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Understanding the Neurobiology of Fear Conditioning and Emergence of PTSD Psychobiology: Commentary on Blanchard et al

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Abstract

In this article we discuss the historical evolution of posttraumatic stress disorder (PTSD) following the Vietnam War with a focus on a article by Blanchard et al. published in the *Journal* in 1991, entitled: “Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with posttraumatic stress disorder” (Blanchard et al., 1991). In this commentary, we discuss the significance of this brief article and developments in the PTSD field before, during, and after the Blanchard publication. Within this context, we discuss the eventual recognition in both the clinical and scientific fields that PTSD had a major neurobiological foundation. Finally, we examine the key implication of these discoveries from an epidemiologic, clinical, and a public health perspective.

Keywords

Posttraumatic stress disorder; Vietnam War; Veterans; Epidemiology; Diagnostic and Statistical Manual of Mental Disorders; Psychobiology

Introduction

During the long publication history of *The Journal of Nervous Mental Disease*, 88 papers have been published that have focused on the Vietnam War, including studies of Vietnam veterans and war refugees. The first one published in the *Journal* on Vietnam veterans was on the prevalence of depressive disorder among US Army returnees by Helzer, et al. in September, 1976 (Helzer et al., 1976). The most recent one published was authored by Benedek in August, 2011 (Benedek, 2011). The Benedek article was a tribute to the late Dr. Eugene Brody’s tenure as Editor and Chief of the *Journal* and was titled, “Posttraumatic stress disorder from Vietnam to today: The evolution of understanding during Eugene Brody’s tenure at *The Journal of Nervous and Mental Disease*.” Since both of us were active on the professional scene in the 1970s when the posttraumatic stress disorder (PTSD) emerged as diagnostic construct (Boscarino at Yale and Figley at Purdue), and both of us are

Vietnam veterans with an interest in PTSD psychobiology, we comment on a brief article by Blanchard et al. published in the *Journal* in 1991 (Blanchard et al., 1991). This article was entitled “Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with posttraumatic stress disorder.”

At the time the Blanchard paper was published in 1991, about the mid-point between the end of the Vietnam War and where we are today, there were 36 articles published in the *Journal* in that decade related to the Vietnam War. While most of these articles in the 1990s focused on descriptive and clinical studies of PTSD among veterans, two focused on the biological aspects of PTSD, including the Blanchard paper. The Blanchard article was published little more 10 years after the PTSD diagnosis was promulgated with the publication of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)* (American Psychiatric Association, 1980). Around this time the VA had established an number of PTSD research centers at major academic centers around the country and, as we discuss below, the results of several large-scale Vietnam veteran studies were made publically available.

The research by Blanchard and colleagues studied plasma norepinephrine samples obtained before and after exposure to auditory stimuli reminiscent of combat. These investigators contrasted responses to these stimuli between two groups of male Vietnam veterans with combat experience. One group with PTSD and one group with no mental disorders. Their results showed a significant 30% rise in plasma norepinephrine for the PTSD group, with no change in the comparison group.

While the Blanchard study was modest by today’s standards (N= 21), it represented one of about a dozen studies published in the late 1980s and early 1990s that helped changed how we thought about PTSD. Specifically, it suggested that PTSD was more than a psychological state -- it had a biological foundation. Below we review developments in the PTSD field before, during, and after the publication of the Blanchard article in 1991 and discuss how we got to where we are today in the field.

The Emergence of PTSD as a Diagnostic Construct

Although United States’ involvement in Vietnam War officially ended in 1975, the impact of that conflict affected society in many ways (Boscarino, 2007). The Vietnam veteran returned home from a conflict that was controversial and unpopular. It became clear to healthcare professionals during the war and shortly afterwards that many returning veterans were experiencing postwar adjustment problems (Boscarino, 2007). During the early post-war period, the work of one of us stood out as a classic in stress research, because it well documented the emotional and psychological trauma many veterans began to manifest by war’s end (Figley, 1978a). Based on this work, *Stress Disorders among Vietnam Veterans: Theory, Research and Treatment*, and that of others, health care researchers and medical professionals in the late 1970s formulated specific etiologic models of the pathogenesis of mental disorders among Vietnam veterans (Boscarino, 2007). These efforts eventually culminated in the inclusion of PTSD in the DSM-III. The symptoms of this disorder came to include increased arousal following an event, re-experiencing of an event, and avoidance of stimuli associated with an event, all which onset after a traumatic event exposure. Once the diagnosis of PTSD emerged in the early 1980s, more accurate assessments of the scope and nature of traumatic stress injuries (and related disorders) among Vietnam veterans and others were possible. These studies of Vietnam veterans, as we suggest below, have lead to research developments and have accelerated the accumulation of knowledge related to the psychobiology of PTSD.

