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Traumatic Brain Injury (TBI): The Progressive Neurodegeneration and Mental Health Decline in United States Veterans

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ABSTRACT

Since the year 2000, the Defense and Veterans Brain Injury Center reported 414,000 documented cases of traumatic brain injuries (TBIs) among individuals serving in the United States Armed Forces (Defense and Veterans Brain Injury Center, 2020). Traumatic events to the head as a result from car accidents, falls, explosions, and gunshot wounds can lead to a disruption of normal cognitive functioning. Roughly 80% of diagnosed TBIs are mild in nature, commonly referred to as concussions, and can range from mild, moderate, severe, and penetrating (O'Neil et al., 2013). However due to the difficulty of diagnosing a TBI most cases go undocumented, or patients do not seek treatment. TBIs that are left untreated can result in progressive neurostructural damage which can lead to the development of dementia-related diseases as well as psychological problems such as post-traumatic stress disorder (PTSD) (McKee et al., 2014). The physical and mental health conditions that can result from sustaining a TBI can drastically impact the lives and families of those injured veterans. With an estimated 8 million adults suffering from PTSD each year as per the National Center for PTSD (2020), researchers must understand how to utilize the linkage between a TBI and PTSD in order to appropriately prevent progressive neurodegeneration and any associated psychological problems (Gradus, 2019).

Previous studies have shown evidence that both single-incidence and repetitive mild TBIs (mTBIs) can lead to atrophy of the grey and white matter in the brain and can promote the acceleration of neurodegeneration in the brain (Gradus, 2019).This chronic neurodegeneration can pose an increased risk for the development of progressive neurodegenerative diseases such as Parkinson's Disease, Alzheimer's Disease, Frontotemporal Lobar Degeneration (FTLD), and

Chronic Traumatic Encephalopathy (CTE) (Gradus, 2019; National Center for PTSD, 2020). Accompanying neurodegeneration are behavioral changes, executive dysfunction, memory loss, and cognitive impairments (DePalma et al., 2018). Researchers have begun to find associations between PTSD and TBI as a result of the disruptions to certain neuropathways from the amygdala and orbitofrontal cortex (DePalma et al., 2018; McKee et al., 2014). This capstone project is a literature review of the neurostructural and cognitive-behavioral changes that result from traumatic brain injuries. The research provided in this paper explores the connections between neurostructural damage and progressive neurodegenerative diseases such as Alzheimer's Disease (AD), FTLD, and CTE. Psychological effects that stem from sustaining a TBI including post-traumatic stress disorder (PTSD) and the increased risk for suicide and self-harm are also discussed.

INTRODUCTION

Traumatic Brain Injury

The Defense and Veterans Brain Injury Center (DVBIC) defines a traumatic brain injury (TBI) as a "blow or jolt to the head that disrupts normal functioning of the brain" (Defense and Veterans Brain Injury Center, 2020). Car accidents, falls, explosions, and gunshot wounds are all common traumatic events that can lead to an individual, whether civilian or soldier, sustaining a TBI. Sustaining an TBI while serving in the military is unpredictable and spontaneous, yet blast exposures from bombs, grenades, and improvised explosive devices (IEDs) remain the most common cause of TBIs sustained in combat (McKee et al., 2014). One group of researchers found that in U.S. troops deployed to Iraq and Afghanistan during Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND), the occurrence of blast related TBIs varied from 15-23%, affecting almost 400,000 troops (McKee et al., 2014; Rosenfeld et al., 2013). Additionally, another group of researchers screened 1 million veterans of the 2.6 million serving from 2007 through 2015. Roughly 20% of the 1 million veterans screened positive on questions pertaining to TBI-sustaining events, immediate symptoms, new or worsening symptoms, and current symptoms. Of the positively screened veterans, almost 10% were positive for a concussion/mild TBI. When these results are compared to the civilian world, the prevalence among civilians is greatly decreased. In a survey of 57,392 civilian trauma cases in the United States, 89 (0.2%) where blast-related injuries, demonstrating how rare traumatic brain injuries are to the general population (Elder et al., 2010). The increasing prevalence of TBIs in combat situations requires an immediate concussive assessment in order to prevent and limit the number of exposures to traumatic events. While the assessments in place are able to flag

soldiers for possible concussive events, many do not self-report the incidences thus leading to difficult diagnoses.

BACKGROUND

TBIs remain one of the most difficult brain injuries to diagnosis correctly among soldiers and it is one of the least understood in terms of the disrupted mechanisms and pathways (McKee et al., 2014). U.S. soldiers can experience reoccurring and progressive long-term effects after sustaining a TBI, with resulting cognitive, behavioral, and physiological changes. Common self-reported symptoms by U.S. soldiers include headaches, cognitive dysfunctions, attention difficulties, and impaired balance, and all will vary with the severity of the sustained TBI. TBI is considered one of the "invisible" wounds sustained during military service due to the lack of external evidence for head or brain injuries. Until imaging and questionaries are obtained through a medical care provider can a TBI diagnosis be given. Diagnosed traumatic brain injuries are classified on a scale of mild, moderate, and severe. The Department of Defense (DOD) and the Department of Veteran Affairs (VA) use 6 criteria in their diagnosis of a TBI, as shown in Table 1: structural imaging, loss of consciousness (LOC), alteration of consciousness (AOC), post-traumatic amnesia (PTA), and the Glasgow Coma Scale (GCS) (shown in Table 2). (O'Neil et al., 2013; Rosenfeld et al., 2013).

