Reduced plasma BDNF concentration associated with cognitive decline in veterans with PTSD

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Abstract: Post-traumatic stress disorder (PTSD) is a trauma and stress related disorder frequently associated with cognitive decline. War veterans with PTSD have a higher risk of developing dementia than veterans without PTSD. Brain derived neurotrophic factor (BDNF) is an important protein that modulates plasticity, memory consolidation and cognitive processes. Lower circulating BDNF levels were related to memory impairment and cognitive deterioration. The aim of this study was to evaluate cognitive deterioration and plasma BDNF concentration in 120 veterans with combat related PTSD, 120 healthy controls, 47 subjects with mild cognitive impairment (MCI) and 76 patients with Alzheimer's disease (AD), and to assess if plasma BDNF concentration might be used as biomarker of cognitive deterioration in PTSD. Veterans with PTSD had significantly decreased plasma BDNF concentration and worse cognitive performances than healthy subjects. Lower plasma BDNF concentration and decreased Mini Mental State Examination and Clock Drawing test scores in PTSD subjects were comparable to results obtained for subjects with MCI. These results suggest that veterans with PTSD should be closely monitored with additional cognitive and biochemical (BDNF determination) tests, in order to early detect and predict cognitive worsening and promote interventions that might help restore blood BDNF levels and cognitive functions.

Key words: Alzheimer's disease; brain-derived neurotrophic factor; cognition; mild cognitive impairment; post-traumatic stress disorder; veterans

1. Introduction

Post-traumatic stress disorder (PTSD) is a trauma and stress related disorder (APA, 2013) that is frequently associated with different comorbidities and with significant cognitive decline (Hayes et al., 2012). Cognitive deterioration includes processing speed, concentration difficulties, deficits in learning, memory, attention, planning, problem solving and executive function (Hayes et al., 2012; Scott et al., 2015). It is assumed that PTSD is characterized by decreased hippocampal and frontal lobe volumes and lower total brain volume (Karl et al., 2006). Meta-analysis, that investigated emotions and cognition, and their interactions, reported that, during emotional and cognitive processing tasks, individuals with PTSD showed significantly greater activation in the striatum compared to controls (Lee et al., 2021). Disruption in social cognition (Couette et al., 2020), disturbances in visual spatial perception and short and long-term visual memory functions, evaluated using the Rey Osterrieth Complex Figure test (Havelka Mestrovic et al., 2020, 2018), were also reported for PTSD. In addition, PTSD was reported as a significant and important risk factor for all-cause dementia in a meta-analysis by Günak et al. (2020). Longitudinal follow up revealed that war veterans with PTSD have a 2-fold-higher risk of developing dementia compared to veterans without PTSD (Kang et al., 2019), and the results were controlled for the possible influence of demographic, medical and neuropsychiatric comorbidities (Yaffe et al., 2010). Although the mechanisms involved are not clear, it is believed that there are common pathways in PTSD and dementia that might accelerate the development of neuropathological alterations in dementia, while PTSD symptoms (hypervigilance and trauma re-experiencing) induce social withdrawal associated with cognitive decline (Bryant, 2019; Desmarais et al., 2020). There is a bidirectional relationship between PTSD and dementia since PTSD increases the risk for late-onset dementia and vice versa (Desmarais et al., 2020). Alzheimer's disease (AD) is a most common cause of dementia characterized by progressive loss of memory and impairment of cognitive functions in older people, while mild cognitive impairment (MCI) is a state between normal aging and AD, assumed to represent a stage that proceeds the development of AD in most cases (Miranda et al., 2019). Subjects with PTSD frequently develop deterioration in concentration, learning and memory, problems in decision-making, and have increased incidence of MCI (Clouston et al., 2019).

Brain derived neurotrophic factor (BDNF) is important in regulating synaptic plasticity and processes related to learning and memory consolidation (Miranda et al., 2019). Altered BDNF signaling and changes in its concentrations affect memory performance in different age-related and neuropsychiatric-related cognitive dysfunctions, such as AD and MCI (Miranda et al., 2019).

In AD patients, lower serum BDNF levels were reported to predict faster cognitive decline, and baseline BDNF serum levels were significantly and independently associated with the rate of cognitive decline in AD (Laske et al., 2011). BDNF has an important role in regulating stress response, and complex role in vulnerability to stress related disorders, such as PTSD, since it is a part of the functional gene-regulatory network (Notaras and van den Buuse, 2020). Namely, it is involved in the pathways that regulate encoding of fear and might potentiate sensitivity to stress, but also in adaptive plasticity during extinction learning in order to suppress trauma related and PTSD-related fear responses (Notaras and van den Buuse, 2020). There are a lot of data regarding the association of the BDNF Val66Met polymorphism (a functional polymorphism affecting the secretion of the mature BDNF protein, hippocampal activity and memory performance) with PTSD (reviewed by Zhang et al. 2016) or cognition in PTSD (Havelka Mestrovic et al., 2020, 2018; Nedic Erjavec et al., 2021). However, there are no data on the association of plasma BDNF levels and cognitive decline in adult PTSD.

