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# Investigating the Differences between Neuropsychological and Physiological Markers in a PTSD-only Group Among Vietnam Veterans

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# Investigating the Differences between Neuropsychological and Physiological Markers in a PTSD-only Group Among Vietnam Veterans

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The Doctorate Program in Clinical Psychology
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CERTIFICATE OF APPROVAL

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Clinical Research Project

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This is to certify that the Clinical Research Project of

Ashtan Alexandra Madsen

has been approved by the
CRP Committee on September 21, 2023
as satisfactory for the CRP requirement
for the Doctorate of Psychology degree
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## Abstract

Individuals diagnosed with posttraumatic stress disorder (PTSD) have demonstrated extinction-resistant symptoms and long-lasting impacts on the brain's functional activity (Krystal et al., 2017; Stark et al., 2015). PTSD illustrates a strong relationship with cognitive functioning, and research has found lower parietal and hippocampal volume and deterioration in brain function and structure, resulting in executive dysfunction, attentional deficits, mood dysregulation, and memory difficulties (Krystal et al., 2017; Stark et al., 2015; Weiner et al. 2017). Sleep has been investigated to better understand its contribution to AD pathologies as well as its impact on PTSD treatment and prognosis. Although sleep's functions are not widely understood, past studies have found that sleep aids in clearing waste, reconsolidating memories, and promoting neuronal connection (National Institute of Neurological Disorders and Stroke, 2006; Pace-Schott et al., 2015). Preliminary research by Weiner et al. (2017) has demonstrated worse global cognitive functioning, lower superior parietal volume, and lower amyloid positivity in people with PTSD, although preliminary results have not indicated PTSD as an increased risk factor for AD (Weiner et al., 2017). Therefore, further assessment of the differences between CSF amyloid, CSF ptau, and PTSD symptoms, specifically sleep, may expand current research on AD risk factors and biomarkers. A total of 179 participants were included in this study and were split into two groups: a PTSD group ($n$ = 96) and a control group ($n$ = 83). A MANCOVA analysis was conducted to assess if one or more mean differences between sleep quality index scores and AD pathology (i.e., CSF tau, CSF p-tau, CSF amyloid beta, CSF amyloid beta 40, and CSF amyloid beta 42/40 ratio) as well as in neuropsychological assessment results were present in a PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans. A statistically significant MANCOVA effect was obtained, Pillai's Trace = 0.28,

$F(6,61) = 3.89$, $p < 0.002$, when assessing differences between sleep quality and AD pathology. However, a statistically significant MANCOVA effect was not obtained, Pillai's Trace = 0.16, $F(11,38) = 0.68$, $p = 0.75$, when assessing differences on neuropsychological assessments. Findings from this study suggest that sleep disturbance is prominent in individuals with PTSD and could be a significant contributor to AD pathologies. However, no difference was found between groups on neuropsychological assessments, illustrating that individuals with PTSD do not differ from those without PTSD in areas assessed by these measures.

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## Contents

# CHAPTER I: INTRODUCTION

## Background

Posttraumatic stress disorder (PTSD) is a complex psychological disorder following exposure to a life-threatening traumatic event(s); (Dayan et al., 2016; Krystal et al., 2017; Stein, 2021). According to the American Psychiatric Association (APA, 2013), PTSD is "a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist attack, war/combat, or rape, or who have been threatened with death, sexual violence or serious injury" (p. 271). Individuals exposed to a traumatic event(s) may experience actual or threatened death, serious injury, or sexual violence, affecting veterans, active military personnel, and civilians alike. Symptoms may include fear-related, trauma-like, avoidance, alterations in cognition and mood, and marked arousal and reactivity (APA, 2013). Individuals who have PTSD may experience flashbacks, physiological reactions, intrusive memories, persistent negative beliefs about oneself, others, or the world, hypervigilance, sleep disturbance, and anxiety (APA, 2013; Krystal et al., 2017).

Individuals diagnosed with PTSD have demonstrated extinction-resistant symptoms and long-lasting impacts on the brain's functional activity (Krystal et al., 2017; Stark et al., 2015). Studies have shown that those with PTSD experience dysregulation, lower parietal and hippocampal volume, and deterioration in brain function and structure, resulting in executive dysfunction, attentional deficits, mood dysregulation, and memory difficulties (Krystal et al., 2017; Stark et al., 2015; Weiner et al. 2017). Because PTSD illustrates a strong relationship with cognitive functioning, theories have been postulated by neuropsychologists about its contribution to dementia and the possibility of PTSD as a risk factor for Alzheimer's disease (AD), a common

form of neurocognitive disorder and age-related dementia (Fiest et al., 2016; Liu et al., 2014; Weiner et al., 2014, 2017, in press).

According to the APA (2013), a neurocognitive disorder is a "decline in mental ability that interferes with independence and daily life" (p. 602). A neurocognitive disorder can be labeled as mild or major, which assesses the level of cognitive impairment (i.e., substantial or modest; APA, 2013). Alzheimer's disease (AD) is a common form of neurocognitive disorder and age-related dementia (Liu et al., 2014; Fiest et al., 2016). It accounts for 70% of all dementia cases and has an age-specific incidence rate, as it doubles approximately every 5.5 years in older populations (Fiest et al., 2016). AD signs and symptoms include cognitive impairments, emotional disturbances, and neuropsychiatric indicators such as delusions, hallucinations, sleep disturbances, and so on (Lanctot et al., 2017). AD pathophysiological markers include the presence of amyloid plaques and tau in the cerebrospinal fluid (CSF) in addition to hippocampal and temporoparietal atrophy, which can be assessed utilizing PET and MRI neuroimaging (Sachdev et al., 2014).

CSF tau and ptau are widely accepted biomarkers of AD in which levels tend to be elevated and reduced, respectively (Meredith et al., 2013; Shaw et al., 2018). Research suggests that tau occurs in a series of fragments in CSF, and the measurement of the subsets of tau species can be used to discriminate the severity of AD (Meredith et al., 2013; Shaw et al., 2018). AD is associated with higher CSF tau, while healthy adults have lower levels of CSF tau (Meredith et al., 2013; Shaw et al., 2018; Weiner et al., 2014, 2017, in press). CSF amyloid plaques are one of the central biomarkers of AD and aid in explaining the development of neurodegeneration resulting in neurocognitive disorders like AD (Blennow et al., 2015). Research posits the amyloid cascade hypothesis, which theorizes that amyloid aggregates into plaques that impair

synaptic function and damage neurons (Blennow et al., 2015). AD is associated with elevated amyloid plaques with lower levels of CSF amyloid beta 42 and 40 (Blennow et al., 2015; Shaw et al., 2018; Weiner et al., 2014, 2017, in press). Healthy adults have higher levels of CSF amyloid beta 42 and 40 (Shaw et al., 2018; Weiner et al., 2014, 2017, in press).

Weiner et al. (2014) proposed a longitudinal study investigating the impact of PTSD and traumatic brain injury (TBI) in the development of dementia, specifically AD. Investigators from the Alzheimer's Disease Neuroimaging Initiative (ADNI) partnered with the Department of Defense (DOD) and the San Francisco Veterans Affairs Medical Center (SFVAMC) to identify veterans who have been diagnosed with PTSD and/or TBI as a result of combat-related trauma or deployment and recruit them as participants for the study (Weiner et al. 2014, 2017, in press). The purpose of the study is to obtain a better understanding of risk factors and the development of AD when experiencing clinical or medical diagnoses such as PTSD. Thus far, the longitudinal study has yet to reveal PTSD as a risk factor for AD but has confirmed previous research regarding PTSD's correlation to cognitive decline and dementia-like symptoms (Weiner et al. 2014, 2017, in press).

PTSD and other mood disorders have been associated with a twofold increase in cognitive impairment and accelerated brain aging compared to individuals without any diagnosed psychological disorders (Clouston et al., 2016; Rafferty et al., 2018). PTSD has also been shown to reduce brain reserve, otherwise known as "cognitive reserve," which can result in greater cognitive impairment, especially in memory (Rafferty et al., 2018; Weiner et al., 2014, 2017, in press). It has been postulated that reduced "cognitive reserve" contributes to PTSD participants' vulnerability to impaired verbal memory, working memory, verbal declarative

memory, executive functioning, and processing speed (Weiner et al., 2014, 2017, in press; Wrocklage et al., 2016).

Past research has illustrated that sleep disturbance could be one of the biological functions contributing to the etiology and maintenance of PTSD in addition to AD pathologies (Pace-Schott et al., 2015). In fact, sleep quality can have differing effects on cognitive, emotional, social, and physical functioning in adults (Bernstein et al., 2019; Lallukka et al., 2017; Miyata et al., 2013). Research has investigated the contribution of sleep to the variability of cognitive performance, especially in the older adult population (Miyata et al., 2013; Nebes et al., 2009). Past studies have postulated that poor sleep may contribute to lower cognitive performance in the domains of working memory, attentional set-shifting, and abstract problem-solving in the older adult population (Miyata et al., 2013; Nebes et al., 2009). Additionally, poor sleep quality has been correlated with poor PTSD prognosis and treatment outcomes (Babson et al., 2012; Pace-Schott et al., 2015; Werner et al., 2020).

**Statement of the Problem**

It remains unclear how biological functions such as sleep could impact AD pathology in individuals with PTSD. Preliminary research by Weiner et al. (2017) has demonstrated worse global cognitive functioning, lower superior parietal volume, and lower amyloid positivity in people with PTSD as compared to individuals without PTSD. Although preliminary results have not indicated PTSD as an increased risk factor for Alzheimer's disease (AD), researchers have primarily investigated amyloid plaques and tau tangles via PET imaging in those with PTSD and TBI thus far (Weiner et al., 2017). Therefore, further assessment of the differences between sleep, CSF amyloid, and CSF tau, specifically in those with PTSD, may expand current research on PTSD's impact on AD risk factors and biomarkers.

**Purpose of the Study**

Although there is promising research to better understand the differences between neuropsychological and physiological factors of PTSD pathology and AD, there is little research that investigates the differences between biomarkers and symptoms of each disorder and their comorbidity among the Vietnam veteran population. Sleep disturbance is a significant PTSD symptom that contributes to the perpetuation of the disorder and has a relation to outcomes in those diagnosed with AD. Therefore, the purpose of this study is to investigate the differences in cognition and sleep quality while assessing the differences between neuropsychological and physiological PTSD and AD biomarkers among a PTSD-only Vietnam veteran group within the DOD ADNI data set.