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0–30 min	> 30 min and < 24 hrs	> 24 hrs
Alteration of consciousness/mental state (AOC)	a moment up to 24 hrs	> 24 hours. Severity based on other criteria	
Post-traumatic amnesia (PTA)	0-1 day	> 1 and < 7 days	> 7 days
Glasgow Coma Scale (best available score in first 24 hours)	13-15	9-12	< 9

Table 1. Classification of TBI severity

BEHAVIOR	RESPONSE	SCORE
Eye Opening Response	Spontaneously	4
	To speech	3
	To pain	2
	None	1
Best Verbal Response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Best Motor Response	Obeying	6
	Localizing	5
	Withdrawal	4
	Flexing	3
	Extending	2
	None	1

Table 2. Glasgow Coma Scale (recreated using CDC guidelines)

A mild TBI (mTBI) is defined as having normal structural imaging, LOC lasting less than 30 minutes, AOC lasting less than 24 hrs, PTA lasting less than 1 day, and a GCS score of 13 to 15. A moderate TBI is defined as having normal or slightly abnormal structural imaging, LOC lasting 30 mins up to 24 hrs, AOC lasting at least 24h hrs, PTA lasting from 1 day to 1 week, and a GCS score of 9 to 12. A severe TBI is defined as having normal or abnormal structural imaging, LOC lasting more than 24 hrs, AOC lasting more than 24 hrs, PTA lasting at least 1 week, and a GCS score less than 9. While a clinical diagnosis exists, TBIs remain one of the most difficult brain injuries to diagnosis correctly among soldiers and the acute and long-term effects have been a poorly researched and explored (McKee et al., 2014). U.S. soldiers can experience persistent and progressive long-term effects after sustaining a TBI, with resulting cognitive, behavioral, and physical changes. Commonly self-reported symptoms by U.S. combat veterans include headaches, forgetfulness, poor concentration, and anxiety. These symptoms typically self-resolve over the course of a few days to weeks, however 10-20% of soldiers report continued unresolved problems (Vasterling et al., 2009). These cognitive dysfunctions, attention

difficulties, impaired balance, and physiological changes all will vary with the severity and classification of TBI.

Although most neurological symptoms are subjective in nature due to veterans self-reporting to their primary care physicians, there are two initial assessments used to for any suspected TBIs. The Military Acute Concussion Evaluation (MACE) is an initial mental status assessment given to veterans who may or may not have been involved in an acute concussive event (Air Force Center of Excellence for Medical Multimedia). The assessment contains 4 sections: a concussion screening, a cognitive exam, a neurological exam, and a symptom screening. The initial concussion screening looks to identify information about the sustained concussive event, whether there was loss of consciousness, alteration of consciousness, and/or post-traumatic amnesia. The cognitive exam focuses on orientation, memory, and recall of the veteran post concussive event. The neurological exam tests for pupil responses to light, speech ability and comprehension, grip strength, and balance. The last section involves symptom screening, which screens veterans for the common complaints of headaches, dizziness, impaired memory, balance problems, nausea/vomiting, tinnitus, and concentration. MACE should be the initial assessment given to any U.S. soldier who has experienced a concussive event within the first 24 hours of the event happening. For those combat veterans who are experiencing symptoms past that window of time or those who have screened positive on the MACE, they are given the Comprehensive Traumatic Brain Injury Evaluation (CTBIE) through the VHA healthcare system. The CTBIE is conducted by a TBI specialist who gathers an in-depth history of the patient's symptoms, the concussive event, review of body systems, physical exam, and administers the Neurobehavioral Symptom Inventory (NSI). A formal diagnosis can be made, and a treatment plan can be implemented based on the conclusive findings (Scholten et al.,

2016). Treatment options and TBI management will be discussed later in the Discussion portion of this paper.

As mentioned previously, blast related TBIs are the leading cause of traumatic brain injuries among U.S. combat veterans, with blast-related mTBIs as the most common form affecting military personnel (McKee et al., 2014). McKee et al. (2014) reports that 60% of TBIs in the combat setting were of blast-related origin, with over 80% of those blast-related incidences resulting in a mTBI diagnosis. A mild TBI (mTBI), commonly referred to as an acute injury or simply a concussion, is typically caused by an impactful force, either directly or indirectly, to the head, face, and/or neck region. A blast related TBI is broken down into four components: primary, secondary, tertiary, and quaternary (Rosenfeld et al., 2013). Primary is characterized by the initial transmission of the blast wave through the skull into the brain. Secondary refers to any projectiles penetrating through the skull into the brain such as shrapnel or bullets. Tertiary is any acceleration, deceleration, or rotational effects on the brain. Quaternary involves other injuries to the head, face, neck and respiratory system such as any chemical or thermal injuries. The primary component of a blast related TBI is involved with all severities of a TBI: mild, moderate, and/or severe. Secondary, tertiary, and quaternary components are associated with only moderate and severe TBIs. Blast related TBIs result in the transmission of acoustic waves through the brain tissue. The blast waves can induce the brain tissue and surrounding blood vessels to expand and contract, resulting in tears and breakage. These tears and damages can lead to cerebral edema, intraparenchymal and subarachnoid hemorrhages, delayed vasospasms, cerebral ischemia, herniations, and aneurysms (McKee et al., 2014; Rosenfeld et al., 2013). Moderate and severe TBIs can also result in damages and eventual atrophy of the grey and white matter in the brain as well as altered glucose metabolism (McKee et al., 2014; Petrie et al.,

2014). Diffuse axonal injuries associated with moderate and severe TBIs cause the brain to elongate and misshape due to rapid acceleration, deceleration, and rotational forces from a blast. Axons that make up the neural circuitry in the brain are extremely susceptible to injury and damage, so when the brain elongates and misshapes as a result of the blast, axons become damaged. These microstructural changes in the white and grey matter and fiber tracts can result in severe neurological and physiological changes. The microvasculature system is compromised which leads to a disruption in the blood-brain barrier as well as focal cortical hypoperfusion (McKee et al., 2014). Additionally, there is a rapid uncontrolled release of neurotransmitters such as glutamate, changes within the sodium (Na^+) channels and sodium-potassium (Na^+/K^+) pumps, massive influx of calcium (Ca^{2+}) ions, efflux of potassium (K^+) ions, and an increase in glucose metabolism (McKee et al., 2014).

