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The Impact of Traumatic Brain Injury on Neuropsychological Functioning and Tau Accumulation Later in Life in Military Veterans

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CERTIFICATE OF APPROVAL

Clinical Research Project

This is to certify that the Clinical Research Project of

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Abstract

The following study examines aging veterans that experience a TBI while in service and compares to older veteran without a history of TBI. The objective is to look at cognitive profile later in life for military veterans with moderate to severe TBI different and compared to older veterans with no history of TBI. Is there a difference in tau accumulations on neuroimaging in military veterans with moderate to severe TBI compared to older veterans without a history of TBI? What is the relationship between the cognitive profile and tau imaging correlates for military veterans with moderate to severe TBI later in life? There were 39 participants in the TBI group and 65 participants in the non-TBI group that participated in neuropsychological testing. Out of the above participants 8 in the TBI group and 19 in the non-TBI group participated in PET ^{18}F-AV1451 imaging to compare Braak regions. The Mann-Whitney U test was used for analysis of neuropsychological tests (Clock score, BNT, TMT-A, & TMT-B). T-test was used for analysis of neuropsychological test category fluency animals and one-way ANOVA was used for the analysis of Auditory Verbal Learning test. Additionally, Mann-Whitney U test was used for the analysis of PET imaging: BRAAK regions 1-2, 3-4, and 5-6. The results suggest no statistically significant differences between TBI and non-TBI groups in neuropsychological tests and Braak regions (all p's > .05). However, there was a trend noticed with TBI group having higher levels of tau in all Braak regions. Ultimately, this study showed that the TBI group and non-TBI did not differ in neuropsychological performance and tau accumulation in BRAAK regions.

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Chapter I: Introduction

Problem Statement

Traumatic brain injury (TBI) is one of the most common and debilitating injuries among military veterans (Long et al., 2009). The leading cause of TBI during battlefield conflict is due to blast injury (McKee, & Robinson, 2014). Other mechanisms of injury are from blunt force trauma from falls, contact sports, and motor vehicle accidents (Long et al., 2009; McKee, & Robinson, 2014). It is possible that TBI due to military injury may impact the brain differently than traditional injuries causing TBI, such as sporting accidents (Long et al., 2009; McKee, & Robinson, 2014). Research consistently shows cognitive deficits that parallel functional and structural damage in moderate to severe TBI resulting from military injuries (Long et al., 2009; McKee, & Robinson, 2014). Furthermore, there is recent evidence that earlier military-related TBI may initiate neurodegenerative processes in the brain that are different from healthy brain aging, including the accumulation of tau proteins (McKee, & Robinson, 2014). However, it is unclear how moderate to severe TBI resulting from military trauma may impact cognitive function later in life, and whether the consequences of the type of injury (military injury vs. other types of TBI) impacts cognitive function and neuroimaging correlates differently (Born, 2005; Cernak, & Noble-Haeusslein, 2009).

The purpose of the study is to investigate cognitive functioning and neuroimaging correlates later in life in military veterans with moderate to severe TBI to individuals without TBI. Findings from the current study will aid in managing TBI outcomes later in life and treatment of military related TBI in the military and veteran population.

Significance of the Study

This study will contribute by enhancing our knowledge of the cognitive profile and imaging correlates of moderate to severe TBI in veteran/military populations many years following injury. Furthermore, this study will provide information regarding existing differences in cognitive performance and imaging correlates between individuals with moderate to severe TBI many years following the initial injury.

Research Questions and Hypotheses

Research question 1. Is the cognitive profile later in life for military veterans with moderate to severe TBI different compared to older veterans with no history of TBI?

Hypothesis 1. Older military veterans with a history of moderate to severe TBI will perform worse than older veterans without a history of TBI on tests that examine language, memory, attention, and executive functioning. Older veterans with a history of TBI will perform worse on the Boston Naming test for language compared to older veterans without TBI. Older veterans with a history of TBI will perform worse on the Auditory Verbal Learning test for memory compared to older veterans without TBI. Older veterans with a history of TBI will perform worse on the Category Fluency (animals) for semantic memory compared to older veterans without TBI. Older veterans with a history of TBI will perform worse on the Clock drawing test and Trail Making Test A and B in attention and executive functioning compared to older veterans without TBI.

Research question 2. Is there a difference in tau accumulations on neuroimaging in military veterans with moderate to severe TBI compared to older veterans without a history of TBI?

Hypothesis 2. Older military adults with a history of TBI will have higher accumulation of tau in the frontal and temporal lobes compared to older veterans with no history of TBI.

Research question 3. What is the relationship between the cognitive profile and tau imaging correlates for military veterans with moderate to severe TBI later in life?

Hypothesis 3. There will be an interaction between performance on language, memory, attention, and executive functioning and accumulation of tau in the frontal and temporal lobes. Older veterans with a history of TBI's performance on the Boston Naming test will relate to tau accumulation in the temporal lobe. Older veterans with a history of TBI's performance on the Auditory Verbal Learning test will relate to tau accumulation in the temporal lobe. Older veterans with a history of TBI's performance on the Category Fluency (animals) test will relate to tau accumulation in the temporal and frontal lobes. Older veterans with a history of TBI's performance on the Clock drawing test will relate to tau accumulation in the frontal lobe.

Background

Prevalence of military related TBI. The leading cause of morbidity and mortality on the battlefield in Operation Iraqi Freedom (OIF) and Operations Enduring Freedom (OEF) is blast injuries (Long et al., 2009). April 2003 to October 2005, 450 casualties taken to Walter Reed Army Medical Center suffered from traumatic brain injury (TBI); 28% needed neurosurgical attention, and 88% of the patients in need of surgery had closed head injuries (long et al., 2009). McKee and Robinson (2014) found service members involved in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND), blast exposure was the leading of mild TBI. Prevalence of mTBI for returning service members range from 15.2% to 22.8% (McKee & Robinson, 2014). Since 2000, more than 300,000 service members have received the diagnosis of TBI (Brix et al., 2017). Explosive Weapons have caused over 73% of

all U.S. military causalities during OEF and OIF (Cernak & Noble-Haeusslein, 2010). Terrorism has increased the use of bombers that are attached to explosive devices (suicide bombers) to ensure maximum harm to the targeted area (Cernal & Noble-Haeusslein, 2010).

Definition of traumatic brain injury. TBI is brain trauma caused by an impact to the head or rapid acceleration and deceleration of the brain within the skull (American Psychiatric Association [APA], 2013).

Military TBI versus TBI from other modalities. Falls (47.2%) is the most common mechanism of TBI in the United States, with being hit/struck by an object (15.4%), then motor vehicle accidents (13.7%) follow (Taylor, Bell, Breiding, & Xu, 2017). In the recent conflicts of OEF, OIF, and OND, service members and civilian have been exposed to explosive weaponry (Cernak & Noble-Haeusslein, 2010) and those involved in these campaigns are 10 times more likely to experience a TBI compared to the general population (Williamson & Mulhall, 2009). Other Mechanisms of injury that cause TBI in the military can be exposure to artillery, rocket, or mortar fire; firing large caliber weapons; and obstacle breaching (Parisian, Georgevitch, & Bahr, 2017). Open head injuries can result from high-velocity projectiles (ammunition rounds) or low-velocity objects (knives) (The Defense and Veteran's Brain Injury Center, 2016).

