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The impact of BDNF Val66Met on cognitive skills in veterans with posttraumatic stress disorder

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Abstract

Posttraumatic stress disorder (PTSD) is a trauma-induced disorder characterized with impaired cognitive function. BDNF modulates cognition and is involved in neuroprotection and neurocognitive processing. The BDNF Val66Met polymorphism was found to influence cognitive functions. In PTSD, carriers of the BDNF GG genotype had better spatial processing of navigation performance, and lower hyperarousal and startle reaction than A allele carriers. The hypothesis was that veterans with PTSD, carriers of the BDNF Val66Met A allele, will show reduced cognitive skills.
The study included 315 male Caucasian combat veterans, with (N=199) or without (N=116) current and chronic PTSD. Cognition was assessed using the Rey-Osterrieth Complex Figure (ROCF) test that determines visual-spatial perception and short and long-term visual memory function.
The results revealed that cognitive decline measured with ROCF test was associated with PTSD. Presence of the BDNF Val66Met GG genotype in veterans with PTSD, but not in veterans without PTSD, showed protective association with visual short-term memory and visual object manipulation after few seconds (executive function), assessed with the ROCF immediate recall test, compared to the A carriers with PTSD.
In conclusion, this was the first study to confirm the association between BDNF Val66Met and memory and attention performed with ROCF in male veterans with PTSD. The results corroborated that the BDNF Val66Met A allele, compared to GG genotype, is associated with poorer short-term visual memory and attention linked with executive functions, in veterans with PTSD.

Keywords

PTSD, BDNF Val66Met polymorphism, cognition, male veterans, Rey–Osterrieth complex figure test

Abbreviations

A: adenine; BDNF: brain derived neurotrophic factor; G: guanine; Met: methionine; PTSD: posttraumatic stress disorder; ROCF: Rey–Osterrieth complex figure test; Val: valine

Introduction

Post-traumatic stress disorder (PTSD) is a trauma-induced stress-related disorder with cognitive decline contributing to the development, maintenance or exacerbation of symptoms [1]. Neuropsychological function is impaired in PTSD [2] including decreased performance in learning,

attention and working memory, executive functions and processing speed. Working and visual memory deficits in PTSD, manifested through persistent re-experiencing of traumatic memories, are probably caused by the decreased hippocampal volume [3] whose smaller size correlated with the progression of PTSD [4,5]. PTSD patients show impaired executive functioning implicating prefrontal cortex (PFC) dysfunction [6], characterized with particular difficulties in the appropriate regulation of PFC regions given the specific task demands [7], but the results across different studies are inconsistent. Disturbed cognition, due to concurrent emotional processing, hypervigilance, or decreased sleep could reduce attention to relevant stimuli thus influencing processing speed [8], which is often associated with prefrontal (i.e. inferior frontal gyrus) activation [9]. In the middle-aged civilian women, higher scores of PTSD symptoms were related to the worse performance on psychomotor speed/attention) and learning/working memory [10].

Brain derived neurotrophic factor (BDNF) modulates cell growth, survival, neuro-differentiation [11], neuroprotection [12], and neuroplastic changes related to cognitive processes [13]. BDNF activity is affected by the single nucleotide polymorphism Val66Met (G/A) of *BDNF* gene, a replacement of valine by methionine [14]. BDNF Val66Met polymorphism affects the transport of BDNF mRNA to dendrites and packaging and secretion of BDNF in neuronal cells, with the A allele associated with disturbances in activity-dependent BDNF release [15]. Moreover, the A allele affected cognitive functions, especially in the delayed recall of episodic memory and reduced hippocampal engagement during encoding and retrieval of a spatial task [16]. Namely, A compared to GG carriers had poorer performance on the memory tasks [17].

There are inconsistent data on the relationship between BDNF Val66Met and PTSD, reporting no [18,19] or a significant [20] association. However, BDNF Val66Met is associated with the main feature in PTSD, fear extinction learning: carriers of the BDNF Val66Met A allele with more severe PTSD had poorer fear extinction than GG carriers with PTSD [21]. The complex relationship between PTSD, trauma, BDNF Val66Met and hippocampal dependent processing affecting navigation skills was reported: BDNF GG genotype carriers were more accurate in judging their own competence at spatial processing of navigation performance than A carriers [22]. BDNF Val66Met was associated with startle response in PTSD, since AA carriers showed increased hyperarousal vulnerability and higher startle scores than the G carries [23]. These data suggest that A allele is a risk allele, while G allele is protective from exaggerated startle reactions [23]. No significant associations between BDNF Val66Met polymorphism with general cognitive ability, memory, executive function, visual processing skills and cognitive fluency were found [24]. Differences might be due to several factors, including gender, age, physical condition, ethnicity, cardio-vascular health status and diagnosis [25,26], valid tests measuring cognitive decline, and different trauma exposure for subjects with PTSD [22]. Only one study determined the association of BDNF Val66Met and memory in civilian women with PTSD, reporting that negative memory bias was significantly increased with increasing numbers of A alleles [27].

