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Pre-Trauma Posttraumatic Stress Disorder Vulnerability Biomarkers

CDT Jacob R. Peterson

ABSTRACT

Posttraumatic Stress Disorder is a stress-related mental disorder that affects only a subset of trauma-exposed populations. While current methods hold strong clinical evidence for preventing/mitigating the development of symptomatic PTSD after the fact, current research is still inconclusive on definitive pre-trauma biomarkers of PTSD vulnerability. It is prudent to recognize vulnerability in a given population, rather than treating the affected individuals post-exposure. Further progression in this field of research could not only improve the speed of reactionary treatment by focusing on susceptible individuals, but also by creating appropriate prophylactic measures. With the military in mind, identification of vulnerable subjects prior to a traumatic situation allows for individual therapeutic preparation (psychologically, pharmacologically, etc...) or re-evaluating an individual's exposure to likely trauma. Application of said methods can help mitigate the psychological damage, costs, & rehabilitation of veterans & soldiers with symptomatic PTSD. Due to current research encompassing a plethora of potential biomarkers, the emphasis of this work is an analysis & review of the most probable. Additionally, the ethical quandaries in utilization of these biomarkers is discussed, akin to the concern surrounding the Human Genome Project.

Introduction

From ancient Greece until our modern times, soldiers returning from war or combat have suffered psychological disturbances. Known by names ranging from Soldier's Heart, Shell Shock, and Combat Fatigue, it has become the 4th most common psychiatric disorder in the United States (Careaga, Girardi, & Suchecki, 2016). However, this mental disorder, characterized by an exacerbated fear response, is not simply limited to combat exposed soldiers. As our ever-growing society presents us with ever increasing external stressors, a significant number of civilians alike have developed Posttraumatic Stress Disorder.

The struggle of our ancient cognitive stress model attempting to cope with modern traumatic, and often chronic, stress has led researchers to regard PTSD as a "maladaptive response to trauma" (Daskalakis, et al., 2016). It is estimated that 7.7 million Americans suffer from PTSD annually and that twenty percent of veterans from Operation Enduring Freedom and Operation Iraqi Freedom were diagnosed (MMS, 2013). Consequently, there is a viable need for PTSD treatment. Current literature has focused on reactionary treatment, employing methods such as cognitive behavioral or processing therapy and utilization of pharmacological treatment such as SSRI's or antidepressants. Support programs and communities have formed around helping individuals cope with PTSD and the military has its own internal program titled BATTLEMIND to assist in patient recovery (Castro, Hoge, & Cox, 2006).

However, this reactionary approach has yet to prove cost effective. Full recovery is estimated at 60% success rate and although many are able eventually manage their symptoms, there is still a cost to their improvement (Vasterling & Brewin, 2005). Annual estimates of all associated PTSD treatment costs total at \$42.3 billion, more than the annual costs of traumatic

brain injury research and spinal cord injury research combined (MMS, 2013). Interestingly though, the 7.7 million Americans with PTSD represent only a small fraction of those exposed to traumatic, stressful events. Although as much as 86% of the population will experience a PTSD qualifying event in their lifetime, less than ten percent will ever develop this mental disorder (e.g., Breslau, 2009, Lukaschek et al., 2013, Wittchen et al., 2012; as cited in Daskalakis, et al., 2016). Succinctly put, not all individuals develop PTSD when exposed to the same trauma.

Modern research has recognized that an individual's probability to develop PTSD depends on individual resiliency and vulnerability factors (Schmidt, Kaltwasser, & Wotjak, 2013). Resiliency is understood as "ability to maintain a state of normal equilibrium in the face of extremely unfavorable circumstances" (Bonanno, 2014; as cited in Ahmed, 2007) . However, unlike resiliency, psychological vulnerability, especially as it pertains to PTSD, is much less understood. As it is unfeasible to remove all potential stressors in society in hopes of eliminating symptomatic development, there is a push to recognize what predispositions an individual has that makes them innately vulnerable to developing PTSD. In support of this, contemporary research has focused on the topic of biomarkers to more effectively diagnose and treat PTSD, with the goal of outright prevention or mitigation.