TBI and neuropsychology. TBI may result in long-term or lifelong cognitive, physical, emotional, and behavioral consequences (Langlois, Rutland-Brown, & Wald, 2006). In cases of mild TBI cognitive problems could result in long-term impairment in daily activities and work responsibilities (Langlois, Rutland-Brown, & Wald, 2006). Additionally, 1 to 3 years post injury, compared with the general population, those who suffer from TBI are 1.8 times as likely to report binge drinking, 11 times as likely to develop epilepsy, and 7.5 times as likely to die (Langlois, Rutland-Brown, & Wald, 2006). Langlois and colleagues (2006) added that there is

1.5 times increased risk of depression, and a 2.3 and 4.5 times increased risk of Alzheimer's disease associated with moderate and severe TBI.

cognitive domains of impact. Cognitive deficits as a result of TBI can interfere with work, relationships, leisure, and activities of daily living (Rabinowitz & Levin, 2014). The impact of cognitive functioning depends on several variables including: severity, complications, injuries to other areas of the body, and the chronicity of the injury (Rabinowitz & Levin, 2014). In moderate to severe TBI cognitive domains typically untouched in mild TBI, may have persistent deficits (Rabinowitz & Levin, 2014). Some of the persistent deficits can include awareness, reasoning, language, visuospatial processing, and general intelligence (Rabinowitz & Levin, 2014). 65% of moderate to severe TBI patients report long-term problems with cognitive functioning (McDonald, Flashman, & Saykin, 2002).

recovery. In moderate to severe TBI in relation to cognitive recovery has a step trajectory in the first year, them with more gradual improvements during the later years (Rabinowitz & Levin, 2014). In severe injuries, impairments are more likely to persist, but some patients may show neuropsychological recovery up to 5 years post injury (Rabinowitz & Levin, 2014).

TBI and imaging. Injuries from blast waves can cause subdural hemorrhages, brain swelling, and diffuse axonal injury (Bolander et al., 2011; Chavko et al., 2011; Leonardi et al., 2011; Long et al., 2009; Moore et al., 2009; Svetlov et al., 2009; Taber et al., 2006; & Taylor & Ford, 2009). Computed tomography (CT) is a procedure that uses computer assisted X-rays to gain visual images of the structure of the brain (MacDonald et al., 2011; Taber et al., 2006; & Taylor & Ford, 2009). Magnetic resonance imaging (MRI) is the measurement of hydrogen atoms when activated by radio frequencies from a magnetic field; once activated, the waves from the hydrogen atoms are measured to determine structure of the brain (MacDonald et al., 2011;

Taber et al., 2006; & Taylor & Ford, 2009). Positron Emission Tomography (PET) is an imaging test that helps reveal how tissues and organs are functioning. PET uses a radioactive tracer to show the functioning of tissues (MacDonald et al., 2011; Taber et al., 2006; & Taylor & Ford, 2009).

Chapter II: Literature Review

Traumatic Brain Injury

According to the DSM-5, the diagnosis of mild to severe form of neurocognitive disorder (NCD) from traumatic brain injury (TBI) can experience an impact to the head or rapid acceleration and deceleration of the brain within the skull (APA, 2013, p. 624). This event can cause a loss of consciousness, amnesia of the event, disorientation and confusion. Disturbances in emotional functioning can also be accompanied with NCD from TBI (APA, 2013, p. 624). For example, a soldier may experience irritability, easy frustration, tension and anxiety following injury (APA, 2013, p. 624). NCD from TBI can cause personality changes of disinhibition, apathy, suspiciousness, and aggression. Some physical disturbances that can occur are headaches, fatigue, sleep disorders, dizziness, photosensitivity, anosmia, and reduced tolerance of certain medications. In more severe cases of NCD from TBI, a soldier can exhibit signs and symptoms of seizures, hemiparesis, visual disturbances, and cranial nerve deficits (APA, 2013, pp. 624-625).

The classification of TBI is in 3 categories, mild, moderate, and severe (Rabinowitz & Levin, 2014). Mild TBI is a classified as a Glasgow Comma Scale (GCS) score of 13-15 (Rabinowitz & Levin, 2014). Individuals with mild TBI would be conscious and able to respond to verbal communication (Rabinowitz & Levin, 2014). Individuals with moderate TBI have a GCS score between 9-12, individuals would likely be conscious but they may experience disorientation and struggling with communication (Rabinowitz & Levin, 2014). Those who suffer from severe TBI have a GCS score between 3 to 8 (Rabinowitz & Levin, 2014). Those in the severe category have complete loss of consciousness, unable to communicate, and may not be able to open their eyes (Rabinowitz & Levin, 2014).

Recovery. Rehabilitation for a physical disability, like paralysis might include: physical exercises, assistive technology, skills training, and involvement of social services (Robinowitz & Levin, 2014). Cognitive rehabilitation therapy (CRT) is treatments designed to improve patients' participation in cognitive demanding activities (Rabinowitz & Levin, 2014). Either by storing cognitive functions or teaching compensatory skills (Rabinowitz & Levin, 2014). Like physical rehabilitation, CRTS might incorporate technologies and services that can help patients reintegrate into their pre TBI lifestyle (Rabinowitz & Levin, 2014).

TBI and Military

Pathophysiology. McKee and Robinson (2014) found in other autopsies of veterans exposed to blast to have a buildup of p-tau in their frontal, temporal, parietal lobes. The exposure to blast occurred between 8 months to 6 years before death (McKee & Robinson, 2014). Diffuse axonal injury (DAI) is caused by shear waves that cause rotational acceleration and deceleration (Bolander et al., 2011; Chavko et al., 2011; Leonardi et al., 2011; Long et al., 2009; Moore et al., 2009; Svetlov et al., 2009; Taber et al., 2006; & Taylor & Ford, 2009). DAI is a result of tissue impacting against other tissue which causes grinding. The axons on the neuron begin to flex or stretch as a result of the movement. DAI can cause swelling within the white matter and between the white and gray matter of the brain (Bolander et al., 2011; Chavko et al., 2011; Leonardi et al., 2011; Long et al., 2009; Moore et al., 2009; Svetlov et al., 2009; Taber et al., 2006; & Taylor & Ford, 2009).

neuronal degeneration. Biochemical and morphological alterations can occur as early as 20 hours to as late as 14 days after primary blast exposure (Cernak & Noble-Haeusslein, 2010; Chavko et al., 2007; Ritenour & Baskin, 2008; & Svetlov et al., 2009). After blast exposure, Cernak and Noble-Haeusslein found considerable metabolic disruptions, and dysfunction of

sodium (Na+), potassium (K+), and adenosine triphosphatase (ATPase) pump (2010, p. 260). Changes in the ATPase pump suggest an imbalance or failure between demand and availability of energy, which would shift pathways of the glucose metabolism from aerobic to anaerobic (Cernak & Noble-Haeusslein, 2010). This shift in pathways can cause impairment in neuronal cell membrane permeability (Cernak & Noble-Haeusslein, 2010).

The enzyme ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) plays an important role in the removal of oxidized, excessive, or misfolded proteins in neurons (Svetlov et al., 2009). Svetlov and colleagues (2009) observed an increase in UCH-L1 in rats 24 hours after exposure to a blast, indicating a strong correlation between UCH-L1 levels in CSF and patients suffering from severe TBI. UCH-L1 has been linked to Parkinson's disease and memory dysfunction (Svetlov et al., 2009).

Glial fibrillary acidic protein (GFAP) helps to maintain astrocyte strength and the shape of cells (Cernak & Noble-Haeusslein, 2010; & Svetlov et al., 2009). Svetlov and colleagues (2009) noticed significant hippocampal accumulation of GFAP, which is a recognized marker for activated glia after the blast. Like GFAP, neuron-specific enolase (NSE) increased between 24 and 48 hours after exposure to blasts (Svetlov et al, 2009). NSE is an enzyme found in normal neurons and used as a marker for neuronal or neuroendocrine tumors (Svetlov et al., 2009). GFAP, NSE, and UCH-L1 levels indicate a blood-brain barrier disturbance after exposure to a severe blast, which can generate events that led to hemorrhages, gliosis, and disturbances in neuronal/glia connections and possibly leads to neuronal degeneration (Svetlov, et al., 2009).

Oxidative stress is associated with the incapacity to repair injury and disruption of the normal mechanisms of cellular signaling, which can activate apoptosis or necrosis (Cernak & Noble-Haeusslein, 2010; Ritenour & Baskin, 2008). Biochemical changes caused by oxidative

stress in the hippocampus correlates with primary blast injury and have been present in recent studies (Cernak & Noble-Haeusslein, 2010; Ritenour & Baskin, 2008). After exposure to a blast, caspase-3 and calpain accumulate in brain tissue; caspase-3 is responsible for activation of apoptosis and calpain is responsible for activation of necrosis (Svetlov et al., 2009).

