Research paper

The interaction of BDNF Val66Met, PTSD, and child abuse on psychophysiological reactivity and HPA axis function in a sample of Gulf War Veterans

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ABSTRACT

Introduction: While the BDNF Val66Met polymorphism has been linked to various psychological disorders, limited focus has been on its relationship to posttraumatic stress disorder (PTSD) and early traumas such as child abuse. Therefore, we assessed whether Val66Met was associated with fear potentiated psychophysiological response and HPA axis dysfunction and whether PTSD status or child abuse history moderated these outcomes in a sample of Veterans.

Methods: 226 and 173 participants engaged in a fear potentiated acoustic startle paradigm and a dexamethasone suppression test (DST) respectively. Fear conditions included no, ambiguous, and high threat conditions. Psychophysiological response measures included electromyogram (EMG), skin conductance response (SCR), and heart rate. The Clinician Administered PTSD Scale (CAPS) and the Trauma History Questionnaire (THQ) were used to assess PTSD status and child abuse history respectively.

Results: Met allele carriers exhibited greater SCR magnitudes in the no and ambiguous threat conditions \(p<0.01\) and \(p<0.05\) respectively. Met carriers with PTSD exhibited greater physiological response magnitudes in the ambiguous (SCR, \(p<0.001\)) and high threat conditions (SCR and heart rate, both \(p \leq 0.005\)). Met carrier survivors of child abuse exhibited blunted heart rate magnitudes in the high threat condition \(p<0.01\). Met allele carriers with PTSD also exhibited greater percent cortisol suppression \(p<0.005\).

Limitations: Limitations included small sample size and the cross-sectional nature of the data.

Conclusions: The Val66Met may impact PTSD susceptibility differentially via enhanced threat sensitivity and HPA axis dysregulation. Child abuse may moderate Val66Met’s impact on threat reactivity. Future research should explore how neuronal mechanisms might mediate this risk.

1. Introduction

Brain derived neurotropic factor (BDNF), is expressed widely throughout the central and peripheral nervous systems and is involved in neurogenesis, cell survival, differentiation, and synapse formation (Martinowich and Lu, 2008). BDNF is concentrated in neural structures critical to learning and memory (e.g. hippocampus, cerebellum; Conner et al., 1997). Earlier research has focused on whether BDNF levels (e.g. serum or plasma) were associated with trauma-related disorders such as posttraumatic stress disorder (PTSD). While some findings have been contradictory, research suggests a relationship between BDNF levels and PTSD such that people with PTSD show lower levels of BDNF (see Suliman et al., 2013 for a review). Nonetheless, it remains unclear how BDNF impacts brain function after trauma exposure. Research linking genes that modulate BDNF, such as BDNF Val66Met, to markers associated with posttraumatic stress symptoms have attempted to resolve some of these inconsistencies (Rakofsky et al., 2012).

Val66Met is a common single nucleotide polymorphism (SNP) that results in a substitution of methionine (Met) for valine (Val) at codon 66 in the pro-domain of the human BDNF protein (Egan et al., 2003). Research has shown that this methionine substitution results in impaired BDNF intercellular packaging and secretion regulation, which may impact the stress response, possibly through hippocampal (Egan et al., 2003) and hypothalamic dysregulation (Tapia-
Arancibia et al., 2004). Given the common occurrence of this SNP, investigations have attempted to link Val66Met to PTSD and other stress-related disorders (Frielingsdorf et al., 2010). Evidence suggests the Met allele may be linked to neuroticism (a possible risk factor for PTSD), anxiety, and depression (Engelhard and van den Hout, 2007; Gatt et al., 2009). Met allele carriers also appear to be at a greater risk for PTSD, possibly due to BDNF overexpression (Zhang et al., 2014). In fear conditioning paradigms, met allele carriers exhibited increased activity in neural structures (e.g. the insula, amygdala, and hippocampus), which are in turn responsible for the regulation of the hypervigilance and heightened startle symptoms associated with PTSD (Lonsdorf et al., 2014).

Recent studies exploring the Val66Met link to PTSD have focused on the fear-potentiated startle response, the largely unconscious defensive psychophysiological response to sudden or threatening stimuli (Ramirez-Moreno and Sejnowski, 2012) and hypothalamic-pituitary-adrenal (HPA) axis reactivity. However, results have been equivocal. For example, one novel investigation using a virtual reality based fear conditioning paradigm revealed that Met allele carriers had difficulty differentiating between fear and safety cues and had stronger startle responses to novel stimuli compared to Val-Val carriers (Mühlberger et al., 2014). Conversely, a recent study that used an acoustic startle paradigm found homozygous Val-Val participants had greater startle magnitudes compared to Met allele carriers in a sample of healthy adults and children (Armbuster et al., 2016). Similarly, one group found Met allele carriers to have an attenuated cortisol response to social stress (Alexander et al., 2010) while others found the opposite (Armbuster et al., 2016).

