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Research article

Significant association between catechol-O-methyltransferase (COMT) Val$^{158/108}$Met polymorphism and cognitive function in veterans with PTSD

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ABSTRACT

Core features of posttraumatic stress disorder (PTSD) are cognitive disturbances. Enzyme catechol-O-methyltransferase (COMT) degrades dopamine primarily in prefrontal cortex. Its functional polymorphism, COMT Val$^{158/108}$Met, affects COMT activity and dopamine availability and is associated with disturbances in cognition. The hypothesis was that PTSD subjects will have worse working memory than healthy controls and that the carriers of the COMT Met allele will show better cognitive performance compared to Val/Val carriers in PTSD and controls subjects. The aim of this study was to assess the differences in cognitive functioning between PTSD and control subjects and to evaluate the association between COMT Val$^{158/108}$Met polymorphism and cognitive function determined using the Rey–Osterrieth complex figure (ROCF) copy, immediate and delayed test. The study included 323 male Caucasian participants of Croatian origin: 205 male combat veterans with PTSD and 118 control subjects. A significant association between the COMT Val$^{158/108}$Met and the ROCF immediate and delayed scores in veterans with PTSD was found. We confirmed, on ethnically homogenous groups of veterans with matched combat experience, that controls had higher ROCF immediate and delayed test scores than veterans with PTSD. In PTSD subjects, the Met carriers of the COMT Val$^{158/108}$Met performed better (i.e. had higher ROCF scores) than Val/Val homozygotes on both ROCF immediate recall and delayed recall test. Our results provide the first evidence that the presence of one or two Met alleles of the COMT Val$^{158/108}$Met might act as a protective variant in working memory tasks in combat exposed veterans with PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a trauma and stressor-related disorder that develops after experiencing or witnessing traumatic or terrifying event in some (i.e. vulnerable), but not all subjects [1]. The characteristic clusters of symptoms include re-experiencing the trauma (including intrusive memories, nightmares, flashbacks, emotional distress and physical reactivity after exposure to traumatic reminders), avoidance of trauma related stimuli, negative changes in thinking and mood, and trauma related arousal and reactivity. Psychological trauma might affect mood, emotions and cognition [2]. Therefore, impairments of the memory, attention, planning- and problem solving, i.e. in working memory and executive control functions, are the most frequent cognitive disturbances in PTSD [3,4].

Cognitive disruptions might be evaluated using the Rey–Osterrieth complex figure test (ROCF): copy, immediate recall and delayed recall [5], a nonlinguistic, neuropsychological test widely used to evaluate visuospatial, organizational, and visual memory skills. Administration consists of copying the figure first by copying it freehand (recognition), and then followed by two free-recall tasks, i.e., reproducing the figure from memory immediately and after a delay during which a different kind of task is administered. Examinees are not told that they will be asked to remember the figure; thus, the second two conditions are regarded as tests of incidental learning and visual working memory [6]. The ROCF is a valuable tool used to evaluate working memory and executive function mediated by the prefrontal lobe [5].

Abbreviations: A, adenine; COMT, catechol-O-methyltransferase; DSM-IV, diagnostic and statistical manual for mental disorders, IV revision; G, guanine; IQ, intelligence quotient; Met, methionine; PTSD, posttraumatic stress disorder; ROCF, Rey–Osterrieth complex figure test; SCID, Structured Clinical Interview; Val, valine

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Dopamine affects cognition, especially in prefrontal cortex, due to its role in attention, vigilance, sleep and arousal. Increased dopaminergic prefrontal activity/availability is associated with improved working memory, attention and other executive functions [7]. Catechol-O-methyltransferase (COMT) degrades catecholamines including dopamine, and COMT affects prefrontal dopamine due to the scarce location of dopamine transporter in this region. The enzymatic activity of COMT is altered by its functional polymorphism COMT Val$^{158/108}$Met that influences dopaminergic activity [7]. COMT Val$^{158/108}$Met, a guanine (G) to adenine (A) transition, results in Valine (Val) to Methionine (Met) substitution at codon 108 in soluble COMT (S-COMT) or codon 158 in membrane-bound COMT (MB-COMT) on chromosome 22 [8]. MB-COMT predominates in the brain [8]. The Met/Met homozygous genotype is associated with significantly reduced thermo-stability and lower COMT activity, slower dopamine degradation and increased prefrontal dopamine availability [[8],9]. Therefore COMT Val$^{158/108}$Met variants (high activity in the Val/Val, intermediate activity in Val/Met, and low activity in Met/Met genotype, respectively) are associated with different dopaminergic phenotypes, cognitive abilities, executive functions and working memory [10,11].

