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BRIEF REPORT

The association between brain-derived neurotrophic factor Val66Met variants and psychotic symptoms in posttraumatic stress disorder

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Abstract

Objectives. Psychotic symptoms frequently occur in veterans with combat-related posttraumatic stress disorder (PTSD). Brain-derived neurotrophic factor (BDNF) plays a major role in neurodevelopment, neuro-regeneration, neurotransmission, learning, regulation of mood and stress responses. The Met allele of the functional polymorphism, BDNF Val66Met, is associated with psychotic disorders. This study intended to assess whether the Met allele is overrepresented in unrelated Caucasian male veterans with psychotic PTSD compared to veteran controls. *Methods.* The BDNF Val66Met variants were genotyped in 576 veterans: 206 veterans without PTSD and 370 veterans with PTSD subdivided into groups with or without psychotic features. *Results.* Veterans with psychotic PTSD were more frequently carriers of one or two Met alleles of the BDNF Val66Met polymorphism than veterans with PTSD without psychotic features and veterans without PTSD. *Conclusions.* The study shows that veterans with psychotic PTSD carried more Met alleles of the BDNF Val66Met than non-psychotic veterans with PTSD or veterans without PTSD. The results might add further support to the hypothesis that psychotic PTSD is a more severe subtype of PTSD.

Key words: *BDNF, polymorphism, PTSD, psychosis, veterans*

Introduction

Psychotic symptoms, such as auditory and visual hallucinations, delusional thinking, paranoia and violent thoughts, are often present in combat veterans with posttraumatic stress disorder (PTSD) (Sautter et al. 2003; Pivac et al. 2004; Kozaric-Kovacic et al. 2005; Kozaric-Kovacic and Pivac 2007; Braakman et al. 2008, 2009; Shevlin et al. 2010). PTSD with secondary psychotic features occurs in 30–40% of patients with combat-related PTSD (Hamner et al. 2004; Kozaric-Kovacic and Borovecki 2005), has a complex clinical presentation and is often misdiagnosed and undertreated. Veterans with PTSD and comorbid psychotic disorder have a greater burden of disease and more severe symptoms compared to veterans with PTSD without psychotic features (Hamner et al. 2004; Shevlin et al. 2010). Although there is no separate classification of a psychotic PTSD subtype in the present diagnostic instruments, a recent meta-analysis (Braakman et al. 2008) and a review based on data from the National Comorbidity Survey (Shevlin et al. 2010) suggested that PTSD with secondary psychotic features might be a separate diagnostic entity. This suggestion is crucial for pharmacological and psychotherapy treatment of psychotic PTSD, which is different and more complex than the therapy of PTSD without psychotic features (Hamner et al. 2004; Braakman et al. 2008).

Brain-derived neurotrophic factor (BDNF) is a neurotrophin located in the hippocampus, neocortex, amygdala, cerebellum and hypothalamus. BDNF plays a role in neuro-development, survival and

