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Department of General Psychology

Department of Neuroscience

Master Degree in Cognitive Neuroscience and Clinical Neuropsychology

Final dissertation

**Cognitive and Psychosocial Outcomes  
of Blast-Induced Traumatic Brain Injury**

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Academic Year 2024/2025

I would like to show my gratitude to Professor Antonini for his professionalism and for his guidance in my work. Also, I would like to thank my friends in Padova, who were always ready to help, who were able to support me during my work, and who gave me the best possible advice. I would like to thank my family and my fiancé, who always were with me and supported me during emotionally hard times. Most of all, I would like to thank the Armed Forces of Ukraine for giving me an opportunity to write this thesis in peace in my hometown. I dedicate this work to all people, who are protecting and supporting the independence of the free nations. As it is written in the Universal Declaration of Human Rights: "Freedom, justice, and peace in the world".  
Glory to Ukraine!

## ABSTRACT

Blast-induced traumatic brain injury (bTBI) is a common consequence of blast exposure, particularly in the military setting. bTBI is differentiated from other types of TBI because of its unique mechanism and pathophysiological features. For the purpose of this thesis, relevant literature from peer-reviewed journals was researched, taking into account neurophysiological and neuroimaging studies. Findings suggest that diffuse axonal injury, astrogliosis, and glial scarring are the main pathologies of this type of brain injury. Moreover, there is a risk of development of chronic traumatic encephalopathy after repetitive bTBI. The aftermath of bTBI is characterized by post-concussion syndrome and psychiatric comorbidities such as post-traumatic stress disorder, depression, and anxiety pathologies. On the cognitive level patients with such brain pathology would deal with issues in memory, executive functions, attention, and processing speed domains. Main psychosocial challenges include substance use, socialization difficulties, anger management issues, stigma, and caregiver burden. The literature review accentuates the need for more studies in this field, especially involving human studies, since a lot of evidence comes only from animal studies, and longitudinal studies. There are still gaps regarding the specific rehabilitation strategies and long-term consequences of individuals with bTBI. Such a complex condition requires addressing the issues in its diagnostic and therapeutic approaches.

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## INTRODUCTION

As long as wars exist, so will the damage and injuries they cause. Military personnel are among those who are most affected by the consequences of war, due to exposure to high-intensity combat environments on the frontlines. The advancements of weaponry were always taking place with the main goals of increasing and maximizing lethality, the number of affected individuals, and overall damage. Nowadays warfare relies on explosive devices such as cannons, mortars, shoulder-fired rockets, and large-caliber machine guns. All of them have the ability to cause blast-related injuries. Moreover, missiles and unmanned aerial vehicles can affect the human body even to a larger extent. The individuals injured by a weapon can have fatal outcomes or be affected by polytrauma, as a result of which the amputation of limbs can happen. The blast explosion also has a profound effect on the brain.

Modern body armor has been developed to significantly decrease the extent of penetrating injuries from blast explosions. However, head injuries remain prevalent. Even though there are improvements in modern helmet design, military personnel are still sustaining traumatic brain injury at an alarming rate. Furthermore, in contemporary warfare, a lot of civilians can become the victims of air strikes and missile attacks. This makes a brain injury even more concerning due to no head protection and therefore a higher risk for severe neurological damage.

Traumatic brain injury was always a major health concern that affects all age groups. TBI has a long history of research, which resulted in a deep understanding of the pathology, specific classification systems, diagnostic tools, and rehabilitation strategies. However, blast TBI remains unique, differing from other types of TBI due to its distinct pathophysiological mechanism.

The Military Health System defines TBI as a “traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: any period of loss of or decreased level of consciousness; any loss of memory for events

immediately before or after the injury; any alteration in mental state at the time of the injury; neurological deficits that may or may not be transient; inter-cranial lesions”.

One of the primary challenges in diagnosing bTBI is the lack of definitive neuroimaging or blood-based biomarkers that can be used to detect it. What adds more challenge is the delayed and subtle symptoms that cannot be easily detected. Moreover, the overlapping symptoms with post-traumatic stress disorder (PTSD), which is a common psychological condition in the military population, complicate the diagnosis. This also may raise the question of whether the symptoms are based solely on the bTBI or on the interaction with PTSD.

Another major issue is that in some cases the bTBI can be neglected or underreported by individuals. This happens mostly because of the misconception that if there are no visible signs of injury, there is no cause for concern. However, affected individuals can have persistent post-concussive symptoms, such as disturbances in the sleeping pattern, and increased sensitivity to light and sound.

Cognitive dysfunctions may emerge over time and they require a lot of attention. Subjective complaints often include memory impairments, difficulties with attention and concentration, and impulsivity.

bTBI has a profound effect on psychosocial functioning. Affected individuals frequently experience social isolation, difficulty maintaining relationships, emotional dysregulation, and impulsive behaviors. It is well-documented that veterans are in higher danger of substance abuse. Together all these factors have a tremendous impact on quality of life and reintegration into civilian society.

Despite being recognized for over a century, bTBI remains under-researched and has many unanswered questions. This literature review aims to synthesize the current knowledge of bTBI, with a main focus on its mechanism of blast, pathophysiology, post-concussion symptoms, psychological consequences, cognitive presentation, and psychosocial consequences.

## Chapter I: BLAST TBI

### 1.1. Traumatic Brain Injury

The aim of this chapter is to provide a general overview of a blast traumatic brain injury (bTBI), starting from a general introduction to traumatic brain injury (TBI). By definition, TBI is a form of acquired brain injury that occurs when a sudden trauma causes damage to the brain (Menon et al., 2010). TBI affects millions of individuals worldwide and leads to physical, cognitive, emotional, and social consequences. If to be precise with numbers, it was estimated in 2019 that worldwide there were 27.16 million cases of individuals who suffered from traumatic brain injury (Guan et al., 2023). Moreover, according to a CDC report of 2021, it was estimated that in the USA 69,000 people died because of the TBI or its complications.

Based on the intensity, TBI can be graded as mild, moderate, and severe. One of the most reliable clinical scales for the severity of TBI is the Glasgow Coma Scale (GCS). It is a 3 - to 15-point scale that assesses eye opening response, verbal response, and motor response of a patient with an acute brain injury (Teasdale & Jennett, 1974). This scale can be used to guide immediate medical care and also to track the level of consciousness. Another measure of TBI severity is the duration of loss of consciousness (Greenwald et al., 2003). Also, sometimes the posttraumatic amnesia (PTA) concept can be used as a measure of severity (Russel, 1932). It takes into account the time that is needed for the patient to regain full consciousness.

The classification of severity of TBI starts with mild. It is expected to see such results of GCS from 13 to 15 points. Loss of consciousness in mild TBI should be less than 30 minutes. The next severity classification is moderate. In this case, the anticipated GCS results are from 9 to 12, while the loss of consciousness should be longer than 30 minutes but less than 6 hours. Finally, the last one is severe TBI. It is characterized by 3 to 8 points in GCS and the loss of consciousness should be longer than 6 hours.

Moreover, traumatic brain injury can be closed or open (penetrating). Penetrating head injury is characterized by breaching of the meninges. Also, it may include the presence of some object inside the brain parenchyma. Another type is perforating brain injury in which the object passes through the brain and exits it. The main attribute of closed traumatic injury is that the skull and meninges are not impaired.

Furthermore, another division of head injuries is based on the emergence time of the consequences of a trauma. Primary injuries are the ones that happen at the moment of injury and are due to straight mechanical force. Moreover, a direct hit can produce indirect damage through the acceleration-deceleration mechanism. For example, deceleration can be seen in car crashes. In this case, the person abruptly halts, while the brain within the skull still has the force to move forward and therefore causes injury by hitting the inner surface of the skull. The primary injuries may include: cerebral contusion, which is a bruising of the cortical surface; laceration, which is a tear in the tissue of the brain; hematoma, which is a bleeding within the skull; the skull fractures. These types of injuries lead to damage of neurons, axons, dendrites, glial cells, and blood vessels, therefore initiating a dynamic series of complex cellular, inflammatory, mitochondrial, neurochemical, and metabolic alternations (Graham et al., 2002).

Secondary injury happens through the cascade of secondary events after the primary injury and happens hours or even days after trauma. Typically it begins with a reduced cerebral blood flow which initiates the cascade of events that provoke damage at the cellular and molecular level (Wagner et al., 2021). It includes ischemic and hypoxic damage, cerebral edema, and increased intracranial pressure. However, the secondary injury effects may be reversible, while the primary ones usually are not alterable (McKee & Daheshvar, 2015).

Further differentiation can be made between focal and diffuse injuries of the brain. Focal damage is done by forces projecting on the skull, which results in compression of the tissue right underneath the cranium at the direct site of the impact (coup) or the tissue at the opposite to the

impact (contra-coup) (Pudenz & Sheldon, 1946). It includes skull fractures, contusions, lacerations, hemorrhage, and hematoma. Also, the focal type is associated with frontal and temporal lobes damage (Capizzi, Woo, & Verduzco-Gutierrez, 2020).

On the other hand, diffuse brain injury encompasses widespread damage, which happens mainly because of acceleration-deceleration forces (Gennarelli et al., 1982). The most common example of this type of trauma is a diffuse axonal injury (DAI). DAI is damage to white matter, that happens due to the acceleration of the head, and therefore axon integrity changes which leads to shearing. Adams et al. (1989) differentiated diffuse axonal injury into three grades of severity. In the first grade axonal injury is mainly seen in the cerebral hemispheres. Second grade injury is marked by a lesion in the corpus callosum, while third grade encompasses a lesion in the dorsolateral quadrant of the rostral brain stem. Other examples of diffuse brain injury are diffuse vascular injury, brain swelling, excitotoxicity, and oxidative stress (McKee & Daheshvar, 2015). It is needed to note that both focal and diffuse injuries are usually found within one patient.

There are differences in the age distribution of TBI incidence. The greatest incidence is seen in three categories: early childhood, late adolescence/early adulthood, and elderly (Bruns & Hauser, 2003). During early childhood, TBI happens mainly because of falls, which can be explained by the yet-developing motor control and balance. In infants, a TBI can be caused by a forceful shaking. This condition is called a shaken baby syndrome. During early adulthood, the leading cause of brain injuries is traffic accidents. For the geriatric population, there is again an increase in the incidence, with falls being a predominant cause. This can be explained by a sensory and motor decline (Bruns & Hauser, 2003).

Also, it was found that generally, TBI is more frequent in males than females (Faul et al., 2010). This can be explained by the fact that men have more chances to be doing injury-prone work or to be involved in dangerous behaviors (Hyder et al., 2007). In the elderly population, the frequency for both genders is the same (Ki Seong et al., 2021). Interestingly, the number of females

who suffer from sports-related TBI is higher than such number of males. A possible interpretation of this is cultural differences by which women would be more prone to reporting the injury (Eapen & Cifu, 2018).

Overall, falls and traffic accidents are the most common causes. Secondly, a big portion of TBIs happen because of violent behaviors, such as beating, and using a cold weapons or a gun. Another major cause for TBIs is professional sports, for example, boxing or American football, in which an athlete could receive a hit to the head or can fall. But also there is a very specific cause for TBI's, which is a blast and it can be seen mostly in the military personnel.

### 1.2. Mechanism of blast injury

“Shell shock” was first described during the times of WWI. Military personnel, who were fighting in this war, were reporting symptoms of amnesia, tremor, headache, poor concentration, dizziness, and tinnitus. Soldiers' status was compared to “what is observed in the “hysterical stupor” or hypnoidal state of civil practice” (Turner, 1915). At that time specialists couldn't differentiate between the neurologic and psychiatric origin of the aforementioned symptoms. Later on, a new term developed: blast traumatic brain injury.