Since cognitive disturbances are core features of PTSD [3,4], and in some studies COMT Val$^{158/108}$Met was associated with cognition [10] and hippocampal volume [12], the hypothesis was that carriers of the Met allele will show better cognitive performance compared to Val/Val carriers in PTSD. The aim of this study was to assess the differences in cognitive functioning between PTSD and control subjects and to evaluate the association between COMT Val$^{158/108}$Met polymorphism and cognitive function measured by the ROCF in Caucasian veterans with combat related PTSD.

2. Materials and methods

2.1. Subjects and cognitive tests

Out of 323 male Caucasian participants of Croatian origin (average age 42.0 ± 7.3 SD), 205 subjects were medication free war veterans with current and chronic combat related PTSD subjects (mean age 44.8 ± 6.4 SD), from the Referral Centre for the Stress-related Disorders of the Department of Psychiatry in University Hospital Dubrava. Control group comprised of 118 healthy subjects (mean age 39.1 ± 8.1 SD). Since the subjects were recruited between 2002 and 2008, PTSD and other comorbid neuropsychiatric disorders were diagnosed using the Structured Clinical Interview (SCID) based on DSM-IV criteria [1] and Clinician Administered PTSD Scale (CAPS). Exclusion criteria were schizophrenia, alcohol or drug abuse, mental retardation, liver diseases and neurological disorders. Cognitive functioning (working memory and executive functions) was measured with the ROCF. The ROCF examines the effectiveness of copying and reproducing complex drawing immediately after observation (ROCF immediate recall) and after 30 min (ROCF delayed recall). The ROCF scores (maximum score of 20 on each subtest) measure individual's memory, visual and spatial abilities, attention and working memory. All subjects signed the consent after being fully informed about the aspects of the study. All studies were conducted with the approval of the Ethics committee of the University Hospital Dubrava and fully compliant with the ethical standards laid down in the 1975 Declaration of Helsinki.

2.2. Blood collection and genotyping

Genomic DNA was isolated from peripheral blood using a salting out method [13]. COMT rs4680 (Val$^{158/108}$Met) polymorphism was genotyped with Applied Biosystems® 7300 Real-Time PCR System apparatus using primers and probes from Applied Biosystems as TaqMan® Drug Metabolism Genotyping Assay (Foster City, CA, USA) and following manufacture's procedures. The 10 µL reaction volume contained around 20 ng of DNA. Assay ID was C_25746809_50.

2.3. Statistical analysis

The results were expressed as median and 25th (Q1) and 75th (Q3) percentiles and evaluated with Sigma Stat 3.5 (Jandell Scientific Corp. San Raphael, California, USA). The χ^2 test was used to evaluate if COMT Val$^{158/108}$Met genotypes were in the Hardy-Weinberg equilibrium and the possible case/control differences in COMT Val$^{158/108}$Met genotype distribution. The ROCF data failed to reach normal distribution (Kolmogorov-Smirnov test). Differences between the ROCF copy, immediate and delayed test scores in carriers of the different COMT genotypes, and afterwards in Val/Val homozygotes vs. Met carriers (i.e. a group with the combined Met/Val and Met/Met genotypes), were evaluated with nonparametric Kruskal Wallis ANOVA and Mann Whitney test, respectively. Linear model was used to evaluate the possible effects of age, placed as covariate variable, as well as diagnosis (PTSD or controls), COMT genotype, general IQ, smoking and education level, which were placed as categorical predictors, on ROCF copy, immediate and delayed test scores. A two-way ANOVA was used to assess the possible interaction between the COMT genotype and diagnosis on the ROCF immediate and ROCF delayed test scores. All tests were two-tailed, with $p < 0.05$.

