The Australian Imaging, Biomarkers and Lifestyle study of ageing (AIBL) Veterans study - Post traumatic stress disorder and risk of Alzheimer's disease

Alby Elias

ORCID 0000-0002-7494-1028

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Department of Psychiatry
Faculty of Medicine, Dentistry and Health Sciences
THE UNIVERSITY OF MELBOURNE

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Abstract

Background

Epidemiological studies have suggested an association between posttraumatic stress disorder (PTSD) and Alzheimer's dementia in Vietnam veterans. These studies, however, did not use biomarkers of Alzheimer's disease (AD) to either confirm the diagnosis or assess the relative prevalence of AD pathology when investigating the risk of dementia in PTSD.

Aim

This study aimed at testing the hypothesis that Vietnam veterans with combat PTSD have an increased risk for Alzheimer's disease in comparison with veteran controls as measured by biomarkers such as amyloid-β (A-β) and tau retention in the brain and regional hypometabolism and atrophy.

Method

Vietnam veterans with a history of PTSD as defined by the Clinicians-Administered PTSD scale (CAPS) score of 40 or above and veteran control subjects as defined by CAPS score of 30 or below and with no current clinical evidence of dementia participated in the study. Outcome measurements were A-β and tau deposition and regional brain metabolism and volumetry. A-β and tau burden was estimated by the Specific Uptake Value Ratio (SUVR) of ^{18}F-florbetaben, and ^{18}F-AV-1451 respectively. ^{18}F-fluorodeoxyglucose positron emission tomographic (PET) scan measured regional brain metabolism, and 3-Tesla T1 MP-RAGE Magnetic Resonance Imaging (MRI) estimated regional volumetry. Comprehensive neuropsychological battery measured cognitive function.

Results

Between March 2014 and June 2017, 83 male Vietnam Veterans (controls, n=30, CAPS=4; lifetime PTSD, n=53, CAPS=73.95; lifetime and current PTSD, n=30, CPAS=52.50) completed the assessments. There was no significant difference between the two groups in the uptake of ^{18}F-florbetaben, ^{18}F-AV-1451 or ^{18}F-fluorodeoxyglucose, or regional brain volumetry. The rate of apolipoprotein E e4 allele was not significantly different between the groups. Compared with control

veterans, the PTSD participants had a significantly lower level of education, predicted premorbid Intelligent Quotient (IQ), and total intracranial volume and higher depression rating score. The Montreal Cognitive Assessment (MoCA) score was significantly lower in the PTSD group than in controls. The group differences in (MoCA) did not remain, however, when adjusted for premorbid IQ or depression in a multilinear regression model analysis.

Conclusions

Posttraumatic stress disorder is not associated with an increased prevalence of biomarkers of Alzheimer's disease. The proxy measures of cognitive reserve, a factor that may delay the onset of Alzheimer's dementia, were relatively low in subjects with PTSD, and this may explain the previously reported higher incidence of dementia in subjects with PTSD compared to age-matched controls.

Declaration

I, Alby Elias, declare that this thesis comprises only my original work towards PhD except where indicated in the preface; due acknowledgement has been made in the text to all other materials used; and the thesis is fewer than the maximum word limit in length, exclusive of tables, maps, bibliographies and appendices as approved by the Research Higher Degree Committee.

Alby Elias

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Role of the candidate

The candidate took part in consenting sessions, collected demographic information (age, gender, educational level, handedness, and age of entry to military), detailed medical history (history of stroke, hypertension, diabetes mellitus, cardiac diseases, sleep apnea, health habits such smoking, family history of dementia and any other health conditions, and medications), conducted a psychiatric evaluation (administration of CAPS, substance use screening, Pittsburgh Sleep Index Questionnaire, and Combat Exposure Scale) and screening for MRI safety particularly metal implants, contacted local hospitals for information on surgical device implants, provided medical cover during the acquisition of scans, and took part in the visual reading of PET scans. The candidate analyzed the data using statistical tests. The candidate then generated discussion based on the interpretation of the findings.

Abbreviations

A-β	Amyloid β (β Amyloid)
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AIBL Study	Australian Imaging Biomarkers and Lifestyle Study
APOE e4	Apolipoprotein E e4
CAPS	Clinician-Administered PTSD Scale
CBF	Cerebral blood flow
CPAP	Continuous Positive Airway Pressure
CR	Cognitive reserve
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDG	Fluorodeoxyglucose
HPA	Hypothalamo-pituitary-axis
ICD	International Classification of Diseases
IQ	Intelligent Quotient
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NFT	Neurofibrillary tangles
OSA	Obstructive sleep apnoea
PART	Primary age related tauopathy
PET	Positron Emission Tomography
PiB Compound	Pittsburgh B Compound
PTSD	Posttraumatic stress disorder
SUVR	Specific Uptake Value Ratio
TBI	Traumatic Brain Injury

TICV	Total Intracranial Volume
WTAR	Wechsler's Test of Adult Reading

Publications and presentations

1. American Psychiatric Association Annual Meeting. Atlanta. May 2016.
2. Alzheimer's Association International Conference. London. July 2017.
3. Alby Elias, Tia Cummins, Fiona Lamb, Regan Tyrrell, Vincent Dore, Rob Williams, Jeffrey V Rosenfeld, Malcolm Hopwood, Victor L Villemagne, Christopher C Rowe. Amyloid-β, Tau, and 18F-Fluorodeoxyglucose Positron Emission Tomography in Posttraumatic Stress Disorder. J Alzheimer's Dis. 2020; 73 (1), 163-173.
4. Alby Elias, Christopher Rowe, Malcolm Hopwood. Risk of dementia in posttraumatic stress disorder. Journal of Geriatric Psychiatry and Neurology. 2020 Sep 10. doi: 10.1177/0891988720957088 (Ahead of print).
5. Alby Elias, Tia Cummins, Fiona Lamb, Regan Tyrrell, Vincent Dore, Rob Williams, Jeffrey V Rosenfeld, Malcolm Hopwood, Victor L Villemagne, Christopher C Rowe. Risk of Alzheimer's Disease in Obstructive Sleep Apnea Syndrome: Amyloid- β and Tau Imaging. Journal of Alzheimer's Disease 66 (2018) 733–741.

Chapter 1

Introduction

Alzheimer's disease (AD), with a relentlessly expanding geriatric population, is one of the major public health problems in the modern era. Leading to a progressive decline in the quality of life, institutionalization, and death, Alzheimer's dementia has an enormous impact on all aspects of human life. Although multiple cognitive domains are affected in Alzheimer's dementia, the loss of memory is the prototype symptom. Memories form the only road to man's past. Interwoven with imagination, memories provide the gateway to the future. Upon progressive loss of memories, the past sinks deeper and deeper into oblivion, and imagination becomes impoverished. Families of patients with dementia become overwhelmed with grief as their loved ones lose identity; care providers confront a daunting endeavour while treating the disease; the social and governmental agencies face an increasing demand for caring of perhaps the most vulnerable individuals. Great strides have been made towards the understanding of the disease mechanism and possible prevention of the disease. The scientific community has yet to see a silver lining in the therapeutics of AD.

The socioeconomic consequences of AD are at a staggering scale (Hurd, Martorell, Delavande, Mullen, & Langa, 2013; James et al., 2014; Nichols et al., 2019). As a dominant or sole pathology, AD accounts for an estimated 60% of dementia ("2019 Alzheimer's disease facts and figures," 2019; Hebert, Weuve, Scherr, & Evans, 2013). In the United States, one person develops Alzheimer's disease every 65 seconds, and this figure is projected to double by 2050 ("2018 Alzheimer's disease facts and figures," 2018; "2019 Alzheimer's disease facts and figures," 2019). The increasing prevalence of dementia arises from the demographic transition that formed an important chapter in human history (Figure 1).

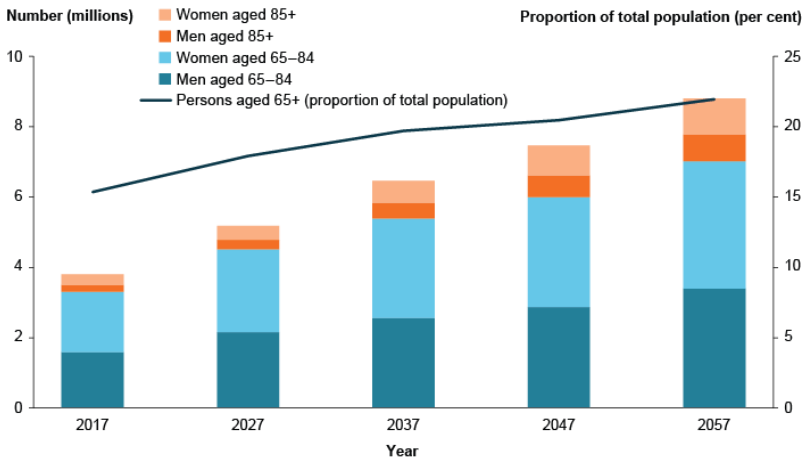

Figure 1. Aging Australian population. Data from the Australian Institute of Health and Welfare 2019.

(https://www.aihw.gov.au/reports/australias-welfare/australias-welfare-2017-in- /contents/ageing-and-aged-care)

Alzheimer's disease is now conceptualized as a distinct pathological process, manifesting in the initial preclinical phase, later mild cognitive impairment (MCI), and eventual dementia. Incurable as it is, dementia in AD results from a neurodegenerative process and follows a downhill trajectory once the syndrome has set in. The corollary is that therapeutic interventions in AD must be based on the identification of risk factors either before the disease process begins or in the early stage to prevent or delay the onset of dementia. The concept of risk factor identification is thus a very major focus in current dementia research. Several risk factors associated with AD have been identified, some are amenable to risk reduction, and others are non-modifiable. Age and genetic abnormalities are arguably the strongest risk factors for AD and are non-modifiable (Jorm & Jolley, 1998; Lindsay et al., 2002; Wisniewski, Wisniewski, & Wen, 1985). Indeed, the multifactorial disease model, as it is used for several diseases, also applies to the late-onset AD. Cardiovascular diseases, head injury, sleep disorders, and psychiatric disorders are implicated in the development of AD and are modifiable or preventable risk factors (Dams-O'Connor et al., 2013; de Bruijn & Ikram, 2014; Kivipelto et al., 2001; Mander, Winer, Jagust, & Walker, 2016; Saez-Fonseca, Lee, &

Walker, 2007; Xue et al., 2015). While the above factors increase the risk, education, premorbid intellectual capacity, bilingualism, and cognitive engagement decrease the risk of dementia (Alladi et al., 2013; Perani et al., 2017; Sando et al., 2008a; Wilson et al., 2007; Wilson et al., 2002).

Posttraumatic stress disorder (PTSD) has recently emerged as a risk factor for dementia and has become a focus for research in cognitive science. Posttraumatic stress disorder is a common and frequently a chronic disorder that develops after a person had exposure to actual or threatened death, serious injury, or sexual violence in one or more of the following ways: direct experience, witnessing the trauma, learning about the trauma or exposure to the aversive aspects of the trauma in the aftermath (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). Exposure to traumatic events is ubiquitous in human life. While the intensity of trauma varies, 75% of the general population experience one or more traumatic events that have the potential to cause PTSD and a quarter to a third of those with traumatic exposure develop PTSD (Green & Lindy, 1994; Yehuda, Southwick, & Giller, 1992). The classical triad of PTSD includes re-experiencing the trauma through intrusive memories or flashbacks, avoidance behaviors, and heightened arousal (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013).

Posttraumatic stress disorder is more common in veterans than in the general population (Dohrenwend et al., 2006; Hoge, Auchterlonie, & Milliken, 2006; Hoge et al., 2004; Seal, Bertenthal, Miner, Sen, & Marmar, 2007; Vasterling et al., 2002). Considering the nature of trauma from war zones, a higher incidence of PTSD in veterans is expected. Combat-related PTSD has been extensively studied. The history of PTSD is closely related to the Vietnam War. Approximately 700,000 Vietnam veterans reported intense psychological trauma (Crocq & Crocq, 2000). One of the characteristic features of the Vietnam War was the persistence of war-related psychological symptoms and the emergence of a delayed syndrome, which was known as Post-Vietnam syndrome (Crocq & Crocq, 2000). Such a delayed but perpetual form of psychological response was later classified as posttraumatic stress disorder and included in the DSM-III in 1980.

Memory disturbance is a feature of PTSD and its diagnostic criteria (American Psychiatric Association, 2013). Research into the cognitive function in PTSD commenced in the early 1990s. Thereafter several studies have demonstrated cognitive impairment in combat-related PTSD (Bremner et al., 1993; Johnsen, Kanagaratnam, & Asbjornsen, 2008; Vasterling, Brailey, Constans, & Sutker, 1998; Vasterling et al., 2002). Meanwhile, commensurate with the cognitive dysfunction in PSTD, both structural and functional neuroimaging studies of patients with PTSD have shown abnormalities in the hippocampus, amygdala, and anterior cingulate cortex. Meta-analyses of volumetric studies have revealed a reduction in volumes of the hippocampus and anterior cingulate cortex in subjects with PTSD (Bromis, Calem, Reinders, Williams, & Kempton, 2018; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015). The hippocampus is involved in encoding and retrieving sequences of events that compose episodic memories (Hasselmo, Wyble, & Wallenstein, 1996). According to functional imaging studies, a pattern of abnormality -hyperactivity in the amygdala and hypoactivity of the cingulate cortex- is appreciable in PTSD (Bremner et al., 1999; Lanius et al., 2001; Rauch et al., 2003; Semple et al., 2000; Shin et al., 2001). Further research showed an accelerated formation of amyloid β (A-β) and tau, the specific biomarkers of AD in animal models of PTSD (Carroll et al., 2011; Justice et al., 2015).

The above findings sparked a series of epidemiological studies that investigated the association between PTSD and dementia in Vietnam veterans. These studies have shown an increased incidence of dementia including Alzheimer's dementia on clinical criteria in patients with PTSD compared with controls (Flatt, Gilsanz, Quesenberry, Albers, & Whitmer, 2018; Mawanda, Wallace, McCoy, & Abrams, 2017; Meziab et al., 2014; Qureshi et al., 2010; Wang et al., 2016; Yaffe et al., 2010). The relationship between PTSD and dementia has thus become a flourishing field of research. Despite the functional and structural abnormalities of the brain structures involved in cognition, the epidemiological studies lacked the neuroimaging or other biomarkers data (Barnes et al., 2012; Mawanda et al., 2017; Qureshi et al., 2010). Efforts at the evaluation of human

biomarkers of Alzheimer's disease, especially A-β and tau, in PTSD have been limited, leaving a gap in this field.

Until recently, an autopsy was the only method to visualize A-β and tau deposition in the brain. Enabling *in vivo* detection of A-β and tau using specific radioactive ligands, amyloid and tau Positron Emission Tomography (PET) represented a breakthrough in AD research (Klunk et al., 2004; Pike et al., 2007; Rowe & Villemagne, 2011). Amyloid and tau imaging studies have identified AD-related pathology in the preclinical phase and set the stage for clinical trials prior to symptom onset. ^{18}F-Fluorodeoxygluocse (FDG) PET estimates brain glucose intake, a proxy measure of brain activity. The advances in nuclear imaging modalities have been rapid and have illuminated the understanding of risk factors for AD pathology. These imaging techniques have the potential to fill the gap between an increased incidence of dementia in PTSD and the underlying pathology of AD. The implication of research into the relationship between AD and PTSD lies in the early detection of risk factors and their modification. Posttraumatic stress disorder is a treatable psychiatric disorder. Also, the presence of PTSD may indicate a high risk of AD, and patients with PTSD may benefit from early detection with the help of a heightened screening process so that the onset of dementia can either be prevented or delayed. Therapeutic interventions and preventive strategies are likely to yield satisfactory outcomes only in the early stages of the disease.

Vietnam veterans are likely to be in an age range matching the preclinical stage of AD and carry biomarkers of AD if they are on the path to Alzheimer's disease. This cohort is therefore well suited for the investigation of the question of increased prevalence of preclinical AD in PTSD. According to Australian data, the lifetime prevalence of PTSD among Vietnam veterans is 21%, and the point prevalence is 16% (O'Toole et al., 1996). This study aimed at investigating the prevalence of biomarkers of AD in PTSD against the background of increased dementia incidence in PTSD.

Chapter 2

Review of Literature

2.1 Alzheimer's Disease

2.1.1 Introduction

2.1.1.1. Disease and syndrome

A disease is a pathological process with its characteristic manifestations, course, and aetiology whereas a syndrome is a constellation of symptoms and signs that indicate a specific condition for which a direct cause is not necessarily identified (Calvo, Karras, Phillips, Kimball, & Wolf, 2003; Smith, 2002). The disease manifests as a syndrome, but a syndrome may have diverse underlying disease processes. A syndrome is the clinical stage of the disease. For example, Alzheimer's disease clinically manifests as a syndrome of dementia at a particular stage in its course. A dementia syndrome can, however, be caused by disparate disease processes such as diffuse Lewy body disease, vascular disease, Pick's disease, normal pressure hydrocephalus, and several others. The World Health Organization defined dementia as a syndrome due to a disease of the brain, usually of a chronic or progressive nature, in which there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment (World Health, 2004). Dementia arising from Alzheimer's disease (AD) is known as Alzheimer's dementia.