To the best of our knowledge, there are no data on the association of the BDNF Val66Met and Rey-Osterrieth Complex Figure (ROCF) test that determines visual-spatial perception and short and long-term visual memory function, in male veterans with PTSD. Therefore, the aims of the study were to 1) evaluate the pattern of change in cognitive function in veterans with or without PTSD using ROCF test; 2) examine the possible association of visuospatial abilities, attention, memory and processing speed with BDNF Val66Met; and 3) confirm if BDNF Val66Met A allele is associated with reduced cognitive skills in veterans with PTSD.

Materials and methods

Subjects and cognitive measurements

The study included only 315 male, medication free, Caucasian combat veterans of Croatian origin, recruited between 2002 and 2008 at the University Hospital Dubrava: 199 war veterans diagnosed with current and chronic combat related PTSD (using the Structured Clinical Interview and Clinician Administered PTSD Scale (CAPS) based on Diagnostic and Statistical Manual for Mental Disorders-IV criteria [28] with median CAPS 58 (51;72) and median age 42 (38;48), and 116 veterans exposed to the same combat experience who did not develop PTSD, with median age 39 (34;43). Exclusion criteria: schizophrenia, mental retardation, dementia, cognitive dysfunction, mood disorders, substance or alcohol abuse. They were mostly married (67%) and 71% finished high schools, with similar social and cultural backgrounds. Veterans were seeking treatment in Veterans PTSD program. They were further referred as cases (veterans with PTSD) and controls (veterans without PTSD).

Visual working memory in cases/controls was evaluated, as described previously [29], using the ROCF test which measures individual's visuospatial abilities, attention, visual memory and processing speed. It consists of replicating the drawing of a complex figure (ROCF copy) and then reproducing it from the memory less than three minutes after observation (ROCF immediate recall) and 30 minutes after observation (ROCF delayed recall). Each subtest has maximum score of 20.

All subjects signed informed consent prior to the study which was approved by the corresponding Ethics committee, fully compliant with the Declaration of Helsinki standards from 1975, as revised in 2008.

Blood collection and genotyping

Genomic DNA was isolated from peripheral blood using a salting out method [30]. BDNF Val66Met (rs6265) polymorphism was genotyped using Applied Biosystems® 7300 Real-Time PCR System with TaqMan® SNP Genotyping Assay (Foster City, CA, USA) primers and probes (Assay ID: C_11592758_10). The reaction was performed following manufacture's protocol in 10 μL reaction volume with approximately 20 ng of DNA. Around 10% of samples were repeated as a quality control for genotyping assays.

Statistical analysis

Data was analyzed using Graph Prism version 7.00 (GraphPad Software, Inc.). Due to deviation from the normal distribution for all tested neuropsychological scales, calculated using the Kolmogorov-Smirnov test, the results were expressed as median and 25^{th} (Q1) and 75^{th} (Q3) percentiles and non-parametric statistical analyses were used. The χ^2 test was used for Hardy-Weinberg equilibrium and to calculate differences in BDNF Val66Met AA, GA and GG genotypes, A vs. GG carriers, and G vs. AA carriers distribution. General linear model analyzed possible effects of diagnosis, age, smoking and education level on ROCF scores. Kruskal Wallis ANOVA and Mann Whitney test were used to determine differences in the ROCF scores depending on BDNF Val66Met genotypes, in cases/controls separately. All tests were two-tailed, with $p < 0.05$. G∗Power 3 Software [31] was used to determine a priori sample size and statistical power [with a = 0.05; expected small to medium effect size = 0.2; and statistical power (1 − b) = 0.800]. The required sample sizes were: for a Mann Whitney test, N = 191; for a χ^2test, N = 241 with df = 2; or N = 197 with df=1; for Kruskal-Wallis ANOVA, N=246. Therefore, the study included N=315 subjects and had adequate sample size and statistical power.

Results

General linear model determined the effects of diagnosis (PTSD or controls), age, smoking and education level, that were placed as fixed factors, and age and general IQ used as covariates on the ROCF copy, immediate and delayed recall test scores (Table 1). Highly significant ($p<0.001$) predictor of both ROCF immediate and delayed recall test scores was diagnosis of PTSD, while other variables

did not contribute to the model. None of the variables was significantly associated with the ROCF copy test scores (Table 1).