**Research Questions and Hypotheses**

The first research question was: are there differences between sleep quality and AD pathology (i.e., CSF ptau and CSF amyloid beta) in a PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans? The Null hypothesis of the first research question was: there will not be any differences between sleep quality and AD pathology (i.e., CSF ptau and CSF amyloid beta) among the two Vietnam veteran groups. The Alternative hypothesis of this research question was: there will be differences between sleep quality and AD pathology (i.e., CSF ptau and CSF amyloid beta) among the two Vietnam veteran groups.

The second research question for this study was: Is there a difference between the neuropsychological tests in the PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans? The Null hypothesis of the second research question was: there will be no difference between the neuropsychological tests among the Vietnam veteran groups.

The Alternative hypothesis for this research question was: there will be a difference between the neuropsychological tests among the Vietnam veteran groups.

**Literature Review**

Posttraumatic stress disorder (PTSD) is a complex mental health disorder following exposure to actual or threatened death, serious injury, sexual violence, or extremely threatening or horrific event(s); (APA, 2013; Dayan et al., 2016; Krystal et al., 2017; Stein, 2021). Recent research has illustrated that the regulation of fear appears to be a significant contributor to PTSD symptoms, especially fear-related symptoms involving hypervigilance, intrusive thoughts, nightmares, flashbacks, and avoidance (Krystal et al., 2017; Levy & Schiller, 2021; Norbury et al., 2021). Studies have demonstrated that trauma-related fear memories tend to be resistant to extinction even when utilizing evidence-based psychotherapy and pharmacological treatments (Krystal et al., 2017; Levy & Schiller, 2021; Norbury et al., 2021). The literature arrives at an uncertain conclusion regarding the reasons surrounding this symptom resistance. However, plausible theories dictate that an underlying biological component such as sleep may contribute to the development of PTSD and its prognosis (Kang et al., 2018; Pace-Schott et al., 2015; Weiner et al., 2014; Werner et al., 2020).

Poor sleep quality has been correlated with poor PTSD prognosis and treatment outcomes (Babson et al., 2012; Pace-Schott et al., 2015; Werner et al., 2020). Poor sleep may be associated with functional impairment as seen in depression (e.g., attention and concentration difficulties) but not mood symptoms such as feelings of sadness or hopelessness (Miyata et al., 2013; Nebes et al., 2009). In fact, sleep disturbance could disrupt the consolidation process where learning and memory are severely impacted and emotional processes where anxiety is exacerbated (Babson et al., 2012; Nebes et al., 2009; Pace-Schott et al., 2015; Werner et al., 2020).

Sleep affects practically every system within the body and although its functions are not widely understood, past studies have found that sleep aids in clearing waste, reconsolidating memories, promoting neuronal connection, and has been known to aid in filtering out toxins that have built up in the brain throughout the day (National Institute of Neurological Disorders and Stroke, 2006; Pace-Schott et al., 2015). Neurotransmitters such as GABA, norepinephrine, and cortisol contribute to the sleep-wake cycle and optimal levels promote healthy, effective sleep (National Institute of Neurological Disorders and Stroke, 2006).

However, research has shown that people with PTSD tend to experience cortisol dysregulation after exposure to a life-threatening traumatic event(s); (Dayan et al., 2016; Krystal et al., 2017; Sopp et al., 2021; Stein, 2021). Those with PTSD illustrate higher levels of cortisol, and past studies have found an association between high cortisol levels and increased sleep disturbances (Babson et al., 2012; Germain et al., 2005; Sopp et al., 2021). It appears that sleep plays an integral role in the perpetuation of PTSD symptoms given that the underlying dysfunction of PTSD persists into the sleep stage and sleep disturbances can be a strong predictor of the development of PTSD (Babson et al., 2012; Germain et al., 2005; Werner et al., 2020).

In addition, research has demonstrated that poor sleep quality and sleep disturbances have been associated with greater Alzheimer's disease (AD) pathology (Ju et al., 2014; Sprecher et al., 2017). In healthy individuals, the clearance of waste products in the cerebrospinal fluid (CSF), also known as the glymphatic system, is enhanced and completed during adequate sleep (Drogos et al., 2016; Jessen et al., 2016; Ju et al., 2014). However, there is a greater deposition of CSF tau and amyloid plaques when sleep is disrupted, which can interrupt sleep-wake rhythms in healthy older adults (Drogos et al., 2016; Ju et al., 2014;). In fact, the "recently discovered macroscopic

waste clearance system" called the glymphatic system depicts the waste elimination of non-waste compounds and neurotoxic waste products such as amyloid beta, which primarily occurs during sleep (Jessen et al., 2016, p. 2583). Research has shown that the glymphatic system dramatically enhances during sleep and clears out the waste like amyloid beta produced during the day while awake (Jessen et al., 2016). Clearance of the accumulation of proteins like amyloid beta and tau is imperative for brain health; therefore, difficulty in the clearance process is problematic leading to neurodegenerative disorders like AD due to the biomarkers, amyloid plaques and tau tangles associated with Alzheimer's (Drogos et al., 2016; Jessen et al., 2016; Ju et al., 2014).

Research has also posited an association between normal sleep-wake cycles and the effect of the APOE gene in which adequate sleep may reduce the impact of the APOE gene on the development of cognitive decline and AD (Drogos et al., 2016; Ju et al., 2014;). The Ɛ4 allele of the apolipoprotein E (APOE) gene is a significant risk factor for AD as it is associated with the pathological progression of brain lesions, cerebral atrophy, and amyloid plaque deposition (Liu et al., 2014). There is also evidence that the sleep-wake cycle directly influences the levels of amyloid plaques in the brain (Ju et al., 2014). Furthermore, poor subjective sleep quality has been associated with elevated CSF amyloid plaque and lower CSF tau levels (Ju et al., 2014; Sprecher et al., 2017). As a result, sleep problems may contribute to greater cognitive impairment and behavioral problems seen in those diagnosed with AD (Shin et al., 2014). Therefore, assessing sleep quality could be a vital aspect in understanding the development of psychological disorders such as PTSD and AD, their psychopathology, and treatment outcomes/prognosis.

### *Measuring Sleep Quality*

The most common measurement of sleep quality is the Pittsburg Sleep Quality Index (PSQI). The PSQI was developed to assess sleep quality in a variety of domains, and scores can be utilized to understand sleep's impact on multiple areas of functioning (Buysse et al., 1988). PSQI scores have been found to be similar in individuals with PTSD, depression, and dementia/AD (Babson et al., 2012; Germain et al., 2005). Research has demonstrated that the Pittsburg Sleep Quality Index has two factors (Perceived Sleep Quality and Efficiency/Duration) that are associated with PTSD (Babson et al., 2012). Additionally, the PSQI has been utilized to assess sleep quality in a variety of domains in individuals diagnosed with AD, in which research has found that individuals with AD illustrate disturbances in the sleep/wake cycles and higher prevalence rates of sleep problems (Shin et al., 2014).

### *Posttraumatic Stress Disorder in Veterans*

Although PTSD can affect all individuals, veterans may have experienced repeated, impactful complex trauma, including military sexual trauma (MST) and combat-related conditions that could influence physical, psychological, and social functioning and could result in chronic PTSD (Kang et al., 2018). According to the U.S. Department of Veterans Affairs (2019), a veteran is "a person who served in the active military, naval, or air service, and who was discharged or released therefrom under conditions other than dishonorable" (p. 1). Combat-related trauma can be defined as "the exposure to military combat or other traumas experienced during military deployments" (Peterson et al., 2021, p. 1).

Veterans with a history of ongoing PTSD but without MCI, dementia, or TBI have increased evidence for AD pathophysiological markers (Weiner et al., 2014, 2017, in press).

According to the National Vietnam Veterans longitudinal study, PTSD symptoms among Vietnam veterans remain stable over time (Steenkamp et al., 2017). However, an exacerbation in symptoms was demonstrated in those with chronic PTSD who were either of African American race, lower education level, younger age at entry into Vietnam, or severe combat exposure, lower social support, or significant past-year stressors (Steenkamp et al., 2017). Research has also postulated an association between the age of exposure to violence or combat and the development of PTSD and symptom severity (Miller-Graff et al., 2016).

Veterans with a history of moderate to severe TBI but without mild cognitive impairment (MCI)/dementia or PTSD, in addition to veterans with ongoing PTSD but without MCI, dementia, or TBI, have increased evidence for AD pathophysiological markers (Weiner et al., 2014, 2017, in press). TBI and/or PTSD reduce brain reserve, which can cause greater cognitive impairment (Weiner et al., 2014). Combat veterans with PTSD show variable reaction times in motor inhibition tasks, with impairments in executive control and increases in impulsivity (Swick et al., 2012; Swick, 2013). PTSD has been associated with deficits in emotional neural tasks and in the cognitive domains of learning and memory, attention, and inhibitory functions (Vasterling & Hall, 2018; Wrocklage et al., 2016).

Neuroimaging has exhibited cortical volume loss and reduced white matter pathways in the prefrontal cortex, hippocampus, and amygdala in PTSD patients, resulting in impaired cortical connectivity, deficits in structural integrity, and damage in synaptic connectivity (Krystal et al., 2017). These biological changes are suggested to be clinically relevant as they have been associated with the cognitive and functional impairments of PTSD (Dayan et al., 2016; Krystal et

al., 2017). Evidence of PTSD biological markers illuminates the transformative and enduring actions of chronic stress responses and helps understand the pathological development of PTSD extinction-resistant symptoms (Dayan et al., 2016).

***Biomarkers and Risk Factors***

Other plausible pathological biomarkers contributing to the development of neurocognitive disorders in veterans diagnosed with PTSD involve atrophy in the hippocampus, elevated levels of cortisol, and disruption in glucocorticoid receptors (Kang et al., 2018). PTSD biomarkers overlap with AD biomarkers regarding hippocampal atrophy; however, it is uncertain the difference between PTSD and other AD pathologies like CSF tau/p-tau and CSF amyloid plaques (Weiner et al., 2014, 2017, in press). Thus far, past researchers have only investigated amyloid plaques via PET and MRI imaging (Weiner et al., 2017).