Defined as a specific structure or process that can be measured in the body to analyze a disease and determine pathology, biomarkers hold promising potential in terms of PTSD diagnosis, cost mitigation, and prevention in vulnerable individuals (Schmidt, Kaltwasser, & Wotjak, 2013) (Lehrner & Yehuda, 2014). While PTSD is currently believed to be an interplay of multiple facets, including biological, environmental, and social interactions, current analysis of biologic and genetic biomarkers provides the most promising avenue for indicators of PTSD vulnerability prior to trauma (Yehuda, 2011). With the aim of supporting the development of

PTSD biomarkers, this review outlines the current state of research on biomarkers for PTSD vulnerability and implicates several likely candidates including structural abnormalities, glucocorticoids, peripheral inflammation, GABA, & environmentally-induced genetic polymorphisms. Following recognition of potential biomarkers is a discussion on the ethical concerns following future implementation, with focus on military implications.

PTSD Overview

In 1980 Post Traumatic Stress Disorder was incorporated in the Third Edition Diagnostic and Statistical Manual of Mental Disorders (Association, 2013). At this time the critical factor for a diagnosis was an extreme stressor identified as “outside the range of usual human experience”

Criterion A: Stressor	Direct exposure; witness, in-person or indirectly; repeated/extreme indirect exposure to details of the trauma
Criterion B: Intrusion Symptoms	Recurrent, involuntary, intrusive memories; Nightmares; Dissociative reactions; Distress; Physiological reactivity
Criterion C: Avoidance	Trauma-related: thoughts or feelings; external reminders
Criterion D: Negative Alterations in Cognitions and Mood	Unable to recall key details of traumatic event; persistent negative beliefs, self-blame or of others, negative emotions; diminished interest in activities; feelings of alienation; constricted affect
Criterion E: Alterations in Arousal & Reactivity	Irritability or aggression; self-destructive or reckless behavior; hypervigilance; exaggerated startle response; concentration problems; sleep disturbances
Criterion F: Duration	Symptom persistence (B-E) greater than one month
Criterion G: Functional Significance	Symptom related distress or functional impairment
Criterion H: Exclusion	Symptoms not due to medication, substance usage, or illness
Specify if:	-With dissociative symptoms: Depersonalization and Derealization -With delayed expression

Table 1: Summarized Criteria for PTSD Clinical Diagnosis (American Psychiatric Association, 2013)

(Friedman, 2017). After two changes to the diagnostic manual, we arrive at the contemporary 5th edition of the DSM and updated criteria used when diagnosing PTSD (see Table 1). Modern

clinical understanding recognizes PTSD as characterized by an exacerbated fear response following a traumatic event that is outside an individual's ability to cope (Careaga, Girardi, & Suchecki, 2016). Exposure to perceived stress that is above this threshold results in the persistence of traumatic memory because of maladaptive psychological and physiological responses. Despite a century and a half of debate in classifying PTSD as a formal diagnosis, there is an increasing acceptance of PTSD as a consequence of the human struggle to deal with extreme external trauma (Hinton & Good, 2016)¹.

The clinical community has come to view PTSD as a psychiatric anxiety disorder characterized primarily of a strong emotional memory. Like other anxiety disorders, PTSD involves an emotional reaction that stems from the anticipation of fearful or threatening stimuli. However, the hallmark PTSD symptoms of hypervigilance and hyperarousal are stimulated by exposure to irrelevant details associated with the context of the trauma. Unique in that a formal diagnosis is reliant upon a traumatic event or exposure, it would seem that the model of classical conditioning best explains this maladaptive stress response (Careaga, Girardi, & Suchecki, 2016). During the time of a traumatic event, cues and external stimuli become associated with the trauma, reinforced by memory consolidation of the events. In a non-pathologic individual, a process known as extinction occurs. This diminishes the unconditioned-condition stimulus relationship, reducing the frequency of the conditioned response. However, in the case of

¹ Although there is growing validity PTSD is a part of the human experience across cultures, it has remained difficult to definitively establish validity as a persistent part of human history. Reviews of literature such as Shakespeare & historical accounts often contain elements of symptomology, leading to the conjecture of a PTSD diagnosis. However, growing understanding of this mental disorder, along with changes in the DSM rubric and symptoms have exacerbated this process. McNally, a proponent for a biocultural perspective, argues that PTSD does in fact exist prior to the modern era, but should be understood contextually. One should account for how levels of resilience and degrees of trauma severity change as society becomes more modernized (Hinton & Good, 2016)

individuals with PTSD, the learning process of extinction is innately faulty and this resistance to the degradation of the memory results in persistent recurrence of the conditioned response (Myers and Davis, 2002, as cited in Careaga, Girardi, & Suchecki, 2016). Even if extinction is initially successful, the unconditioned stimulus can spontaneously renew or reestablish a relationship with the conditioned response. It is likely that the strength of acquisition under which the memory is made correlates with resistance to extinction. Thus, it would seem trauma that exceeds an individual's ability to cope would have a stronger conditioning and decreased efficacy in memory extinction.

