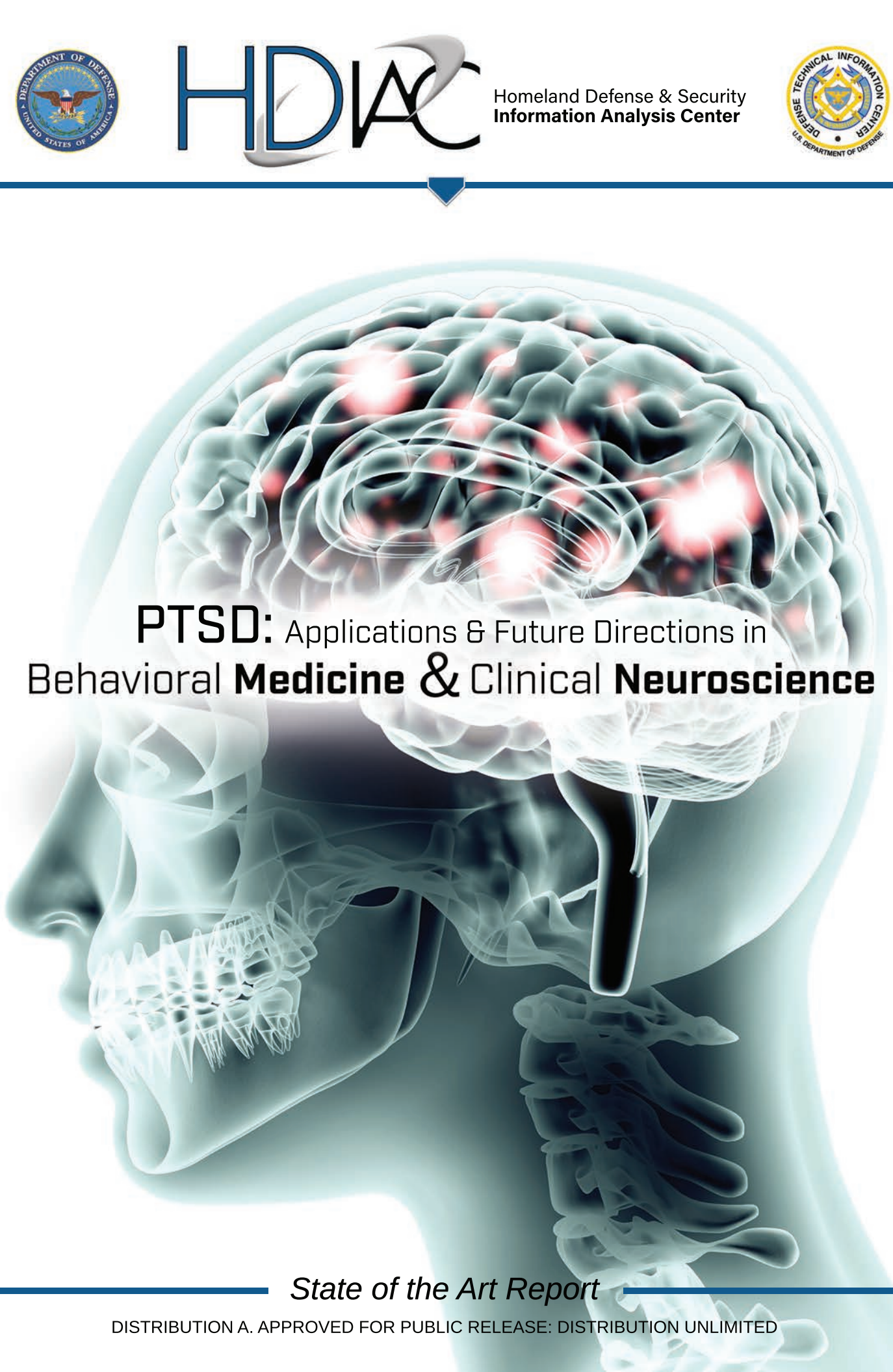

Homeland Defense & Security
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PTSD: Applications & Future Directions in Behavioral **Medicine** & Clinical **Neuroscience**

State of the Art Report

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State of the Art Report (SOAR)

PTSD: Applications and Future Directions in Behavioral Medicine and Clinical Neuroscience

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Eric Luster is a U.S. Army veteran and Bronze Star recipient with more than fifteen years of experience in the information technology/telecommunications industry including management, network, and mission feasibility analysis, systems integration, entrepreneurship and person-centered design. As founder of Movement Interactive, he has focused on developing wearable technologies that detect and report concussions and Traumatic Brain Injury. Mr. Luster was awarded a Masters of Business Administration in Information Technology in 2007 from Western International University and is completing his Doctor of Business Administration degree. Mr. Luster was named one of Arizona's top 35 entrepreneurs under 35 for 2015, was an Excellence Award winner for the Oklahoma State University Veteran Entrepreneurial Program in 2014, and was recognized by the Clinton Global Initiative as one of the 'Top Five Black Student Leaders to Watch in 2014.'

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Acronyms

ACC ..... Anterior-cingulate Cortex
ADC ..... Apparent Diffusion Coefficient
APA ..... American Psychiatric Association
APOE ..... Apolipoprotein E
BFB ..... Biofeedback
BOLD ..... Blood Oxygenation Level-Dependent
CAPS ..... Central Auditory Processing Syndrome
CBF ..... Cerebral Blood Flow
Cho ..... Choline
CPT ..... Cognitive Processing Therapy
Cr ..... Creatin
CSF ..... Cerebrospinal Fluid
CT ..... Computerized Tomography
CTE ..... Chronic Traumatic Encephalopathy
DAI ..... Diffuse Axonal Injury
DARPA ..... Defense Advanced Research Projects Agency
DFN ..... Default Mode Network
DMN ..... Default Mode Network
DNA ..... Deoxyribonucleic Acid
DoD ..... Department of Defense
DSM ..... Diagnostic and Statistical Manual of Mental Disorders
DTI ..... Diffusion Tensor Imaging
DWI ..... Diffusion Weighted Imaging
ECF ..... Extracellular Fluid
EEG ..... Electroencephalograph
EMDR ..... Eye Movement Desensitization and Reprocessing
EMG ..... Electromyogram
ERC ..... Event-related Potential
ERP ..... Event-Related Potential
fMRI ..... Functional Magnetic Resonance Imaging
GABA ..... Gamma Aminobutyric Acid
HAMD ..... Hamilton Rating Scale for Depression
HC ..... Hippocampal
HDFT ..... High Definition Fiber Tractography
HF ..... High Frequency
HPA ..... Hypothalamic-pituitary-adrenal
HRV ..... Heart Rate Variability
IAF ..... Individual Alpha Frequency
LF ..... Low Frequency
LOC ..... Loss of Consciousness
MCC ..... Mid-cingulate Cortex

MEG ..... Magnetoencphalography
MMPI ..... Minnesota Multiphasic Personality Inventory
mPFC ..... Medial Prefrontal Cortex
MRE ..... Magnetic Resonance Elastograph
MRI ..... Magnetic Resonance Imaging
MRS ..... Magnetic Resonance Spectroscopy
MRT ..... Master Resilience Training
mTBI ..... Mild Traumatic Brain Injury
MVA ..... Motor Vehicle Accident
NAA ..... N-acetyl Aspartate
NFB ..... Neurofeedback
OEF ..... Operation Enduring Freedom
OIS ..... Operation Iraqi Freedom
PCC ..... Posterior Cingulate Cortex
PCS ..... Post-concussion syndrome
PDHA ..... Post Deployment Health Assessment
PE ..... Prolonged Exposure Therapy
PG ..... Progesterone
PHG ..... Parahippocampal Gyrus
PRESTINT ..... Predeployment Stress Inoculation Training
PTH ..... Posttraumatic Headache
PTSD ..... Post traumatic stress disorder
Pz ..... Parietal Midline
qEEG ..... Quantitative Electroencephalography
RAM ..... Restoring Active Memory
RCT ..... Randomized Control Trial
RNA ..... Ribonucleic Acid
RSA ..... Respiratory Sinus Arrhythmia
RS-fMRI ..... Resting State Functional Magnetic Resonance Imaging
SC ..... Superior Colliculus
SCID-IV ..... Structured Clinical Interview for the DSM-IV
sLORETTA ..... Low Resolution Brain Electromagnetic Tomography
SNP ..... Single Nucleotide Polymorphism
SPECT ..... Single Photonemission Computed Tomography
SRTS ..... Stress Resilience Training System
STG ..... Superior Temporal Gyrus
SUD ..... Substance Use Disorders
SWI ..... Susceptibility Weighed Imaging
TBI ..... Traumatic Brain Injury
TOVA ..... Test of Variables of Attention
VA ..... Department of Veterans Affairs
VE ..... Virtual Environments
VH ..... Virtual Humans

Executive Summary

Global conflict and political instability have increased our nation's military operations and deployments. Missions occur more frequently, in unpredictable environments, resulting in less time for soldiers to recover mentally and physically. Many active duty service members return from combat with symptoms related to post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI). Although research in these areas is on-going, accurate reporting and assessment and effective interventions are lacking. Understanding the progression of PTSD, the neural mechanisms involved, and the compounding impact of mTBI and other comorbidities is imperative. Increased knowledge will enable the military to improve in first-line interventions, including predictive and resilience training.

This State of the Art Report (SOAR) presents recent research in behavioral medicine and clinical neuroscience as it relates to PTSD, which often occurs with mTBI and other comorbidities. Current gaps in knowledge and treatment ineffectiveness underscore the need for the military to more specifically and comprehensively address military-related PTSD and mTBI in active duty soldiers and veterans. Of particular interest are new scientific perspectives driving research and shifting paradigms; innovative technologies for delivering interventions; and emerging research in predictive and resilience training.

SOAR Sections provide a brief history and overview of military-related PTSD, highlight the need for more comprehensive assessments and evidence-based interventions, explore the critical role played by the neurobiological correlates of PTSD, examine complications and prevalence of combat-related mTBI as it relates to PTSD, provide insight into advancing technologies able to address previously 'hidden' injuries and symptoms, discuss unique mobile training and treatment capabilities, analyze the science and role of building resilience prior to deployment, and finally, consider the future implications of shifting to an ideal that accommodates the presented evidence.

Information presented in this SOAR is from empirically derived research, ranging from small cohorts to meta-analyses, and primarily focuses on military-related PTSD whenever possible.

Symptoms of combat-related PTSD have been recorded for centuries. With advances in science and in technology, what was once considered or even dismissed as poor coping is now known to have significant neurobiological correlates, including biomarkers, possible genetic predispositions, and numerous comorbidities. Because PTSD is complex, researchers are exploring novel, evidence-based approaches, which are discussed in Section 2.

Section 3 reviews compelling evidence of the neural signature of PTSD from recent functional magnetic resonance imaging (fMRI) studies and the emerging unique brain activity patterns associated with PTSD detectable by quantitative electroencephalography (qEEG). Although applied neuroscience is an evolving discipline, mounting evidence shows the benefits of bio- and neurofeedback as non-trauma focused techniques for addressing PTSD. Neurofeedback and heart rate variability (HRV) biofeedback are now being used in Department of Veteran Affairs (VA) hospitals, on military bases, in remote training, and in optimal performance training in war fighters.

Soldiers returning from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) have reported cognitive difficulties, including memory loss, sleep difficulties, and suicidal depression. An increasing amount of research is focused on the misdiagnosis of mTBI as primary PTSD. Section 4 provides insight into mTBI, its nature and course, comorbid factors, and treatment. Special attention is given to the pathophysiology of mTBI, and specifically to the unique characteristics of blast injuries found in recent research.[1]

Researchers are interested in why some soldiers are vulnerable to PTSD and others are resilient. Combat veterans return with varying levels of needs, some of which are persistent and difficult to address. Novel approaches, such as resilience building/training, discussed in Section 5, have been explored.

This SOAR aims to bring understanding and apreciation of the physiological correlates of PTSD and assist in developing a more proactive aproach in preparing military through resilience training. This SOAR fashions a novel perspective on where the research is leading, highlighting a feasible and necessary shift in the military's approach in addressing PTSD. The authors summarize research and inform about the state of the field while highlighting gaps in research and emphasizing emerging scientific evidence.