Although clinical evidence of the adverse psychological effects of combat exposure to go back as far the US Civil War, the etiology of these syndromes were neither clearly understood nor well defined (Boscarino, 2007). However, after review war trauma studies and other findings related to natural disaster and concentration camp survivors, in 1975 Dohrenwend concluded that there was clear and compelling evidence many individuals develop functional psychiatric disorders after extreme stressor exposures that were not present before these exposures (Dohrenwend, 1975). In 1973, two years before Dohrenwend's article was published, Robert Jay Lifton's classic book, *Home from the War: Vietnam Veterans - Neither Victims nor Executors*, was published (Lifton, 1973). Thus, within the span of about five years several major works related to the mental health status of Vietnam veterans and others exposed to psychological trauma were published, including the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (American Psychiatric Association, 1980). These publications created a major paradigm shift in American psychiatry, which would eventually affect the practice of psychiatry worldwide (Boscarino, 2007).

Initial Vietnam Veteran Studies

Initial studies of the postwar experiences of Vietnam veterans provided the first clinical and scientific evidence linking combat exposures in Vietnam to post-service adjustment difficulties also observed among previous veterans (Figley, 1978a; Figley, 1978b; Figley and Sprenkle, 1979; Figley and Southerly, 1980; Stretch and Figley, 1984). One difficulty was that these early studies were limited because of biases associated with using non-representative samples. Another problem was the use of non-standardized mental health measures or the use of measures that assessed only mental health symptoms. Thus, although clinicians had observed that individuals exposed to combat exhibited certain syndromes, linking these symptoms to past combat exposure was problematic because of existing methodological shortcomings at the time (Boscarino, 2007).

When DSM-III was being written in the 1970s, however, clinicians and others involved with Vietnam veterans were successful in eventually incorporating these syndromes into DSM-III under the diagnostic nomenclature defining post-traumatic stress disorder, originally labeled the "post-Vietnam syndrome" (Boscarino, 2007). Once PTSD was included in DSM-III, undertaking large-scale, systematic mental health studies of Vietnam veterans were feasible and had other research and clinical benefits. During this early research period, Robert Laufer's "Legacy Study," which while not based on a true probability study, stood out as a landmark investigation (Frey-Wouters and Laufer, 1986). This is because it included over 1,000 subjects (both Vietnam veterans and civilians) and used several standard symptom scales common in the 1960s and 1970s. At the time, this study provided the best assessment of the mental health status of Vietnam veterans and served as a benchmark for future studies (Boscarino, 2007). However, since the Legacy Study was considered primarily a "convenience" sample questions remained.

Later Vietnam Veteran Studies

As part of Public Law 98-160, the US Congress in 1983 mandated that research on Vietnam veterans be undertaken to determine "the prevalence and incidence of post-traumatic stress disorder and other psychological problems in readjusting to civilian life." In addition to Public Law 98-160, the US Congress passed other public laws mandating studies of the "health effects" of Vietnam service. As a consequence of these new laws, several well-designed cohort studies of Vietnam veterans were undertaken during the late 1980s (Boscarino, 2007). These studies avoided many of the shortcomings of previous research, chiefly because of advancements in sampling and measurement that evolved from earlier

research. One of these measurement advances included the availability of the *Diagnostic Interview Schedule* (DIS), which for the first time permitted the gathering of DSM-III psychiatric diagnoses by means of population surveys, something previously not possible (Robins et al., 1981). This later research confirmed that Vietnam combat veterans had higher rates of postwar adjustment difficulties, mental health disorders, medical morbidity, and higher postwar mortality than non-combat veterans or comparable non-veterans (Boscarino, 2007). Importantly, these studies indicated that the postwar adjustment difficulties and health problems experienced by these veterans were often due to combat exposures in Vietnam, not the selection biases or measurement inadequacies that had affected earlier studies (Boscarino, 1995).