3. Results

In all subjects linear model was used to test the effect of age, general IQ, smoking, education status, COMT genotype and diagnosis on the ROCF copy, immediate and delayed test results, which were set as dependent variables. None of the predictors showed significant effect on the ROCF copy test results ($R^2 = 0.712$: $F_{age} = 0.831$, $p_{age} = 0.149$; $F_{IQ} = 1.422$, $p_{IQ} = 0.174$; $F_{smoking} = 0.301$, $p_{smoking} = 0.588$; $F_{education} = 0.900$, $p_{education} = 0.478$; $F_{genotype} = 0.772$, $p_{genotype} = 0.473$; $F_{diagnosis} = 0.013$, $p_{diagnosis} = 0.911$). Linear model revealed that diagnosis had highly significant effect on the ROCF immediate test ($R^2 = 0.771$: $F_{diagnosis} = 16.106$, $p_{diagnosis} < 0.001$) and on the ROCF delayed test ($R^2 = 0.846$: $F_{diagnosis} = 39.378$, $p_{diagnosis <} 0.0001$) scores. Other predictors did not show any significant effect on the ROCF immediate test ($F_{age} = 0.141$, $p_{age} = 0.710$; $F_{IQ} = 0.811$, $p_{IQ} = 0.731$; $F_{smoking} = 0.378$, $p_{smoking} = 0.543$; $F_{education} = 0.262$, $p_{education} = 0.900$; $F_{genotype} = 1.725$, $p_{genotype} = 0.197$) and on the ROCF delayed test ($F_{age} = 0.639$, $p_{age} = 0.431$; $F_{IQ} = 0.935$, $p_{IQ} = 0.583$; $F_{smoking} = 0.534$, $p_{smoking} = 0.471$; $F_{education} = 1.325$, $p_{education} = 0.285$; $F_{genotype} = 0.829$, $p_{genotype} = 0.447$) scores.

The distribution of the COMT Val$^{158/108}$Met genotypes did not deviate from Hardy-Weinberg equilibrium ($\chi^2 = 1.246$; $p = 0.264$), and did not differ significantly ($\chi^2 = 0.435$; df = 2; $p = 0.805$) between veterans with PTSD and control subjects (Table 1).

Since linear model revealed a significant effect of diagnosis on the ROCF test results, Kruskal-Wallis ANOVA was used separately in PTSD and control subjects (Fig. 1). It showed that control subjects had similar scores on the ROCF copy ($H = 2.045$; df = 2; $p = 0.360$), immediate ($H = 3.083$; df = 2; $p = 0.214$) and delayed ($H = 2.824$; df = 2; $p = 0.244$) test depending on genotype. Among PTSD subjects, the ROCF copy ($H = 0.364$; df = 2; $p = 0.834$), immediate ($H = 5.938$; df = 2; $p = 0.051$) and delayed ($H = 5.790$; df = 2; $p = 0.055$) test scores did not differ significantly between carriers of Met/Met, Met/Val

Table 1
The frequency of the COMT Val$^{158/108}$Met genotypes (Met/Met, Met/Val and Val/Val) among veterans with PTSD and control subjects.

COMT Val$^{158/108}$Met genotypes	PTSD N (%)	Controls N (%)
Met/Met	63 (30.7)	32 (29.4)
Met/Val	95 (45.9)	57 (46.7)
Val/Val	48 (23.4)	29 (23.8)

COMT: catechol-O-methyltransferase; PTSD: posttraumatic stress disorder.