1. Introduction

1.1 PTSD Introduction

Post-traumatic stress disorder (PTSD) can develop in people exposed to a traumatic, physically dangerous, and often times, life-threatening event. Combat places military personnel at particularly greater risk for developing stress disorders compared to the general population.[2,3] Multiple deployments characterize recent conflicts and further increase exposure and, therefore, risk for developing PTSD.[4] Comorbid mental and physical health conditions including anxiety, depression, substance use,[5,6] sleep problems,[7] and mild traumatic brain injury (mTBI)[8] often accompany military-related PTSD. From a practical and clinical perspective, these conditions complicate diagnosis and treatment.[9]

There have been remarkable developments in the understanding of the etiology and pathophysiology of PTSD since the 1970s. Advances in PTSD knowledge, treatment, and access result from the integration of theory and evidence from recent research on resilience and the expanding research in the behavioral sciences and neurosciences.[10] Researchers and clinicians have a better understanding of how trauma-related stress influences, and is influenced by, behavioral and neurobiological correlates, such as cognition, emotion, genetics, biochemical response, and physiological reactivity.[11]

This knowledge is being used to apply evidence-based approaches in research and clinician training efforts throughout the Department of Defense (DoD) and the Department of Veterans Affairs (VA). Despite clinically meaningful improvements in response to interventions, treatment attrition rates remain high and, compared to active controls, interventions are only considered marginally superior compared to active controls.[12] Consequently, many soldiers report persistent symptoms and even continue to meet diagnostic criteria for PTSD six months post-treatment.[13,14]

PTSD follows a chronic course. Left untreated, it can result in lifelong dysfunction.[15,16] With efficacy studies showing PTSD treatment is currently lagging behind,[17] there is an immediate and imperative need for further development and testing of novel and effective evidence-based treatments.[18] As physiological factors further confound PTSD diagnosis and treatment, researchers and clinicians must become more competent in discerning root causes for presenting symptoms, including understanding the role of genetic predisposition, using biomarkers for measuring susceptibility, and evaluating the effects of mTBI.[19,20,21,22]

The following section provides a foundation for subsequent SOAR sections. Though combat-induced stress symptoms have been noted for centuries, questions remain regarding the onset, progression, and course of what is now called PTSD. A brief history of PTSD in the military, prevalence rates, comorbidities, current standards of care, and barriers to treatment efficacy are included in the discussion.

2. PTSD History and State of the Field

2.1 PTSD History and Diagnostic Criteria

Though the term PTSD is only a few decades old, the struggle to define, research, and understand the cluster of symptoms associated with PTSD has been ongoing for centuries. Historically, various terms have been applied to a constellation of symptoms, including soldier's heart, irritable heart, shell shock, war neurosis, and battlefield fatigue. The American Psychiatric Association (APA) first adopted the term post-traumatic stress disorder in 1980.

PTSD remains a widely debated and controversial condition and diagnosis. With numerous theoretical underpinnings supporting various routes of etiology, onset, and course, PTSD is complex. Diagnostic criteria for PTSD, according to the most recent APA Diagnostic and Statistical Manual of Mental Disorders (DSM-V), recategorizes PTSD from an anxiety disorder to a trauma and stressor-related disorder (see Table 1).[23]

Despite the new designation, APA executive director of research and education, Darrel Regier, MD, MPH, acknowledges "It is very important to have a better paradigm than what we have been using to look at somatic presentation of mental disorders, and the relationship of disorder in other organ systems."[24] This statement reflects the current thinking that PTSD diagnosis and subsequent treatment may not adequately capture and account for the pathophysiology of the condition. For example, new research reveals PTSD susceptibility likely increases with blast-related mTBIs,[25] which raises questions on best approaches for diagnosis and treatment.

The disturbance, regardless of its trigger, causes clinically significant distress or impairment in the individual's social interactions, capacity to work or other important areas of functioning. It is not the

Table 1: DSM-V Criteria for PTSD

Diagnostic criteria for PTSD include a history of exposure to a traumatic event that meets specific stipulations and symptoms from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, **and** alterations in arousal and reactivity**. The sixth criterion concerns** duration of symptoms; **the seventh assesses** functioning**; and, the eighth criterion clarifies symptoms as** not attributable to a substance or co-occurring medical condition**.**

The diagnostic criteria identify the trigger to PTSD as exposure to actual or threatened death, serious injury or sexual violation. The exposure must result from one or more of the following scenarios, in which the individual:

- Directly experiences the traumatic event
- Witnesses the traumatic event in person
- Learns that the traumatic event occurred to a lose family member or close friend (with the actual or threatened death being either violent or accidental)

or

- Experiences first-hand repeated or extreme exposure to aversive details of the traumatic event (not through media, pictures, television or movies unless work-related)

The disturbance, regardless of its trigger, causes clinically significant distress or impairment in the individual's social interactions, capacity to work or other important areas of functioning. It is not the physiological result of another medical condition, medication, drugs or alcohol.

physiological result of another medical condition, medication, drugs, or alcohol.

PTSD research and knowledge expanded rapidly in recent decades and is drastically different than the initial psychopathology defined in the first DSM. Research breadth now extends from prevalence, assessment, comorbidity, and randomized controlled trails of various treatment methods to phenomenology, psychophysiology, and neural mechanisms of PTSD.[26,27,28,29,30] This increased understanding substantially impacts how PTSD is assessed and treated, as discussed in the following sections.

2.2 Prevalence Rates in Veterans and Active Duty Military

Increasing prevalence rates of PTSD and comorbidities, especially mTBI, require a closer look into the process of diagnosing and the progression and course of this condition. Estimates of lifetime prevalence for PTSD in Vietnam veterans range from 11% to 30%, depending on criteria strictness.[31,32] Hoge and colleagues'[33] seminal study estimates that 12% to 20% of service members deployed to Afghanistan and Iraq, respectively, screened positive for PTSD. This is consistent with other estimations of 10% to 25% found by Tanielain & Jaycox.[34] Estimates for National Guard reserve soldiers range from 11% to 25%, depending on time post-deployment.[35,36] While percentages may seem relatively low overall, they translate to 138,197 possible cases of PTSD in soldiers deployed between 2002 and early 2015.[37]

Typically, variations in statistics are the result of differing methodologies and samples, assessments, and data analyses. Inaccuracies in self-reporting and shortcomings within the assessment process are characteristics of military-related PTSD. An attempt to grasp the gravity and impact of this condition requires dependable data obtained from service members, their families, and health services and providers.

Currently, there are barriers to obtaining accurate data about PTSD. These include under-reporting due to stigma and fear of job change/loss and over-reporting of symptoms by those seeking compensation, and comorbidities.[38] Reger et al. (2008) report having an appreciation for military culture, or the social, political, environmental milieu of the military, is requisite and profoundly shapes our contextual understanding of this condition and its effects.[39]

Self-reporting, especially under-reporting, remains a significant barrier in PTSD assessment.[40] Specifically, research finds military personnel under report for reasons of fear, guilt, or shame.[41] For example, the stigma of showing weakness by reporting mental health symptoms contradicts the highly valued trait of stoicism. By its very nature, stoicism is characterized by emotional and mental control under times of pressure; it is analogous to being a capable, level-headed leader—one who is dependable and consistent.[42] These are critical characteristics in wartime decision-making.

A 2004 study of OEF and OIF military service members found that over 60% of the sample feared being perceived as "weak" and over 60% also feared adverse treatment, such as job loss, from their superiors.[43] In response to soldiers' denial of symptoms or under-reporting, the military is actively engaged in conversation about how to define PTSD:

> Certain military leaders, both active and retired, believe the word "disorder" makes many soldiers who are experiencing PTSD symptoms reluctant to ask for help. They have urged a change to rename the disorder posttraumatic stress "injury", a description that they say is more in line with

> the language of troops and would reduce stigma. But others believe it is the military environment that needs to change, not the name of the disorder, so that mental health care is more accessible and soldiers are encouraged to seek it in a timely fashion. Some… also question whether "injury" is too imprecise a word for a medical diagnosis.[44]

2.3 Comorbidities

Comorbidity, the presence of one or more additional diseases or disorders co-occurring with a primary disease or disorder, further complicates the assessment, diagnosis, and course of PTSD.[45] Co-occurring mental and physical health conditions may include anxiety, depression, substance use, sleep problems, and mTBI.[46] Some of these conditions have been shown to have unique and compounding effects on PTSD.[47]

Recent studies show PTSD is moderately to highly correlated with other anxiety and affective diagnoses (*r* is .43-57 and .44-.50, respectively).[48] Co-occurrence rates are especially high among military and veteran populations,[49,50,51] which may reflect the contributions of other environmental, psychological, and biological risk factors; specifically cited are personality and genetic factors and mTBI.[52] Miller et al.[53] identified three personality subtypes, with the internalizing subtype as characteristic of PTSD and depression co-occurrence.

PTSD and co-occurrence substance use disorders (SUDs) are high in military populations. A 1997 study found over half of male Vietnam veterans diagnosed with SUD also met criteria for PTSD.[54] More recent studies reveal similar findings among OEF and OIF veterans.[55,56] Some researchers suspect the co-occurrence could be present in 60% to 80% of OEF and OIF veterans.[57] Kruse et al.'s[58] review proposed mechanisms explaining such high co-occurrence. Self-medication, high-risk, susceptibility, and third-variable hypotheses suggest poor coping skills, personality factors, neurobiological differences, and genetic vulnerabilities contribute to risk.

Clinically, anger is considered a hyper-arousal PTSD symptom and is one of growing concern, as it is a common complaint reported by many soldiers post-deployment. Studies show PTSD is significantly associated with increased levels of anger and aggression in veterans and active duty military.[59] Recently, multiple studies indicate that as many as one-third of veterans returning from Iraq and Afghanistan have significant problems with aggression.[60,61,62,63] Notably, a 2006 meta-analysis found larger effect sizes for combat-related PTSD and anger compared to a civilian population of PTSD and anger.[64] The mechanisms influencing these rates is unclear, although a synthesis of trauma stress and neurobiological effects or factors is implicated.

Post-deployment assessments of active-duty military reveal sleep disturbance as the most frequently reported complaint.[65,66] Of those deployed to Iraq or Afghanistan, almost two-thirds endorse symptoms of insomnia upon their return.[67] Furthermore, prevalence of sleep difficulties is especially high among those meeting PTSD diagnostic criteria. An estimated 90% of soldiers returning from Iraq and Afghanistan meeting criteria for PTSD reported sleep difficulties.[68] While the etiology of sleep issues and their role as a symptom or exacerbator of mental health problems requires further investigation, evidence indicates that sleep deprivation places military personnel at higher risk for experiencing mental health problems.[69]

Combat exposure increases risk of traumatic brain injury (TBI), which has emerged as a significant cause of morbidity in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) soldiers. Penetrating TBI is usually identified and treated quickly, if it is not fatal, while mild TBI (mTBI) may be missed. Mild TBI is defined as an injury from an external force from a blast, fall, or accident.[70] Conventional neuroimaging techniques, such as Functional Magnetic Resonance Imaging (fMRI), do not typically pick up on temporal conditions of the brain and these types of electrophysiological injuries. Now, more than ever, mTBI is of particular concern as it is considered a "signature" injury" of OEF and OIF[71] and accounts for most of the TBI cases in the military. Between 2000 and mid 2016, more than 290,000 soldiers were diagnosed with mTBI.[72]

> Unlike more severe Traumatic Brain Injury (TBI), the disturbance of brain function from a mild TBI (mTBI) is related more to dysfunction of brain metabolism rather than to structural injury or damage. The current understanding of the underlying pathology of mTBI involves a paradigm shift away from a focus on anatomic damage to an emphasis on neuronal dysfunction involving a complex cascade of ionic, metabolic and physiologic events.

Soldiers returning from deployment report persistent post-concussive symptoms, including sleep difficul-

ties, impaired memory and concentration, headaches, and affective problems.[74] Mild TBI symptoms may "look" similar to PTSD, and mTBI may exacerbate and increase risk for PTSD.[75] A study by Hoge et al.[76] found that, even after controlling for combat exposure, the association between TBI and PTSD remains. Unfortunately, available military equipment, i.e. helmets, are not yet able to prevent damage from these blasts.[77,78] Novel technologies with remote capabilities for use in theater are needed to more quickly and effectively diagnose mTBI injuries. Various eye-tracking technologies and analysis platforms, such as Tobii and Imotions, respectively; monitoring technologies, such as those created by Movement Interactive, LLC; and training technologies such as the Listening Program by Advanced brain Technologies, are being developed.

While TBI and mTBI are critical to diagnosing and accurate symptom assessment of PTSD, these are also wounds that are considered "invisible,"[79] which may be a deterrent to reporting. Section 5 provides a more detailed review of the pathophysiology and sequelea of mTBI, as well as insight into advances in detection and treatment.

Successful reintegration into a civilian community, family life, and employment, while coping with mental and physical impairments, can be difficult. The effects associated with comorbid conditions and the inherent overlapping symptoms appear to intensify reintegration issues.[80] Thorough PTSD treatment is aimed at mitigating these issues but remains challenging given the number and, often times, severity of comorbid issues. Thorough PTSD treatment begins with reliable reporting, comprehensive assessment, accurate diagnosis, and appropriate treatment planning.

2.4 Assessment

Trauma assessments vary in format and in scope, ranging from self-report measures to more comprehensive, clinician-guided diagnostic tools.[81] Often comorbidity with other conditions, such as mTBI, and symptom overlap with other psychiatric diagnoses complicate the course and severity of PTSD and, consequently, the assessment.[82,83] Structured diagnostic interviews increase diagnostic accuracy.[84] The Clinician-Administered PTSD Scale (CAPS), for example, which assesses diagnostic criteria and symptom severity, is widely employed and has good diagnostic utility.[85] The Structured Clinical Interview for the DSM-IV (SCID-IV)[86] is another valid and reliable interview tool, although it does not assess frequency, severity, or effects of prior trauma.