2.1.1 Dementia: prevalence and incidence

Prevalence refers to the proportion of people who have a specific disease in a defined population at a given point of time (Rothman, 2012). In common use, this is point prevalence in

contrast to 12-month prevalence, which is the proportion of individuals who had the illness in a given 12-month period (Figure 2). Lifetime prevalence is the proportion of individuals who had the disease at any time in life. The prevalence of dementia may vary according to the criteria of symptoms used, the geographical location, and the age groups studied. The age-standardized prevalence of dementia in the population aged above 60 years is 5%-10% ("2019 Alzheimer's disease facts and figures," 2019; Prince et al., 2013). The prevalence is 0.9 % in the age group 60-64 years; 1.5% in the age group 65-69; 3.6% in the age group 70-74 years; 6.0% in the age group 75-79 years; 12.2% in the age group 80-84 years; 24.8 % the age group above 85 years (Prince et al., 2013). The prevalence varies according to the geographical regions, with the lowest rate in Africa and the highest in Latin America (Prince et al., 2013). Trends in the dementia prevalence suggest lower rates in developing countries and higher rates in developed countries. This may reflect increased screening processes and detection rates in developed countries. Whereas the prevalence is 6.9 in North America, it is 6.4 in Australasia and 6.2 in Europe (Prince et al., 2013). A systematic review and meta-analysis of studies conducted in Europe between 1993 and 2018 have shown age and gender-adjusted prevalence of 7.1% (Bacigalupo et al., 2018).

Incidence is a measure of the probability of occurrence of a disease that develops during a specified period in a defined population. The epidemiological data of dementia are derived mainly from prevalence studies. Incidence studies are much less common because of the requirement of a considerable amount of resources (Fiest et al., 2016). For this reason, a meta-analysis is used to pool the data and estimate the dementia incidence. According to a meta-analysis, the annual incidence of dementia among individuals aged above 60 years was 4.1 per 1000 in the community setting (Fiest et al., 2016). As in the case of prevalence, there are variations in the incidence with age and geographical areas. An earlier meta-analysis reported a lower incidence of dementia in the United States (U.S), 2.4 among individuals of 65 to 69 years of age (Jorm & Jolley, 1998). The incidence exponentially increased to 27.5 among individuals aged between 85-89 years. In Europe, the incidence among individuals above 90 years was very high, 66.1 suggesting no plateauing with advancing age (Jorm & Jolley, 1998). A lower incidence has been reported in this age group later

(Corrada, Brookmeyer, Paganini-Hill, Berlau, & Kawas, 2010). The incidence increased from 12.7% per year in the 90–94-year age group to 21.2% per year in the 95–99-year age group. The highest incidence was recorded in centenarians, 40.7% per year.

There is a dearth of national studies that systematically surveyed dementia prevalence and incidence in Australia. The usual solution was to use the data derived from meta-analyses and apply them to the population data. However, given the reduction in dementia risk factors, for instance, cardiovascular risk factors in Australia, the relevance of the overseas data to the Australian population is limited (Australian Government 2020). A recent study has utilized administrative linked database to estimate dementia incidence in Australia (Welberry, Brodaty, Hsu, Barbieri, & Jorm, 2020). The incidence rates increased from 0.4 cases per 1000 person years in the 55–59-year group to 79 cases per 1000 person years in those aged 90 years or older.

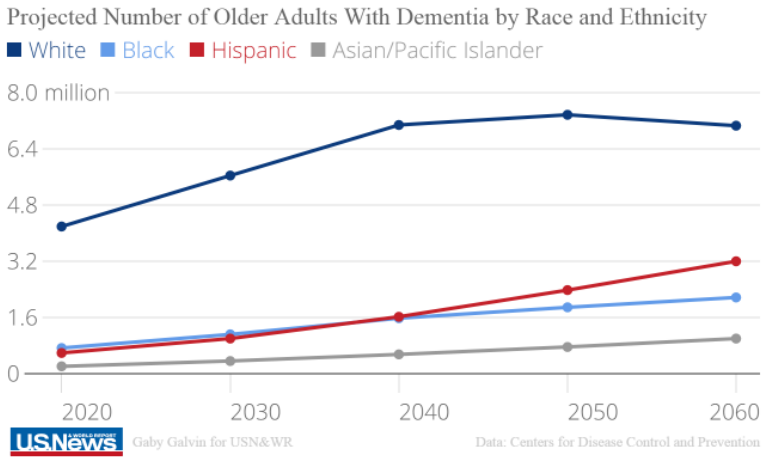

Figure 2. The projected magnitude of dementia. Source: Centers for Disease Control and Prevention, Atlanta, Georgia. U.S.A.

The commonest form of dementia arises from Alzheimer's disease (Clarfield, 2003; Fratiglioni et al., 2000; Schoenberg, Anderson, & Haerer, 1985). In the United States, 50-70% of all dementias were due to AD (Esiri, Nagy, Smith, Barnetson, & Smith, 1999; Katzman, 1986;

Kokmen, Beard, Offord, & Kurland, 1989). In Europe, as of 2000, its prevalence was 4.4% in people aged above 65 years (Lobo et al., 2000). The U.S data showed a prevalence of Alzheimer's dementia of 11% in those aged above 65 years and 32% above 85 years (Hebert et al., 2013). According to a meta-analysis, the prevalence of dementia due to AD among individuals aged above 65 years was 40.2 per 1000 persons (Fiest et al., 2016). The annual incidence of Alzheimer's dementia was 0.4% in the age group 65-69 years, 1.0% in the age group 70-74 years, 2.0% in the age group 70-75 years, 3.3% in the age group 80-84 years, and 7.6%-8.4% in individuals aged above 85 years (Hebert et al., 2013; Rajan, Weuve, Barnes, Wilson, & Evans, 2019). The pooled annual incidence in the age group above 60 years was 34.1 per 1000 persons in the community (Fiest et al., 2016).

2.1.1.2.1. Recent trends: Is dementia incidence declining?

For reasons that remain largely inexplicable, recent incidence and prevalence studies have shown declining age-adjusted rates of dementia (Langa et al., 2008; Matthews et al., 2013; Prince et al., 2016; Prince et al., 2013; Satizabal et al., 2016). The first report, published from the United States in 2008 (Langa et al., 2008), showed a diminishing rate of cognitive impairment from 1993 to 2002 in people aged over 70 years. A population-based cohort study, popularly known as the Rotterdam study, compared dementia incidence between a subcohort of subjects aged 60-90 years that started in the year 1990 and a subcohort of similar age that began in 2000 (Schrijvers et al., 2012). The incidence was insignificantly lower in the 2000 cohort for all age strata. The mortality was lower in the 2000 subcohort, which also showed larger brain volumes. The Medical Council Research Cognitive Function Aging Study (CFAS) estimated the prevalence of dementia during 2008-2011 in England and Wales. It found a lower prevalence (6.5%) than what was expected (8.3%) from the 1989-1994 prevalence (Matthews et al., 2013). A recent study assessed dementia incidence over three decades and observed a steady decline in the age and sex-adjusted cumulative hazard rates of dementia (Satizabal et al., 2016). The trends, however, showed the opposite pattern in Japan. The prevalence and incidence of Alzheimer's dementia and all-cause

dementia increased during 1985-2002. This trend was attributed partly to improved survival of patients with dementia. The latest study of this series has observed no secular trend in the rate of dementia, showing that the results are not blending with harmony (Rajan et al., 2019). A recent meta-analysis revealed significant heterogeneity among studies but found a non-significant trend towards a decreasing incidence of dementia (Roehr, Pabst, Luck, & Riedel-Heller, 2018).

Interpretation of the above studies warrants caution. Response bias may be an underlying reason for a lower prevalence found in recent studies. For instance, in the Medical Council Research Cognitive Function Aging Study, the response rate from the earlier cohort was 80%, but it was reduced to 56% from the later cohort (Matthews et al., 2013). Inter-rater variability, the inclusion of patients in the nursing homes, and changing diagnostic systems have the potential to affect the outcome and produce varying results. However, higher education and better control of vascular diseases may account for the above reported declining rate of dementia.

In Australia age-standardised death rate for cardiovascular diseases including coronary artery disease decreased substantially from 1968 to 2006 (Australian Government 2020). Therefore, the described trends in dementia incidence and prevalence may be relevant to the Australian population. Nonetheless, given that there is no baseline primary data regarding dementia incidence or prevalence in Australia, there is limitation in extrapolating the above findings to the Australian population.

2.1.2 Historical overview

The progress in the field of dementia closely parallels the advancement of science from the early concepts of dementia to hypothetically driven modern research. In this journey, scientists wielded tools and techniques invented by disciplines other than medicine, particularly physics and chemistry, that enabled microscopic examination of tissues with special staining techniques and *in vivo* imaging studies. Descriptions suggestive of dementia can be found in the relics from ancient

times. Around the year 2000 BC, Egyptians noted that old age was associated with loss of memory (Boller & Forbes, 1998). Solon, who is known as the founder of legal thinking in Athens, wrote that judgment could be impaired by pain, violence, drugs, old age, and persuasion by women (Freeman, 1927). In the Middle Age, dementia did not evoke notable writing because of deadlier epidemics such as plague. Several terms that denoted a condition resembling dementia were used in the ancient literature. They were *amentia, anoea, senility, idiocy, imbecility, and insanity*. The first use of the term 'dementia' is debatable. Some authors claim that the term was used in France as early as in 1381, although it is widely believed that Phillip Pinel was one of the first authors who used this term (Berrios, 1987). In Blancard's *Physical Dictionary*, the word dementia appeared as an equivalent of 'anoea,' a term that referred to the poverty of imagination and judgment (Berrios, 1987). The earliest adjective 'demented' was found in the Oxford Dictionary of 1644. Esquirol described dementia as a 'cerebral affection characterized by sensibility, intelligence, and will compromising' (Boller & Forbes, 1998). Based on the association with the aging process, he separated dementia from 'idiotica' (mental retardation of today), a condition characterized by weakness of intelligence. Dementia was later divided into acute, chronic, and senile forms. Georget contributed to the notion of the irreversibility of the dementia process (Berrios, 1987). Morel studied the association between dementia and brain atrophic changes. He proposed that dementia was associated with neuropathological changes different from aging. Kraepelin detached dementia from 'praecox dementia' (dementia of the young, which is schizophrenia today) (Figure 4). For Griesinger, dementia was a state of mental weakness without delirium. He described dementia as a state of growing incapacity for any deep emotion, loss of memory and loss of the power to reproduce ideas, and fast forgetting for the latest events or those that took place during the dementia state, but not infrequently with preservation of older memories related to a distant past. He observed that complete remission never occurred.

Around the dawn of 20’th century, the biological theories of mental illnesses pervaded scientific discourses in Germany. Alois Alzheimer was a German psychiatrist and pathologist (Figure 5). In 1901 Alzheimer observed a 51-year old patient named Auguste Deter while he was

working in Frankfurt asylum. Deter suffered from progressive changes in her personality with a decline in memory (Cipriani, Dolciotti, Picchi, & Bonuccelli, 2011). Her condition deteriorated to the extent of disorientation and unintelligible speech. In her last days, she was apathetic and bedridden.

On August 8, 1906, Deter died from septicaemia. In the meantime, Alzheimer moved to Munich, to work with Kraepelin. When Kraepelin was working on the illnesses in senile patients, Alzheimer was interested in the laboratory work of senile diseases. He remembered Deter and asked for her records and brain to be sent to Munich. There he examined Deter's brain and observed characteristic histological changes: severe loss of neurons and the presence of plaques and tangles. His tissue preparations did not include the hippocampus or entorhinal cortex (Graeber & Mehraein, 1999). On November 3, 1906, Alzheimer presented his findings at the meeting of Southwest German Psychiatrists. His conclusions did not elicit interest or comments; the audience appeared to be more interested in the following lecture on compulsive masturbation. "So then, respected colleague Alzheimer, I thank you for your remarks; clearly, there is no desire for discussion," the chairman concluded the session (Dahm, 2006). Undaunted Alzheimer's published his findings in 1907 under the title 'A characteristic serious disease of the cerebral cortex' as a short abstract (Cipriani et al., 2011). Later in the Handbook of Psychiatry, Kraepelin introduced the term 'Alzheimer's disease' for the first time.

Today dementia is conceptualized as an acquired chronic disorder of impaired memory and at least one other cognitive dysfunction, such as executive dysfunction, apraxia, or aphasia. There are many forms of dementia. One classification divides them into progressive dementias and reversible dementias. The proportion of potentially reversible dementias is small, constituting 9%-19.1% of all dementias (Bello & Schultz, 2011; Clarfield, 2003). Reversible causes of dementia include vitamin B12 deficiency, normal pressure hydrocephalus, subdural haemorrhage, infectious diseases, and depression.

Summary

Alzheimer's disease is a pathological process encompassing a pre-clinical phase, mild cognitive impairment, and dementia syndrome. It gives rise to the commonest form of dementia. Both the prevalence and incidence steadily increase with age, but recent studies show a trend towards declining age-adjusted incidence of dementia. The descriptions of dementia with changing concepts are seen throughout history, and the notion that it was associated with irreversible pathological changes different from aging appeared in the 18'th century. Alois Alzheimer, while working with Emil Kraepelin, discovered the characteristic pathological lesions associated with a peculiar syndrome of dementia, which later came to be known by his name. Today dementia is defined as a syndrome of impairment of chronic nature in multiple cognitive domains. While most dementia syndromes are progressive in nature, a few are reversible with treatments.

2.1.3. Diagnosis of dementia

2.1.3.1. Clinical Diagnosis of dementia

"There is no disease that you either have or don't have—except perhaps sudden death and rabies. All other diseases you either have a little or a lot of."

Geoffrey Rose. *Epidemiologist*

There is no single, unanimously accepted diagnostic method of Alzheimer's dementia. The diagnostic approaches vary across settings. For example, primary care physicians may take a clinical approach different from diagnostic imaging studies at a memory clinic or specialist centre.

These methods are different from the approach taken by an academic research centre where comprehensive diagnostic measurements such as estimation A-β and tau burden are undertaken.

Two antithetical views prevail in society. One notion is that impairment in cognition is an inevitable part of aging. The other view is that all cognitive changes found with aging are signs of dementia. These views underscore the importance of appropriate diagnostic evaluation and screening for people reporting cognitive symptoms. A presumptive clinical diagnosis of Alzheimer's dementia can be made based on symptoms and signs. The International Classification of Diseases, 10'th edition (ICD-10), and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) provide diagnostic guidelines for the diagnosis of Alzheimer's dementia (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013; World Health, 2004). The ICD-10 defines dementia as a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Unlike in delirium, consciousness remains unaffected. The above symptoms must be present for at least six months and are associated with impairment of Activities of Daily Living (ADLs). They have a gradual onset and progressive course over the years. The symptoms may be brought into clinical attention following a critical life event that could unmask the deficits, for instance, the death of the spouse.

In the DSM-V, both amnesia and dementia are subsumed under a new entity known as Major Neurocognitive Disorder (MNCD). According to the DSM-V, there should be evidence of significant cognitive decline from a previous level of performance in one or more areas of cognitive domains viz., complex attention, executive function, learning, and memory, language, perceptual, motor, or social cognition (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). The decline may be based on:

A 1. A concern of the individual, a knowledgeable informant or the clinician that there has been a significant decline in cognitive function; and

A 2. Substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities.

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder.

(E.g., major depressive disorder, schizophrenia).

In the fall of 1983, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) convened a group to formulate the diagnostic criteria and describe the clinical diagnosis of Alzheimer's dementia (McKhann et al., 1984). The medical history, clinical examination, neuropsychological testing, and laboratory assessments were incorporated into the diagnosis. According to the criteria, a diagnosis of probable Alzheimer's dementia can be established by deficits in two or more areas of cognition, progressive worsening of cognitive functions, age of onset between 40 and 90 years, most commonly after 65 years of age and absence of other diseases that could better account for cognitive dysfunctions. The criteria, commonly referred to as the NINCDS-ADRDA criteria, have been quite successful, surviving for more than a quarter of a century. These criteria demonstrated 81% sensitivity and 70 % specificity when tested against pathological diagnosis (Knopman et al., 2001).

Given the tremendous advances that occurred in the past 25 years, the National Institute on Aging (NIA) and Alzheimer's Association (AA) have put forward recommendations to revise the NINCDS-ADRDA criteria. The diagnostic guidelines for Lewy body disease did not exist at the time of the NINCDS-ADRDA criteria; voluminous literature on mild cognitive impairment (MCI) has emerged after the NINCDS-ADRDA criteria; neuroimaging findings in the field of dementia have expanded in the past 25 years. The new criteria have embodied the advances gained in these

areas (Albert et al., 2011; Jack et al., 2011). The proposed three stages of the new criteria are preclinical AD, MCI, and dementia due to AD. Individuals who do not have clinical symptoms but have brain changes of AD would meet the diagnosis of preclinical AD. Patients with mild cognitive symptoms who can perform daily tasks would classify for MCI. Individuals who have cognitive symptoms and signs and are unable to perform daily requirements would meet the criteria for dementia. This classification reflects a long preclinical phase of AD that may begin 20 years or more before the manifestation of symptoms (Jack et al., 2009; Villemagne et al., 2013).