*The Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5;* APA, 2013) does not discuss biological markers as part of the pathological development when describing the symptoms of PTSD. However, the *DSM-5* does describe the biological markers and physiological pathology of neurocognitive disorders, which demonstrate high comorbidity with PTSD among veterans (Kang et al., 2018). Research has suggested a higher risk of dementia in veterans with PTSD compared to those without and an increased likelihood of developing a neurocognitive disorder if the veteran experienced combat-related trauma (Kang et al., 2018). It is also hypothesized that factors such as occupation, education, and intellectual/social activity can impact cognition, and these factors could advance cognitive decline and the incidence of AD (Kang et al., 2018; Weiner et al., 2014, 2017, in press).

Other significant risk factors for AD include age and depression (Weiner et al., 2014, 2017, in press). Age has been recognized as a significant risk factor for the development

of AD (Miller-Graff et al., 2016; Weiner et al., 2014, 2017, in press). AD affects approximately 50% of individuals over the age of 85 and has an age-specific incidence rate (Fiest et al., 2016; Weiner et al., 2014, 2017, in press). Recent research also has postulated that depression, especially diagnosed later in life, can be a significant risk factor for dementia, specifically AD (Bellou et al., 2017; Rafferty et al., 2018).

***Cognitive Reserve***

The combination of AD and PTSD risk factors in addition to other psychosocial aspects (e.g., daily functioning and sleep quality) are included in "cognitive reserve," which has been defined as the "ability to optimize or maximize normal performance, and compensation, an attempt to maximize performance in the face of brain damage by using brain structures or networks not engaged when the brain is not damaged" (Stern, 2002, p. 448). Cognitive reserve can be used to describe healthy individuals and those who have sustained or experienced brain damage (Stern, 2002, 2012, in press). There are two models explaining cognitive reserve, which include passive models and active models (Stern, 2002, 2012, in press). Passive models suggest the construct of brain reserve capacity, depicting a critical threshold wherein once there is a depletion of the threshold and then functional impairment on a clinical level emerges (Stern, 2002, 2012, in press). Active models suggest that the brain actively attempts to compensate for brain damage by using other brain structures or networks to compensate for the areas that were injured or damaged (Stern, 2002, 2012, in press).

Individuals diagnosed with a neurocognitive disorder like Alzheimer's Disease (AD) experience memory deficits in the areas of prospective memory, free recall, cued recall, implicit learning, short-term and long-term memory, and recognition memory (Henry, 2021; Sachdev et al., 2014). Past studies suggest that cognitive reserve can aid in the aforementioned progressive,

insidious deficits by increasing the brain's tolerance of these changes to maintain a semblance of function (Stern, 2002, 2012, in press). Research findings also suggest PTSD includes reduced cognitive reserve, resulting in elevated functional impairment compared to individuals with AD (Brenner et al., 2009; Weiner et al., 2014).

### *Neuropsychological Assessments*

Neuropsychological evaluations are utilized to assess overall cognition, cognitive impairments, and provide diagnostic clarity in cases that depict deficits in the primary neuropsychological domains (Schaefer et al., 2023; Weiner et al., 2014, 2017, in press). Domains of functioning are evaluated and compared to normative data sets to properly investigate the cognitive deficits that may be present. Although neuropsychological assessments may be primarily used to assess neurocognitive disorders such as AD and dementia, other psychological disorders (e.g., PTSD) may illustrate similar cognitive deficits. PTSD has demonstrated cognitive impairment similar to individuals who have been diagnosed with AD such as memory impairments (Henry, 2021; Sachdev et al., 2014; Weiner et al., 2014). PTSD is associated with a variety of behaviors (e.g., sleep disturbance) that may contribute to cognitive impairments and the development of AD (Weiner et al., 2014, 2017, in press). Neuropsychological assessments like the Pittsburg Sleep Quality Index (PSQI) demonstrate similar global scores between PTSD and AD in addition to other psychological disorders (Babson et al., 2012; Germain et al., 2005).

### *Aim of Current Study*

Research findings suggest PTSD includes reduced cognitive reserve (Brenner et al., 2009; Weiner et al., 2014). However, past literature has not examined the differences between chronic PTSD symptoms (e.g., sleep disturbances and quality) and AD pathologies such as CSF ptau and CSF amyloid beta (Weiner et al., 2014, 2017, in press). Past research has highlighted

the effects PTSD may have on AD pathology; nevertheless, there has been minimal research on the differences between PTSD and AD biomarkers (Weiner et al., 2014, 2017, in press). Recent research has illustrated a relationship between sleep deprivation, PTSD, and AD in that sleep deprivation has demonstrated a bidirectional relationship with PTSD and AD (Delic et al., 2021). However, this relationship triad has yet to be investigated as it pertains to the risk of developing AD (Delic et al., 2021; Weiner et al., 2014, 2017, in press). Therefore, exploring the differences between PTSD symptoms and AD pathology may be an essential area of research to better understand the interaction between the factors of sleep and AD pathology in those with PTSD (Babson et al., 2012; Germain et al., 2005; Weiner et al., 2014, 2017, in press).

The aim of this study is to investigate the differences between sleep and AD pathology in Vietnam veterans with PTSD who have experienced combat-related trauma. Sleep disturbance is a significant PTSD symptom that contributes to the perpetuation of the disorder and has a relation to outcomes in those diagnosed with AD. Therefore, the purpose of this study is to investigate the differences in cognition and sleep quality while assessing the differences between neuropsychological and physiological PTSD and AD biomarkers among a PTSD Vietnam veteran group within the DOD ADNI data set.

# Chapter II: Methods and Materials

## ADNI Data Use Agreement

Data utilized in the preparation of this dissertation were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 with the DOD ADNI beginning in 2017, a collaborative study, and was led by the Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI has been to assess whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), and other biological markers, in addition to clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The purpose of the DOD ADNI was to examine the possible connections between traumatic brain injury (TBI, posttraumatic stress disorder (PTSD), and signs and symptoms of AD on Vietnam Veterans as they age. For up-to-date information, visit www.adni-info.org.

Since the data used in this study was obtained from the ADNI database, the principal investigators within the ADNI contributed to the design and implementation of the ADNI and provided data, however, they did not participate in the analysis or the writing of this dissertation. In addition, data was provided and generated by the Alzheimer's Disease Metabolomics Consortium (ADMC) regarding the biofluid collection and DNA sequencing within the ADNI study.

Additionally, data collection and sharing for this project was funded by the ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012).

## Participants

### *Study Cohort Recruitment, Eligibility, and Selection*

Participants in this study were from the DOD ADNI data set (Weiner et al., 2014, 2017, in press). All study participants underwent a pre-screen evaluation conducted by the San Fransico VA Medical Center (SFVAMC) that determined eligibility for inclusion in the DOD ADNI study. Vietnam veterans who met basic PTSD or control criteria according to the inclusion and exclusion criteria outlined in this chapter were mailed a letter describing the study and asking them to call the screening center. Veterans who did not respond to the letter were contacted directly by phone by screening center staff. Advertisements were placed to which veterans can respond by calling the screening center. Ads were placed on Craigslist, newspapers, veterans' newspapers, magazines, and websites. Flyers were also posted at study sites. Staff conducted outreach at veterans' events and within veterans' organizations. Recruitment letters were sent to participants who met the basic eligibility criteria of being a Vietnam veteran with or without PTSD or Traumatic Brain Injury (TBI) from the VA Compensation and Pension records and Department of Defense (DOD) service records. A Traumatic Brain Injury (TBI) was defined as a loss of consciousness, post-traumatic amnesia > 24 hours, and/or alteration of consciousness or mental state > 24 hours. Eligibility was determined by a trained research associate at the San Fransico VA Medical Center (SFVAMC) who conducted an initial screening and Clinical Psychological Interview by telephone. Staff at participating ADNI clinics furthered assessed eligibility for all interested participants.

Exclusion criteria included mild cognitive impairment (MCI) or dementia, history of psychosis or bipolar affective disorder, history of alcohol or substance abuse/dependence within

the past 5 years; MRI-related exclusions (e.g., aneurysm clips, metal implants that are determined to be unsafe for MRI, or claustrophobia), or contraindications for lumbar punctures, PET scan, or other procedures within the study; any major medical conditions must have been stable for at least 4 months, with no seizure disorder or any systematic illness affecting brain function during the past 5 years, no clinical evidence of a stroke, and no history of relevant severe drug allergy or hypersensitivity; and any participants with current clinically significant unstable medical comorbidities that pose a potential safety risk.

***PTSD Participant Group***

The PTSD participant group consists of 65 Vietnam War veterans with PTSD but without traumatic brain injury (TBI), MCI, or dementia. The inclusion criteria for the PTSD participant group included: veterans from the Vietnam War, 50-90 years of age, who met the Structured Clinical Interview for *The Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (SCID-IV; *DSM-IV*; First et al., 2008) criteria for current/chronic PTSD, had a minimum current Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990) score of 50, had PTSD symptoms contributing to PTSD diagnosis that were be related to a Vietnam War related trauma, and must live within 150 miles of ADNI clinic. The exclusion criteria for the PTSD participant group included: MCI/dementia, documented or self-report history of mild/moderate-severe traumatic brain injury (TBI), any history of head trauma associated with injury onset of cognitive complaints, and loss of consciousness for > 5 minutes.

The Structured Clinical Interview for *Diagnostic and Statistical Manual for Mental Disorders*, 4th Edition (SCID-IV, *DSM-IV*; First et al., 2008) is a semi-structured interview with the sole purpose of determining whether an individual meets diagnostic criteria for any *DSM-IV* disorder. The SCID-IV is intended to assess both current and lifetime symptoms where the

interviewer documents the age, onset, and severity of the disorder (First et al., 2008; Glasofer et al., 2015). First, open-ended questions regarding demographic information, chief complaint, history of present illness, any past psychiatric disturbance episodes, treatment history, and current functioning are asked by the interviewer. Afterward, multiple close-ended questions (i.e., yes/no) related to diagnostic criteria are asked by the interviewer. The close-ended questions are grouped according to Axis I or II disorders and its criteria. If a participant does not meet the minimum diagnostic criteria within each series of questions, then the interviewer is instructed to skip the remaining questions and move on to the next disorder and its criteria. Specifically in the DOD ADNI study, the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) was utilized (Weiner et al., 2014, 2017, in press). These questions assess mood disorders, psychotic disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, and current adjustment disorders. Investigators with appropriate training complete the interviews with each participant who is knowledgeable of diagnostic evaluation and criteria.

The Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990) is a structured diagnostic interview that assesses posttraumatic stress disorder (PTSD) diagnostic criteria and symptom severity. The CAPS assesses all PTSD criteria with its associated features (e.g., dissociation), global ratings of distress, impairment, response validity, and symptom severity (Blake et al., 1990; Weathers et al., 2017). It also investigates both dichotomous (present/absent) and continuous individual symptoms of PTSD and provides a separate assessment for symptom frequency and intensity (Blake et al., 1990; Weathers et al., 2017). CAPS has behaviorally anchored prompts and rating scales that enable it to assess trauma-related symptoms that are inherently linked to trauma such as loss of interest, difficulty concentrating, and flashbacks (Blake et al., 1990; Weathers et al., 2017). The CAPS is a thoroughly validated and highly

recognized assessment tool in the field of traumatic stress in specifically investigating PTSD criterion and symptoms (Blake et al., 1990; Weathers et al., 2017).

### *Control Participant Group*

The control participant group consists of 65 Vietnam War veterans without PTSD, TBI, MCI, or dementia and is comparable in age, gender, and education. The inclusion criteria for the control participant group included: veterans from the Vietnam War, 50-90 years of age, comparable in age, gender, and education with the PTSD participant group utilizing the pre-screening process, may be receiving VA disability payments for something other than PTSD or no disability at all, and must live within 150 miles of ADNI clinic. The exclusion criteria for the control participant group included: MCI or dementia, presence of PTSD by SCID-I or a CAPS score of > 30, documented or self-report history of mild/moderate-severe TBI, any history of head trauma associated with injury onset of cognitive complaints, loss of consciousness for > 5 minutes, history of PTSD or current PTSD, and any other exclusionary criteria applied to the PTSD participant group.

## Neuropsychological Assessments

All participants completed a baseline and 12-month follow-up comprehensive neuropsychological evaluation assessing global cognition, sleep quality, executive functioning, episodic learning and memory, and mood. Measures were chosen from the DOD ADNI neuropsychological battery within the data set that pertains to specific areas relating to this study's research questions and hypotheses (see Table 1). The aforementioned chosen neuropsychological assessments for this study were as follows: Clinical Dementia Rating Scale (CDR; Morris, 1993), Auditory Verbal Learning Test (AVLT; Rey, 1964), Logical Memory (WMS-R – LM; Weschler, 2009), Boston Naming Test (BNT; Kaplan et al., 1983), Trail Making

Test (TMT; Reitan, 1958), Clock Drawing Test (CDT; Goodglass & Kaplan, 1983), Pittsburg Sleep Quality Index (PSQI; Buysse et al., 1988), Functional Assessment Questionnaire (FAQ; Pfeffer et al., 1982), and Geriatric Depression Scale – Short Form (GDS-SF; Sheikh & Yesavage, 1988).

**Table 1**

*Neuropsychological Assessments*

| Domain | Test | Description | Range |
|---|---|---|---|
| Global Cognition | Clinical Dementia Rating Scale | Measures cognitive status and stability | 0-3 |
| Learning and Memory | Auditory Verbal Learning Test | Measures verbal memory using multiple list-learning trials | 0-75 |
| | Logical Memory | Measures episodic memory using stories | 0-25 |
| Language | Boston Naming Test – 30-item Odd Version | Measures confrontation naming and lexical retrieval abilities | 0-30 |
| Information Processing | Trail Making Test – Part A | Measures speeded visual search and scanning | 0-150 |
| Executive Functioning | Trail Making Test – Part B | Measures cognitive flexibility in a number and letter set-shifting task | 0-300 |
| Visuo-Constructional | Clock Drawing Test | Measures visual constructional abilities | 0-5 |
| Sleep | Pittsburg Sleep Quality Index | Measures overall sleep quality and efficiency | 0-21 |
| Activities of Daily Living | Functional Assessment Questionnaire | Measures competency in completing complex daily tasks | 0-30 |
| Mood | Geriatric Depression Scale – Short Form | Measures symptoms of depression in older adults | 0-15 |

### *Clinical Dementia Rating Scale*

Overall cognitive functioning and detection of dementia symptoms were assessed utilizing the Clinical Dementia Rating Scale (CDR; Morris, 1993). The CDR consists of four versions with varying levels of semi-structured interviews with participants and informants. Each of the four versions produces a global score based on the following cognitive areas: memory,

orientation, judgment and problem-solving, community affairs, homes and hobbies, and personal care. Global CDR scores range from 0 (“no dementia”) to 3 (“severe dementia”) and are automatically calculated when entered into the electronic scoring system. The CDR’s internal consistency is .80 and deemed clinically valid in adequately detecting prodromal AD (Chapman et al., 2015; McDougall et al., 2020).

### *Auditory Verbal Learning Test*

Verbal memory function was assessed using the Auditory Verbal Learning Test (AVLT; Rey, 1964). The AVLT has five presentations of a 15-word list that are given followed by an attempted recall. There is a 15-word interference list (List B) that is then followed by a recall of the previous list (List A). Delayed recall and recognition are also tested utilizing the lists. The AVLT has a maximum score of 15 for each recall and 21 for the forced choice recognition test in which participants who score lower than 8/15 on recall and 10/21 on recognition demonstrate possible MCI or dementia. Raw scores are then transformed into *z*-scores based on normative data in which participants who score 1.5 standard deviations below the mean demonstrate impaired memory function. The AVLT has an internal consistency of .80 and regarding the validity, there is considerable statistically significant evidence that demonstrates the AVLT as a reliable construct and measurement of memory function (Magalhaes et al., 2012; Snow et al., 1988).

### *Logical Memory*

To measure episodic memory, the Logical Memory test from the Weschler Memory Scale–Revised (WMS-R – LM; Weschler, 2009) was utilized. LM is a free recall of one short story (Story A) that consists of 25 bits of information that will be elicited immediately after it is read aloud to the participant and again after a 30-minute delay. The LM for older adults has a

maximum score of 25, with higher scores indicating greater episodic memory and lower scores indicating difficulties with episodic memory. The LM has an internal consistency of .90 and considerable evidence has been demonstrated for LM as a valid measure of episodic memory (Soble et al., 2018).

### *Boston Naming Test*

Language functioning, specifically sensitivity to aphasia, was assessed utilizing the Boston Naming Test (BNT; Kaplan et al., 1983). The BNT contains 60 object drawings ranging in difficulty from commonly known (e.g., bed) to rarely known (e.g., abacus), and the participant will identify each object encountered. If participants are unable to name the object spontaneously, then the administrator can provide two types of prompting cues (one phonemic, one semantic). Scoring counts the number of spontaneously given correct responses, the number of cues given, and the number of responses following a phonemic and semantic cue. Discontinuation criteria were six consecutive failures, with or without a cue. The BNT has a maximum score of 60 representing intact language functioning with no indication of aphasia and lower scores indicating impaired language functioning with a possible aphasia. The BNT has an internal constancy ranging from $r$ = .78 to .96 across various studies (Pedraza et al., 2011). For the purposes of the DOD ADNI study, only the odd-numbered items from the full standard test were administered, with a maximum score of 30 being obtained (Weiner et al., 2017).

### *Trail Making Test*

Attention, cognitive flexibility, and executive functioning were measured using the Trail Making Test (TMT; Reitan, 1958). The TMT includes two versions, A and B, where participants are asked to connect 25 circles as fast but as accurately as possible. Version A is all numbers

that need to be connected in sequential order, while version B alternates between numbers and letters. Raw scores are calculated in seconds and then converted to a scaled score that translates to a *T*-score utilizing normative data. Participants who score 1.5 standard deviations below the mean based on the normative data demonstrate difficulties with attention, cognitive flexibility, and executive functioning. The TMT has an internal consistency of .77 and has demonstrated considerable statistically significant evidence for construct and concurrent validity (Stanczak et al., 1998).

### *Clock Drawing Test*

Constructional abilities were assessed using the Clock Drawing test (CDT; Goodglass & Kaplan, 1983). CDT contains two conditions where participants are first asked to draw the face of a clock with all the numbers and hands included, then asked to draw a copy of a model clock that is provided by the administrator. Five areas are scored including circular face, symmetry of number placement, the correctness of numbers, presence of two hands, and presence of two hands set to ten after eleven, with the highest score being a five and the lowest score being a zero. Higher scores indicate intact constructional abilities and lower scores demonstrate impairment in those abilities. CDT's internal consistency is 0.75 in accurately detecting patients with MCI or dementia (Cacho et al., 1999; Smedslund et al., 2017).

### *Pittsburg Sleep Quality Index*

To measure sleep quality, the Pittsburg Sleep Quality Index (PSQI; Buysse et al., 1988) was used. It is a self-report measure that contains 19 items assessing sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances (including nightmares), use of sedative-hypnotics, and daytime energy and dysfunction during the past month. The sum scores for

each of the seven components yields one global score, which ranges from 0-21 where higher scores indicate worse sleep. The PSQI's completion time ranges between 5-10 minutes. The PSQI has an internal consistency coefficient of .83 and a reliability coefficient of 0.83 (Backhaus et al., 2002; Buysse et al., 1988). The PSQI's validity has illustrated statistical significance that attests to the construct and concurrent validity (Buysse et al., 1988).