Explosive blast serves a property of a unique injury mechanism for the whole body, as well as for the brain. Mainly it is characterized by a sudden release of energy in a short period, inside of a small volume, and as a result it creates shock and pressure waves (Moore & Jaffee, 2010). Overpressure is the outcome of the enormous release of energy and is described as “near-instantaneous pressure rise above atmospheric pressure” (Cernak, 2015). When the blast wind reverses back to the epicenter, there is a sharp decline in pressure, which may even reach the sub-atmospheric level, after which pressure returns to an ambient level. If the explosion occurs in a plain field with no surfaces near it will be considered the simplest form of the blast wave, as described in Friedlander waveform (Friedlander, 1955). It describes an ideal form of a blast from a spherical source. However, this model works great in theory, in real life blast happens usually in a

space that is surrounded by solid surfaces or it can even happen indoors. The shock wave reflection and reverberation heightens the intensity of blast consequences due to an increase in the blast pressure and the blast wind's speed. Numerous reflections may interact with the primary wave, as well as between each other, therefore creating a complex wave (Ben-Dor, Igra, & Elperin, 2001). Also, because the blast wind is non-linear it poses a difficulty in the prediction of the exact characteristics of the reflected waves (Kulkarni et al., 2013)

Moreover, there is a slightly different mechanism for enhanced-blast explosive devices. There is a primary blast that will distribute other explosives, which in turn will produce a secondary explosion. Since the area of a high-pressure wave gets bigger and increases the duration of the overpressurization phase (DePalma et al., 2005), it makes the effect of an explosion more harmful.

Cernak (2015) describes five factors for understanding the degree of damage for person from the explosion. They include: the highest point of the pressure wave, the time duration of the overpressure, the medium of the explosion, the distance from the blast epicenter, the presence of surrounding walls or a confined area. When the blast wave reaches the person there are two things that happens. One part of the wave is reflected from the body, while the other part is absorbed.

In the literature, it is possible to find a distinction between five types of injuries from a blast. Primary injury, also known as barotrauma, involves the interaction of a shock wave with a body, so it mainly happens in the proximity to the epicenter. The most vulnerability to this type of injury is shown by air-filled organs. These organs get damaged by pressure changes at tissue-density interfaces because of a mismatch between high-frequency stress waves and low-frequency shear waves (Guy, Glover, & Cripps, 1998).

Typically seen examples of a primary blast injury are a rupture of the tympanic membrane, ruptures of the viscera, and pulmonary damage. A pressure rise of even 5 psi above atmospheric pressure can cause the damage to tympanic membrane (Jensen & Bonding, 1993). Because of this,

the rupture of an eardrum can be used as a marker for any other blast-related injuries. Primary blast-induced TBI remains a difficult injury to predict and diagnose (Hoge et al., 2008).

The main damage to the lungs is caused by the rupture of alveolar capillaries, which provides the exchange of an optimized gas (Buchacker et al., 2019). Respiratory problems arise from intrapulmonary hemorrhage and edema (Gorbunov et al., 2005). Also, an occlusion of blood vessels leading to the spinal cord and brain may happen due to acute gas embolism from pulmonary dysfunction (DePalma et al., 2005).

Secondary blast injury is caused by parts of the explosive device that are propelled by an explosion, resulting in penetrating or blunt trauma. It can be either caused by the casing of the explosive device or by metallic fragments, such as nails and screws, that are contained inside of the device. A larger number of people experience the secondary blast injury than a primary one. This can be explained by the fact that debris can travel a considerable distance and therefore be more damaging.

Tertiary blast damage is caused by strong blast wind that displaces objects or the body of the person. For example, the body can be accelerated by the wind and eventually strike another object or the dislocated object can hit the body. These will result in blunt trauma, bone fractures, and penetrating injuries. Another mechanism for a tertiary injury is the crush or a collapse of the building that affects a person's body.

Crush syndrome is a traumatic compression of muscle tissue with resulting acute kidney injury (Lovallo, Koyfman, & Foran, 2012) and is seen in people who are trapped underneath the rubble. Another syndrome that can be manifested during tertiary damage is compartment syndrome. It occurs when there is increased pressure within a closed osteofascial compartment, which results in impaired local blood circulation (Torlincasi, Lopez, & Waseem, 2017). If left untreated it leads to local ischemia and as a result to necrosis.

Moreover, another effect of the blast injury to internal organs is the possibility of hemorrhage and subsequent production of autacoids, molecules that are produced when required and act locally in the tissue where they were produced (Hasselink, 2017). The release of autacoids in systemic circulation activates the neuroendocrine-system and contributes to following secondary brain injury mechanisms (Cernak et al, 1991).

Quaternary injuries are the ones that are not directly attributable to blast, but that result from the blast effects (Kinch, Fullerton, & Stewart, 2019). These are attributed to all damage that is done to the body, which is not included in the previous three types of injuries. The type of damage is characterized by burns, toxic inhalations, and complications of chronic and pre-existed illnesses. Exacerbation of psychological issues, such as depression or anxiety, can happen, too.

Some researchers also mention the existence of the quinary blast effects (Kluger et al., 2007). It is caused by the application of “dirty bombs” that contain radioactive, biological, or chemical materials that are vaporized after explosion.

### 1.3. Specifics of blast TBI

Literature suggests that blast TBI has its specifics regarding the presentation of injury. Understanding the pathophysiological properties of bTBI is important for planning the treatment and management of symptoms.

Methods for studying the blast damage in the brain are varied, including postmortem studies on the human brain, advanced neuroimaging techniques, and biomarker analysis. Animal studies are also helpful in studying this specific type of brain damage. In this case, the animal of choice will be exposed to a controlled blast, which can be done using blast tubes, which generate a shockwave with the help of explosive charges, or shock tubes, where compressed air or gas is used for the generation of shockwave. In most studies, mice or rats are used, but it is also possible to find research where larger species are used as rabbits, sheep, or pigs.

In the literature, it is possible to find multiple examples of the neuropathology that is present as a result of bTBI. Typically during mild blast TBI (mbTBI), there are no signs of macroscopic damage that could be seen in the conventional neuroimaging methods. However, on the deeper level, it is possible to find microscopic signs of the traumatic injury.

One of the main mechanisms for bTBI is a rotational and translational acceleration of the brain (Ommaya & Hirsch, 1971; Goldstein et al., 2012), which leads to diffuse axonal injury (DAI). Du and colleagues (2023) in their study, using the finite element model, found that during the acceleration peak, the sagittal rotation causes axonal damage. This can be explained by the fact that parenchyma's movement is constrained by falx cerebri and tentorium cerebelli. After the initial peak, the fixed-point movement pattern of the head induces the further stretch of axons because of the distortion in the axonal direction. Properties of axons as: the viscoelasticity, anisotropic arrangement of tracts, and large surface-to-volume ratio of the axon membrane to the axon's cytoplasm were shown to pose a vulnerability for axons during acceleration-deceleration injuries (Johnson et al., 2013).

For finding signs of certain pathology on the microscopic level biomarkers can be used. For diagnosing DAI there are certain biomarkers like amyloid precursor protein (APP), neurofilaments, glial fibrillary acidic protein (GFAP), S-100 $\beta$ , and tau protein (Zurek et al., 2011; Zhang et al., 2024). In the post-mortem a study on veterans with history of blast Ryu and colleagues (2014) found the presence of APP-immunoreactive axonal varicosities or spheroids in the medial frontal white matter, mostly in the superior and middle frontal gyri, and in the anterior and middle temporal lobe. Therefore, axons were characterized by irregular swellings. Moreover, these lesions were located in close proximity to blood vessels. In some cases varicosities were observed in the corpus callosum, the superior cerebellar peduncle, and in the cerebellum, specifically next to deep nuclei.

In another study using diffusion tensor imaging (DTI), a significant decrease of the anisotropy was found in the middle cerebellar peduncle (Mac Donald et al., 2013). As reported by

Garman et al. (2011) DAI, evidenced by axonal spheroids, was seen in the blast-injured rats mostly in the cerebellar white matter, but also to some extent in the internal and external capsule, the thalamic pathway, the optic nerve tract, the cerebral and cerebellar peduncles. In another study by Säljö and colleagues (2022), where they used rat brains, APP immunoreactivity was found in the temporal, cingulate, and piriform cortices, and thalamus. The immunoreactivity peaked at 18 hours after injury and remained at high levels until 21 days later.

Another marker of bTBI that is widely researched is scarring of the brain. Astrogliosis happens when astrocytes, which are a type of glial cells that protect and support neurons in the CNS, show reactivity to brain injury by rapid changes in their morphological, molecular, and functional aspects. The main purpose of astrogliosis is to isolate the damaged cells from a healthy one and to synthesize neurotrophins that are needed for neuronal recovery (Franke & Illes, 2014).

Astrocytosis is a part of astrogliosis and marks the increase in the number of astrocytes in a specific area mostly due to injury. Reactive astrocytosis was found in the blast-exposed brains of mice, particularly across the cerebral cortex, hippocampus, brainstem, internal capsule, cerebellum, and corticospinal tract (Goldstein et al., 2012)

Prolonged astrogliosis can result in the formation of astroglial scarring, which allows us to retrospectively determine where neuronal injury occurred. In the post-mortem case study of Shively and colleagues (2016), researchers were looking for signs of astroglial scarring in the brain specimens of active-duty members. GFAP was used in this case as a biomarker of scarring. It was found that most of the scarring was near the structures of different densities, for example at the boundary of white and grey matter, around blood vessels, near ventricles and structures lining them, subpial region. An explanation for such pattern of scarring is in the spallation, implosion, and inertial effects of the blast mechanics (Benzinger, 1950), specifically due to the differences of the wave force of energy passing between denser and lighter structures, compression of gas bubbles in

cerebrospinal fluid and blood vessels that pose a tearing effect on the brain parenchyma, and differences in elasticity of different matters.

Furthermore, severe bTBI has certain characteristics that differentiate it from a non-blast brain injury. Patients typically showcase diffuse cerebral edema and hyperemia, which presents within hours after exposure and has high severity, unlike in other types of TBI (Ling et al., 2009).

Using animal models it was shown that blast shock waves (BSW) pose a threat to the integrity of the blood-brain barrier. In a study by Abdul-Muneer et al. (2013), it was shown that mild-intensity BSW can trigger the generation of free radicals, which in turn would lead to oxidative stress in brain capillaries. Next, this provoked the loss of tight junction proteins, that in normal circumstances preserve the integrity of the blood-brain barrier. Another outcome of a reduced number of tight junction proteins is the edema around cerebral vessels.

However, the different intensity of an injury is reported by other researchers, who used a milder BSW. In a study by Readnower et al. (2010), it was reported that the breakdown of the blood-brain barrier was limited to layer I of the cortex, while Kelley et al. (2007) identified the injury throughout the neocortex, hippocampus, and thalamus.

More intense BSW, in turn, leads to direct interference of the blood-brain barrier. This is evidenced by extravasation of immunoglobulin G near capillaries and therefore by the presence of small scattered vascular lesions (Yeoh et al., 2013). It was shown that both lower and higher-intensity blast shock waves can promote the disruption, degeneration, and inflammation of the blood-brain barrier (Shetty et al., 2014).

Another finding that suggests the blood-brain barrier compromise is the increase in VEGF concentration (Dvorak et al., 1995). In the study by Kwon et al. (2011), it was shown that rats that experienced a single mild blast had higher levels of VEGF. Another biomarker for the permeability of the blood-brain barrier, glia specific protein NF-H (Anderson et al., 2008), was also increased.

The elevated serum protein markers were elevated 2 months after the blast injury. This may indicate long-lasting ongoing pathological changes.

In a study by Lotan et al. (2018), researchers were looking for signs of cerebral microhemorrhages in military service members. Interestingly, in none of the blast affected individuals microhemorrhage was observed, while for a blunt TBI, microhemorrhage is a neuroimaging biomarker. Also, the results may be undermined by the fact that the mean time between testing and getting bTBI was 9.4 years. Another study on this matter was conducted by Liu and his colleagues (2016). Only 43 out of 603 patients had signs of cerebral microhemorrhage, therefore researchers concluded that detection ability may decrease with time after the injury.

#### 1.4. Chronic neuropathological bTBI danger

Repetitive blasts experienced by a person in life can not only cause immediate neuropathological patterns, that are mentioned above but also have some long-term consequences that are pronounced later in life. It has been shown in a number of studies that multiple brain injuries throughout the lifespan increase the developmental likelihood of degenerative diseases. One of the explanations is that traumatic brain injury boosts the progressions of certain diseases and they would have an early onset.

One such outcome is chronic traumatic encephalopathy. It is a specific form of tauopathy, that has intracellular aggregates of hyperphosphorylated tau. Previously, this type of encephalopathy was seen in contact sports like boxing, martial arts, American football, and hockey, where athletes experienced repetitive mild traumatic brain injuries. For example, in a study where two professional boxers were examined, neuronal and astrocytic neurofibrillary tangles were found in superficial cortical layers, especially in deep sulci and around blood vessels (McKee et al., 2013). The onset of symptoms may not be exhibited until years or even decades after brain injuries (McKee et al., 2009). Clinical symptoms of chronic traumatic encephalopathy include the onset of

dementia with a prior decrease in memory and executive functioning, impulsivity, apathy, irritability, and aggression (Bailes et al., 2014).