Self-report measures with validity scales are useful as a complement to structured interviews, as they assess symptoms and severity while also providing indicator scores of malingering, exaggerating symptoms for secondary gain, and of under-reporting. The Minnesota Multiphasic Personality Inventory Second Edition (MMPI-2)[87] is often used, as is the Mississippi Scale for Combat-Related PTSD.[88] While there exists perhaps only one report of established guidelines for assessment,[89] a multi-method approach, using evidence-based assessments, generally can discriminate presenting symptomatology and yield a more accurate and comprehensive case conceptualization.

2.4.1 Shortcomings of Current Assessment Approaches[90]

The range of PTSD prevalence rates may be attributable to how assessment tools are used. As a result, criteria required for positive PTSD diagnosis can vary, resulting in under- or even over-diagnosing.[91] When overlapping symptoms and comorbidities are present, a more comprehensive, multi-method assessment or diagnostic approach is imperative. Keane[92] and others suggest that measuring aspects of psychophysiological activity and reactivity is not often used and may be helpful. For example, such assessment results could reveal an mTBI as a primary diagnosis or a comorbidity. Moreover, physiological measures may better detect PTSD hyper-arousal symptoms, such as anger and aggression. Psychophysiological assessments and interventions are covered in more detail in Section 3.

2.4.2 PTSD Risk and Additional Considerations in Assessment

Research suggests some disorders may develop secondary to PTSD,[93,94,95,96] while other disorders, such as anxiety and affective disorders, may predispose an individual to developing PTSD.[97] This is important, because understanding the etiology, or cause, of PTSD informs the approach to assessment. Research indicates etiological factors include genetics, early-life trauma, and exposure to disasters and combat.[98] Other documented risk factors influencing vulnerability to PTSD include prior psychiatric history, prior trauma, autonomic hyperarousal, and traumatic brain injury.[99] Evidence increasingly suggests the effects of trauma are cumulative,[100,101] which places soldiers with multiple deployments at increased risk for developing PTSD. A recent meta-analysis confirms this cumulative risk, finding individuals exposed to childhood trauma also are at increased risk for developing military-related PTSD.

The study also found increased risk among those with less education, decreased social support during and after deployment, war-zone exposure, war-related injuries, and those of younger age at deployment.[102] Mild TBI also increases risk for PTSD and depression.[103]

It is notable that specific genetic variations substantially contribute to risk in developing PTSD.[104,105] Evidence indicates genetics may account for symptom overlap in some co-occurring conditions, such as depression, over other psychological or environmental factors.[106]

Research also suggests effects are likely mediated by gene-environment interactions, involving polymorphisms of specific genes which impact the hypothalamic-pituitary-adrenal (HPA) axis function.[107] The HPA is presumed to play a significant role in trauma and stress related conditions.[108,109] (See also Figure 1)

Consequently, a more integrated hypothesis is that prior trauma experiences may lead to certain conditions through a developmental process where genetic variations interact with neural circuits or pathways that regulate emotion.[110] It may be possible to inform pre-deployment resilience training and screening, if this research can explain mediation of risk and resilience.

2.5 PTSD Treatment and Standards of Care

Recommended PTSD interventions consist of working through trauma experiences and the cognitive and emotional sequelea, or previous events, associated with the trauma.[112] Although randomized controlled trials increased in number over the past decade, few have offered compelling and consistent hope for effective treatment.[113] The VA commissioned a report from the Institute of Medicine (now the National Academy of Medicine) documenting the efficacy of current treatments for military-related

Figure 1

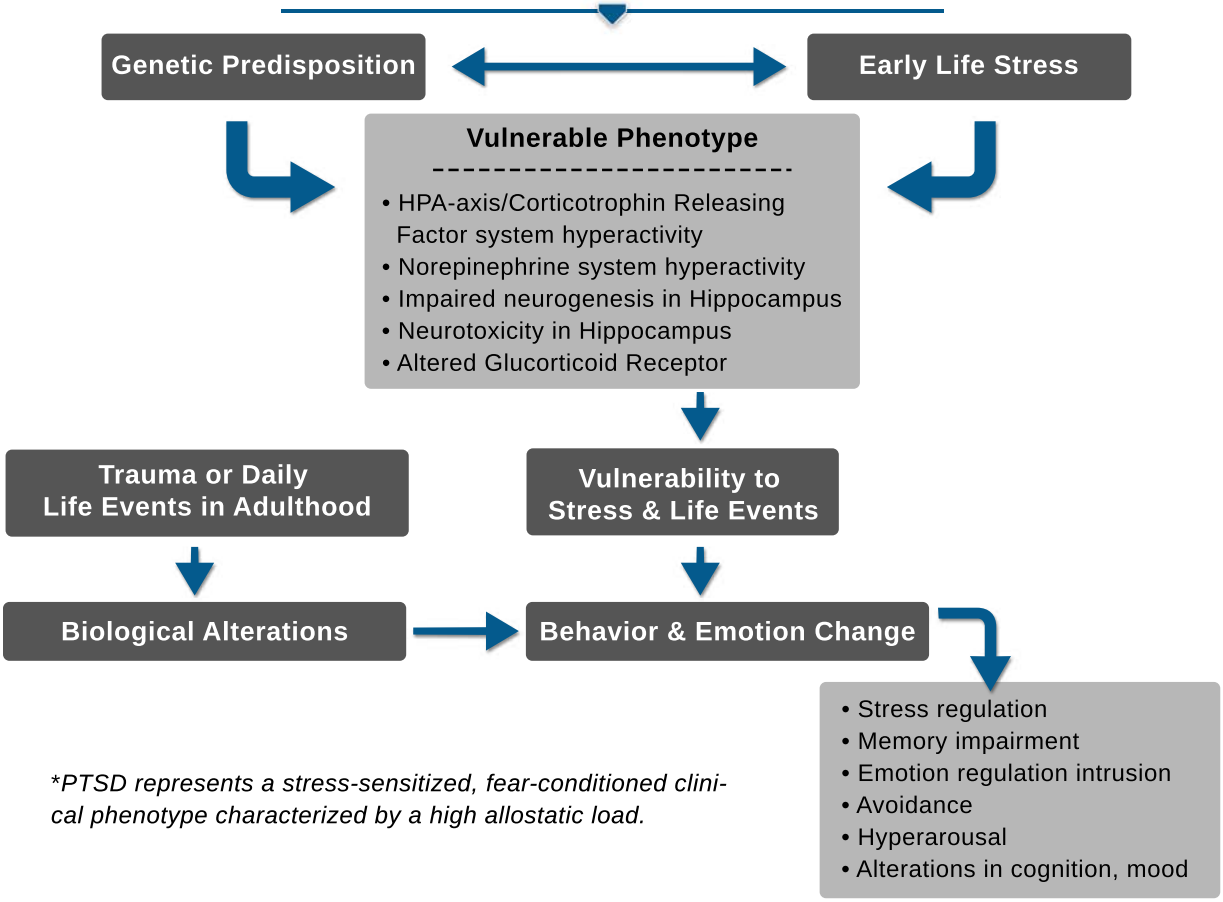

Figure 1: *Pathways of PTSD development.*[111]

PTSD. The 2007 research outcomes were based on 90 randomized clinical trials, 53 of which were considered psycho-therapeutic interventions and 37 of which were pharmacological interventions. The report found exposure therapy to be the only psychotherapeutic modality with sufficient evidence as an intervention for PTSD, and there was insufficient evidence to support pharmacological interventions.[114,115]

2.5.1 Effectiveness of Current Treatment Approaches

According to a recent review, most trauma research looks at traumas in civilian populations, such assaults and motor vehicle accidents (MVAs). There is a paucity of published research studies on combat-related PTSD treatment in military populations. Furthermore, the existing military PTSD studies show only modest effect sizes for treatments,[116] highlighting the need for new and more effective approaches.

Treatments, such as Cognitive Processing Therapy (CPT) and Prolonged Exposure Therapy (PE), have been shown to be most effective and, in civilian studies, have large and comparable pre-post treatment effects for CPT, PE, and Eye Movement Desensitization and Reprocessing (EMDR).[117,118]

In the military, however, nonresponse rates to these PTSD treatments remain high, and, therefore, symptom amelioration remains negligible in some veterans and active duty military.[119,120] An overview of first-line PTSD interventions is in Table 2.[121]

CPT, PE, and EMDR interventions are considered trauma-focused therapies that have been widely studied and generally involve assessment and attention to dysfunctional trauma-related cognitive and emotional processes. Manualized and typically requiring at least 12 in-office sessions, these interventions have been adopted to aid in standardizing care for veterans.[122,123] However, most efficacy studies primarily focus on civilian populations. Those conducted using CPT in a military population may show statistically significant changes initially but non-significant at six- and 12- month post treatment follow-up assessments. In a recent review of Randomized Controlled Trials (RCTs) for military-related PTSD,[124] authors summarized:

> …trials of CPT for military-related PTSD have included both veterans and active-duty personnel with combat or military sexual trauma, have shown high methodological rigor (although fidelity problems were present in 1 trial), and have had large effect sizes when compared with no treatment (waitlist) or treatment as usual. However, CPT was marginally superior to active, non–trauma focused control comparisons.

Fewer methodologically robust trials exist for PE interventions for combat-related trauma in military populations.[125] Similarly, the EMDR trials have been fairly brief interventions and conducted with small sample sizes prior to military presence and combat in Afghanistan.[126,127,128] Additional studies are needed to establish efficacy for PE and EMDR specifically with a military population[129,130] and should include post-treatment assessment at six and 12 months. As

Table 2. Descriptions of First-Line Interventions

- Cognitive therapy: Focuses on modifying dysfunctional thoughts, beliefs, and expectations by identifying, challenging, and replacing maladaptive cognitions. Cognitive processing therapy (CPT) is the most widely used example of cognitive therapy in the Departments of Defense and Veterans Affairs.
- Exposure therapy **(PE):** Comprises psychoeducation, imaginal or narrative exposure (targeting trauma memories), in vivo exposure (targeting external stimuli or situations that the patient avoids because of the trauma), and processing of thoughts and emotions, with the aim of confronting, rather than avoiding, feared memories and stimuli. Prolonged exposure therapy (PE) is the most widely used example of exposure therapy in the Departments of Defense and Veterans Affairs.
- Eye movement desensitization and reprocessing **(EMDR):** Asks patients to attend to emotionally disturbing material in brief sequential doses while focusing on an external stimulus, typically therapist-directed lateral eye movements. Additionally, treatment involves identifying bodily sensations associated with the image, identifying an aversive cognition associated with the trauma, and identifying an alternative positive cognition to replace the aversive cognition.
- Stress inoculation training **(SIT):** Teaches anxiety-management skills including relaxation training, breathing retraining, positive thinking and self-talk, assertiveness training, and thought stopping. It may also include cognitive restructuring and exposure, although these are optional elements.

of 2011, no EMDR RCTs had been conducted within the VA or DoD since commencing OIF and OEF.[131]

Other PTSD treatments include non-trauma focused therapies, alternative and complimentary approaches, and physiological-based interventions. Non-trauma focused therapies include, but are not limited to, group, family, psychodynamic, and pharmacological therapies. Mindfulness-based stress reduction, relaxation, and deep breathing have not been found efficacious at this time.[132,133] Preliminary evidence is promising in the areas of applied neuroscience and psychophysiology, such as neurofeedback[134] and biofeedback.[135,136] While RCTs exist for some long-standing approaches to treating military-related PTSD, additional research is needed in all areas, from trauma- and non-trauma focused interventions to physiological-based interventions to complimentary and alternative approaches.

With research increasingly focused on biological factors and physiological correlates of PTSD, comes the responsibility to address PTSD more comprehensively. Time commitment, access, and emotional intensity are likely to remain particularly challenging treatment aspects for veterans and especially active-duty military.[137] Novel technologies and application of current interventions to mobile platforms may offer more accessibility for veterans and soldiers and increase symptom oversight and maintenance capabilities for service providers.[138,139]

Advances in understanding PTSD and its progression should be informing more comprehensive assessments; producing accessible, novel, and technological therapeutics and interventions, See Appendix A for example.

3. Neurophysiology of PTSD: Electrophysiological Measures, Methods, and Evidence-Based Applications

3.1 Functional Imaging Techniques: fMRI

Several types of functional imagining techniques are used to investigate the impact of trauma on the human brain, enabling researchers and clinicians to identify the neural signature. Functional Magnetic Resonance Imaging, for example, uses the blood oxygen level-dependent (BOLD) signal to reveal activation patterns in the brain.[140] The patterns have been studied under several different approaches, including the use of tasks which are chosen to target brain regions hypothesized to be involved with PTSD. Emotional recall tasks, memory encoding tasks, the counting or emotional Stroop task, and the auditory continuous performance task are among those used. Symptom provocation approaches, which involve exposing the subject to trauma-related visual or auditory stimuli, such as combat sounds and/or images and personal traumatic scripts, also are used.[141,142]

PTSD subjects also can be studied while their brain is “at rest”, without any task or stimuli.[143] These approaches enable researchers to study differences in brain functioning in PTSD patients and to compare results to those of healthy controls with no history of trauma, as well as subjects with a history of trauma who have not developed PTSD. Thus, with the various types of trauma studied (MVAs, combat, sexual assault, natural disaster, etc.), the various types of approaches used (task, symptom provocation, rest), and the various comparison groups (healthy, trauma with no PTSD, etc.), there is great diversity within fMRI research resulting in a wide variety of findings. Despite the range of methods and subjects, several common themes emerge and repeatedly point to the same structures being involved with PTSD.