In the classic biological model, the long term stress response associated w/ PTSD originates primarily from the Hypothalamic-Pituitary-Adrenal (HPA) axis. During exposure to an external stressor the amygdala will recognize said stressor and signal the hypothalamus. The hypothalamus in turn will engage the sympathetic division of the autonomic nervous system. This process, known as the Sympathomedullary (SAM) Pathway, results in the production of epinephrine and norepinephrine via direct stimulation of the adrenal medulla and other bodily neurons. Best suited for immediate reaction to stress, physiological responses such as increased heart rate, respiratory ventilation, and elevated glucose metabolism ready the body for the classic "Fight or Flight" scenario (Stangor, 2017). To return the body to homeostasis, parasympathetic stimulation reduces these elevated physiological processes.

A simultaneous hormonal response occurs in response to an external stressor, involving the stimulation of the HPA axis. Although slower acting, the resulting changes can last for several hours due to a cascade of hormonal signals increasing in strength sequentially. When the amygdala stimulates the hypothalamus to promote SNS activation, it also prompts hypothalamic release of corticotropin releasing hormone. CRH initiates the release of adrenocorticotropic

hormone in the pituitary gland and this ACTH signals the release of stress steroid hormones, known as glucocorticoids, from the adrenal glands. Structures that mediate the HPA axis include the hippocampus, with a glucocorticoid inhibiting feedback loop, and the pre-frontal cortex, which is also able to limit the strength of the stress response.

Due to the high comorbidity of PTSD²³, current diagnostic criteria limits efficacy and accuracy of clinical evaluation (Schmidt, et al., 2015). Definitive biomarkers promote a streamlined method to not only properly identify pathology development but also to effectively treat both pre- and post-trauma. Current methods are also extensively reactive, relying on the exposure to trauma to validate a diagnosis. It has been proposed that to prevent the sequelae associated with PTSD, treatment should be administered during the “golden hours” after exposure⁴. Current short-term treatment and prevention involves the usage of medication such as benzodiazepines or SSRI’s⁵, while psychological intervention generally employs mediated debriefings. However, long term dependency on medication hardly constitutes a full recovery and there is supporting evidence the preventative measure of psychological debriefings is ineffective (Delahanty, 2011).

As research progresses in this field, a growing consensus lies in the fact that PTSD is

² A review of epidemiological studies has shown that 75-88% of adults and adolescents with PTSD meet criteria for at least one other psychiatric disorder, most often major depression (Lehrner & Yehuda, 2014)

³ Analysis of genetic vulnerability to developing PTSD following trauma exposure suggests a similar gene contributes to vulnerability for alcohol abuse. (Norman, et al., 2012)

⁴ Akin to the three-hour window after a thrombotic cerebrovascular accident, or a similar one-hour period after a myocardial infarction, there is likely a limited time frame to treat an individual post-trauma, preventing future development of symptoms (Zohar, Sonnino, Juven-Wetzler, & Cohen, 2009)

⁵ Benzodiazepines are utilized for reducing short term anxiety but have little evidence in preventing PTSD symptoms later on. Conversely, SSRI’s are not administered for acute symptomology, but to prevent future PTSD symptoms.

likely a complex interplay of multiple dysregulated physiological processes⁶. Resulting symptoms can be classified into four clusters⁷, and in the search for appropriate biomarkers there is a probability that finding erroneous processes determinant of each cluster would more effective than a systemic approach (Schmidt, Kaltwasser, & Wotjak, 2013). However, when looking at vulnerability factors, caution should be exercised. The systems implicated are varied, which still promotes a comprehensive view rather than attributing pathological development to a single causal factor. However, it has been found that the genetic expression and biological processes involved in the stress response play a substantial role⁸. Acknowledging the influence of environmental, psychological, and social factors, what follows is a proposal of some of the most promising avenues of research in identifying biological contributors to PTSD.