The most widely used diagnostic definition of a TBI, taken from the Department of Defense and Department of Veterans Affairs, states that normal structural imaging on CT and MRI scans may or may not be present based on the severity of the TBI. Mild TBIs and some moderate TBIs typically do not show any abnormalities on imaging scans, while severe TBIs may show abnormalities. CT scans are the preferred choice during the first 24 hours after sustaining a traumatic brain event. CT scans are able to detect any early bleeds and any cerebral or bony pathology (Lee & Newberg, 2005). However, after 24 hours MRI scans are the preferred choice as they are able to detect any hematomas, axonal injuries, or small neuronal damage (Lee & Newberg, 2005). The pathophysiology of any blast related TBI is distinctive and varies across individuals depending on the blast energy, distance from the initial blast, body orientation, use of armor protection, the environment, and the frequency of blasts (Rosenfeld et al., 2013). All of

these blast related effects play an important role in the pathological presentation of each TBI for each individual veteran.

As mentioned above in the TBI diagnosis, most patients present with normal structural imaging after sustaining a TBI. The use of MRI to detect any brain abnormalities has been proven unreliable within the first 24 hours due to scans showing the absence of abnormalities when in fact there may be some present (MacDonald et al., 2011). When T2 MRI scans do show abnormalities, common findings include cerebral microhemorrhages, contusions, gliosis, and encephalomalacia (Riedy et al., 2016). However, the common presentation of no visible damage from CT or MRI scans does not mean there is an absence of any abnormalities (Elder et al., 2010). Additional scans and tests must be done in order to determine the extent of the brain injury. Diffusion tensor imaging studies have shown that soldiers who have sustained a TBI or currently experience PTSD have disrupted white matter integrity (Davenport et al., 2015). Diffusion tensor imaging (DTI) has become a widely popular diagnostic tool to determine the severity of neuronal damage. DTI is a type of magnetic resonance imaging (MRI) that is extremely sensitive to the diffusion rate of water in brain cells and tissue, measuring the structural integrity of the surrounding white matter (Taber et al., 2015). Water diffuses through grey matter at similar rates in every direction yet will diffuse differently through white matter depending on the surrounding structure. The direction of water diffusion within the white matter is controlled and bound by certain physical boundaries such as myelin and axon membranes (Chanraund et al., 2010). This causes the water to diffuse more easily down the controlled direction of the axon compared to perpendicularly, making the diffusion highly angiotrophic. Thus, when there are structural and integrity changes within the white matter, the rate of diffusion through the white matter will be uncontrolled and multidirectional, creating low

anisotropy. This allows researchers to pinpoint and detect any subtle neurostructural changes within the white matter and fiber tracts. Neuroanatomy changes as a result of TBIs have been found in the cingulum, uncinate fasciculus, anterior and posterior limbs of the internal capsule, cerebellar peduncles, and the genu of the corpus callosum (Petrie et al., 2014).

Another useful tool that has been proven to detect changes within the neuronal axons is amyloid precursor protein immunohistochemistry (McKee & Robinson, 2014). This type of test uses amyloid precursor proteins to visualize traumatic axonal injuries (TAIs) around small blood vessels in the corpus callosum, fornix, subcortical U-fibers, and the cerebellum. This test looks for accumulations of hyperphosphorylated tau (p-tau) in the form of neurofibrillary tangles (NFTs) and hemosiderin-laden macrophages (McKee & Robinson, 2014). Researchers have specifically linked these NFTs and hemosiderin-laden macrophages to axonal injuries, breaches of the blood-brain barrier, and neuroinflammation, which are all extremely important determiners for soldiers sustaining a TBI.

Neuroanatomy and Neural Pathways

Blast-related TBIs, whether mild, moderate, or severe, all can change the composition of the neuroanatomy in the brain. The cerebrum, amygdala, hippocampus, orbitofrontal cortex, frontal lobe, and temporal lobe, to name a few, are all heavily impacted as a result of sustaining a traumatic brain injury. Injury to these structures can lead to downstream effects causing memory problems, cognitive defects, behavioral abnormalities, and neuronal damage. The neuronal pathways and connections that allow humans to function as their baseline “normal” become disrupted. The limbic system is the epicenter for memory and emotion processing. The structures that comprise the limbic system provide the link between our emotions and our drive-related behaviors, as well as memory tasks and our reactions to sensory and internal stimuli (Felten &

Shetty, 2005; Vanderah & Nolte, 2018). It is a grey area in terms of the structures and boundaries within the limbic system, which include the cingulate gyrus, hippocampus, amygdala, septal nuclei, hypothalamus, and olfactory bulbs. While all of these structures are vulnerable to damage, the important TBI-related neuroanatomy includes the amygdala and hippocampus.