Blast injury pathophysiology. Physicians are faced with great difficulty examining brain injuries due solely to primary blast waves (Bolander et al., 2011; Cernak & Noble-Haeusslein, 2010; Chavko et al., 2011; Huang et al., 2009; Leonardi, Bir, Ritzel, & VandeVord, 2011; Long et al., 2009; MacDonald et al., 2011; Moore et al., 2009; Ritenour & Baskin, 2008; Svetlov et al., 2009; & Taber et al., 2006). Most soldiers and civilians seek medical treatment due to exposure to an IED for external injuries from the secondary and subsequent waves, meaning it is difficult to determine if injuries to the brain are from primary blast waves or a combination of all waves. For the victims that did not experience external injuries and chose not to seek medical attention, they can experience cognitive disturbances at a later time. This may be diagnosed as a psychological disorder such as post-traumatic stress disorder (PTSD) (Bolander et al., 2011; Cernak & Noble-Haeusslein, 2010; Chavko et al., 2011; Huang et al., 2009; Leonardi et al., 2011; Long et al., 2009; MacDonald et al., 2011; Moore et al., 2009; Ritenour & Baskin, 2008; Svetlov et al., 2009; & Taber et al., 2006).

Primary Blast Wave: Once an IED has been detonated, a high-pressure blast wave changes the atmospheric pressure, which causes expansion of gases (Born, 2005; Cernak & Noble-Haeusslin, 2010; Ritenour & Baskin, 2008; Taber, Warden, & Hurley, 2006). The comparison of hurricane-force winds of 200km/h and an estimated overpressure of 1.72kPa (0.25 psi) to primary blast wave of 2,414 km/h and an estimated overpressure of 690 kPa (100 psi) shows the destructive force of a primary blast wave (Cernak & Noble-Haeusslin, 2010).

Structures, vehicles and confined spaces can amplify the destructive force (Born, 2005; Cernak & Noble-Haeusslin, 2010; Ritenour & Baskin, 2008; Taber et al. 2006). Victims exposed to the primary blast suffer injuries 2-3 times more severely in a vehicle or confined space (Cernak & Noble-Haeusslin, 2010).

Primary blast waves involve two phases; a compression of surrounding air known as the positive phase and a sudden drop in pressure creating a vacuum which is the negative phase (Taber et al., 2006). The dynamics change in the two phases once they enter a different medium. An example of mediums would be water or human tissue. These changes are measured by impact pressure, velocity and wave duration (Chavko et al., 2007). Chavko and colleagues (2007) measured primary blast waves in rats to determine if damage can occur. They found a significant difference in pressure wave formation depending on the orientation of the rat. If the rat was facing the blast, the positive phase lasted longer than what was recorded in the air; however, if the rat was perpendicular to the blast, the second phase lasted longer. Chavko and colleagues (2007) also found that the shape of the pressure wave was different in the brain compared to the air, indicating a change in velocity of the wave, and that the reflection of the wave or complex wave changes in different densities. Two types of energy are formed during the blast wave, stress waves and shear waves (Ritenour & Baskin, 2008). The stress waves, also known as longitudinal pressure forces, travel at supersonic speeds, which create the "Spalling" effect, meaning the medium changes from air to tissue. The "Spalling" effect can be compared to boiling water. Shear waves cause erratic movement of tissue and possible detachments of tissue (Ritenour & Baskin, 2008).

When exposed to a primary blast wave, the positive phase of the wave travels across the skull with great force causing the skull to compress (Bolander et al., 2011; Chavko et al., 2011;

& Leonardi et al., 2011). When the vacuum effect of the negative phase occurs, the skull expands. After both phases of the blast have occurred, the skull flexes back to its original state. Rapid compression and decompression of the skull is known as skull flexure. Intracranial pressure is when the event causes a pressure change in the brain's environment (Bolander et al., 2011; Chavko et al., 2011; & Leonardi et al., 2011). The blast waves can dynamically deform the skull (flexures) and can cause localized regions of high and low pressures through the brain (Chavko et al., 2011). The slightest skull flexure from a non-lethal blast can produce damaging effects without physical contact to the head (Chavko et al., 2011). Injuries from primary blast waves can cause subdural hemorrhages, brain swelling, and diffuse axonal injury (Bolander et al., 2011; Chavko et al., 2011; Leonardi et al., 2011; Long et al., 2009; Moore et al., 2009; Svetlov et al., 2009; Taber et al., 2006; & Taylor & Ford, 2009).

Secondary Blast waves are the result of a few factors like the components of the IED fragment after the explosion and the primary blast wave propel the fragments faster than the speed of sound in all directions, creating a missile or ballistic hazard (Born, 2005; Taber et al. 2006). These components of the IED could also be nails, screws, nuts, bolts or any other solid objects to heighten the deadly effect (Born, 2005). Or other fragments from an armored vehicle or existing debris (Born, 2005). The primary blast dislodges metal material from the vehicle and propels it into the victims riding in the vehicle (Born, 2005; Taber et al., 2006).

Tertiary blast waves (3rd stage) is after denotation of the IED. This is were the victim becomes the projectile (Born, 2005; Cernak & Noble-Haeusslein, 2010; Moore et al. 2009; Taber et al., 2006). This acceleration and deceleration of the victim and possibly slamming into structures and other objects is the primary source of injury in this stage (Born, 2005; Cernak & Noble-Haeusslein, 2010; Moore et al., 2009; Taber et al. 2006).

In ICP, Wojnarowicz and colleagues (2017) found that ICP as a result from a shock wave in mouse models can result in no tissue damage if the head is immobilized during the shock wave. They observed hippocampal-dependent learning and memory deficits in blast-exposed mice were prevented once their heads where immobilized. The cause injury during a shock wave is the result of the head freely moving (bobblehead effect) while exposed (Wojnarowicz et al, 2017).

Long-term impact of TBI. McKee and Robinson (2014) found hyperphosphorylated tau (p-tau) abnormalities in individuals with axonal injury, breach of blood-brain barrier, and in neuroinflammation. In a study analyzing military veterans with blast exposure to young-adults athletes with histories of concussive injury. Evidence of tau neuropathology was found in the brains of blast-exposed veterans. This find was indistinguishable from the tau neuropathology of those who were athletes with histories of repeated concussive injury, indicating a link between blast injuries and CTE pathology (Wojnarowicz, Fisher, Minaeva, & Goldstein, 2017). Additionally, Wojnarowicz and colleagues (2017) found in mouse models blast-related injuries that are related to human CTE neuropathology, including cellular accumulation of phosphorylated tau protein and pre-tangle tau protein neuropathology.

TBI Neuropsychological Profile

Cognitive deficits that can occur in all severities of TBI including: decreased mental flexibility, trouble shifting sets, impaired attention, poor planning, lack of organization, problems with sequencing, impaired judgment, deficits in verbal fluency, problems with working, and an increase in impulsivity (Kraus et al, 2007). Kraus and colleagues (2007) examined the relationship between both white matter integrity and white matter load with neuropsychological

function. They found a significant correlation between composite white matter load and executive, attention, and memory domains.

Correlations between executive function and body of the corpus callosum, splenuim of the corpus callosum, corticospinal tracts, external capsule, forceps major, forceps minor, anterior corona radiate, inferior frontoocciptial fasciculus, anterior corona radiata, posterior corona radiata, superior longitudinal fasciculus, sagittal stratum, and cingulum fibres (Kraus et al, 2007). Areas correlated with attention were forceps major and posterior corona radiata (Kraus et al, 2007). Rabinowitz and Levin (2014) state that cognitive and behavioral functions can be impaired as a result of moderate to severe TBI including: cognitive executive functions of memory acquisition and retrieval, top-down control of attention, planning, judgment, and cognitive aspects of decision-making; behavioral executive functions of emotional aspects of decision-making, motivation, and impulsivity.