Potential Biomarkers

Neuroimaging has implicated several key structural and functional abnormalities within the corticolimbic system which is responsible for modulating the HPA axis. Specifically, in the amygdala, hippocampus, and prefrontal cortex, it is probable that HPA dysregulation arises from morphological changes in these parts of the brain. Initiating the stress response prior to HPA activity, the amygdala is mediator of fear conditioning, the amygdala is directly involved in

⁶ While this work focuses on the physiologic and biologic pathologies associated with PTSD, it should be noted that a holistic view inclusive of social and environmental vulnerability factors would facilitate a more plausible etiology. This acknowledgement also promotes further elucidation of environmental alterations on genetic expression and acquired resiliency factors. (Yehuda, 2011)

⁷ Criteria B-E

⁸ In a study analyzing the development of PTSD amongst monozygotic versus dizygotic twins, Yehuda's results supported this statement. Based on her findings, there was a greater incidence of developing PTSD in the monozygotic twins over the dizygotic (2011).

associating the details of traumatic event during the formation of emotionally charged memories related to said trauma (Hinton & Good, 2016). Additionally, it plays roles in memory acquisition and consolidation, with many arguing that the basolateral region is also the site of classical conditioning (Careaga, Girardi, & Suchecki, 2016). PTSD patients exhibit exacerbated hyperresponsiveness, even at rest, when compared to controls but it is believed that pre-existing abnormalities within the amygdala can represent a predisposed vulnerability (Careaga, Girardi, & Suchecki, 2016). Acknowledging that chronic stress is a consequence of our society, amygdala alterations become clear. Chronic stress has been found to increase basolateral synaptic connectivity both structurally and functionally (Daskalakis, et al., 2016). Persistent exposure to stressful situations and recurring activation of the HPA axis has been suggested to lead to increased hypersensitization and over consolidation of the emotional context (Sanford et al, 2000; as cited in Vaiva, et al., 2004). However, it is also known that the amygdala is mediated by the PFC and hippocampus, the latter of the two influencing long term memory consolidation (Hinton & Good, 2016).

The hippocampus is responsible for connecting the fear experienced in a traumatic event to the contextual details. Aside from acquiring and expressing this contextual fear memory, it also updates previously developed schema with new information (Careaga, Girardi, & Suchecki, 2016). Pertaining directly to the HPA axis, the hippocampus regulates glucocorticoid secretion via a negative feedback mechanism. One of the most consistent findings in PTSD patients is a diminished hippocampal volume, averaging around seven percent compared to controls (Daskalakis, et al., 2016). An animal study by Daskalakis (2016) showed that vulnerable animals were characterized by shorter dendritic lengths and lower density in hippocampal. It is known

HPA axis activation during a traumatic event elevates cortisol and that elevated levels of glucocorticoids have been found to lead to neuronal loss and dendritic shrinkage (Vasterling & Brewin, 2005). This results in impaired long term potentiation along with impaired context processing and synaptic plasticity (Careaga, Girardi, & Suchecki, 2016) (Daskalakis, et al., 2016). These changes are likely another result of chronic stress and predispose affected individuals to developing PTSD (Schmidt, et al., 2015) (Careaga, Girardi, & Suchecki, 2016).

The third structure implicated within the corticolimbic system is the prefrontal cortex. Tasked with controlling executive cognitive actions, its role within the stress response is to regulate the fear expression derived from previously learned schema. Of interest is the medial region which modulates fear expression by excitatory signaling and is negatively correlated PTSD severity (Careaga, Girardi, & Suchecki, 2016). Symptomatic patients exhibit inhibited activation in this region, leading to the conclusion that a structurally impaired PFC can result in an increased fear response to trauma. Additionally, the medial PFC is involved in fear extinction. An under active PFC is understood to elicit an impaired fear extinction process, a trait characteristic of PTSD patients (Hinton & Good, 2016). Individuals with an under active PFC may be vulnerable to traumatic stressors, developing a heightened fear expression without extinction while resilient individuals are able to extinguish such memories (Charney, 2004; cited in Ahmed, 2007).

As the culminating product of the activation of the HPA axis, glucocorticoids hold a predominant focus as likely biomarkers for clinical utilization. Glucocorticoids play a role in enhancing the emotional memory consolidation of traumatic events. Responsible for enhancing neurotransmitter levels by indirect neuronal stimulation, cortisol contributes to the heightened

state of vigilance and awareness during stress. Although a basal level is yet to be determined for the general population, current research indicates a diminished level of glucocorticoids to be correlated with a higher vulnerability for developing PTSD.