The amygdala is the control center for emotional responses, especially fear. Two kinds of sensory inputs project to the amygdala for processing and responses: general senses (such as taste, touch, smell, visual, and sounds) and physical and emotional senses. These inputs into the amygdala are then processed and projected outward to other surrounding structures such as the hypothalamus, septal nuclei, hippocampus, olfactory regions, basal ganglia, and other cerebral cortical structures. These projections allow the amygdala to bridge the connections between the "perception of objects and situations with the appropriate emotional response" (Vanderah & Nolte, 2018). Typically, these emotional responses relate to fear or danger, but that is not always the case. Projections from the thalamus allow the amygdala to process things in the outside world, while projections from other limbic structures and the hypothalamus allow the amygdala to process the body's current emotional and physiological condition. Outputs from the amygdala utilize these inputs to tell other structures how to respond. Outputs for emotional responses are sent to the hypothalamus, brainstem, and ventral striatum. Outputs for emotional memories and storage are sent back through the limbic system and hypothalamus, while outputs involving heightened awareness are sent to sensory cortices (Vanderah & Nolte, 2018).

Normal activation of the amygdala results in attentive fear. We typically stop what we are doing in a frozen state, become very in-tune to our surroundings, and then experience aggression with either fight or flight responses via our sympathetic nervous system. Activation of the sympathetic nervous system results in responses such as increased heart rate, pupil dilation, and

blood vessel dilation in the muscles. These primal responses allow us to react to a perceived threat, increasing our odds in survival. Since the amygdala sends projections to the hippocampus, situations that heavily activate the amygdala will tell the hippocampus to store memories of the events in order to remember next time a similar situation arises. Ratliff et al. (2019) found significant neurostructural changes to the basolateral amygdala during research studies on rats sustaining blast related TBIs (Ratliff et al., 2019). By mimicking the blast explosions as those found overseas in combat zones, the researchers were able to expose rats to these blasts to determine the traumatic effects on the amygdala. The researchers found a significant increase in the number of dendritic branching, dendritic spine densities, and increased signaling within the amygdala. The researchers hypothesized that the increased signaling within the amygdala can be attributed to increased feelings of fear and hyperarousal, which can overtime lead to the development of PTSD (Ratliff et al., 2019).

The hippocampus is another limbic structure which is extremely important to traumatic events and how we as humans process our responses to the situation. The hippocampus is a structure found in the medial aspect of the anterior temporal lobe which resembles a seahorse shape (Felten & Shetty, 2011). The functional aspect of the hippocampus is memory formation, specifically consolidating short-term memories into long-term storage. The hippocampus contains a wide range of connections throughout the brain and within itself, with information going to regions of the neocortex, temporal lobe and additional limbic structures such as the amygdala (Felten & Shetty, 2011). Memory formation and storage involves explicit memory, which are memories involving objects, stimuli, and information that is easily recalled and known (Felten & Shetty, 2011). This includes information on specific personal events, dates, and facts. Implicit memories, the ability to learn how to do tasks or skills unconsciously, are not dependent

on the hippocampus and rely on other surrounding brain structures. Storage of explicit memories are dependent on the hippocampus and other structures in the medial temporal lobe. Within the hippocampus are CA1 neurons containing pyramidal cells (Felten & Shetty, 2011). These hippocampal cells are vulnerable to damage and apoptosis which can lead to long-term cognitive, learning, and memory problems. Damage to these structures can lead to memory consolidation problems, affecting immediate and short-term memories, confusion, and disorientation (Felten & Shetty, 2011). Aungst et al. (2014) found substantial neuronal cell loss in both the ipsilateral and contralateral hippocampus in patients with repeated mTBIs. Additionally, they found a significant increase in the number of activated microglial cells, potentially serving as both neuroprotective and neurotoxic agents (Aungst et al., 2014). The neuronal cell loss and increased microglial presence leads to deficits in hippocampal functioning and a disruption in the synaptic transmission between cells, something commonly found in chronic neuroinflammation and neurodegeneration. This will play a role in the next section in regard to certain neurodegenerative diseases involving memory deficits.

Wright et. al (2017) demonstrated in their research that rats sustaining a blast-related traumatic brain injury can lead to progressive neuronal damage and eventual neuronal loss. The researchers linked their results from rats to soldiers sustaining TBIs while in combat. They hypothesized that a TBI can lead to progressive atrophy of the motor cortices with degeneration of the corticospinal tracts (Wright et al., 2017). Wright et al. (2017) also found a reduction in neurons with increased TDP-43 in the motor cortex, reduced spinal cord motor neurons, and increased expression of muscle atrophy markers. The atrophy of the motor cortex due to reduced neurons and pathologic TDP-43 is important because it leaves the brain susceptible for

progressive neurodegenerative diseases such as Alzheimer's Disease, ALS, CTE, and FTLD. Specific neurodegenerative diseases will be discussed in the section below.

Progressive Neurodegenerative Diseases

Traumatic brain injuries, whether mild, moderate, or severe, can result in a complete disruption in the normal processing of brain structures. Through repeated TBI exposures or increased severity, these brain injuries can lead to progressive pathophysiological presentations which include neuronal apoptosis, oxidative stress, neuroinflammation, diffuse axonal injuries, and excitotoxicity (Blennow et al., 2012). This is extremely concerning for those individuals serving within the United States military who are constantly at risk for TBI exposure, especially blast-related, while overseas. These individuals are at a high risk for sustaining a TBI, which puts them at an even higher risk for developing or triggering neurodegenerative diseases and PTSD (Omalu et al., 2011). McKee and Robinson (2014) found evidence in their studies that even a single TBI can lead to long-term gray and white matter atrophy, accelerate any present neurodegeneration, and can increase the risk of Alzheimer's Disease, Parkinson's Disease, Chronic Traumatic Encephalopathy, and motor neuron diseases such as ALS. They additionally found that those individuals sustaining a moderate to severe TBI were at a 50% increased risk for developing dementia-related diseases (McKee & Robinson, 2014). Due to these increased risks, TBIs, especially moderate and severe, have become an extremely important risk factors for progressive neurodegenerative diseases (Shahim et al., 2020). The connections between TBIs and the mechanisms in which contribute to neurodegenerative diseases will be discussed below.