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neuronal function, synaptic plasticity, memory formation and processing, learning, mood, cognition, molecular and behavioural responsiveness to stress and regulates serotonergic, glutamatergic, cholinergic, and dopaminergic neurotransmission (Russo-Neustadt 2003; Gratacos et al. 2007). Therefore, it is a good candidate for various psychiatric disorders including PTSD. The most frequently studied BDNF single nucleotide polymorphism (SNP) is a single base pair substitution G196A (Val66Met), in which valine (Val) is replaced with methionine (Met) at position 66 in the pro-BDNF sequence (Egan et al. 2003). The Met variant of the BDNF Vall66Met SNP is associated with decreased activity-dependent BDNF secretion from the cultured hippocampal neurons (Egan et al. 2003). The combined Met/Met and Met/Val genotypes are more frequently found in suicide victims exposed to stressful life events in childhood compared to those without stressful experiences (Pregelj et al. 2011), in suicide completers who committed suicide with violent methods compared to controls (Pregelj et al. 2011) and in Alzheimer's patients with psychotic compared to those with non-psychotic symptoms (Pivac et al. 2011). A few studies evaluated the association between BDNF Val66Met and PTSD, with small numbers of patients, and found no significant association (Lee et al. 2006; Zhang et al. 2006). A hallmark of PTSD is a reduced ability to suppress the traumatic fearful memories, and the Met allele of the BDNF Val66Met has been reported to be significantly associated with a decreased activation of the ventro-medial prefrontal cortex, indicating impaired fear extinction (Frielingsdorf et al. 2010). Since Met carriers are overrepresented in schizophrenia and psychotic disorders (Gratacos et al. 2007), although see also (Kawashima et al. 2009), the hypothesis of this study was that the Met allele of the BDNF Val66Met SNP would be overrepresented in veterans with PTSD with psychotic features. As there are significant ethnic differences in the BDNF Val66Met (Pivac et al. 2009), the aim of the study was to assess the distribution of the BDNF Val66Met variants in large groups of Caucasian male veterans, exposed to a comparable combat-related traumatic experience, subdivided into veterans with or without PTSD, with or without psychotic symptoms.

Methods and materials

Participants

The study included 576 male unrelated Caucasians from Croatia, older than 18 years (mean age 42.3 ± 7.1 years), who were active duty soldiers between 1991–1995 in the Croatian armed forces, with comparable traumatic combat experience (3.0 ± 1.0 years). Subjects were categorized as veterans with current and chronic PTSD ($N = 370$, 76 with and 294 without secondary psychotic features) and combat exposed veterans who did not develop PTSD ($N = 206$); the groups were matched on age (average age 40.75 ± 4.55 years, range 34–59). Veterans were recruited from the University Hospital Dubrava, from 2003 to 2009, and 8–14 years elapsed since trauma. The majority of war veterans were married (69%) and 71% finished high schools. All veterans had similar social and cultural backgrounds, were all Croatian citizens, born and living in Croatia. The diagnostic procedures and inclusion and exclusion criteria have been described in detail previously (Kozaric-Kovacic and Pivac 2007). The subjects were seeking treatment in our Veterans PTSD program. The diagnosis of PTSD was made by a team of psychiatrists during a comprehensive screening evaluation, using the Structured Clinical Interview for DSM-IV (SCID), and based on DSM-IV criteria, while psychotic and PTSD symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Clinician Administered PTSD Scale (CAPS), respectively. Veterans were subdivided into those with mild (range 46–65 CAPS scores), moderate (range 66–95 CAPS scores) and severe (range 96–136 CAPS scores) PTSD symptoms. The exclusion criteria were a history of any psychiatric disorders, comorbid substance abuse, and traumatic experience other than combat-related experience. Patients with comorbid depression (MDD) and anxious depressive disorder, which were secondary to the primary PTSD, were included. Psychotic symptoms were more strongly associated with characteristics of PTSD (they were combat-related: scenes of war, ugly faces of dead people and slaughtered, massacred, or disintegrated (dismembered) bodies, images of screaming soldiers or enemies trying to kill them, sounds of fire, bombing, shell and rocket fire, irrational guilty feelings, etc.), than with characteristics of a psychosis or major depressive disorder with psychotic features. Psychotic symptoms were defined as evidence of hallucinations or delusions during the mental status examination, with a score of at least 4 (moderate severity) on the positive items on the PANSS (delusions, conceptual disorganization, hallucinatory behaviour, suspiciousness/persecution), two negative items (emotional withdrawal and passive/apathetic social withdrawal), eight items out of the general psychopathology subscale (guilt feelings, depression, motor retardation, unusual thought content, disorientation, disturbance of volition, poor impulse control and active social avoidance), and two items on the supplementary subscale (anger and affective lability). The procedure

was fully explained and all veterans provided written informed consent to the treating psychiatrists. The study was approved by the Ethics committee of the University Hospital Dubrava and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Genetic analysis

