia were 66.67±8.24 and 72.21±7.64 years old, respectively. Dementia patients comprised of patients with Alzheimer's disease (N=31), Fronto-temporal dementia (N=12), Lewy Body Dementia (N=2) and Vascular dementia (N=1). Diagnosis of dementia was assigned according to results of cognitive testing, analysis of cerebrospinal fluid, as well as imaging using magnetic resonance and single photon emission computed tomography.

All individuals gave their detailed medical history, and underwent complete physical, neurological and psychological examinations. Written informed consent was obtained from all participants, after explaining the aims and procedures of the study, under guidelines approved by the Ethics committee of the Zagreb University Hospital Center, Zagreb, Croatia. All human studies have been carried out with the full cooperation of participants, adequate understanding, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Cognitive testing

The determination of the neurological status of these patients utilized the Mini Mental Status Examination (MMSE), Neuro-Psychiatric Inventory (NPI), Alzheimer's Disease Assessment Scale-Cognition (ADAS-COG), Clock Drawing Test (CDT), Word pairs learning and recall/ Picture pairs learning (WPLCR/PPLR) and recall test and Visual association test (VAT), performed by experienced neurologists.

Mini mental state examination (MMSE)

Brief measure of cognitive status commonly used in dementia centers. It consists of different questions that are rated with 0 or 1 point. Scores ranges from maximum of 30=no impairment to 0=most severe impairment.

Neuropsychiatric inventory (NPI)

Questionnaire constructed to assess behavioral disturbances occurring in dementia patients. It consists of several different parts that are focused on delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibiton, irritability, apathy and aberrant motor activity. Both the frequency and the severity of each behavior are determined. Information for the NPI is obtained from a caregiver familiar with the patient behavior.

Alzheimer's disease assessment scale-Cog (ADAS-Cog)

Widely used and well-known scale constructed to assess the level of cognitive impairment in Alzheimer's disease. It consists of 11 different items. The rating scale of 0–5 reflects the degree of severity of dysfunction. A rating of 0 signifies no impairment on a task while a rating of 5 is reserved for the most severe degree of impairment. Scores ranges from 0 to 70, with 0=no impairment and 70=most severe impairment.

Visual association test (VAT)

VAT is computerized test of sustained visual attention conceptually similar to the Conrinuous Performance Test in that it requires participants to continously search a visual array for a target. On each trial, participants were shown an array of 20 identical letters presented pseudorandomly on the screen and were instructed to continously scan the array until one of the letters changed. Participants were instructed to respond to the change by pressing the space bar as quickly as possible. If a transformation occured and the participant did not respond within 60 sec, that trial was considered »timed out« and was added to the end of the session. A total of 24 trials equally distributed over the eight delay intervals (starting at 5 sec and then occuring every 15 sec) were run for each subject. Participant's reaction time between the actual transformation and the participant's response was collected.

TABLE 1
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SUBJECTS WITH DEMENTIA

	Dementia; N=46
Sex female/male	24/22
Age	69.7±8.2
Duration of disease	2.5±1.8
Age at onset	67.2±8.3
Education	10. 2±4.4
MMSE	16.5±6.5
MMSE modified	54.5±22.0
CDT	5.0±2.4
ADAS	45.2±14.7
NPI	11.7±11.8
VAT	2835±4244

Word pairs learning and recall/Picture pairs learning and recall

Test measures verbal and visual memory. The test consists of 10 pairs of words, with 5 pairs connected by logical association and 5 pairs of randomly connected words. Patient is asked to memorize words and after it to speak out the word that is missing in the pair. The process is repeated 3 times. The number of corrected, uncorrected and unanswered words is measured as well as the time requested for the answers. In the Picture pairs learning instead of the words pictures are presented for the patients.

COMT polymorphism analysis

DNA was extracted from blood using the DNeasy Blood and Tissue Kit (Qiagen) according to manufacturer's instructions. In DNA samples COMT Val158/108Met polymorphism was genotyped in ABI Prism 7000 Sequencing Detection System apparatus using Taqman-based allele-specific polymerase chain reaction assay, according to the procedure described by the Applied Biosystems (Applied Biosystems, Foster City, CA, USA). The primers and probes were purchased from Applied Biosystems.

Statistical analysis

The results, expressed as means (X) ± standard deviations (SD), were evaluated with Sigma Stat 3.5 (Jandell Scientific Corp. San Raphael, California, USA) using one-way analysis of variance (ANOVA), followed by the Tukey's test. The Hardy-Weinberg analysis was used to test the equilibrium of the population. The differences in the genotype frequencies were evaluated using a χ^2-test. The level of significance was set to $\alpha=0.05$.