Alzheimer's Disease

Researchers have determined that TBIs are one of many risk factors for late-life dementias, including Alzheimer's Disease (AD) (Mortimer et al., 1991). The relationship between this type of head trauma and Alzheimer's Disease has been established, yet it is very difficult for physicians to determine without looking at the neuropathology of the patient (Daneshvar et al., 2011). There is however a correlation with veterans having a history of traumatic brain injuries and higher prevalence of Alzheimer's-disease pathology (Danesvhar et al., 2011). The pathology of Alzheimer's Disease within veterans diagnosed with TBIs are similar to civilian patients with the AD diagnosis. There is a presence of amyloid-ß neuritic plaques and phosphorylated-tau (p-tau) neurofibrillary tangles (NFTs) (McKee et al., 2013). These amyloid-ß proteins are formed from amyloid-precursor proteins by ß-secretase and gamma secretase (Blennow et al., 2012). Amyloid-precursor protein has been found to be upregulated as a response to traumatic brain injuries, which in turn accumulate around the neurons and axons in the brain as a result of the axonal damage (Blennow et al., 2012).

Parkinson's Disease

Parkinson's Disease is another progressive neurodegenerative disease that has been connected to higher prevalence due to a history of traumatic brain injuries. Bower et al (2003) determined that the association between traumatic brain injuries and development of Parkinson's Disease varies by the severity of TBI sustained. There is a similar but different neuropathology to Alzheimer's Disease with instead a presence of alpha-synuclein-positive Lewy bodies within the brainstem (McKee et al., 2013). These alpha-synuclein proteins are the primary building blocks of Lewy bodies, and accumulate as a response from the axonal damage from traumatic brain injuries.

Frontotemporal Lobar Degeneration

Frontotemporal Lobar Degeneration (FTLD) is a progressive neurodegenerative disease characteristic of atrophy of the frontal and temporal lobes in the brain, that can lead to a type of dementia called frontotemporal dementia (Heyburn et al., 2019). Frontotemporal dementia (FTD) is one of the most common types of dementia found in individuals under the age of 65 and has an even higher occurrence within the veteran community (Heyburn et al., 2019). Three types of FTD exist including behavior, non-fluent, and semantic. FTD-Behavior involves behavior changes such as disinhibition, apathy, and impulsivity. FTD-Non-Fluent involves difficulty in speech production, while FTD-Semantic involves impaired speech comprehension (Heyburn et al., 2019). Those veteran patients with a history of TBIs were 3.33 times more likely to develop FTD and had earlier ages of onset for symptoms compared to patients with no previous TBI diagnoses (Heyburn et al., 2013). The neuropathology of FTLD involves an accumulation of phosphorylated-tau (p-tau) and TDP-43, a DNA and RNA binding protein that controls the expression of many different types of genes (McKee et al., 2013). The TDP-43 proteins become hyperphosphorylated and ubiquitinated, breaking off into pathological fragments that accumulate in the cytoplasm. Studies have shown that in as little as one sustained TBI, accumulation of the TDP-43 fragments can occur leading to significant changes in cognition and behavior (Heyburn et al., 2019).

Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative disease that is characterized by widespread accumulation of hyperphosphorylated-tau (p-tau) as neurofibrillary tangles (NFTs), typically caused by single, episodic, or repetitive trauma to the head (McKee et al., 2013; Omalu et al., 2011). CTE is marked by structural changes within the

brain such as atrophy of the cerebral cortex, medial temporal lobe, thalamus, and hypothalamus (McKee & Robinson, 2014). In addition to widespread atrophy, there is enlargement of the lateral and third ventricles and thinning of the corpus callosum and septum pellucidum (McKee & Robinson, 2014). Structural changes within the limbic system such as damage to the hippocampus, medial temporal lobe, and fornix, lead to behavioral changes, executive dysfunction, memory loss, and other cognitive impairments (McKee & Robinson, 2014). These behavioral and cognitive changes typically will begin insidiously but will progress over years and have detrimental effects. There are currently four symptom stages of CTE that range from headaches and loss of attention (Stage I) to more severe symptoms such as executive dysfunction (Stage III) and dementia (Stage IV) (McKee et al., 2013). Researchers have shown that symptoms typically will be present 8-10 years after sustaining a TBI (McKee & Robinson, 2014). Repetitive TBIs can increase the development of the disease, with researchers finding cases of CTE in veterans of the Iraq and Afghanistan conflicts who had been exposed to explosive blasts (McKee & Robinson, 2014). Neuropathological studies of postmortem brains from veterans with a history of TBIs and blast exposures showed CTE that was consistent with NFL athlete CTE case studies, further demonstrating the link between TBIs and this progressive neurodegenerative disease. (Goldstein et al., 2012).