One commonly reported finding is that of altered functioning of the amygdala, a structure of the limbic system believed to play a role in quickly identifying and assessing threatening stimuli and in fear conditioning.[144] Functional MRI research has repeatedly found the amygdala to be over active and hyper responsive in PTSD patients.

There is also evidence to suggest that this pattern of activity is present in the acute stage of PTSD, and the degree of responsivity can distinguish PTSD with great sensitivity and specificity.[145,146] Additionally, decreased amygdala activity may be a protective factor against developing PTSD.[147]

The medial prefrontal cortex (mPFC) is another region commonly reported in the fMRI literature. This region of the frontal lobe, which includes the anterior cingulate cortex, subcallosal cortex, and medial frontal gyrus,[148] plays a role in a variety of tasks including executive functions, decision making, and memory functioning and allows associations to be made between situations and adaptive responses.[149] In studies of patients with a clinical diagnosis of PTSD, this region has been reported to be under active and/or fails to activate to the same degree compared to studies of subjects without PTSD.

Evidence also suggests that mPFC activation is inversely correlated with the severity of PTSD symptoms.[150] However, this is a large region and it has

been noted that the majority of findings showing reduced activity have been in the rostral and ventral portions of the mPFC, while the dorsal portions may show normal or increased responsivity in PTSD patients.[151] The hippocampus, important in memory functioning, has also been implicated in PTSD; however, the findings have been mixed, with some reporting decreased hippocampal activation and others reporting increased activation.

While the hippocampus is dysregulated in PTSD, the direction of dysregulation found may depend on the methodologies employed.[152] The insula, particularly the anterior insula, which has reciprocal connections with the amygdala and plays a role in awareness of psychological states, has been reported to show higher levels of activation in PTSD.[153] While these regions have most consistently been reported in fMRI research, findings regarding the thalamus are of interest and may help explain aspects of PTSD symptomology.

The thalamus has been reported to show lower levels of activation in PTSD subjects when using 4-T field strength. Researchers hypothesized that excessive arousal from trauma leads to dysregulation of thalamic processing, which leads to a dysregulation of sensory information being transmitted to the cingulate cortex, frontal cortex, amygdala, and hippocampus. Thalamic dysregulation may underlie dissociative symptoms and flashbacks.[154] Recent research has attempted to provide greater specificity to these fMRI findings. Using an activation likelihood estimation meta-analysis, Boccia et al.[155] explored whether different traumatic events produce different activation patterns. Using data from 38 individual experiments, authors reported trauma from physical or sexual abuse, combat, and natural disaster impact the brain differently. PTSD from physical or sexual abuse resulted in clusters of activation in the bilateral anterior cingulate cortex (ACC) and mid-cingulate cortex (MCC), precuneus, superior occipital gyrus, and middle frontal gyrus. PTSD from combat revealed clusters of activation in the bilateral hippocampus, ACC, and superior temporal gyrus (STG). PTSD due to natural disaster results in clusters of activation in the right superior frontal gyrus and STG, left middle frontal gyrus, and bilateral parahippocampal gyrus. A representation of the functional neuroanatomy of PTSD has been proposed by Vermetten & Lanius, 2012,[156] as shown in Figure 2.

Figure 2

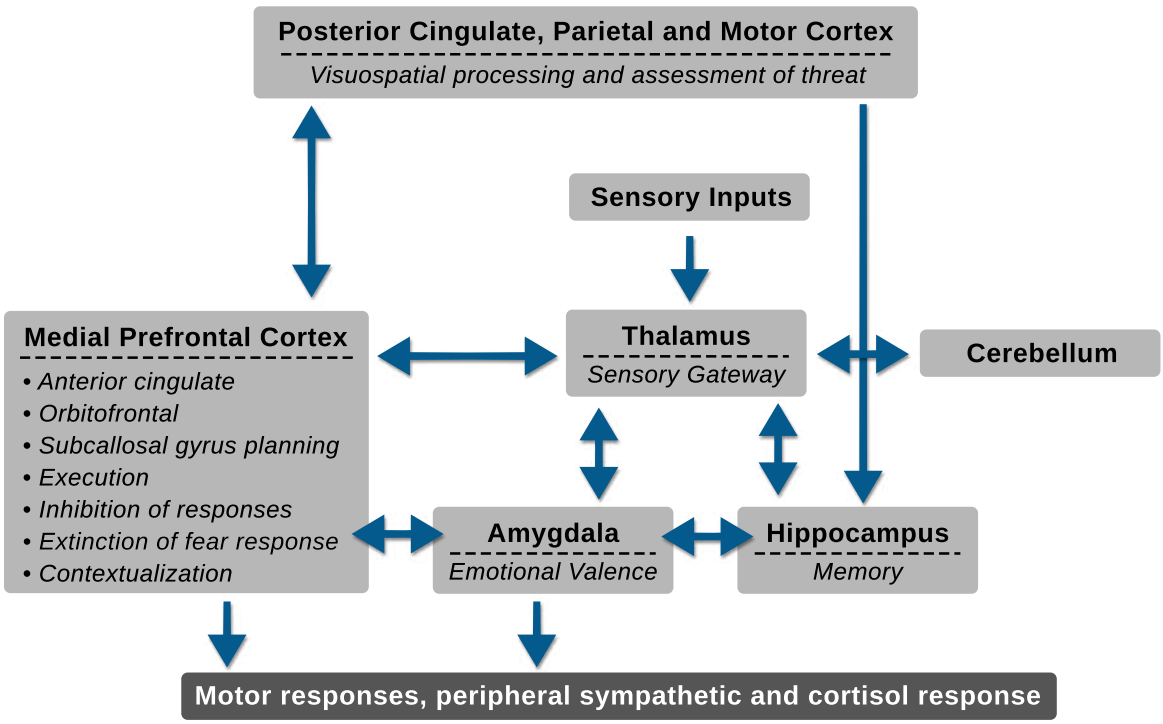

Figure 2: *Functional neuroanatomy of post-traumatic stress disorder.*[157]

Researchers generally agree that specific regions of the brain are impacted by specific types of trauma and that the functional connectivity and coordination of multiple brain areas is necessary to carry out complex processes. In fMRI research, functional connectivity analysis uses statistical methods to identify regions with correlated activity.[158]

The amygdala appears to significantly influence activity in the visual cortex, subcallosal gyrus, and anterior cingulate in PTSD subjects. Additionally, the theory that under activation of the mPFC results in a failure to inhibit the amygdala was not supported, but rather it appears that the amygdala has influence over the frontal regions.[159] Functional connectivity analysis also reveals hemispheric differences, with greater correlation of the right posterior cingulate, right caudate, right parietal lobe, and right occipital lobe in PTSD subjects compared to traumatized subjects without PTSD. Researchers hypothesize that this pattern accounts for the nonverbal nature of memory recall in PTSD.[160] Functional connectivity of the posterior cingulate cortex (PCC)/precuneus also is disrupted in PTSD subjects with a lack of connectivity between this region and other regions in the default mode network.

Researchers hypothesize that this disconnection of the PCC/precuneus is associated with the disruptions in self-referential processing noted in PTSD. However, this finding was studied only in subjects with early childhood trauma and may not generalize to other trauma populations.[161] Additionally, functional connectivity of the PCC with the perigenual anterior cingulate and right amygdala has been associated with current PTSD symptoms, and the connectivity with the right amygdala may predict future symptoms.[162] Although fMRI research has shed considerable light on the neural signature of PTSD, additional studies are needed to fully understand the impact of trauma on the human brain.

Despite the advances made by fMRI, it has limitations. For example, perhaps the greatest limitation is the poor temporal resolution with fMRI recording changes 4 to 6 seconds after the actual brain activation occurs. The technique is expensive, and the MRI scanner is extremely loud, which can make traumatized subjects very uncomfortable.[163] Therefore, the electroencephalogram (EEG) and other imagining techniques have been used. The fMRI's temporal resolution weakness is the strength of EEG, which can record brain responses in milliseconds. Traditional EEG lacks the spatial resolution of fMRI, although newer analytic techniques, such as Low Resolution Electromagnetic Tomography (sLORETA), have greatly improved EEG spatial resolution. Additionally, EEG's relatively low cost, non-invasive nature, and wide availability make it a viable option to study the impact of trauma on the brain.

3.1.1 Functional Imaging Techniques: qEEG

Similar to fMRI research, EEG research is mixed and varied with numerous ways to quantitatively analyze the EEG. In quantitative analysis, the raw EEG is subject to mathematical and statistical processes that go beyond traditional visual inspection of the EEG. One way to quantitatively analyze the EEG is by investigating changes in magnitude or power of various EEG frequencies (delta, theta, alpha, beta, etc.) to see if differences in EEG activity are noted within PTSD populations. Imperatori et al.[164] reported a widespread increase in theta activity in the parietal regions and the frontal regions and Begic et al.[165] reported increased theta (4-7 Hz) over the central regions, increased beta 1 (13.5-18 Hz) over frontal, central, and left occipital regions, and increased beta 2 (18.5-30 Hz) over frontal regions. Alpha frequencies are the most frequently studied band of activity, and alpha activity has been found to be globally decreased in PTSD compared to those with depression and healthy controls.[166] Decreased alpha 2 power also was directly related to clinical arousal scores on the Clinician Administered PTSD Scale (CAPS).[167]

Jokic-Begic & Begic[168] compared 79 veterans with PTSD to 37 veterans without PTSD and noted decreased alpha 1 (7.5-9.5 Hz) over the frontal, central, and occipital regions; more pronounced in the left hemisphere; and increased beta 1 over the frontal and central regions in the PTSD group. This pattern of decreased alpha activity (and increased beta activity) is consistent with over-arousal symptoms noted in PTSD.[169] Because the alpha frequencies are believed to be generated by the thalamus, this difference may reflect disturbances of the thalamus, which has been hypothesized to be associated with sensory dysregulation in PTSD.[170,171]

In addition to changes in alpha power, asymmetries in alpha activity between hemispheres, particularly in the frontal regions, also have been investigated. This frontal alpha asymmetry model has been popular; however, a recent review of the studies shows little empirical support. Meyer et al.[172] reviewed eight studies comprising approximately 139 PTSD subjects, and all but one study failed to find significant group differences in trait (at rest) frontal alpha asymmetry. Meyer et al. also studied state (during

an emotional task) frontal alpha asymmetry and reported higher right hemisphere frontal activation in response to trauma-related stimuli, but not unrelated negative stimuli, in the PTSD group. Finally, a slight difference in individual alpha frequency (IAF) has been observed in PTSD subjects, with a higher IAF noted in the left hemisphere at 9.9 Hz compared to the right hemisphere at 9.6 Hz.[173]

3.1.2 Functional Connectivity Analysis: sLORETA

Another way to quantitatively analyze the EEG is through functional connectivity, evaluating the strength and connection between brain regions Using sLORETA, a mathematical technique designed to estimate the source of EEG from activity recorded at the surface. Imperatori et al.[174] found increased EEG connectivity of the alpha frequencies between the precuneus and right inferior parietal region in PTSD subjects compared to healthy controls. Lee et al.[175] also noted disruptions in functional connectivity strength and efficiency when comparing 33 PTSD subjects with 30 healthy controls. Researchers found PTSD subjects had decreased connection strength and communication efficiency in beta and gamma frequencies within frontocentral regions. Additionally, connection strength in beta frequencies significantly correlated with depressive symptoms, and connection strength in the gamma frequencies was significantly correlated with arousal. Re-experiencing, increased arousal, and severity of PTSD symptoms were significantly correlated with communication efficiency in the beta and gamma frequencies.

Using another form of connectivity analysis, Kim et al.[176] found increased non-linear interdependence in fronto-parieto-temporal regions of the left hemisphere and decreased interdependence in the fronto-parieto-occipital regions of the right hemisphere. By evaluating dynamic complexity, rather than connectivity, which is a method to determine the number of independent variables that comprise the EEG signal, researchers found PTSD subjects had globally reduced complexity of their EEG waveforms compared to healthy subjects. Researchers hypothesized this was related to disruption in cortical information processing that is exhibited by PTSD patients.[177]

3.1.3 Functional Connectivity Analysis: Event Related Potentials

The measured brain response that is the direct result of a specific sensory, cognitive, or motor event, known as event related potential (ERP), also has been used to evaluate differences within PTSD subjects. ERP takes advantage of the temporal resolution available in EEG analysis, allowing the investigation of millisecond differences in processing of visual and auditory stimuli. In a recent review by Lobo et al.,[178] 22 ERP studies were analyzed. Consistent, significant associations were observed for the slope of the P2 response for auditory stimuli, with the P2 slope positively correlated with PTSD symptom severity. Researchers hypothesized that this relationship reveals the auditory hyper reactivity seen in PTSD and may reflect deficiencies in cortical inhibition that normally protect an individual from overstimulation. Studies[179] evaluating the P3 component, which relates to processes of attention and working memory, have produced contrasting results, but there is evidence to suggest a relationship between PTSD symptom severity and the P3 ERP.