Goldstein et al. (2012) conducted a study in which they examined the postmortem brains of military veterans and compared them to the brains of professional athletes, who sustained repetitive concussive injuries. All four military subjects had tau-immunoreactive neurofibrillary tangles around blood vessels and glial tangles in the inferior and dorsolateral frontal, parietal, and temporal cortices. A similar pattern of neurofibrillary tangles was found in athletes in the inferior and dorsolateral frontal cortices, but not in the parietal and temporal cortices.

In the same study, researchers also tested the mouse brain following a blast exposure for a deeper understanding of the issue. Notably, even after a single blast mice had signs of CTE neuronal pathology: cellular accumulation of phosphorylated tau and pre-tangled tau, myelinated axonopathy, and microvascular damage. This neuropathology developed within 2 weeks after exposure to a blast.

Following a blast mice showed hippocampal-dependent learning and memory deficits. One of the testing conditions in the study was head immobilization. It was used in order to eliminate the effect of head acceleration from a blast wind. Results showed that this condition significantly reduced the memory deficits. Therefore, the authors concluded that head acceleration which happened because of intense blast winds was a pathogenic mechanism leading to neurotrauma.

Another related phenomenon is cellular senescence during which there is a cessation of the cell's replication ability (Hayflick, 1965). In most cases, it is a natural response to a telomere loss after extensive proliferation, but oxidative stress, genotoxic damage, proteasome inhibition, and oncogene activation can trigger cellular senescence, too (Hernandez-Segura et al., 2018). On the one hand, this process has a protective function, since it prevents damaged cells from future division. On another hand, molecules that are secreted by senescent cells form a senescence-associated secretory phenotype (SASP), which in its turn has inflammatory properties.

Arun and colleagues (2020) decided to investigate the matter of senescent cells following exposure to blast. This was tested by single or coupled repeated blasts on rat brains. As was predicted, the SA- $\beta$ -gal activity, which is an enzyme activity that is used as a biomarker of senescent cells, was higher following repeated blast exposure. Also, at 1 month time after the blast, the SA- $\beta$ -gal activity was the highest one, compared to 24 hours and a year time points.

An increased amount of biomarkers was found in the areas that are responsible for processing visual signals, specifically in the dorsolateral thalamic nucleus, geniculate, and superior colliculus. It was connected to a probable early degeneration of vision in affected rats. In another study (Magone & Shin, 2014) it was shown that 68% of military members without initial eye injury still have long-term visual dysfunction.

Furthermore, SA- $\beta$ -gal activity was pronounced in the auditory cortex. It was mentioned above that rupture of a tympanic membrane can be one of the first signs of blast-related injury, however, auditory dysfunction can occur even without a rupture of a tympanic membrane (Fausti et al., 2009). Authors suggested that disturbance of hearing may be explained by disruption of auditory cortex structures. Another structure in which levels of SA- $\beta$ -gal were elevated is the hippocampus.

Certain studies refer to a higher occurrence of CTE in military personnel, who also participated in contact sports. Priemer et al. (2022) weren't able to find a strong link between blast exposure and CTE, however relative risks for having CTE were higher in those service members who were engaged in sports and in general had higher occurrences of civil TBI.

Some researchers, such as Tripathy and his colleagues (2019) for instance, entirely disagree on this matter and support the idea that the amount of phosphorylated tau of military service members is equivalent to the one found in age-matched control, however in their study only two participants out of eighteen had a history of blast exposure.

The field of CTE is rather a new one and contradicting results of the studies regarding CTE link to blast exposure only highlight the importance of and more needed future research on this matter.

## CHAPTER 2: Exploring the aftermath of bTBI

### 2.1. Physical symptoms and Post-concussion syndrome

Typically for most people, who received a diagnosis of mild bTBI, symptoms resolve without any complication in a short period of time but there are still a lot of cases where people exhibit a range of different pathological symptoms for a prolonged period. Especially people who experienced more than one TBI have increased risks. This is explained by the fact that the brain doesn't have enough time to return to its pre-injurious state.

One such possibility is that people would experience physical and somatic symptoms. They are included in the post-concussion syndrome (PCS). Even though this syndrome is controversial in the sense of its definition, etiology, course, and prognosis, it is still mentioned in a major number of studies. There are even differences in diagnosing PCS using DSM-IV or ICD-10, since the criteria are different, which adds more to the debate. Also, the criteria for PCS are not specific to concussion and the presentation symptoms can be found in subjects, who never had a cranial trauma. This questions the specifics of diagnosing a PCS.

Some of the most common symptoms of PCS include: dizziness, headache, fatigue, sleeping disorders, and hypersensitivity to light and noise. Blast exposure increases the probability of experiencing such symptoms as tinnitus, troubled sleep, irritability, and most notably headaches (Tsao, 2017), which are in line with the diagnosis of PCS. Other characteristics of PCS are cognitive in nature, so they will be discussed in the next chapter. Most symptoms resolve in 2 weeks, however, if symptomatology is continued for more than 3 months there is a diagnosis of persistent post-concussive syndrome.

Regarding the time of symptoms presentation, it must be noted that for severe and moderate bTBI symptoms will be expressed immediately, while for the mild form, symptoms may emerge immediately or can be delayed. In a study by MacGregor, Shannon, & Dougherty (2021) it was found that headache, tinnitus, sleep problems, and other symptoms were higher for 91-365 days,

than for the first 90 days after injury in service members. Only dizziness presentations were found to be higher in the first 90 days.

One of the most frequent complaints after TBI is a headache or migraine, which can be long-lasting, present almost all the time, or coming and going. 74% out of 246 veterans who received a diagnosis of mTBI after a blast had headaches of different intensities for 30 days after trauma (Patil et al., 2011). Also, a certain number of these people were diagnosed with migraine headaches and chronic daily headaches.

Another common neurological issue is chronic pain, which can persist for a long time. Headache can be one of the types of chronic pain, but others can be differentiated, too. Neuropathic pain is caused by a disruption to the central or peripheral nervous system and is characterized as a tingling, burning sensation, or pain that is not relevant to the actual injuries. Another type is central pain syndrome, which is caused by damage to the central nervous system. This type of pain can be restricted to a specific body area or affect a large part of the body. Uddin et al. (2019) hypothesized that chronic back pain in veterans with blast TBI is caused by thalamic sensitization.

Any form of TBI poses a risk for developing post-traumatic epilepsy (PTE), and blast TBI is no exception. Research shows that 10-25% of veterans with closed-head trauma have a risk of developing PTE (Chen et al., 2009). Immediate seizures can happen right after the blast and indicate the severity of the injury, but typically they are not associated with a long-term risk of epilepsy. However, when seizures occur later after initial injury they are more predictive of PTE. Additionally, up to 15% of veterans may not have a first seizure until five or even more years after trauma.

Lightheadedness and vertigo, commonly known as dizziness, are one of the most prevalent self-reported symptoms after bTBI reported by military members. Vertigo can be described as a subjective feeling of motion or spinning, while lightheadedness is described as a sensation of nearly

fainting. Even though there is a difference in the presentation of the two symptoms in most studies they go together by dizziness.

Vertigo has a vestibular nature of its origin, as it is involved with balance. Also, as it was presented earlier, primary blast injury often involves rupture of the eardrum and overall injury of the inner ear. After injury vestibular symptoms, which also include nausea and vomiting, last for 6 months or longer (Cohen et al., 2002), however vestibular adaptation processes in the semicircular canal, a structure in the inner ear, takes place before the symptoms fade. This inconsistency may suggest a different origin of dizziness (Akin & Murnane, 2011). Another source of vestibular symptoms may lie in the disruption of work of the cerebellum and brainstem, as they are central nervous system parts of the vestibular system.

In the study by Scherer et al. (2011) it was shown that vestibular pathologies in blast-affected service members involve both central (cerebellum and brainstem) and peripheral (inner ear structures) hypofunction. Central involvement is seen more with nystagmus, while peripheral with dizziness. Nystagmus, characterized by involuntary oscillations of the eyes, may occur in patients, who have the sensation of motion and there is a compensatory eye movement that tries to correct the imbalance.

Shifting from a vestibular component of somatic symptoms, it is vital to address visual dysfunctions. Dysfunctions in vision are shown to be present for as long as 5-6 years after the blast injury. 68% of patients in the research by Magone & Shin (2014) reported visual complaints. This number even increased to 87.5% if the patient experienced multiple blasts during deployment.

Most frequently the visual dysfunctions associated with bTBI are related to oculomotor functions. Capó-Aponte et al. (2012) assessed patients who experienced issues with vergence, evidenced by large exophoria, decreased fusion ranges, receded near point of convergence, deficits in pursuit and saccadic eye movements, reduced amplitude of accommodation, and monocular accommodative facility. All of these problems with near oculomotor function lead to problems in

reading abilities, pronounced by low reading speed and comprehension. Moreover, researchers found that a lot of servicemen showed signs of hyperphoria, a condition in which one eye deviates upwards relative to the other one, which can be missed because of the compensation technique of tilting the head.

Photophobia is another prevalent visual problem that is reported by servicemen. It is described as intolerance to bright, or sometimes even moderate levels of light, which causes painful sensations. This symptom is debated to be either caused directly by head injury or it can be a by-product of another symptom, such as headache. Light sensitivity was present in 55% of patients after bTBI (Magone & Shin, 2014). Also, it is associated more with blast TBI than with non-blast TBI. In a study by Goodrich et al. (2013) 67% of blast-related TBI patients reported experiencing light sensitivity opposing to 33% of non-blast-related TBI patients. Even though photophobia is a common symptom that is seen in military personnel, it isn't well-researched.

Additionally, it is reported in some literature that those servicemen who experience visual deficits have more chances to also have auditory disturbances, one of which is sensitivity to loud noises (Lew et al., 2009). This makes a person experience a dual sensory impairment, which might exacerbate psychological and cognitive problems.

Tinnitus is a perception of a sound, often described as a ringing one, without the external stimulus for it and is one of the most reported auditory symptoms in the general population. Mild TBI in veterans is associated with the occurrence of 75,7% incidence of tinnitus (Oleksiak et al., 2012). Moreover, there is a difference between the occurrence of tinnitus; it may be constant or intermittent. The intermittent tinnitus before deployment would increase the incidence of post-deployment constant tinnitus (Clifford et al., 2019). A greater number of blast TBIs and higher intensity of combat are two factors that increase the likelihood of this symptom and their duration. Interestingly, in the rat study, it was found that tinnitus presentation one month after blast exposure

is associated with decreased spontaneous firing of neurons in the auditory cortex, while at three months time post-blast this pattern changes to hyperactivity (Luo, Pace & Zhang, 2017)

Other frequently mentioned complaints after blast TBI include: the difficulty understanding speech in the presence of some background noise, issues with understanding long or rapid speech, and issues with understanding what is told on the phone (Gallun, Papesh & Lewis, 2016). All of these subjective complaints were supported by behavioral test batteries for auditory processing disorder. Some people showcase persistent patterns for more than 10 years after injury, suggesting chronic effects on processing auditory information.

Another problems that become relevant after blast TBI are disturbances that interfere with the duration and quality of sleep. It may include trouble falling asleep, nighttime awakenings, trouble waking up, sleep deficiency, daytime sleepiness, and others. The main issue with this disturbance is that it affects the quality of life in general and may worsen all of the other symptoms. Even though sleep disturbance is one of the symptoms of PCS, it was demonstrated that this disturbance can predict the persistence of post-concussive symptoms.

Also, this is extremely relevant to the military topic, since it can increase the number of misjudgments and errors during deployment, which potentially can lead to accidents and compromise safety. These problems in military personnel can start even before the TBI. The main factors for them would be stress, traumatic experiences, and intense tempo of work.

Veterans, who experienced TBI during their deployment, are 41% more likely to develop any sleep disorder, including sleep apnea, insomnia, hypersomnia, and sleep-related movement disorder, than those who didn't experience TBI (Leng et al., 2021). In the study, it was shown that the probability of developing a sleep disorder is maintained for 14 years after injury.

The exact mechanism of how TBI causes sleep disturbances is not well understood and requires more research. However, for instance, in one study it was found that rats subjected to a blast had glial scarring on the hypothalamus (Shively et al., 2016). The hypothalamus is responsible

for the production of neuropeptide orexine, which is essential for supporting wakefulness. Another key role in sleep modulation is played by the suprachiasmatic nucleus (SCN) of the hypothalamus, which takes part in the regulation of the sleep-wake cycle.