Among these newer generation of studies was the *National Vietnam Veterans Readjustment Study* (NVVRS). This national study, which involved a large random sample of Vietnam theater and non-theater veterans (in addition to civilian, non-veterans), was considered one of the most comprehensive psychosocial assessment at the time it was conducted in the late 1980s. The NVVRS findings were a wake-up call for the American mental health community. Among other things, the NVVRS suggested that 15% of male Vietnam veterans were current PTSD cases (9% of female veterans) and that 31% of male veterans (27% of female veterans) had PTSD in their lifetimes (Kulka et al., 1990). The NVVRS further confirmed that the PTSD-positive veterans often had disrupted lives in almost every domain, including in employment and in family relationships.

As significant as the psychosocial consequences of the war were for Vietnam veterans, their postwar experiences went beyond only psychosocial outcomes. For example, the “Vietnam Experience Study” (VES), another national landmark study conducted in the late 1980s, revealed that Vietnam veterans had higher rates of postwar mortality in the first 5 years after discharge, primarily due to suicides, homicides, drug overdoses, and motor vehicle accidents (Centers for Disease Control, 1987). Furthermore, VES findings related to the postwar morbidity experienced by these veterans confirmed that Vietnam “theater” veterans as a group had higher rates of health care utilization and reported themselves to be in poorer physical health, in comparison to veterans without Vietnam service (Center for Disease Control, 1988a; Centers for Disease Control, 1988b). In addition, when the postwar health status of Vietnam veterans was examined by whether the veteran had PTSD, PTSD-positive veterans had substantially higher postwar rates (i.e., 50–150% higher prevalence) of many major chronic diseases, including circulatory, nervous system, digestive, musculoskeletal, and respiratory diseases, even controlling for the major risk factors for these conditions (Boscarino, 1997).

Another compelling study provided additional evidence linking PTSD to adverse health outcomes was a VES study that examined the causes of death among 15,288 male US Army veterans 30 years after military service (Boscarino, 2006). These findings indicated that postwar mortality for all-cause, cardiovascular, cancer, and external causes of death (including, motor vehicle accidents, accidental poisonings, suicides, homicides, and injuries) was associated with PTSD among Vietnam “theater” veterans. For Vietnam “era” veterans with no Vietnam service, PTSD was associated with all-cause mortality. This study suggested, among other things, that Vietnam veterans with PTSD were at about twice the risk of postwar death from multiple causes 30 years after military service than veterans without PTSD (Boscarino, 2006).

What can be concluded from this research is that while combat exposure and service in Vietnam had a negative impact on the veteran’s health status, it was whether the veteran developed PTSD from these exposures that had the greatest adverse impact health status in the long-term.

Emergence of PTSD Psychobiology

As suggested, in the Blanchard study (Blanchard, et al., 1991), there are reasons to expect alterations in neuroendocrine system functioning in chronic PTSD cases, because changes in the hypothalamic-pituitary-adrenal system and the sympathetic arm of the autonomic nervous system had been observed following severe stressor exposures (Tsigos and Chrousos, 2002; Yehuda and LeDoux, 2007). Evidence suggests that the adverse physiologic arousal often observed during recollection of traumatic events is associated alterations in the neuroendocrine functions linked to the sympathetic-adrenomedullary and hypothalamic-pituitary-adrenocortical stress axis activation (Tsigos and Chrousos, 2002; Yehuda and LeDoux, 2007). In the case of PTSD, it is thought that these neuroendocrine alterations reflect the consequences of a state of physiopsychological conditioning that occurs following stressor exposures. Furthermore, while this “conditioning” response is initiated in the central nervous system (CNS), it is subsequently carried out by multiple endocrine mechanisms that have wide-ranging effects on the body and nervous system. One large-scale study, also based on the VES and involving thousands of veterans, found that Vietnam theater veterans with PTSD not only had lower cortisol levels, but that past combat exposure levels were associated with plasma cortisol concentrations in an inverse “dose-response” relationship, suggesting neuroendocrine system dysregulation (Boscarino, 1996).