Although there have been numerous investigations of EEG patterns associated with PTSD, a clear theme has not emerged. This may be due, in part, to the wide variety of EEG aspects analyzed, various analytic methods used, poorly defined EEG frequency bands (i.e. alpha (8-13 Hz), low alpha, high alpha, or IAF, and failure to control for medication effects. However, given the strengths of EEG (low cost, non-invasive nature, and wide availability), it should be pursued in PTSD research to increase understanding of the neural signature of and to identify underlying traumatic brain injuries.

3.2 Evidence-based Treatment Approaches in Applied Psychophysiology

In addition to understanding the neural signature of trauma and improving diagnosis, applied neuroscience can inform treatment and help individuals heal from PTSD. One promising applied neuroscience technique is biofeedback, which involves small sensors being placed on the body to record various aspects of physiology, such as muscle activity, heart rate, skin conductance, and brain function. This information is then converted into visual and auditory displays, which helps PTSD subjects become more aware of these aspects of physiology. With practice, individuals can learn to regulate and change their physiology, thereby improving self-regulation. One form of biofeedback investigated in PTSD subjects is EEG biofeedback, often referred to as neurofeedback (NFB).

3.2.1 Neurofeedback

One of the earliest published investigations of NFB

in PTSD was conducted in the early 1990s by Peniston and Kulkosky.[180] Vietnam combat veterans with PTSD were randomized to an alpha-theta neurofeedback group which received thirty 30-minute training sessions, or a treatment as usual control group. The neurofeedback group was pre- and post-tested using the Minnesota Multiphasic Personality Inventory (MMPI), a standardized psychometric test of adult personality and psychopathology. The NFB group showed a decrease of 10 MMPI scales and all subjects reduced medication. The control group had a decrease of only 1 MMPI scale, and only one subject was able to reduce medication. At 30-months follow-up, all control subjects had relapsed while only three of the neurofeedback group showed signs of PTSD.

An uncontrolled study by Peniston et al.[181] trained 20 Vietnam veterans with chronic PTSD and alcohol abuse with thirty 30-minute alpha-theta neurofeedback sessions. Following training only four of the 20 subjects reported nightmares or flashbacks. There are methodological flaws in these studies, such as no randomization, no control group, and inconsistencies in reporting and techniques applied.

Critics[182,183] have argued that it is not clear what the "Peniston Protocol" actually is. The titles and summaries suggest that these are neurofeedback interventions, but temperature biofeedback, autogenic training, rhythmic breathing techniques, desensitization, guided imagery, and possibly other therapeutic techniques also are mentioned. While it is unclear if the improvements in these groups was due solely to neurofeedback, a comprehensive biofeedback self-regulation training program resulted in significant improvement in a difficult to treat population.

Since the early 1990s, other studies have focused on neurofeedback as an intervention. Walker[184] reported training 23 PTSD patients to reduce high frequency beta (21-30 Hz) activity and increase 10 Hz activity. The location of the training was determined by qEEG findings. All subjects were asked to rate their anxiety on a scale from 1 to 10. Four patients declined neurofeedback training, and they were used as a no-treatment control group. All patients who completed training reported a clinically significant reduction in anxiety, whereas the four who declined neurofeedback reported that their anxiety levels remained constant over the same three-month period.

Smith,[185] also reviewed by Reiter et al.,[186] trained 10 males with combat related PTSD in a two-phase neurofeedback protocol, which included 10 sessions rewarding 15-18 Hz at C3-Fpz and 12-15 Hz at C4-Pz while inhibiting 4-7Hz. This was followed by 20 sessions of alpha-theta training at the parietal midline (Pz). A significant improvement in depression was noted with a decrease in HAMD scores, and improved commission errors and variability of response time was measured by Tests of Variable Attention (TOVA) scores. However, this study did not include randomization, controls, or follow-up.

In 2016, Gapen and colleagues[187] published a proof-of-concept study for the use of neurofeedback with treatment-resistant PTSD. Seventeen participants completed 40 training sessions and were randomly assigned to either training at temporal and parietal locations T4-P4 or temporal locations T3-T4. Training included rewarding 12-15 Hz and inhibiting 4-7 Hz and 22-36 Hz. The reward band was adjusted if signs of over- or under arousal were reported following the training sessions. Neurofeedback training significantly reduced PTSD symptoms as measured by the Davidson Trauma Scale, and the changes were believed to precede improvement in affect regulation as measured by the Inventory of Altered Self-Capacities.

An interesting study, conducted by Kluetsch et al.,[188] involved neurofeedback training of 21 PTSD subjects with childhood trauma. Subjects were trained for 30 minutes with an alpha desynchronization protocol, which involved reducing alpha (8-12 Hz) activity at the parietal midline location Pz. Functional MRI scans and EEGs were recorded at baseline and following training. Analysis of EEG changes indicated a decrease in alpha amplitude during neurofeedback training, followed by a significant increase in resting alpha activity after training. This rebound in alpha activity was correlated with participants' reports of increased calmness. Analysis of fMRI data revealed increased connectivity in the salience network with the right insula and increased connectivity of the default mode network with bilateral PCC, right middle frontal gyrus, and left medial prefrontal cortex — networks that have been shown to be dysregulated in PTSD. This is an important study as it begins to explain the possible mechanisms behind the effects of neurofeedback training in PTSD. It is also important as it demonstrates that a relatively simple, single channel, neurofeedback protocol can regulate large scale brain networks that have been reported to be dysregulated in PTSD. While more research is needed to draw firm conclusions regarding the efficacy of neurofeedback in the treatment of PTSD, these studies reveal the possible benefits of this training

and make further research in this area worthwhile.

3.2.2 Biofeedback: Heart Rate Variability

In addition to neurofeedback, another applied psychophysiology technique that has become popular and shows promise in addressing PTSD is heart rate variability (HRV). When heart rate is analyzed on a beat-to-beat basis, there is a change in time intervals between each heartbeat. This variability is the result of a complex interplay among multiple physiological systems and reflects regulation or dysregulation of the autonomic nervous system.[189] This physiological measure is showing promise in the treatment and, possibly, the prevention of PTSD.

HRV is reduced in some PTSD subjects. In a meta-analysis of 11 studies involving 379 subjects, a significant effect size was found for reduced high frequency (HF), low frequency (LF), and reduced HRV as measured by RMSSD and SDNN, various ways to assess and measure HRV[190] — with these measures being significantly reduced in PTSD subjects when compared to controls.[191] Reduced HRV reflects an imbalance between the sympathetic and parasympathetic systems and has been associated with chronic stress, psychological disorders, and inadequate functioning of self-regulatory systems.[192] It may also be a marker to identify PTSD. Given this relationship between reduced HRV and PTSD, HRV biofeedback has been used to help increase HRV and reduce PTSD symptoms. HRV biofeedback, as described by Leher et al.,[193] involves identifying an individual's resonant frequency breathing rate (typically around six breaths per minute) and then training the individual to use paced breathing, with feedback on respiration and HRV provided by biofeedback software.

Using respiratory sinus arrhythmia training, which is similar to HRV training but without measuring and using an individual's resonant frequency, Zucker et al.[194] randomly assigned 38 participants to a biofeedback group or progressive muscle relaxation group. While both groups had a slight reduction in PTSD symptoms, the biofeedback group had a significantly greater decrease in depression symptoms, with the improvement in HRV predicting improvement in PTSD. Tan et al.[195] found that veterans with PTSD had significantly depressed HRV compared to controls. Twenty veterans with PTSD were randomly assigned to treatment as usual or HRV biofeedback (8 weeks of 30 minute HRV biofeedback training and home breathing practice for 20 minutes twice a day) and compared to 10 healthy control participants. Treatment as usual had no significant effect on HRV or PTSD symptoms (decreasing the CAPS score by 9%). However, HRV biofeedback significantly increased HRV, decreased PTSD symptoms, and decreased CAPS score by 18%. The greatest decrease was found on the avoidance/numbing cluster of the CAPS. Also evaluating this technique with combat veterans, Ginsberg et al.[196] randomly assigned participants to an active HRV biofeedback group or a sham HRV biofeedback group. Preliminary data showed the active group reduced the severity of PTSD, while the sham (pacebo-type) group showed only a negligible change.

Not all randomized trials have found HRV biofeedback to be effective. Lande et al.[197] randomly assigned active duty service members with PTSD to either treatment as usual or treatment as usual with HRV biofeedback. The addition of HRV biofeedback was found to have no effect on PTSD or depression symptoms. It should be noted that the HRV biofeedback deviated significantly from that used in other studies. In this study, participants were trained twice a week for 20 minutes for three weeks for a total of six sessions. Additionally, no home training practice was mentioned. Because all forms of biofeedback, including HRV, are considered training rather than a treatment, repeated practice is essential and is a key component recognized by clinicians and researchers.[198] The participants in the Lande et al.[199] study only practiced HRV a total of six times which likely did not change autonomic nervous system functioning enough to impact PTSD symptoms. Therefore, preliminary evidence indicates there is clinical improvement in PTSD when HRV biofeedback is integrated into treatment.

In addition to treatment of PTSD, there is initial and modest evidence that altered autonomic nervous system activity, as measured by LF/HF HRV ratio, can identify military personnel with a vulnerability to developing PTSD.[200] HRV can be determined in a simple five minute procedure. Although this type of longitudinal research can be time consuming. It is well worth effort if this relationship is established. That is, if such a simple procedure can identify military personnel at risk for PTSD, steps can be taken prior to deployment to help individuals learn to regulate arousal and possibly protect themselves from the negative effects of trauma. HRV training prior to deployment has been investigated by Lewis et al.[201] Participants were chosen from a convenience sample of platoons from the U.S. Army 82nd Airborne Division at Fort Bragg, NC, and randomly assigned to a Predeployment Stress Inoculation

Training (PRESTINT) intervention group or control group. The 469 participants in the PRSTINIT group received breathing training and HRV biofeedback, while the 422 participants in the control group received a didactic presentation on stress management. The goal of the intervention was to provide participants with stress management techniques that could help them recover from stressful events and relax prior to sleep. Researchers found that HRV increased following the PRESTINT training, and this increase persisted following a simulated combat stressor. More research is needed to determine if this type of predeployment training will improve physiological regulation during combat and if it can protect military personnel from the long term consequences of trauma.

3.3 Emerging Technologies: Clinical and Remote Applications

While applied psychophysiology techniques of neurofeedback and HRV hold great promise for the identification, treatment, and possible prevention of PTSD, the most exciting aspect is the way technology is changing the face of how these techniques are delivered. Clinical biofeedback has historically been provided by trained clinicians within the confines of an office. While a trained clinician is still a critical component, technology is expanding how services can be provided. The development of EEG headsets, the reduced cost of computers, and the internet enable clinicians to remotely train clients anywhere in the world. Additionally, EEG headsets that interface with smart phones or tablets will enable individuals to train under the supervision of a clinician, but on their own time and with increased frequency, even when deployed. HRV is particularly useful in this type of training, and there are numerous applications on smart phones and tablets that allow for HRV biofeedback at a minimal cost. Biofeedback applications can be extremely useful in helping individuals regulate their physiology in situations, such as combat, where medication and other therapies are not practical or are not available.

4. Mild Traumatic Brain Injury

4.1 Introduction and Background

The most underreported, under diagnosed, and underestimated brain trauma is mTBI, or concussion, which accounts for 90% of TBI and millions of trauma cases every year.[202] It is a public health problem within the general population and is increasingly more common in sports and military populations.[203,204,205] A Defense and Veterans Brain Injury Center (DVBIC)[206] analysis of surveillance data released by the DoD reported 33,149 U.S. military personnel were diagnosed with a TBI in 2011 alone,[207] and the military has reported over 350,000 mTBIs since 2000 .

Mild TBIs in the civilian population are caused primarily by falls, MVAs, being struck by an object, and assaults. Most individuals experience one or more symptoms related to their injury, such as headache, dizziness, insomnia, impaired memory, and/or lowered tolerance for noise and light, but will return to a previous level of function within three to six months. However, approximately 10% to 15% of patients may go on to develop chronic post-concussive symptoms. These symptoms can be grouped into three categories: somatic (headache, tinnitus, insomnia, etc.), cognitive (memory, attention, and concentration) difficulties, and emotional/behavioral (irritability, depression, anxiety, and behavioral dyscontrol). Patients who have experienced mTBI are also at increased risk for psychiatric disorders, such as depression and PTSD, compared to the general population.

In contrast to civilians, the primary causes of TBI in veterans of Iraq and Afghanistan are blasts, blast plus MVAs, MVAs alone, and gunshot wounds. Exposure to blasts is unlike other causes of mTBI and may produce different symptoms and natural history. For example, veterans seem to experience post-concussive symptoms for longer than the civilian population; some studies show most will still have residual symptoms 18-24 months after the injury. In addition, many veterans have multiple medical problems. The comorbidity of PTSD, history of mild TBI, chronic pain, and substance abuse is common and may complicate recovery from any single diagnosis.