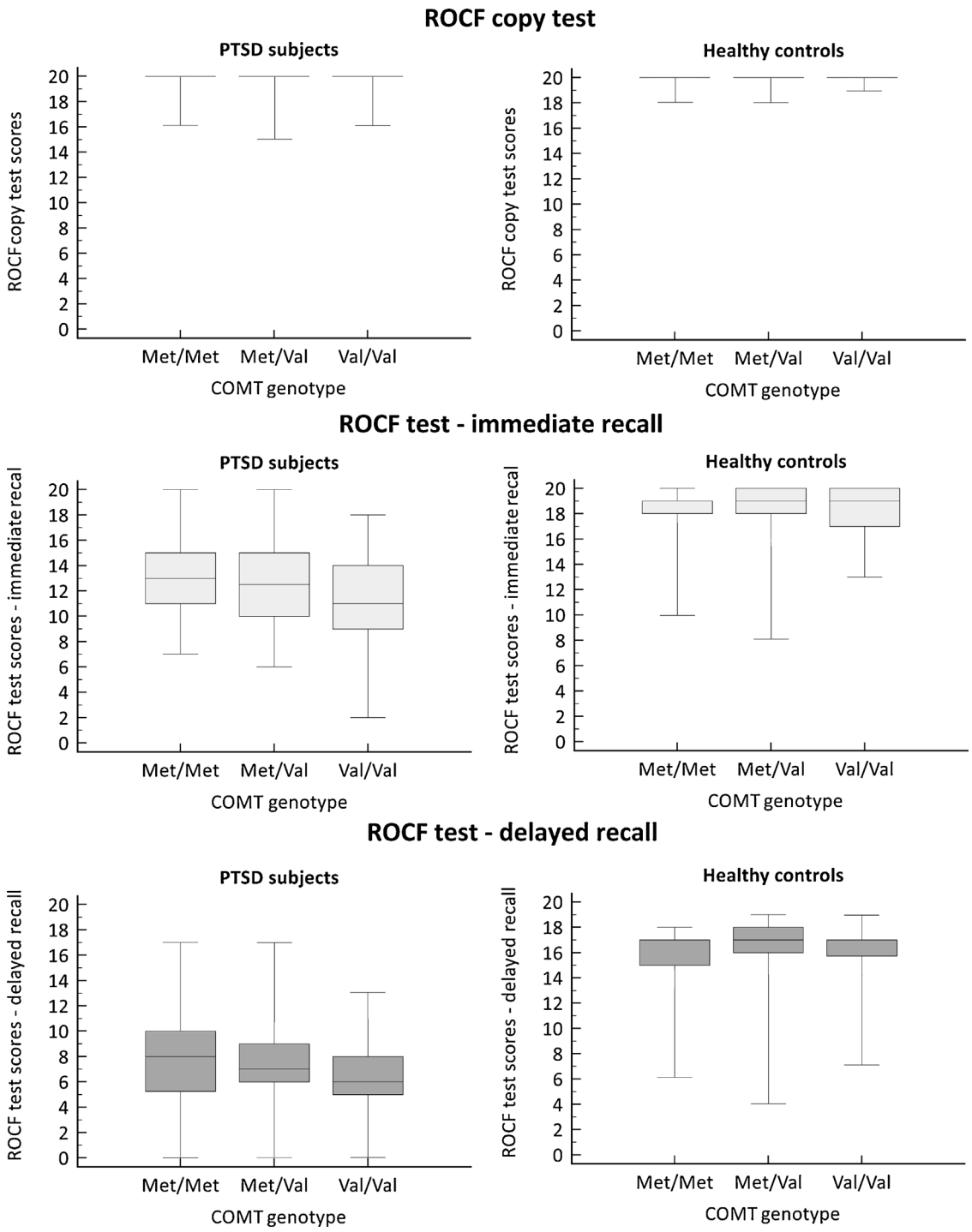

Fig. 1. The ROCF copy, immediate, and delayed scores achieved by veterans with PTSD and healthy controls depending on COMT Val$^{158/108}$Met genotype. Central box represents the interquartile range (Q1–Q3) while the middle line represents the median. Whiskers represent minimum and maximum values.

and Val/Val genotypes. However, Val/Val carriers had slightly lower scores on immediate and delayed ROCF tests compared to other genotype carriers (Fig. 1).