Table 1. Effects of diagnosis, age, general IQ, smoking and education level on ROCF copy, immediate and delayed test scores

Predictor	ROCF copy	ROCF immediate recall	ROCF delayed recall
Diagnosis	F=0.843; p=0.360	F=132.877; **p<0.001**	F=222.422; **p<0.001**
Education level	F=0.612; p=0.654	F=0.117; p=0.976	F=0.965; p=0.428
Smoking	F=0.004; p=0.949	F=0.971; p=0.326	F=0.055; p=0.815
Age	F=0.045; p=0.832	F=0.673; p=0.413	F=0.392; p=0.532
General IQ scores	F=0.092; p=0.762	F=1.308; p=0.255	F=2.913; p=0.091
Model	R^2=0.020	R^2=0.555	R^2=0.682

Veterans with PTSD had significantly (p<0.001; Mann Whitney test) lower ROCF immediate test scores than controls, confirming the effect of diagnosis on the ROCF immediate and delayed recall scores. Both groups had decreased ROCF delayed recall scores; however, cases had significantly (p<0.001) lower scores than controls (Supplementary Table 1, Fig. 1). Both groups had maximum, similar ROCF copy test scores that evaluated visual memory.

Out of 315 subjects, 63.5% had GG, 34.0% had GA and 2.5% had AA BDNF Val66Met genotype, respectively. This distribution was in the Hardy-Weinberg equilibrium (χ^2=2.046; df=2; p=0.359). Minor allele frequency (MAF) was 0.195 which is in concordance with estimated MAF of 0.200 in European population [32]. The frequency (χ^2 test) of BDNF Val66Met genotypes, A vs. GG carriers and G vs. AA carriers, respectively, did not differ significantly between cases/controls (Supplementary Table 2, Fig. 2).

The differences in the ROCF copy, immediate and delayed recall test scores between AA, GA or GG genotype carriers, or between A vs. GG carriers, or between G vs. AA carriers, were evaluated in cases/ controls separately (Supplementary Table 3, Fig. 3). Both groups had maximum scores on the ROCF copy test regardless of the BDNF Val66Met genotype: these ROCF copy scores did not differ significantly between carriers of the BDNF genotypes, A vs. GG carriers, or G vs. AA carriers in cases/controls (Supplementary Table 3, Fig. 3). In controls, no significant differences were observed in the ROCF immediate recall scores between carriers of different genotypes, A vs. GG carriers or G vs. AA carriers (Supplementary Table 3, Fig. 3). In veterans with PTSD, the ROCF immediate scores did not differ significantly in BDNF genotype carriers, or G carriers and AA homozygotes (Supplementary Table 3, Fig. 3). However, A carriers had significantly (p=0.040) lower ROCF immediate recall test scores than GG carriers (Supplementary Table 3, Fig. 3). There were no significant differences in the ROCF delayed recall scores between AA, GA or GG genotypes, A vs. GG carriers or G vs. AA carriers in cases/controls (Supplementary Table 3, Fig. 3). In confirmation (Supplementary Table 1, Fig. 1), veterans with PTSD, subdivided into A vs. GG carriers had significantly lower ROCF immediate working visual memory (p<0.001) and ROCF delayed visual memory (p<0.001) scores than corresponding control A vs. GG carriers (Supplementary Table 1, Fig. 1).

Discussion

This study found that ROCF test was associated with BDNF Val66Met polymorphism in male veterans with PTSD. Namely, the presence of the GG homozygous genotype in veterans with PTSD, but not in veterans without PTSD (controls), showed protective association with visual short-term memory and visual object manipulation after few seconds (executive function), assessed with the ROCF immediate recall test, compared to the A carriers with PTSD. No significant associations were found with the ROCF delayed scores, measuring long term visual memory, object manipulation and visual constructional abilities in long term memory system, or in ROCFT copy test scores, between carriers of the BDNF Val66Met genotypes in veterans with and without PTSD. In line with previous results [29], veterans with PTSD had significantly lower ROCF immediate and delayed recall test scores than veterans without PTSD.

Significant positive association between BDNF Val66Met GG genotype and ROCF immediate recall test agrees with better cognitive performance in GG homozygotes than A carriers in both healthy and clinical populations [22]. In policemen and military, GG carriers, opposed to A carriers, more accurately judged their competence at allocentric spatial processing [22], suggesting that BDNF modulates navigation behavior [22]. The A substitution negatively affects BDNF intracellular trafficking and activity-dependent secretion in hippocampus, where it is highly expressed [16]. In addition, A carriers have slightly smaller hippocampal volume than GG homozygotes [33], which could consequently lead to impaired memory and cognitive function. In contrast, no significant association between BDNF Val66Met polymorphism and cognitive function in healthy subjects [34], or a protective effect of the A allele on several cognitive domains [33] in subjects with Alzheimer's disease [35] and traumatic brain injury [36] was reported. Different BDNF Val66Met effects on cognition in neurodegenerative/neuropsychiatric disorders might result from the different etiology of these disorders. Similarly to our data, majority of the studies in patients with psychiatric disorders [16,17] or healthy individuals [22] associate the presence of the GG homozygous genotype with better executive function and memory. Acute and chronic stress reduced BDNF expression [37], while exposure to chronic stress during late adolescence in A carriers increased fear memory and elevated the risk of developing PTSD in adulthood [37]. However, studies analyzing BDNF Val66Met polymorphism and cognitive functioning in PTSD patients are scarce.