To calculate the global score for the PSQI, each of the seven component scores is obtained, each scored from 0 to 3. Initially, component scores needed to be transformed from the DOD ADNI response range of 1-4 to the PSQI scoring range of 0-3. Next, each component area was summed up to then be added together resulting in one global score. Component 1 was subjective sleep quality, question 6, and the responses were scored from 0 (very good) to 3 (very bad). Component 2 was sleep latency, questions 2 and 5a, and the responses were scored from 0 (< 15 minutes) to 3 (> 60 minutes) and 0 (not during the past month) to 3 (three or more times a week), respectively. Scores from questions 2 and 5a were summed together to create a total subscore and then recoded to be scored from 0 (subscore = 0) to 3 (subscores = 5-6), yielding a final component 2 score. Component 3 was sleep duration, question 4, and responses were scored from 0 (> 7 hours) to 3 (< 5 hours). Component 4 was sleep efficiency, questions 1,3, and 4, and was calculated by dividing the number of hours slept by the number of hours in bed multiplied by 100%.

The number of hours slept was question 4 and the number of hours in bed was calculated from responses to questions 1 (time going to bed at night) and 3 (time getting up in the morning). Sleep efficiency percentages were scored from 0 (> 85%) to 3 (< 65%). Component 5 score was sleep disturbance, questions 5b-5j, were scored from 0 (not during the past month) to 3

(three or more times a week). The scores from 5b to 5j were added together to create a total subscore that was scored from 0 (subscore = 0) to 3 (subscores = 19-27), yielding a final component 5 score. Component 6 was the use of sleep medication, question 7, and the responses were scored from 0 (not during the past month) to 3 (three or more times a week). Lastly, component 7 was daytime dysfunction, questions 8 and 9, and responses were scored from 0 (not during the past month) to 3 (three or more times a week) and 0 (no problem at all) to 3 (a very big problem), respectively. Scores from questions 8 and 9 were summed together to create a total subscore and then recoded to be scored from 0 (subscore = 0) to 3 (subscores = 5-6), yielding a final component 7 score. A global PSQI score was the sum of the seven component scores. There are five additional questions about bed partners, if applicable, but these questions are not included in the global score.

***Functional Assessment Questionnaire***

To assess a participant's engagement in daily living, a study companion or qualified partner was interviewed using the Functional Assessment Questionnaire (FAQ; Pfeffer et al., 1982) to discuss the participant's ability to complete ten complex activities of daily living. Some examples of the ten activities assessed include financial responsibilities, household chores, and personal care. The study companion or qualified partner rates each item with a score of 0 ("normal") to 3 ("dependent"). Scores are then summed up together (range 0-30) with a cutoff point of 9 which is dependent on three or more activities. The FAQ has an internal consistency of .72 and demonstrates excellent inter-rater reliability (Manero et al., 2014).

***Geriatric Depression Scale – Short Form***

Depression was assessed utilizing the Geriatric Depression Scale – short form (GDS-SF; Sheikh & Yesavage, 1988). It is a self-report scale designed to identify symptoms of depression

in the older adult population. The scale consists of 15 items in a yes or no type of response format based on how the individual has felt over the past week. A total greater than four in column A responses (i.e., the yes column) indicates depression. The GDS-SF has an internal consistency of .83 and regarding the validity, there is considerable statistically significant evidence that demonstrates the GDS-SF as a valid and reliable measurement of depression (Zalsman et al., 1998).

**Physiological Tests - Biofluids Collection**

***Cerebral Spinal Fluid (CSF)***

A lumbar puncture (LP) was utilized to collect CSF to assess CSF ptau and CSF amyloid plaque levels. An overnight fast with a minimum of 6 hours was necessary for the biofluid collections. The expected time for a collection was at 8 o'clock in the morning. A neurologist specifically trained in performing LPs completed this procedure for all participants. To administer this procedure, the neurologist inserts a small caliber atraumatic needle (22-gauge Sprotte needle) into the space between two vertebrae in the lower spine. The needle is moved carefully into the CSF-filled space surrounding the spinal cord. The CSF sample is collected by gravity into a labeled polypropylene container. The first one to two milliliters of CSF is discarded to clear any blood from the minor trauma. Participants are given a local anesthetic during the procedure to minimize pain and discomfort. A total of 20 milliliters (about ½ tablespoons) of spinal fluid is taken as a baseline for each participant in the study. Two milliliters are used for standard tests such as cell counts, glucose, and total protein. The remaining CSF is frozen upright in dry ice for 20 minutes before being packaged to be shipped via Federal Express overnight delivery to the Penn AD Biomarker Fluid Bank Laboratory (Weiner et al., 2014, 2017, in press). The CSF sample should be received by the Penn AD Biomarker Fluid Bank

Laboratory within 24 hours. Clinical Lab Reports will be faxed to each investigator within 48 hours of specimen receipt at the laboratory, indicating the levels of tau, p-tau, and amyloid (Weiner et al., 2014, 2017, in press).

Total tau, p-tau, and amyloid were measured using the highly automated Roche Elecsys immunoassays on the Cobas e601automated system (Weiner et al., 2014, 2017, in press). Amyloid 42 and amyloid 40 were measured in CSF using a validated ultra-performance liquid chromatography-mass spectrometer (UPLC-MS/MS; Weiner et al., 2014, 2017, in press). Total tau and p-tau were measured in CSF using a validated high-performance liquid chromatography-mass spectrometer (HPLC-MS/MS; Weiner et al., 2014, 2017, in press).

A Roche Elecsys immunoassay is an "in vitro diagnostic test for the quantitative determination of the total tau, p-tau, and amyloid beta in CSF and is intended to be used on Cobas e601 immunoassay analyzers" (Cobas, 2020, p. 1). Elecsys immunoassays are electrochemiluminescence immunoassays employing the quantitative sandwich principle where CSF samples are measured with a plate-based ELISA (Cobas, 2020; Schindler et al., 2018). The assay has a total duration of 18 minutes with two incubation periods utilizing a monoclonal IL-6-specific antibody and the Elecsys for amyloid beta 42 and 40 and total tau (Cobas, 2020; Schindler et al., 2018). Results are determined by "a calibration curve that is instrument-specifically generated by a two-point calibration and master curve provided by an e-barcode" on the CSF samples (Cobas, 2020, p. 2). Amyloid beta 42 has a measuring range of 200-1700 pg/mL and total tau has a measuring range of 80-1300 pg/mL (Cobas, 2020; Shaw et al., 2018). Cutoff levels for leaning toward an MCI are > 300 pg/mL for total tau, > 80 pg/mL for p-tau, and < 700 pg/mL for amyloid beta 42 and 40 (Cobas, 2020; Delmotte et al., 2021; Shaw et al., 2018).

### *DNA Sequencing*

A blood sample was collected for DNA sequencing and APOE genotyping at baseline for all study participants after passing the screening criteria for the DOD ADNI study (Weiner et al., 2014, 2017, in press). Whole blood was collected in a single 10 mL EDTA lavender top tube. APOE genotyping was done utilizing the 10 mL whole blood sample (Weiner et al., 2014, 2017, in press). DNA was extracted by Cogenics, Inc. from a 3 mL aliquot of EDTA whole blood sample to assess a participant's APOE genotype (Weiner et al., 2014, 2017, in press). Cogenics used a QIAmp DNA Blood Maxi Kit and the amplification refractory mutation system to extract the APOE genotype. "B lymphocytes were transformed with the Epstein-Barr virus to establish lymphoblastoid cell lines (LCLs)" and to enhance gene expression in which the "polymerase chain reaction amplification was followed by the HhaI restriction enzyme digestion" (Saykin et al., 2010, p. 267). Specific differential amplification setups for allele 2, allele 3, and/or allele 4 in addition to 4% Metaphor Gel and ethidium bromide staining were used to determine the presence or absence of haplotypes, i.e., the target allele (Saykin et al., 2010; Zhong et al., 2016).

## Design

This study was correlational and comparison, with a between-subjects design utilizing the DOD ADNI data set, which is established data compiled on Vietnam War veterans. Participants had completed neuropsychological self-report pen/paper questionnaires with a person administering the questionnaires, in-person and telephone interviews, underwent biofluid collection to assess their genetics and CSF levels, and completed neuroimaging via PET and MRI. However, for the purposes of this specific study, the PTSD and control group data will be

investigated, explicitly neuropsychological tests assessing cognition, sleep, mood, PTSD, and AD in addition to the biofluid collection of CSF ptau and amyloid plaque levels and APOE genotype.

***Data Analysis***

Descriptive statistics for demographics and biomarkers were calculated separately for the PTSD participant group and the Control participant group. A MANCOVA was performed to determine the difference between sleep index scores and AD pathology and the difference between neuropsychological tests. Significance was set a priori at $p < 0.05$ and all analyses were conducted using Jamovi Version 1.6.15.

***Power Analysis***

A power analysis utilizing G*power 3.1.9.7 was conducted to indicate the necessary number of participants required to detect a difference 80% of the time when one exists. The alpha fixed was at .05, the beta was fixed at .8, there were three covariates, and two groups. The G*power indicated that 150 participants are necessary to detect a difference within the data. The G*power is a more conservative approach to power analysis, and there are 179 participants in the sample, which is over what is needed. The more traditional and liberal approach is to have 30 people per group, and there is twice that amount per group. Additionally, the data includes highly sensitive biomarkers, including CSF biomarkers and neuropsychology tests that are sensitive to the impact of PTSD.