Cognitive Recovery

CRTs were designed to tackle problems with attention, communication, memory, and executive functioning (Rabinowitz & Levin, 2014). An example of a CRT is Goal Management Training (GMT), which focuses on treating executive functioning deficits based on goal processing theories and sustained attention (Rabinowitz & Levin, 2014). In GMT is to periodically pause the patient's ongoing behavior to monitor performance and define goal hierarchies (Rabinowitz & Levin, 2014). Christensen and colleagues (2008) found that cognitive recovery could be related to time. They added that early intervention improved cognitive functioning compared to waiting (Christensen et al, 2008). Initiating an exercise routine at specific stages of recovery also improved neuroplasticity (Christensen et al, 2008; Griesbach, Hovda, & Gomez-Pinilla, (2009).

Military Profile versus Non-military Profile

Prominent complaint of military service members that have TBI resulting from blast exposure is headaches and tinnitus, which is not commonly reported by non-blast TBI individuals (Leuthcke, Bryan, Morrow, & Isler, 2011). Service member returning from Iraq with chronic headaches, 41% had experienced mild head or neck trauma, with 67% was the result of blast injuries (Leuthcke, et al, 2011). Belanger and colleagues (2009) found that those who suffered from blast related TBI experience other psychological symptoms that non-blast related TBI did not report. They found a trend of those with blast related TBI reported more PTSD symptoms compared to non-blast TBI (Belanger et al. 2009). Immediately after injury non-blast TBI was associated with greater frequency and longer duration of loss of consciousness, immediate balance problems, nausea, and vomiting (Leuthcke, et al, 2011). However, Leuthcke and colleagues (2011) found no significant differences between blast and non-blast mild TBI in cognitive performance 2 years post injury. They concluded that severity of injury did predict cognitive sequelae instead of modality of injury (Leuthcke, et al, 2011).

TBI imaging

Computed tomography (CT) is a procedure that uses computer assisted X-rays to gain visual images of the structure of the brain (MacDonald et al., 2011; Taber et al., 2006; & Taylor & Ford, 2009). Magnetic resonance imaging (MRI) is the measurement of hydrogen atoms when activated by radio frequencies from a magnetic field; once activated, the waves from the hydrogen atoms are measured to determine structure of the brain (MacDonald et al., 2011; Taber et al., 2006; & Taylor & Ford, 2009). CT and MRI scans can be used to detect brain swelling, hemorrhage, and edema (MacDonald et al., 2011; Taber et al., 2006; & Taylor & Ford, 2009). Moderate and severe stages of TBI can be detected using CT and MRI scans, but mild TBI, CT

and MRI scans show minimal or no intracranial abnormalities (Huang, et al., 2009; MacDonald et al., 2011; Taber et al., 2006; & Taylor & Ford, 2009). Patients who suffer from mild TBI suffer from difficulties in information processing, memory and deficiencies in cognitive functions, but conventional MRI scans show no abnormalities (Taylor & Ford, 2009). The lack of detection in mild TBI may miss the critical connections in the brain that may be damaged or severed at a microscopic level (Taylor & Ford, 2009).

Diffusion tensor imaging (DTI) is an advanced MRI involving the measurement of the directionality of water diffusion (Huang, et al., 2009; MacDonald et al., 2011). The DTI can detect the integrity of fibers in the white matter (Huang et al., 2009). DTI is more sensitive to patients who may not exhibit external injuries and have milder forms of trauma (Huang et al., 2009; MacDonald et al., 2011). Huang and colleagues (2009) evaluated 10 patients suffering from mild TBI from civilian related accidents and military personnel exposed to explosions. All but one patient in the study had normal CT and MRI scans. All patients were evaluated to determine the extent of damage through DTI and MEG technology (Huang et al., 2009). Huang and colleagues (2009) found diffused axonal injury despite having unremarkable CT and MRI imaging.

Positron Emission Tomography (PET) is imaging test that helps reveal how tissue and organs are functioning (Saint-Aubert et al., 2017). A PET uses a radioactive drug (tracer) to show activity (Saint-Aubert et al., 2017). In recent years, there has been the development of a radioactive tracer that targets the cerebral tau (Saint-Aubert et al., 2017). This breakthrough allows for the opportunity to examine imaging that looks for tau build up in humans and animal models (Saint-Aubert et al., 2017). McKee and Robinson (2014) found in a 45-year-old male Army veteran with single exposure to a close-range IED blast at autopsy to have multiple areas

of perivascular p-tau in the frontal, parietal, and temporal cortices with a predilection for sulcal depths and superficial cortical layers. These findings in this Army veteran are diagnostic of CTE stage IV (McKee & Robinson, 2014).

Tauopathy

Tau protein plays a role in the physical stabilization of microtubule assembly in axons, and pathologically forms hyperphosphorylated aggregates in the brain in Alzheimer's Disease and tauopathies (Harada, et al., 2016). Tauopathies include some variations of frontotemporal lobar degeneration, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), tangle predominant senile dementia (TPSD), argyrophilic grain disease (AGD), and chronic traumatic encephalopathy (CTE) are also neurodegenerative conditions characterized by the accumulation of tau protein in the brain (Harad, et al., 2016). CTE is associated with repetitive TBI and prevalent among contact sports and military personnel exposed to blast while in combat (Harad, et al., 2016). The accumulation of tau is highly associated with neuronal loss, severity of dementia, and neurodegeneration, unlike amyloid plaque, which is associated AD (Harad, et al., 2016). The migration of tau from the medial temporal lobe, such as the entorhinal cortex and hippocampus into the neocortical areas leads to synaptic dysfunction, glial activation, leading to neuronal loss, causing progressive cognitive impairment (Harad, et al., 2016). Tau deposits in CTE have similar histopathological characteristics as neurofibrillary tangles and neuropil threads, neurofibrillary tangles were focally in superficial cortical layers (Harad, et al., 2016).

Early human PET studies successfully demonstrated high retention of ^{18}F-AV1451 in regions known to contain high density of tau deposits in patients with AD with low white matter retention (Harad, et al., 2016). Harad and colleagues (2016) reported a strong association was observed between the amount of radiotracer and the severity of dementia. A

large multicenter study of ^{18}F-AV1451 is ongoing (Harad, et al., 2016). A case report on posterior cortical atrophy (visual variant of AD) demonstrated that ^{18}F-AV1451 binding in the posterior brain regions correspond to reduced ^{18}F-FDG uptake and clinical symptom (Harad, et al., 2016). Case reports of non-AD tauopathies such as frontotemporal dementia with MAPT mutation P301L, suspected CTE, PSP, and CBS also demonstrated elevated binding of ^{18}F-T807 in frequent areas of tau aggregates in those conditions (Harad, et al., 2016). However, these findings have not yet been fully validated by imaging-autopsy studies (Harad, et al., 2016).

What is not known

Most of the studies found evaluate TBI within 6 years of injury. Very little research has looked at what occurs in military TBI in older adulthood. Most studies using Tau ^{18}F-AV1451 is for the purposes of AD, CTE, and other neurodegenerative diseases.

Research Questions and Hypotheses

Research question 1. Is the cognitive profile later in life for military veterans with moderate to severe TBI different compared to older veterans with no history of TBI?

Hypothesis 1. Older military veterans with a history of moderate to severe TBI will perform worse than older veterans without a history of TBI on tests that examine language, memory, attention, and executive functioning. Older veterans with a history of TBI will perform worse on the Boston Naming test for language compared to older veterans without TBI. Older veterans with a history of TBI will perform worse on the Auditory Verbal Learning test for memory compared to older veterans without TBI. Older veterans with a history of TBI will perform worse on the Category Fluency (animals) for semantic memory compared to older veterans without TBI. Older veterans with a history of TBI will perform worse on the Clock

drawing test and Trail Making Test A and B in attention and executive functioning compared to older veterans without TBI.

Research question 2. Is there a difference in tau accumulations on neuroimaging in military veterans with moderate to severe TBI compared to older veterans without a history of TBI?

Hypothesis 2. Older military adults with a history of TBI will have higher accumulation of tau in the frontal and temporal lobes compared to older veterans with no history of TBI.

Research question 3. What is the relationship between the cognitive profile and tau imaging correlates for military veterans with moderate to severe TBI later in life?