The aim of this study was to compare cognitive deterioration and plasma BDNF concentration in veterans with combat related PTSD, and compare these data with the findings in healthy controls and subjects with MCI or AD, and to assess if plasma BDNF concentration might be used as biomarker of cognitive deterioration in PTSD. The hypothesis of this study was that cognitive performance and plasma BDNF concentration will be reduced in veterans with PTSD compared to control subjects and that this decline will be similar to the results obtained in subjects with MCI or AD.

2. Materials and Methods

2.1. Subjects

The study included Caucasian male subjects: 120 veterans with combat related PTSD, 120 healthy control subjects, 47 subjects with MCI and 76 subjects with AD. All participants were recruited in the Clinics for Psychiatry Vrapce, Zagreb, Croatia.

2.2. Clinical evaluations

Diagnosis of PTSD was done with Structured clinical interview (SCID) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria (APA, 2013). Subjects with PTSD were exposed to similar traumas during the Homeland war in Croatia. Inclusion criteria were in- and out-patients who signed informed written consent. Exclusion criteria for PTSD subjects were: drug abuse, alcohol dependence or pathophysiological changes

in the liver, such as fibrosis, sclerosis, cirrhosis and malignant liver disease [alcoholic liver cirrhosis (K70.3), alcoholic liver fibrosis and sclerosis (K70.2) and hepatocellular carcinoma (C22.0), according to International Classification of Diseases, 10 revision /ICD-10/], schizophrenia, bipolar disorder, adult ADHD, AD (according to DSM-5 criteria), current or recent (previous 3 months) use of medication. Control subjects were also evaluated in Clinics for Psychiatry Vrapce, and underwent the same inclusion/exclusion criteria.

The diagnosis of AD and MCI was done according to the criteria listed in DSM-5 (APA, 2013) and the criteria of the National Institute of Neurological and Communication Disorders and Stroke, which is part of the American National Institute of Health (NINCDS-ADRDA; National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association).

Cognitive status in all participants was tested using a Mini-Mental State Examination (MMSE) (Boban et al., 2012) and Clock Drawing test (CDT) (Agrell and Dehlin, 1998; Shulman, 2000). The study was approved by the Ethics Committee of the University Psychiatric Hospital Vrapce, Zagreb, Croatia, and were carried out in line with the Helsinki Declaration (World Medical Association, 2013). All subjects have signed either informed consent prior to study procedures, or the consent forms were explained in details to the patients with AD or subjects with MCI and their caregivers.

2.3. Blood sample collection

Whole blood samples were collected at 8 a.m., following an overnight fast, in 8.5 ml yellow-top Vacutainer tubes with 1.5 ml of acid citrate dextrose anticoagulant. Sampling was performed during the routine laboratory visits. After a series of centrifugation of the whole blood, plasma was separated for BDNF analysis and stored at -20 °C.

2.4. Measurement of plasma BDNF concentration

BDNF concentration in plasma was determined using a commercial enzyme-linked immunosorbent assay (ELISA) according to the manufacturer’s instructions (Quantikine ELISA, R&D Systems, Minneapolis, USA), as described before (Sagud et al., 2016). All samples were measured in duplicates and plasma samples were diluted 1:2. The absorbance of each sample, standards and blanks was measured using a microplate reader set to 450 nm with wavelength

correction set to 570 nm. The intra- and inter-assay coefficients of variations were less than 10%. The concentrations of samples in each plate were calculated based on a standard curve.

2.5. Statistical analysis

The results were evaluated with Sigma Stat 3.5 (Jandel Scientific Corp., San Jose, California, USA). Normality of data distribution was confirmed with the Kolmogorov-Smirnov test. Since the variables did not follow normal distribution, non-parametric tests were applied and the results were expressed as median and Q1-Q3 range. Kruskal-Wallis ANOVA by ranks was used to compare four groups, with the Dunn's multiple comparisons test for post-hoc comparisons. Age, MMSE and CDT scores and BDNF concentrations were correlated using Spearman's correlation coefficient. All tests were two-tailed, and α was set at 0.05.

G∗Power 3 Software (Faul et al., 2007) was used to calculate the needed sample size and statistical power. With expected moderate effect size = 0.25, and statistical power set to 0.800, the required sample size was N=180 for Kruskal-Wallis ANOVA and N=84 for correlation. Since the study included 363 participants, it had the needed sample size to detect differences between groups.