Blood samples (8 ml) were drawn using plastic syringes with 2 ml of acid citrate dextrose anticoagulant at 08.00 h. The DNA was isolated from blood using the "salting-out" method (Miller et al. 1988). The dbSNP ID for Val66Met is rs6265. The BDNF Val66Met polymorphism was genotyped in a total volume of 10 µl, containing 30–100 ng of DNA, with the ABI Prism 7000 Sequencing Detection System apparatus (ABI, Foster City, USA). Genotyping was carried out using the Taqman-based allele-specific polymerase chain reaction assay, according to manufacturer's instructions. The primers and probes were purchased from Applied Biosystems as TaqMan® Drug Metabolism Genotyping Assay (assay ID: C_11592758_10).

Statistics

The results, expressed as means ± standard deviations or numbers and percents, were evaluated with Sigma Stat 3.5 (Jandell Scientific Corp. San Raphael, CA, USA). Differences in clinical scores or age were assessed using one-way analysis of variance (ANOVA) and Tukey's test. The distribution of the BDNF genotypes and the presence of the Hardy–Weinberg equilibrium (HWE) were evaluated by a χ^2-test. The power of calculation (*power*), which should be 0.800, was evaluated using Sigma Stat 3.5. Standardized residuals (*R*) were evaluated using Microsoft Excel to determine which genotype contributed to the significance in the χ^2-test statistics, and if the absolute *R* value was greater than 2.00 (http://www.acastat.com/Statbook/chisqresid.htm), it revealed a major influence on a significant χ^2 statistics. The level of significance was set to $\alpha = 0.05$, with two-tailed *P* values.

Results

The clinical variables for the 370 veterans with PTSD are presented in Table I. As expected, veterans with psychotic PTSD had significantly higher total and subscale scores in the CAPS and PANSS than veterans with PTSD without psychotic symptoms (Table I).

The distribution of the BDNF Val66Met variants was determined in all 576 veterans (Table II). The genotype distribution in all PTSD veterans ($\chi^2 = 0.828$; df = 1; $P = 0.363$) or in veterans without PTSD ($\chi^2 = 1.927$; df = 1; $P = 0.162$) was in the expected HWE. However, when veterans with PTSD were subdivided into veterans without or with psychotic features, there was a significant deviation from the HWE in veterans with psychotic PTSD ($\chi^2 = 4.761$; df = 1; $P = 0.029$), but not in veterans with PTSD without psychotic symptoms ($\chi^2 = 0.040$; df = 1; $P = 0.842$).

The frequency of the Met/Met, Met/Val and Val/Val genotypes ($\chi^2 = 2.426$; df = 2; $P = 0.297$), Met and Val alleles ($\chi^2 = 1.625$; df = 1; $P = 0.202$), or Met carriers (the combined Met/Met and Met/Val genotypes) versus the homozygous Val/Val genotype ($\chi^2 = 1.095$; df = 1; $P = 0.295$) did not differ significantly when all veterans with PTSD (with and without psychotic symptoms) were compared to veterans without PTSD. To evaluate the possible effect of the severity of PTSD symptoms, or the presence of the comorbid depression (MDD and anxious depressive disorder), regardless of the

Table I. Clinical variables in veterans with PTSD, subdivided into those with psychotic features (psychotic PTSD) and veterans with PTSD without psychotic features (PTSD).