Hypothesis 3. There will be an interaction between performance on language, memory, attention, and executive functioning and accumulation of tau in the frontal and temporal lobes. Older veterans with a history of TBI's performance on the Boston Naming test will relate to tau accumulation in the temporal lobe. Older veterans with a history of TBI's performance on the Auditory Verbal Learning test will relate to tau accumulation in the temporal lobe. Older veterans with a history of TBI's performance on the Category Fluency (animals) test will relate to tau accumulation in the temporal and frontal lobes. Older veterans with a history of TBI's performance on the Clock drawing test will relate to tau accumulation in the frontal lobe.

Chapter III: Methods

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The DOD ADNI database consists of 39 male Vietnam veterans with diagnosis of moderate to severe TBI. The control group is 65 male Vietnam veterans with no history of TBI. The participants' ages ranged from 60.87 years to 85.16 years, with a mean age of 70.58 years. In the TBI group, 39 participants completed neuropsychological tests and out of these individuals 8 completed PET ^{18}F-AV1451 imaging. In the control group, 65 participants completed neuropsychological tests and out of these individuals 19 completed PET ^{18}F-AV1451.

Inclusion and Exclusion criteria

Inclusion criteria for TBI group is diagnosis of moderate to severe TBI, military service, and male. Exclusion criteria for TBI group is diagnosis of other psychological disorders, mild cognitive impairment, dementia, substance abuse, and female. Inclusion criteria for the control group is male, and military service. Exclusion criteria for the control group is female due to not enough female participants in the database, diagnoses of TBI, psychological disorders, mild cognitive impairment, dementia, and substance abuse.

Neuropsychological tests

Boston Name Test: Neuropsychological assessment tool to measure confrontational word retrieval in individuals suspected of neuropsychological impairment (Kaplan, Goodglass, & Weintraub, 1983). BNT contains 60 line drawings graded in difficulty (Kaplan, Goodglass, & Weintraub, 1983). Naming difficulties may be rank ordered along a continuum. Items are rank ordered in terms of their ability to be named, which is correlated with their frequency (Kaplan, Goodglass, & Weintraub, 1983).

The Auditory Verbal Learning test: Neuropsychological assessment tool to evaluates verbal learning and memory (Schmidt, 1996). The participant is then asked to repeat all words from the list that he/she can remember (Schmidt, 1996). This procedure is carried out a total of five times (Schmidt, 1996). The examiner then presents a second list of 15 words, allowing the participant only one attempt at recall of this new list (Schmidt, 1996). Immediately following this, the participant is asked to remember as many words as possible from the first list (Schmidt, 1996). After a 20-minute delay, the participant is again asked to recall as many words as possible from the first list (Schmidt, 1996). The participant is then read a list of words and asked to indicate whether each word was from the first list (Schmidt, 1996).

Category Fluency (animals) is a neuropsychological assessment tool to measure semantic memories (Lezak et al., 2012). It is used to diagnose ADHD, and cognitive impairment in persons with neurodegenerative diseases (Lezak, et al, 2012). The Clock drawing is a neuropsychological assessment tool to screen individuals for signs of neurological impairment and evaluates executive functioning and attention (Adunsky, Fleissig, Levenkrohn, Arad, & Nov, 2002; Suhr, Grace, Allen, Nadler, & McKenna, 1998; McDowell & Newell, 1996).

The Trail Making Test (TMT) is a neuropsychological assessment tool to measure visual search, scanning, speed of processing, mental flexibility and executive function (Tombaugh, 2004). The TMT consists of two parts, TMT-A requires a participant to draw lines sequentially connecting 25 numbers enclosed in circles that are distributed on a sheet of paper. The TMT-B's requirements are similar with the exception that the participant must alternate between numbers and letters. The scores on TMT-A and TMT-B represent the amount of time required to complete the task (Tombaugh, 2004).

Tau imaging

DOD ADNI participant pre-screening procedures consisted of screening all participants for inability to cooperate or have claustrophobia (Gray, et al., 2012). They also screened for inability to lie on the scanner bed for at least 30 minutes. Insured none of the participants exceeded total radiation dose exposure for annual amount as per US Code of Federal Regulations (CFR) Title 21 Section 361.1. PET technician insured proper head positioning and checked positioning and readjusting the position of participants head thought imaging process (Gray, et al., 2012).

DOD ADNI used ^{18}F-AV1451 provided by Avid Radiopharmaceutical, Inc. PET scans were transferred to the laboratory of Neuroimaging at University of Southern California Berkeley and UC San Francisco (Mohamed, et. al, 2019). Prior to imaging day an ECG was conducted on a separate day to determine anything clinically significant. Bazett's corrected QT (QTcB) interval was evaluated and must not exceed >458 msec in males in order for the participants to be included (Mohamed, et. al, 2019). On imaging day a physician or licensed medical professional evaluated the participants prior to administration of ^{18}F-AV1451 injection to insure suitability to undergone the scan. Participants a single IV bolus injection

of approximately (370 MBq) 10 mCi of ^{18}F-AV1451 followed with a saline flush. Roughly 75 minutes after injection, a continuous 30 minute brain scan (6 frames of 5 minute duration). Adverse events were continuously monitored during the ^{18}F-AV1451 imaging session. Those that experienced any adverse events remained at the imaging center until resolved or stabilized. Follow-up phone call to all participants were conducted between 2 to 3 business days following imaging (Mohamed, et. al, 2019). Risks involved in ^{18}F-AV1451 injection is primarily radiation exposure. Due to ^{18}F-AV1451 being an experimental compound and in clinical evaluation, the risks from this agent are not fully known.

The DOD ADNI's Tau-PET imaging pre-processing, the standard uptake value (SUV) was calculation voxel wise (Mohamed, et. al, 2019). SUV images were reoriented to FSL orientation and resampled to 1.5x1.5x1.4mm^3 to match with the MNI template's resolution. The SUV maps were coregistered to each participant's T1-weighted image (Mohamed, et. al., 2019).

Tau PET imaging was performed on subset of participants during the baseline DOD ADNI clinic visit. Tracer used Tau ^{18}F-AV1451 tracer, which binds with p-tau. The dataset includes a broad set of regional flortaucipir means and their corresponding Freesurfer-defines volumes. This set includes cortical and subcortical regions of interest and reference regions such as cerebellar grey matter and eroded hemispheric white mater. There is approximate uptake in the anatomical Braak stages by calculating volume-weighted means of groups of FreeSurfer-defined regions, specified in the "Braak ROIs" section.

Braak region 1. Consists of left and right entorhinal cortex.

Braak region 2. Consists of left and right hippocampus.

Braak region 3. Consists of left and right parahippocampal region, left and right fusiform gyrus, left and right lingual, and left and right amygdala.

Braak region 4. Consist of left and right middle temporal lobe, left and right Cingulate (CaudAntCing, RosAntCing, PostCing, IsthmCing), left and right insula, left and right inferior temporal, and left and right anterior temporal lobe.

Braak region 5. Consists of left and right Frontal Lobe and left and right Parietal Lobe.

Braak region 6. Consists of left and right Occipital lobe (pericalcarine, postcentral, cuneus), left and right Sensory-Motor Cortex (precentral, and left and right paracentral).

Data manipulation

In this study the method of identifying eligible veterans by using the VA eligibility data set. Selected participants that were in the cohort for TBI only and Control. Excluded participants with PTSD and PTSD/TBI from the VA eligibility data. Identified participants based on SCRNO number for neuropsychological battery tests on a data set NEUROBAT. Most participants were given neuropsychological battery tests at different points in time. Selected only the baseline assessment for the purposes of this study. Test selected for analysis were Boston Naming Test total (BNT), Trails A (TMTA) and B (TMTB), Clock drawing total score (CLOCK), Auditory Verbal Learning Test immediate recall total (AVLTLEARN), 30-minute recall (AVLTDELAY), and recognition (AVLTRECOG), and Category Fluency animals total (ANIMALS).

Most participants were given PET imaging at different points in time. Selected participant imaging when first imaged, which fell on different points in time (baseline, 12 month follow-up, and tau visit). Imaging was viewed based on Braak regions, variables were BRAAK 1-2, BRAAK 3-4, BRAAK 5-6.