Due to this trend, all subjects were subdivided into Met carriers (the combined Met/Met and Met/Val genotype) and Val/Val homozygotes (Fig. 2). The ROCF copy test scores did not differ significantly (Mann Whitney test) between Val/Val homozygotes and Met carriers in control subjects ($U = 1203.50$; $Z = -1.429$; $p = 0.153$), or in veterans with PTSD ($U = 3685.00$; $Z = -0.190$; $p = 0.849$). In control subjects, there was no significant difference in the ROCF immediate test ($U = 1221.00$; $Z = 0.449$; $p = 0.653$), or in the ROCF delayed ($U = 1129.00$; $Z = 1.035$; $p = 0.301$) scores between Met carriers and Val/Val homozygotes (Fig. 2). In contrast, among PTSD subjects, Met carriers showed significantly better performance (i.e. higher test scores) than Val/Val homozygotes on both ROCF immediate ($U = 2931.00$; $Z = -2.338$; $p = 0.019$) and delayed ($U = 2997.50$; $Z = -2.158$; $p = 0.031$) test results (Fig. 2).

To assess the possible interaction between the studied variables, two-way ANOVA was used. It revealed no significant interaction between the COMT genotype and diagnosis on the ROCF immediate ($F = 1.997$; $df = 2, 317$; $p = 0.137$) or ROCF delayed ($F = 1.397$; $df = 2317$; $p = 0.249$) test scores. Further, this analysis confirmed the significant