Current research has elucidated several correlations between glucocorticoid levels (specifically cortisol), receptor levels, and associated vulnerability to PTSD development. Prior to trauma, subjects who developed PTSD were found to have lower basal levels of cortisol (Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016). Concerning their associated receptors, a study conducted by van Zuiden (2011) has drawn a correlation between elevated pre-deployment glucocorticoid receptor levels, and the predictability of developing higher intensity PTSD symptoms. Additionally, a Dutch study, titled Prospective Research in Stress Related Military Operations (PRISMO), came to a similar conclusion, predicting a greater intensity in symptoms post-deployment. Acknowledging the physiologic up-regulation process⁹ to be a probable link connecting the abnormal levels of glucocorticoids and their receptors, it can be surmised that low basal cortisol levels are a symptomatic PTSD vulnerability factor. In support of this, Careaga (2016) found that administering corticosterone 12 hours before exposing rats to a traumatic stressor prevented behavior & cognitive alterations. Additionally, it has also been found that vulnerable patients exhibit chronically diminished levels of cortisol post-exposure to trauma (Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016).

However, there is seemingly contradictory evidence concerning cortisol's effects pre- &

⁹ Upregulation is a process by which cells increase the amounts of a cellular component in response to an external stimulus. The complimentary process is known as downregulation. Pertinence for this discussion involves the body-wide balance of a hormone and corresponding levels of its receptor to maintain a balance in hormonal expression.

post-trauma. It has been found that high levels during an etiological traumatic event enhance memory consolidation and associated hypermnesia¹⁰ (Careaga, Girardi, & Suchecki, 2016). Discussed previously, cortisol is produced in massive amounts and the end of the HPA axis, before seemingly dropping off. Steudte-Schmiedgen (2016) hypothesize that cortisol secretion after trauma is multi-staged, characterized by initially elevated cortisol levels, followed by hypercortisolic levels. This is likely a result of the innate HPA negative feedback mechanism. However, while high cortisol levels enhance memory consolidation, elevated levels also serve the purpose of inhibiting retrieval of the same traumatic memories (Careaga, Girardi, & Suchecki, 2016). The latter is further supported by the finding that simultaneous hydrocortisone administration improves reactionary therapeutic intervention (Daskalakis, et al., 2016).

Based on the previous, this work proposes the following model as an explanation for the fluctuations in cortisol levels and their impact on PTSD development: Vulnerable individuals express chronically low levels of cortisol with upregulated receptor levels. During a traumatic experience, the significant cortisol of the HPA axis can produce a much stronger memory consolidation because of the interaction of both elevated cortisol and receptor levels. After the traumatic experience, the HPA feedback mechanism, having received insult from excessive cortisol levels, inhibits cortisol production to chronic levels of hypocortisolism. Thus, memory retrieval is minimally impaired and the robustly consolidated traumatic memory remains overtly persistent.

If the previous holds true, then a plausible vulnerability biomarker would be circulating

¹⁰ Hypermnesia relates to extreme memory consolidation of irrelevant details and is thought to be facilitated by glucocorticoid release.

cortisol levels. A proposed method involves analyzing the cortisol levels in an individual's hair (Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016). Because of its lipophilic nature, hormone concentrations can be evaluated over a period. Additionally, such a process would be minimally invasive and promote ease in both participant involvement and sample storage. Current methods have already been implemented in the German Armed Forces experiment by Bundeswehr, assessing cortisol levels before and after deployment (Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016). More importantly, prophylactic treatment would have a central focus on administering a substance such as hydrocortisone (Daskalakis, et al., 2016). Although likely other etiology contributors have yet to be determined, there is promising evidence that correcting low glucocorticoid tone could reduce vulnerability.

Alongside its purpose in the stress response, cortisol is also responsible for mediating the inflammation process, which has been identified as placing individuals at risk prior to trauma (Hodes, et al., 2014). Implicating the immune system due to its intimate relationship, peripheral inflammation has several potential biomarkers that affect PTSD vulnerability. In study titled Marine Resiliency Study, an analysis of approximately 2,600 previously deployed Marines, researchers recognized a significantly greater elevation in C-reactive protein versus controls, which was determined as a possible pre and post deployment predictor for PTSD (Eraly, et al., 2014). A marker for inflammation, CRP is secreted following Interleukin-6.

IL-6, one of many of the substances known as cytokines that are secreted by the immune system, has been reportedly elevated in PTSD patients (Daskalakis, et al., 2016). In mice experiments, this particular cytokine elevation was linked to expression of PTSD susceptible phenotypes, in comparison to both control and mice that displayed resiliency (Hodes, et al.,

2014). Furthermore, IL-6 levels have been negatively correlated with social interaction behavior (Daskalakis, et al., 2016) (Hodes, et al., 2014). During peripheral inflammation the blood-brain barrier increases in permeability, permitting cytokine entry and subsequently promoting cerebral-induced cytokine production (Daskalakis, et al., 2016). By removing IL-6 from the body, or inhibiting its entry into the brain, researchers have found that resilience is promoted by limiting the emotional response to stress (Hodes, et al., 2014).