Our data, obtained in veterans with PTSD, but not in veterans without PTSD (controls), showed lower short term visual memory scores in BDNF Val66Met A carriers, which could correspond to the poorer processing of the visual and spatial information in A compared to GG carriers [22]. We confirmed working memory problems and attention deficits occurring in PTSD. In our study veterans with PTSD, carriers of the A allele or GG carriers, had significantly reduced ROCF immediate and delayed scores compared to control A allele or GG carriers. These results, obtained in male veterans with PTSD, partially agree with recent results [27] in civilian women with PTSD: A allele carriers had significantly poorer immediate memory, while heterozygous women (but not homozygote AA carriers) had lower delayed memory performance than controls, measured with a Repeatable Battery for the Assessment of Neuropsychological Status [27]. However, this study, in contrast to ours, did not detect significant differences in the immediate memory performance between carriers of different BDNF Val66Met genotypes subdivided according to the diagnosis [27]. A greater negative memory bias in women with PTSD carrying A allele than controls, where negative memory bias showed increasing trend with higher number of A alleles in women with PTSD [27], as well as poorer processing of traumatic information of veterans with PTSD that carry A allele [22] was also found. These differences were not detected in healthy subjects [22, 27]. In line with our results, animal study found poor performance in stress

exposed BDNF$^{+/Met}$ mice, suggesting that these mice are more susceptible to stress-induced working memory impairments [38].

The effect BDNF Val66Met polymorphism on cognitive and executive functions was affected by aging [39]. In our study, age, education and smoking were not significantly associated with working memory, attention and visual perception, assessed by ROCF test. On the other hand, the diagnosis of PTSD was shown to be a highly significant predictor of the decreased executive performance and worse working visual memory, since veterans with PTSD had significantly lower ROCF immediate and ROCF delayed scores, but not ROCF copy test scores, than veterans without PTSD, which is in line with our previous data [29] and data in civilian women with PTSD [27]. Possible sex differences in the cognition and BDNF Val66Met genotypes were excluded since the present study included only male veterans with or without PTSD.

Limitation are that the study included only male subjects, and the cognition was assessed using only the ROCF. However, due to the sex differences in *BDNF* Val66Met polymorphism and its sex-specific role in cognition [40], we excluded the possible influence of sex.

Conclusion

This is the first study to evaluate the association between BDNF Val66Met and memory and attention performed with ROCF in male veterans with PTSD. We have confirmed that the A allele of the BDNF Val66Met is associated with poorer short-term visual memory and attention linked with executive functions, compared to the GG carriers in veterans with PTSD.

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References

[1] R.L. Aupperle, A.J. Melrose, M.B. Stein, M.P. Paulus, Executive function and PTSD: disengaging from trauma, Neuropharmacology. 62 (2012) 686-694. doi:10.1016/j.neuropharm.2011.02.008.

[2] J.P. Hayes, M.B. Vanelzakker, L.M. Shin, Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies, Front. Integr. Neurosci. 6 (2012) 89. doi:10.3389/fnint.2012.00089.

[3] C.R. Brewin, The nature and significance of memory disturbance in posttraumatic stress disorder, Annu. Rev. Clin. Psychol. 7 (2011) 203-227. doi:10.1146/annurev-clinpsy-032210-104544.

[4] N. Kitayama, V. Vaccarino, M. Kutner, P. Weiss, J.D. Bremner, Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis, J. Affect. Disord. 88 (2005) 79-86. doi:10.1016/j.jad.2005.05.014.

[5] F.L. Woon, S. Sood, D.W. Hedges, Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis, Prog. Neuropsychopharmacol. Biol. Psychiatry. 34 (2010) 1181-1188. doi:10.1016/j.pnpbp.2010.06.016.

[6] A.R. Polak, A.B. Witteveen, J.B. Reitsma, M. Olff, The role of executive function in posttraumatic stress disorder: a systematic review, J. Affect. Disord. 141 (2012) 11-21. doi:10.1016/j.jad.2012.01.001.

[7] R.L. Aupperle, A.N. Stillman, A.N. Simmons, T. Flagan, C.B. Allard, S.R. Thorp, S.B. Norman, M.P. Paulus, M.B. Stein, Intimate Partner Violence PTSD and Neural Correlates of Inhibition, J. Trauma. Stress. 29 (2016) 33-40. doi:10.1002/jts.22068.

[8] J.C. Scott, G.E. Matt, K.M. Wrocklage, C. Crnich, J. Jordan, S.M. Southwick, J.H. Krystal, B.C. Schweinsburg, A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder, Psychol. Bull. 141 (2015) 105-140. doi:10.1037/a0038039.