Another factor influencing post-concussive symptoms are medications that can be prescribed. Some of them might interfere with normal sleeping patterns and might as well provoke dizziness and vertigo.

Furthermore, there is a strong link between physical symptoms and comorbid PTSD. A lot of research is done on the topic of what is the stronger factor influencing PCS symptoms - PTSD or TBI. Also, there is an overlap in symptoms of PCS and PTSD, for example sleep disturbance and headache. In a lot of studies after controlling for symptoms of PTSD the association between TBI history and post-concussion symptoms drops. This suggests that post-concussion symptoms are influenced more by psychological issues, than by the physiological effects of TBI. It was found that such symptoms associated with TBI as dizziness and postural imbalance are mediated by PTSD in the first place, rather than being part of PCS (Hoge et al., 2004). However, it is a closed loop since all of the factors are found to be interacting with each other. A more ecological hypothesis is that there is a pathophysiological mechanism that starts the post-concussive symptoms and later on they are maintained by comorbid psychological distress, which frequently itself has a neural basis (McCrea, 2008). Also, this highlights the strong link between psychological well-being and physical symptoms.

## 2.2. Post-traumatic stress disorder

The military environment especially a war zone not only poses a higher threat of receiving a physical injury but also has an increased danger of having a traumatic experience. Things like losing a comrade in a battle, witnessing civilian casualties, or suffering a traumatic amputation as a result of polytrauma are some of the examples of traumatic events that can bring a huge imbalance

in the mental health of a military personnel. This potentially can lead to post-traumatic stress disorder (PTSD).

In order to receive a PTSD diagnosis, a person is supposed to present a set of different symptoms. The defining characteristic of PTSD is that a person was exposed to actual or threatened death, serious injury, or violence. It can be either direct experience or witnessing such in person. Another important feature of this disorder is intrusive symptoms, for instance, distressing memories, dreams, and flashbacks. People with PTSD also tend to avoid stimuli that are associated with the traumatic experience. Such things as specific places, people, or situations can be avoided in order to lower the recurrence of unwanted thoughts.

In addition to already presented symptoms, there are also negative mood and thought alternations. The person would be prone to experience emotions like guilt, fear, shame, and anger. The thinking of one person would be biased toward the negativity. Typically people who are dealing with trauma would be perceived as being emotionally numb.

People, who experienced an intense traumatic event, frequently exhibit alternations in arousal and reactivity. Symptoms like increased irritability, hypervigilance, reckless behaviors, sleep disturbance, including restless sleep, difficulty falling or staying asleep, problems with concentration, and exaggerated startle response are commonly presented. Interestingly, nearly 6% of people who are diagnosed with PTSD have no perception of having a clinical problem. This highlights problems with rational evaluation of a person's own situation.

Post-traumatic stress disorder can be diagnosed in people who received a head injury. PTSD is one of the psychiatric disorders that may escalate the disability in people with mTBI. Also, there is data that suggests that blast-related TBI is a greater predictor of post-traumatic stress symptoms than non-blast mTBI (Kennedy et al., 2010). One of the explanations for such results is the environment in which blast exposures typically take place.

Regarding the prevalence of PTSD, it was found that nearly 20% of service members report symptoms of PTSD (Tanielian & Jaycox, 2008), while in the general population the lifetime prevalence is nearly 4%. It can be clearly seen that the military environment is a risk factor for a traumatic experience. The numbers increase even more dramatically if to take into account active duty members together with veterans who have a history of mTBI. The estimated percentage of those diagnosed with PTSD is from 33 to 39% (Carlson et al., 2011).

There is a possibility to observe a certain correlation between various neurobehavioral factors and PTSD. For example, in one of the studies it was reported that the number of blast TBIs with loss of consciousness during deployment has a positive correlation with the severity of PTSD (Ruff et al., 2012).

Another noticeable point is that some of the symptoms might overlap with PCS, like sleeping problems, concentration difficulties, and others. This might present some challenges in correct diagnosis of a person who simultaneously had a traumatic experience and TBI. The issue lies in the fact that PTSD may be underdiagnosed.

In the context of investigating the links between two pathological states, data from studies focused on neural deficits offer helpful insights. Similar to TBI, in PTSD it is common to see white and grey matter dysfunctions due to oxidative stress, neuroinflammation, and excitotoxicity (Kaplan et al., 2018).

Numerous studies were conducted on topic of the PTSD and TBI using MRI scanning. For example, in the study by Lindemer and colleagues (2013), it was found that patients with comorbid PTSD and TBI had a reduced cortical thickness in bilateral superior frontal regions. In this study, the results were compared to individuals with PTSD alone and they showed statistical significance after contrasting two groups.

Another well-researched and established neural basis for PTSD is the involvement of the amygdala. It is known that the amygdala is a key player in the regulation of fear and stress. In the

course of PTSD, it shows hyperactivity, which correlates with increased emotional response. Although in the literature there is no direct link between blast TBI and amygdala dysfunction. However, it can be hypothesized that, as part of a limbic system, the amygdala may exhibit hyperactivity which could be evidenced by overall emotional instability. There is some evidence to support this matter in patients who are simultaneously diagnosed with two pathologies. For example, in one study that used voxel-based and surface-based morphometry, reductions in volume were detected in bilateral anterior amygdala in veterans with both conditions compared to their comrades with either TBI or PTSD alone (Depue et al., 2014).

Spielberg and colleagues (2015) conducted a graph theory-based research. Two weakly connected networks, especially the right prefrontal cortex and hippocampus, were identified to be related to re-experiencing symptoms. Taking into account the presented earlier symptoms of PTSD, re-experiencing the traumatic event through flashbacks is one of the main intrusive symptoms. However, in this study the weakened connections were found only in individuals with TBI, highlighting the increased vulnerability to PTSD after injury.

Spadoni, Hyang & Simmons (2018) in their article suggested that disruption in prefrontal cortex functioning following a TBI may lead to the amplification of PTSD symptomatology. This was backed by magnetoencephalography (MEG) results in which slow-wave activity in ventromedial and dorsolateral frontal regions, corresponding to TBI, was co-occurring with reduced activity in high-frequency bands in the identical regions, corresponding to PTSD.

These findings demonstrate the involvement of both frontal and limbic regions and they confirm the specific neural alternations that are evidenced uniquely in dually diagnosed groups. This can be hypothesized to lead to the presentation of overlapping symptomatology of two distinct disorders. Presented facts only highlight the already established idea of the importance of a continued investigation into roles and interplay of frontal and limbic regions in TBI and PTSD (Spadoni, Hyang & Simmons, 2018).

Another important concept regarding PTSD is the hypothalamic pituitary adrenal (HPA) - axis. It connects in central nervous system structures and peripheral tissues in order to regulate hormones, specifically glucocorticoids. This integration of systems main function is to preserve and restore homeostasis in stress conditions (Burford, Webster, & Cruz-Topete, 2017). Times of prolonged stress and emotional disturbances may disturb the efficiency of the HPS-axis and cortisol release.

The study by Ramos-Cejudo and colleagues (2021) focused on the measure of corticotropin-releasing factor (CRF) in veterans with PTSD and TBI. CRF is the essential mediator of HPA-axis responses to stress and anxiety. It is released by the paraventricular nucleus of the hypothalamus and then triggers the secretion of adrenocorticotrophic hormone by the anterior pituitary gland. In the PTSD alone and PTSD together with TBI groups, a significant reduction in CRF levels was observed. The control group and TBI-only group didn't present such levels of CRF. This suggests that a decrease in CRF is associated with PTSD independent of TBI. The authors also suggested that alternatively, low serum levels of CRF are risk factors for TBI. The future research should be aimed at the validation of CRF serum levels as a biomarker for PTSD.

Numerous studies emphasize considering the difference between the civilian and military population when investigating stress response since the HPA-axis functioning can differ between groups. For example, Pierce and Pritchard (2016) found interesting differences regarding diurnal rhythms in female veterans and civilians. Diurnal rhythms are related to the peak cortisol level in the morning and its the lowest point in the evening. The flattened diurnal rhythms as expected were found in veterans and civilians with PTSD, however, surprisingly such results were also shown by veterans without PTSD. These findings offer a perspective that changes in cortisol can be related to military experience alone, not only PTSD.

In the research of Golier et al. (2014), it was demonstrated that cortisol reactivity was higher in the veterans who had the war zone exposure when compared to their colleagues who didn't have an experience in the same setting. These results were not dependent on the diagnosis of PTSD.

The aforementioned studies highlight the fact that specifics of military service, such as increased likelihood for trauma and living under constant stress, can promote a change in the HPA-axis and therefore the desensitized stress response.

### 2.3. Other Mental Health Comorbidities

As anticipated, the incidence of other mental health problems except PTSD, which receives the most attention in the academic field, is also high in the military population. It is estimated that 70% of military personnel who sustained head injuries are diagnosed with at least one mental health disorder (Chin & Zeber, 2020). These include anxiety issues and depression, which are among the most diagnosed ones in individuals with bTBI.

Talking about gender differences, it is well-documented that women are at higher risk for being diagnosed with any psychiatric disorder in the military setting than men. One of the hypotheses for such gender differences is the fact that women are more subjected to sexual abuse, which itself can be a reason for mental health struggles (Chin & Zeber, 2020).

The US Department of Veteran's Affairs named depression a service-connected condition secondary to TBI due to its high presentation among service members and veterans. Common symptoms of depression include feelings of sadness and emptiness, reduced interest in things that brought pleasure, loss of energy, and feelings of worthlessness (DSM-IV, 1994). It can be accompanied either by insomnia or excessive sleepiness, weight loss, or weight gain.

The prevalence of depression has different estimates. For instance, the highest number of 87.46% among Operation Enduring Freedom and Operation Iraqi Freedom veterans was reported by Dismuke-Greer and colleagues (2018). Vasterling et al. (2012) in the research demonstrated that

31.3% of service members at post-deployment were screened positive for depression. An even lower estimation of 20% was reported by Tanielian et al. (2008).

Reasons for such different numbers are due to differences in diagnostic, rating methods, and the amount of time that passed after the deployment. One of the crucial problems in the military setting is that personnel are reluctant to report any mental health issues or to seek medical help. One of the explanations is that it is rooted in the cultural traditions of the military's resilience and strength, while admitting struggles would be viewed as weakness.

Anxiety disorders are marked by excessive fear, constant worrying, and nervousness. This excessive emotionality is typically concerned with the anticipation of future events. This may lead to avoidance behaviors and affect normal functioning. In the general population, it is estimated that 4.05% of people have a diagnosis of any of the anxiety disorders (Javaid et al., 2023). In the study by Chin & Zeber (2020), the reported incidence of anxiety among military service members with TBI is 37%.

As for any other pathological state, during mental health issues, it is important to report them as soon as possible to see the best results in diagnosis and treatment. Also, it may prevent the possible worsening of existing symptoms or the emergence of new ones. It is also shown in the literature that struggling with depression or anxiety in the course of the two weeks after TBI increases the risk for long-lasting post-concussive symptoms (Hou et al., 2012).

Additionally, veterans who are diagnosed with depression are susceptible to increased suicidality. This risk is furthermore elevated by the comorbid presentation with PTSD. Interestingly, Bryan and colleagues (2013) found that loss of consciousness during a TBI was connected to a decreased likelihood of suicidality. One proposed explanation for this finding is that longer loss of consciousness diminishes the ability to recall traumatic events of the blast or things that preceded it. Also, service members with more severe forms of TBI were evacuated from the war zone and received more comprehensive medical care, which helped to mitigate the risks.

It is well documented in the literature that in the general population there is a high comorbidity of PTSD and depression. In the military population there is the same trend, the simultaneous occurrence is estimated as high as 73.4% (Kennedy et al., 2019). Researchers shifted more attention to PTSD during studies about suicidality in a military context, which has a higher risk factor for suicidal ideation than depression. Moreover, the comorbidity of these two pathologies intensifies each other, and the risk of suicidality marks even higher. Since there are a lot of individuals who have a diagnosis of depression, and who also received a diagnosis of military setting TBI, more attention is needed in investigating the possible suicidal thoughts and how all of the aforementioned factors influence each other.

Notable are results regarding the fact that the number of blast exposures and subsequent TBIs do not impact the prevalence of mood and anxiety symptoms (Kennedy et al., 2019; Walker et al., 2015). Such data contradict the previous findings demonstrated in animal research, where the number of experienced TBIs elevated the risks for emotional disturbances.