Results

There were no significant differences in the genotype ($\chi^2=3.923$; d.f.=6; p=0.687) frequency between male and female healthy subjects and patients with dementia. Since no significant gender related differences were found, the data for male and female subjects in the further analyses were collapsed. The observed genotype distribution in healthy control subjects ($\chi^2=0.825$; $p>0.05$), or in patients with dementia ($\chi^2=0.999$; $p>0.05$) did not differ significantly from the expected Hardy–Weinberg equilibrium.

No significant differences in the genotype ($\chi^2=0.185$; d.f.=2; p=0.912) frequency between healthy subjects and patients with dementia were detected. In subsequent analyses we evaluated genotype-induced differences in demographic and neurocognitive data in patients with dementia. One-way ANOVA revealed significant (p=0.026–0.043) genotype-induced differences in the MMSE scores (Table 2), and in VAT duration of numbers test, VAT time of response to numbers test, VAT average response to numbers test and WPLCR/PPLR unanswered (Table 3). Namely, carriers of Met/Val (p=0.031) or Val/Val (p=0.015) genotype had significantly (Tukey's test) higher MMSE scores than Met/Met carriers (Table 3). The post-hoc analysis (Tukey's test) of the results obtained through neurocognitive testing showed that carriers of Met/Met genotype had significantly longer VAT duration of numbers test (p=0.024), VAT time of response to numbers test (p=0.024), and VAT average response to numbers test (p=0.024), and significantly greater number of unanswered questions to WPLCR/PPLR (p=0.022) when compared to carriers of Met/Val genotypes (Table 3). Age of the groups differed significantly (F=57.378; df=3,107; p<0.001), since healthy subject were significantly younger than patients with dementia.

Discussion

Our preliminary results showed similar frequency of COMT genotypes between male and female healthy subjects and male and female patients with dementia. This finding concurs with previous studies showing similar genotype distributions of COMT polymorphism in patients with Alzheimer's disease and control subjects[8,18]. Additionally, in line with previous report[19], there were no significant differences in COMT genotype distribution in relation to gender. Patients with dementia differed significantly when subdivided into Met/Met, Met/Val or Val/Val genotypes with respect to MMSE scores, VAT duration of numbers test, VAT time of response to numbers test, VAT average response to numbers test and WPLCR/PPLR unanswered. Namely, carriers of Met/Met genotype had significantly lower scores of MMSE than carriers of Met/Val or Val/Val genotypes, indicating more severe symptoms of dementia. In addition, carriers of Met/Met genotype needed significantly longer time to respond to VAT duration of numbers test, VAT time of response to numbers test and VAT average response to

TABLE 2
COMPARISONS OF THE DEMOGRAPHIC AND COGNITIVE PERFORMANCES AMONG THE COMT VAL/158MET GENOTYPIC GROUPS IN PATIENTS WITH DEMENTIA

Dementia COMT				
	AA (Met/Met) N=11	AG (Met/Val) N=23	GG (Val/Val) N=12	ANOVA
Age	68.6±7.8	70.2±7.6	69.7±10.3	F=0.125; p=0.883; df=2,43
Duration of disease	2.4±1.3	2.0±1.8	3.3±2.2	F=1.869; p=0.167; df=2,43
Age at onset	66.2±7.7	68.2±7.7	66.4±10.3	F=0.258; p=0.754; df=2,43
Education	10.1±4.1	9.3±4.6	11.2±4.4	F=0.896; p=0.416; df=2,42
MMSE	12.3±5.7	17.8±7.1*	17.7±4.4**	F=3.397; p=0.043; df=2,43
MMSE modified	42.4±23.5	56.6±22.2	60.4±17.7	F=2.165; p=0.127; df=2,42
CDT	4.2±2.8	5.0±2.4	5.9±1.8	F=1.552; p=0.224; df=2,43
ADAS	57±5.0	44.5±17.0	40.8±11.8	F=1.816; p=0.185; df=2,43
NPI	5.6±4.0	19.7±15.4	7.3±5.3	F=3.464; p=0.058; df=2,15
NPI depression	0.0±0.0	2.4±4.5	1.2±1.8	F=0.959; p=0.406; df=2,15
NPI anxiety	0.2±0.4	3.6±5.8	1.5±1.8	F=1.213; p=0.325; df=2,15
NPI euphoria	0.2±0.5	v1.3±2.4	0.0±0.0	F=1.362; p=0.286; df=2,15
NPI apathy	3.0±1.9	4.4±4.3	3.5±4.8	F=0.199; p=0.822; df=2,15
NPI desinhibition	0.2±0.5	0.9±1.6	0.7±1.6	F=0.333; p=0.722; df=2,15
NPI irritability	0.4±0.5	3.0±4.0	0.5±1.2	F=1.950; p=0.177; df=2,15
NPI aberrant behavior	1.6±3.6	4.1±5.6	0.0±0.0	F=1.807; p=0.198; df=2,15