3. Results

Demographic and clinical parameters for all four groups of subjects are presented in Table 1 and evaluated using Kruskal Wallis ANOVA by ranks followed by the Dunn's multiple comparisons test. Included participants differed significantly by age ($p<0.001$) since subjects diagnosed with MCI and AD were significantly older than healthy controls and PTSD patients (Table 1). As expected, subjects diagnosed with PTSD, AD or MCI had significantly lower ($p\leq0.050$; Dunn's multiple comparisons test) MMSE scores compared to scores in healthy control subjects (Table 1). Patients with AD have the lowest MMSE scores when compared to the other groups of subjects (Table 1). The same trend was detected when comparing CDT scores between groups (Table 1). Healthy control subjects had the highest CDT scores, while AD patients had the lowest CDT scores (Table 1). Interestingly, PTSD patients had significantly lower CDT scores than subjects with MCI (Table 1).

Significant differences were found in plasma BDNF concentration between healthy controls, PTSD subjects, subjects diagnosed with MCI or AD (Figure 1). Significant differences ($F=40.22$; $df=3$; $p<0.001$) were the results of the higher plasma BDNF concentrations in healthy control

subjects (1.740, 1.000-3.630) compared to PTSD subjects (0.785, 0.455-1.735), subjects diagnosed with MCI (0.800, 0.335-1.835) or AD subjects (1.070, 0.575-2.180). The lowest BDNF plasma concentration was detected in PTSD subjects, even when compared to individuals with AD ($p \leq 0.050$; Dunn's multiple comparisons test).

Since participants differed by age, to evaluate possible effect of age on plasma BDNF levels, Spearman correlation was used. In all subjects together, there was no significant correlation ($p=0.171$) between age and BDNF plasma concentration (Table 2). The possible correlation between age and BDNF plasma levels in individual diagnostic groups was evaluated and confirmed no significant correlation between age and peripheral BDNF concentration in healthy controls subjects, subjects with PTSD, subjects with MCI or subjects with AD (Table 2). No significant correlation was found between severity of cognitive symptoms, evaluated with MMSE and CDT, and BDNF plasma concentration in healthy subjects, veterans with PTSD, subjects with MCI and patients with AD (Table 2). However, when all subjects were evaluated together, a significant positive correlation was detected between plasma BDNF levels and both MMSE ($p<0.001$) and CDT ($p=0.003$) scores (Table 2).

In order to confirm the effect of diagnosis on BDNF plasma levels, and correct for the possible effect of cognitive decline (MMSE and CDT scores) and age difference, multiple linear regression analysis (with diagnosis, age, MMSE scores, and CDT scores as independent variables) was used. Multiple linear regression analysis with plasma BDNF concentration as dependent variable revealed a significant model ($F(4,358)=2.80$; $p=0.026$; $R_{adj}^2=0.019$). The model was significant due to the effect of diagnosis ($p=0.014$) and age ($p=0.034$), with no significant effects of MMSE ($p=0.302$), and CDT ($p=0.117$) scores on plasma BDNF concentration.

4. Discussion

This study is the first to evaluate the association between plasma BDNF concentration and cognition in veterans with PTSD, and compare these data with those in subjects with MCI, patients with AD and healthy control subjects. The results revealed that plasma BDNF concentration was significantly reduced in veterans with PTSD compared to age matched healthy subjects, and that veterans with PTSD, although younger than MCI subjects, had similarly decreased BDNF concentration and similar cognitive deterioration as subjects with MCI. Lower BDNF concentration in veterans with PTSD compared to healthy subjects is not

consistent with previous results suggesting higher plasma and serum BDNF concentration in subjects with PTSD, compared to control subjects (Mojtabavi et al., 2020). However, Mojtabavi and colleagues (2020) did not evaluate cognition in their PTSD sample. Therefore, disturbances in cognitive tasks in veterans with PTSD might explain the reduced plasma BDNF concentration found in our veterans with PTSD. In addition, differences might be due to the fact that these included participants had different clinical backgrounds (such as childhood sexual abuse, PTSD developed antepartum, after earthquake, road traffic accident or combat), other psychiatric disorders or hepatocellular carcinoma (Mojtabavi et al., 2020), while our study excluded liver diseases and included only combat related PTSD. Differences might also be due to inadequate statistical power or small sample size, ranging from 10 to 102 (Mojtabavi et al., 2020).

However, the unexpected result was that veterans with PTSD had even lower plasma BDNF concentration than patients with AD, who had reduced plasma BDNF concentration compared to healthy control subjects. This finding might be explained by the fact that higher BDNF levels are associated with the early stage of AD, when compared to patients with late stage of AD (Laske et al., 2006), suggesting that our patients diagnosed with AD are still in the early stages of the disease. In conformation, the median MMSE score was 17.5 for our AD patients, suggesting moderate dementia (13-20 scores). Therefore, either some compensatory effect, or treatment with donepezil (Leyhe et al., 2008), mood stabilizers (Ventriglia et al., 2013) or vortioxetine (Dvojkovic et al., 2021; Sagud et al., 2016) that increase plasma BDNF concentration, might explain higher plasma BDNF levels in patients with AD.