Cognitive Behavioral Changes

The effects of traumatic brain injuries within the veteran community go beyond the structural and neuronal damages that occur. When neurological structures in the brain are damaged, upstream and downstream pathways become disrupted leading to a wide range of cognitive and behavioral changes. Structural damage and neuronal loss around the inferior temporal lobe, nucleus basalis, septal nuclei, and amygdala has been shown to lead to irritability,

impulsivity, explosivity, and increased aggression (McKee et al., 2013). Others have self-reported poorly controlled anger, social isolation issues, attention difficulty, poor concentration, paranoia, insomnia, and depression (McKee & Robinson, 2014). Structural damage to the subcallosal and inferior orbital frontal cortex and brainstem has been shown to lead to depression, mood lability, headaches, and suicidality (McKee & Robinson, 2014; McKee et al., 2013). As mentioned above, damage to the limbic structures results in numerous impairments in learning and memory such as amnesia, mental confusion, and speech hesitancy. These behavioral and cognitive changes, executive dysfunction, and memory loss are all characteristic to patients who have sustained traumatic brain injuries.

Polytrauma Clinical Triad

The Polytrauma Clinical Triad was developed as a way to categorize the co-occurrences of chronic pain, Post-Traumatic Stress Disorder (PTSD), and TBIs within the veteran community (Blakey et al., 2018). These three co-occurrences have been associated with suicidal ideation, violent impulses, increased pain intensity, drug abuse, and Major Depressive Disorder (Blakey et al., 2018). Since the War on Terror began in 2001, suicide and self-harm has become an increasingly major issue and concern among the veteran community. In a 2010 report by the Department of Defense, suicide rates in all the service branches increased from roughly 10 per 100,000 people in 2001 to 20 per 100,000 people in 2010 (U.S. Department of Defense, 2010). These rates continue to increase as veterans are increasingly exposed to the dangers of war and blast exposures.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition categorizes Post-Traumatic Stress Disorder (PTSD) as a trauma-and-stressor-related disorder that comes as a result from exposure to a traumatic or stressful event (American Psychiatric Association, 2013).

The diagnostic criterion for PTSD is shown in Table 3, which shows the criteria for adults, adolescents, and children over the age of 6. Within the veteran community, diagnosis for PTSD results from the initial exposure to the traumatic events of combat and subsequent symptoms within 6 months according to the ICD-10 (Substance Abuse and Mental Health Services Administration, 2014). PTSD is characterized by frontal lobe dysfunction, executive dysfunction, impulsivity, emotional lability, disinhibition, and impairments in attention and memory, specifically working memory (Vasterling et al., 2009). These presiding symptoms come as a result of damage to key structures within the brain including the prefrontal cortex, amygdala, hippocampus, and white matter damage within the fronto-striatal fibers, fronto-limbic circuits, fronto-parieto-occipital fibers, brainstem fibers, and callosal fibers (Elder et al., 2010; Yeh et al., 2014). Sustaining a traumatic brain injury can damage these functional structures and further increase the risk for development of PTSD symptoms, especially within the veteran community (Elder et al., 2010). In addition to structural damage, PTSD has been found to be associated with high white matter integrity within the bilateral anterior thalamic radiations, cingulum, and frontotemporal tracts (Davenport et al., 2015).

Post-Traumatic Stress Disorder (PTSD) has been shown to be associated with TBIs and suicide risks within the veteran community (Hoge et al., 2008). Loignon et al. (2020) has found that the combination of combat military settings overseas and TBI diagnoses present far greater risks for developing PTSD in veteran soldiers. They found that sustaining a traumatic brain injury can lead to an initial PTSD diagnosis, severe PTSD symptoms compared to non-TBI veterans, and a longer PTSD remission, with a roughly 16% lifetime prevalence in the military community (Gates et al., 2012; Loignon et al., 2020). This increased risk is due to the overlap of physiological and psychological symptoms from both TBIs and PTSD. Both TBIs and PTSD

have been shown to be associated with neuropsychological impairments, ranging from problems with attention, learning, memory, and executive function (Vasterling et al., 2009). Unlike TBI-related impairments that can show up shortly after the traumatic event, PTSD symptoms take a slower approach that can last years longer than TBI symptoms (Vasterling et al., 2009). However, the context and location in which the traumatic brain injury was sustained is thought to be determinant of how PTSD develops and progresses within an individual (Vasterling et al., 2009). The neuropsychological processes that occur immediately after sustaining a TBI affects the progressive development of PTSD. Within 24 hours after sustaining a TBI, there is an emotional response formed to the traumatic event and short-term consolidation of memories, including trauma memory (Vasterling et al., 2009). Fear conditioning also occurs, activating certain biological pathways in response to stress, such as the HPA axis, autonomic nervous system, cell-mediated immunity, and sleep/wake cycles (Bryant, 2001). These consolidated traumatic memories and emotional responses are then later resurfaced due to certain triggers or events as PTSD progresses in an individual.

Hoge et al. (2008) found a 44% prevalence in PTSD symptoms in 2525 soldiers who screened positive for sustaining an mTBI, further suggesting the strong association between mTBI and PTSD. In another study looking at veterans from Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn, 80% of soldiers exposed to a blast-related TBI with early symptoms of CTE were also diagnosed with PTSD (McKee & Robinson, 2014). These types of combat injuries play an increased role in PTSD and long-term health effects including cardiovascular diseases and neurological disorders (Schneiderman et al., 2008). With the association between TBI and PTSD, it is however clinically difficult to determine whether the presenting symptoms are a result of sustaining a TBI or just PTSD (Stein & McAllister,

2009). When looking at TBI and PTSD, one can view each as the opposite end of a spectrum. On the TBI end, there is organic brain disease and structurally damaged areas of the brain, while on the PTSD end there is psychologically reactive damage (Elder et al., 2010). Table 4 displays the differences among PTSD and TBI symptoms. While each end of the spectrum may have their own differences, the middle of the spectrum allows for heavy overlap in physiological and psychological symptoms. These overlapping changes in the brain can lead to disrupted neural connections and pathways that can present with behavioral and cognitive dysfunction. Research is still evolving, although there is recent evidence that TBIs are more highly associated with PTSD than any other type of injury sustained in combat (Hoge et al., 2008).