2.1.3.2. Pathological diagnosis of dementia

An autopsy continues to be the method by which the definite diagnosis of AD is made. Gross morphological changes seen in the brain of patients with AD are non-specific, particularly in old age. Brain weight and cortical thickness differ between patients and healthy controls in early-onset dementia, but not so well in late-onset dementia in advanced age (Perl, 2010; Terry, 1986). Hippocampal atrophy and increased volume of the inferior horn of the lateral ventricle may be seen in the early disease. As the disease progresses, widened sulci throughout the cortex and atrophy in the posterior temporal, parietal, and frontal lobes become prominent while primary motor and sensory cortices remain unaffected (Perl, 2010).

Microscopically the loss of synaptic components, along with the loss of neurons, is a prominent morphological alteration in AD. Denervation is marked in cortical regions but also found in subcortical regions, notably in the cholinergic system of the basal forebrain. Plaques and tangles are the two defining lesions of AD. Originally described as plaques and tangles, the microscopic lesions have later undergone chemical analysis. Amyloid beta-peptide was first sequenced by chromatography from the meningeal vasculature of patients with Alzheimer's disease and Down's syndrome more than three decades ago (Glenner & Wong, 1984). Masters et al. isolated and purified the amyloid protein and elucidated amino acid composition, mass, and sequencing (Masters et al., 1985). A dense deposition of amyloid plaques with abnormal neurites is the

pathological hallmark of AD. The plaque is composed of a central mass of A-β surrounded by abnormally configured neuronal processes viz., the neurites, reactive astrocytes, and glial cells. A-β is present in all plaques. Abnormal neurites represent degenerated processes of neurons, typically dendrites. Neurites are present in primitive and classic forms of senile plaques (SP) but absent in compact senile plaque, which is composed of a large mass of amyloid. Thioflavin S and Congo red can stain the plaques. Senile plaques can be observed in several regions of the brain, but they are densest in the cerebral cortex sparing the sensory and motor areas. A dense deposition of senile plaque with neuritic activity is a specific marker of AD because these features are absent in other neurodegenerative diseases.

Neurofibrillary tangles (NFT) are intracytoplasmic fibrillar structures composed of abnormally phosphorylated tau proteins. Tau is a microtubule-stabilizing protein found in neurons. Neurofibrillary tangles are argentophilic and Thioflavin S positive. Unlike senile plaques, NFT damage cellular structures within the cytoplasm and cause neuronal death. Abnormally phosphorylated tau proteins form the core of NFT (Bancher et al., 1989). Tau proteins are a set of six isoforms of phosphoproteins formed by alternate mRNA splicing of microtubule-associated protein tau (MAPT) gene located on chromosome 17q21. The function of tau proteins is to facilitate the assembly of tubulin to the microtubule. It is hypothesized that in the hyperphosphorylated forms, diverse types of tau proteins pair up to form paired helical filaments (PHF) that tangle together (Grundke-Iqbal et al., 1986). Tangling disrupts microtubules, the structures that maintain the integrity and transport system of neurons. Oligomeric and aggregated NFT play a determinant role in synaptic death (Ballatore, Lee, & Trojanowski, 2007). Compared with A-β plaques, NFT have shown better correlation with cognitive deterioration in AD (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Markesbery et al., 2006). Tau deposition in the temporal lobe closely tracked the onset and progression of dementia and predicted a longitudinal decline in episodic memory independent of Aβ accumulation (Guillozet, Weintraub, Mash, & Mesulam, 2003).

The presence of neuropil threads (NT) is another pathology seen in AD. They represent degenerating processes of neurons, axons, and dendrites with tangles. They are argentophilic and Thioflavin S positive. Amyloid angiopathy-a condition produced by deposition of amyloid fibrils in small to medium-sized leptomeningeal and cortical vessels-is present in the clear majority of patients with AD (Esiri et al., 1999). Congo Red staining imparts a yellow-green birefringence to the fibrillar substance, and hence it is also known as congophilic angiopathy. Although it is absent in some patients with Alzheimer's pathology, it is present in almost all patients with intense deposition of plaques and tangles (Esiri et al., 1999). This condition may occur without amyloid plaques, but its presence depends on the age of the patient, the area of the brain studied, and the severity of plaques.

There are various pathological criteria for the diagnosis of AD. In the CERAD method, the brain regions examined are the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, hippocampus, entorhinal cortex, and midbrain, including substantia nigra. The density of neuritic plaque in the most widespread region is described as sparse, moderate, or severe and then combined with the age of the person to get age-specific plaque score. One hundred microscopic fields are examined in this method. The result is then correlated with clinical history to make a diagnosis of definite, probable, or possible AD. Neurofibrillary tangles are not used in the CERAD criteria.

The National Institute on Aging (NIA) criteria are rather prescriptive. According to the NIA criteria, three regions of the neocortex (the frontal, temporal, and parietal lobes), amygdala, hippocampus, and subcortical areas are examined. In individuals, less than 50 years of age, more than 2-5 neuritic SP or NFT must be seen anywhere in the neocortex per field during the examination of 200 fields. More than 8 SPs are required in each field for the diagnosis of AD in individuals aged between 50-65; more than 10 SP are required for individuals aged between 66-75 years, and more than 15 SP are needed for those aged above 75 years (Khachaturian, 1985).

In 1997, the National Institute on Aging/Reagan Institute of the Alzheimer Association Consensus Recommendations for the Post-mortem Diagnosis of AD emerged (Davis, Schmitt, Wekstein, & Markesbery, 1999b). The criteria required the presence of dementia for the diagnosis, and the emphasis was to diagnose pathology as an explanation of the underlying cause for dementia (Davis et al., 1999b). A proposition for revised criteria broadened the diagnosis to include preclinical disease and mild symptoms (Hyman et al., 2012). The revised criteria disentangled clinicopathologic AD from the neuropathologic AD. The clinicopathologic AD is an entity that consists of symptoms of cognitive dysfunctions and behavioral changes in the presence of neuropathological changes of AD. In contrast, the neuropathologic AD is identified during post-mortem examination independent of clinical symptoms. The criteria recommend an ABC staging protocol for the neuropathological lesions of AD, according to three morphologic characteristics: β/amyloid plaques (A), the Braak and Braak staging of NFT (B), and the CERAD score for neuritic plaques (C). According to Braak and Braak, the different stages were classified based on immunocytochemical methods. These stages include

1. Transentorhinal stages I-II: clinically silent cases;
2. Limbic stages III-IV: incipient Alzheimer's disease;
3. Neocortical stages V-VI: fully developed Alzheimer's disease (Braak & Braak, 1995).

2.1.4 Aetiological mechanism of the disease

Except for trisomy 21 and autosomal dominantly inherited AD, the aetiology of Alzheimer's disease is multifactorial. Despite, a relatively homogeneous microscopic pathology characterized by plaques and tangles, the aetiology of AD fits into a heterogeneous model, in which what often appears as genetic abnormalities are the causes of early-onset disease and, age, cardiovascular morbidities, and other lifestyle factors such as exercise, sleep disorders, and low level of education are the risk factors for late-onset type. Although the aetiology of early-onset familial AD is genetic, no single gene abnormality explains all cases of AD. The genetic defects vary from trisomy 21 to mutations in amyloid precursor protein (APP) and presenilin 1 and 2. Whereas the overproduction

of A-β leads to neuritic plaque in early-onset AD, reduced clearance of A-β is the pathological mechanism in late-onset disease. While the pathophysiology of early-onset is relatively well understood, that of late-onset AD is not so. The clearance pathway of A-β in humans has been elucidated, and impaired clearance has been postulated as the principal mechanism of A-β accumulation in late age (Mawuenyega et al., 2010; Roberts et al., 2014).

The presence of apolipoprotein E e4 (APOE e4) leads to decreased clearance of A-β from the brain and consequent A-β deposition (Blacker et al., 1997; Castellano et al., 2011; Harold et al., 2009; Sando et al., 2008b). In a Finnish study, the age of onset in the late-onset disease was significantly reduced by APOE e4 in a dose-dependent fashion from a mean age of 78 years in the absence of an e4 allele to 69 years with two e4 alleles (Lehtovirta et al., 1995). A-β, in this instance, is followed by NFT that spreads from the medial temporal lobe to the association cortices culminating in cognitive decline and eventual dementia.

In the second situation, several, but not so well-defined factors such as vascular lesions and sleep disturbances, impair A-β clearance (Gupta & Iadecola, 2015; Xie et al., 2013b). In mice, sleep resulted in a 60% increase in the interstitial space leading to increased clearance of A-β during sleep (Xie et al., 2013a). The role of vascular lesions in accelerating A-β retention has been clearly documented (Esiri et al., 1999; Gottesman et al., 2017; Lewis et al., 2006; Snowdon et al., 1997; Vemuri et al., 2015b; Zekry et al., 2002). The relationship between vascular lesions and the accumulation of A-β has been largely described as synergistic (Snowdon, 1997; Zekry et al., 2002), notwithstanding the findings that suggest an independent contribution rather than interaction (Vemuri et al., 2015a). Increased A-β retention that subsequently follows occurs in the late age within the late-onset AD, in the late eighth decade and after. In the presence of an increased A-β deposition, NFT progresses from the medial temporal lobe to the association cortices. In the absence of A-β, NFT becomes confined to the medial temporal lobe and leads to age-related cognitive decline, not dementia. A peculiar feature of AD pathology in the late stage of late-onset AD is the weak relationship between A-β and clinical expression of the disease. Protective

mechanisms, for example, a high level of education and bilingualism as well as unfavourable factors like vascular disease, play an essential role in mediating the link between A-β deposition and clinical manifestations of the disease.

Thal phases and Braak & Braak stages describe the hierarchical progression of Aβ and NFT, respectively (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Thal, Rub, Orantes, & Braak, 2002). While Aβ initially builds up in the association cortex and then propagates inwards to allocortex and finally to the brainstem and cerebellum, tau deposition typically begins in the allocortex and then progresses outwards to the association cortex and finally to primary and secondary cortices. There is substantial support to consider tau as downstream effect of Aβ (Hardy & Selkoe, 2002; Stancu, Vasconcelos, Terwel, & Dewachter, 2014) notwithstanding rare instances of NFT without significant Aβ in patients with clinical diagnosis of Alzheimer's dementia, a quandary that some authors (Jellinger & Attems, 2007) view as a subset of AD called tangle dominant dementia and others as an entity separate from AD pathology. Current knowledge of the role of Aβ and tau in the pathogenesis of AD, although confronting dilemmas, is expanding, and the relationship may be best described as synergistic at this stage (Nisbet, Polanco, Ittner, & Gotz, 2015).

Summary

Both the International Classification of Diseases and related disorder (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) provide clinical features and guidelines for the diagnosis of dementia. Dementia is renamed as Major Neurocognitive Disorder in the DSM-V. The syndrome is characterized by a decline in multiple cognitive domains such as complex attention, executive function, learning, and memory, language, perceptual, motor, or social cognition. Impairment in cognitive function, either noticed by a knowledgeable person of the patient or documented by a neuropsychological evaluation and interfering with daily function, is essential for the diagnosis. National Institute of Neurological

and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) formulated the diagnostic criteria for Alzheimer's dementia in1983. The National Institute on Aging and Alzheimer's Association made recommendations to revise the criteria given tremendous advances in the field. Consistent with a long preclinical phase, for instance, with the accumulation of A-β for approximately 20 years before the onset of symptoms, the new criteria have proposed a three-stage diagnosis: preclinical phase, mild cognitive impairment (MCI) and dementia. In the preclinical phase, pathological changes progress without manifestations; in the MCI stage, cognitive symptoms appear, but not significant enough to cause impairment of function; in the final stage of dementia, multiple cognitive symptoms produce significant impairment. In dementia, atrophy restricted to the hippocampus in the early stage becomes extensive later to involve the posterior temporal, parietal, and frontal lobes along with the widening of sulci and ventricles. At the microscopic level, the deposition of β-amyloid and neurofibrillary tangles is the defining lesion in AD. A dense deposition of amyloid plaques with abnormal neurites is the pathological hallmark of AD. The plaque is composed of a central mass of β-amyloid surrounded by abnormally configured neuronal processes-the neurites, reactive astrocytes, and glial cells. Neurofibrillary tangles (NFT) are intracytoplasmic fibrillar structures composed of abnormally phosphorylated tau proteins. The progression of NFT is believed to occur closer to the development of symptoms and consequently has shown a better correlation with neuronal damage and cognitive deterioration than β-amyloid. While Aβ initially builds up in the association cortex and then propagates inwards to allocortex and finally to the brainstem and cerebellum, tau deposition typically begins in the allocortex and then progresses outwards to the association cortex and finally to primary and secondary cortices. There is substantial support to regard tau as a downstream effect of Aβ. The relationship between β-amyloid and tau may be best described as synergistic at this stage.

2.1.5. Evaluation of cognitive function and neuropsychological assessments

Cognition includes an array of mental functions varying from consciousness to the complex problem-solving skills. It encompasses individual domains such as orientation, including visuospatial awareness, attention, memory, language, and executive function.

2.1.5.1. Memory: Memory is defined as a process of encoding, storing, and retrieving information about outer and inner stimuli or presentation of past information to the central nervous system that can be used to react and position the organism towards new stimuli (Jahn, 2013). Broadly there are two types of memory, explicit or declarative memory, and implicit or non-declarative memory (Ullman, 2004). Declarative memory is conscious, intentional recollection of previous experiences, information, and concepts (Ullman, 2004). Implicit memory refers to the retrieval of previous experiences, essentially learned information, unconsciously. There are two types of declarative memory, episodic memory, and semantic memory. Episodic memory involves retrieval of an event with time and space of its occurrence and autonoetic consciousness, a subjective sense of experiencing it (Tulving, 1985). It is also described as an autobiographical episode. Autonoetic consciousness accompanies memories and enables the subject to be aware of the self in time and space. With episodic memory, people relive the experience. In contrast, semantic memory is the retrieval of information without locating it in time and space. It is, therefore, independent context retrieval.

Working memory refers to the system or mechanism underlying the maintenance of task-relevant information during the performance of a cognitive task (Baddeley & Hitch, 1974). It involves a temporary holding of information while cognitive tasks are performed. Declarative memory and working memory are affected in the early stages of AD. The impairment of semantic memory manifests in language functions, such as verbal fluency and naming.

2.1.5.2. Visuospatial orientation and construction: Visuospatial function involves the identification of a stimulus and its location in space. Visuospatial construction is the ability to see an object or picture as a set of parts, and then to construct a replica of the original from these parts (Mervis, Robinson, & Pani, 1999). Alzheimer described visuospatial deficit more than a century ago: 'She could not find her way about her home….' (Alzheimer, 1906). The brain regions responsible for visuospatial tasks are superior parietal lobule, parieto-occipital junction, premotor areas, and Brodmann area 5 (immediately posterior to primary somatosensory cortex).

2.1.5.3. Executive function: Executive function is a broad term; there is little consensus on its definition. Broadly, executive functions refer to a family of top-down mental processes that are required during cognitive control of behavior (Wahba, 2004). There is a general agreement on the three core components of executive function: inhibitory control, working memory, and cognitive flexibility or set-shifting (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; Miyake et al., 2000). Higher-order functions such as reasoning, problem-solving, and planning develop from these components.

2.1.6. Standardized tools for formal cognitive assessment

Cognitive scientists and researchers have developed a variety of cognitive assessment tools. There is no single tool regarded as the best for all settings. The tools vary in their psychometric properties. The standard tools are the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Clinical Dementia Rating Scale (CDR).

2.1.6.1. Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975): The Mini-Mental State Examination (MMSE) is a common screening test used for the assessment of cognitive functions. It is used to determine cognitive changes over time as well as the therapeutic response in clinical trials (Strauss, Sherman, & Spreen, 2006). The MMSE is aw 30-point questionnaire and a sensitive test to supplement a clinical diagnosis of dementia. It assesses orientation, attention,

immediate and short-term memory, language, ability to follow a three-step task, and constructional ability. The test-retest reliability coefficient of the MMSE over 24 hours is 0.89 (Folstein, Folstein, & McHugh, 1975). It is used to screen dementia and delirium in a wide range of settings: medical wards, community clinics, and research. Folstein proposed a cut-off point of 24 to aid the diagnosis of dementia, and this yielded 75.5% sensitivity and 100% specificity with a Positive Predictive Value (PPV) of 100% (Folstein, Folstein, & McHugh, 1975). Other authors suggested higher cut-off points, particularly for screening highly educated individuals (Morales, Gonzalez-Montalvo, Bermejo, & Del-Ser, 1995). The administrative time, when used by an experienced professional, is 5-10 minutes. The advantages of the MMSE are easiness to administer and good reliability and validity. It is suitable in acute care settings, primary health care centers, and residential care facilities to assess global cognitive status in older people. The drawback of the MMSE is the lack of sensitivity in detecting early dementia. It has low sensitivity for mild cognitive impairment (MCI); 80% of patients with MCI scored above 26 on the MSSE (Tombaugh, Kozak, & Rees, 1999). It does not measure executive function.