Mean ± SD	PTSD with psychotic features (*n* = 76)	PTSD without psychotic features (*n* = 294)	ANOVA; df = 1,368; *power* = 1.00	
			F	*P*
CAPS total scores	104.1 ± 8.0	69.0 ± 12.1	571.051	0.001
PANSS total scores	103.9 ± 12.8	53.7 ± 5.6	2619.059	0.001
PANSS positive subscale scores	27.2 ± 3.8	7.6 ± 1.3	5441.472	0.001
PANSS negative subscale scores	13.7 ± 3.4	8.9 ± 2.0	242.262	0.001
PANSS general psychopathology subscale scores	52.1 ± 6.7	30.7 ± 4.8	1016.569	0.001
PANSS supplementary items subscale scores	10.4 ± 1.7	6.1 ± 3.7	96.197	0.001
Age (years)	42.03 ± 6.83	43.37 ± 6.44	2.681	0.109
Range (years)	(29 – 60)	(29 – 61)		

n is the number of subjects. CAPS, Clinician Administered PTSD Scale; PANSS, Positive and Negative Syndrome Scale; *power* = power of calculation.

Table II. The BDNF genotype and allele count and frequencies (percentages) in male veterans with PTSD with psychotic features (psychotic PTSD), with PTSD without psychotic features (with PTSD) and in veterans without PTSD.

BDNF Val66Met	Veterans with PTSD with psychotic features *n* (%)	Veterans with PTSD without psychotic features *n* (%)	Veterans without PTSD *n* (%)
Met/Met genotype	1 (1.3)	11 (3.7)	3 (1.4)
Met/Val genotype	35 (46.0)	89 (30.3)	63 (30.6)
Val/Val genotype	40 (52.6)	194 (66.0)	140 (68.0)
$\chi^2 = 10.082$; df = 4; $P = 0.039$; *power* = 0.718; $R = 2.08$ for Met/Val genotype in veterans with psychotic PTSD			
Met allele	37 (24.3)	111 (18.9)	60 (14.9)
Val allele	115 (75.7)	477 (81.1)	343 (85.1)
$\chi^2 = 7.002$; df = 2; $P = 0.030$; *power* = 0.653; $R = 1.78$ for Met allele in veterans with psychotic PTSD			
Met carriers	36 (47.4)	100 (34.0)	66 (32.0)
Val homozygotes	40 (52.6)	194 (66.0)	140 (68.0)
$\chi^2 = 6.023$; df = 2; $P = 0.049$; *power* = 0 .578; $R = 1.81$ for Met carriers in veterans with psychotic PTSD			

n is the number of subjects. Frequencies (%) are shown in parentheses. BDNF: brain-derived neurotrophic factor; Met, methonine; Met carriers, the combined Val/Met + Met/Met genotypes; Val, valine; *power* = power of calculation; *R* = absolute value of the residual.

presence of psychotic symptoms, on the distribution of the BDNF Val66Met variants, veterans were subdivided into those with mild, moderate and severe PTSD symptoms, and in those with or without comorbid depression. There were no significant differences in the frequency of the BDNF Val66Met genotypes ($\chi^2 = 5.532$; df = 4; $P = 0.237$, *power* = 0.425), alleles ($\chi^2 = 1.00$; df = 2; $P = 0.605$, *power* = 0.127), or Met carriers versus Val/Val homozygotes ($\chi^2 = 1.356$; df = 2; $P = 0.508$) between all veterans with PTSD with mild, moderate and severe PTSD symptoms. The frequency of the genotypes ($\chi^2 = 2.889$; df = 2; $P = 0.236$, *power* = 0.297), alleles ($\chi^2 = 2.557$; df = 1; $P = 0.110$, *power* = 0.342) or Met carriers versus Val/Val homozygotes ($\chi^2 = 1.959$; df = 1; $P = 0.162$, *power* = 0.270) did not differ significantly between all veterans with PTSD comorbid with MDD and anxious depressive disorder compared to veterans with PTSD without any comorbidities.

Significant differences were detected in the frequencies of the BDNF Val66Met variants between veterans with PTSD with or without psychotic symptoms and veterans without PTSD (Table II). These differences were the result of the significantly higher frequency of the Met/Val genotype in veterans with psychotic PTSD ($R = 2.08$) compared to other groups.

Genotype groups (Met/Met, Met/Val or Val/Val) did not differ significantly in the mean total and subscale scores in the CAPS and PANSS in veterans with PTSD with or without psychotic symptoms (data available on request).