A study by Heldt and colleagues (2014) investigated the effect of receiving a closed-head blast injury in anesthetized rats. Results showed that injury potentiated the anxiety response in mice, even though they were under anesthesia, meaning there was no conscious memory of the traumatic event. These findings suggest the existence of a biological basis for emotional deficits after bTBI and that it can be presented without the explicit recollection of events. Therefore there is a neurobiological mechanism for emotional regulation that is challenged by bTBI.

Vasterling and colleagues (2020) in their research found that war zone mild TBI is significantly associated with anxiety, while moderate and severe TBIs are significantly associated with severe depression with anxiety symptoms. Another key finding is that after adjusting for deployment-related stress, TBI still was a risk factor for long-term negative emotional stability.

These connections also work in another direction. Mental health issues might result in higher risks of sustaining TBI during military service. The work by Albrecht and colleagues (2024)

clearly demonstrated such findings in veterans older than 55. In this study, findings revealed that rates for depression, PTSD, anxiety, and substance use disorders prior to service were significantly higher in those individuals who later sustained a TBI during deployment than in individuals who did not. Furthermore, it is noted that pre-injury depression and anxiety are predictive of long-term post-concussive symptoms, which are present after 3 months post-injury.

In conclusion, it is estimated that for veterans with TBI and comorbid psychiatric disturbances annual medical costs reach approximately \$1 billion (Dismuke-Greer et al., 2018), which marks a substantial economic burden. The high prevalence of veterans who have such comorbidities, together with the increased risks that they bring with them, highlight the need for improving the health care efficiency and accessibility for affected individuals. Additionally, a more thorough screening of the mental health prior to deployment might reduce the risks for TBI.

## CHAPTER 3: Cognitive consequences of bTBI

### 3.1. Memory problems

The amount of different neurological pathologies and post-concussive symptoms after blast TBI can't go unnoticed in the cognitive performance of the affected individuals. Some of the cognitive deficits may be transient, while others might be permanent, depending on the severity of TBI.

One of the most prominent cognitive deficits is the one concerning the memory domain. Memory is composed of multiple components, each with its distinct neural basis. Damage to any of these brain areas can lead to impaired memory performance.

Broadly speaking, memory can be divided into three stages: encoding the information, storing the exact information over time, and retrieving the needed piece of information on demand. Moreover, this cognitive function can be further categorized as short-term memory, long-term memory, and prospective memory.

To begin with, the transient memory problem that can be noticed right after the injury when the individual is still confused is post-traumatic amnesia. In the study by Walker and colleagues (2013), 87 active-duty personnel and veterans who sustained blast-related brain injury were examined regarding their initial experience after the blast. Substantial gaps in memory were reported by 17.2% of participants, while not continuous memory for the events were reported by 13.8%. It is also worth mentioning, that 20.7% of individuals mentioned that they experienced loss of consciousness.

Digging deeper into memory functioning right after the events of the blast injury, the study by Palombo et al. (2015) offers valuable insights. In this study, veterans who received the diagnosis of mTBI were asked to recall the events of the blast during the semi-structured interview. Certain patterns started to emerge in their narratives.

On the one hand, it was found that the group with blast-related mild TBI had narratives that were less coherent compared to their colleagues who didn't receive the diagnosis. This goes in line with previous research suggesting that such event as blast exposure, along with confusion and disorientation that are associated with it, can reduce the efficient encoding of memories. Moreover, the lack of coherence can be due to information retrieval deficits.

On the other hand, individuals with head injuries included more episodic details in their narrative than those who didn't sustain an injury after blast exposure. This finding is rather a counterintuitive one, however, the authors offered some hypotheses to explain it. One such explanation is that events with high personal significance and emotional relevance are better remembered. For people with blast-related TBI, the event of injury holds a lot of emotional significance. As well as in general, negative experiences are more vividly remembered.

It is proposed in the study that the generation of event details and organization of these details into a coherent narrative depends on two distinct cognitive mechanisms. The mechanism for details generation is linked to the successfulness of the encoding, while the organization of these details is connected to post-encoding processes, such as consolidation and integration with prior knowledge.

After blast exposure, a common memory complaint is the rapid forgetfulness in daily tasks, such as remembering a phone number or the beginning of a long sentence. These difficulties are linked to such domains as short-term memory, which is responsible for holding information for a brief period of time without manipulating it. The cognitive function relies on the activation of prefrontal and parietal cortices. In the civilian population with mTBI, deficits in the short-term memory subset of Memory Assessment Scale (MAS) were associated with reduced fractional anisotropy of the DLPFC, which is a measure of axonal density and myelination (Cho et al., 2022). After the blast similar effects are expected to be seen.

Anderson and his colleagues (2021) mention the functioning of short-term memory after blast exposure in rats in their research. Animals that did not receive any medication following repeated blast exposures overall showed a trend for reduced short-term memory efficiency at nearly one-month post-injury. This finding highlights the delayed and time-dependent presentation of a deficit, which authors explained by secondary-injury processes, such as inflammation taking place during that period.

Another animal study that investigated short-term memory functioning was done by Sajja et al. (2015). In this study effect on memory was tested by the Novel Object Recognition Test (NOR) at one and three months post-blast. The results showed that functioning was decreased at both time periods, however, there were no significant differences in results between two time periods in the blast group. Such findings were linked to the loss of neurons, secondary inflammation, and synaptic dysfunction in the prefrontal cortex and hippocampus. Similar significant findings were demonstrated by Cho et al. (2013). However, in this study, researchers testing with NOR on rats was performed during the sub-acute stage, specifically two weeks after trauma.

Another issue that can be noticed is regarding long-term memory. It may include complaints like forgetting certain words during conversation, having hard times remembering recent or distant past events, and details of them, asking questions repeatedly during a conversation, getting lost in familiar neighborhoods, and forgetting where an item was placed before.

A neural substrate responsible for long-term memory deficits is believed to be the hippocampus. A lot of research is done regarding degenerative diseases like Alzheimer's. It is shown that neurodegenerating processes start at the entorhinal cortex and hippocampus. Later the pathology spreads to lateral frontal, parietal, and frontal structures.

An interesting study was done by Wooten and colleagues (2021) on the topic of apolipoprotein E4 and its association to close blast exposure in veterans. Individuals who are carriers of APOE e4 have higher risks of developing Alzheimer's disease. It was hypothesized that

carriers of this gene would present more cognitive decline after the blast than individuals without this gene. The individuals' memory was tested with the California Verbal Learning Test - II (CVLT-II) and its three assessments for short-delay free recall, long-delay free recall, and long-delay recognition in the verbal memory domain. Carriers of  $\epsilon 4$ , who also experienced a close blast, showed worse performance in short-delayed and long-delayed free recall, however, no differences were found for long-delay recognition. It is believed that recognition is an easier form of a memory task, therefore deficits in this type of task would suggest a more serious decline in cognitive functioning.

In the study by Baalman et al. (2013), researchers evaluated recognition memory in rats after single blast wave exposure with the help of a novel object recognition task. Two weeks post-injury, rats were trained for 10 minutes with identical objects. After 1 hour break, rats were put back into the testing room in which one of the learned objects was replaced with a novel one. Injured rats spent a significantly lower amount of time with new objects when compared to a control group. This finding suggests problems in the memory domain, specifically in recognizing the object that was encountered before.

As a result of blast exposure the presented cognitive deficits involving memory can also be linked to the disruption of the hippocampus normal functioning. An animal study by Ratliff et al. (2020) found decreased dendritic branching, distribution, and density in the hippocampus of injured mice. Taking into account the main functions of dendrites, the reduction in dendritic morphology is associated with negative effects on such abilities of neurons as generation, propagation, and timing of action potentials.

In another study by Manohar et al. (2020), it was found that blast-exposed rats showed a significant decrease in hippocampal neurogenesis and cell proliferation. 45-days post blast rats were tested with a maze task to look for any differences in spatial memory acquisition. Test and control groups showed similar results in the learning process, however, two weeks after acquisition training

test group results were significantly lower. Rats in the testing condition showed no long-term memory recall of the maze that was learned before.

Another important concept in the field of memory is prospective memory, which is sometimes called “remembering to remember”. It refers to the ability to remember and execute actions that are planned for the future. It is a key component in daily tasks, such as remembering to take medication, attending daily appointments, or dates for specific events in the future. Moreover, prospective memory can be divided into two types: time-based, when it involves a specific time for doing some action, and event-based when there is a need to perform an action that is triggered by a specific event. Event-based prospective memory is believed to be an easier form of a task, since the event itself serves a functional cue, while time-based one is more challenging since it requires an independent recall with no reminder.

Prospective memory also plays a critical role in how the individual adheres to the prescribed treatment plan from a healthcare provider, therefore the overall prognosis highly depends on this aspect. Veterans, like any other individuals, may face problems in prospective memory after brain injury.

Pagulyan and colleagues (2017) demonstrated that prospective memory deficits are a sensitive marker for a general cognitive decline. In this research, veterans were evaluated using the Memory for Intentions Test (MIST), which consists of eight tasks that varied depending on the amount of time before the instructed task needs to be executed, which ranges from 2 to 15 minutes, with event- or time-based nature of a cue, and required response type. Veterans with bTBI showed significantly lower total MIST scores. As hypothesized, the lowest scores were observed in the most challenging tasks, which included the 15-minute delayed recall and time-based task. Another important finding is that veterans who had comorbidity with PTSD performed significantly worse than the one with bTBI alone.

One of the explanations for lower performance on the time-based prospective memory tasks was proposed by Sheppard et al. (2023). In this study, it was discovered that veterans with blast exposure exhibited significantly reduced time-monitoring behavior during a required task compared to veterans without blast exposure.

Overall, the memory complaints of veterans after bTBI are undeniable. The available animal studies give the idea about the pathological mechanisms of persistent memory deficit, however, it would be beneficial to see more research with human subjects. In the field of prospective memory, there are numerous studies on veterans, however, there is an issue with neuropsychological tests that are being used since a lot of them are criticized for lack of ecological validity.

### 3.2. Executive functions

Another cognitive domain in which issues may arise for veterans is high-order thinking abilities, known as executive functions. Key roles of the executive functions include goal-directed behavior, active manipulation of learned material, self-regulation, emotional control, and problem-solving. Executive functions are usually based on easier cognitive abilities and may be constituted of a combination of abilities. They are used in everyday life and their disruption is easily noticeable. For instance, after bTBI an individual may find it exhausting to engage in everyday planning or making a list, to have problems in counting a change in the store, to be late to meetings, to have troubles with impulse control, and to present higher levels of irritability.

As the more demanding cognitive domain executive functions are mainly controlled by a most evolutionary novel part of the brain - the prefrontal cortex. Therefore after a bTBI a disruption in this neural substrate is expected to be seen. For instance, in the study by Matthews and colleagues (2011), it was found that veterans with bTBI present a lower fractional anisotropy (FA) in multiple white matter tracts of the prefrontal cortex.

Moreover, another role in the regulation of these functions is taken by basal ganglia structures, even though these nuclei mainly take part in the motor control. In the study by Terry et

al. (2024) the increased FDG uptake was found in the left portion of the globus pallidus (GP), part of the basal ganglia, of the blast-exposed veterans. The increased work of the left GP mediated the executive function disruption, which was assessed by the Behavior Rating Inventory of Executive Function (BRIEF). One of the explanations for the increased glucose uptake is the compensatory strategy, meaning that after trauma the same area needs to work more in order to have the same behavioral outcome. Even though the imaging resolution of the PET scan is low and authors couldn't differentiate between affected subregions of GP, they hypothesized that it was ventral pallidum. Such decision is explained by the central roles of this subregion, which include regulation of reward, motivational, and emotional processes (Smith et al., 2009).

One of the well-researched executive functions is inhibition. Inhibition is crucial during the post-traumatic period because when its' normal functioning is disturbed it may lead to the reckless behaviors and the emergence of addictions. Veterans are a vulnerable group that has higher chances of developing gambling problems, substance addiction, and dependency issues. After a bTBI, it may be hard for veterans to control their impulses and refrain from engaging in the fast rewarding behaviors. The lack of thinking about the consequences of one's actions adds its weight to such impulsive behaviors.