In our study veterans with PTSD had similar BDNF concentration as subjects with MCI suggesting a higher risk of cognitive deterioration (Fujiwara et al., 2021). Findings from the literature regarding blood BDNF levels in MCI are inconsistent and meta-analysis reported similar (although slightly reduced) serum BDNF levels in subjects with MCI compared to healthy controls (Ng et al., 2019). In line with the effect of age on BDNF and on cognitive function (Miranda et al., 2019; Ng et al., 2019), multiple linear regression confirmed that diagnosis and age significantly affected plasma BDNF concentration in our study.

Altered BDNF levels were found in AD, indicating the lack of neurotrophic support in the physiopathology of AD and progression to neurodegeneration in older age or MCI (Diniz and Teixeira, 2011). In agreement with our data, circulating BDNF levels were found decreased in AD (Laske et al., 2006; Ng et al., 2019) and reduced peripheral BDNF levels were also detected

in AD subjects with MMSE scores lower than 20, when compared to control subjects (Kim et al., 2017). Opposed to the findings of the meta-analyses (Kim et al., 2017; Ng et al., 2019), in present study and study by Forlenza and colleagues (2006) BDNF concentration was found to be lower in MCI subjects, revealing reduction in trophic support and contributing to progressive neurodegeneration. In line with our findings, similar blood BDNF levels were found among subjects with MCI and patients with AD when controlled for the effect of age, sex, and drug use (Kim et al., 2017). In our study lower plasma BDNF levels were associated with diagnosis and age, but not with MMSE or CDT scores, according to the multiple regression analysis. However, correlation analysis revealed a significant positive correlation between plasma BDNF levels and both MMSE and CDT scores when all groups were merged together. It has been reported that MMSE scores are important moderators that might explain the heterogeneity of the reported findings of circulating BDNF levels in dementia (Ng et al., 2019). In our study all groups of subjects (veterans with PTSD, subjects with MCI and patients with AD) had significantly lower plasma BDNF concentration and also significantly reduced MMSE and CDT scores compared to healthy subjects, showing cognitive decline. This reduction in BDNF might indicate a lack of neurotrophic support and consequent alterations in synaptic plasticity and memory process, including memory consolidation (Miranda et al., 2019). These results collectively suggest that decreased BDNF is associated with cognitive disturbances in these groups of participants. The possible influence of sex was excluded since we included only male subjects, while possible influence of age and diagnosis was detected.

Regarding cognitive tasks, veterans with PTSD had reduced MMSE and CDT scores compared to healthy control subjects who were matched for age, and similar MMSE scores as older individuals with MCI. In agreement with our findings, the MMSE scores were significantly reduced in subjects with PTSD compared to control subjects (Fayyazi Bordbar et al., 2012). However, the unexpected result was that veterans with PTSD had even lower CDT scores than subjects with MCI. These results suggest that cognitive deficits are more pronounced in veterans with PTSD than in control subjects of the general population, and that this cognitive decline, evaluated with MMSE, is similar as in older subjects with MCI, while cognitive tasks of drawing clock are worse than in MCI individuals. In line with cognitive decline in PTSD, in our previous studies, other groups of Croatian veterans with PTSD had cognitive deterioration evaluated using the Rey Osterrieth Complex Figure test, showing deficits in visual spatial perception and short and long-term visual memory functions (Havelka Mestrovic et al., 2020, 2018), and developed cognitive decline that was evaluated using the PANSS cognition subscale scores

(Nedic Erjavec et al., 2021). In a smaller Italian study, within 4 years follow-up, lower MMSE scores were detected in 17% of patients with PTSD suggesting matched criteria for dementia (Bonanni et al., 2018). After a longer follow up of 6-10 years, 13% of PTSD population developed semantic frontotemporal dementia, while 16% of patients with dementia had a history of PTSD (Bonanni et al., 2018). Since our study does not have a longitudinal design, we cannot demonstrate how many PTSD veterans have developed dementia. However, the MMSE score for 120 PTSD subjects included in this study ranged from 22-25 and median was 25, suggesting a state between mild dementia (21-24 scores) and normal cognition. It is unclear whether cognitive deterioration develops prior to PTSD or is a complication of PTSD. Longitudinal assessment of veterans prior to combat and after the deployment might answer this question. Some studies have found that lower cognitive function before trauma increased the risk of developing PTSD (Brewin et al., 2000; Parslow and Jorm, 2007), while reduced pre-trauma visual immediate memory was related to higher post-deployment PTSD symptom severity in veterans (Marx et al., 2009). Therefore, veterans with PTSD deserve to be closely monitored with cognitive and biochemical (BDNF determination) tests, to be able to early detect and predict cognitive worsening and to promote interventions that might increase blood BDNF levels and improve cognitive functions. These strategies include medication such as memantine and donepezil, but also exercise, diet, increased physical activity, intellectual stimulation and yoga (reviewed in Ng et al. 2019), interventions aiming to increase BDNF and slow progression of dementia.