Discussion

This is the first evidence of the significant differences in the frequencies of the BDNF Val66Met variants in veterans with and without combat-related PTSD, further subdivided into PTSD groups with or without psychotic symptoms. In line with the data showing that the Met allele of the BDNF Val66Met polymorphism is associated with psychotic disorders (Gratacos et al. 2007), our results supported our hypothesis that veterans with psychotic PTSD are more frequently carriers of the Met/Val genotype, and the Met allele than veterans with PTSD without psychotic symptoms, or veterans without PTSD. In addition, this finding is consistent with our recent results showing that psychotic male patients with Alzheimer's disease were more frequently Met carriers than carriers of the Val/Val homozygous genotype of the BDNF Val66Met polymorphism (Pivac et al. 2011). We are not aware of any direct comparison of the BDNF Val66Met SNP distribution between psychotic and non-psychotic subtypes of PTSD. In agreement with other studies (Lee et al. 2006; Zhang et al. 2006), no significant association was found in the frequency of the BDNF Val66Met variants between veterans with or without PTSD.

Veterans with psychotic PTSD have been shown to be non-responders to antidepressant treatment, however they respond well to monotherapy with atypical antipsychotics (Pivac et al. 2004; Kozaric-Kovacic et al. 2005; Kozaric-Kovacic and Pivac 2007). As shown by the significantly higher total and subscale scores in the CAPS and PANSS, veterans with psychotic PTSD had more severe PTSD symptoms than veterans with PTSD who did not develop psychotic symptoms. The categorization of veterans into those with mild, moderate, and severe PTSD symptoms (according to the CAPS scores) showed that the Met allele status was strongly associated with psychotic symptoms and the more severe type of PTSD, but not with the severe type of PTSD in

the absence of psychotic symptoms. Although MDD is significantly associated with the Met allele of BDNF in male subjects (Verhagen et al. 2010), our results showed no significant association between the BDNF polymorphism and MDD in veterans with PTSD, compared to veterans with PTSD without any comorbidity. These data are in line with the evidence that particular peripheral markers, such as concentrations of plasma cortisol, cerebrospinal fluid corticotrophin releasing hormone, platelet serotonin, and activity of platelet monoamine oxidase and plasma dopamine beta hydroxylase, are higher in psychotic compared to non-psychotic PTSD (Sautter et al. 2003; Hamner et al. 2004; Pivac et al. 2006, 2007; Braakman et al. 2008, 2009; Shevlin et al. 2010). We might speculate that early intervention for this more severe subtype of PTSD, complicated with psychotic features, would be treatment with atypical antypsychotics as monotherapy, or as add-on therapy with antidepressants. In addition, our data might also suggest that therapy aimed to normalize BDNF function (Frielingsdorf et al. 2010), would improve treatment response in PTSD, especially in the psychotic subtype of PTSD, which is associated with a higher frequency of the BDNF Met allele.

Although the advantage of this study was the inclusion of 576 unrelated Caucasian male veterans controlled for the severity of PTSD and comorbid depression, who were exposed to comparable traumatic experiences, and therefore the effect of ethnicity and gender on BDNF Val66Met was excluded, a possible limitation is a relatively small sample size when veterans were subdivided into groups with or without PTSD, and/or psychotic symptoms, as the power of calculation decreased below the desired 0.800. Therefore, the risk of type II error might be resolved by a large, multicentre study comparing BDNF polymorphisms in psychotic versus non-psychotic PTSD. Despite this limitation, this study represents the first evidence of a higher frequency of one or two Met alleles of the BDNF Val66Met in veterans with psychotic PTSD compared to veterans with PTSD without psychotic features or without PTSD. Since this study included only veterans with combat-related PTSD, the results cannot be readily generalized to other trauma victim populations, and therefore studies with other PTSD populations are warranted.

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Statement of Interest

None to declare.

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