2.1.6.2. Montreal Cognitive Assessment (Nasreddine et al., 2005**)**: It is a 30-point cognitive test designed to detect the mild form of cognitive impairment in individuals scoring 24 to 30 points on the MMSE. The cut-off score is 26. Along with the measurement of attention, delayed recall, and visuospatial abilities, the MOCA assesses executive function using alternation tasks adapted from the Trail Making Test Part B, phonemic fluency task, and two-item verbal abstraction task. Language is assessed by a three-item confrontation naming task using low familiarity animals (lion, camel, rhinoceros), repetition of two syntactically complex sentences, and language fluency. Trained professionals can administer the test in 10 minutes. The MoCA has 83%-90% sensitivity to detect MCI and 94% -100% sensitivity to detect mild dementia, but the specificity is 50%-87% **(**Esiri et al., 1999**;** Nasreddine et al., 2005**)**. The test-retest reliability is high (r=0.92). The correlation between the MMSE and the MOCA is also high (r=0.87).

2.1.6.3. Clinical Dementia Rating (Hughes, Berg, Danziger, Coben, & Martin, 1982**)**: The CDR was developed at Washington University School of Medicine for the evaluation of the staging of dementia. It is based on s semi-structured interview with the patient and the informant. It is a five-point scale starting from 0 that denotes no cognitive impairment up to a score of 3, which indicates severe dementia. A score of 1 indicates mild cognitive impairment, and 2 denotes moderate cognitive impairment. The score is derived from an interview with the patient and informant and the judgment of the administrator. The six domains measured by CDR are memory, orientation, judgment, problem- solving skills, community affairs, home and hobbies, and personal care. It has good inter-rater reliability. **(**Hughes et al., 1982**)**. The CDR has established reliability and criterion validity.

2.1.7. Neuropsychological Tests

2.1.7.1. Logical Memory tests of Wechsler's Memory Scale (WMS): The Wechsler Memory Scale is the most commonly used measure of memory (Abikoff et al., 1987; Wechsler, 1987). The Logical Memory Test (LMT) is one of the seven subsets of WMS. It is a task indented to measure the index of auditory-linguistic memory. The test consists of the recall of auditorily presented story passages. The examinee is then asked to remember as many details as possible both immediately (LMT 1) and after 25-30 minutes delay (LMT 2). A recognition test of yes or no response follows the delay. An advantage of the LMT is its strong psychometric properties. The internal consistency in a sample of adults aged 16-69 years was 0.82 for the LMT 1 and 0.86 for the LMT2. The test-retest reliability was 0.72 for the LMT 1 and 0.67 for the LMT2. Regarding the construct validity, the LMT correlated with other measures of memory, for example, the California Verbal Learning Test (CVLT). The disadvantages of the LMT include its heavy reliance on verbal memory and limited applicability to individuals with language difficulties.

2.1.7.2. Wechsler Adult Intelligence Scale (WAIS-III) Digit Span: David Wechsler developed the Wechsler Intelligence Scale and first published it in 1939. These tests were designed to measure

intellectual performance by adults. The scale was subsequently revised, and the WAIS-III was published in 1997 (Wechsler 1997). The WAIS-III-digit span is one of the seven verbal performance tests. This test has two parts, digit span backward and forward. The test measures sustained attention and working memory.

2.1.7.3. Rey-Osterrieth Complex Figure Test (ROCFT): After Rey developed the Copy Figure Test in 1941, Osterrieth standardized it in 1944 (Osterrieth, 1944; Rey, 1964). It is a commonly used test to measure visuospatial constructional skills and visual memory. The ROCFT has three test components: copy, immediate recall, and delayed recall. In the first step, the examinee is given the ROCF stimulus card and asked to draw the same figure. After this step, the examinee will be instructed to draw from what could be remembered and eventually draw the same figure after 30 minutes delay. The test involves measures of accuracy, location, and organization. The ROCFT can also measure motor coordination and strategic planning. Validity studies in the geriatric population showed the sensitivity of ROCFT to Alzheimer's disease (Berry, Allen, & Schmitt, 1991). Interrater and test-retest reliability, and internal consistency were adequate to good for recall trials of the ROCFT but not so for copy trial (Berry et al., 1991).

2.1.7.4. Rey Auditory Verbal Learning Test (AndrÈ Rey, 1964). The RAVLT measures short-term verbal memory, verbal learning, and recognition. The test consists of a list of 15 nouns that are read out to the examinee at the rate of one noun per second for five consecutive trials. Each trial is followed by a free recall period. Upon completion of trial five, an interference list that contains 15 words is presented in the same manner as the first list, followed by a recall of the interference list. During the sixth trial, the examinee is asked to recall as many words as possible from the original list. In the last trial, a story that incorporates all the words from the initial list is presented, and the examinee is then asked to identify words recognized from that list. The RAVLT can be used as a quick screening measure for the evaluation of patients with suspected verbal learning and memory impairments (Rosenberg, Ryan, & Prifitera, 1984).

2.1.7.5. Verbal fluency tasks: Verbal fluency tests are used to assess cognitive impairment. Verbal fluency has two components, letter fluency, and categorical fluency. Patients with Alzheimer's dementia have relatively more impairment of categorical fluency, whereas patients with TBI demonstrate impairment on the letter fluency tests (Capitani, Rosci, Saetti, & Laiacona, 2009). In the case of letter fluency, education accounts for more variation than age does, but in the case of categorical fluency, age is a stronger predictor than education (Tombaugh et al., 1999). In the letter fluency test, the examinee is required to say words starting with a specific letter as many as possible over five minutes. In the categorical fluency test, names from a specific category, for instance, animals have to be articulated.

2.1.7.6. Trail Making Tests: In 1938 Partington and Leiter introduced a connection test (Partington & Leiter, 1949). There are two parts. In part A, the examinee has to connect randomly distributed circled and sequential numbers as fast as possible. This is known as the Trail Making Test part A. In part B, randomly distributed circled sequential numbers alternating with sequential letters should be connected from the number to letter and then letter to number order as fast possible. The second component is known as the Trail Making Test Part B. The tests measure the speed of cognitive processing. The test scores reflect the performance on several cognitive domains: attention, visual processing, sequencing, working memory, and executive function (Salthouse, 2011). The Trail Making Tests are commonly used tests in the neuropsychological battery.

2.1.7.7. Wechsler's Test of Adult Reading (WTAR): The Hold tests indirectly estimate premorbid intelligence by assessing measures that are relatively unaffected by neurological insults (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). The word pronunciation test is a commonly used hold test. The WTAR is one of the word pronunciation tests that provide an estimate of premorbid intelligence (Green, Melo, et al., 2008). The test requires the task of reading irregularly spelled words (Venegas & Clark, 2011). The use of irregular words is a reflection of prior learning and is based on the correlation between reading ability and intellectual functions. The WTAR was co-normed with the WAIS-III. During administration, the examiner presents the word card and asks

the examinee to pronounce each word. The examinee can give only one pronunciation of a word. The changing grapheme to phoneme translation in the prompts makes it challenging to apply standard pronunciation rules and pronounce the word without prior learning. The maximum raw score is 50. The WTAR raw score is then converted to a predicted premorbid IQ score after taking the demographic data (e.g., age) into account. The WTAR moderately correlated with the level of education, and the performance declined with aging from 45 to 54 years. Normative data exists for the U.S. and U.K samples. The test has excellent internal consistency coefficients ranging from 0.90 to 0.97 for the U.S sample. The test-retest correlation was good (>0.90). The WTAR has high correlations with other measures of IQ, for example, the AMNART (r=0.90), WAIS-III VIQ (r=0.75), and FSIQ (r=0.73) in the U.S. sample. The performance on WTAR appears to be a reasonable predictor of premorbid intellectual function. The WTAR has been studied in patients with mild to moderate Alzheimer's dementia, MCI, TBI, and cognitively asymptomatic patients (Green, Melo, et al., 2008). The limitation of the WTAR is that it mostly predicts verbal intellectual ability, not memory ability. It cannot be applied to individuals with a pre-existing learning disability.

Summary

Memory, visuospatial orientation, constructional skills, executive function, and language are the commonly assessed cognitive domains by a neuropsychological battery. Memory involves encoding, storing, and retrieving information to the central nervous system. Declarative memory is a conscious, intentional recollection of materials, whereas implicit memory is the retrieval of learned information without conscious effort. Episodic memory, a type of declarative memory, is the process of recollection of past events with autonoetic experience of space and time. Impairment of episodic memory is one of the earliest manifestations of Alzheimer's dementia. Visuospatial function refers to the identification of a stimulus in space. Visuospatial construction is the ability to see an object as a set of parts and then to construct a replica of the original from these parts. From a broad perspective, executive function refers to cognitive control

that includes but not limited to set-shifting. The MMSE, being easy to administer, is used in a wide variety of health care settings. By assessing orientation, attention, immediate and short-term memory, language, ability to follow simple tasks, and constructional ability, the MMSE can supplement a diagnosis of dementia. It is not meant to assess executive function or screen early dementia. On the other hand, the MoCA assesses executive function, fluency task, and abstract thinking and has 83%-90% sensitivity to detect mild cognitive impairment, albeit with a limited specificity of 50%-87%. The Clinical Dementia Rating scale, mainly an instrument to classify the severity of dementia, measures memory, orientation, judgment, and problem- solving, along with the assessment of community affairs, home and hobbies, and personal care. The Logical Memory Tests of Wechsler's Memory Scale measure verbal memory. The Wechsler Adult Intelligence Scale Digit Span measures sustained attention and working memory. The Rey-Osterrieth Complex Figure Test has three tasks: copy (visuospatial orientation and construction), immediate drawing from visual memory, and delayed drawing. The Rey Auditory Verbal Learning test involves sophisticated measurement of short-term verbal memory, verbal learning, and recognition. Verbal fluency tasks assess language function. Impairment in categorical fluency occurs in the early stage of Alzheimer's dementia in contrast to traumatic brain injury, which predominantly affects the letter fluency task. The Trail Making Tests are used to assess visual processing speed and executive function. Word pronunciation is a hold test that is relatively resistant to neurological insults and a reflection of premorbid intelligence. The Wechsler's Test of Adult Reading is used to measure word pronunciation skills. It indirectly estimates premorbid intelligence.

2.1.8. Mild Cognitive Impairment

2.1.8.1. Origin of the term

Impairment in cognitive functions, occurring in association with neither dementia nor healthy aging, was recognized long ago. The diagnosis of dementia requires a substantial degree of cognitive and functional impairment. However, a proportion of patients who developed dementia

had a transitional phase of subtle signs of cognitive decline before the syndrome of dementia emerged. Identification of this transitional stage is important for early intervention and research that may generate insight into the pathological mechanisms of dementia. Various terms were in place to describe this clinical entity, which was subthreshold for dementia, namely dementia prodrome, benign senescent forgetfulness, mild cognitive impairment, cognitive impairment, no dementia, inter alia. Later, the term mild cognitive impairment survived time. Mild cognitive impairment is now recognized as a clinical syndrome, characterized by impairment in cognitive functions that is not severe enough to cause significant impairment of Activities of Daily Life (ADL) (Langa & Levine, 2014). In the case of Alzheimer's disease or MCI due to Alzheimer's disease, it is essentially a symptomatic pre-dementia phase.

2.1.8.2. The concept

Conceptually MCI is considered as a dynamic stage on a continuum between the preclinical phase of Alzheimer's disease and dementia (Figure 7). The features of MCI overlap with healthy aging on one side and with dementia on the other side. The DSM-V recognizes a syndrome characterized by subtle features of cognitive impairment that are distinct from aging but do not represent dementia. It is called mild neurocognitive syndrome, which is equivalent to MCI (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). Bedside cognitive evaluations, other investigations such as neuropsychological testing, biomarkers, and neuroimaging, are, therefore, required to delineate this syndrome from healthy aging and dementia. There is no consensus on a single set of diagnostic criteria. Subjective memory compliant, objective evidence of cognitive deficits, and preserved ADL are the commonly seen features of MCI. There are different subtypes of MCI; if only memory domain is affected it is called amnestic-MCI (aMCI), and if multiple cognitive domains, viz., language, executive function, and visuospatial skills are involved then it is called multiple domain MCI (md-MCI) (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). Within md-MCI if memory is affected, then it is md-MCI+, and if memory impairment is absent then it is md-MCI-. The least common type is single non-memory

domain MCI. Multiple domain-MCI reflects a greater extent of the disease and has a higher probability of progression to dementia compared with single-domain MCI.

2.1.8.3. Epidemiology and clinical features

The prevalence of MCI varies widely from 3%-40% depending on the geographical regions, age, and the criteria used (Ward, Arrighi, Michels, & Cedarbaum, 2012). Differences in the diagnostic criteria and the settings in which assessments were made caused heterogeneity within MCI and variability in progression to dementia. Clinically, subjective compliant of cognitive decline, in some cases verified by a knowledgeable informant, is the first criterion of MCI. Additionally, there may be objective cognitive deficits. The changes in cognitive function are typically over the years. The rapid deterioration in days, weeks, or months suggests vascular events, neoplasms, metabolic disorders, or prion diseases. For further evaluation of cognitive function, the MoCA is proposed as a useful tool. It was specially developed for the screening of MCI (Nasreddine et al., 2005; Smith, Gildeh, & Holmes, 2007). With a cut-off point of 25/26, the MoCA has a sensitivity of 80%-100% and specificity of 50%-76% for diagnosing MCI.

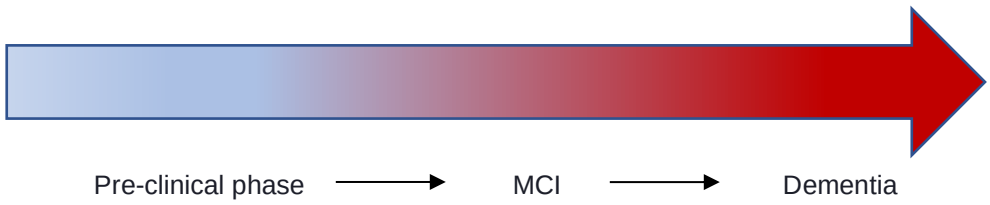

Figure 3. Mild cognitive impairment: a transitional phase between the preclinical stage and dementia on a continuum

2.1.8.4. Diagnostic evaluation

Structural and functional imaging, along with biochemical tests (for instance, CSF $A\beta_{42}$ estimation), add valuable information regarding the underlying aetiology of MCI. For example, a

decreased volume of the right hippocampus and smaller baseline thickness of the right entorhinal cortex on Magnetic Resonance Imaging (MRI) implies an increased risk of progression to dementia (Soldan et al., 2015). Earlier findings suggested that white matter abnormalities on MRI were associated with progression to dementia (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000), but a later study that controlled for other factors did not find vascular lesions or white matter hyperintensity as predictors of progression (Prins et al., 2013). These modalities have only limited use in routine clinical practice because of the lack of standardization and validation. The importance of structural imaging is more in the exclusion of other intracranial lesions such as stroke, subdural hematoma, normal pressure hydrocephalus, and tumours that may cause MCI than in confirming neurodegenerative diseases that would result in dementia. Functional imaging such as FDG PET and amyloid PET can narrow down the diagnostic considerations in the evaluation of MCI (see below).

2.1.8.5. Prognosis and progression to dementia

The clinical importance of MCI is its potential for a progression to dementia. Only a small proportion of patients with MCI develop dementia every year. The conversion rate is dependent on the type and severity of MCI, the settings, and age. In the clinic-based samples, annual conversion rate is 10%-15% (Grober, Lipton, Hall, & Crystal, 2000; Petersen et al., 1999) while it is 3.8% to 6.3% in the community-based samples (Morris et al., 2001; Ritchie, Artero, & Touchon, 2001). Older age is an important predictor of the progression to dementia (Brodaty, Connors, Ames, & Woodward, 2014). According to a meta-analysis, the annual conversion rate (ACR) to all types of dementia is 9.6%; the ACR to Alzheimer's dementia is 8.1% (Mitchell & Shiri-Feshki, 2009). Baseline performance in memory measures and executive function is a strong predictor of future dementia (DeCarli et al., 2004). If a neurodegenerative condition is presumed, then amnestic-MCI and multidomain-MCI + usually represent prodromal AD whereas impairment in non-memory domains such as executive function and visuospatial function indicate the likelihood of non-AD dementia, for example, Lewy Body dementia (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller,

2006; Ferman et al., 2013). A deficit in episodic memory is most commonly seen in patients who progress to Alzheimer's dementia (Prins et al., 2013). Theoretically, any kind of MCI may precede vascular dementia. Biomarkers are significant predictors of progression from MCI to dementia. Hypometabolism in the inferior parietal cortex, posterior cingulate cortex, and precuneus on FDG PET, apolipoprotein E e4 and decreased $A\beta_{42}$ levels in CSF are predictors of progression to dementia (Cerami et al., 2014; Prins et al., 2013).