Research with Vietnam combat veterans suggests, in effect, that PTSD-positive veterans tend to have lower cortisol levels. Paradoxically, however, they also tend to have higher catecholamine concentrations, together with heightened responses of the stress system to traumatic memories and other stimuli associated with the original trauma (Blanchard et al., 1991; Yehuda and DeDoux, 2007). Thus, the physiological findings for PTSD-positive Vietnam veterans suggest that past traumatic stress exposures have resulted in neuroendocrine alterations that may make veterans potentially susceptible to a host of inflammatory diseases, although the specific biologic pathways for these associations are uncertain at this time (Boscarino, 2012). Consistent with these clinical findings, it has recently been reported that PTSD was associated not only with early onset ischemic heart disease (Boscarino, 2008), but also with autoimmune diseases, including psoriasis and rheumatoid arthritis (Boscarino, 2004; Boscarino et al., 2010).

In summary, PTSD among Vietnam veterans has been associated with significant alterations in their neurophysiology and with an increased risk for many chronic diseases. However the specific causal pathways for these diseases, and whether they can be prevented or not, are uncertain at this time (Boscarino, 2011; Boscarino, 2012).

Traumatic Stress Studies with Other Populations

Following the first Persian Gulf War (PGW) in 1991, large scale epidemiologic studies were used to evaluate the health impact of this conflict for military personnel who served in that theater (Hallman et al., 2003). This PGW research has established a link between service in the PGW and mental illness, post-service injury, chronic fatigue syndrome, and other multi-symptom conditions. While the reasons for these associations are still being investigated, results from this research are being used to inform a new generation of veterans, the men and women deployed to the Afghanistan and Iraq theaters of war following the September 11, 2001 attacks (Hoge et al., 2006). For these recent conflicts, military personnel were being assessed both before deployment and after return, something rarely done in the past, but often desired after combat exposures had occurred (Boscarino, 2007). These newer prospective cohort studies offer both researchers and clinicians alike much more robust data with which to assess the impact of warzone stressor exposures.

Finally, after the September 11 attacks in New York City in 2001, investigative teams funded by the National Institutes of Health (NIH) to assess this event, including our team, used prospective cohort studies together with DSM measurements that were originally developed for Vietnam veterans and other trauma populations (Boscarino et al., 2012b; Boscarino et al., 2012c; Boscarino et al., 2011; Boscarino and Adams, 2009; Boscarino et al., 2006). In short, the field of “psychiatric epidemiology” has emerged as a subspecialty within the field of biomedical research (Tsuang et al., 2011), in part, informed by the original work with Vietnam veterans over the previous decades and the development of the DSM-III and DIS (Boscarino, 2007). This epidemiologic research is now being used to study the impact of traumatic stress exposures among a broad range of exposed populations.

To understand risks for PTSD genetically, we recently assessed the cumulative burden of polymorphisms located within four genetic loci previously associated with PTSD among patients at risk for PTSD (Boscarino et al., 2012a). For this we completed diagnostic interviews and collected DNA samples among 412 randomly selected patients to determine if *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* single nucleotide polymorphisms (SNPs) were cumulatively associated with risk for PTSD. In bivariate analyses, we found that a count of specific PTSD risk alleles located within *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genetic loci (allele range = 0–6, mean count = 2.92, SD = 1.36) was associated with lifetime ($t[409] = 3.430$, $p = 0.001$) and early onset PTSD ($t[409] = 4.239$, $p = 0.000028$). In logistic regression, controlling for demographic factors, personality traits, and trauma exposures, risk-allele count remained associated with both lifetime (odds ratio [OR] = 1.49, $p = 0.00158$) and early onset PTSD (OR = 2.37, $p = 0.000093$). Interaction effects were also detected, whereby individuals with higher risk-allele counts and higher trauma exposures had an increased risk of lifetime PTSD (allele count $\times$ high trauma, $p = 0.016$) and early onset PTSD (allele count $\times$ high trauma, $p = 0.016$). Those with no or few risk alleles appeared resilient to PTSD, regardless of exposure history.