[9] N. Usui, T. Haji, M. Maruyama, N. Katsuyama, S. Uchida, A. Hozawa, K. Omori, I. Tsuji, R. Kawashima, M. Taira, Cortical areas related to performance of WAIS Digit Symbol Test: a functional imaging study, Neurosci. Lett. 463 (2009) 1-5. doi:10.1016/j.neulet.2009.07.048.

[10] J.A. Sumner, K. Hagan, F. Grodstein, A.L. Roberts, B. Harel, K.C. Koenen, Posttraumatic stress disorder symptoms and cognitive function in a large cohort of middle-aged women, Depress. Anxiety. 34 (2017) 356–366. doi:10.1002/da.22600.

[11] M.M. Poo, Neurotrophins as synaptic modulators, Nat. Rev. Neurosci. 2 (2001) 24-32. doi:10.1038/35049004.

[12] C.R. Bramham, E. Messaoudi, BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis, Prog. Neurobiol. 76 (2005) 99-125. doi:10.1016/j.pneurobio.2005.06.003.

[13] M. Miranda, J.F. Morici, M.B. Zanoni, P. Bekinschtein, Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain, Front. Cell. Neurosci. 13 (2019) 363. doi:10.3389/fncel.2019.00363.

[14] T. Mizui, K. Ohira, M. Kojima, BDNF pro-peptide: a novel synaptic modulator generated as an N-terminal fragment from the BDNF precursor by proteolytic processing, Neural. Regen. Res. 12 (2017) 1024-1027. doi:10.4103/1673-5374.211173.

[15] G. Baj, D. Carlino, L. Gardossi, E. Tongiorgi, Toward a unified biological hypothesis for the BDNF Val66Met-associated memory deficits in humans: a model of impaired dendritic mRNA trafficking. Front. Neurosci. 7 (2013) 188. doi:10.3389/fnins.2013.00188.

[16] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell. 112 (2003) 257-269. doi:10.1016/s0092-8674(03)00035-7.

[17] A.R. Hariri, T.E. Goldberg, V.S. Mattay, B.S. Kolachana, J.H. Callicott, M.F. Egan, D.R. Weinberger, Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance, J. Neurosci. 23 (2003) 6690–6694. doi:https://doi.org/10.1523/JNEUROSCI.23-17-06690.2003.

[18] N. Pivac, D. Kozaric-Kovacic, M. Grubisic-Ilic, G. Nedic, I. Rakos, M. Nikolac, M. Blazev, D. Muck-Seler, The association between brain-derived neurotrophic factor Val66Met variants and psychotic symptoms in posttraumatic stress disorder. World. J. Biol. Psychiatry. 13 (2012) 306–311. doi:10.3109/15622975.2011.582883

[19] K.E. Bountress, S.A. Bacanu, R.L. Tomko, K.J. Korte, T. Hicks, C. Sheerin, M.J. Lind, M. Marraccini, N. Nugent, A.B. Amstadter, The effects of a BDNF Val66Met polymorphism on posttraumatic stress disorder: a meta-analysis, Neuropsychobiology. 6 (2018) 1–7. doi:10.1159/000489407.

[20] L. Zhang, D.M. Benedek, C.S. Fullerton, R.D. Forsten, J.A. Naifeh, X.X. Li, X.Z. Hu, H. Li, M. Jia, G.Q. Xing, K.N. Benevides, R.J. Ursano, PTSD risk is associated with BDNF Val66Met and BDNF overexpression. Mol. Psychiatry. 19 (2014) 8–10. doi:10.1038/mp.2012.180.

[21] K.L. Felmingham, D.V. Zuj, K.C.M. Hsu, E. Nicholson, M.A. Palmer, K. Stuart, J.C. Vickers, G.S. Malhi, R.A. Bryant, The BDNF Val66Met polymorphism moderates the relationship between Posttraumatic Stress Disorder and fear extinction learning. Psychoneuroendocrinology 91 (2018) 142-148. doi:10.1016/j.psyneuen.2018.03.002.

[22] J.K. Miller, S. McDougall, S. Thomas, J. Wiener. The Impact of the Brain-Derived Neurotrophic Factor Gene on Trauma and Spatial Processing. J. Clin. Med. 6 (2017) pii:E108. doi:10.3390/jcm6120108.

[23] L. Zhang, X.X. Li, X.Z. Hu, Post-traumatic stress disorder risk and brain-derived neurotrophic factor Val66Met, World. J. Psychiatry. 6 (2016) 1–6. doi:10.5498/wjp.v6.i1.1.

[24] S.D. Mandelman, E.L. Grigorenko, BDNF Val66Met and cognition: all, none, or some? A meta-analysis of the genetic association, Genes. Brain. Behav. 11 (2012) 127-136. doi:10.1111/j.1601-183X.2011.00738.x.