2.1.8.6. Mild cognitive impairment due to Alzheimer's disease

This construct has arisen from the recognition that individuals with AD pathology go through a transitional phase of progressive cognitive decline before dementia. In 2011, the National Institute of Aging and Alzheimer's Association formed a working group to develop diagnostic guidelines for MCI due to AD. The working group put forward two types of diagnostic guidelines, core clinical criteria, and research criteria (Albert et al., 2011; Jack et al., 2011). Clinical diagnostic guidelines are for routine clinical evaluation, and the criteria for MCI include 1. Concern regarding a change in cognition, in comparison with previous cognitive level as reported by the patient, an informant, or a clinician; 2. Impaired performance in one or more cognitive domains that is greater than what would be expected from patient's age and education, typically 1.5 standard deviations below the published norms; 3. Preservation of independence in the activities of daily life; 4. No dementia.

The lines between healthy aging and MCI and then between MCI and dementia are difficult to draw in real life. A documented progressive decline over time rather than a one-off assessment is helpful in identifying MCI due to AD. Although independence in ADL is preserved in MCI, patients often find it challenging to perform complex tasks, for example, fiscal management that they used to execute before. During cognitive assessments, word-list learning test with multiple trials is particularly useful as it measures episodic memory. The tests that can measure episodic memory include the RAVLT, the California Verbal Learning Test, and the Logical Memory Test 1 and 2.

Given that multiple cognitive domains can be affected in MCI, it is vital to evaluate other cognitive functions such as attention, processing speed, language, executive function, and visuospatial skills.

2.1.8.7. Amyloid PET imaging in mild cognitive impairment

The Aβ PET imaging has provided transformative information about the progression of MCI in the presence of an increased Aβ deposition in the brain (Hatashita & Wakebe, 2017; Villemagne et al., 2011). Patients with MCI progressed to Alzheimer's dementia within a shorter period if they had a higher annual rate of brain Aβ deposition (Hatashita & Wakebe, 2017). With a positive amyloid scan, 67% of patients progressed to dementia in two years in contrast to 5% with a negative scan (Villemagne et al., 2011). The conversion rate with a positive scan is up to 82% in three years against 7% with a negative scan (Okello et al., 2009). Apolipoprotein e4 was associated with an accelerated decline in cognitive function and shorter duration for progression (Rawle et al., 2018). Age was not significantly different at baseline between subjects who progressed to dementia and those who did not (Hatashita & Wakebe, 2017; Villemagne et al., 2011). Pooled analysis demonstrated that the sensitivity and specificity of ^{11}C-PIB-PET for predicting long-term progression to AD ranged from 83.3% to 100% and 41.1% to 100%, respectively (Ma et al., 2014). A Cochrane systematic review and meta-analysis estimated the sensitivity and specificity of ^{11}C-PIB-PET in predicting progression from MCI to dementia (Zhang et al., 2014). The pooled data showed a sensitivity between 83%-100% and specificity between 46% and 88% but the studies examined mostly had short follow-up periods and the specificity is higher in studies with a longer follow-up.

Summary

Mild cognitive impairment refers to cognitive symptoms that represent neither healthy aging nor dementia, but a dynamic process that falls along a continuum between healthy aging

and dementia. The symptoms are significant enough to differentiate them from otherwise healthy aging but inadequate to cause impairment in function and, therefore, subthreshold for dementia diagnosis. Mild cognitive impairment manifests as subjective memory complaint, objective evidence of cognitive deficits, preserved general cognition, and intact ADL. Mild cognitive impairment due to Alzheimer's disease is essentially a symptomatic but pre-dementia phase, a transitional stage that allows potential therapeutic interventions to work and research into the risk factors of dementia and its course. Because MCI often overlaps between healthy aging and dementia, neuropsychological evaluation and measurement of biomarkers of AD are required to identify the specific cause and prognosis. Given the differences in the diagnostic criteria used, age groups studied, and the level of education, MCI is regarded as a heterogeneous syndrome leading to variation in the risk of progression to dementia. There are different types of MCI, single-domain MCI affecting only one cognitive function and multidomain MCI affecting more than one cognitive domain, and the latter carries a higher risk of future dementia, especially if it involves the memory domain. The progression to dementia, if occurs, is a slow process usually taking several years. Apart from the subtypes of MCI, the risk of progression to dementia depends on other factors like the clinical setting and presence or absence of biomarkers. In the clinic-based population, the annual conversion rate is 10%-15%, while it is 3.8% to 6.3% in the community-based samples. White matter abnormalities on MRI do not predict progression to dementia in MCI, but hippocampal atrophy does. Other biomarkers that indicate future dementia risk include characteristic patterns of hypometabolism on FDG PET scan and apolipoprotein E e4 allele. A positive amyloid scan is the most reliable predictor of progression to dementia. The rate of conversion in three years is 82% with a positive amyloid scan and 7% with a negative scan. A systematic review and pooled analysis found 83%-100% sensitivity and 46% and 88% specificity for a positive ^{11}C-PIB-PET scan.

2.1.9 Risk factors associated with Alzheimer's disease

The importance of identifying risk factors lies in the potential of prevention through risk modification. Numerous risk factors of AD have been identified, but prospective studies that assessed these risk factors are very few.

2.1.9.1. Socio-demographic factors

2.1.9.1.1. Age: Age is the single most definite risk factor of Alzheimer's disease. AD pathology is related to dementia for all age groups, although the strength of this relationship is stronger for individuals below the age of 90 years (Dolan et al., 2010; Haroutunian et al., 2008; Savva et al., 2009). One meta-analysis found that the incidence of dementia rose exponentially with age up to 90 years (Jorm & Jolley, 1998). The proportion of people with Alzheimer's dementia show a steadily increasing pattern with age: three percent of people aged between 65- and 74 years, 17 percent of people aged between 75 and 84 years and 32 percent of people aged above 85 years suffer from Alzheimer's dementia (Hebert et al., 2013). Some people never develop dementia during a feasible life span (Jorm, Dear, & Burgess, 2005), and data from Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) project showed that the age-specific risk reduced after 90 years (Lautenschlager et al., 1996). These findings suggest that dementia is not an inevitable attendant of aging. Nonetheless, the highest incidence (61.1) is in individuals above 90 years of age (Jorm & Jolley, 1998).

The relationship between Alzheimer's pathology and clinical dementia is less evident in nonagenarians and centenarians compared with younger age (Haroutunian et al., 2008). Many elderly subjects with Alzheimer's disease pathology do not develop dementia (Bennett et al., 2006; Driscoll et al., 2006; Roe, Xiong, Miller, & Morris, 2007).

Episodic memory loss occurs in both normal aging and dementia (Mitchell & Shiri-Feshki, 2009; Small, Schobel, Buxton, Witter, & Barnes, 2011). Neurofibrillary tangles (NFT) in the medial

temporal lobe are also seen in both aging with and without dementia, and they are associated with impairment in episodic memory (Mitchell et al., 2002). Atrophy in healthy aging and AD overlap in the hippocampus and entorhinal cortex (Raji, Lopez, Kuller, Carmichael, & Becker, 2009). The key difference between normal aging and aging with dementia is the extent of NFT. In aging without dementia, NFT is confined to the medial temporal lobe, whereas in dementia, it spreads to the inferior temporal lobe and then to the association cortex and eventually to primary and secondary cortical regions. The critical factor that determines the spread of NFT is the presence of Aβ. Neurofibrillary tangles progresses with the accumulation of Aβ, and in its absence, aging without dementia ensues (Maass et al., 2018). Neurofibrillary tangles without significant retention of Aβ is associated with hippocampal atrophy and reduced cognitive performance (Josephs et al., 2017). The cognitive impairment is typically minimal but may vary from normal performance to profound deficit. This entity is now identified as primary age-related tauopathy (PART) and characterized by the presence of NFT with minimal Aβ (Thal amyloid phase ≤2) and Braak and Braak staging ≤ IV (usually III or lower) (Crary et al., 2014). Besides lack of progression of NFT and the absence of Aβ, features such as low frequency of apolipoprotein E e4, absence of involvement of posterior hippocampus and hippocampal sclerosis distinguish PART from Alzheimer's disease.

2. 1.9.1.2.Gender: Prevalence studies have found an increased risk of dementia in women (Jorm, Korten, & Henderson, 1987; Rocca et al., 1991). Whereas some authors have shown a higher overall incidence (Gao, Hendrie, Hall, & Hui, 1998; Nichols et al., 2019) others have found the same only in older age (Jorm & Jolley, 1998). In a two-wave community study that combined the initial and later incidence of dementia in residents aged above 85 years, the overall incidence was found to be higher in women than in men (Gussekloo, Heeren, Izaks, Ligthart, & Rooijmans, 1995). In a three-year follow-up study, the age-adjusted odds ratio for women was 3.1 for Alzheimer's dementia (Fratiglioni et al., 1997). These findings were replicated by another longitudinal study that indicated a higher risk of dementia in women than in men after the age of 80 years (Letenneur et al., 1999). The same study also found a higher incidence in men than in women before the age of 80. The increased risk remained after adjusting for education (Letenneur et al., 1999). On the other

hand, the Framingham study did not find a significant difference in the incidence of dementia between men and women (Bachman et al., 1993). It was a 10-year follow-up study of the incidence of Alzheimer's dementia in a general population sample. One explanation is that more women than men survive into the risk period of AD so that women are overrepresented in the AD population and when adjustments were made for survival the increased risk in women was only mild (Rocca, Amaducci, & Schoenberg, 1986; Rocca et al., 1991; Schoenberg, 1986).

2.1.9.1.3. Education and premorbid intelligence

Prospective studies have proposed that high levels of education reduce the risk of dementia (Letenneur et al., 1999; Ott et al., 1995; Stern et al., 1994). The Framingham study reported a higher age-adjusted risk of dementia with grade school education or less compared with high school diplomas (Cobb, Wolf, Au, White, & D'Agostino, 1995). There is no evidence that higher education affects pathological processes associated with dementia, however (Brayne et al., 2010). Instead, education mitigates the dementia effects of neurodegenerative pathology (Brayne et al., 2010). These findings have led to the hypothesis that education acts as neurocompensation rather than neuroprotection. The famous Nun study has demonstrated that a lower level of education combined with small head circumference was associated with a four-fold increased risk of late-onset dementia. In contrast, either factor alone did not result in an increased risk (Mortimer, Snowdon, & Markesbery, 2003). Either higher education or larger head size afforded protection in terms of the expression of dementia at a later age (Mortimer et al., 2003). The Lancet Commissions identified less education (none or primary education only) as a modifiable risk factor (Livingston et al., 2020; Livingston et al., 2017). The population attributable risk fraction (PAF) is the percentage reduction in the incidence of dementia when a particular risk factor is eliminated. The PAF for education is the second highest, next to hearing loss (Livingston et al., 2017).

Out of 14 prevalence studies, ten studies identified an increased risk of dementia with low education, whereas four studies found no such relation (Sharp & Gatz, 2011). A total of 42 studies

investigated the relationship between the incidence of dementia and education. A clear majority of these studies showed an increased dementia risk with a low level of education (Sharp & Gatz, 2011). A recent meta-analysis has provided further information about the dose-response trend in the risk of Alzheimer's dementia; the dementia risk was reduced by 7% per year of education (Xu et al., 2016).

In the Nun Study, low linguistic density, as reflected in early life autobiographies, was found to be associated with impaired cognitive performance and Alzheimer's disease in late life (Snowdon et al., 1996). The Scottish Mental Health Survey revealed an association between childhood mental ability and late-onset dementia, but not early-onset dementia (Whalley et al., 2000). A recent study showed an inverse relationship between intelligence scores measured at the age of 11 years and the incidence of dementia after the age of 65 (Russ et al., 2017). In a retrospective cohort study, higher IQ and mental activity in the adolescent age were independently found to be associated with a reduced risk of dementia (Fritsch, Smyth, Debanne, Petot, & Friedland, 2005).

2.1.9.1.4. Genetic risk factors

2.1.9.1.4.1 Chromosomal abnormalities. The most definitive aetiology for Alzheimer's disease is the genetic abnormality seen in Down's syndrome-the trisomy of 21'st chromosome ("2019 Alzheimer's disease facts and figures," 2019). It represents the highest risk, and almost all patients with Down's syndrome develop Aβ deposition by the age of 40-50 years and clinical dementia by the age of 60 years (Wisniewski et al., 1985). Down's syndrome was the first genetic disease implicated in AD.

Apart from Down's syndrome, three other genetic abnormalities cause AD. Mutations of genes coding for the Amyloid Precursor Protein (APP), presenilin I, and presenilin II show Mendelian inheritance and cause autosomal dominantly inherited AD. Proteins coded by these genes are involved in the metabolic pathway of Aβ, and mutations result in overproduction of Aβ,

particularly the form with 32 amino acids that has the greatest neurotoxicity (Hardy, 1997). Several mutations involving the APP gene are described in the familial early-onset AD. Mutations affecting the presenilin I gene that is located on chromosome 14 account for most of the familial AD (Hardy, 1997). Presenilin II gene is located on chromosome 1. Mutations involving this gene are rare. They are described in families with a history of German origin and later migration to the Volga river in Russia and then to different parts of the world (Cummings, Vinters, Cole, & Khachaturian, 1998). In spite of the causal role of mutations of APP, presenilin I, and presenilin II genes, they cause only 1% of AD. Patients with such mutations develop dementia before the age of 65 years.

2.1.9.1.4.2. Family history of dementia: Individuals who have one affected member in the immediate family are at higher risk of developing AD than those without an affected immediate family member (Fratiglioni, Ahlbom, Viitanen, & Winblad, 1993; Green et al., 2002). According to a meta-analysis of case-control studies, the risk of dementia was 3.5 times higher if there was dementia in the first-degree relative. Still, this risk was non-specific because higher incidence was found when the first-degree relatives had other neurological diseases suggesting a selection bias of the samples studied (Mayeux, Sano, Chen, Tatemichi, & Stern, 1991). The risk becomes higher if there are two or more affected members (Lautenschlager et al., 1996). The children of conjugal AD couples had a cumulative risk of 54% by the age of 80 years, which was 1.5 times greater than the sum of the risks to children having affected mothers or fathers, and nearly five times greater than the risk to children having normal parents. The children of affected fathers had a cumulative risk that was 1.4 times higher than the corresponding risk to children of affected mothers.

2.1.9.1.4.3. Apolipoprotein E: Apolipoprotein (APOE) e4 allele is the most influential genetic risk factor for late-onset AD (Corder et al., 1993; Farrer et al., 1997; Hashimoto et al., 2012). Apolipoprotein is a protein that plays a crucial role in cholesterol transport and coded by genes situated on chromosome 19, which has three alleles, e2, e3, and e4. e3 is the most common form, and e2 is the least common. e2 decreases, and e4 increases the risk of dementia. Apolipoprotein e4 is composed of 299 amino acids, and the differences in amino acids 112 and 158 give rise to

the isoforms, e2, e3, and e4. In the brain, APOE is produced in abundance by astrocytes. It regulates the clearance of lipoproteins from plasma and transport of lipids within tissues by serving as the ligand for binding to various cellular receptors. In the central nervous system, it acts as the principal lipid transport vehicle by redistributing lipids to growing and regenerating axons after injury. Apolipoprotein e4 facilitates Aβ oligomerization and its clearance in an isoform dependent fashion, e4 < e3 < e2. Aβ binding to APOE e4 results in Aβ -APOE e4 complex, which is internalized by the Very Low-Density Lipoprotein (VLDL) receptor more slowly than Aβ-APOE e2, and Aβ-APOE e3 complexes. Immunohistology techniques showed that senile plaques in the brains of patients with AD were embedded with APOE (Namba, Tomonaga, Kawasaki, Otomo, & Ikeda, 1991).

A meta-analysis of clinic-based and autopsy data concluded that the inheritance of AD was significantly increased for people with APOE genotypes e2/e4 (2.6 times) e3/e4 (3.2 times) and e4/e4 (14.9 times). The risk was decreased for people with a genotype e2/2 (Farrer et al., 1997). Apolipoprotein e4 is associated with increased Aβ deposition in the form of senile plaques as well as lower age at onset of dementia (Castellano et al., 2011; Polvikoski et al., 1995). The increased risk is seen for all ages and all ethnic groups, although it is robust before the age of 70 years and in Caucasians (Farrer et al., 1997). According to amyloid Positron Emission Tomography (PET) imaging data, APOE e4 was more prevalent in the positive ^{11}C -PIB PET scans than in the negative scans (Barthel et al., 2011) and ^{11}C -PIB retention was more in APOE e4 carriers than in non-carriers (Rowe et al., 2007). Among patients with MCI, those with APOE e4 had worse cognitive deficits and smaller hippocampal volume compared with subjects without APOE e4, suggesting distinct cognitive and imaging profiles in APOE e4 carriers (Farlow et al., 2004). Moreover, APOE e4 was associated with an increased risk of progression of MCI to Alzheimer's dementia (Petersen et al., 1995). Finally, the presence of APOE e4 in cognitively asymptomatic individuals signifies accelerated cognitive decline and earlier onset of dementia in comparison with the absence of APOE e4 (Caselli et al., 2011; Caselli et al., 2007). These findings show that apolipoprotein E e4

implies a substantial risk of AD, and it is associated with cognitive decline and AD pathology relatively early when compared with a non-APOE e4 status.