# Chapter III: Results

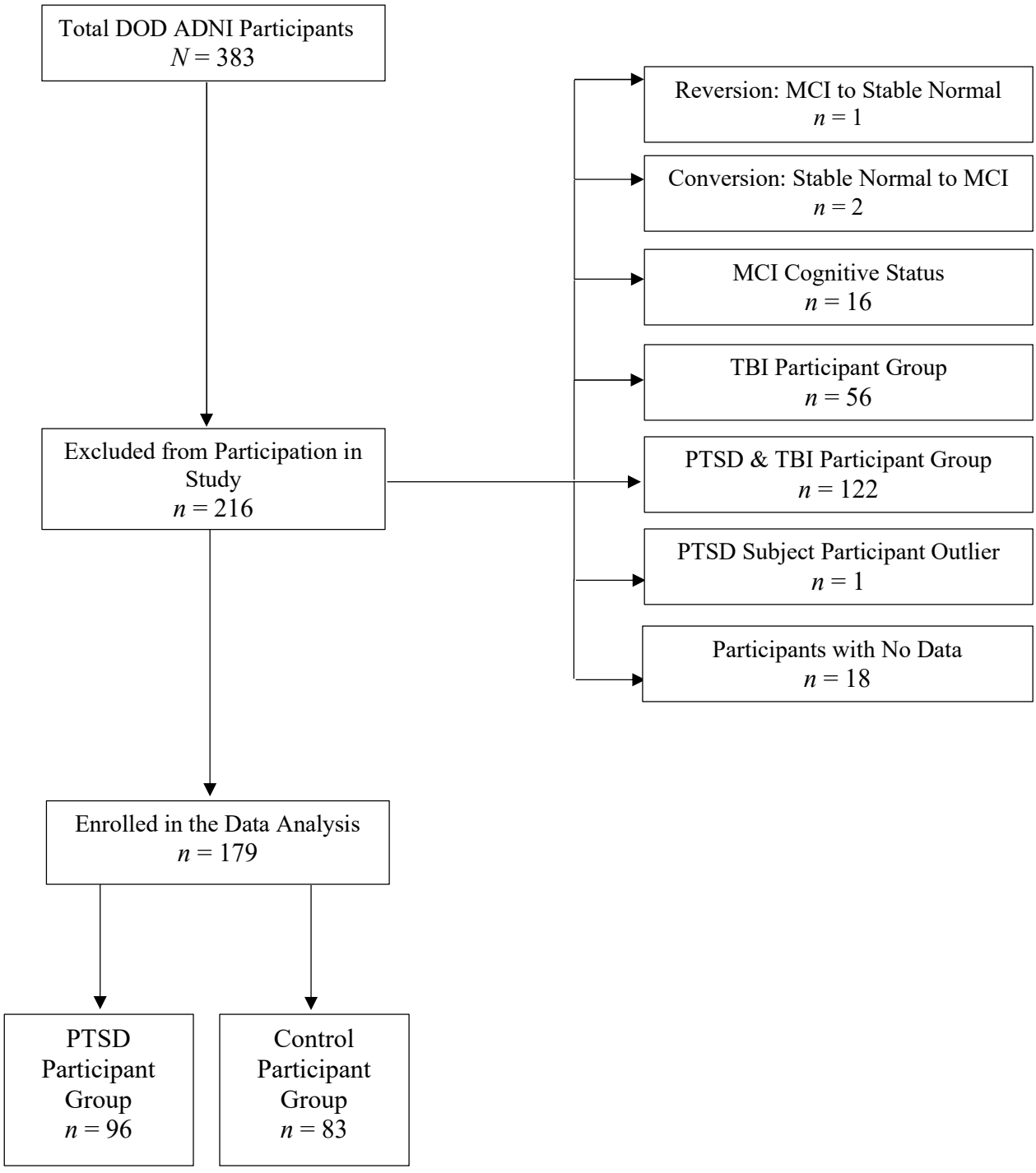
## Results

### *Demographic Characteristics*

Of the 383 participants who were eligible and completed the DOD ADNI's neuropsychological protocol and biofluids collection, 96 who were in the PTSD participant group and 83 who were in the Control participant group were included in this study. Therefore, a total of 179 participants comprised the descriptive statistics and data analysis. A total of 216 participants were excluded from this current study upon analyzing the participant data. Of the 216 participants, 19 were removed due to a reversion from MCI to stable normal cognition ($n$ = 1), conversion from stable normal cognition to MCI ($n$ = 2), or an MCI ($n$ = 16). Then, 56 participants were excluded due to being in the Traumatic Brain Injury (TBI) only group, and 122 participants were excluded due to being in the PTSD and TBI group. Next, one outlier was removed following the completion of the data analysis due to the possibility of this participant's scores skewing the results. Finally, 18 participants were not included in the data analysis due to having missing data as they did not complete any of the neuropsychological protocol or biofluid collections. See Fig. 1 for details on participant inclusion and exclusion criteria.

**Figure 1**

*Participant Inclusion and Exclusion Criteria*



At baseline, the overall participant pool was age 69 ± 5 years with an education level of 15 ± 2 years, 99% of the participants were male, 91% self-identified as non-Hispanic, and 80% self-identified as white. The characteristics for the entire participant pool and the between-group differences for the PTSD group and the control group are presented in Table 2. It is noted that the final 197 participants included in this study's data analysis had 19 participant data points missing from the demographic categories of age, gender, race, ethnicity, and education. Those participants chose not to answer about their demographic characteristics. Additionally, 78 participants' data was missing from the APOE status for AD genetic and biomarker characteristics. CSF ABETA, AB40, AB4240, total tau, and p-tau were also missing participant data that ranged from 126-128, which were not included in the AD genetic and biomarker characteristics.

**Table 2**

*Baseline Demographic Characteristics*

| | Total N=179 | PTSD n=96 | Control n=83 | *p*-value |
|---|---|---|---|---|
| *Demographic Characteristics* | | | | |
| Age, years | 69±5 | 68±3 | 71±5 | <0.001* |
| Gender, % male | 99 | 95 | 83 | 0.35 |
| Race, % white | 80 | 73 | 71 | 0.13 |
| Ethnicity % non-Hispanic | 91 | 83 | 80 | 0.06 |
| Education, years | 15±2 | 15±2 | 14±2 | <0.001* |
| *AD Genetic and Biomarker Characteristics* | | | | |
| APOE Status, % yes | 34 | 15 | 11 | 0.59 |
| CSF ABETA, pg/mL | 1225.22±545.46 | 1327.43±506.83 | 1114.73±570.68 | 0.08 |
| CSF AB40, pg/mL | 17206.62±5532.06 | 17320.00±5568.58 | 17084.05±5567.55 | 0.85 |
| CSF AB4240, pg/mL | 0.07±0.02 | 0.08±0.01 | 0.07±0.02 | 0.007* |
| CSF total tau, pg/mL | 221.83±85.18 | 214.11±71.07 | 229.97±98.24 | 0.42 |
| CSF p-tau, pg/mL | 19.50±9.06 | 18.26±7.62 | 20.85±8.20 | 0.21 |
| *Neuropsychological Assessments* | | | | |
| Clinical Dementia Rating Total | 0.08±0.35 | 0.13±0.39 | 0.02±0.27 | 0.03* |
| Auditory Verbal Learning Total | 48.14±11.18 | 46.59±9.42 | 49.57±12.50 | 0.13 |
| Auditory Verbal Learning Delayed | 12.50±2.22 | 12.52±2.33 | 12.48±2.13 | 0.92 |
| Auditory Verbal Learning List B | 4.76±1.66 | 4.49±1.53 | 5.00±1.74 | 0.07 |
| Logical Memory Total | 12.05±3.41 | 11.76±3.23 | 12.58±3.55 | 0.10 |
| Boston Naming Test Total | 28.02±2.02 | 27.41±2.26 | 28.59±1.58 | <0.001* |
| Trail Making A Total | 35.88±10.86 | 36.75±10.19 | 35.07±11.46 | 0.37 |
| Trail Making B Total | 90.82±40.98 | 94.00±40.55 | 87.96±41.45 | 0.40 |
| Clock Drawing Total | 4.51±0.68 | 4.42±0.75 | 4.59±0.60 | 0.14 |
| Pittsburg Sleep Quality Total | 7.77±3.20 | 8.32±3.48 | 7.11±2.60 | 0.01* |
| Functional Assessment Total | 0.62±1.33 | 0.94±1.65 | 0.21±0.51 | 0.04* |
| Geriatric Depression Total | 2.85±3.12 | 4.49±3.30 | 0.83±1.12 | <0.001* |

*$p < 0.05$; Values denoted as mean ± standard deviation or frequency; AD = Alzheimer's Disease; APOE = apolipoprotein E; CSF = cerebrospinal fluid

There were between-group differences for age ($x^2 = 4.80$, $p < 0.001$), education ($x^2 = 4.67$, $p < 0.001$), and ABETA 42/40 ratio ($x^2 = 2.76$, $p = 0.007$) in which the PTSD group has a lower age and higher education level as well as an elevated ABETA 42/40 ratio. ABETA and ethnicity were close to the *p*-value cutoff yet were still not statistically significant as were the rest of the demographic and AD genetic and biomarker characteristics.

A Mahalanobis distance was completed to look at multivariate normality. Since there were two groups being compared, the PTSD group and the control group, the data was split up to look at them individually. The cutoff for influential outliers was based on 5 degrees of freedom since there were 5 DVs, chi-squared = 20.52, $p <$. 001. There were three Mahalanobis distances that surpassed this cutoff in the PTSD participant group, Mahal = 38.00 (ID = 212520); Mahal = 24.14 (ID = 410221); Mahal = 20.56 (ID = 171027). Then Cook's distance was utilized to corroborate whether these three individuals were influential (Cook's > 1 is considered influential). There was only one influential outlier that met both criteria, Mahal = 38.00, Cook's = 2.93 (ID = 212520). There were no multivariate outliers in the Control participant group.

Additionally, in each of the statistical analyses for both of the research questions the variables of age, APOE status, and global depression scores were covariates that were controlled. To ensure that these three factors did not play a role in the results of the data analysis, they were controlled for when assessing the differences between each of the dependent variables in the PTSD and control groups.

***Research Question 1***

The first research question was: are there differences between sleep quality and AD pathology (i.e., CSF ptau and CSF amyloid beta) in a PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans? A one-way multivariate analysis of covariance (MANCOVA) was conducted to test the hypothesis that there would be one or more mean differences between sleep quality index scores and AD pathology (i.e., CSF tau, CSF p-tau, CSF amyloid beta, CSF amyloid beta 40, and CSF amyloid beta 42/40 ratio) in a PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans. A statistically significant MANCOVA effect was obtained, Pillai's Trace = 0.28, $F(6,61) = 3.89$, $p$

< 0.002. Furthermore, there was a significant effect of amyloid beta in the Control group, $F(1,66) = 8.38$, $p = 0.005$. There was also a significant effect of amyloid beta 42/40 ratio in the PTSD group $F(1,66) = 13.33$, $p < 0.001$. Additionally, there was a significant effect of sleep quality index scores in the PTSD group $F(1,66) = 14.33$, $p < 0.001$. MANCOVA results for research question 1 are presented in Table 3.