[25] M. Verhagen, A. van der Meij, P.A. van Deurzen, J.G. Janzing, A. Arias-Vasquez, J.K. Buitelaar, B. Franke, Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity, Mol. Psychiatry. 15 (2010) 260-271. doi:10.1038/mp.2008.109.

[26] W. Lu, C. Zhang, Z. Yi, Z. Li, Z. Wu, Y. Fang, Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naive patients with schizophrenia, J. Mol. Neurosci. 47 (2012) 505-510. doi:10.1007/s12031-012-9750-4.

[27] H. Hori, M. Itoh, F. Yoshida, M. Lin, M. Niwa, Y. Hakamata, K. Ino, R. Imai, S. Ogawa, M. Matsui, T. Kamo, H. Kunugi, Y. Kim, The BDNF Val66Met polymorphism affects negative memory bias in civilian women with PTSD, Sci. Rep. 10 (2020) 3151. doi:10.1038/s41598-020-60096-1.

[28] American Psychiatric Association, Diagnostic and statistical manual of mental disorders: DSM-IV, Washington, DC (1994).

[29] A. Havelka Mestrovic, L. Tudor, M. Nikolac Perkovic, G. Nedic Erjavec, Z. Kovacic Petrovic, D. Svob Strac, M. Konjevod, N. Pivac, Significant association between catechol-O-methyltransferase (COMT) Val158/108Met polymorphism and cognitive function in veterans with PTSD, Neurosci. Lett. 666 (2018) 38-43. doi.org/10.1016/j.neulet.2017.12.033.

[30] S.A. Miller, D.D. Dykes, H.F. Polesky, A simple salting out procedure for extracting DNA from human nucleated cells, Nucleic. Acids. Res. 16 (1988) 1215. doi:10.1093/nar/16.3.1215.

[31] F. Faul, E. Erdfelder, A.G. Lang, A. Buchner, G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences, Behav. Res. Methods. 39 (2007) 175-191. doi:10.3758/bf03193146.

[32] The 1000 Genomes Project Consortium, A global reference for human genetic variation, Nature. 526 (2015) 68–74. doi:10.1038/nature15393.

[33] F. Harrisberger, K. Spalek, R. Smieskova, A. Schmidt, D. Coynel, A. Milnik, M. Fastenrath, V. Freytag, L. Gschwind, A. Walter, T. Vogel, K. Bendfeldt, D.J. de Quervain, A. Papassotiropoulos, S. Borgwardt, The association of the BDNF Val66Met polymorphism and the hippocampal volumes in healthy humans: a joint meta-analysis of published and new data, Neurosci. Biobehav. Rev. 42 (2014) 267–278. doi:10.1016/j.neubiorev.2014.03.011.

[34] N. Avgan, H.G. Sutherland, L.K. Spriggens, C. Yu, O. Ibrahim, C. Bellis, L.M. Haupt, D.H. Shum, L.R. Griffiths, DNF variants may modulate long-term visual memory performance in a healthy cohort, Int. J. Mol. Sci. 18 (2017) pii:E655. doi:10.3390/ijms18030655.

[35] T. Nagata, S. Shinagawa, K. Nukariya, H. Yamada, K. Nakayama, Association between BDNF polymorphism (Val66Met) and executive function in patients with amnestic mild cognitive impairment or mild Alzheimer disease, Dement. Geriatr. Cogn. Disord. 33(2012), 266–272. doi:10.1159/000339358.

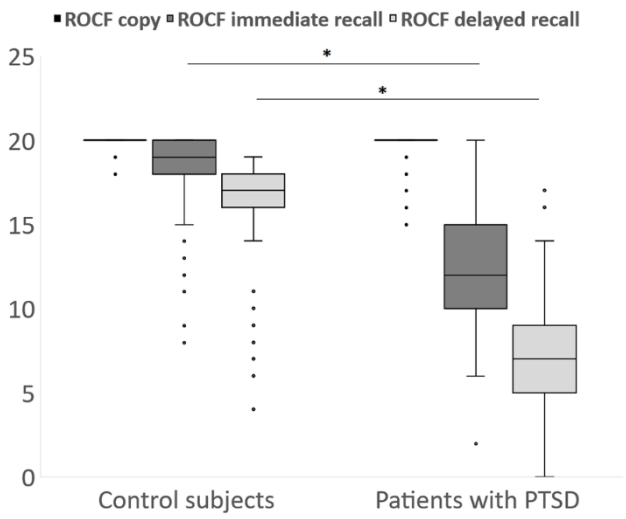
[36] A.K. Barbey, R. Colom, E. Paul, C. Forbes, F. Krueger, D. Goldman, J. Grafman, Preservation of general intelligence following traumatic brain injury: Contributions of the Met66 brain-derived neurotrophic factor, PLoS ONE, 9 (2014) e88733. doi:10.1371/journal.pone.0088733.