Limitations and strengths of the study should be acknowledged. First limitation is a cross sectional design, therefore due to lack of longitudinal follow up, we are not able to detect how many PTSD subjects developed dementia. The other limitation is that we included only male combat veterans with PTSD, hence we could not generalize these findings to civilian PTSD subjects or to female subjects. Since the main aim was to evaluate BDNF levels and cognitive decline in veterans with PTSD, the inclusion of comparative groups of older MCI and AD subjects could not be omitted. Another limitation is that, although healthy control subjects and veterans with PTSD were medication free, subjects with MCI and AD were on their usual treatment regimen. Strengths are in the inclusion of ethnically homogenous population for all groups, only male subjects, and for the comparator group for PTSD veterans we included age matched healthy control subjects. This study has adequate sample size (N=363) and needed statistical power. In addition, as recently suggested, all BDNF determinations were done by

researchers who were blind to diagnoses of subjects, and using and R&D System-Quantikine BDNF ELISA assays, reported to be specific for mature human BDNF (Ng et al., 2019).

Funding

This research was funded by the Croatian Academy of Sciences and Arts grant no. 1452H05, project: The role of BDNF in cognitive alterations in PTSD - possible application in prevention and treatment of these symptoms (PI Nela Pivac), and by the Croatian Science Foundation research grant no. IP-2019-04-6100, project: Therapeutic potential of neurosteroids and neurotrophins in dementia (PI Dubravka Svob Strac).

Acknowledgments

We are extremely grateful to all the subjects who took part in this study.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committees of the University Hospital Dubrava, Zagreb (protocol code: none; 20 February 2006) and University Psychiatric Hospital Vrapce, Zagreb, Croatia (protocol code 23-209-/4-19; 26 June 2019). Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

Agrell, B., Dehlin, O., 1998. The clock-drawing test. Age Ageing 27, 399–403.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. Arlington, VA.

Boban, M., Malojčić, B., Mimica, N., Vuković, S., Zrilić, I., Hof, P.R., Simić, G., 2012. The reliability and validity of the mini-mental state examination in the elderly Croatian population. Dement. Geriatr. Cogn. Disord. 33, 385–392. https://doi.org/10.1159/000339596

Bonanni, L., Franciotti, R., Martinotti, G., Vellante, F., Flacco, M.E., Di Giannantonio, M., Thomas, A., Onofrj, M., 2018. Post Traumatic Stress Disorder Heralding the Onset of Semantic Frontotemporal Dementia. J. Alzheimers. Dis. 63, 203–215. https://doi.org/10.3233/JAD-171134

Brewin, C.R., Andrews, B., Valentine, J.D., 2000. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J. Consult. Clin. Psychol. 68, 748–766. https://doi.org/10.1037//0022-006x.68.5.748

Bryant, R.A., 2019. Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. World Psychiatry 18, 259–269. https://doi.org/10.1002/wps.20656

Clouston, S.A.P., Diminich, E.D., Kotov, R., Pietrzak, R.H., Richards, M., Spiro, A. 3rd, Deri, Y., Carr, M., Yang, X., Gandy, S., Sano, M., Bromet, E.J., Luft, B.J., 2019. Incidence of mild cognitive impairment in World Trade Center responders: Long-term consequences of re-experiencing the events on 9/11/2001. Alzheimer's Dement. (Amsterdam, Netherlands) 11, 628–636. https://doi.org/10.1016/j.dadm.2019.07.006

Couette, M., Mouchabac, S., Bourla, A., Nuss, P., Ferreri, F., 2020. Social cognition in post-traumatic stress disorder: A systematic review. Br. J. Clin. Psychol. 59, 117-138. https://doi.org/10.1111/bjc.12238

Desmarais, P., Weidman, D., Wassef, A., Bruneau, M.-A., Friedland, J., Bajsarowicz, P., Thibodeau, M.-P., Herrmann, N., Nguyen, Q.D., 2020. The Interplay Between Post-traumatic Stress Disorder and Dementia: A Systematic Review. Am. J. Geriatr. psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry 28, 48–60. https://doi.org/10.1016/j.jagp.2019.08.006

Diniz, B.S., Teixeira, A.L., 2011. Brain-Derived Neurotrophic Factor and Alzheimer's Disease: Physiopathology and Beyond. NeuroMolecular Med. 13, 217–222.

https://doi.org/10.1007/s12017-011-8154-x

Dvojkovic, A., Nikolac Perkovic, M., Sagud, M., Nedic Erjavec, G., Mihaljevic Peles, A., Svob Strac, D., Vuksan Cusa, B., Tudor, L., Kusevic, Z., Konjevod, M., Zivkovic, M., Jevtovic, S., Pivac, N., 2021. Effect of vortioxetine vs. escitalopram on plasma BDNF and platelet serotonin in depressed patients. Prog. Neuro-Psychopharmacology Biol. Psychiatry 105, 110016. https://doi.org/https://doi.org/10.1016/j.pnpbp.2020.110016

Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191. https://doi.org/10.3758/BF03193146

Fayyazi Bordbar, M.R., Talaei, A., Heydari Yazdi, A., Dastgheib, M.-S., Rezaei Ardani, A., 2012. Cognitive Deficits and Memory Disturbances in Patients with Chronic Post-Traumatic Stress Disorder. Zahedan J. Res. Med. Sci. ZJRMS 14, 73–78.