After a bTBI there are differences in the neural processing during the inhibition task compared to individuals without any TBI, as well as to civilian TBI. This matter was investigated by Fischer and colleagues (2014). In their research participants were undergoing functional MRI while performing an inhibitory task. Specifically a Stop Signal Task was introduced, in which it is needed for participants to respond as quickly as possible to a stimulus and to abort the action when the stop signal is displayed at a variable time point (McMorris, 2016).

During a successful inhibition response, both civilian and blast TBI groups showed hypoactivation in such regions as medial prefrontal, precuneus, and inferior parietal, which are associated with default mode network (DMN).

The differences between the two groups emerged during the unsuccessful inhibition. The bTBI group results demonstrated hyperactivation in the left caudate nucleus and left posterior region of the cerebellum, while on the other hand, hypoactivation was presented by the civilian TBI group. The caudate nucleus is associated with negative response feedback, therefore authors suggest that such outcome is associated with the increased cognitive interpretation of the negative response. Such findings highlight the difference in brain functioning as an outcome of two different types of TBI.

Inhibition is also closely related to depression, which as presented before, is a common comorbidity in military veterans after bTBI. In a study by Bjork et al. (2016), a positive correlation was found between the preservative and commission errors, which are estimates of disinhibition, and was measured by a Continuous Performance Test (CPT-II), and depression score.

A lot of studies on this topic find a stronger correlation between mood disorders and problems in inhibition, than with bTBI. For instance, a study by Swick and his colleagues (2012) stresses the fact that PTSD is a stronger predictor of impulsive errors than bTBI. It would be beneficial to see more research regarding this since disinhibition is a core executive function, which disruption affects the individual's standard of living.

Another important component of executive functions, that is susceptible following a brain trauma, is working memory. Its main function is to manipulate the information in a short period of time and before memory starts to decay. Moreover, in civilian research on working memory functioning after TBI, it is regarded as a sensitive indicator of an overall cognitive dysfunction (Frencham et al, 2005).

This ability is important, especially in mental arithmetics and is used in such everyday tasks as for example counting a change. Logically, as a measure of working memory, there are a lot of tests using mathematical problems. For instance, in the study of Rice et al. (2020), it was shown that blast-exposed military servicemen showcase significantly diminished scores in solving arithmetical

problems when compared to the civilian population. Also, it was shown that military subjects required in general more time to process information.

Tasks on arithmetics can also be found in the working memory index (WMI) of the Wechsler Adult Intelligence Scale (WAIS-IV). In this set of tasks veterans with mild bTBI also showcase lower scores, however, the deficit was not detected in the follow-up period of 12 months (Martindale, Ord, & Rowland, 2020).

There are differences in the work of brain areas involved in working memory between different etiologies of brain trauma. In the research of Pagulayan et al. (2018), they decided to use fMRI during the evaluation of working memory with Auditory Consonants Trigrams (ACT). Even though there were no significant differences between veterans with a history of blast TBI and veterans without such history in the neuropsychological measure, there were findings in regard to activation of the working memory network. The blast-exposed group demonstrated resting state hyperconnectivity of frontal regions, which is an expected finding after TBI. Specifically, the increase in connectivity between the frontal working memory network to cerebellum is associated with better performance on the working memory testing measure only for blast-exposed group. This is largely explained by the compensatory mechanism that is needed in order to bring the functionality level back to the pre-traumatic one. It is worth noting that, such finding was found to be not related to the measure of PTSD in servicemen.

Even though case studies lack generalizability, they offer in-depth research into one individual's history, medical profile, and deficits exploration. Moreover, they are influential for future research on the same topic, because they may offer valuable hypotheses. One of the case studies regarding executive function was done on a retired veteran who sustained multiple blast injuries during his career by Hayes, Morey, & Tupler (2012). The contrast between premorbid above-average intelligence, which is suggested by vocabulary and information measures of WAIS-III, and the neuropsychological functioning presented after numerous blast explosions are striking.

Most of the deficit was seen in tests regarding such domains of executive functions as sequencing, set switching, category fluency, and problem-solving. He showed an impaired below average in Trial Making test B (letter number sequencing). Moreover, he made a lot of preservative errors in the Wisconsin Card Sorting Test, which were in the low-average range.

Such neuropsychological findings correlate with the results of DTI. Compared to age and sex-matched controls, the individual showed signs of decreased fractional anisotropy in projections of white matter to frontal and parietal cortices. Therefore the subjective complaints of participants were evidenced by the results of neuropsychological testing and functional alternations in frontoparietal regions.

As it was shown, executive dysfunction is a common outcome of the bTBI, which involves disruption in multiple brain regions, but most profoundly in the frontal cortex. There are some studies on this specific topic, however, it would be beneficial to see more studies that focus on the number of sustained bTBI and whether the effects are exacerbated over time in relation to executive functions.

### 3.3. Attention

Attention is regarded as one of the cognitive domains and its functioning can be impaired as a result of a bTBI. In the literature, regarding civilian TBI, it can be found that attention deficits may persist for a long time after the injury (Vanderploeg, Curtiss, & Belanger, 2005). It is a fundamental part of cognition that supports other cognitive processes such as learning and processing new information, problem-solving, goal-directed behavior, and others.

Attention could be divided into multiple components, of which some are relevant to blast consequences. The first one is sustained attention, or when a person is supposed to maintain attention on the same stimuli for an extensive period of time. After a blast injury, individuals can experience problems with maintaining their focus on a needed task. For instance, it may be hard to

concentrate on a conversation or to read a long instruction. Also, distractibility plays an important role in this concept.

A study by Bonnelle et al. (2011) looked at the functioning of sustained attention after brain injury using a fMRI. Sustained attention was measured by the Choice Reaction Time task, in which participants needed to sustain their attention for a long time, specifically for 144 trials, and it showed the effect of fatigue and losing the focus on task. It was found that dysfunction of sustained attention was associated with the increase of DMN activation, specifically in areas of the precuneus and posterior cingulate cortex. Furthermore, it was shown that the connection of the precuneus to other “parts” of a network at the very beginning of the task was predictive of the final result, even before any behavioral response.

Another component of attention is selective attention. This refers to the situation when there are multiple environmental stimuli, and an individual can successfully attend to the relevant stimulus while at the same moment ignoring the irrelevant one. For instance, in a crowded place, full of people who are having conversations, an individual can attend to one specific speaker and ignore others. This is described by Cherry (1953) as a “cocktail party problem”.

Selective attention after an explosive brain injury was discussed in the research of Bressler, Goldberg, & Shinn-Cunningham (2017). In their study, the auditory task was used, in which two melodies were playing and the participant was beforehand asked to attend to a specific one, while the other was a distractor. At the end of testing, it was required to answer a specific question regarding the tested melody. Before testing the hearing of all participants was also assessed, those who had signs of a hearing loss were eliminated from the study. Also, during a task EEG was used to record the neural activity.

The participants who sustained the explosive injury showcased significantly worse performance and their selective attention deficit was proved. The result was also validated by weaker ERPs in frontal EEG channels. It can be found in the literature that primary, secondary, and

tertiary blast injuries can impact the normal functioning of brain regions that are also responsible for attentional control network (Taber et al., 2006).

In the aforementioned study of Martindale et al. (2020), some results were found regarding deficits in divided attention. This is another component of attention, which is responsible of processing of two stimuli at the same time. For instance, it is the ability to perform two tasks simultaneously as talking on the phone while driving. In the study, it decrements in the successful complication of Trial Making Test B, which involves sequencing between letters and numbers. The severity of the injury, as well as the number of experienced injuries, were found to exacerbate the performance on this task.

Moreover, during a neuropsychological assessment, the distractibility or lack of attention may interfere with testing and lower performance scores. Because of this reason, it is important to assess the attention domain first before moving to other cognitive abilities, since it can lead to misinterpretation of testing results.

### 3.4. Processing Speed

One of the cognitive functions that is extremely sensitive towards any brain damage is processing speed. Speed of mental processing is usually measured by the amount of time that is needed to process a certain set of information. Moreover, it is one of the first cognitive abilities that are age-sensitive. As a result of blast exposure processing speed is affected, too, as evidenced by research on this topic.

In the civilian TBI studies, the slower speed of information is evidenced in such tasks as Trail Making Test A (connecting numbers in ascending order), Hayling Test (logical sentence completion), N-back (response when the previously seen stimulus is repeated) (Dymowski et al., 2015). For instance, in the study of Martindale and colleagues (2020) similar results are seen in the blast-exposed individuals in the simplest measure of processing speed - Trail Making Test A.

However, authors suggested that presented lower performance wouldn't be associated with functional impairment and therefore stress on the further replications.

In the study of Combs and colleagues (2015), it was found that veterans with TBI had a poor performance on processing speed, which was measured by subtests of the Processing Speed Index of WAIS-IV, including Digit Symbol Coding.

A lot of studies explore if decreased functioning of processing speed is worsened by psychiatric problems. In the aforementioned study difficulties in processing speed were found in veterans with TBI, who also had a higher prevalence of psychiatric comorbidities. It was also suggested that it is rather comorbidity of two pathological states, for instance, a TBI combined with PTSD, that result in such an outcome, and not solely the psychiatric component accounting for the deficit.

Research, that was done by Brenner et al. (2009), also found worse performance on processing speed tasks in retired servicemen with TBI. Similarly to the previous study, no significant differences were found between groups with TBI only and with comorbid PTSD. In their discussion authors suggested that PTSD may be linked to cognitive decline in other domains.

On the other hand, there are studies in which the TBI group with comorbid PTSD shows lower performance in processing speed (Nelson et al., 2009). Another study found a decline in processing speed to be associated only with PTSD, specifically the hyperarousal symptoms, while bTBI with LOC was not a significant predictor (Wrocklage et al., 2016).

Disruption in this cognitive ability would influence other more complex abilities, especially the one related to executive functions. In the study of Nelson et al. (2009) on veterans with TBI, it was found that decreased processing speed accounted for 43% performance variance on the Trial Making Test B, which originally measures divided attention and task switching. Additionally, 50% of the variance in performance on the Stroop task, which measures predominantly inhibition, was also dependent on speed of information processing.

What might be the case, is that in a lot of studies, measures for processing speed are classified as measures to assess attention or executive functions. Even though processing speed is important for these cognitive domains, it is important to be able to separate them in research. Moreover, taking into account the age decline in this cognitive ability, it is important to compare results to the age-matched control group.

## CHAPTER 4: Psychosocial consequences of bTBI

### 4.1. Military footprint

In the previous chapter, the well-documented consequences of bTBI on servicemen were explored. However, brain injury doesn't solely affect the neurologic aspects and their interconnected functions. Each of the things that are influenced by bTBI, such as physical and mental health, as well as cognition, will have their role in the reintegration of a person in the community, interpersonal relationships, occupation, and others.

It would be reasonable to start with an explanation of how the military experience can change the person. A military environment can be described as having a strong presence of structure and guidance to rules. From the very first days in the military, people are taught to follow orders and to have a strong respect toward the higher-ranked personnel. After a certain time in the military, when the person gets used to certain norms and practices, the military mindset emerges. Krueger (2000) explained it as an “organizational structure that fosters a common set of values, with associated attitudes, beliefs, and behaviors that are shared by all uniformed service members.”.

In this context, the person usually struggles with self-identity and with their own vision of a situation. After a considerable time in such an enclosed and strict structure, it certainly will be hard to adapt to a civilian context, where a person would be responsible for his own life choices.

Among the problems that might be faced by veterans when they are trying to integrate into civilian life is a lower sense of self and purpose. One of the first explanations for a probable identity crisis is the lack of understanding regarding what to do in future civilian life. Typically, people join the military at a considerably young age, and for their whole lives, they are studying and doing things that can't be utilized in civilian life. This discrepancy in the high knowledge of military skills and complete loss in the civilian skills that are valued in a job market might create difficulties in adaptation.

In the research, it is shown that a lot of servicemen after deployment think about returning to military jobs again since there is no place for them in civilian life. The willingness to come back to the battlefield is fueled even more by feelings of brotherhood that were experienced there. In the military circle, servicemen can find an understanding of the troubles they are going through. At the same time, the feeling of isolation in society would deepen the social alienation and psychological problems.

However, being unfit for civilian life is not the only reason why veterans can express these types of thoughts. Another reason can be the emotional dependence on the risk-taking opportunities the military offers. During the stressful and sometimes life-threatening situations that are faced during deployment, the sympathetic nervous system is activated and responds by releasing adrenaline. This hormone provokes certain physiological changes that will increase the alertness and energy. Over repeated exposures to such circumstances, the individual can develop psychological dependence due to experiencing the adrenaline rush. Moreover, it can be explained by the widely accepted dopamine theory of reward and addictions (Nutt et al., 2015).