**Table 3**

*MANCOVA – Research Question 1*

| | Value | *F* | Sum of Squares | df | *p*-value |
|---|---|---|---|---|---|
| Cohort – Pillai's Trace | 0.28 | 3.89 | | 6,61 | 0.002* |
| CSF ABETA | | 8.38 | 1588310.96 | 1,66 | 0.005* |
| CSF AB40 | | 0.32 | 8432594.18 | 1,66 | 0.57 |
| CSF AB4240 | | 13.33 | 4347.97 | 1,66 | <0.001* |
| CSF total tau | | 0.63 | 91.81 | 1,66 | 0.43 |
| CSF p-tau | | 1.13 | 0.00 | 1,66 | 0.29 |
| PSQI Global Score | | 14.33 | 113.65 | 1,66 | <0.001* |

*$p < 0.05$

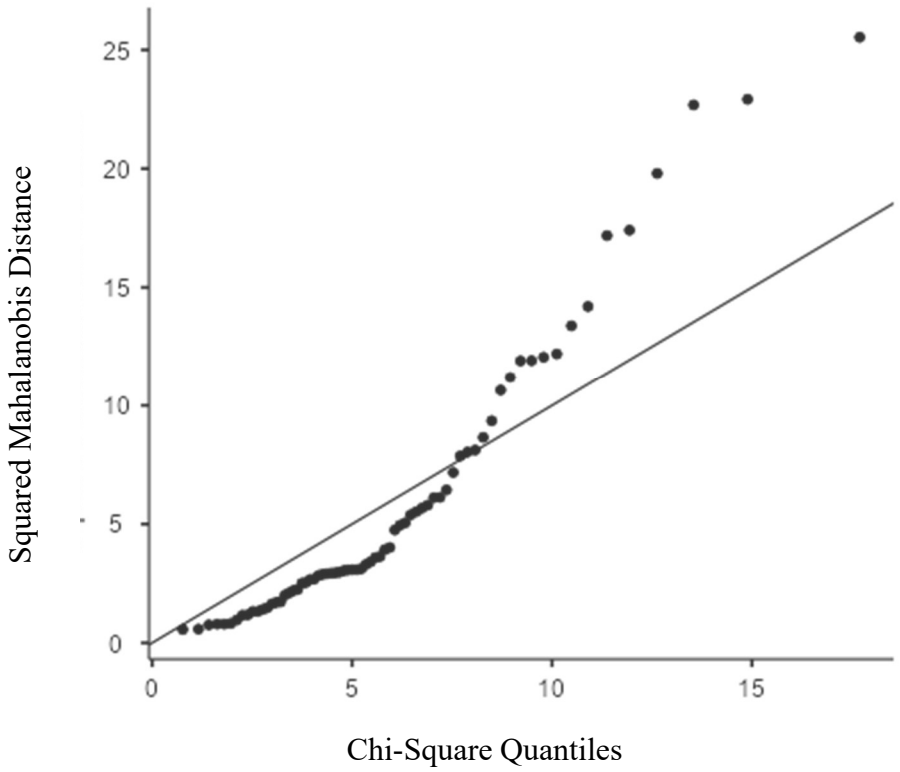
Therefore, the null hypothesis is rejected and concludes that there is a difference between sleep quality index scores and CSF amyloid beta in the PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans.

The dependent variables (i.e., CSF amyloid beta, CSF amyloid beta 40, CSF amyloid beta 42/40 ratio, CSF total tau, CSF p-tau, and PSQI global score) represent a relatively normal distribution. Both random sampling and independence of observations are assumed to be met. The Shapiro-Wilk is statistically significant for the dependent variable ($p < 0.001$) but there is a large sample size for each group ($N > 30$), so it is reasonable. Therefore, the normality assumption has been met. Levene's test has a *p*-value is that less than .05 ($p = .002$). Therefore,

the homogeneity of variance assumption has not been met because there is a difference between the two groups. See Fig. 2 for MANCOVA normality assumptions.

**Figure 2**

*Multivariate Normality Plot*




*Note.* Q-Q plot depicting the multivariate normality MANCOVA assumption for Research Question One.

***Research Question 2***

The second research question for this study was: Is there a difference between the neuropsychological tests in the PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans? A one-way multivariate analysis of covariance (MANCOVA) was conducted to test the hypothesis that there would be one or more mean differences between the neuropsychological assessments in a PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans. A statistically significant MANCOVA effect was

not obtained, Pillai's Trace = 0.16, $F(11,38) = 0.68$, $p = 0.75$. Furthermore, there is no significant effect of the Clock Drawing Test (CDT) [$F(1, 48) = 0.02$, $p = 0.89$], Trail Making Test A (TMT-A) [$F(1,48) = 0.10$, $p = 0.76$], Trail Making Test B (TMT-B) [$F(1,48) = 0.01$, $p = 0.94$], Boston Naming Test (BNT) [$F(1,48) = 0.29$, p = 0.59], Auditory Verbal Learning Test (AVLT) [$F(1,48) = 1.62$, $p = 0.21$], Logical Memory Test (LMT) [$F(1,48) = 2.62$, $p = 0.11$], and Clinical Dementia Rating Scale (CDR) [$F(1,48) = 1.93$, $p = 0.17$] in the PTSD group. However, there is a significant effect of the Functional Assessment Questionnaire (FAQ) in the PTSD group $F(1,48) = 4.43$, $p = 0.04$. MANCOVA results for research question 2 are presented in Table 4.

**Table 4**

*MANCOVA – Research Questions 2*

| | Value | *F* | Sum of Squares | df | *p*-value |
|---|---|---|---|---|---|
| Cohort – Pillai's Trace | 0.16 | 0.68 | | 11,38 | 0.75 |
| FAQTOTAL | | 4.43 | 4.49 | 1.48 | 0.04* |
| CLOCKSCOR | | 0.02 | 0.01 | 1,48 | 0.89 |
| COPYSCOR | | 0.12 | 0.02 | 1,48 | 0.74 |
| TRAASCOR | | 0.10 | 10.02 | 1,48 | 0.75 |
| TRABSCOR | | 0.01 | 7.93 | 1,48 | 0.93 |
| BNTTOTAL | | 0.29 | 1.12 | 1,48 | 0.59 |
| AVDELTOT | | 1.08 | 5.06 | 1,48 | 0.30 |
| LIMMTOTAL | | 2.62 | 27.27 | 1,48 | 0.11 |
| AVTOTB | | 0.94 | 2.72 | 1,48 | 0.34 |
| CDGLOBAL | | 1.93 | 0.10 | 1,48 | 0.17 |
| AVTOTAL | | 1.62 | 169.16 | 1,48 | 0.21 |

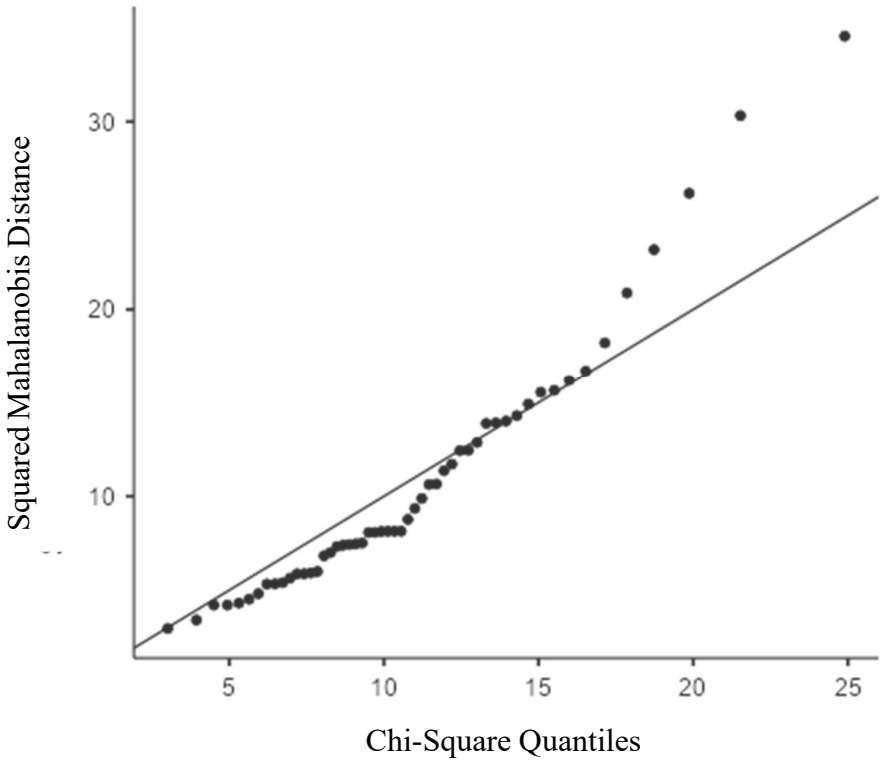
*$p < 0.05$

Therefore, the null hypothesis failed to be rejected and concludes that there is no difference between neuropsychological assessments in the PTSD group compared to the control group (i.e., no PTSD or TBI group) among Vietnam veterans.

The dependent variables (i.e., FAQ total, CDT scoring, CDT copy scoring, TMT-A scoring, TMT-B scoring, BNT total, AVLT delayed total, LM total, AVLT list B, CDR global score, and AVLT total) represent a relatively normal distribution. Both random sampling and independence of observations are assumed to be met. The Shapiro-Wilk is statistically significant for the dependent variable ($p < 0.001$) but there is a large sample size for each group ($N > 30$), so it is reasonable. Therefore, the normality assumption has been met. Levene's test has a *p*-value is that less than .05 ($p = .005$). Therefore, the homogeneity of variance assumption has not been met because there seems to be differences between the groups. See Fig. 3 for MANCOVA normality assumptions.

**Figure 3**

*Multivariate Normality Plot*




*Note.* Q-Q plot depicting the multivariate normality MANCOVA assumption for Research Question Two.