Forlenza, M.J., Miller, G.E., 2006. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. Psychosom. Med. 68, 1–7. https://doi.org/10.1097/01.psy.0000195780.37277.2a

Fujiwara, Y., Ihara, K., Hachisu, M., Suzuki, H., Kawai, H., Sakurai, R., Hirano, H., Chaves, P.H.M., Hashizume, M., Obuchi, S., 2021. Higher Serum Brain-Derived Neurotrophic Factor Levels Are Associated With a Lower Risk of Cognitive Decline: A 2-Year Follow Up Study in Community-Dwelling Older Adults. Front. Behav. Neurosci. 15. https://doi.org/10.3389/fnbeh.2021.641608

Günak, M.M., Billings, J., Carratu, E., Marchant, N.L., Favarato, G., Orgeta, V., 2020. Post-traumatic stress disorder as a risk factor for dementia: systematic review and meta-analysis. Br. J. Psychiatry 217, 600–608. https://doi.org/10.1192/bjp.2020.150

Havelka Mestrovic, A., Tudor, L., Nedic Erjavec, G., Nikolac Perkovic, M., Svob Strac, D., Kovacic Petrovic, Z., Pivac, N., 2020. The impact of BDNF Val66Met on cognitive skills in veterans with posttraumatic stress disorder. Neurosci. Lett. 735, 135235. https://doi.org/https://doi.org/10.1016/j.neulet.2020.135235

Havelka Mestrovic, A., Tudor, L., Nikolac Perkovic, M., Nedic Erjavec, G., Kovacic Petrovic, Z., Svob Strac, D., Konjevod, M., Pivac, N., 2018. Significant association between catechol-O-methyltransferase (COMT) Val(158/108)Met polymorphism and cognitive function in veterans with PTSD. Neurosci. Lett. 666, 38–43. https://doi.org/10.1016/j.neulet.2017.12.033

Hayes, J.P., Hayes, S.M., Mikedis, A.M., 2012. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. Biol. Mood Anxiety Disord. 2, 9. https://doi.org/10.1186/2045-5380-2-9

Kang, B., Xu, H., McConnell, E.S., 2019. Neurocognitive and psychiatric comorbidities of posttraumatic stress disorder among older veterans: A systematic review. Int. J. Geriatr. Psychiatry 34, 522–538. https://doi.org/10.1002/gps.5055

Karl, A., Schaefer, M., Malta, L.S., Dörfel, D., Rohleder, N., Werner, A., 2006. A meta-analysis of structural brain abnormalities in PTSD. Neurosci. Biobehav. Rev. 30, 1004–1031. https://doi.org/https://doi.org/10.1016/j.neubiorev.2006.03.004

Kim, B.Y., Lee, S.H., Graham, P.L., Angelucci, F., Lucia, A., Pareja-Galeano, H., Leyhe, T., Turana, Y., Lee, I.R., Yoon, J.H., Shin, J. Il, 2017. Peripheral Brain-Derived Neurotrophic Factor Levels in Alzheimer's Disease and Mild Cognitive Impairment: a Comprehensive Systematic Review and Meta-analysis. Mol. Neurobiol. 54, 7297–7311. https://doi.org/10.1007/s12035-016-0192-9

Laske, C., Stellos, K., Hoffmann, N., Stransky, E., Straten, G., Eschweiler, G.W., Leyhe, T., 2011. Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. Int. J. Neuropsychopharmacol. 14, 399–404. https://doi.org/10.1017/S1461145710001008

Laske, C., Stransky, E., Leyhe, T., Eschweiler, G.W., Wittorf, A., Richartz, E., Bartels, M., Buchkremer, G., Schott, K., 2006. Stage-dependent BDNF serum concentrations in Alzheimer's disease. J. Neural Transm. 113, 1217–1224. https://doi.org/10.1007/s00702-005-0397-y

Lee, M.-S., Anumagalla, P., Pavuluri, M.N., 2021. Individuals with the post-traumatic stress disorder process emotions in subcortical regions irrespective of cognitive engagement: a meta-analysis of cognitive and emotional interface. Brain Imaging Behav. 15, 941–957. https://doi.org/10.1007/s11682-020-00303-9

Leyhe, T., Stransky, E., Eschweiler, G.W., Buchkremer, G., Laske, C., 2008. Increase of BDNF serum concentration during donepezil treatment of patients with early Alzheimer's disease. Eur. Arch. Psychiatry Clin. Neurosci. 258, 124–128. https://doi.org/10.1007/s00406-007-0764-9