Cytokines have also been implicated neuronal and structural alterations. The cytokine transcription factor labelled Nuclear Factor-Kappa Beta (NF- κ B) is part of an immunosuppressive cascade that ultimately affects neuron structure and function (Daskalakis, et al., 2016). Although present throughout the entire body, concentrations within the hippocampus in PTSD patients have associated it with characteristic hippocampal loss and stress vulnerability (Hodes, et al., 2014).

Partial modulation of the HPA axis, and by extension the inflammatory process, comes from the neurotransmitter Gamma-Aminobutyric acid (GABA). The predominant inhibitory neurotransmitter in normal human physiology, GABA works to reduce neuronal excitability. This is done primarily by binding to Type A GABA receptors, reducing environmental reactivity, hyperarousal, and anxiety (Nutt, 2000, as cited in Vaiva, et al., 2004) (Lu, Liu, Jiang, Pan, Ho, & Ho, 2017). Removed from the common focus on the HPA, immune system (Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016) GABA has gained recognition as a potential biomarker because of negative correlations between GABA levels and PTSD symptom severity (Trousselard, et al., 2016). It has thus been proposed that individuals with genetically

low GABA levels are resultantly vulnerable to developing stress-related anxiety disorders.

Based on clinical research and observations, it has been proposed that GABA inhibition leads to a heightened response to stress (Vaiva, et al., 2004). An experiment using the Stroop Color and Word Test¹¹ found a correlation between reduced plasma GABA levels and increased severity of PTSD symptoms. The conclusion of this by Trousselard (2016) was that the symptomatic individuals suffered increased brain excitability, originating from either low basal GABA levels or impaired secretion in response to trauma. Regarding the former, it has been found that GABA concentrations are reduced in the parieto-occipital lobe, temporal cortex, and anterior cingulate (Trousselard, et al., 2016). However, there is even greater implication of the effect of GABA and its receptor in the corticolimbic system.

PTSD neuroimaging studies have found abnormalities in the corticolimbic circuit of the hippocampus, amygdala, and prefrontal cortex. GABA-A receptors are comprised of alpha, beta, and gamma subunits that vary in concentration among the corticolimbic structures. Alpha5, densely located in the hippocampus, has been implicated in the formation of spatial memory and increased expression explaining the impaired memory in PTSD patients (Trousselard, et al., 2016). Meis and Pape (2001, as cited in Vaiva, et al., 2004) have found that increased GABAergic activity correlates with reduced stress vulnerability. The alpha2 subunit, responsible for neuronal signaling rate, is significantly concentrated in all three structures, but reduced expression in the PFC has been associated with impaired extinction of traumatic memories. Reduced expression of gamma2 subunits in the PFC leads to impaired synaptic plasticity (Lu, Liu, Jiang, Pan, Ho, & Ho, 2017). Responsible for mediating synaptic inhibition, this subunit is

¹¹ The Stroop Color and Word Test has been classically administered to elicit a stress response within the corticolimbic system.

also more commonly known as a prerequisite for the binding of benzodiazepines. Current clinical use of benzodiazepines, generally Clonazepam, is effective in short term treatment of symptomatic PTSD. By increasing receptor concentration, they strengthen GABA signaling and reduce anxiety (Trousselard, et al., 2016). Additionally, they suppress opposing excitatory glutamate activity (Vaiva, et al., 2004). However, sustained symptom resolution requires sustained pharmacologic treatment. Experiment analysis of GABA levels during trauma versus that of several weeks later, implicated a potential clinical biomarker (Vaiva, et al., 2004) GABA levels below .21 mmol/ml indicated a strong negative correlation between PTSD severity. This tool has the potential to not only be a reactionary measure of severity but also a prophylactic measure of vulnerability.