In summary, we found that a cumulative risk-allele count involving SNPs located within the *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* genes, respectively, was associated with PTSD. Furthermore, level of trauma exposure interacted with risk-allele count, such that PTSD was increased in those with higher risk allele counts and higher trauma exposures (Boscarino et al., 2012a).

FKBP5 polymorphisms are known to regulate the cortisol-binding affinity and nuclear translocation of the glucocorticoid receptor. *COMT* polymorphisms have been found to affect fear extinction and are thought to play a role in the etiology of anxiety disorders. The *CHRNA5* gene has been associated with smoking and nicotine dependence. PTSD is known to be associated with cigarette smoking. This loci has recently been associated with PTSD and is likely involved in mammalian fear circuitry (Boscarino et al., 2012a). Research suggests that the *CRHR1* gene regulates HPA axis function in conjunction with exposure to early life trauma. It has been suggested that corticotrophin releasing hormone (CRH) is associated with alterations in memory formation in PTSD and that this hormone influences hippocampus regulation of the HPA axis. Since the four SNPs studied encompass fear circuitry, addiction biology, and other key neurobiologic circuits, we think these genetic findings may have implications for neuropsychiatric research and treatment as this relates to PTSD (Boscarino, 2012; Boscarino et al., 2012a).

Implications for Research and Treatment

Synthesizing the scientific findings related to the postwar experience of the Vietnam veteran over the past three decades suggests that neurobiological models are required to understand the impact of this experience, generally, and that there is the need for multi-factorial PTSD

models, in particular. Such models are consistent with the observation that both pharmacotherapy and cognitive-behavioral psychotherapy are reported effective in treating PTSD (Boscarino, 2007). In the case of pharmacotherapy, the pathophysiology of PTSD appears to involve the cholinergic, noradrenergic, and other biological pathways involving the amygdala and mammalian fear circuitry systems (Boscarino et al., 2012a). Consequentially, drugs known to potentiate these biologic mechanisms have been found to have a positive effect (Yehuda and LeDoux, 2007).

In the case of cognitive-behavioral therapy, this approach has been effective in reducing PTSD-related symptoms and can be traced back to an innovation introduced by Wolpe (Wolpe, 1958). Desensitization and elimination of the link between stressful stimuli and unwanted cognitive states can be achieved by increasing control of aversive arousals, by enhancing anxiety management, and by other known behavioral-psychological techniques (Boscarino, 2007). Although the underlying interventional mechanisms differ for pharmacological versus cognitive-behavioral therapy (e.g., pharmacokinetic vs. psychologic), the outcomes are similar. That is, the psychopathology and underlying pathophysiology would be reduced and fewer adverse patient symptoms manifested, hence, lowering the risk of other adverse outcomes (Boscarino, 2007).

Thus, one would expect that as trauma-related symptoms were reduced through pharmacotherapy or psychotherapy, the risk for adverse health outcomes would also decrease. Recent research has partially confirmed this hypothesis in NYC following the September 11 attacks. For example, we reported that NYC adults that received emergency crisis counseling at work shortly after the attacks, not only had better mental health outcomes, but also better outcomes in terms of binge drinking and alcohol dependence, lowering the possibility of adverse health outcomes in the future (Boscarino et al., 2011; Boscarino et al., 2006).

Conclusion

We suggest that just as what has been true with other areas of medicine – orthopedic surgery, plastic surgery, and emergency medicine – developments in military medicine and in veterans' healthcare, in particular, often are translated into medical advances for non-military populations. Although the findings discussed chiefly involved veterans exposure to combat, these results are applicable to other trauma-exposed populations. Thus, despite the medical and mental health suffering caused by Vietnam War -- or perhaps because of it -- the postwar experiences of the Vietnam veteran have resulted in significant scientific and professional practice advances in our knowledge of the nature and consequences of human stress exposures. These advances will likely lead to future medical advances not currently imagined. We think that the Blanchard study represented the commencement of our understanding of the neurobiology of PTSD and fear conditioning thanks, in part, to *The Journal of Nervous and Mental Disease* and to Dr. Brody's tenure as Editor and Chief.

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