2.1.9.3. Cardiovascular diseases

Apolipoprotein e4 is a risk for both AD and cardiovascular diseases. A Finnish study found an association between increased levels of low-density lipoprotein (LDL) and APOE Ee4 (Gronroos et al., 2007). In another prospective study, Framingham Cardiovascular Risk Profile predicted progression to Alzheimer's dementia in MCI, and this risk was escalated with APOE E e4 (Viticchi et al., 2017). Epidemiological data suggested that hypertension is a risk factor for dementia (Kivipelto et al., 2001). Population-based studies provided evidence supporting an association between diabetes mellitus and Alzheimer's dementia (Barbagallo & Dominguez, 2014). Central obesity is known to increase the risk of dementia (Whitmer et al., 2008) particularly in women (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003). Impaired clearance of Aβ is another mechanism of increased risk of AD in cardiovascular diseases.

2.1.9.4. Traumatic brain injury

Traumatic brain injury (TBI) refers to the dysfunction of normal brain functions secondary to mechanical trauma to the head or penetration of the skull by a foreign object. Loss of consciousness for more than 30 minutes defines moderate TBI. If the duration of post-traumatic amnesia is more than 24 hours, then it constitutes severe TBI. Studies that have investigated the causal link between dementia and TBI have provided conflicting findings. Earlier, a meta-analysis of 11 case-control studies indicated an increased relative risk for AD (RR=1.82) in TBI (Mortimer et al., 1991). Although a stronger association was observed with the family history of dementia and gender, adjustment for family history, alcohol use, and education did not amend the association between TBI and dementia. Other authors replicated this finding (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003). A large follow-up study of more than 5000 participants showed an

increased risk of dementia with moderate to severe TBI for all age groups. With mild TBI, the risk was seen only in a higher age group, 65-74 years compared with 55-64 years (Gardner et al., 2014). A recent retrospective cohort study of older veterans with TBI showed a 60% higher risk of dementia with TBI, and this risk persisted after adjusting for potential confounders viz., demographic factors, and medical and psychiatric morbidities (Barnes et al., 2014). A research group from the Duke University assessed military records and the late occurrence of dementia in World War II Navy and Marine veterans (Plassman et al., 2000). The findings suggested that AD risk increased by the severity of TBI; the risk was inconclusive for mild TBI, 2.32 times higher for moderate for TBI, and 4.51 times higher for a severe head injury. Epidemiological studies that suggested an increased risk of dementia in TBI have not been supported by a recent biomarker study that did not show increased deposition of Aβ in veterans with TBI (Weiner et al., 2017).

Few prospective epidemiological studies, case-control studies, and systematic reviews failed to show an association between late-onset dementia and traumatic brain injury, however (Dams-O'Connor et al., 2013; Godbolt et al., 2014; Lindsay et al., 2002; Mehta et al., 1999). Moreover, subjects had to recall their experience of head injury, and for this reason, case-control studies suffered from recall bias. These mythological limitations. Therefore, the association between TBI and dementia is far from being conclusive.

2.1.9.5. Sleep and Alzheimer's disease

The research into the relationship between AD and sleep disorders has gained momentum recently. Studies addressing such a relationship began in the 1980s. Smallwood et al. studied the relationship of sleep apnoea to age, gender, and dementia (Smallwood, Vitiello, Giblin, & Prinz, 1983). Further studies have suggested an association between Alzheimer's dementia and sleep apnoea and revealed that the severity of apnoea correlated with the severity of dementia (Hoch et al., 1986; Reynolds et al., 1985). A study of Chinese nonagenarians and centenarians showed an association between sleep quality and cognitive function (Chang-Quan, Bi-Rong, & Yan, 2012).

Cognitive impairment was associated with poor sleep quality, longer sleep latency, and lower sleep efficiency percentage. In another study, the Aβ burden in the medial prefrontal lobe was correlated with NREM sleep Slow Wave Activity impairment (Mander et al., 2016).

Natural sleep or anaesthesia is associated with a 60% increase in the interstitial space and an increased convective exchange of cerebrospinal fluid with interstitial fluid in animal models. The expansion of interstitial space helped convective fluxes of interstitial fluid and increased the rate of Aβ clearance during sleep (Xie et al., 2013a). The findings derived from animal studies are consistent with amyloid imaging studies in humans (Mander et al., 2016). In a cross-sectional study of community-dwelling older individuals, Spira et al. observed an increased amyloid deposition in subjects with shorter sleep duration (Spira et al., 2013). Older individuals with insomnia had a faster progression to dementia from normal cognitive functioning compared with those who did not report insomnia (Osorio et al., 2011). Sleep Disordered Breathing is associated with earlier onset of both MCI and AD compared with subjects without SDB. This progression could be delayed by continuous positive airway pressure (CPAP) treatment (Osorio et al., 2015). Moreover, the adverse effect of the Apolipoprotein E e4 allele has been attenuated by better sleep consolidation (Lim et al., 2013).

2.1.9.6. Other Risk factors: popular dementia studies

2.1.9.6.1. The Nun Study

The Nun study epitomized the longitudinal investigation of aging and Alzheimer's research. The study began in 1991 and involved 678 Catholic nun sisters from the Notre Dame congregation. The sisters lived in a relatively homogenous environment; this might have eliminated environmental and lifestyle confounders that could affect dementia outcomes. As part of the study, the sisters underwent serial cognitive assessments, and many agreed to donate their brains for autopsy (Riley, Snowdon, & Markesbery, 2002; Snowdon, 2003; Snowdon et al., 1996).

The Nun study provided insights into the risk factors of dementia and the link between neuropathology and clinical disease. There was a broad range in cognitive and physical function among the nun sisters, along with variable neuropathology despite homogenous living conditions. Some sisters became centenarians, and the oldest sister lived up to the age of 107 years. The investigators accessed archives of the convent and found that the linguistic density of autobiographies, written in their 20s, correlated with a reduced risk of dementia in late life. Some nuns were models of healthy aging with preserved cognition in the presence of AD lesions. Detailed analysis of the lesions in one sister showed widespread diffuse plaques extending to the hippocampus, and NFT that were confined to the mesial temporal lobe sparing association cortex. In an exceptional circumstance, one sister retained cognitive function, albeit extensive NFT corresponding to Braak and Braak score of 6 and homozygous apolipoprotein E e4.

2.1.9.6.2. Australian Imaging Biomarkers and Lifestyle study of Ageing (AIBL)

The AIBL study was launched in November 2006. The participants aged above 60 years have been recruited to one of three groups: the cognitively normal controls, MCI, and Alzheimer's dementia. By 2017 the study has recruited 989 cognitively asymptomatic individuals. The AIBL research found that APOE had a dose-dependent impact on A-β levels and episodic memory. Such a relationship was significant with e4 heterozygotes and the strongest with e4 homozygotes (Rowe et al., 2007). The study also revealed that the correlation between amyloid burden as measured by Pittsburgh B Compound (PiB) scan and decline in cognition was weak. Still, progression from MCI to dementia of Alzheimer's type was 67% in subjects with high PiB uptake and 5% in those with low PiB uptake (Villemagne et al., 2011).

2.1.9.6.3. European Studies of Dementia (EURODEM) Network

The European Studies of Dementia (EURODEM) network pooled data from several studies conducted in Denmark, France, the Netherlands, and the United Kingdom. The data were obtained from 528 incident dementia patients aged 65 years and above and 28,768 person-years of follow-up (Launer et al., 1999). The association between a particular risk factor and dementia was estimated by the Relative Risk (RR) at 95% Confidence Intervals (CIs) using a Standard Poisson program to calculate the measurements. Given that the follow-up period was relatively short, with a mean of 2 years, this method was similar to the risk estimated by Cox's proportional hazards regression. The results showed that a family history of dementia in two or more first-degree relatives, a lower level of education, and smoking history increased the risk of dementia. The significance of education was found only in women, and the smoking effect was stronger in men. A prevalent study suggested a reduced risk of dementia with smoking (Jones, Sahakian, Levy, Warburton, & Gray, 1992) possibly because of the memory-enhancing effects on nicotine receptors (Graves et al., 1991), but the findings could not be replicated by another study (Brenner et al., 1993).

2.1.9.6.4. Canadian Study of Health and Aging

A large Canadian prospective study of aging showed an increased risk of AD with a lower level of education, higher age, and APOE e4 allele (Lindsay et al., 2002). Non-steroidal anti-inflammatory drugs, coffee and wine consumption, and regular physical activity were associated with diminished risk. There was no association between dementia and a family history of dementia, gender, history of depression, estrogen replacement therapy, head trauma, antiperspirant or antacid use, smoking, high blood pressure, heart disease, or stroke.

2.1.10 Psychiatric disorders as risk factors for Alzheimer's disease

2.1.10.1. Depressive disorders: For a long while, late-onset depression was regarded as a harbinger of dementia (Alexopoulos et al., 1997; Kral & Emery, 1989). There is mounting evidence supporting an association between depression and cognitive decline and eventual dementia (Byrne & Pachana, 2010). This hypothesis rested mainly on two observations: the chronic course and cognitive impairment in late-onset depression. The term pseudodementia was coined by Leslie Kiloh to describe a syndrome that mimicked dementia and recovered when the underlying psychiatric disorder-mostly depression-remitted (Kiloh, 1961). The term was originally applied to any psychiatric disorder that presented with cognitive impairment, but later it became synonymous with cognitive deficits seen in depression. The name pseudo implied that there was no neurodegenerative process behind dementia.

Long term follow-up data of 18 years showed that 39 out of 44 patients with depression and pseudodementia (89%) developed dementia at the end of the study (Smith & Kiloh, 1981). Some of these patients recovered from depression as well as cognitive deficits of pseudodementia. These findings were replicated in a UK follow-up study of 182 patients over 5-7 years; 71.4% of patients with pseudodementia developed dementia compared with 18.2% of cognitively intact subjects(Saez-Fonseca et al., 2007). Alexopoulos et al. demonstrated that geriatric depression with pseudodementia had a 4.69-times higher chance of developing into irreversible dementia later in the course of illness compared with patients with depression without pseudodementia. Irreversible dementia occurred in depressed patients with pseudodementia (43%) much more frequently than in those with depression without pseudodementia (12%) (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993). A meta-analysis of case-control studies and prospective studies showed that the risk of dementia doubled with previous depression (Jorm, 2001). The link between geriatric depression and Alzheimer's dementia has become stronger with neuroimaging findings. A meta-analysis of voxel-based morphometric studies has shown that amygdala and parahippocampal volumes may be reduced in Major Depressive Disorder (Bora, Fornito, Pantelis, & Yucel, 2012).

Cortical grey matter volume was also found to be significantly reduced in depression (Bora et al., 2012). Reduced hippocampal volumes in depression were associated with deficits in visual and verbal memory performance (Hickie et al., 2005). Hippocampal volume was not altered in early-onset depression or with the total duration of depression (Lloyd et al., 2004).

There are a few hypotheses concerning the relationship between depression and Alzheimer's dementia. One explanation is that depression is an early manifestation of dementia. Others point out that depression brings forward the recognition of dementia by added impairment in cognition and motivation (Jorm et al., 2005). The third hypothesis is that depression causes damage to medial temporal lobe structures leading to dementia. Another possibility is the impact of vascular lesions in the brain, specifically, chronic small vessel disease on mood (vascular depression) and cognition (vascular dementia).

Summary

Numerous risk factors of Alzheimer's disease have been investigated using varying methodology. Among several risk factors for Alzheimer's disease identified, age is the strongest. The relationship between age and dementia is epidemiologically linear with increasing prevalence with advancing age. When it comes to AD pathology and manifest disease, the association is convoluted, however, and compounded by confounding factors such as vascular lesions. High Aβ burden results in dementia in the younger old, typically below 80 years, but such a relation is not straight forward in nonagenarians and centenarians where other pathology is more frequent. Many older individuals have a high burden of Aβ without dementia. This disparity is believed to reflect a higher threshold for neurofibrillary tangles to cause dementia in individuals aged above 90 years compared with the young-old and earlier manifestation of dementia with APOE e4 in those aged below 70 years. The converse is equally valid, older

persons with relatively low β-amyloid burden may develop dementia, and increased vascular lesions mediate this risk. With aging, tau deposition in the medial temporal lobe accounts for impairment of episodic memory, which can occur without dementia, but in a syndrome called primary age-related tauopathy (PART). In the absence of abnormal Aβ, this is confined to the medial temporal lobe. With an increased deposition of β-amyloid, tau accumulation will progress to the cortical areas with consequent dementia. Apolipoprotein e4, by reducing the clearance of Aβ, plays a critical role in the genesis of dementia in this regard. Coming to gender differences, the findings are not uniform or conclusive, although the available data show a trend towards an increased prevalence of dementia in women aged above 80 years. Genetic abnormalities represent the highest risk for Alzheimer's dementia, typically young-onset dementia. Dementia is almost certain in Down's syndrome by the age of 50-60 years, while specific mutations in amyloid precursor protein or in presenilin I and II imply 100% risk for offspring. Apolipoprotein e4 is another genetic risk factor for dementia, particularly in the homozygous state (e4/e4). Cardiovascular risk factors, perhaps by interfering with the clearance of β-amyloid, increase the risk of dementia. There is robust evidence suggesting the protective role of premorbid intelligence, education, and bilingualism in delaying the onset of dementia if not preventing dementia forever. These factors confer protection not by reducing the pathological process of Alzheimer's disease but enhancing cognitive reserve, which can buffer the pathological load. The association between traumatic brain injury and Alzheimer's dementia remains elusive; epidemiological studies that suggested an increased risk have not been supported by biomarker studies (Weiner et al., 2017). On the other hand, mounting data indicate an increased risk of dementia in the presence of sleep disorders. The proposed mechanisms include enhanced clearance of β-amyloid with an expansion of extracellular space during sleep.

2.2. Posttraumatic Stress Disorder and the Risk of Dementia

2.2.1 Introduction

Posttraumatic stress disorder is a stress response syndrome that follows exposure to catastrophic trauma. A diagnosis of PTSD cannot be made without a history of exposure to trauma. It is an epitome of a syndrome that occurs at the interface of external trauma and an internal responsive brain (Shalev & Marmar 2017). The trauma is of such a nature that it is outside the range of ordinary human experiences posing a threat to life or personal integrity of oneself or others (Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, 5th Edition, 2013). The most commonly studied traumatic situations were those involving a victim of crime, sexual assault, natural disasters, and combat exposure (Kessler, Chiu, Demler, Merikangas, & Walters, 2005).

2.2.2 History of Posttraumatic Stress Disorder

Intense psychological reactions after experiencing extreme stressors are seen throughout recorded history. Post-trauma psychological reactions were included in Lucretius' De Rerum Natura, which was written in the 50 BC (Crocq & Crocq, 2000). The history of PTSD is, in a way, the history of war-related traumas, which is almost as old as humanity. In the Gisli Súrsson Saga, there is a description of a war hero who is unable to stay alone at night after he experienced dreams of battle scenes (Figley & Boscarino, 2012). The psychological syndrome that originated in the aftermath of wars was known under various names: war neurosis, the irritable heart of soldiers, shell shock syndrome, and combat neurosis. During the first World War, approximately 80,000 troops with shell shock syndrome entered army hospitals, and a quarter of them required admission to psychiatric hospitals (Gersons & Carlier, 1992). Based on this diagnosis, a further 200,000 soldiers were exempted from services. At one stage, English psychiatrists believed that traumatized soldiers had symptoms of 'hysteria,' and the remedy was to ignore it or not to talk about it (Gersons

& Carlier, 1992). Admissions of soldiers to psychiatric institutions followed. The greatest despair was in the unknown origin of the syndrome. The term 'shell-shock' syndrome came from an erroneous judgment of doctors who believed that the syndrome resulted from micro-sections of exploded bombs trapped in the brain (Gersons & Carlier, 1992). This term was later abandoned when it was noted that individuals developed the syndrome without direct exposure to bombs. There was a suggestion that the syndrome represented simulation, and those afflicted with it must be imprisoned and executed. But the generals did not agree with such drastic measures. The contributions of a French psychologist Myers are worth remembering in this context. Myers and colleagues used the technique of hypnosis and helped affected soldiers relive painful memories and gain emotional balance. It was in the aftermath of the First World War that post-combat psychological reactions were given adequate attention. Abram Kardiner, who treated World War I veterans between 1922 and 1925, published a book based on his experience (1947). He pointed out that the acute form of post-combat psychological syndrome must be treated immediately to avoid its progression to a chronic intractable form. He also recognized that the syndrome was a 'psychoneurosis' given prominent physical symptoms.