Planned Analysis

Analysis of data was through IBM's Statistical Package for the Social Sciences (version 25). Normality was assessed for the continuous variables of CLOCKSCOR (mean=4.63, SD=.69), BNTTOTAL (mean=28.39, SD=1.63), TRAASCOR (mean=35.55, SD=13.26), TRABSCOR (mean=88.97, SD=40.23), AVDEL30MIN (mean=6.26, SD=3.85), AVDELTOT (mean=12.57, SD=2.10), AVTOTLRN (mean=48.93, SD=11.74), CATANIMSC (mean=20.60, SD=4.92), Braak region 1-2 (mean=2.25, SD=.24), Braak region 3-4 (mean=2.20, SD=.16), Braak region 5-6 (mean=1.97, SD=.15). The tests of normality indicated violation of normality ($p < .05$) on CLOCKSCOR, BNTTOTAL, TRAASCOR and TRABSCOR, AVDEL30MIN, and AVDELTOT. CATANIMSC, AVTOTLRN, Braak regions 1-2, 3-4, 5-6 were not significant indicating normality, (see Table 1).

Table 1
Tests of Normality

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
CLOCKSCOR	.42	104	.00*	.59	104	.00
BNTTOTAL	.25	103	.00*	.84	103	.00
TRAASCOR	.14	104	.00*	.86	104	.00
TRABSCOR	.16	104	.00*	.78	104	.00
AVTOT1	.14	104	.00*	.94	104	.00
AVDEL30MIN	.11	104	.01*	.97	104	.01
AVDELTOT	.18	104	.00*	.91	104	.00
AVTOTLRN	.06	104	.20	.99	104	.72
CATANIMSC	.07	104	.20	.99	104	.54
BRAAK1-2	.11	27	.20	.97	27	.51
BRAAK 3-4	.11	27	.20	.98	27	.79
BRAAK 5-6	.09	27	.20	.97	27	.49

Note. * $p < .05$, violation of normality.

Hypothesis 1. Mann-Whitney U test was used for the analysis of neuropsychological tests: CLOCKSCOR, BNTTOTAL, TRAASCOR and TRABSCOR. T-test was used for the analysis of neuropsychological test CATANIMSC. One-way ANOVA was used for the analysis of AVDEL30MIN, AVDELTOT, AVTOTLRN. The null hypothesis was that there would be no differences in neuropsychological test scores (clock, BNT, TMT A & B, category animals, and auditory verbal learning test) between the TBI group and non-TBI group. The alternate hypothesis was that the TBI group's performance on neuropsychological test would be worse than the non-TBI group.

Hypothesis 2. Additionally, Mann-Whitney U test was used for the analysis of PET imaging: BRAAKs 1-2, 3-4, and 5-6. The null hypothesis was there would be no difference in Braak regions (1-2, 3-4, 5-6) between the TBI group and non-TBI group. The alternate hypothesis was that the TBI group's Braak regions would have a high presence of p-tau compared to the non-TBI group.

Hypothesis 3. Multiple regression to examine if there is a relationship between neuropsychological tests (CLOCKSCOR, BNTTOTAL, TRAASCOR, TRABSCOR, CATANIIMSC, AVDEL30MIN, AVDELTOT, AVTOTLRN) and Braak regions (BRAAK1-2, BRAAK3-4, BRAAK 5-6). The null hypothesis was there would be no relationship between performance on neuropsychological test scores and p-tau amounts in the Braak regions. The alternate hypothesis was that there would be a relationship between performance on neuropsychological tests and p-tau amounts in the Braak regions.

Chapter IV: Results

Neuropsychological Testing

A Mann-Whitney U test was used to determine whether there was a difference in CLOCKSCOR between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the clock scores of TBI (*Md* = 5, *n* = 39) and non-TBI (*Md* = 5, *n* = 65), *U* = 1,117.5, *z* = -1.27, *p* = .20, *r* = -.12. Although not statistically significant, there were differences in the mean rank for non-TBI (m = 50.19) and for TBI group (m = 56.35; see Figure 1).

Figure 1
Independent Samples Mann-Whitney U Test

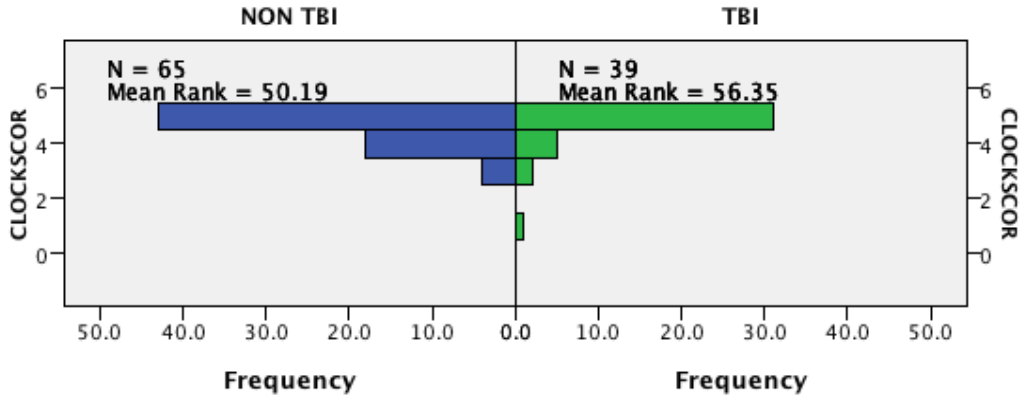

Figure 1. Shows mean ranks for each group on the clock score.

A Mann-Whitney U test was used to determine whether there was a difference in BNTTOTAL between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the BNTTOTAL of TBI (*Md* = 28.5, *n* = 38) and non-TBI (*Md* = 29, *n* = 65), *U* = 1,442.5, *z* = 1.46, *p* = .143, *r* = .14. Although not statistically significant, there were differences in the mean rank for Non TBI (m = 55.19) and for TBI group (m = 46.54; see Figure 2).

Figure 2
Independent Samples Mann-Whitney U Test

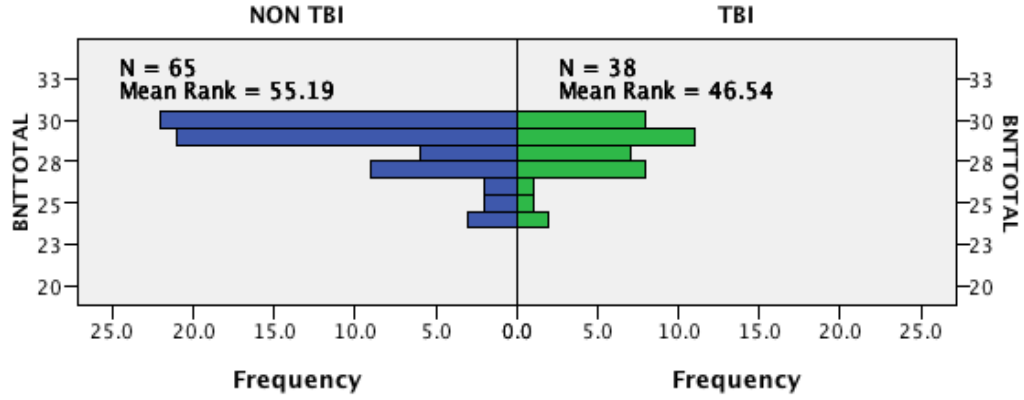

Figure 2. Shows mean ranks for each group on the BNTTOTAL.

A Mann-Whitney U test was used to determine whether there was a difference in TRAASCOR between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the TRAASCOR of TBI (*Md* = 31 , *n* = 39) and non-TBI (*Md* = 34, *n* = 65), *U* = 1,437, *z* = 1.14, *p* = .26, *r* = .11. Although not statistically significant, there were differences in the mean rank for Non TBI (m = 55.11) and for TBI group (m = 48.15; see Figure 3).