(*p=0.031 *vs*. AA genotype; **p=0.015 *vs*. AA genotype; Tukey's test)

numbers test, and they showed significantly greater number of unanswered questions to WPLCR/PPLR when compared to carriers of Met/Val genotypes. Better performance in several neurocognitive tests in carriers of Met/Val genotype in our patients with dementia is in agreement with the findings that healthy older adults with Val/Met genotype performed better on measures of verbal declarative memory and delayed recall than both homozygous groups[20]. The similar age range between our and former[20] study might suggest that younger subjects who are Met/Met homozygotes have the optimal dopamine signaling in the prefrontal cortex, while in older

TABLE 3
COMPARISONS OF THE COGNITIVE PERFORMANCES IN SUBJECTS DIVIDED INTO COMT VAL158/108MET GENOTYPES IN PATIENTS WITH DEMENTIA. VAT, WPLCR/PPLR WORD PAIRS TIME OF CORRECT ANSWERS, WPLCR/PPLR WORD PAIRS TIME OF UNCORRECT ANSWERS, REVERSE NAMING TIME CORRECT, REVERSE NAMING TIME UNCORRECT (SEC)

Dementia COMT				
	AA (Met/Met) N=11	AG (Met/Val) N=23	GG (Val/Val) N=12	ANOVA
VAT duration/sec	1957±656	3738±5836	1828±245	F=0.785; p=0.465; df=2,30
VAT duration of letter test	936±584	869±84	955±155	F=0.388; p=0.682; df=2,30
VAT duration of numbers test	1020±257	840±96*	872±92	F=3.953; p=0.030; df=2,30
VAT time of response to letter test	412±414	239±84	325±155	F=1.815; p=0.180; df=2,30
VAT time of response to numbers test	390±257	210±96*	243±94	F=3.920; p=0.031; df=2,30
VAT average response of letter test	11.4±11.5	6.6±2.3	9.0±4.3	F=1.817; p=0.180; df=2,30
VAT average response of numbers test	10.8±7.1	5.8±2.6*	6.7±2.6	F=3.924; p=0.031; df=2,30
WPLCR/PPLR picture pairs – correct answers	6.3±5.4	10.0±5.6	9.6±6.1	F=0.976; p=0.388; df=2,31
WPLCR/PPLR picture pairs – uncorrect answers	17.0±9.1	19.8±5.4	20.0±6.2	F=0.502; p=0.610; df=2,31
WPLCR/PPLR unanswered	1.7±2.4	0.2±0.5**	0.4±0.7	F=4.103; p=0.026; df=2,31
WPLCR/PPLR time of correct answers	56.6±48.8	65.5±25.5	59.6±33.1	F=0.207; p=0.814; df=2,31
WPLCR/PPLR time of uncorrect answers	350.3±232.3	304.5±120.0	343.6±133.8	F=0.337; p=0.716; df=2,31

(* p=0.024 *vs*. AA genotype; **p=0.022 *vs*. AA genotype; Tukey's test)

age, Met/Val heterozygotes have the optimal dopamine signaling, since older age is related to reduced dopamine signaling and prefrontal cortex function[20]. However, our results are not in line with the previous data on the association of the COMT genotypes and various cognitive functions in healthy subjects[12,14,15,19,21,22], since carriers of the Met/Met and Val/Met genotypes took less time to perform the task on Trail Making test B[19], showed better performance on the Digit Span Forward (a measure of attention and visuospatial working memory[15]), or on matrix reasoning (a measure of nonverbal reasoning) and block design (a measure of constructional ability), good indicators of general reasoning ability and fluid intelligence[22], or on Letter number sequencing test[12] (a test that requires storage and manipulation of information) and had decreased number of perseverantive errors in Wisconsin Card Sorting Test and in Continuous Performance Test[14].