In times of war, the post-traumatic psychological syndrome was rediscovered. In the intervening years, both the medical community and the patients themselves minimized the symptoms. A detailed account of the psychological consequences of combat trauma was published in 1941. This was formed from the experience of survivors of World War II and prisoners of war camps. The distinguishing feature of World War II was the total war that killed millions of civilians (Crocq & Crocq, 2000). Armies were unprepared to deal with the psychological crisis. Psychiatrists were viewed not only as useless but also a burden. In December 1942, Winston Churchill wrote to the Lord President of the Council, and it read: - "I am sure it would be sensible to restrict as much as possible the work of these gentlemen [psychologists and psychiatrists]." In 1943 the term 'exhaustion' was used to describe all psychological reactions arising from the combat duty. Grinker and Spiegel described 65 clinical scenarios and classified post-combat psychological syndromes into an acute response and a delayed syndrome that included 'war neurosis' (Grinker and Spiegel

1945). The story of a group of French civilians is intriguing in this context (Crocq, Macher, Barros-Beck, Rosenberg, & Duval, 1993). They were conscripted to the German army but later held in captivity in Russia. They were bilingual people with cultural roots in both heritages. They fought for Germany under threat. When the Soviet Army captured them, they were treated as German soldiers, but later sent to France. Post-war France was gripped by guilt after their early surrender to the Nazi army. French people believed that the incorporation of these soldiers into the German army was a form of treason. A survey showed long-lasting symptoms in these soldiers that persisted over decades. A good majority of them (82%) reported intrusive recollections and nightmares of their wartime captivity, many tried to suppress thoughts or feelings associated with the trauma and experienced a foreshortened sense of the future, and others went through survivor guilt.

2.2.3. The Vietnam War

The Vietnam War was a conflict that occurred between North Vietnam and the government of South Vietnam from November 1, 1955, to April 30, 1975. The Soviet Union, China, and other communist forces supported the North Vietnamese Army, and the United States, South Korea, Australia, Thailand, and other anti-communist allies supported the South Vietnamese army. The People's Army of North Vietnam and the political organization of South Vietnam, known as the National Liberation Front (also known as Viet Cong), fought against the U.S and allied forces occupation in South Vietnam. Gradual withdrawal of the U.S forces began in the early 1970s as part of a process called Vietnamization. It was a policy of the Richard Nixon administration to end U.S. involvement in the Vietnam War. Vietnamization was a program to expand, equip, and train South Vietnamese forces and assign to them an ever-increasing combat role, at the same time steadily reducing the number of U.S. combat troops. The Vietnam War ended on April 30, 1975, with the capture of Saigon, the capital of South Vietnam by the People's Army of Vietnam and the National Liberation Front. The war resulted in a huge toll, with an estimate of 966,000 to 3.1 million deaths (Hirschman, Preston, & Loi, 1995). 58,220 U.S. service members also died in the conflict,

and a further 1,626 remained missing in action (Leland, Oboroceanu, Library of, & Congressional Research, 2010).

The psychological consequences of combat-related trauma attracted widespread attention following the Vietnam War. This perpetual form of post-combat psychological symptoms was commonly termed as post-Vietnam syndrome. Subsequently, the psychological symptoms following combat exposure were relabelled as Posttraumatic Stress Disorder (PTSD) and included in the 3'rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 (Crocq & Crocq, 2000). A problem remained, however, because the diagnostic nomenclature was based on consensus, not an empirically validated disorder. The consensus-based diagnosis led to repercussions in the period afterward, and socio-political debate surrounding the validity of PTSD had roots in the origin of the disorder as a new entity (Mezey & Robbins, 2001). Summerfield argued that PTSD represented a political transformation from a war focused state of affairs to a patient-centred approach, legitimization of victimhood, and moral exculpation to soldiers (Summerfield, 2001).

2.2.3.1. Australian involvement in the Vietnam War

The Vietnam War marks an important landmark in Australian history. It was Australia's longest war until surpassed recently by its long-term commitment to the War in Afghanistan. The Australian Vietnam troop was the largest contribution to a foreign conflict since World War II. Australia's involvement in the Vietnam War began in 1962 with a small commitment of 30 military advisors. Over the next decade, the commitment increased to a peak of 7672 Australian personnel following the Menzies Government's decision to upgrade the involvement in South Vietnam. Australian and New Zealand military forces had gained experience in jungle warfare and counterinsurgency while assisting the British during the Malayan Emergency during 1948-1960. The Australian Government had introduced conscription for compulsory military service under the National Service Act of 1964 to boost the size of the Army by providing a greater number of

infantrymen. The National Service Act (1964) was an Australian federal law, which required males to serve in the Army for twenty-four months of continuous service, followed by three years in the Reserve. Public opinion polls in the late 1960s did not favour Australia's involvement in the Vietnam War. The withdrawal of the Australian force commenced in November 1970 and completed in January 1972. Approximately 60,000 Australians served in the war; 521 were killed, and more than 3,000 were wounded (Australian War Memorial).

2.2.4. Controversies about the diagnosis of Posttraumatic Stress Disorder

The term posttraumatic stress disorder was born to an age of philosophical discourse on the futility of war, contentious socio-political views of stress-related syndromes, and antipsychiatry movements. It was met with advocacy programs and a sense of mission for victims of trauma. The term PTSD was also used to identify psychological damage and claim compensation (Shalev & Marmar, 2017). The resulting controversies shifted the focus from the intended purpose of the diagnosis of PTSD as a descriptor of stress syndrome to a socio-economic construct. It has been argued that achieving an understanding of PTSD is not the province of medicine but of war and sociology. The notion that a single etiological factor-the war trauma-caused the syndrome perpetuated the debate. Such an attribution to an etiological factor was an exception to the contemporary psychiatric classification that did not make assumptions about the underlying causes of mental disorders. The post hoc attribution fallacy ("after this and therefore because of this") led to an implicit assumption that stress causes PTSD, despite the fact PTSD did not develop in a majority after exposure to trauma. Additionally, the U.S Institute of Medicine reported that three decades of studies in the field of PTSD had not produced a cohesive body of evidence (Shalev & Marmar, 2017).

Summary

Posttraumatic stress disorder represents a morbid stress response to catastrophic trauma, the events that are outside ordinary human experiences and threatening to life or integrity of oneself or others. Intense psychological reactions in the aftermath of wars are recorded throughout history. Post-war psychiatric symptoms received little scientific attention until World War I when Abraham Kardiner recognized the potential for chronic intractable nature of the illness and the accompanying physiological symptoms. It was after the Vietnam War that a perpetual form of post-combat adverse psychological reactions attracted global attention. This chronic form of post-war psychiatric syndrome came to be known as the post-Vietnam syndrome. Diagnostic and Statistical Manual of Mental Disorders included the syndrome in its 3'rd edition and renamed it as the posttraumatic stress disorder in 1980. The Vietnam War began in 1955 and ended in 1975. The war resulted in a huge toll, with an estimate of the number of Vietnamese soldiers and civilians killed varied from 966,000 to 3.1 million. It was Australia's longest war until surpassed recently by its long-term commitment of combat forces to the War in Afghanistan. Controversies surrounded the validity of the diagnosis of PTSD and served to act as a distractor by shifting the focus from the diagnosis of a stress response syndrome and victim advocacy to social, political, and economic dimensions.

2.2.5. Incidence and prevalence of Posttraumatic Stress Disorder

Posttraumatic Stress Disorder, with a lifetime prevalence rate of 6.4%, poses significant challenges to public health (Kessler et al., 2005). According to the DSM-IV criteria, the 12-month prevalence of PTSD was1.5% (Rosenman, 2002). This rate was much lower than the figure found in North America (3.9%) (Kessler, Mickelson, & Williams, 1999). Had this data been extrapolated to the whole population of Australia, it would have given 179 093 diagnoses of PTSD during a

year. Posttraumatic stress disorder was historically assessed for each traumatic exposure and this approach created challenges when respondents reported multiple traumas.

Women are at higher risk of developing PTSD compared with men (Kessler et al., 1994; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The gender difference in the incidence is a pressing conclusion from the trauma literature (MacGregor, Clouser, Mayo, & Galarneau, 2017; Olff, Langeland, Draijer, & Gersons, 2007) Such an increased risk has been observed in a military context as well; the prevalence of PTSD among U.S. navy health personnel was higher in women than in men after adjusting for combat exposure severity, previous psychiatric history, and demographics (MacGregor et al., 2017). The proposed reasons for the higher incidence in women include their stronger perception of threat and loss of control, increased vulnerability to sexual assaults, and gender-specific psychobiological reactions to trauma (Olff et al., 2007).

2.2.5.1. Risk factors for posttraumatic stress disorder

Posttraumatic stress disorder does not develop in the majority of victims exposed to trauma (Blake et al., 1990; Breslau, Davis, Andreski, & Peterson, 1991; Lewis et al., 2019). This implies that certain risk factors operate in the development of PTSD. The risk factors for PTSD have been studied after both combat and non-combat traumatic exposures. Identified risk factors varied across studies and populations studied.

A systematic review and meta-analysis have summarised and divided risk factors into pre-trauma factors, peri-trauma factors and post-trauma factors (Tortella-Feliu et al., 2019). Childhood adversities and a family history of psychiatric disorder are important pre-trauma risk factors. Trauma related risk factors include the severity of trauma, meaning of the trauma, injuries, and bereavement. Trauma severity is a strong risk factor and was previously identified as the strongest risk factor in another review (Brewin, Andrews, & Valentine, 2000a). A significant correlation between the severity of injury and the risk of development of PTSD has not been consistently

reported, however (Sareen, 2014). Depressive symptoms and acute stress symptoms in the aftermath of trauma predict the future development of PTSD (Tortella-Feliu et al., 2019).

It was found that after exposure to assaultive violence, victims who had IQ greater than 115 had reduced risk of PTSD (Breslau, Lucia, & Alvarado, 2006). After earthquakes, low education level or socio-economic status, and prior trauma acted as risk factors for PTSD in adults (Tang, Deng, Glik, Dong, & Zhang, 2017). Neuroticism and childhood trauma were found to be the risk factor PTSD in the older population (van Zelst, de Beurs, Beekman, Deeg, & van Dyck, 2003). In a twin study, early age at exposure to trauma, exposure to multiple traumas, history of depression in father, low level of education at entry to military, pre-existing conduct disorder, and major depressive disorder emerged as risk factors (Koenen et al., 2002). After combat exposure, lower rank, being unmarried, low educational attainment and a history of childhood adversity were associated with the development of PTSD.

2.2.5.2. Posttraumatic Stress Disorder in War Victims

Posttraumatic Stress Disorder is common in war veterans (Figure 4). It is estimated that 20-30% of Vietnam veterans developed this disorder (Blake et al., 1990) whereas the prevalence among veterans returning from Iraq and Afghanistan was found to be 17% (Hoge et al., 2004). The essential criterion for PTSD is exposure to a catastrophic trauma which threatens one's or others' life (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). War veterans are at an elevated risk of such exposures. Once thought to be a distinct syndrome, war-related stress disorder later came to be known as combat PTSD. According to the US studies, the combat-related PTSD has a prevalence rate varying from 2% to 17%. (Dohrenwend et al., 2006; Hoge et al., 2006; Seal et al., 2007). Among Vietnam veterans, the point prevalence ranged from 2.2% to 15.2% (Eisen et al., 2004; Thompson, Gottesman, & Zalewski, 2006) (Centers for Disease Control, 1989). Australian data showed a lifetime prevalence of 21% and point prevalence of 16% in Vietnam veterans (O'Toole et al., 1996).

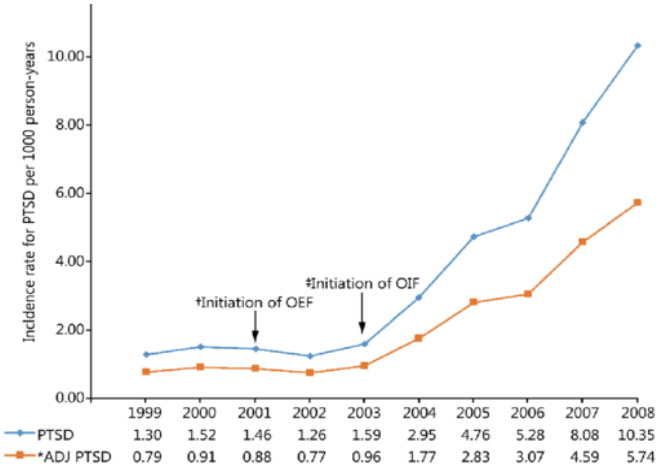

Figure 4. Annual unadjusted and adjusted incidence rates of posttraumatic stress disorder among all active-duty US service members between 1999 and 2008. †. Operation Enduring Freedom in Afghanistan, OEF; ‡. Operation Iraqi Freedom in Iraq, OIF

(Source of publication: Cameron KL, Sturdivant RX, Baker SP. Trends in the incidence of physician-diagnosed posttraumatic stress disorder among active-duty U.S. military personnel between 1999 and 2008. Military Research 2019; 6(1): 8. Copyright permission link- https://creativecommons.org/publicdomain/zero/1.0/) (Cameron, Sturdivant, & Baker, 2019)

According to the National Vietnam Veterans Readjustment Study (NVVRS), a congressionally mandated program, nearly one in every three Vietnam veterans developed PTSD (Hamner, 1992). The NVVRS rates of 30.9% lifetime PTSD and 15.2% current PTSD were regarded as unusually high. The NVVRS was widely discussed in view of the unexpected large figures and revisions of the original data on the basis of clinical severity showed lower prevalence rates (Dohrenwend et al., 2006). Compared with other wars, the Vietnam War has been described as a ‘‘low-intensity’’ war for the U.S. forces as measured by rates of combat stress breakdowns and personnel killed or wounded in action (Jones & Wessely, 2001). In line with this discrepancy, the Centers for Disease Control and Prevention (CDC) reported lower estimates (14.7% lifetime

PTSD and 2.2% current PTSD after the Vietnam War) compared with the NVVRS rates (Centers for Disease Control and Prevention, 1989; https://www.cdc.gov/nceh/veterans/default1c.htm). These prevalence rates were comparable with other sources (Eisen et al., 2004; Thompson et al., 2006). Another study found a prevalence rate of 18.7% for lifetime diagnosis and 9.1% for current diagnosis (Dohrenwend et al., 2006). A 25-year follow-up of the National Vietnam Veteran Longitudinal Study conducted between 2011 and 2013 estimated a prevalence of 17.0% of lifetime PTSD, and 4.6 % of current and subthreshold PTSD (Marmar et al., 2015). Overall, U.S. combat veterans had a prevalence of PTSD two to four times higher than in U.S civilians.

2.2.6. Diagnosis of Posttraumatic Stress Disorder

A diagnosis of PTSD requires antecedent traumatic events that are markedly distressing and ‘‘outside the range of usual human experience’’—especially events that threaten the life or physical integrity of the individual or someone close. The definition also includes witnessing death or serious injury to others (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). According to the Diagnostic and Statistical Manual of Mental Health, fifth edition (DSM-V), the following criteria must be met for a diagnosis of PTSD.

Criterion A defines the nature of trauma that can cause PTSD. The types of trauma implicated in PTSD include exposure to death, threatened death, actual or threatened serious injury, and sexual violence. The trauma exposure could be direct involvement or indirectly to the aftermath of trauma (e.g., work of first-aid responders, police, paramedics, etc.). The exposure can also be in the form of witnessing trauma or learning that a family member or close friend was exposed to trauma.

Criterion B covers the symptoms related to re-experiencing the trauma. They are unsolicited distressing memories of the traumatic event, nightmares, flashbacks, emotional distress, and physical reactivity after exposure to reminders of the trauma.

Avoidance symptoms form criterion C. One of the essential symptoms of PTSD is the avoidance of trauma-related cues, thoughts, or feelings.

Criterion D covers the negative thoughts and feelings after trauma exposure, inability to recall an important aspect of trauma, the blame of the self, negative affect, decreased level of activities, sense of isolation, and reduced capacity for positive affect.

Criterion E describes hyperarousal symptoms, which include hypervigilance, heightened startle reaction, concentration difficulties, sleep disturbances, irritability, and destructive behavior.

Criterion F is a duration specifier. The symptoms must be present for more than a month.

Criterion G requires significant functional impairment (e.g., social, occupational, etc.).

Criterion H specifies exclusions. The symptoms are not due to medication, substance abuse, or other disorders.

The International Classification of Diseases 10'th edition (ICD-10) included PTSD under neurotic and stress-related disorders. According to the ICD-10 criteria, PTSD arises as a delayed or protracted response to a stressful event or situation of exceptionally threatening or catastrophic nature. Such trauma is presumed to cause pervasive distress in almost everyone. However, ICD-10 criteria recognize predisposing factors that could lower the threshold for the emergence of PTSD syndrome after trauma exposure. Symptoms described in ICD-10 are similar to those in DSM V.

A diagnosis of PTSD is sometimes made using PTSD rating scales. Two commonly used scales are the Posttraumatic Diagnostic Scale (PDS) and the Clinician-Administered PTSD Scale (CAPS). The PDS is a self-reporting diagnostic scale with good psychometric properties (Foa et al., 2016). The administration of the PDS does not require a trained professional. The CAPS is considered as the gold standard for PTSD diagnosis (Weathers, Keane, & Davidson, 2001).