# Chapter IV: Discussion and Conclusions

## Findings

This study aimed to explore the differences between sleep and AD physiological biomarkers in Vietnam veterans with PTSD who have experienced combat-related trauma. Sleep quality, neuropsychological psychopathology, and AD pathology were investigated in a PTSD group and a control group among Vietnam Veterans within the DOD ADNI data set. It was hypothesized that there would be differences between sleep quality index scores and AD biomarkers (i.e., CSF tau/ptau and amyloid beta) as well as a difference between neuropsychological assessments between the two Vietnam veteran groups. There were significant differences, with a *p*-value less than 0.05, between groups on the sleep quality index scores, functional assessment scores, amyloid beta, and amyloid beta 42/40 ratio. Aside from sleep quality index scores on the PSQI and functional assessment scores on the FAQ, neuropsychological assessment scores on the Auditory Verbal Learning Test, Logical Memory, Boston Naming Test, Trail Making Test A & B, Clock Drawing Test, Clinical Dementia Rating Scale, and Geriatric Depression Scale yielded no significant differences, with a *p*-value greater than 0.05, between the PTSD group and the control group.

Sleep quality and day-to-day functionality were the only differences found for the neuropsychological assessments among the two Vietnam veteran groups, illustrating that individuals with PTSD may not differ cognitively from those without PTSD but possibly experience more difficulties with sleep and daily functioning. Furthermore, both sleep quality and day-to-day functionality could be poorer for individuals with PTSD compared to those

without PTSD. However, the sleep quality index scores were mildly different between the two Vietnam veteran groups while the daily functioning scores had a rather large difference between them. Therefore, findings from this study suggest that poor sleep quality could be possible in individuals with PTSD but daily functioning impairment seems to be a significant difficulty in people with PTSD.

It may be proposed that individuals with PTSD could experience a more impaired ability to complete activities of daily living (Krystal et al., 2017; Stark et al., 2015; Weiner et al. 2014, 2017, in press). Findings from this study supported past research regarding individuals with PTSD experiencing severe functional impairment, which contributes to extinction-resistant symptoms (Kang et al., 2018; Pace-Schott et al., 2015; Weiner et al., 2014; Werner et al., 2020). Corroborating with previous studies where PTSD is linked to worse global cognitive functioning and dementia-like symptoms, it appears that functional impairment could also be comorbid with PTSD demonstrating a dysfunction with activities of daily living (e.g., financial responsibilities, grocery shopping, etc.) and cognitive impairments (Bonfils et al., 2022; Weiner et al. 2014, 2017, in press). Yet, sleep quality results were not as drastic as expected given past research on PTSD and sleep disturbance's potential for disruption in cognitive, emotional, and biological functions (Kang et al., 2018; Pace-Schott et al., 2015; Weiner et al., 2014; Werner et al., 2020).

Alternatively to previous studies, it appears that the two Vietnam veteran groups did not have differences regarding other areas of cognitive functioning, indicating that the DOD ADNI participants in this study performed similarly cognitively. Compared to past research, results from this study did not illustrate executive dysfunction, attentional deficits, severe mood dysregulation, and memory difficulties as expected in a PTSD group (Krystal et al., 2017; Stark et al., 2015; Weiner et al., 2017). Overall, the PTSD group did demonstrate worse

neuropsychological scores compared to the control group; however, compared to standardized norms for a similar population based on age, gender, and education, the two Vietnam veteran groups performed in the average range for executive functioning (i.e., TMT-B) and attention and concentration (i.e., TMT-A) but performed in the low average to moderately impaired range for learning (i.e., BNT and AVLT), memory (i.e., LM), and spatial reasoning (i.e., CDT). The PTSD group did illustrate mild depression scores, while the control group did not report any symptoms of depression.

Differences were also found for CSF amyloid beta and CSF amyloid beta 42/40 ratio between the PTSD group and the control group. The PTSD group had worse amyloid beta 42/40 ratio scores and they were below the cutoff score for healthy individuals. Nevertheless, there was only a slight difference between the two Vietnam veteran groups regarding the CSF amyloid beta biomarkers. All of the other AD pathologies, including CSF tau, CSF p-tau, and CSF amyloid beta 40, were not different between the two veteran groups. Past research indicates that PTSD has comorbidities with other mental health disorders (e.g., Major Depression) and neurocognitive disorders like AD, and the findings in this study support individuals with PTSD having worse CSF amyloid beta levels compared to healthy individuals and reporting mild depression scores (Krystal et al., 2017; Stark et al., 2015; Weiner et al., 2014, 2017, in press).

Comparing the two Vietnam veteran groups, it appears that sleep quality, daily functional impairment, and AD pathology are different. Results from this study did demonstrate individuals with PTSD seem to experience daily functional impairment and lower CSF amyloid beta compared to a control group. However, since sleep quality only had a mild difference between the two groups, it is uncertain the exact extent sleep quality may be different in individuals with PTSD compared to those without PTSD. Previous research has suggested that poor sleep quality

could disrupt many bodily and daily functions, such as the glymphatic system and completing financial responsibilities (Drogos et al., 2016; Jessen et al., 2016; Ju et al., 2014). The glymphatic system occurs during sleep where amyloid beta and other neurotoxins are filtered out through the CSF, and amyloid beta and tau biomarkers are the primary indicators for MCI and AD (Drogos et al., 2016; Jessen et al., 2016; Ju et al., 2014; Weiner et al., 2014, 2017, in press). Additionally, sleep aids in optimal brain health to maintain concentration and active response time which is beneficial in completing daily tasks effectively (National Institute of Neurological Disorders and Stroke, 2006; Pace-Schott et al., 2015).

Compared to previous research, findings from the current study only mildly emphasized sleep disturbance and the potential impact on overall biopsychosocial functioning like the glymphatic system (Jessen, Munk, Lundgaard, & Nedergaard, 2016; Drogos et al., 2016; Ju et al., 2014). Disruptions in sleep potentially result in poor waste elimination and build-up of amyloid beta and tau/p-tau in the brain (Drogos et al., 2016; Jessen et al., 2016; Ju et al., 2014). Exploring how poor sleep quality impacts the levels of CSF amyloid beta in individuals with PTSD could provide further knowledge on the development and progression of AD (Drogos et al., 2016; Jessen et al., 2016; Ju et al., 2014; Weiner et al., 2014, 2017, in press). Thus, the current study provides an opportunity to investigate the role sleep quality may have in AD pathogenesis and whether higher rates of sleep disturbance in PTSD are etiologically linked to the higher risk of AD in individuals with PTSD.

**Limitations**

Although there were statistical findings in this study, there were some limitations that should be noted such as the missing participant data and the lack of female representation in the groups. There was a large proportion of missing participant data within the sample pool.

The largest missing data was in the AD biomarkers and pathology characteristics, which were one of the primary variables investigated and statistical findings reported in this study. It appears the missing AD biomarkers may not have given consent during the biofluid collection phase of the DOD ADNI longitudinal study. Therefore, it is uncertain how these participant's results could have impacted the current study's findings. However, a majority of the missing data from the AD biomarkers and pathology were in the PTSD participant group. It may be likely that individuals with PTSD may struggle to complete certain tasks due to past trauma symptoms or could be more defensive due to their diagnosis compared to the control participant group. Both the missing data and non-missing data were comparable in demographic characteristics, which was aided by the matching processes when completing the screening portion of the research study.

The sample size was adequate and was greater than the necessary sample size to detect a difference. However, the sample itself had some limitations that could have impacted the results of the study. There was only one female included in the participant data and the population was predominantly white males with 80% of the participant poll identifying as white/Caucasian. Therefore, these findings can only be summarized and applied to white males within the veteran population, which leaves unanswered questions regarding females' and other minority groups' sleep quality and its correlation to AD pathologies and biomarkers.

**Recommendations**

Findings from this study could expand our understanding of functional impairment in individuals with PTSD and its importance in overall biopsychosocial functioning. These findings provide additional research that PTSD has comorbid symptoms with other mental health disorders such as AD and depression, which could have lasting effects on the brain and overall

well-being of the individual. The DOD and Veteran healthcare systems around the United States could use this study to further investigate various evidence-based psychotherapies that may help with functional impairment in veterans with PTSD. Therefore, findings from this study could aid in the development of effective interventions and strategies that promote effective daily functioning that could aid individuals with other mental health or neurocognitive disorders.

This study demonstrated that sleep is still being investigated in regards to its functioning and impact on an individual's overall well-being, but it is universally known that it is primary in the survival of all people. This study added the possibility that sleep, especially quality sleep, may play a larger role in the maintenance of biopsychosocial health in people with PTSD but it continues to remain uncertain at this time. Therefore, it may be helpful if future studies investigated the assessment of sleep quality utilizing either collateral information from reliable partners or conducted polysomnography instead of a self-report questionnaire. The current study excluded the collateral portion of the PSQI; therefore, further research could provide an additional understanding of sleep quality in individuals with PTSD. Also, it may be beneficial for future research to explore effective strategies for functional impairment as that was found to be significantly different in the PTSD group. Past research has demonstrated that individuals with AD experience irreversible functional impairment as the disease progresses; however, the same may not be true for people with PTSD. Therefore, further investigating functional impairment in PTSD and strategies to aid in its negative effects could be beneficial for understanding its progression and treatment outcomes.

Since the current study utilized only Vietnam veterans, future studies could use veteran participants from recent wars (e.g., Afghanistan or Iraq) that could include a more culturally

diverse population compared to the Vietnam veteran population used in this study. There was only one female participant in the entire DOD ADNI data set; thus, female representation in the participant sample in future studies would be ideal in order to assess sleep quality, daily functioning, and AD biomarkers and pathologies differences within women. Additionally, the DOD ADNI data set was predominantly white, thus, the sample in this study did not include a large portion of other races or ethnicities. It is presumptuous to generalize the current study's findings to an entire population due to the predominantly white male-oriented participant pool. Therefore, investigating similar factors within a larger and more culturally diverse participant sample would provide a better understanding of sleep quality, daily functioning, and AD pathology in veterans with PTSD.

This study also had missing data for neuropsychological assessments and biofluid collections, primarily in the PTSD group. One plausible theory for the lack of data in the PTSD group is the challenging aspect of the tasks, which may be too overwhelming for people diagnosed with PTSD. Thus, future research may benefit from integrating mindfulness or relaxation strategies to reduce emotional discomfort for individuals with PTSD to promote higher participation rates in challenging aspects of research (e.g., physiological tests, biofluid collections, or functionality questionnaires).

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