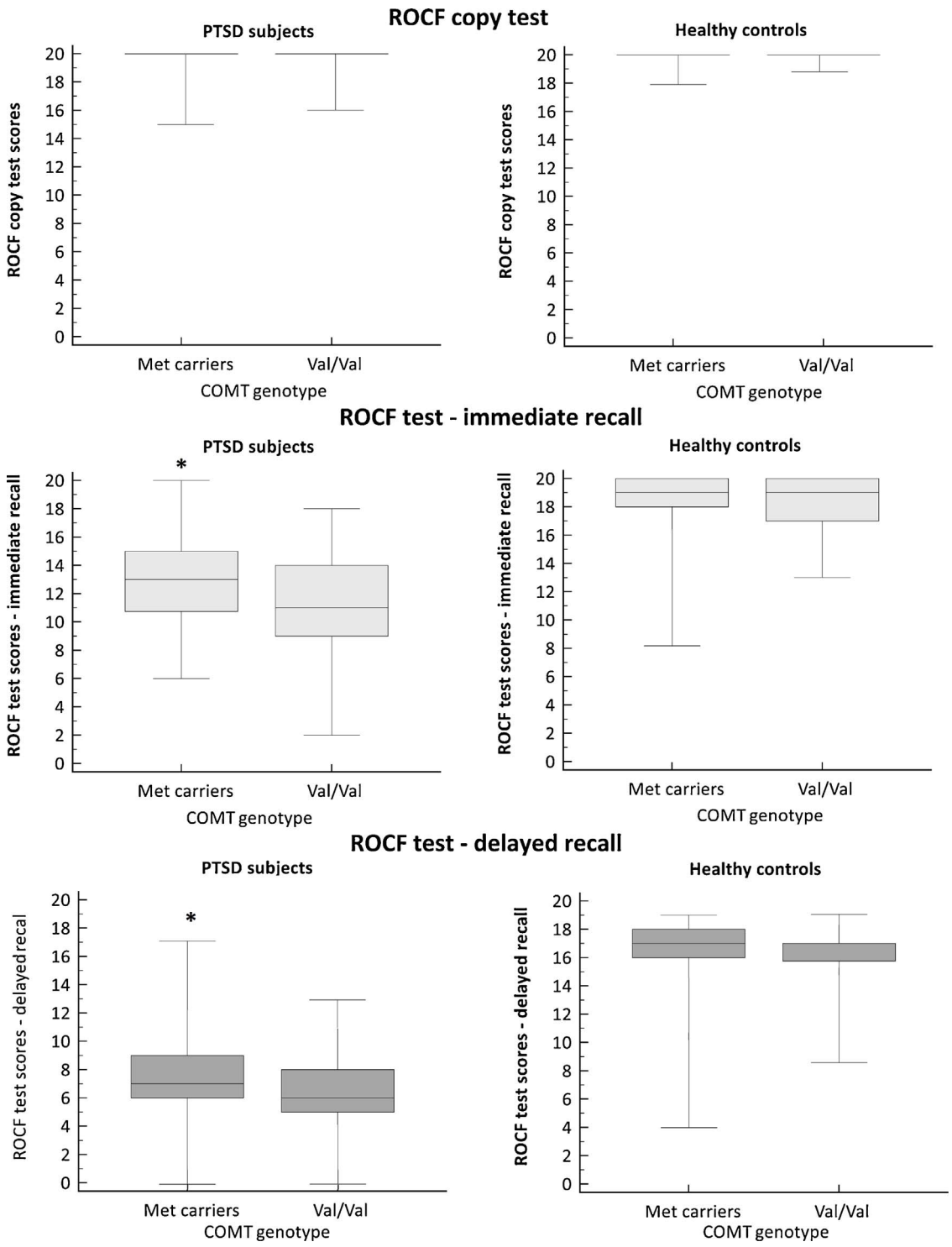

Fig. 2. The ROCF copy, immediate, and delayed scores achieved by veterans with PTSD and healthy controls subdivided according to the COMT Val$^{158/108}$Met genotype into Met carriers and Val/Val homozygotes. Central box represents the interquartile range (Q1–Q3) while the middle line represents the median. Whiskers represent minimum and maximum values, *$p < 0.05$.

effect of diagnosis on the ROCF immediate ($F = 284.7$; $df = 1, 317$; $p < 0.0001$) and ROCF delayed ($F = 436.9$; $df = 1317$; $p < 0.0001$) test scores. However, no significant influence of the COMT genotype on the ROCF immediate ($F = 1.582$; $df = 2, 317$; $p = 0.207$) or ROCF delayed ($F = 2.258$; $df = 2317$; $p = 0.106$) test scores was detected.

In addition, to evaluate if COMT genotype is related to working memory regardless of PTSD status, the group (PTSD + controls) was analyzed as a whole. There was no significant difference in the ROCF copy ($H = 0.886$; $df = 2$; $p = 0.642$), immediate ($H = 1.893$; $df = 2$; $p = 0.388$) and delayed ($H = 1.750$; $df = 2$; $p = 0.417$) test scores between the carriers of Met/Met, Met/Val and Val/Val genotypes, when both PTSD and control subjects were examined together (Kruskal Wallis ANOVA). This was confirmed since ROCF copy ($U = 9118.00$; $z = -0.822$; $p = 0.411$), immediate ($U = 8577.00$; $z = -1.255$; $p = 0.210$) and delayed ($U = 8532.00$; $z = -1.318$; $p = 0.187$) test scores did not differ significantly (Mann Whitney test) between the Met

carriers and Val/Val homozygotes when case/controls were merged.

4. Discussion

The main findings of this study are: 1) the ROCF immediate and delayed test scores, but not the ROCF copy test scores, were influenced by the diagnosis of PTSD; 2) frequency of the COMT Val$^{158/108}$Met genotypes did not differ between veterans with PTSD and control subjects; 3) COMT Val$^{158/108}$Met was significantly associated with the ROCF immediate and delayed scores in veterans with PTSD, but not in control subjects; and 4) within veterans with PTSD, Met carriers performed better (i.e. had higher ROCF scores) than Val/Val homozygotes on both ROCF immediate recall and delayed recall test.