Due to this psychological dependence on adrenaline, ex-military servicemen would often associate civilian life with an absence of emotions and no “rush feeling” that they used to have. Therefore, it is quite common for them to engage in risk-taking activities, such as extreme sports, combat martial arts, reckless driving, and sexual risky behaviors. In a lot of situations, the striving for risk-taking may end with certain criminal charges.

In cases when such people don’t have the option to return to a military career again, they are prone to searching for other dangerous job opportunities that would fulfill their need for strong emotions. For instance, in this scenario, career choices would be firefighting and rescue services, law enforcement, private security, and mercenary jobs.

Talking about the cultural aspect of a military setting, it can be described as having all of the characteristics of a collectivistic culture, while most modern Western societies are formed on

individualistic ones. The collectivistic patterns of behavior can be described by loyalty, respect, commitment, and selfless service. The values that are promoted in the specific example of military culture are hypermasculine and include strength, toughness, insensitivity, and increased aggressiveness (Keats, 2010). Taking all of these characteristics into account, it becomes evident that for a person who spent most of the years in such a structure, it would take time to adapt again to Western societal norms.

For instance, considering such quality as toughness, in the military, it would be hard for a person to acknowledge any issues that are faced after the deployment. The idea of being viewed as weak and problematic in society would lower the person's willingness to ask for social and emotional support. The expression of particular vulnerabilities in mental and physical symptoms would require a lot of courage to shift from the built psychological military barriers (Pietrzak et al., 2009).

Exaggerated aggressiveness can be regarded as one of the symptoms of PCS and also as a by-product of a military culture. Especially this issue is more pronounced in individuals who were subjected to complex trauma during a deployment. In a study by Bailie et al. (2015), it was found that veterans with TBI reported a clinically significant level of anger, while the control group without TBI had normal results. Another research study found that increased anger rates among veterans are associated with difficulties in employment, health issues, functional issues, and arrest rates (Turgoose & Murphy, 2018; Etchin et al., 2022).

While some emotions as aggression can be increased in their manifestation, others can be lowered. For instance, there is a phenomenon known as emotional numbing, during which there is difficulty to experience and express emotions in situations that require a certain emotional response (Foa & Cahill, 2001). Especially during the post-deployment period, the problems with emotions are mostly noticeable.

Mitchell (2018) divided emotional problems into two categories: neutrality and overreaction. It is typical that veterans would showcase an emotional neutrality to major life events, when before the service the same event would result in great joy. Also, the negative event wouldn't evoke any high feelings. On the other hand, as it was shown with aggression, certain emotions may be heightened due to the slightest stimuli. This can happen with irritation or sadness.

Overall, military service is a unique environment that changes individuals who were once there and these changes can be noticed in civilian life. There needs to be a deeper understanding of military culture and its influence on the personality of a person.

#### 4.2. Alcohol and Substance Use

The challenges that are presented to the servicemen affected by blasts require the person to learn to live with them and cope with them in a functionally rational way. While some already discussed consequences may differ in their duration, being short-term or long-term, they still are more visible in the clinical assessment than the psychosocial consequences, which are more covert. Therefore, it is equally important to shed light on the psychosocial effects of bTBI as well.

To begin with, increased alcohol and substance consumption in servicemen is a common issue, especially after a bTBI, that will result in problems in all of the other psychosocial areas of life and will negatively affect the recovery prognosis after trauma. For instance, in the study by Petrie et al. (2014), higher rates of alcohol use were found in veterans who sustained a bTBI, as opposed to the ones who didn't sustain a brain injury.

The emergence of such habits may be connected to the irrational way of coping with stress, life difficulties, chronic pain, and sleep problems, however, this tactic may lead to further exacerbation of these issues. Moreover, there are differences in how substances and alcohol affect the brain that sustained the injury.

It is important to understand the mechanism by which substance use after blast exposure worsens existing symptoms. There is extensive research on this topic using animal models since people tend to withhold information regarding their substance use for various reasons.

The study by Nawarawong and colleagues (2019) found evidence that blast exposure can increase drug-seeking behaviors, even without a history of pre-injury intake. In their animal study, blast-exposed rats during the extinction period showed more drug-seeking behaviors of oxycodone than rats in the sham condition. This was the only significant finding regarding multiple blast-exposed rats.

Of special interest are studies that investigate the differences between repetitive and single-blast exposure. For instance, Schindler and colleagues (2021) investigated this issue in alcohol abuse using a rat model. Compared to the sham group, both the single and repetitive blast groups showed increased sensitivity to the sedative properties of alcohol. However, only the repetitive blast group showed an increase in the locomotor stimulation effect of ethanol, which was evidenced by hyperactivity. Moreover, repetitive blast exposure resulted in a specific consumption pattern. When the ethanol was placed for free access, the repetitive blast group had higher rates of alcohol consumption in the first two hours of access, which suggested the binge drinking pattern.

In the same study, researchers were simultaneously looking at the data from self-report questionnaires of veterans who sustained bTBI. The data from the questionnaires suggested that veterans with bTBI were engaging in “risky” drinking behavior, which was characterized by high alcohol intake and high frequency. The veterans without bTBI didn’t present the same drinking behavior, which suggests the effect of bTBI.

In the civilian TBI, there are well-documented cases of reduced substance tolerance after brain injury (Oddy et al., 1985). Even though there are no studies on this matter after bTBI, the same outcome is expected. After injury, the brain’s response to substances, such as alcohol or drugs, can change because of neurochemical and structural alternations. The individual would experience a

stronger effect from the smaller amount of substance, compared to the amounts used pre-injury. The main danger is in the fact that a person would try to intake the same amount of substance as before the injury, however, this might result in an overdose.

Emotional disturbance is among the most likely reasons for engaging in substance abuse. As it was presented earlier, the prevalence of PTSD is particularly high after bTBI. Almost 50% of people with diagnosed PTSD will also be diagnosed with alcohol or substance use disorder during their lifetime (Kessler et al., 1995). The military service, together with traumatic experience, can provoke the emergence of distressing flashbacks. To deal with this issue, individuals may engage in maladaptive ways of coping, such as substance use.

Taking into account the structural alternations that can result from injury, alcohol and substance use can also add to this. For instance, alcohol use is associated with significant cortical and subcortical decrease in volume in such structures as the frontal lobe, limbic system, and cerebellum (Sullivan & Pfefferbaum, 2005).

As documented with extensive research, there are a number of cognitive deficits that are presented after military service in combination with blast exposure. These cognitive issues, which already can impair normal functioning, can be detrimentally worsened by accompanying substance use. Specifically, alcohol consumption would further impair such abilities as executive functions and memory (Oscar-Berman & Marinkovic, 2007).

Substance and alcohol use poses a negative impact on the interpersonal relations of an individual. Emotional detachment, social isolation, problems with trust, and caregiver burden can lead to a vicious circle of mental health issues and comorbid psychiatric disorders, which, in turn, would only sustain the usage of substances. Furthermore, the usage of substances can increase the levels of aggression, which therefore can be a reason for violent behaviors that would further detriment social functioning.

As presented above, substance use is a significant risk for individuals who are recovering from a brain trauma. Moreover, it is a factor that is modifiable by the individual, and it can ensure the normal rehabilitation process. It is important for healthcare providers to check for issues regarding substance use and educate individuals about associated risks to ensure the most effective recovery.

#### 4.3. Difficulties in Socialization

People who did their service and are then trying to return to civilian lifestyle might face with problems in this reintegration process. The increasing number of veterans in various countries highlights the need for understanding the specific reasons that interfere with a healthy reintegration process. It is undeniable that meaningful governmental programs are essential for the desired outcome, which might involve legal protection, social and financial help during the adaptation process, and access to healthcare services.

First of all, veterans who come back to civilian life after the real experience of combat and who experience service on the frontline may lack the feeling of safety. Coming from an environment, where everything seemed to be a danger and had a real risk of death, having a mind set on being cautious of everything in the surroundings, it might be hard to accept the quick change to safe civilian life. After the whole mentality is set to the “fight” mode, it may be complicated to switch it back. Veterans might showcase extreme suspiciousness and overreaction to normal, everyday situations, which in its turn would cause problems in socialization. This type of behavior might be overlooked by the society.

Adding to this, veterans might not understand the huge difference between combat and civilian life. A lot of servicemen, share the experience of misunderstanding how two completely different settings can exist at the same time. On the one hand, there is a peaceful civilian life, while on the other, there is a cruel war side of the world. Another issue, is that servicemen might have a

judgemental way of thinking about people who didn't serve. In turn, this can lead to interpersonal conflicts.

Even when veterans decide to participate in the social activities of their community, there can be consequences of bTBI that will hinder it. As presented before, there is a long list of possible PCS symptoms that can interfere with normal functioning. For instance, as a result of bTBI, there might be an increase in sensitivity to loud noises, which would withdraw a veteran from large events or big groups of people. Moreover, due to neural overload, participation in social events can also be challenging. When presented with too many social stimuli, the nervous system would quickly become exhausted.

The first to notice problems in the socialization of veteran is often would be their family. The challenges experienced by individuals, who return from the frontline, have a negative effect on family relationships as well. It can be supported by existing statistics: veterans and their families have higher rates of divorce, homicide, and child neglect (Watson Institute for International and Public Affairs, 2015). In a study by Sayers et al. (2009), three-fourths of interviewed veterans reported experiencing family problems in the past week. The most frequently stated issues included a feeling of being a guest in their household, reporting that their children were afraid or were not warm towards them, and being unsure about their family role. Moreover, having experienced a life-threatening military accident doubles the likelihood of break-ups and divorce (Wasemann et al., 2024). One of the explanations for such problems in personal relationships is that families learn to function without one of their family members and the family roles of the absent member are taken by others, usually by spouses, therefore there needs to be an adjusting period for this matter to go back to pre-deployment level.

Another significant family problem is child maltreatment, which can be presented in such forms as physical abuse, sexual abuse, emotional abuse, neglect, and exposure to intimate partner violence. In the Canadian study by Afifi et al. (2021), it was found that overall child maltreatment

prevalence was 62.5% among armed forces members and veterans. The highest prevalence out of different types of maltreatment was shown by physical abuse (44.2%) and sexual abuse was the lowest (11.6%). Furthermore, in the study by Wesemann et al. (2024), it was found that veterans who were subjected to life-threatening incidents, for example a blast nearby, had a more significant deterioration in relationships with their children compared to those veterans who didn't experience such incidents.

Also, more family issues were reported by veterans who have comorbid depression, anxiety, or PTSD. It was reported that dysfunctional child communication patterns were also associated with having a diagnosis of PTSD and other mental disorders in the last 12-months (Afifi et al., 2021).

In order to decrease the dysfunctional family communication patterns, not only the veteran but also the family should be involved in the process of reintegration. First of all, children and spouses should be psycho-educated about PCS and all of its accompanying symptoms. It is crucial for them to understand that there is an organic cause for the new and bizarre behaviors of veteran, that might be unpleasant for them. There should be a deep understanding of what their family member is going through and what the rehabilitation process could involve. The engagement of family members in the re-adaptation process would strengthen the family ties. It is shown in the literature that psychoeducation can decrease levels of conflict in families. Moreover, families may try family therapy for even better results in order to have a deeper understanding of each other's feelings and behaviors.

The socialization problem can not only be viewed through the prism of a serviceman, but also through their caregivers. Caregivers, who are usually the wives of veterans, are crucial for socialization, since they provide emotional support and help with reintegration into family and community life. Therefore caregivers would be the first to experience issues in communication, aggression, and emotional instability of veterans. In the study of Maddah et al. (2024) main problems of veteran's spouses were identified. Most frequently such problems as sleep disturbances,

apathy towards self-care and caring for veterans, depression, feelings of being ignored, dissatisfaction with marital life, and financial burden were reported.

Another important factor for successive social integration is the level of income. It was found in the study by Pugh et al. (2009), that veterans with lower income also reported lower levels of social support and family functioning. Lower income is also correlated with difficulties in community reintegration. Another finding in the research was that moderate and severe levels of TBI lead to problems in reintegration. TBI also was positively correlated with low scores on a family functioning questionnaire.

On the job market veterans, who are also fighting the consequences of military brain trauma, could also face certain difficulties. Issues with cognitive abilities, psychological struggles, and physical symptoms might interfere with the successful completion of job tasks. Also, it might be hard for retired servicemen to fit into the civilian job market. Certain governmental programs for career transition and retraining are beneficial for better integration. Social services can take their share in assisting people in finding and adapting for suitable jobs.