A. The patient must have been exposed to a stressful event or situation (either brief or long-lasting) of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone.

B. There must be persistent remembering or "reliving" of the stressor in intrusive "flashbacks", vivid memories, or recurring dreams, or in experiencing distress when exposed to circumstances resembling or associated with the stressor.

C. The patient must exhibit an actual or preferred avoidance of circumstances resembling or associated with the stressor, which was not present before exposure to the stressor.

D. Either of the following must be present:

    1. Inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor
    2. Persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor), shown by any two of the following:
        a. Difficulty in falling or staying asleep.
        b. Irritability or outbursts of anger.
        c. Difficulty in concentrating.
        d. Exaggerated startle response.

E. Criteria B, C, and D must all be met within 6 months of the stressful event or at the end of a period of stress.

Table 3. ICD-10 Diagnostic Criteria for Post-Traumatic Stress Disorder (PTSD) (adapted)

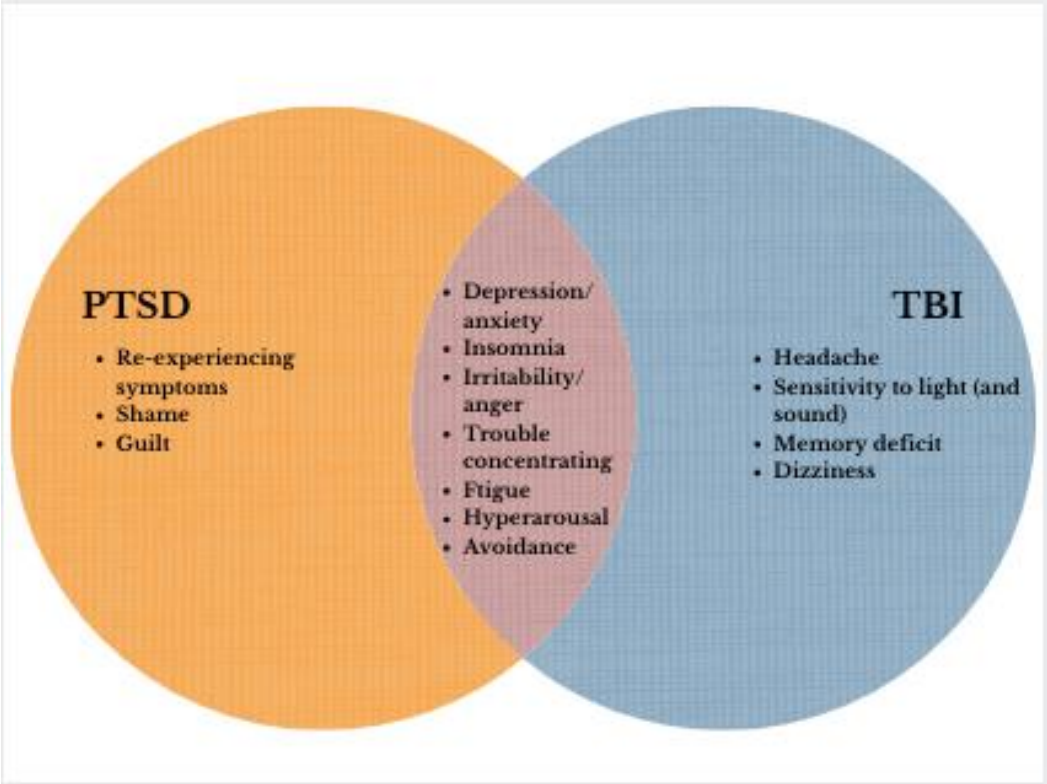

Figure 1. Relationship between PTSD and TBI (adapted from Stein & McAllister, 2009)

RESEARCH STRATEGIES

Literature Review

A literature review was completed in order to describe and detail the complexities behind traumatic brain injuries and their role in physiological and psychological changes within U.S. combat veterans. Two major TBI databases were used to collect information on combat veterans who have served during Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND). The Comprehensive Traumatic Brain Injury Evaluation (CTBIE) database includes combat veterans who have served in the Iraq and Afghanistan, separated from the military, enrolled in the VHA healthcare system, and received a comprehensive TBI evaluation. The National Patient Care Database (NPCD) includes other combat veterans enrolled in the VHA healthcare system who have received inpatient or outpatient TBI diagnoses as part of routine clinical care. Definitions and criteria for the psychological disorders mentioned in this paper were taken from the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) and the International Statistical Classification of Diseases and Related Health Problems, 10th Edition (ICD-10).

DISCUSSION

Treatment/Management

The awareness for treatment of traumatic brain injuries has drastically increased over the years. Dedicated research centers and rehabilitation centers for both military veterans and civilians have popped up across the United States. In order for treatments to be effective, researchers and healthcare workers need to understand the structural and neuronal damages and changes that the brain endures after sustaining a TBI (McKee & Robinson, 2014). The psychological effects need to equally be addressed as well, as research has shown the link between TBI and cognitive changes such as PTSD. By addressing the brain injuries and psychological stress, healthcare teams can efficiently treat and manage their patients' symptoms both short-term and long-term prognoses (Srinivasan et al., 2019). Rosenfeld et al. (2013) suggests the evidence-based clinical practice model to manage mTBI symptoms. They recommend a multidisciplinary team approach, using extensive rehabilitation programs, cognitive rehabilitation, ophthalmological assessments, periodic neuroimaging to manage the progression, and posture and gait assessments, and retraining if the soldiers need it (Rosenfeld et al., 2013). The benefit to a multidisciplinary approach allows for complete management of symptoms and to watch for any neurodegeneration. The quicker the team can determine if any neurodegenerative disease is present, the sooner they can begin treatments to help prevent further damage or disease progression.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) has become useful in research studies by Peskind et al (2011). FDG-PET imaging allows researchers to measure certain neurobiological substrates that are associated with repeated blast-related mTBIs. The