Marx, B.P., Doron-Lamarca, S., Proctor, S.P., Vasterling, J.J., 2009. The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes

among Iraq-deployed Army soldiers. J. Int. Neuropsychol. Soc. 15, 840–852. https://doi.org/10.1017/S1355617709990488

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

Mojtabavi, H., Saghazadeh, A., van den Heuvel, L., Bucker, J., Rezaei, N., 2020. Peripheral blood levels of brain-derived neurotrophic factor in patients with post-traumatic stress disorder (PTSD): A systematic review and meta-analysis. PLoS One 15, e0241928. https://doi.org/10.1371/journal.pone.0241928

Nedic Erjavec, G., Nikolac Perkovic, M., Tudor, L., Uzun, S., Kovacic Petrovic, Z., Konjevod, M., Sagud, M., Kozumplik, O., Svob Strac, D., Peraica, T., Mimica, N., Havelka Mestrovic, A., Zilic, D., Pivac, N., 2021. Moderating Effects of BDNF Genetic Variants and Smoking on Cognition in PTSD Veterans. Biomolecules 11, 641. https://doi.org/10.3390/biom11050641

Ng, T.K.S., Ho, C.S.H., Tam, W.W.S., Kua, E.H., Ho, R.C.-M., 2019. Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 20, 257. https://doi.org/10.3390/ijms20020257

Notaras, M., van den Buuse, M., 2020. Neurobiology of BDNF in fear memory, sensitivity to stress, and stress-related disorders. Mol. Psychiatry 25, 2251–2274. https://doi.org/10.1038/s41380-019-0639-2

Parslow, R.A., Jorm, A.F., 2007. Pretrauma and posttrauma neurocognitive functioning and PTSD symptoms in a community sample of young adults. Am. J. Psychiatry 164, 509–515. https://doi.org/10.1176/ajp.2007.164.3.509

Sagud, M., Nikolac Perkovic, M., Vuksan-Cusa, B., Maravic, A., Svob Strac, D., Mihaljevic Peles, A., Zivkovic, M., Kusevic, Z., Pivac, N., 2016. A prospective, longitudinal study of platelet serotonin and plasma brain-derived neurotrophic factor concentrations in major depression: effects of vortioxetine treatment. Psychopharmacology (Berl). 233, 3259–3267. https://doi.org/10.1007/s00213-016-4364-0

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

Shulman, K.I., 2000. Clock-drawing: is it the ideal cognitive screening test? Int. J. Geriatr. Psychiatry 15, 548–561. https://doi.org/10.1002/1099-1166(200006)15:6<548::aid-gps242>3.0.co;2-u

Ventriglia, M., Zanardini, R., Bonomini, C., Zanetti, O., Volpe, D., Pasqualetti, P., Gennarelli, M., Bocchio-Chiavetto, L., 2013. Serum Brain-Derived Neurotrophic Factor Levels in Different Neurological Diseases. Biomed Res. Int. 2013, 901082. https://doi.org/10.1155/2013/901082

World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310, 2191–2194. https://doi.org/10.1001/jama.2013.281053

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K.E., Neylan, T., Kluse, M., Marmar, C., 2010. Posttraumatic stress disorder and risk of dementia among US veterans. Arch. Gen. Psychiatry 67, 608–613. https://doi.org/10.1001/archgenpsychiatry.2010.61

Zhang, L., Li, X.-X., Hu, X.-Z., 2016. Post-traumatic stress disorder risk and brain-derived neurotrophic factor Val66Met. World J. psychiatry 6, 1–6. https://doi.org/10.5498/wjp.v6.i1.1

Table 1. Comparison of age, MMSE scores and CDT scores between healthy controls (HC), veterans with PTSD, subjects with MCI and AD patients. Data are presented as median (25th - 75th percentile).

	Subject groups				Kruskal-Wallis ANOVA (*df*=3)	
	HC (*n*=120)	**PTSD** (*n*=120)	**MCI** (*n*=47)	**AD** (*n*=76)	***H***	***p***
Age (years)	59.0 (50.5-68.5)	59.0 (55.0-65.0)	72.0[a,b] (67.5-76.5)	75.0[a,b] (69.5-79.5)	141.29	<0.001
MMSE	30.0 [c] (30.0-30.0)	25.0[a,c] (22.0-25.0)	26.0[a,c] (22.5-27.0)	17.5[a] (13.0-21.0)	296.67	<0.001
CDT	5.0 (5.0-5.0)	3.0[a] (1.0-3.0)	4.0[a,b,c] (3.0-5.0)	1.0[a,b] (0.0-2.0)	200.29	<0.001

[a] <0.050 vs. HC (Dunn's multiple comparisons test); [b] <0.050 vs. PTSD (Dunn's multiple comparisons test); [c] <0.050 vs. AD (Dunn's multiple comparisons test)

Table 2. Correlation between plasma BDNF concentration and age, MMSE scores and CDT scores in healthy controls (HC), veterans with PTSD, subjects with MCI or AD, and in all included subjects.