Mild TBI is caused by physical trauma that shears or damages brain tissue. This trauma can lead to a cascade of delayed neurodegenerative events that may include diffuse axonal injury (DAI), activation of excitotoxic inflammatory cascades, and transneuronal degeneration.[208,209,210] Mild TBI is considered a “silent epidemic” because many of the acute and long-term complications may not easily be observed during initial assessment.[211,212,213,214] While initial damage in mTBI may be minimal, the chronic neurodegenerative effects can persist for weeks or months post-injury and lead to significant cognitive, sensory, behavioral, and psychiatric dysfunctions.[215] More than 82% of the 352,619 brain injuries reported during military operations from 2000 to mid 2016

were classified as mTBIs, thus underscoring mTBI as a major health issue in the U.S. military.[216] The growing global awareness of the frequency of mTBI in contact sports, coupled with the emergence of blast-related injuries in the military, has heightened the urgency to understand the underlying mechanisms of mild brain trauma and to improve therapeutic interventions.

The signs and symptoms of mTBI can be vague, a diagnostic challenge that is made more difficult by patients who may underreport their injury by ignoring or hiding their symptoms or overreport, exaggerating their symptoms. Reliable witness accounts and directed questions to evaluate for loss of consciousness (LOC), post-traumatic amnesia, and confusion are necessary for diagnosis.[217,218,219]

Following the International Classification of Diseases update in late 2015, the Assistant Secretary of Defense clarified the mTBI definition as follows:

> Concussion/Mild TBI is characterized by the following: Confused or disoriented state which lasts less than 24 hours; or loss of consciousness for up to 30 minutes; or memory loss lasting less than 24 hours. Excludes penetrating TBI. A CT scan is not indicated for most patients with a Mild TBI. If obtained, it is normal .

A few years earlier, the American Congress of Rehabilitation Medicine defined mTBI as characterized by a blow to the head (e.g., striking an object, being struck) accompanied by evidence of physiological disruption of brain function [i.e., loss of consciousness (LOC) less than 30 min, altered mental state (AMS), posttraumatic amnesia (PTA) less than 24 hours, and neurological deficits.[220,221,222] While the some diagnostic symptoms of LOC, AMS, and PTA are generally limited in duration to the TBI event itself, some physical (e.g., headaches and sleep disturbance), behavioral (e.g., irritability and disinhibition), postural and stability (balance), and cognitive (e.g., difficulty in concentrating and memory problems) symptoms can persist for several days, weeks, or months.[223,224]

TBI can induce neurological, cognitive, and behavioral symptoms collectively referred to as post-concussion symptoms (PCS). Prominent neurological symptoms include headache, vomiting, nausea, problems with balance, vision, dizziness, fatigue, drowsiness, sensitivity to light or noise, and sleep disturbances. The cognitive symptoms consist of problems with attention, concentration, memory, processing speed, and executive functions (e.g., working memory and decision making). Common behavioral symptoms include anxiety, irritability, aggression, and depression.[225,226,227,228,229,230]

Recently, there has been a growing interest in subconcussive or repetitive mTBI that involve multiple low-impact injuries associated with domestic violence, contact sports, or military activities.[231,232,233,234,235] Repetitive mTBI impacts have been shown to cause significant cumulative brain damage and have been hypothesized to cause early dementia and Alzheimers.[236,237,238,239] Repetitive mTBI has been associated with deficits in several functional areas, including speed of information processing, memory and attention, and executive functions, including verbal learning and delayed recall.[240,241]

Approximately 20% of U.S. soldiers who served in Iraq and Afghanistan have experienced a head injury during deployment.[242,243] Explosions, or blasts, are the most common cause of brain injuries in soldiers. The blast TBI has been called the “invisible wound”. Many service members present with debilitating neurological symptoms, but clinical biomarkers for this condition have yet to be fully established, and the underlying pathophysiology is now being investigated, i.e. Shively et al., 2016.[244]

Current research has shown military personnel with mild brain injuries caused by explosive blasts had outcomes similar to those with mild brain injury from other causes. A blast injury consists of several phases. After the initial blast wave, a blast wind follows with the potential of reaching hurricane speeds, hurling objects in its path. This flying debris can cause penetrating trauma, known as secondary injury, and tertiary injury can result from acceleration of the head causing it to impact against a solid object, a component of many blast TBIs. The secondary and tertiary injuries are similar to a sports-related mTBI.

Recent data indicates that there might be a predictable pattern of physical damage to human brain after a blast exposure, which standard clinical neuroimaging techniques currently cannot detect. Analysis of brain tissues from military veterans who suffered from blast-related injuries showed a neuroanatomical pattern of interface astrogliosis, or scarring.[245] The neuroanatomical locations of the scarring support the concept that persistent symptoms of blast-exposed individuals may correlate with damage to particular structures with potential interference or alteration of their functions. In the human brain, astrocytes respond to local damage and are

detectable within hours; astroglial scarring can be seen in the ventromedial prefrontal (orbitofrontal) cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, anterior insular cortex, amygdala, hypothalamus, and hippocampus—all neuroanatomical areas associated with PTSD. This scarring pattern is not present in the non-blast brain injury cases. More research needed to support this hypothesis.

4.2 Pathophysiology

Mild TBI is a form of diffuse injury caused by significant mechanical stresses, despite a lack of resulting overt morphological damage. The biomechanical forces perceived to inflict the majority of brain damage are rotational or angular acceleration–deceleration forces rather than the linear counterparts.[246,247,248] Researchers believe these rotational forces acting on the midbrain and thalamus cause a transient disruption of the reticular activating system, resulting in the LOC often associated with concussion.

The shearing forces (acceleration, deceleration, or rotational forces) from acute brain injury cause neuropathophysiological changes to the microscopic structure of the brain.[249] These consist of diffuse axonal injury caused by density differences between the gray and white matter of the brain. However, the gray-white junction is not the only area where pathological changes are seen; changes also are seen in the internal capsule, midbrain, and pons. Oxidative stress, cytotoxic injury, and excitatory neurotoxicity caused by the release of proinflammatory cytokines are also implicated.[250,251] Data has shown that there is hormonal dysregulation in trauma-induced hypothalamic malfunction. Disturbances in hormone regulation have been observed in TBI and may be the cause of disturbances in the sleep-wake cycle associated with PTSD. Research shows that there is a disruption of hormonal regulation in women who sustain a mTBI in contact sports, and recovery may be prolonged because of this dysregulation.[252,253] This research should be applied to women in the armed services who suffer TBIs.

Evidence indicates that the severity of metabolic changes initiated by a concussive event is directly related to the length and degree of neurological recovery.[254] In addition, these changes have been implicated to cause a window of vulnerability following injury that should dictate return-to deployment guidelines.

4.3 Comorbidities

4.3.1 Post Traumatic Headache

Post traumatic headache (PTH) is the most common symptom of mTBI and is among the most debilitating long-term sequelae in individuals who have a prolonged recovery. Headaches that present de novo and are temporally related to the traumatic injury are typically characterized as headaches attributed to trauma or injury to the head and/or neck.[255] Although the most common headache type is migraine, many other headache subtypes have been described in the literature, including tension-type headache.[256] Whatever the individual experience, all PTH patients have head pain that is sometimes severe. Many also get an upset stomach and become sensitive to bright lights and loud noises.[257,258] PTH currently lacks well-established, evidence-based treatment guidelines. Most treatment recommendations are based on expert opinion and typically mirror the established treatments for specific types of headaches.

4.3.2 Post-traumatic Stress Disorder

PTSD has emerged as one of the signature impairments of the conflicts in Iraq and Afghanistan.[259] More than 138,000 active duty soldiers and veterans have been diagnosed with PTSD since 2002.[260] While the adverse mental and physical health outcomes associated with PTSD are well documented —including depression, anxiety, substance abuse, hypertension, obesity, and cardiovascular disease — the relationship between PTSD symptoms and chronic headaches among military personnel has received less attention.[261] PTSD causes clinically significant distress or functional impairment in an individual's social interactions, work capacity, and ability to carry out his/her normal routine. Although mTBI and PTSD have distinguishing characteristics, there is a considerable overlap of symptoms. By pursuing the mission for effective treatment by experienced clinicians, gathering accurate information, and enlisting the support of peers and family, it is possible to develop an effective treatment strategy for mTBI and PTSD

4.3.3 Chronic Traumatic Encephalopathy

In athletic and military environments, the link between repetitive, mTBI, and neurodegenerative disease has received considerable attention. This interest, in large part, has been driven by increas-

ing numbers of reports of chronic traumatic encephalopathy (CTE) in autopsies of former athletes or military personnel.[262,263,264] CTE is a neurodegenerative disease associated with repetitive head trauma. Although initially believed to affect only boxers, the at-risk population has expanded to include football and hockey players, wrestlers, and military veterans. This progressive neurodegenerative disorder is characterized by the accumulation of hyper-phosphorylated tau protein that begins focally and then spreads to involve most of the central nervous system.[265] In its early stages, CTE symptoms include difficulty concentrating, depression, and behavioral and personality changes.[266] As the disease progresses, patients may have short-term memory loss and cognitive changes, and then, in its late stage, dementia. Parkinsonism and signs of motor neuron disease can also occur, along with difficulties with gait and speech. The likelihood of progression from brain injury to clinical manifestation is unknown, however, and factors that are reliably associated with progression have yet to be identified.

4.4 Future Directions in Detection

4.4.1 Genetics

TBI triggers a cascade of pathophysiological events involving all cellular levels, including the genome; protein mediators, such as ribonucleic acid (RNA); proteins, and serum antibodies.[267,268,269,270,271] Considerable efforts have been made to better understand the prognostic features that influence recovery following TBI. Genetic factors appear to play a significant role in how these processes are involved in TBI and may play a significant role in the patient's recovery and rehabilitation process.

The genes proposed to be associated with TBI can be roughly categorized into two categories: those that influence the extent of the injury (e.g., pro-and anti-inflammatory cytokines) and those that effect repair and plasticity (e.g., neurotrophic genes).[272,273,274] A growing body of research has attributed a role for genetic factors in the inter-individual variability observed in TBI, and in predicting functional and cognitive outcome following brain injury.[275] These variations are a result of alterations in the deoxyribonucleic acid (DNA) sequence within a given gene and are referred to as genetic polymorphisms. Polymorphisms can arise from insertions or deletions of short lengths of DNA within a particular gene, interfering with the normal function of the gene, or at a single nucleotide. When a single nucleotide is responsible for the modification in the DNA, it is referred to as a single nucleotide polymorphism(SNP). SNPs are the most common type of genetic variation, occurring once every 100 to 300 nucleotides, amounting to approximately 10 million in the human genome. A SNP can reside within the coding sequence of a gene where it may alter the amino acid composition of a protein or within a noncoding region of a gene, such as a promoter or intron, where it may influence expression of the gene and protein production.[276]

The study of genes that influence outcome following TBI is increasing. Evidence is rapidly accumulating in the literature, particularly in the last decade, focusing on the predictive properties of genetic polymorphisms alluding to an inherent pre-disposition to TBI outcome.[277,278,279,280] Numerous genes have been implicated in the pathophysiology and outcome following moderate to severe TBI. More recently, considerable attention has focused on genes associated with mild and repetitive mild TBIs, notably among combat veterans and professional athletes.[281,282,283,284] Although inheriting a single defective allele of a specific gene may predispose an individual to better or worse outcome following injury, it is becoming increasingly apparent that recovery from TBI is multifaceted, involving the interaction of numerous genes from multiple pathways.[285,286,287,288,289] The apolipoprotein E gene (APOE) has emerged as a candidate for predicting TBI recovery, with APOEε4 identified as a susceptibility marker for poor outcome, despite large discrepancy in its reported influence post-TBI.[290,291,292]

In summary, how genes interact with one another following TBI is not fully understood and requires extensive research. Most genetic research has been conducted in adult populations, despite the observation that the vast majority of TBIs occur in children and young adults. Additional TBI-genetic research studies are essential to facilitate both the prediction of outcome and clinical management in TBI population.

4.4.2 Biomarkers

The clinical use of protein biomarkers in the diagnosis of mTBI has multiple advantages. First, biomarker measurements from peripheral tissues (e.g., blood, saliva, or urine) are minimally invasive and are inexpensive to process and analyze. Second, if the level of a biomarker indicates brain damage (or a lack thereof), a clinician or researcher can better able determine if brain imaging is necessary and what treatment options are best. For severe and moderate TBI, neuroimaging and electrophysiological modalities are being routinely used in the clinical setting for TBI diagnosis and prognosis. For mild and

chronic TBI, the molecular biomarkers detected in bio-fluids, such as blood serum, urine, saliva, cerebrospinal fluid (CSF), and extracellular fluid (ECF), are more practical and economical.[293,294,295] Sensitive and specific biomarkers reflecting brain injuries, repair, and regeneration can provide important information regarding TBI pathophysiology and can serve as candidate markers for predicting abnormal computed tomography (CT) findings in mild TBI.