A final consideration in the search for a viable PTSD biomarker is not only an individual's innate predisposition, but also how environment-induced gene expression potentially contributes to vulnerability. It has been proposed that susceptibility to developing PTSD is a product of heritability (Daskalakis and Yehuda, 2014b, Perroud et al., 2014, Yehuda et al., 2015b, Yehuda et al., 2014a; as cited in Daskalakis, et al., 2016). Monozygotic vs dizygotic twin studies focusing on this suggestion have found that 34 percent of PTSD symptoms can be attributed to intergenerational transmission (True et al., 1993; as cited in Ahmed, 2007) and it has been previously established that there is a correlation between impaired glucocorticoid production in infants and maternal stress during pregnancy (Yehuda, 2011). However, in addition to this proposal is the notion that environmental interaction can affect polymorphic gene expression and modify their functioning longstanding (Stedte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016). In the case of PTSD, distinct genes may interact with traumatic

events early on in life, resulting in vulnerability to PTSD upon exposure to future trauma (Daskalakis, et al., 2016). It has been shown that GABA gamma2 subunit expression is affected in such a way, but the largest emphasis has been directed on the protein FKBP5 (Lu, Liu, Jiang, Pan, Ho, & Ho, 2017).

FKBP5 is chaperone peptide that serves to negatively regulate glucocorticoid receptors and inhibit both glucocorticoid signals and transcription (Daskalakis, et al., 2016). Studies have shown that there is a negative association linking differing polymorphic FKBP5 expression and childhood trauma (Binder et al., 2008 Boscarino et al., 2011 Yehuda et al., 2009, Xie et al., 2010; as cited in Bomyea, Risbrough, & Lang, 2012). Additionally, these polymorphisms can be found in adulthood, with low plasma levels predictive of high PTSD symptoms (Van Zuiden, Willemen, Vermetten, Maas, Heijen, & Kavelaars, 2011). Not only were levels low, but there was also a decrease in the expression of the binding sites. It is found that in PTSD subjects these polymorphisms, which normally associate with increased glucocorticoid resistance and FKBP5 resistance, are instead associated with increased glucocorticoid sensitivity and inhibited FKBP5 expression (Binder et al., 2004, 2008, Ising et al., 2008, Binder, 2009, Mehta et al., 2011; as cited in Bomyea, Risbrough, & Lang, 2012). As such, normal response of stress sensitive genes, and their transcription, have been altered (Daskalakis, et al., 2016). Based on these findings, it can be postulated that trauma changes the function of both the HPA axis and FKBP5 expression. Although uncertain, researchers have proposed that there may be damage to both the expression FKBP5 and HPA axis function (Bomyea, Risbrough, & Lang, 2012). Thus, FKBP5 may negatively impact limbic maturation from trauma exposure, permanently altering HPA signaling in these structures.

There are several caveats when implicating specific genes. When searching for a gene responsible for PTSD vulnerability, the tendency is to view them as also promoting non-resiliency. However, an experiment by Daskalakis (2014; as cited Daskalakis, et al., 2016) discovered that vulnerability and resiliency to stress are two separate entities. Resiliency is not achieved by reversing the expression of a vulnerability gene. To promote resiliency and reduce vulnerability, the respective genes must independently be activated/inhibited.

Ethical Concerns

Although present research is lacking for identification of clinical biomarkers, one should consider the potential implications of developing definitive disease markers. Just as PTSD is likely an interplay of multiple physiological processes, if biomarkers were implemented as primary diagnostic tool, there would be a complex interaction of both positive and negative consequences surrounding those in question. Directly impactful at a clinical level, diagnostic biomarker-assisted validation may also impact subjects at social and psychological levels. As such, the ethical implications should be considered in development and continued pursuit of appropriate PTSD biomarkers.

PTSD biomarkers would appear to be the most beneficial in a clinical setting. With early information, efforts can be better distributed to monitor at risk individuals. Treatment progression could theoretically be manipulated more effectively and tailored to the individual. Earlier interventions post-trauma would also increase in frequency and targeted pre-deployment resilience training could become a cost effective way to mitigate symptom development. Despite these benefits, there are still potential costs to clinical PTSD biomarker development. When individuals are aware they are constantly monitored, effects derived from constant observation

can occur, skewing acquired data.

The cost/benefit of PTSD biomarkers relates to both the pre-trauma recognition of risk factors as well as validation and appropriate treatment of a post-trauma diagnosis. Due to the selective nature in which PTSD develops, a harmful stigma has grown that can impact the identity of symptomatic individuals. However, identification of biomarkers validates an individual's symptoms, potentially reducing the stigma from observing individuals and providing a clinical justification of what may be perceived as abnormalities. However, objective legitimization of a mental disorder within a military setting is likely to be detrimental (Yehuda, 2011). In the context of an environment where mental toughness and resiliency are valued, validation of PTSD symptoms can be translated as an inherent weakness. It is conceivable, even in a civilian context, that a definitive biology-based diagnoses can result in an individual regarding themselves as untreatable or damaged. In military operations, such beliefs from the soldier and his peers can be detrimental to unit cohesion and trust.