associated neurobiological substrates can signify certain somatic, cognitive, and behavioral symptoms that are commonly reported by veterans from the Iraq and Afghanistan conflicts. The ability to track and measure neurobiological substrates via the FDG-PET imaging can play a significant role in diagnosis and treatment. The ability to use imaging tools in help diagnose and treat TBI patients will drastically improve care in addition to what is already deemed standard care. Healthcare teams typically use several factors such as injury severity, the initial GCS given in the field, age, medical comorbidities, and any associated injuries to establish a plan of care. As treatment progresses, they will monitor the patient's response to therapy and adjust the protocols based upon the type of TBI sustained, either global or focal injury (Srinivasan et al., 2019).

The ability to test for neuro-biomarkers will significantly improve the approach to diagnosing TBIs and the associated treatment plans. Not only will treatments improve, but healthcare teams will also be able to assess and monitor the progression of the injury in real time, adjusting care as needed. Currently, there are no objective biomarkers that can pinpoint exact symptoms and injury progression, yet researchers have begun to focus on a few biomarkers that have been consistently associated with traumatic brain injuries and neuronal damage: GFAP, NfL, S-100ß, tau, MBP, and UCH-L1. GFAP, otherwise known as glial fibrillary acidic protein, is an intermediate filament protein expressed by astrocytes in the central nervous system that typically marks the mechanical strength of cells (Okonkwo et al., 2013). Researchers have hypothesized that when there is astrocyte brain damage due to a TBI, GFAP is able to cross the disrupted blood-brain barrier and become detected in the peripheral blood. Okonkow et al. (2013) found an association between the levels of plasma GFAP and the Glasgow Coma Scale scores. The serum levels of GFAP increased as the GCS scores decreased, and these elevated levels were consistently found in subacute and chronic TBI cases (Shahim et al., 2020). In

addition, Yue et al. (2019) found that the plasma levels of GFAP in patients after sustaining a TBI correlated with the intracranial injury shown on CT scans. The researchers concluded that GFAP would be a great diagnostic tool to help early detection of TBI and determine whether more imaging is necessary for each patient. UCH-L1, otherwise known as ubiquitin C-terminal hydrolase L1, is a degradation enzyme expressed specifically by neurons in the brain. UCH-L1 is able to cross the disrupted blood-brain barrier when there is neuronal damage after a sustained TBI. Researchers have found elevated blood levels of UCH-L1 during the acute phase of a TBI as well as in severe TBI cases (Shahim et al., 2020; Yue et al., 2019). Tau is a protein associated with the structural stability of microtubules of unmyelinated axons in the central nervous system. Similar to UCH-L1 and GFAP, tau is able to cross the disrupted blood-brain barrier as a result of neuronal damage caused by a TBI. Although Shahim et al. (2020) found elevated blood levels of tau in patients with a TBI, there was no significant correlation to severity, outcome, or imaging. Since tau is associated with neurodegenerative diseases, the researchers concluded that the accumulation of tau as a result of a TBI can contribute to the progression of those diseases. While UCH-L1 and GFAP have been shown to be useful diagnostic biomarkers, NfL has become an increasingly popular and more effective diagnostic marker. NfL, otherwise known as neurofilament light chain protein, is a structural component of the cytoskeletons of axons. NfL is typically expressed in large myelinated subcortical axons, which are vulnerable to breakdown during a TBI event (Shahim et al., 2020). Damage to the cytoskeleton of these subcortical axons allows NfL to become detected in the peripheral blood, crossing the disrupted blood-brain barrier like GFAP and UCH-L1. Shahim et al. (2020) found that blood levels of NfL can help healthcare teams determine the severity of the TBI, whether mild, moderate or severe, and can help serve as control levels to compare months and years post-injury.

RECOMMENDATIONS FOR FUTURE STUDIES

As mentioned in the Discussion, the continued research into biomarkers that can help identify and target treatments for soldiers diagnosed with a TBI is crucial. The more biomarkers and the more information we have about what they mean cellularly and physiologically can help rehabilitation programs individualize their programs and the soldier's needs. These neuro-biomarkers can dramatically help in the initial assessments of TBI, becoming a diagnostic tool to help confirm any abnormalities in neuroimaging and head CT scans (Yue et al., 2019). The fact that a simple blood test can tell a wealth of knowledge can hopefully be implemented in the future to combat zones. Combat medics overseas would be able to test right then and there in the field, and quickly diagnose and provide first-line treatment rather than have time pass to truly diagnose a TBI. In addition to serum biomarkers, future studies must look into specific rehabilitation treatments to aid in a more complete and increased recovery. Such protocols should include restorative practices that focus on the mechanisms that help promote and build neuroplasticity like addressing sleep needs, exercise, and nutrition (McKee & Robinson, 2014). Pharmacological agents should be researched and trialed to help reduce any cognitive deficits in solders sustaining a TBI, especially soldiers who are constantly suffering from PTSD and suicidal tendencies. These therapeutic agents should take a holistic approach to treating the soldiers, providing care for the structural damages from the TBI itself and also the invisible cognitive wounds that may appear months to years later.

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