It has recently been reported that differences in the effects of the COMT variants on the dopaminergic inputs on cortical function, and therefore on cognitive functions, might be induced by altered dopaminergic regulation in health and disease[23]. Namely, schizophrenic patients who have impaired cortical dopaminergic tone, with the Met/Met genotype (with lower dopamine degradation) have more »normal« dopamine levels than patients with Val/Val genotype (which metabolize dopamine more effectively). On the other hand, healthy subjects with Val/Val genotype, i.e. those with increased dopamine degradation, have optimal cortical dopaminergic activity compared to control subjects with Met/Met genotype[23]. In contrast, a recent review[24] discussed the association between indices of cognitive functions and COMT variants, and concluded that Met allele carriers perform better than Val carriers in healthy subjects and in schizophrenia patients, while carriers of Val allele show better cognitive performances in ADHD and in Parkinson's disease, suggesting a compley interplay between genetic, developmental and environmental backgrounds and pathophysiological processes[24]. The opposing effects of Met/Met, Met/Val or Val/Val genotypes on cognition might be explained by the complexity of the cognitive functions assessed by various cognitive tests[22], by the significant effect of age, since COMT Val158/108Met polymorphism modulates age-related changes in cortical physiology underlying cognitive functions[25], or by the significant gender interaction with COMT genotypes to impact cognitive function[13]. Since a myriad of genes is responsible for memory and other cognitive functions, it has been proposed that a constellation of genes, rather than a specific gene per se, may be required to account for the majority of variance in memory functioning[21].

Some of the shortcommings of our study are the possibilities of type 1 and type 2 errors due to the performance of multiple cognitive tests and due to the modest size of the groups, especially after subdivisions accordig to the genotypes[5]. In order to avoid both types of errors, future studies should include large samples.

Conclusion

Our preliminary data showed significantly impaired performance in several neurocognitive tests in carriers of Met/Met genotype in patients with dementia compared to either Met/Val or Val/Val genotype carriers. Although Met/Met genotype with more dopamine available in the frontal cortex should be associated with better neurocognitive test results than Met/Val or Val/Val genotype, our data on demented patients did not confirm this hypothesis. Further study on larger sample of patients with dementia, that will have a large statistical power, is needed to clarify the role of COMT polymorphism in cognitive functions.

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N. Pivac

»Rudjer Bošković« Institute, Division of Molecular Medicine, Bijenička 54, Zagreb, Croatia
e-mail: npivac@irb.hr

ASOCIJACIJSKA STUDIJA FUNKCIONALNOG POLIMORFIZMA KATEHOL-O-METILTRANSFERAZE I KOGNITIVNIH FUNKCIJA U BOLESNIKA S DEMENCIJOM

S A Ž E T A K

Funkcionalni polimorfizam Val158/108Met katehol-o-metiltransferaze (COMT), koji se odlikuje zamjenom valina (Val) i metionina (Met), povezan je s kognitivnim funkcijama u normalnom mozgu, starijom dobi i raznim demencijama. Katehol-o-metiltransferaza je odgovorna za razgradnju dopamina i drugih kateholamina, posebice u frontalnom korteksu. Stoga je za očekivati da nosioci alela s nižom aktivnošću enzima (Met) imaju bolje rezultate određenih neurokognitivnih testova. Studija je obuhvatila 46 bolesnika s demencijom i 46 zdravih starijih ispitanika. Bolesnicima je utvrđeno neurološko stanje koristeći test MMSE (od eng. Mini Mental Status Examination) i niz različitih neuroloških testova. Na uzorcima DNA provedena je genotipizacija. Bolesnici s demencijom su pokazali značajne, o genotipu ovisne, razlike u provedenim testovima. U odnosu na nosioce Val/Val genotipa, nosioci genotipa Met/Met su imali značajno niže rezultate na MMSE, značajno duže vrijeme trajanje, vrijeme odgovora i prosjek odgovora brojeva na testu vizualnog povezivanja (eng. Visual Association Test; VAT) te znatno veći veći broj neodgovorenih pitanja na testu WPLCR/PPLR (od eng. Word Pairs Learning and Recall/Picture Pairs Learning and Recall). Preliminarni rezultati su pokazali da bolesnici s demencijom, koji su nosioci genotipa Met/Met, ostvaruju značajno lošije rezultate na različitim neurokognitivnim testovima u odnosu na bolesnike nosioce genotipova Val/Val ili Val/Met. Iako bi genotip Met/Met trebao biti povezan s više raspoloživog dopamina u frontalnom korteksu, što se povezuje s boljim rezultatima neurokognitivnih testova u tih bolesnika, naši podaci nisu potvrdili tu hipotezu. Kako bi se razjasnila uloga polimorfizma COMT u kognitivnim funkcijama, potrebne su daljnje studije s većim brojem ispitanika.