In 2008 the United States government passed the Genetic Information Non-Discrimination Act (Issues in Genetics: Genetic Discrimination, 2017) in response to public concern over the growing research concerning the Human Genome Project. To combat rising fear that available genetic information could impair an individual's opportunities, GINA effectively diverted the potential for genetic discrimination from Health Insurance providers and potential employers¹² (Friedman, 2017). However, this law did nothing to protect pathological biomarker information. This raises both ethical and legal dilemmas regarding future abuse and subsequent discrimination. If an individual's predisposition to developing PTSD after trauma is

¹² Active military personnel are exempt from the legal protection offered by GINA. This decision was made with the intent to maximize the efficacy to which troops are trained for combat. (Baruch & Hudson, 2008)

made available, in the military or otherwise, it becomes an ethical quagmire if situations necessitate such exposure (Yehuda, 2011). In terms of the military alone, it could be considered negligent to deploy a soldier with definite biomarkers into a combat arms branch. Yet this also begins to infringe on an individual's right to serve. In the civilian sector, Emergency Services personnel may be denied employment if they exhibit biologic risk factors. Even though this protects the employer from future litigation, it can still be argued that discriminatory practices have occurred.

Concerns are also present for those that test negative for PTSD biomarkers. Although genetic expression and physiologic processes contribute to PTSD development, they are not all inclusive. Individuals who do not display these biomarkers may be lured into a false sense of security or impunity to developing post-trauma symptoms (Lehrner & Yehuda, 2014). Additionally, those who are initially symptomatic yet test negative may feel that their suffering has become invalidated. With inaccurate testing results a possibility, this confounds biomarker utilization.

Despite the current state of research concerning PTSD biomarkers, consideration of the potential impacts of this line of research should be heavily weighed. Although identification of biomarkers provides a diagnostic tool that is sorely lacking, the cost of their implementation can be quite high. As Baum & Savulescu have argued (Yehuda, 2011), once PTSD biomarkers are accepted into mainstream clinical evaluation, views will shift from justifying why biomarkers are not valid, to another in which it becomes negligent not to. Thus it is incumbent that all consequences be considered before reaching a point when biomarkers are the norm without acknowledging all implications.

Lastly, future research should focus on populations chronically exposed to traumatic events. Military personnel are arguably the most at risk populations, yet their inclusion in experimental groups is grossly overshadowed by utilization of civilians. To illustrate, in a meta-analysis of eleven PTSD studies incorporating neuroimaging pre- and post-therapy, Lehrner was only able to locate a single experiment utilizing an appropriate military sample (Yehuda, 2011). For diagnostic military biomarkers to hold consistent validity and reliability, an experimental population must be pulled from this subset of society. It is probable that with further evaluation of a population exposed to chronic and atypical trauma, demographic differences will be discovered¹³.

Conclusion

PTSD has become much more widely recognized and understood in recent decades. However, we still have much to learn about this disorder. Such a debilitating mental disorder plays a serious role of the health of individuals who have gone through extreme trauma, and this can eventually influence others around them as well. There is great cost to society in treating individuals who suffer from PTSD, not only in money but in lives that have been irreversibly traumatized. With turmoil continuing worldwide and the stress of society ever increasing, there is a strong probability that incidence of PTSD will grow if left unchecked.

¹³ Of interest is a proposal by Yehuda (2011), who contests that genes may play a significant role in establishing this variance. A genetic predisposition may in fact contribute to increased risk of environmental exposure. Succinctly, innate genetic expression may cause behavioral tendencies that increase the frequency of trauma experiences. Along with potential environmental alteration of gene expression, this prompts an opportunity for further insight into at-risk populations.

There is promise on the horizon that an indicator of individual vulnerability may soon end the need for reactionary treatment in favor of prophylactics. However, the ethical questions surrounding PTSD biomarker integration deserves thoughtful deliberation; while they have the potential to do a great deal of good, they also have the possibility to negatively affect those they were meant to help as well. As of now research in this field is still developing and a lot of uncertainties must be clarified before an absolute conclusion can be made as to how to best utilize what we know about the relationship between PTSD and biomarkers. It is incumbent that we educate ourselves as much as possible in order to take the most ethical and beneficial course of action in the time that we live. The purpose of PTSD biomarkers should be to do the greatest amount of good possible with the least number of repercussions. Whether this is actually feasible remains to be seen.

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