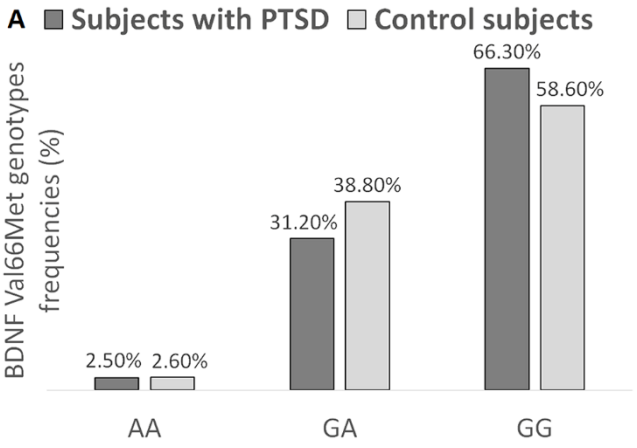
[37] M. Aas, U.K. Haukvik, S. Djurovic, Ø. Bergmann, L. Athanasiu, M.S. Tesli, T. Hellvin, N.E. Steen, I. Agartz, S. Lorentzen, K. Sundet, O.A. Andreassen, I. Melle, BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses, Prog. Neuropsychopharmacol. Biol. Psychiatry. 46 (2013) 181–188. doi:10.1016/j.pnpbp.2013.07.008.

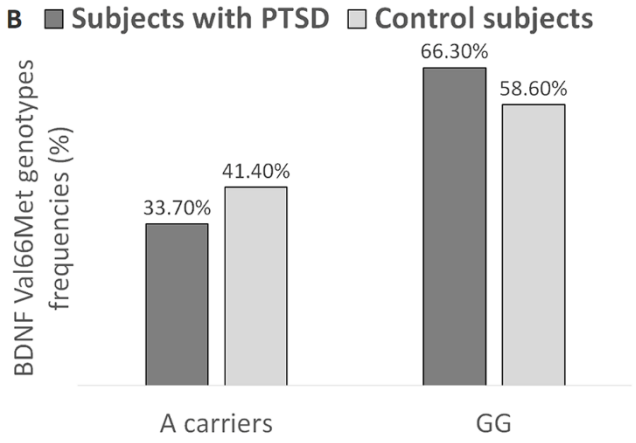
[38] H. Yu, D.D. Wang, Y. Wang, T. Liu, F.S. Lee, Z.Y. Chen, Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants, J. Neurosci. 32 (2012) 4092–4101. doi:10.1523/JNEUROSCI.5048-11.2012.

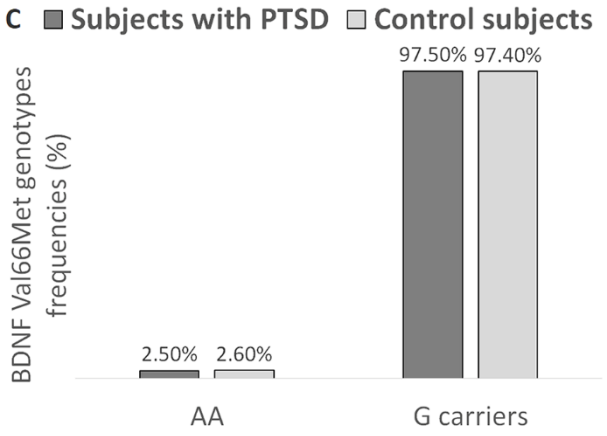
[39] K.M. Kennedy, E.D. Reese, M.M. Horn, A.N. Sizemore, A.K. Unni, M.E. Meerbrey, A.G. Kalich Jr, K.M. Rodrigue, BDNF val66met polymorphism affects aging of multiple types of memory, Brain. Res. 1612 (2015) 104–117. doi:10.1016/j.brainres.2014.09.044.