Communication with other veterans can have a significant role during the reintegration process. Veteran communities or support groups can be beneficial for their participants. During the meetings, veterans can share their struggles with people who have similar experiences, which will promote the feeling of being understood and heard. People who were in the same situation can offer valuable insights for others, who are trying to reintegrate into society.

These support groups would help veterans feel less isolated, however, there is another side to such homogenous group meetings. Being surrounded by people who were in the same situation may lead to re-traumatization and would again create a closed community of people, like in the military, taking progress a couple of steps back. The communication in such a support group would hinder veterans from a real need for socialization with “outsiders” since they already found good

listeners and emotional support in people from the same setting. Moreover, such groups might lead to further exacerbation of alcohol abuse problems.

Social support can be provided not only by humans but by animals, too. Scotland-Coogan (2019) decided to examine the impact of training with dogs on combat veterans. After 14 weeks of training, improvements in the domains of anger, socialization, and interpersonal relationships were documented.

#### 4.4. Stigmatization

Social stigma is one of the prevailing problems in the healthcare system and is a factor influencing a person's psychosocial functioning. Stigma stemming from society may be related to fear, disgust, and avoidance of people who deviate from certain societal norms, as people with certain psychological and physical states. In the case of veterans, it may involve bTBI, PCS, and their symptoms.

This issue of stigma can be linked to the mind-body dualism by Descartes (1984), which views them as two different entities. Because of this, people would fail to see a connection between physical state and psychological or behavioral response. Although nowadays it is proved that these two entities are interconnected, therefore a physical state would affect psychological functioning. In most cases, veterans' psychological difficulties can be explained by the organic cause of the blast-related injuries.

Also, civilians may view people with bTBI as a danger to society due to their possible aggressive outbursts, and overall uncontrollable emotions and behavior, as it is usually portrayed in media. For the elimination of negative stereotypical thoughts, it is needed for society to understand that it is not the personality, nor the veteran's will to behave in a specific way, but rather the effect of the organic cause. On the other hand, society may stigmatize veterans because of viewing them as victims of war or as ones who receive too many benefits from the government. Despite the

reasoning behind stigmatization, it may lead to isolation, more issues in adapting to civilian life, and a worsening of psychological state.

As a part of the reintegration process, veterans with bTBI require a lot of help from society, which becomes scarce with the presence of stigmatization. On the one hand, society as such is not well educated about the traumatic experiences that influenced a great number of veterans. Even the understating for an ordinary civilian of the amount of affected individuals would shift their thinking pattern. In the media, there are a lot of portrayals of veterans as dangerous individuals, which fuels discriminatory behaviors in society.

Because of such incompetence in the matter, civilians have no willingness to help this group of people. On the other hand, individuals affected by bTBI have no desire to share their condition with others because of fear of being stigmatized. These give rise to the vicious circle of misunderstanding.

Moreover, in the research, it is presented that individuals affected by some issues may engage in self-stigma. In this case, even the individual believes in the public stereotypes, agrees with them, and internalizes them (Corrigan & Watson, 2002). Such a phenomenon is also associated with low self-esteem. For instance, in one study on veterans with PTSD, most of the participants shared an idea that civilians perceived them as responsible for their condition since they volunteered for military service (Mittal et al., 2013).

The worst-case scenario that can happen after deployment for veterans with brain injury after feeling pressure from society is suicidal ideation and behavior. This issue was presented earlier as one of the consequences of a disturbed psychiatric state, however, it is important to discuss it as part of the psychosocial consequences since a lot of factors influence its occurrence.

In the research, it can be seen that in the first year after quitting the military, the suicide risk is elevated, comparing the periods of service to one year of civilian life. For instance, in the study by Shen et al. (2016), it was found that the suicide rate in the first three months of civilian life is

three times higher when compared to other time groups. In male veterans, TBI specifically marks as a factor for increased suicidal ideation. In the study by Wisco et al. (2014), after controlling for comorbid mood symptomatology, TBI was responsible for a 55% increased risk of suicidal ideation.

The military stigma towards complaining about physical health and stigmatized views on people who admit certain problems as weak leads servicemen to deny any of the PCS issues and therefore to develop suicidal ideation. Pompili, Mancinelli, and Tatarelli (2003) in their study, stress the fact that suicide by itself can be a source of stigma. The common thoughts about people who committed or attempted it would be that they are shameful, selfish, and sinful. This would again prevent servicemen from seeking help if they have existing thoughts about suicide. Interestingly, relatives of people who committed suicide can suffer from stigma, too.

Taking these into account, it can be concluded that factors such as an existing PCS and suicidal ideation, or even the previous attempt, become more dangerous when they are stigmatized. The more attention all of these matters receive from the public, as well as from veterans, the less danger it poses.

Caregivers of veterans with bTBI can also experience stigma. In the research of Phelan et al. (2018), multiple ways by which caregivers, who are usually wives or parents of affected individuals, are affected by stigma are presented. From the questionnaires and interviews, it was found that there is a presence of caregiver stigma-by-association, which refers to the stigma that is experienced by a caregiver personally and beliefs that they are devalued by other people because of their care. Another type of stigma is a family one. This has to do not with one person at a time but with the whole family as one entity and certain ideas that a family with an individual affected by bTBI might expect poor treatment. Last but not least, the caregiver has strong ties with an affected individual and therefore would be affected by a stigma that is aimed toward a veteran.

All of these stigma factors would affect the behavior of caregivers. For instance, they would try to avoid social situations where it is possible to be met with discrimination. Such isolation

would only increase the already existing burden and reintegration difficulties. Caregivers who are influenced by stigma also report having higher levels of anxiety, depression, and stress issues, overall poor emotional well-being, and lowered self-esteem (Phelan et al., 2011). Certain governmental initiatives for counseling access for caregivers might be beneficial in order to overcome psychological issues and stress. Also, social support groups where caregivers can share their experiences would be helpful.

## DISCUSSION

This literature review tried to encompass such topics regarding bTBI as pathophysiology, physical symptoms, cognitive impairments, and psychosocial consequences. The available number of researches confirms that a bTBI has a different pathophysiology than a conventional TBI. The main differences can be explained by the existence of a unique mechanism of a blast, which is characterized by a sudden release of energy and overpressure. As a result, there are five distinct types of injuries, each mostly affecting a specific body organ and having its own acting process. It is important to note that blast can result not only in TBI but in a complex polytrauma.

A crucial point to address regarding the differentiation of bTBI from other types of brain injury is biomarkers. Moreover, biomarkers are relevant to avoid ambiguity between PTSD and bTBI because the overlapping symptoms may complicate the diagnosis. As was presented in the previous parts, there are certain biomarkers to indicate signs of blast exposure, such as diffuse axonal injury, neuronal injury, vascular abnormalities, and blood-brain barrier permeability. However, there is a lack of definitive biomarkers due to ongoing controversies and deficient replications of research findings. Another issue is in the fact that certain biomarkers do not strongly correlate with cognitive and neurobehavioral changes (Agoston et al., 2012). Therefore, more work should be done in future studies to address this issue and for the development of long-term biomarkers to track the recovery of a patient.

In the review, the topic of repetitive bTBI was explored, along with the possibility of the development of chronic traumatic encephalopathy (CTE). Examining this topic, it was found that no studies have particularly investigated the factors responsible for initiating degenerative processes in the brain. Despite all of the complexities in conducting longitudinal studies, it would be beneficial to undertake such type of research to track the disease progression and identify the probable risk factors for developing CTE following repeated bTBI.

Continuing with a discussion of limitations it is reasonable to include the common issue in research on this matter. First of all, the subjective report of a blast event and its proximity to it adds a lot of ambiguity to the results of different studies. The distance to the epicenter of an explosion can dramatically change the number of injuries. Another explanation is that people can have false memories or no memories at all due to loss of consciousness, therefore their data would be compromised. Moreover, a lot of studies are focused on samples of individuals who experienced a blast injury up to 10 years prior to the research and it marks a tremendous time gap. In order to gain more understanding of this topic, some future studies should include people in the acute phase of bTBI.

Secondly, there are certain issues with post-concussion syndrome assessment. The first problem emerges because there are different diagnostic criteria in separate diagnostic manuals. This makes it hard to rationally summarise the data of different research. There certainly are symptoms that are experienced by affected individuals on a daily basis, however, there is another reason to report the symptoms rather than to get some help with them. For some the motivation would be simply to get the insurance money. So it is interesting to understand the real number of people who are struggling with post-concussion symptoms.

Considering psychiatric disorders that are often comorbid to bTBI and to military service overall, multiple crucial points emerge. As it was seen in the previous parts a lot of studies confirm the notion that post-concussion symptoms are better explained by PTSD than by bTBI. This again raises questions about the specificity of the diagnostic criteria of PCS. Anxiety and depression disorders have a negative effect on the prognosis of a bTBI as they usually occur after injury. To ensure the best possible outcome for the individual it is important to take them as important treatment targets (Benavides et al., 2021).

Regarding the cognitive presentation of bTBI, there are several critical thoughts to be noted. It would be beneficial to see future studies that explore the discrepancy between the high self-report

of cognitive difficulties and the low amount of individuals who actually show a clinically significant impairment on cognitive tests. One possible perspective is that a comparison with premorbid levels of cognitive domains can be used. However, in the majority of cases, an individual has not done any of the tests beforehand. In this situation, it can be advised to use a National Adult Reading Test (NART), which has irregular words to estimate the premorbid abilities. Another interpretation of this misbalance in subjective and objective results is the psychological nature of them. For instance, it may be related to depression that results in cognitive bias. This means, that an individual perceives their cognitive abilities worse than they are in reality. Low motivation can also play its role and have an effect on activities that require cognitive skills. One more explanation is that an individual, knowing that he can possibly have certain troubles with cognition, will just adhere to this fact and attribute any smallest error to impairment, which will only reinforce their belief.

Future research should also examine such cognitive ability as a language after the blast. Especially, taking into account that pathologies in the auditory cortex and inner ear structures are quite common after an explosion.

As it is common in practice, a lot of servicemen return to their duties after sustaining a bTBI. What can be proposed to be implemented in the military guidelines, is the incorporation of neuropsychological testing as part of the assessment process before duty. The evaluation should consider an individual's decline following a blast since the individual recovery trajectory can vary.

Although numerous studies have been discussed in this literature review, there is still a need for greater precision in research to leave out the existing vagueness in certain topics. With the help of future research addressing these significant gaps, it would be possible to improve the diagnosis, track progression, and develop effective rehabilitation for individuals who have suffered from bTBI.

## CONCLUSION

This thesis tried to synthesize the existing literature on the topic of bTBI, along with its cognitive and psychosocial consequences. The uniqueness of bTBI was proved by the specific pathophysiological mechanism, which marks it distinct from other types of traumatic brain injury. These take into account five specific types of injuries from a blast exposure. Macroscopically the damage to the brain may be not apparent. However, microscopically bTBI has such neuropathological changes as diffuse axonal injury, axonal varicosities near blood vessels, astroglial scarring at the boundaries of structures of different densities, blood-brain barrier disruption, and neuroinflammation that are well-documented. In addition, there is also evidence that repetitive bTBI can contribute to the development of chronic traumatic encephalopathy.

A number of post-concussion symptoms were presented and affected vestibular, oculomotor, and auditory functions. Moreover, psychological conditions such as PTSD, anxiety, and depression regularly co-occur in the course of bTBI and might complicate the diagnosis. Cognitive impairments, presented by memory, attention, executive functions, and processing speed difficulties, are also documented across studies. All of these disruptions in cognitive and physical functioning present a challenge for the psychosocial functioning in civilian life for military personnel. Due to this bTBI individuals may also have concerns with emotional regulation, risk-taking behaviors, and social integration.

A number of limitations in the research regarding bTBI are present. It would be beneficial to see in the future studies indicating specific biomarkers. Furthermore, longitudinal research is needed to keep track of the recovery trajectories and evaluate the interventions for the cognitive and psychosocial recovery of patients. Lastly, to mitigate the risks, it is needed to implement the standardized return-to-duty neuropsychological assessment of military personnel who received a diagnosis of bTBI. Given the growing number of affected individuals today, multidisciplinary

research involving clinical neuropsychology, neurology, and neuroscience is essential on this matter to see improvements in the diagnosis, treatment, and rehabilitation.

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