In TBI, neuronal and glial cells at and around damage sites release brain-derived cell-type-specific proteins into the peripheral blood stream.[296] Representative biomarkers are derived from acute neuronal, axonal, astroglial, and endothelial injuries or secondary inflammatory and reparative processes such as inflammation, oxidative stress, excitotoxicity, and other host-derived pathophysiological mechanisms.[297] In particular, early biomarkers of structural damage, such as S100 calcium-binding protein B, glial fibrillary acidic protein, and ubiquitin carboxyl-terminal hydrolase L1 may be used to assist physicians in assessing a brain injury and determining whether to order a head CT scan for patient with a mTBI. Because biological markers can become abnormal within hours and remain abnormal for days or weeks after injury, they can be used to predict prolonged complications or to monitor recovery. Though numerous candidate biomarkers have proven a positive association with TBI outcome, they showed low specificity or sensitivity when used individually. Combining biomarkers into a panel may provide more information than individual biomarkers.[298]

The heterogenetic and multifactorial nature of secondary responses in TBI make it difficult to find cellular biomarkers for diagnosis, prognosis, and management of TBI. It is imperative to find more accurate TBI-specific markers to take the place of central nervous system-restricted markers. Although great progress has been made with the aid of advanced technologies, there is still a need for fast and reliable diagnostic instrumentation, especially on a sports playing field or in a combat zone to determine when the individual can return to play or deployment.

4.4.3 Imaging

An essential goal of neuroimaging after TBI are to assist in prevention of secondary damage, to emphasize favorable biomarkers with potential for neurodegenerative disease detection, and to obtain prognostic information about long-term outcome. Neuroimaging methods, such as CT and MRI are the conventional neuroimaging techniques generally used for the initial clinical evaluation and acute vital management of intracranial problems following TBI.[299] CT is the imaging modality that is used to exclude serious intracranial injury and provide an early assessment of the extent of brain injury.[300] MRI is indicated in acute TBI when neurologic examination is not consistent with CT findings and provides more sensitivity in detection of white matter abnormalities.[301] Advanced structural neuroimaging techniques are susceptibility-weighted-imaging (SWI), diffusion-weighted-imaging (DWI), diffusion-tensor-imaging (DTI) and high-definition-fiber-tractography (HDFT). Advanced functional neuroimaging methods include MR spectroscopy (MRS), functional MR imaging, magnetic resonance elastography (MRE), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG).[302] These techniques are beneficial for finding abnormalities in the brain related to long-term traumatic sequelae, and the focus of ongoing research is to identify structural and functional correlations while analyzing fiber tracts.[303] (Table 1)

SWI is the detection of small amounts of altered blood and blood products during neuroimaging.[304] An important advantage of SWI is the detection of microbleeding. It suggests the presence of diffuse axonal injury and is not seen on conventional imaging in the acute phase of injury. Its presence may be a useful indicator of the severity of brain injury and may assist clinicians in identifying elevated risk for poor social cognitive function in the post-acute recovery period. Microbleed lesions detected by SWI on the frontal, parietal, and temporal lobes may correlate with higher incidence of depression after TBI.[305]

DWI measures patterns of water diffusion based on surrounding temperature, structures, and tissue damage.[306] Areas with a high degree of diffusion, such as the cerebrospinal fluid, will be hypointense, or less intense and appearing darker, on DWI and display a high apparent diffusion coefficient (ADC) value.[307] Unlike SWI, DWI has the ability to explain the pathophysiology of non-hemorrhagic diffuse axonal injury. White matter ADC is particularly useful for predicting outcomes.[308]

DTI measures the movement of water molecules in tissue and white-matter brain regions using fractional anisotropy to determine disruptions in flow. The lower the fractional anisotropy value, the more likely there is a microstructural abnormality.[309]

HDFT tracks fibers from the cortex to subcortical targets with high resolution.[310] It also reveals more than 250,000 fibers with 256 possible directions,

Table 3: Neuroimaging Modalities for TBI		
Neuroimaging Modality	**Attributes**	**Limitations**
Diffusion Tensor Imaging (DTI)	White matter track integrity	Fractional Anisotropy measurement-by interstitial fluid content
Diffusion-Weighted Imaging (DWI)	Non Hemorrhagic diffuse axonal injury	heterogeneity with Large standard deviation of the ADC changes
Functional MRI (fMRI)	Neuronal activity with cerebral oxygen consumption (BOLD)	Physics based factors of signal and the field of inhomogeneity generated by deoxyhemoglobin
High Definition Fiber Tractography (HDFT)	Structural Brain connectivity	Restricted ability to determine crossing of fibers within a voxel
Magnetic Resonance Elastography (MRE)	Measures brain mechanical properties (stiffness)	Must create a vibrational field to measure brain mechanical properties
Magnetic Resonance Spectroscopy (MRS)	Intracellular neuronal metabolic status	limited spatiotemporal resolution and small brain fields are challenging to analyze
Magnetoencephalography (MEG)	Magnetic fields of postsynaptic ionic currents	Absence of standard analyzing protocols
Single-photon Emission Computed Tomography (SPECT)	Regional cerebral blood flow	Blood flow changes after TBI do not always correspond to metabolism
Susceptibility-weighted Imaging (SWI)	Diffuse axonal injury and detecting Microbleed	Sensitive to motion artifacts and long acquisition time

enabling MEG detects magnetic fields generated by currents flowing in neurons through a group of sensors surrounding the head.[329] During MEG imaging, the subject may perform auditory, visual, and/or tactile tasks or undergoes electrical stimuli. The MEG detector examines neuronal change and reorganization during tasks between different brain regions; it can identify abnormal connections between multiple suspected epileptogenic regions following TBI.[330,331]

MRS is a neuroimaging technique that reflects intracellular metabolic status as evidence of microscopic injury.[332,333] Common neuronal markers used during MRS include N-acetyl aspartate (NAA), a neuronal mitochondrial marker that decreases with neuronal loss or dysfunction; creatine (Cr), a marker for intact brain energy metabolism; and choline (Cho), a marker for membrane disruption, synthesis or repair. Increased amounts of Cho detected in white matter is a breakdown product after myelin damage.[334,335,336] Various studies indicate that NAA levels and NAA to creatinine ratios are reduced in TBI as a result of neuronal loss and/or dysfunction. Reduced NAA levels are predictive of long-term functional outcomes in TBI.

Brain perfusion SPECT imaging is a functional nuclear imaging technique performed to assess regional cerebral perfusion by using a radioactive labeled tracer.[337,338,339] SPECT scans can display areas of impaired brain function following TBI, including focal cerebral blood flow (CBF) reduction near the focal site of injury and asymmetrical hypoperfusion in the prefrontal, temporal, and parietal or occipital lobes. SPECT discloses regions of hypoperfusion correlated with severity of acute injury, loss of consciousness, cognitive deficit, and brain atrophy.[340] SPECT can detect brain activation changes during complex cognitive tasks in patients with chronic symptoms following TBI.[341]

4.5 Monitoring

EEG biofeedback, or neurofeecback, is a well-established non-invasive diagnostic method for neurological monitoring, prognostic, and follow-up evaluation after TBI. EEG, which records neuroelectric activity in the brain from electrodes placed on the scalp, has been in use for almost a century as a research tool. It detects specific, but subtle, deficits in neurocognitive function associated with TBI in areas of the brain involved with attention, perception, memory, and visual and sensory processing.[342,343,344] EEG may also play a role in treatment of brain injury. Young mTBI patients showed improvement in cognitive functions and concussion symptoms.[345,346] Additionally, thalamo-cortical connection in follow-up MRI was increased after EEG neurofeedback therapy.[347]

Quantitative measures of altered brain electrical behavior may provide quantitative, early assessment

of neuropsychiatric disorders. This pursuit is important as changes in brain electrical behavior following TBI can be persistent. Slobounov et al. (2012) found that 85% of the mTBI patients who presented significant EEG alterations in the immediate post-injury period still presented altered EEGs up to 12 months post-injury.[348]

4.6 Treatment

Progesterone (PG) is a well-known hormone that primarily regulates the reproductive system, but it may have other uses. In several animal models of TBI acts as a form of neuroprotection.[349,350,351,352] This neuroprotective hormone is produced in the brain by neurons and glial cells, the cells by which PG's neuroprotective actions are believed to be derived. Cerebral edema, inflammation, apoptosis, and oxidative stress include some of the pathophysiologic changes that occur after TBI. PG acts as an anti-oxidant and upregulating gamma aminobutyric acid (GABA), a neurotransmitter, and seems to provide additional neuroprotection by reducing cerebral edema and decreasing inflammation and apoptosis. Reducing inflammation is achieved through downregulating the expression of proinflammatory cytokines though microglia and astroglial cells.

Hypothermia is one of the most promising treatments for TBI due to its ability to attenuate prolonged neurological deficits and improve functional outcomes.[353,354,355] Induced hypothermia aims to fight against such detrimental effects. Positive results were achieved by reducing hypoxic events following TBI with the use of brain tissue oxygen–guided cerebral perfusion pressure management and therapeutic mild hypothermia.[356,357,358,359,360] Although the mechanisms responsible for the actions of hypothermia in the treatment of TBI are not yet clear, mild induced hypothermia seems to have an association with the expression connexin-43 and glutamate-transporter-1 in the hippocampus following TBI in rats. Jackson et al., 2016[361] hypothesized that mild hypothermia, using a specialized head and neck cooling unit during the window vulnerability, may provide benefits for the brain along with reducing brain temperature.[362,363]

TBI frequently results in an impaired ability to retrieve memories formed prior to injury and a reduced capacity to form or retain new memories following injury. Despite the scale of the problem, there are few effective therapies available to mitigate the long-term consequences of TBI on memory issues. Through the Restoring Active Memory (RAM) program, the Defense Advancd Research Projects Agency (DARPA) seeks to accelerate the development of technology to address this public health challenge and help service members and others overcome memory deficits by developing new neuroprosthetics to bridge gaps in the injured brain. The goal of the RAM Replay program is to develop new closed loop, non-invasive systems that leverage the role of neural replay in the formation and recall of memory to help individuals better remember specific episodic events and learned skills. The RAM Replay program aims to non-invasively detect, model, and facilitate real-time correlates of replay in humans, leveraging neurophysiology, as well as physiological state and external elements in the surrounding environment.[364]

Many veterans with mTBI and PTSD become isolated as they withdraw from social contact. Cognitive behavioral therapy requires veterans to negotiate daily activities and interactions, such as attending appointments. Virtual environments (VEs) and virtual humans (VHs) hold the potential to address these problems. VEs are computer-generated, immersive, and interactive virtual reality constructs for simulation and learning.[365] VHs are specialized types of automated virtual reality human figures, which display lifelike movement, appearance, and gestures and are able to recognize and respond to human speech or textual communication. VHs are an excellent means to present social challenges, probe or train attitudes and beliefs, and teach social strategies and coping mechanisms. VEs and VHs provide opportunities for interaction between patients and therapists in fully immersive, customizable, controlled, and low-threat environments. These environments have the potential for infinite repetitions of assessment or training tasks. VEs allow for creation of simulated realistic environments in which performance can be tested and trained in systematic fashion.

The subtleties of TBI research stretch beyond a monotherapeutic approach to target single receptors or specific mechanisms, and an approach that encompasses both the multiple direct and indirect injury mechanisms must be developed in order to provide effective treatment for TBI.[366] Continued research is needed to determine the magnitude and socioeconomic and medical impact of military service related TBI, identify preventable and modifiable risk factors to reduce injury, and develop and evaluate evidence -based interventions.