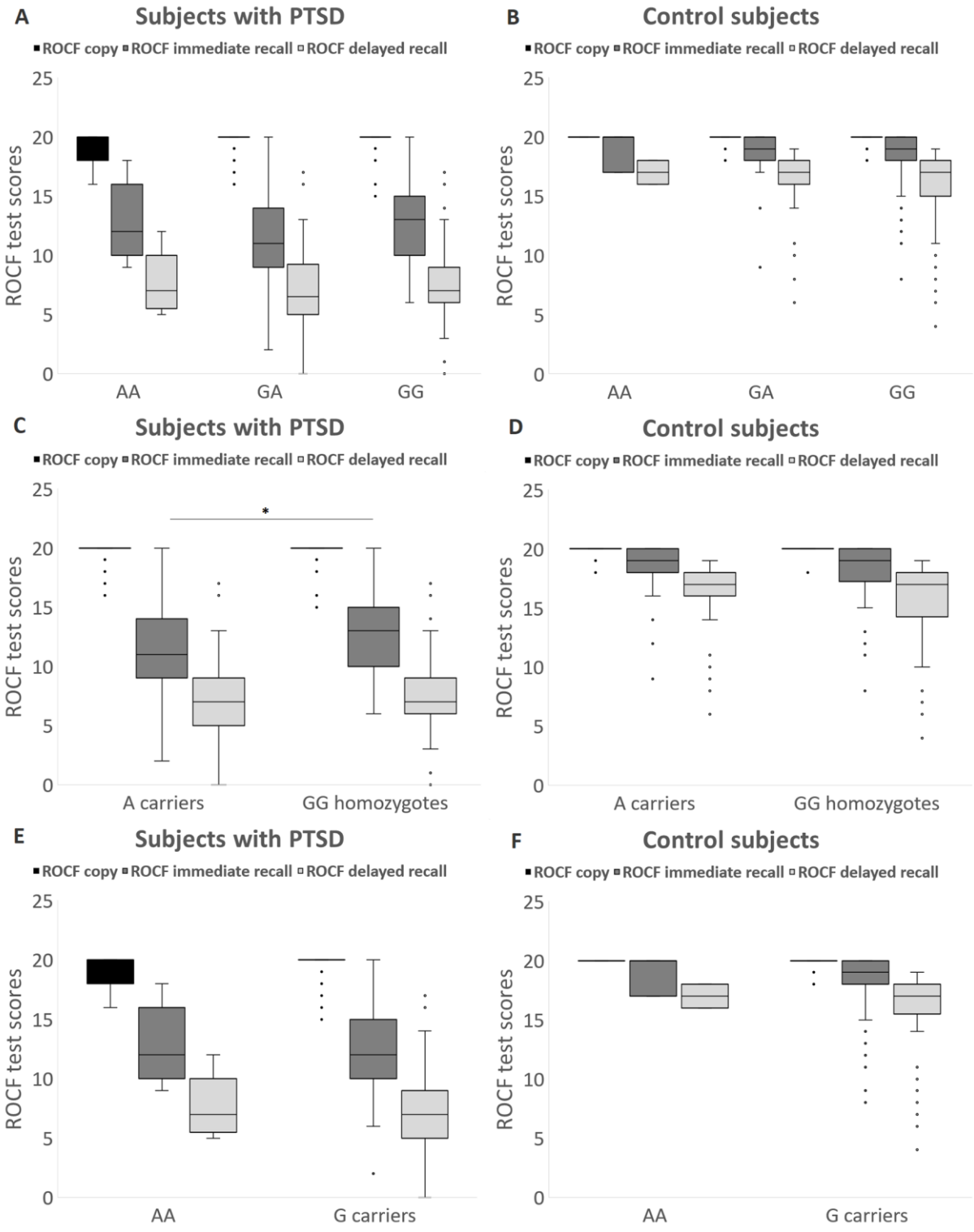
[40] K.R. Laing, D. Mitchell, H. Wersching, M-E. Czira, K. Berger, B.T. Baune. Brain-derived neurotrophic factor (BDNF) gene: a gender-specific role in cognitive function during normal cognitive aging of the MEMO-Study? Age. 34 (2012) 1011–1022. doi: 10.1007/s11357-011-9275-8.


ROCF copy
ROCF immediate recall
ROCF delayed recall
25
20
15
10
5
0
*
*
Control subjects
Patients with PTSD


A
Subjects with PTSD
Control subjects
BDNF Val66Met genotypes frequencies (%)
2.50%
2.60%
31.20%
38.80%
66.30%
58.60%
AA
GA
GG


B
Subjects with PTSD
Control subjects
BDNF Val66Met genotypes frequencies (%)
33.70%
41.40%
66.30%
58.60%
A carriers
GG


C
Subjects with PTSD
Control subjects
BDNF Val66Met genotypes frequencies (%)
2.50%
2.60%
97.50%
97.40%
AA
G carriers


A
Subjects with PTSD
ROCF copy
ROCF immediate recall
ROCF delayed recall
ROCF test scores
25
20
15
10
5
0
AA
GA
GG
B
Control subjects
ROCF copy
ROCF immediate recall
ROCF delayed recall
ROCF test scores
25
20
15
10
5
0
AA
GA
GG
C
Subjects with PTSD
ROCF copy
ROCF immediate recall
ROCF delayed recall
*
ROCF test scores
25
20
15
10
5
0
A carriers
GG homozygotes
D
Control subjects
ROCF copy
ROCF immediate recall
ROCF delayed recall
ROCF test scores
25
20
15
10
5
0
A carriers
GG homozygotes
E
Subjects with PTSD
ROCF copy
ROCF immediate recall
ROCF delayed recall
ROCF test scores
25
20
15
10
5
0
AA
G carriers
F
Control subjects
ROCF copy
ROCF immediate recall
ROCF delayed recall
ROCF test scores
25
20
15
10
5
0
AA
G carriers