Figure 3
Independent Samples Mann-Whitney U Test

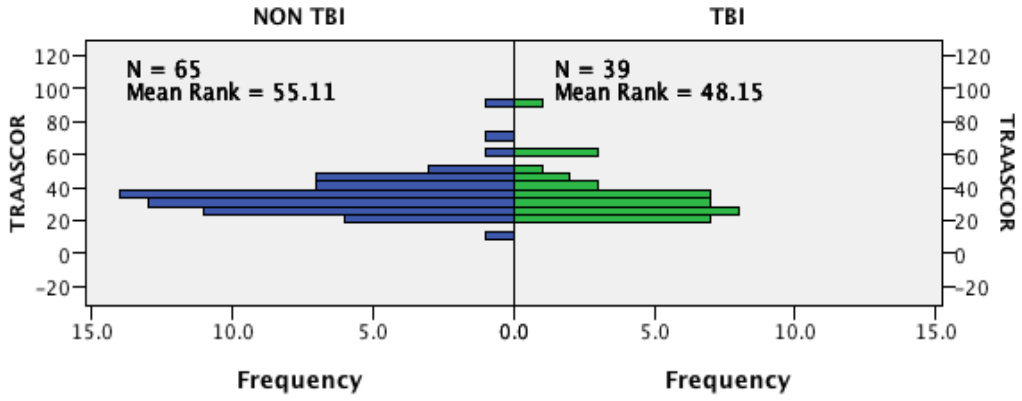

Figure 3. Shows mean ranks for each group on the TRAASCOR.

A Mann-Whitney U test was used to determine whether there was a difference in TRABSCOR between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the TRABSCOR of TBI (*Md* = 79, *n* = 39) and non-TBI (*Md* = 82, *n* = 65), *U* = 1,307.5, *z* = .27, *p* = .79, *r* = .03. Although not statistically significant, there were differences in the mean rank for Non TBI (m = 53.12) and for TBI group (m = 51.47; see Figure 4).

Figure 4
Independent Samples Mann-Whitney U Test

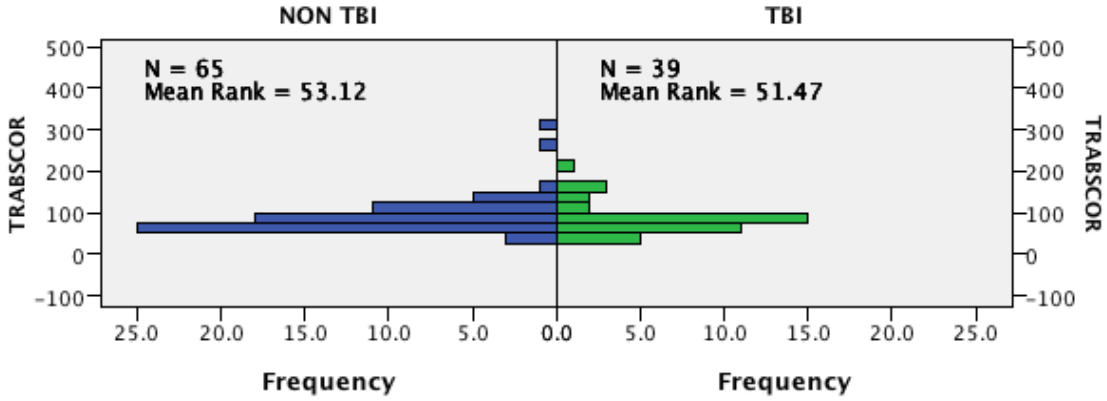

Figure 4. Shows mean ranks for each group on the TRABSCOR.

An independent-samples t-test was conducted to compare the CATANIMSC score for TBI and non-TBI. The Levene's test for Equality of variance is .1 indicating that the assumption of equal variances has not been violated. There was no significant difference in scores for TBI (*M* =20.72 , *SD* = 4.38) and non-TBI (*M* =20.52 , *SD* = 5.26; *t* (102) = 1.94, *p* = .85, two-tailed). The magnitude of the differences in the means (mean difference = .20, 95% *CI*: -1.79 to 2.18) was very small (eta squared = .0004).

A one-way between-groups analysis of variance was conducted to explore the impact of the status of TBI on (AVDELTOT), (AVDEL30MIN), and (AVTOTLRN). The Levene's test for homogeneity of variance for AVDELTOT (Sig.= .80), AVDEL30MIN (Sig.= .93) and

AVTOTLRN (Sig.=.88) indicating no violation of the assumption of homogeneity of variance. There was not a statistically significant difference at the $p < .05$ of level in AVDELTOT scores for the groups: F (1,102) = .57, p = .45. The actual difference in mean scores between the groups was very small. The effect size, calculated using eta squared was .01. There was not a statistically significant difference at the $p < .05$ of level in AVDEL30MIN scores for the group: F (1,102) = .18, p = .67. The actual difference in mean scores between the groups was very small. The effect size, calculated using eta squared, was .002. There was not a statistically significant difference at the $p < .05$ of level in AVTOTLRN scores for the group: F (1,102) = .31, p = ..58. The actual difference in mean scores between the groups was very small. The effect size, calculated using eta squared, was .003.

PET Imaging ^{18}F-AV1451

A Mann-Whitney U test was used to determine whether there was a difference in BRAAK 1-2 between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the BRAAK 1-2 of TBI (Md = 2.27, n = 8) and non-TBI (Md = 2.2, n = 19), U = 66, z = -.53, p = ..62, r = -.10. Although not statistically significant, there were differences in the mean rank for non-TBI (m = 13.47) and for TBI group (m = 15.25; see Figure 5).

Figure 5
Independent Samples Mann-Whitney U Test

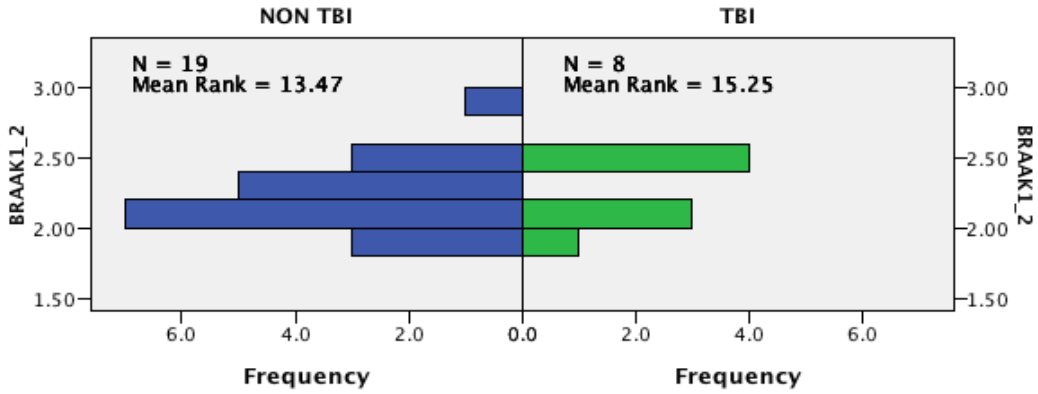

Figure 5. Shows mean ranks for each group on the BRAAK 1-2.

A Mann-Whitney U test was used to determine whether there was a difference in BRAAK 3-4 between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the BRAAK 3-4 of TBI (*Md* = 2.25, *n* = 8) and non-TBI (*Md* = 2.18, *n* = 19), *U* = 63, *z* = -.69, *p* = .52, *r* = -.13. Although not statistically significant, there were differences in the mean rank for non-TBI (m = 13.32) and for TBI group (m = 15.62; see Figure 6).