5. Resilience Training

5.1 Introduction

In World War II, there were more psychiatric causalities than physical casualties. Approximately 98% of individuals who participated in combat for over 60 consecutive days experienced emotional breakdowns.[367] Combat readiness consists of both physical and psychological readiness. Military training involving the use of weapons and physical conditioning has been a primary focus of pre-deployment training; they are essential to ensure military personnel are ready for combat and harsh physical conditions. Resiliency training is provided in order to give soldiers the best possible chance at survival and success before, after, and during their service. The United States Army's Comprehensive Soldier and Family Fitness program (CSF2), which is an element of the US Army's Ready and Resilient Campaign, is an example of this type of training. Established in 2009, this program is used to increase resilience among soldiers, their families, and Army civilians.[368]

An increasing amount of attention is now being directed towards soldiers' psychophysiology, or the combination of psychological and physiological aspects of readiness. Greater understanding of the etiology and course of PTSD has brought a deeper appreciation for the physiological and neurobiological correlates of this condition.[369] Furthermore, individuals can be trained to consciously alter these correlates, even moderators perhaps of trauma development, e.g. Nagpal et al., 2013.[370] Research emphasizes readjustment from combat zone deployments requires both pre- and post-deployment preparation.[371]

Identifying risk factors and building resilience are increasingly critical research areas, as larger numbers of military personnel are exposed to battlefield experiences that can result in numerous and sometimes chronic mental and physical ailments, including anxiety, depression, and heightened arousal.[372] To better address these symptoms, in 2003 the DoD and the VA implemented mandatory screening protocols for all service members returning from OIF and OEF deployments. The Post Deployment Health Assessment (PDHA)[373] is designed to detect psychological, psychosocial, and physical issues associated deployment-related exposures.[374,375] Specifically, mandates require mental health assessments 120 days before deployment, between 90 and 180 days after deployment, 180 days to one year after deployment, and 18 to 30 months after deployment.[376] Valuable information regarding common issues emerged as a result of these mandatory screenings. To further improve military capability to diagnose PTSD in service members, the U.S. Congress introduced the National Defense Authorization Act for FY 2012 (10 USC § 1074m), which requires individual person-to-person, mental health assessments by licensed mental health providers for each service member.[377]

Existing approaches for dealing with psychological and physiological stress have been largely reactive and focused on treatment after deployment.[378] Current research indicates that using proactive strengthening and resilience training techniques prior to deployment can significantly lower risk or severity of PTSD symptoms later. Resilience training regimens focus on promoting self-regulation, which research indicates is associated with better psychological adjustment.[379] When individuals suffering from PTSD experience self-regulation impairments, their ability to logically make critical and timely decisions is impaired. This impairment often causes individuals to experience increased emotional distress, periods of dissociation, loss of trust in relationships and meaning in life, and chronic, seemingly idiopathic health problems.[380,381,382]

5.2 Financial Burden of Post-deployment Transition

The financial burden of postdeployment transition is tremendous. A 2010 study[383] found that of 49,425 veterans newly diagnosed with PTSD, only 9.5% attended nine or more VA mental health sessions in the first year of diagnosis. And yet, during 2012, the DoD spent approximately $294 million, and the VA spent nearly $3 billion to treat PTSD for active service personnel and veterans, respectively. Still, treatment effectiveness is typically short-lived,[384] and there are significant treatment fidelity issues marked by low attendance and rising attrition rates.[385] Research by Brenner et al., 2009[386] reflects the military's efforts to address these concerns and looks at resilience training prior to deployment as a way to mitigate PTSD onset, severity, and cost of treatment post deployment.

5.3 Physiological and Psychological Resilience

The relationship between psychology and physiology is increasingly important to the military.[387,388] Research indicates that high-intensity physiological effort with inadequate recovery often leads to degraded military performance.[389] In addition, physiological measurements, such as real-time cardiovascular impact and HRV are useful screening

tools to identify personnel who better cope with an increased amount of risk during active duty.[390]

The military has introduced initiatives, such as Comprehensive Soldier Fitness (CSF), which tests for psychological fitness and provides soldiers with self-improvement courses and Master Resilience Training (MRT). The courses are instructor-led and address positive emotion, engagement, relationships, meaning, and accomplishment, which are the building blocks of resilience and growth.[391] Psychological resilience is the ability to adapt of life tasks in highly adverse conditions. The application of physiological resilience consists of training and awareness for adapting from adverse to non-adverse environments. Training is a primary objective for all military personnel.[392] The Global Assessment Tool (GAT), an online assessment tool employed in CSF, is a self-report survey that measures psychosocial fitness in emotional, social, family, and spiritual domains.[393]

5.4 Existing Applications in Resilience

The Mental Gym™ method proposed by Oded[394] is a practical mental training program that assists soldiers facing extreme psychological stress to establish a balance between physical and emotional aspects within their everyday tasks. This method combines a variety of modalities, including biofeedback, mindfulness, neurofeedback, imagery, stress inoculation techniques, and attentional training and problem-solving methods.[395]

Physiological measures are intended to provide a window into how the brain and body respond to stress. Often times, changes detected in heart rate, brainwaves, sweat gland response, and muscle activity are indicators of stress. Whereas these changes are typically covert to an individual, they are easily seen in physiological signals measured by biomedical devices. For example, service members may know when they were experiencing stress, but managed to hide the stress from themselves and others. In some instances, these objective, bio-medical devices measuring stress responses reveal that soldiers are more stressed than they believe themselves to be. Hence, biofeedback enhances internal awareness, and, for soldiers who are encouraged to suppress their emotions, biofeedback training may cause an adverse emotional reaction. Stress indicators such as blood pressure, respiration, and heart rate are indicators of stress that measured and trained in the Mental Gym™ method to help soldiers recognize that they are experiencing stress.[396] While it is possible to teach mental skills without biofeedback, increasing numbers of military outfits are using Mental Gym™.[397] and other programs that combine a number of methodologies to improve self-awareness.

Another method to help avert PTSD involves a performance enhancement and resilience training program developed and implemented for both pre- and post-deployment Reserve Officers Training Corps (ROTC) cadets at California State University in Fullerton, CA. This method combines multimodal biofeedback training, a psychophysiological stress profile, and a skills-based group educational program to help reduce stress reactivity and assist in promoting autonomic nervous system flexibility. HRV biofeedback training, breathing rate, and hand-surface temperature are particularly emphasized in this method.[398]

ROTC cadets enrolled in this program were instructed to practice breathing at the program-determined resonance frequency twice a day for 20 minutes using a device known as the EZ-Air™ pacer bar.[399] Additional sessions included breathing at resonance frequency with feedback through a device known as the Thought Technology Infiniti™ device. This was followed by multimodality biofeedback (surface electromyography, skin conductance level, and respiration) combined with an additional technique each week, such as autogenic training, imagery, and progressive muscle relaxation.[400] This study mirrored the research conducted by Sack, et al.,[401] which is the first to identify a decreased Respiratory Sinus Arrhythmia (RSA) in response to a traumatic reminder and an association between low baseline RSA and sustained conditioned arousal in PTSD.

A third method for averting PTSD on the battlefield and other stressful military situations involves the Stress Resilience Training System (SRTS), which shows how a software training application can provide an effective, individualized method for minimizing the negative impacts of stress on the battlefield while eliciting potentially positive impacts on battlefield performance and overall performance.[402] This method provides information to the individual, skills training, and practice to build capacity for coping and performance while exposed to stress. Increased resilience results from transferring resilience knowledge into measurable skills that are developed through practice and applied to life situations. The effectiveness of resilience skill practice increases as the intensity of the session increases, progressing from cognitive knowledge-based modules to bio-

feedback techniques modules to biofeedback-controlled games.[403] Like the other methods mentioned, SRTS looks at HRV as a measure of stress.[404]

Seven evaluations, including a usability study, controlled experiments, and field evaluations, were conducted to evaluate SRTS effectiveness. The results demonstrate that the SRTS program helps users to manage their stress by reducing stress symptoms while improving job performance.[405] In addition, like many of the other resilience training programs, SRTS uses computer-based software games to help military personnel to manage stress in a simulated environment, increasing the availability and lowering the cost of training.

Research and applications for building and training psychological and physiological resilience in soldiers are increasing. Effectiveness of these approaches can have profound benefits for the soldier, soldiers' families, military budget, and the development of personalized and mobile training tools.

6. Conclusion

Post-traumatic stress disorder is a complicated and disabling condition affecting many of our country's active and veteran military service men and women. Missions are longer, with multiple tours leading to less mental and physical recovery time,[406] negatively affecting service members' health and mental wellbeing. Researchers need to better understand the effects of trauma experience on the mind, brain and body. Extant research provides a guide for next steps to improve reporting, assessment and effective interventions. Specific translation of research to development, testing, and application of emerging evidence, especially novel technological methodologies and evidence-based techniques, is essential to improving the future mental and physical of military service members and veterans.

Clear themes and factors have emerged as a result of military research through private research, universities, DoD, and VA initiatives. A number of factors contribute to the etiology and pathophysiology of PTSD, ranging from prior trauma experiences and comorbidities to specific demographic factors and psychobiological indicators. Indeed, theoretical underpinnings in behavior, biology, and nosology research form the multi-faceted lens through which researchers view the effects of trauma. Research in trauma establishes cognition, emotion, memory, sleep, neurocircuitry, neuroplasticity, and multiple other factors as unique stress effects or contributors. Research in blast-related mTBI suggests it is pathophysiologically different than other mTBI and PTSD, although the symptom overlay sometimes makes diagnosis challenging. A growing amount of research is finding that genetics, personality, and other neurobiological risk factors significantly contribute to the complexity of PTSD. Hence, attention must be given to additional physical and environmental factors that may moderate the relationship between comorbidities and PTSD.

Although this SOAR focuses on combat-related PTSD and mTBI and changes in their diagnosis and treatment, the military must address the violent outcomes of these untreated or under-treated conditions. Depression and violence, are more frequently leading to suicide, sexual assault, and even homicide, making increasing resilience pre- and post-deployment a high priority.[407]

With recent discoveries in the neuro- and pathophysiology of PTSD comes the opportunity to target more specific areas of research and to more wholly, not just comprehensively, address this condition. Moreover, we may be able to overcome barriers associated with underreporting by destigmatizing PTSD as more psychophysiological in nature. The addition of valid psychophysiological assessments to confirm PTSD diagnosis and to discriminate primary mTBI can also overcome over-reporting issues and help identify root causes of symptoms, respectively. Scientific discoveries and advances in technologies are changing the landscape of detection and treatment capabilities for PTSD, mTBI, and other conditions. Improvements in technology enable clinicians to measure biometric data, such as heart rate variability and brain activity, and psychological data, with mobile applications, to personalize evidence-based treatment and resilience training. This SOAR reviews the current state of the field and the scientific research that is changing it. We attempt to synthesize specific points of progress made while also highlighting areas of need.

We hope to encourage research to pursue diverse and innovative approaches to address PTSD. In conclusion, research indicates a need to expand our current understanding of this highly complex condition, in order to more appropriately assimilate emerging science and technology, where necessary, to yield improvements in knowledge and standards of care.

Appendix A

Virtual Reality Neuro-Rehab for Stroke Holds Promising Applications for PTSD and mTBI

Brain injury and disease have a long history of being divided into the physical and the psychological, roughly mapping onto the fields of neurology and psychiatry, reinforcing the idea that there is a distinction between the mental and the physical, the practical and the theoretical.[408] The divide between the fields has influenced approaches to therapeutics-- physical therapy for neurological impairment and psychotherapy for psychiatric illness. Physical therapy is centered on touch and movement, whereas psychotherapy is based on verbalization and thought content. At their core, both types of intervention are behavioral; they focus on task-based and context-based training, practice, and feedback. The concept of deliberate practice is as applicable to purely cognitive activities, like chess, as it is to more physical activities, like sports and music.[409] However, despite this methodological overlap, physical and cognitive therapies operate on non-overlapping domains in terms of their effects. There is evidence that these two approaches can have overlapping effects and that gaming and virtual reality can promote and exploit this overlap.

Researchers are currently conducting an early intervention trial for moderate to severe hemiparesis after stroke that combines video gaming and exoskeletal robotics. A customized game is based on a highly immersive virtual oceanic environment in which the patients control a simulated dolphin that responds to the patient's desired direction in extrinsic space. The goal is to have the patient make a large number of exploratory arm movements in the short-lived sensitive period after stroke, when plasticity responsiveness to training are maximal.[410] The dolphin has to jump and spin, catch fish, and battle sharks. The game was designed to promote intrinsic motivation, which promotes more enjoyment, creativity, and flexibility than motivation obtained from extrinsic rewards.[411] The fish and sharks become more intelligent as the levels progress, which makes this game require both cognitive strategizing as well as skilled motor execution. In pilot studies, researchers observed that the game created a joyous, playful state in patients and a degree of engagement not usually seen in a hospital setting.

A combination of motor and cognitive training may have benefits in patients with TBI who have multifaceted cognitive impairment, including problems with executive function, visuo-spatial abilities, and working memory.[412,413] Recent work in healthy participants suggests that designed, sport-like activities can target both physical fitness and cognition and can mutually enhance each other.[414] Specifically, Moreau and colleagues found that 8 weeks of training at a designed sport showed larger gains on cognitive measures than a group that had cognitive training alone. This is likely through increasing time on task, motivational effects on performance, and the generalizability of the learning effects. The apparent generalizability of combined motor and cognitive training stands in stark contrast to the lack of benefit of training on games that target a specific cognitive function, such as those offered by the now discredited company Lumosity.[415,416,417]

The usefulness of immersive sport-like video games and virtual reality for PTSD is not known at this time, although the boundary between TBI and PTSD is blurring, with evidence that PTSD also is associated with neural injury.[418,419] Because PTSD is common after stroke,[420] it is assumed that all these disorders are associated with neural injury and that, like stroke, TBI and PTSD will respond to motivating and immersive training experiences. At the current time, cognitive behavioral therapy (CBT) is the gold standard for the treatment of PTSD and TBI.[421] CBT for PTSD can be considered analogous to the standard occupational, physical, and speech therapies given after stroke. Treatments need to be more enjoyable and more intrinsically motivating if their frequency goes beyond once a week sessions with a therapist. This can only realistically be achieved through the use of technology, as it simply is not feasible for a therapist(s) to provide several hours of CBT every day to a single patient for weeks, but CBT can be provided by technology and gaming.

It is time to bring a more holistic, fully immersive experience to patients with PTSD and TBI that exploits both the aesthetic and motivating effects of gaming with the neuroscience of plasticity after brain injury.

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