	Plasma BDNF (ng/ml)							
	HC (*n*=120)		**PTSD** (*n*=120)		**MCI** (*n*=47)		**AD** (*n*=76)	
	r_s	***p***	r_s	***p***	r_s	***p***	r_s	***p***
Age	-0.022	0.813	0.015	0.874	-0.037	0.804	0.091	0.436
MMSE	-0.110	0.232	-0.014	0.880	-0.183	0.219	-0.201	0.082
CDT	0.102	0.269	-0.017	0.850	0.025	0.866	-0.051	0.664

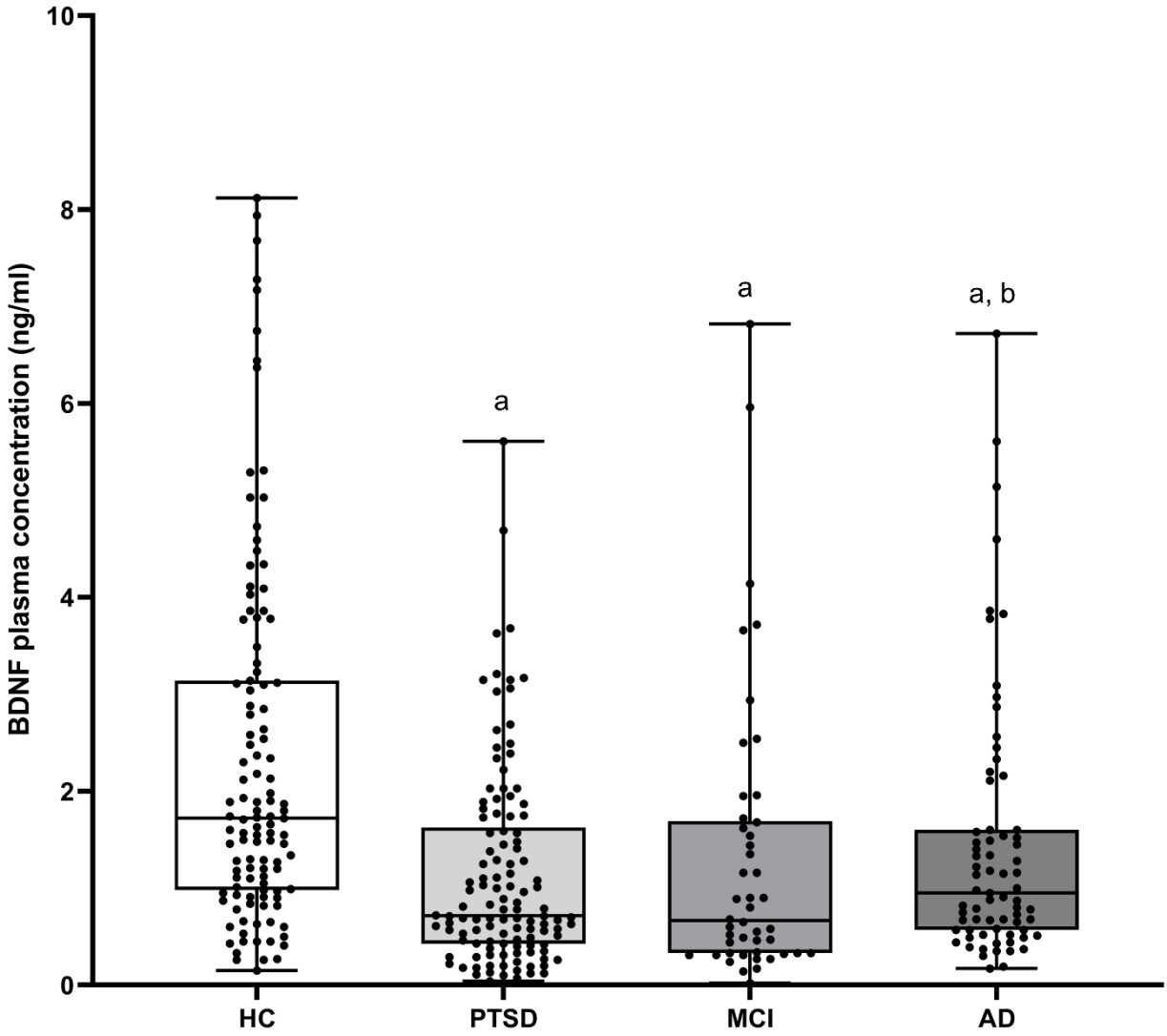

Figure 1. BDNF plasma concentration in healthy controls (HC), veterans PTSD, subjects with MCI and AD patients.

[a] <0.050 vs. HC (Dunn's multiple comparisons test); [b] <0.050 vs. PTSD (Dunn's multiple comparisons test)