Early trauma such as child abuse impacts brain development across the life span (Dannlowski et al., 2012) and is a strong risk factor for PTSD (Duncan et al., 1996). Key structures in the limbic system that are rich with BDNF continue to develop throughout childhood (Giedd et al., 1996). Animal models suggest neural BDNF expression is adversely affected by early environmental insults (Ognibene et al., 2008). Thus, lower BDNF levels as a result of early trauma and genetic predisposition may increase the risk of adverse psychological outcomes in humans. In a sample of depressed participants, Met allele carriers who were exposed to child abuse had lower BDNF serum levels compared to Val-Val carriers. In contrast Met allele carriers without child abuse exposure had higher BDNF levels compared to Val-Val counterparts (Elzenga et al., 2011). While evidence suggests adult survivors of child abuse exhibit greater startle response magnitudes compared to individuals who were not exposed to child abuse (Jovanovic et al., 2009), it remains unclear how Val66Met might impact startle response within the context of early trauma. Thus, exploring a possible Val66Met × child abuse interaction on psychophysiological response and HPA axis reactivity would move us closer to understanding the etiology of PTSD as well as differential posttraumatic stress responses in trauma-exposed individuals.

We investigated whether the BDNF Val66Met polymorphism is associated with psychophysiological reactions to startling sounds over successive trials across three different threat conditions in a sample of Veterans. We also assessed whether this SNP was associated with HPA axis reactivity to a dexamethasone suppression test (DST). We hypothesized Met allele carriers would exhibit greater psychophysiological response magnitudes compared to homozygous Val-Val carriers. We also hypothesized Met allele carriers would exhibit greater dexamethasone suppression compared to Val-Val allele carriers. In addition, we examined whether Val66Met interacts with either child abuse or PTSD diagnosis on psychophysiological response and cortisol levels after DST.

2. Materials and methods

2.1. Participants

We conducted secondary data analyses on Veterans from a cross-sectional study of the effects of Gulf War deployment on the brain. Gulf War Veterans were recruited between 2002 and 2007 through contacts with physicians at VA clinics in Northern California using methods described elsewhere (Apfel et al., 2011). Inclusion criteria for the broader study was being a US veteran of the First Persian Gulf War; exclusion criteria included severe physical impairment or medical illness, current or lifetime history of psychosis or of suicidal or homicidal ideation, and a history of neurological or systemic illness affecting central nervous system functioning (for a complete list of exclusion criteria please see Apfel et al., 2011). The University of California San Francisco and Veterans Administration Committees on Human Research and the Department of Defense Human Subjects Research Review Board approved all research. This research was carried out in accordance with The Code of Ethics of the World Medical Association and all participants provided consent to be included in this study. Of the 369 Veterans from the original sample, 226 of them engaged in the psychophysiological response task and provided a blood plasma sample from which we extracted and analyzed DNA. 149 Veterans were Val-Val carriers, 67 were Val-Met carriers, and 10 were homozygous Met-Met carriers in the overall sample. A subsample of 173 participants provided blood plasma samples and engaged in the DST. Of those, 119 were Val-Val carriers, 46 were Val-Met carriers, and 8 were Met-Met carriers. Both the overall samples and the DST subsample conformed to the Hardy-Weinberg equilibrium ($\chi^2 = 0.90; p = 0.63$ and $\chi^2 = 1.07; p = 0.26$ respectively) and there were no significant differences between the minor allele frequencies of the three most representative races in our sample regarding this particular SNP ($\chi^2 = 0.26; p = 0.61$; National Institutes of Health HapMap Project, Bethesda MD).

Demographic variables were obtained by self-report as prior literature has linked them to differential traumatic stress response (Neylan et al., 2005). Current PTSD symptoms were evaluated by a Ph.D. level clinical interviewer using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). Criterion A was used to assess whether participants had experienced any traumatic event in adulthood (DSM-IV-TR 4th ed., text rev.; APA, 2000). Participants were diagnosed with PTSD based upon frequency and severity of their CAPS scores (e.g. the “1, 2” rule) and the DSM-IV-TR algorithm. Of the ninety-four participants who were exposed to adult trauma, seventy-four endorsed military-related trauma exposure. Twenty participants reported non-military/civilian trauma exposure and of those, only two had PTSD and were retained in subsequent analyses. All subjects with PTSD had combat-related trauma exposure. Twenty-six participants reported paramilitary adult trauma exposure but none of these individuals had PTSD. Exposure to child abuse occurring prior to the age of 16 years old was assessed using the last six items of the Trauma History Questionnaire (Green, 1996).

2.2. Psychophysiological assessment

Three indices of psychophysiological response were collected by trained technicians, who were blind to participants’ psychometric status. The participant’s left eye blink electromyogram (EMG) activity, skin conductance response (SCR) level, and heart rate electrocardiograph EKG were assessed during a two-minute baseline period. Participants were fitted with headphones and told that they would hear potentially startling sounds. They were asked to focus their eyes on a monitor in front of them. A Coulbourn Instruments Lablinc V Modular System binaurally presented 106-dB(A), 40 ms white noise bursts with 0-millisecond rise and fall times separated by inter-trial intervals of between 30 and 50 seconds in each threat condition. In the “no threat” condition, participants were instructed that they would not be shocked...
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