Figure 6
Independent Samples Mann-Whitney U Test

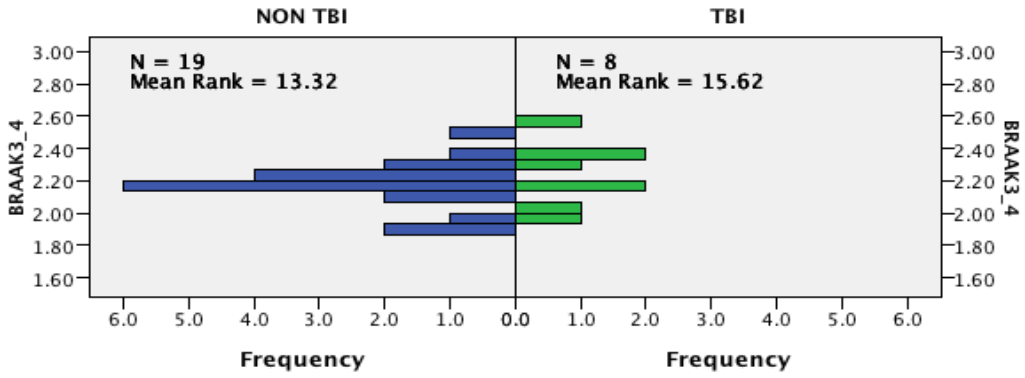

Figure 6. Shows mean ranks for each group on the BRAAK 3-4.

A Mann-Whitney U test was used to determine whether there was a difference in BRAAK 5-6 between the TBI group and the non-TBI group. The Mann-Whitney U test revealed no statistically significant difference in the Braak region 5-6 of TBI (*Md* = 2.09, *n* = 8) and non-TBI (*Md* = 1.96, *n* = 19), *U* = 46, *z* = -1.593, *p* = .12, *r* = -.31. Although not statistically significant, there were differences in the mean rank for non-TBI (m = 12.42) and for TBI group (m = 17.75' see Figure 7).

Figure 7
Independent Samples Mann-Whitney U Test

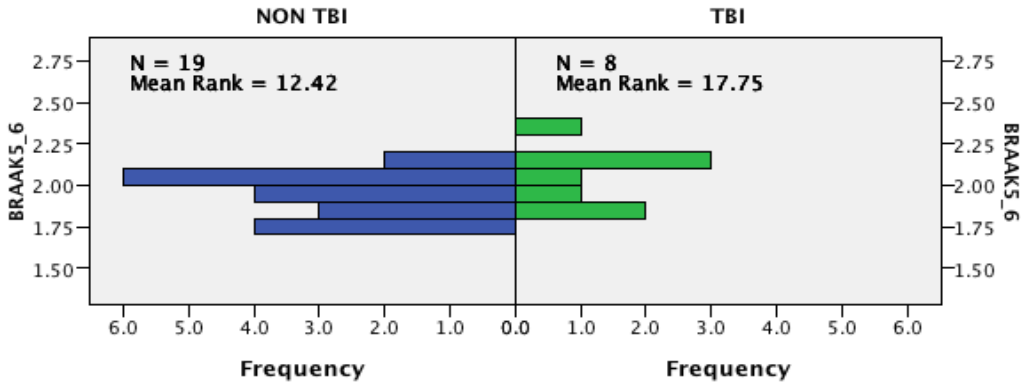

Figure 7. Shows mean ranks for each group on the BRAAK 5-6.

Relationship Between Neuropsychological Testing and PET Imaging ^{18}F-AV1451

Given that the statistical analysis performed on neuropsychological tests and Braak regions were not significant, multiple regression analysis was not indicated.

Chapter V: Discussion

The purpose of the study was to investigate cognitive functioning and neuroimaging correlates later in life in military veterans with moderate to severe TBI to individuals without TBI. The hypothesis that was no statistical significant differences in language, memory, attention, and executive functioning related to neuropsychological tests on the Boston Naming, Auditory Verbal Learning, Category Fluency (animals), Trail Making Test A and B, and the Clock drawing test between the TBI group and non-TBI group. The null hypothesis was retained indicating that there would be no differences in neuropsychological test scores between TBI group and the non-TBI group. Interestingly, even though there was not a statistical significant difference, the performance on neuropsychological tests Boston Naming and Trail Making Test A and B were not the same showing that the TBI group preformed lower than the non-TBI group.

In the second hypothesis, there was no statistically significant differences in levels of tau between the TBI group and non-TBI group. The null hypothesis was retained indicating that there was be no differences in Braak regions (1-2, 3-4, 5-6) between the TBI group and non-TBI group. However, a trend was observed of higher levels of tau in the TBI group when compared to the non-TBI group that did not reach statistical significance. Harad and colleagues (2016) reported a strong association between the amount of density of tau deposits and the development and severity of dementia. This trend in the TBI group could indicate additional risk factors of dementia.

As a result of the findings in the first and second hypotheses, analysis of the third hypothesis was not investigated. The lack of statistical significance found in performance on neuropsychological tests and levels of tau suggests there would be no statistically significant

relationship. Therefore, retaining the null hypothesis of there would be no relationship between performance on neuropsychological test scores and p-tau amounts in the Braak regions.

According to Langlois and Colleagues (2006), traumatic brain injury may result in long-term or lifelong cognitive, physical emotional, and behavioral consequences. Those who have a history of experiencing a moderate and severe TBI are more likely to be 1.5 times increased risk of depression, and a 2.3 to 4.5 times increased risk of Alzheimer's disease when compared to the general population (Langlois, Rutland-Brown, & Wald, 2006). In recent battlefield conflicts, researchers have identified that the most common and debilitating injuries among military veteran as TBI (Long et al., 2009). Research consistently shows cognitive deficits that parallel functional and structural damage in moderate to severe TBI resulting from military injuries (Long et al., 2009; McKee, & Robinson, 2014). Furthermore, there is recent evidence that earlier military-related TBI may initiate neurodegenerative processes in the brain that are different from healthy brain aging, including the accumulation of tau proteins (McKee, & Robinson, 2014).

This study has contradicting results about the implications of moderate and severe TBI on cognitive functioning and imaging when compared to current literature. The clinical implications indicate no significant differences in aging in those that have experienced a TBI earlier in life compared to others that had not experienced a TBI. Some factors that could have played a role in this study's results in the possibility of resilience. The TBI participants did not have a history of cognitive impairment, psychological disorders, and substance abuse. These individuals could have had early interventions that would have benefited them in emotional, psychological, physical functioning. Considering these individuals served in an era were the socio-political climate was not supportive of veterans. These individuals may have identified

coping strategies that through a supportive environment, like immediate medical attention after injury, continued access to health services, socially supportive members in their community, and lifestyle factors. Furthermore, continued exploration of these participants with history of TBI in this study could reveal protective factors that prevent or limit neurodegenerative aging.

Limitations

There were several limitations to this study. One of the limitations was in the ADNI DOD database's inclusion and exclusion criteria and available participant data set limitations on the hypotheses investigated in this study. Specifically, the exclusion of veteran's with history of TBI with either mild cognitive impairment or dementia. This exclusion restricted some of the opportunity to investigate possible relationships between TBI, aging, and neurodegenerative processes. This restriction prevented further investigation in whether the diagnoses of mild cognitive impairment and dementia correlated with the participants' TBI experienced in military service.

Additionally, the available number of participants in each group was not equal between groups with only 39 participants in the TBI group and 65 in the non-TBI completing neuropsychological testing. Out these groups only 8 participants completed PET ^{18}F-AV1451 imaging for the TBI group and 19 participants completed PET ^{18}F-AV1451 imaging for the non-TBI group. Due to the size of the sample, the non-significant results could have been influenced by power of the analyses. Additionally, this study only looked at male Vietnam veterans, due to only one female was in the DOD ADNI database. The lack available female participants limits the results to male Vietnam veterans. Based on this study it is unknown if there would have been different outcomes in neuropsychological testing and imaging.

However, considering the era of the Vietnam war and the roles of females played in the military this limitation may not be resolved for this specific era of veterans.

Recommendations

The purpose of this study was to investigate cognitive functioning and neuroimaging correlates later in life in military veterans with moderate to severe TBI to individuals without TBI. Although the findings of this study were not significant, future studies of TBI and aging are necessary. Recommendation for future studies includes continuing the investigation of aging veterans with a history of TBI with a larger sample size. Having a larger sample size may yield different results compared to this study. Additionally, including individuals that have mild cognitive impairment or dementia may also yield different findings. Continued investigation of TBI and aging could aid in managing TBI outcomes and differential diagnoses later in life and the treatment of military related TBI in theater and after for the military and veteran populations.

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