Control subjects performed better on the ROCF immediate and delayed tests than PTSD subjects. Worse results on the ROCF immediate and delayed tests in veterans with PTSD corroborate with cognitive disturbances in PTSD [14], and agree with previous preliminary results obtained on a different, but much smaller group of Croatian war veterans with PTSD [15]. Impaired working memory in PTSD [4] is consistent with the significantly lower performance on measures of learning, immediate and delayed verbal memory [14], and reduced verbal and visual working memory [16] in veterans with PTSD. Even special operations warfighters, who were exposed to acute military stress, but did not have a diagnosis of PTSD, showed impaired working memory and poor ROCF copy and recall performance after exposure to the realistic levels of acute (i.e. interrogation) stress [17]. Acute stress conditions incapacitated warfighters to copy and recall information and also diminished working memory, a cognitive function important in military service as soldiers need to rapidly reveal, retain and manipulate new information needed for executive cognitive operations [17]. In contrast to these conditions [17], where subjects were evaluated 15 min after exposure to a high acute stress, in our study all subjects were evaluated years after trauma. In addition, 6 h after this form of acute stress, all special operations warfighters had normal ROCF copy and recall performances [17], which agrees with our data obtained in healthy subjects. Since in a previous study, age, gender, and IQ affected the results of the ROCF [18], in this study, the ROCF scores were controlled for these variables. The possible influence of gender on the ROCF was excluded since only male subjects were included in the study. In contrast to data obtained in normal volunteers [18], but in agreement with data in drug naïve subjects with PTSD [14], measures of immediate and delayed recall of verbal and visual explicit memory material were not affected by different IQ or years of education. In addition, our study revealed a lack of significant effect of smoking and age on the ROCF results. Our results are confirmed by the previous studies [[14],14], showing that memory deficits, especially impaired working memory, are related to PTSD. Recent meta-analysis confirmed impairments in verbal learning and memory, speed of processing, and attention/working memory, suggesting that therapeutic strategies should focus on improving these neurocognitive dysfunctions in PTSD [4].

To the best of our knowledge, this is the first association study to analyze COMT Val$^{158/108}$Met and the ROCF immediate and delayed scores in veterans with PTSD. The significant difference in ROCF immediate and delayed scores was detected between different COMT Val$^{158/108}$Met genotype groups in veterans with PTSD, but not in control subjects. This result confirms the significant relationship between COMT Val$^{158/108}$Met variants and working memory in PTSD, and not between COMT Val$^{158/108}$Met polymorphism and diagnosis of the PTSD itself, since COMT Val$^{158/108}$Met genotype distribution did not differ between veterans with PTSD and control subjects. This is in line with data showing that COMT Val$^{158/108}$Met polymorphism was not significantly associated with diagnosis of PTSD [19]. However, the literature data on this topic are inconsistent. The presence of the COMT Met/Met genotype significantly increased the risk of developing PTSD regardless of the severity of traumatic load [20]. Either Met/Met or Val/Val genotype was associated with more severe PTSD symptomatology [21]. Carriers of the Met allele had better functional outcome but lower rate of PTSD following mild traumatic brain injury [22]. However, the Met allele was also related to higher rate of PTSD after exposure to urban violence [23]. Nevertheless, the recent meta-analysis confirmed that COMT Val$^{158/108}$Met was not significantly associated with PTSD [19].

The data regarding the association between COMT Val$^{158/108}$Met and cognitive function are divergent [10,11,12,22,24,25,26,27,28]. Better performance on the ROCF immediate and delayed recall test among veterans with PTSD who were Met carriers, compared to Val/Val homozygotes, agrees with findings showing that carriers of the Val/Val genotype with PTSD frequently had more reductions in hippocampal volume [12] and worse memory retrieval [24] than Met carriers. It was also shown that PTSD subjects with Val/Val genotype had reduced functional connectivity between the hippocampus and prefrontal cortex during memory encoding-related activation patterns than Met carriers [25]. These differences in cognitive performance in carriers of different COMT genotypes might be due to the cortical hypodopaminergia in carriers of the Val/Val genotype, associated with worse cognitive performance, and deficits in executive and working memory functions [26]. All these findings might be explained with the lower dopamine availability in Val/Val carriers, suggesting an interaction between traumatic experience, lower dopamine and atrophy of the hippocampal and prefrontal regions, leading to the development and maintenance of PTSD and memory deficits in PTSD [12]. In contrast, Val/Val genotype carriers showed higher hippocampal activation after exposure to childhood trauma, which correlated with less PTSD symptoms and more trait resilience [27]. Regardless of the differences in traumatic experiences, these data suggest that COMT Val$^{158/108}$Met might moderate the effect of traumatic stress on hippocampal function and subsequent development of resilience to psychopathology.

Our results provide the first report that the presence of one or two Met alleles of the COMT Val$^{158/108}$Met might act as a protective variant in working memory tasks in combat exposed veterans with PTSD.

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