Summary

The prevalence of PTSD is higher in veterans than in the general population. One in every three Vietnam veterans developed PTSD. Women are at higher risk of developing PTSD compared with men. The diagnostic criteria provided by the DSM-V and the ICD-10 are more or less the same. The criteria specify the nature of trauma, re-experiencing symptoms with autonomous physiological arousal symptoms upon exposure to reminders of the trauma, avoidance behavior, negative symptoms such as inability to recollect important aspects of trauma, and hypervigilance. The trauma implicated in PTSD is of catastrophic nature, outside ordinary human experiences. Rating scales have been developed to assist research into PTSD. A commonly used scale is the Clinician-Administered PTSD Scale (CAPS).

2.2.7. Posttraumatic Stress Disorder and cognitive impairment

2.2.7.1. Psychopathology and cognitive biases in Posttraumatic Stress Disorder

Aversive but intrusive memories lie at the heart of the psychopathology of PTSD. Remembrance and avoidance of the reminders of trauma involve the consolidation and conservation of traumatic memories (Shalev & Marmar 2017). Overgeneralization of aversive memories, emotional dysregulation, and heightened threat sensitivity are associated with hyperarousal and hypervigilance. Fear conditioning is perhaps the most discussed theory in PTSD. Fear is arguably the strongest emotion preserved across the species during evolution.

Impairment in contextual learning, enhanced cue conditioning, and delayed extinction of fear processing are seen in PTSD. There is evidence supporting a predominance of emotional

memories that are sensory, fast, related to aversive aspects of the trauma, and perceived as immediate rather than past (Ehlers & Clark, 2000). Therefore, emotional memories seem to predominate, generalize, and fail to extinguish (Lissek & Grillon, 2010). Cognitive biases have been repeatedly observed in PTSD. Attentional, judgment, and memory biases are the best-studied biases. Attentional bias is a phenomenon where a mild threat results in disruption of ongoing cognitive activities due to an automatic redirection of attentional resources to that stimulus (Lissek & Grillon, 2010). It is a selective engagement with emotionally laden stimulus (Vasterling & Arditte Hall, 2018). Attentional bias is believed to play an essential role in the development and maintenance of PTSD symptoms. Because of the constant redirection of attention to mild threat, the salience of innocuous stimuli increases, leading to chronic hyperarousal (Mathews & MacLeod, 2002). The attentional bias has been studied using trauma-related words within a Stroop paradigm that represent mildly threatening stimuli. The studies have assessed the task performance during exposure to trauma-related words using two information-processing paradigms: a dot-probe paradigm and an emotional Stroop task. In a study of motor vehicle accidents, victims with PTSD showed attentional deficits in response time compared with those without PTSD (Bryant & Harvey, 1997).

Memory bias refers to the selective retrieval or recognition of traumatic events in contrast to neutral stimuli (Vasterling & Arditte Hall, 2018). Cognitive dysfunction in PTSD is complex; it manifests as intrusive memories as well as impoverished memories (Elzinga & Bremner, 2002). Intrusive memories take the form of flashbacks and re-enactment of the original trauma (Witvliet, Ludwig, & Laan, 2001). In patients with PTSD, enhanced processing of implicit memory (non-declarative memory) leads to increased access to information about traumatic events and subsequent intrusive recollections (Elzinga & Bremner, 2002). Vietnam veterans with PTSD showed greater implicit memory for trauma-related words than neutral words compared with control subjects (Zeitlin & McNally, 1991). Implicit memories underlie fear conditioning which is one of the proposed mechanisms of symptom manifestations in PTSD. Attempts to supress trauma related memories were followed by rebound of the same memories (Shipherd & Beck, 2005). Disruption of

regulations that control reactivation of unwanted memories has been suggested in PTSD (Mary et al., 2020). Hyperarousal in PTSD results from the generalization of the conditioned fear that becomes resistant to extinction (Elzinga & Bremner, 2002). Impoverished memories in PTSD are deficiencies in explicit memory (declarative memory) of sensory elements of the trauma, its perceived meaning, and physiological and psychological reactions that accompanied trauma (Elzinga & Bremner, 2002). In a World War II campaign, 5% of soldiers of had no recollection of the events that just took place, and many suffered from episodes of blackouts (Archibald & Tuddenham, 1965).

The impairment in verbal declarative memory is consistently observed in PSTD from a variety of trauma (Bremner et al., 1993; Golier et al., 2002; Jenkins, Langlais, Delis, & Cohen, 1998; Johnsen, Kanagaratnam, & Asbjørnsen, 2008; Samuelson et al., 2006; Uddo, Vasterling, Brailey, & Sutker, 1993; Vasterling et al., 1998; Xie et al., 2013a). The tools used in the studies were the California Verbal Learning Test, paired-association learning from the Wechsler Memory Scale (WMS), and narrative recall such as the Logical Memory subset of the WMS. In general, verbal memory impairment is more profound than visual memory impairment (Wignall et al., 2004). The pattern of memory deficits suggests impairment in the initial acquisition and learning phase of memory rather than the retention phase (Samuelson, 2011). Studies did not show significant deficits in delayed recall in PTSD when the initial acquisition was controlled (Johnsen, Kanagaratnam, & Asbjornsen, 2008; Vasterling et al., 1998; Vasterling et al., 2002). A meta-analysis of studies before 2006 showed memory impairment in PTSD with a small to moderate effect size, a finding that was replicated by Scott et al., in 2015. (Brewin, Kleiner, Vasterling, & Field, 2007; Scott et al., 2015a). Impairment was found to be more pronounced in war veterans than in civilian groups (Johnsen, Kanagaratnam, & Asbjornsen, 2008). Veterans with PTSD showed deficits in olfactory identification compared with veterans without PTSD suggesting orbitofrontal dysfunction in this disorder (Dileo, Brewer, Hopwood, Anderson, & Creamer, 2008; Vasterling, Brailey, & Sutker, 2000). This deficit was observed despite the uncompromised performance on cognitive measures assessing pre-frontal functions, and it remained significant after adjusting for

depression and substance abuse disorder. The olfactory identification deficit was associated with poor impulse control and aggression in PTSD (Dileo et al., 2008).

Summary

Impairment in contextual learning, enhanced cue conditioning, and delayed extinction of fear are the proposed mechanisms of psychopathology in PTSD. In PTSD, emotional memories of sensory and aversive aspects of trauma persist and predominate over declarative memories. Emotional memories of trauma generalize and sometimes fail to fade. Generalization of fear causes hyperarousal symptoms. Attentional, judgmental, and memory biases are important cognitive biases in PTSD. Attentional bias occurs when a mild threatening stimulus results in redirection of attention to that stimulus. There are two types of memory biases in PTSD, enhancement of implicit memories, and impoverishment of declarative memories. Augmented implicit memories result in increased access to the information of trauma leading to reliving of trauma through flashbacks. Deficits in declarative memory arise from an impaired acquisition rather than retention. PTSD may also be associated with olfactory dysfunction.

2.2.7.2. Cognitive dysfunction in combat-related Posttraumatic Stress Disorder

The studies that evaluated cognitive function in combat-related PTSD employed various measurement methods and recruited different types of control groups. For instance, while most studies used CAPS to assess PTSD (Cohen et al., 2013; Dileo et al., 2008; Dretsch et al., 2012; Geuze, Vermetten, de Kloet, Hijman, & Westenberg, 2009; Samuelson et al., 2006; Woodward et al., 2006; Yehuda, Golier, Tischler, Stavitsky, & Harvey, 2005a) some studies used the Structured Clinical Interview for DSM (SCID) (Bremner et al., 1993; Gurvits et al., 1993; Vasterling et al., 1998; Vasterling et al., 2000; Vasterling et al., 2002) and a few others administered the Mississippi Scale for Combat-Related PTSD (Beckham, Crawford, & Feldman, 1998; Sarac-

Hadzihalilović, Kulenović, & Kucukalić, 2008). Some studies had healthy controls without trauma exposure (Bremner et al., 1993; Dileo et al., 2008; Golier et al., 1997; Yehuda et al., 1995) and others had control subjects with a history of trauma exposure.

Several studies showed significant cognitive deficits in veterans with PTSD, but they had relatively smaller sample sizes. Vasterling et al. demonstrated deficits in sustained attention and learning in veterans with PTSD (n=19) compared with veterans without PTSD (n=24). This study recruited veterans who served Operation Desert Storm. The degree of deficits correlated with the severity of PTSD (Vasterling et al., 1998). Another study of Vietnam veterans compared memory and intelligence between veterans with PTSD and trauma unexposed healthy controls (Bremner et al., 1993). The study reported significantly lower scores on the tests for immediate recall, total recall, long-term storage and retrieval, and delayed recall of the verbal and visual components of the Selective Reminding Test in the PTSD group than in the control group. This study matched the control group for age, race, sex, educational background, and alcohol abuse. Subsequent reports showed that veterans with PTSD (n=26) had impairment in attention on digit span and Continuous Performance Test and deficits in recall in comparison with veterans without PTSD (n=21). The cognitive deficits remained after adjusting for general intellectual functions, combat exposure, and substance abuse (Vasterling et al., 2002). One study involved participants aged above 65 years and analysed learning and memory in three groups: those who had no exposure to trauma (n=15), a group with exposure to trauma, but no PTSD (n=20) and the third cohort with PTSD (n=35) (Yehuda et al., 2005a). Learning and memory were impaired in the PTSD group when compared with the trauma-unexposed group, but there was no significant difference in comparison with the trauma-exposed non-PTSD group. Another study examined several neuropsychological functions in veterans with PTSD and alcohol abuse (n=30), with PTSD and no alcohol abuse (n=37), with alcohol abuse but no PTSD (n=30) and neither PTSD nor alcohol abuse (n=31) (Samuelson et al., 2006). The authors found significant deficits in verbal learning, attention, and processing speed independent of alcohol use. Moreover, the cognitive deficits in the PTSD group remained upon adjusting for the effects of depression, education, premorbid intellectual function, and attention. Uddo et al. reported impairment in attention and verbal and visual memory in Vietnam combat

veterans with PTSD (n=16) when compared with veterans without PTSD (n=15) (Uddo et al., 1993).

Trail Making Tests in Vietnam veterans showed mixed results. After excluding substance abuse, major depressive disorder, anxiety disorder, and compensation seeking status, veterans with PTSD performed poorly on the Trail Making Test B in comparison with veterans without PTSD, but the performance on the Trail Making Test A was influenced by anxiety and compensation seeking status (Beckham et al., 1998). In a study of active soldiers, although PTSD was associated with an impaired performance of the working memory domain in comparison with asymptomatic healthy soldiers, the group difference did not remain when anxiety and depression were controlled for (Beckham et al., 1998).

Dutch peacekeeping veterans with PTSD showed significant deficits in learning and immediate and delayed verbal memory compared with control veterans (Geuze et al., 2009). The cognitive deficits were not accounted for by intelligent quotient. A study of Bosnian combat veterans compared cognitive functions in those with PTSD (n=20) and without PTSD (n=20) (Koso & Hansen, 2006). Impairment in attention, executive function, and memory was found in the PTSD group. Subjects did not have substance abuse or loss of consciousness, and they were matched for age and education. There was no significant difference in general intellectual function between the groups. Nonetheless, a limitation of this study was the probable co-morbid affective disorders among veterans with PTSD (Koso & Hansen, 2006). These findings were replicated by another study of Bosnian veterans that used the Rivermead Behavioral Memory Test (RBMT). Veterans with PTSD showed impaired declarative memory, both immediate and prolonged (Sarac-Hadzihalilović et al., 2008).

A twin study assessed verbal memory, executive functions, and attention in veterans with PTSD (n=19) and their twins without PTSD (n=24) (Gilbertson et al., 2006). Veterans with PTSD

and their co-twins with neither combat exposure nor PTSD had mostly the same cognitive impairment. This study suggested that neurocognitive impairment in PTSD represented familial predisposition rather than trauma-induced deficits. A recent study assessed various cognitive functions, viz., processing speed, executive function, letter fluency, categorical fluency, and verbal learning and recognition in veterans with PTSD (n=196) in a cohort (n=535) of adult outpatients aged below 65 years after excluding dementia and neurological illnesses (Cohen et al., 2013). Compared with patients without PTSD, those with PTSD performed poorly on several domains of cognitive function, particularly in tests involving processing speed, executive function, and learning. Nevertheless, upon adjustment of vascular risk factors and depression, the difference remained significant only in the processing speed.

In spite of the above-described results showing an association between PTSD and cognitive impairment, the largest studies found no evidence of cognitive impairment in PTSD. One study comprised of three samples: Vietnam veterans with PTSD (n=241), veterans with generalized anxiety disorder (n=241), and healthy control veterans (Zalewski, Thompson, & Gottesman, 1994). This study failed to demonstrate significant differences among the groups in cognitive performance (Zalewski et al., 1994). Another large study involved four groups: veterans with PTSD and no other psychiatric disorder (n=236), with PTSD and other psychiatric disorders (n=128), with no PTSD but other psychiatric disorders (n=242) and with neither PTSD nor any other psychiatric disorder (n=1835). There was no association between PTSD and cognitive impairment upon controlling demographic factors and psychiatric morbidities (Barrett, Green, Morris, Giles, & Croft, 1996). In a well-controlled study, albeit with small sample size (PTSD, n=19, control group, n=13) PTSD was found to be associated with several neuropsychological functions, but upon controlling the effect of depression, alcohol abuse, intelligent quotient and previous learning difficulties only deficits in attention and explicit memory remained significant (Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001). A meta-analysis reported multiple cognitive deficits in PTSD independent of depression, substance abuse and head injury (Scott et al., 2015b). The impairment in verbal learning had the strongest effect size. Premorbid Intelligent Quotient (IQ) had a significant impact on the effect size.

Few trends are visible as regards the cognitive outcomes in combat PTSD. When the studies involved trauma-unexposed controls cognitive impairment was found in veterans with PTSD (Scott et al., 2015a). However, the comparison between PTSD and trauma-exposed controls attenuated the association between PTSD and cognitive impairment (Scott et al., 2015a; Yehuda, Golier, Tischler, Stavitsky, & Harvey, 2005b). The studies that involved lifetime instead of current PTSD and trauma exposed controls observed no evidence of cognitive impairment (Barrett et al., 1996; Zalewski et al., 1994). The presence of confounders such as depression, anxiety, and vascular risk burden either eliminated or weakened the difference in cognitive performance between the controls and veterans with PTSD (Beckham et al., 1998; Cohen et al., 2013; Scott et al., 2015a). In no study, have all the potential confounders been removed or controlled, but several studies excluded most of these confounders or analysed them as covariates, and still demonstrated cognitive impairment in PTSD (Scott et al., 2015a; Vasterling et al., 2002; Yehuda et al., 2005b). Premorbid intellectual function has an influence on the risk of development of PTSD as well as the cognitive impairment associated with PTSD (Kremen et al., 2007; Macklin et al., 1998; Parslow & Jorm, 2007). Lower premorbid intelligence was associated with PTSD and when this factor was controlled, the cognitive impairment in PTSD was no longer significant. Various cognitive domains such as memory, processing speed, categorical fluency and executive function have been studied in PTSD, but deficit in declarative memory is the most pronounced impairment.

2.2.7.3. Cognitive dysfunction in Posttraumatic Stress Disorder arising from other contexts

In a study of refugees from former Yugoslavia, participants with PTSD (n=21) had a lower score on attention, executive functions, and visuospatial functions compared with those without PTSD (n=13) (Kivling-Boden & Sundbom, 2003). In Holocaust survivors, learning was found to be significantly impaired in subjects with PTSD (n=36) in comparison with survivors without PTSD (n=26). In contrast, there was no significant difference in recent memory (Yehuda et al., 2006). Similarly, in another study of refugees learning was significantly impaired in people with PTSD

(n=21) compared with those without PTSD (n=21), but the difference between the groups was no longer present after adjusting for depression (Johnsen, Kanagaratnam, & Asbjornsen, 2008).

Posttraumatic stress disorder has been studied in survivors of natural disasters. The participants were relatively young, with an age range of 27-42 years and the time since disaster varied from 9 months to four years. A study of survivors of bushfire in Australia found that attention, recent memory, and executive dysfunction were significantly impaired in victims with PTSD (n=38) when compared with a large control group (n=955), although the effect size was weak (Parslow & Jorm, 2007). This study analysed cognitive function before and after trauma and found that PTSD symptoms were significantly associated with pre-trauma neurocognitive deficits. Eren-Kocak et al. studied cognitive function in survivors of the 1999 earthquake in Turkey. Their study included three groups viz., victims with current PTSD (n=11), past PTSD (n=14), and no PTSD (n=18). The authors noticed that victims with current PTSD had significant impairment in executive dysfunction and verbal fluency (Eren-Kocak, Kilic, Aydin, & Hizli, 2009). However, upon controlling depression, they found no difference in visuospatial functions, learning, or memory.

Posttraumatic stress disorder is more common in women than in men (Kessler et al., 1995). Ironically, studies of cognitive function in women have been very limited. A recent study has investigated cognitive function in 14,151 civilian women with a history of exposure to physical assault and natural disaster (Sumner et al., 2017). The participants were female nurses. The study found impairment in psychomotor speed, attention and learning, and working memory in PTSD after adjusting for depression, health behaviour and medical comorbidities.

Summary

The studies that assessed cognitive function in PTSD showed heterogeneity in the types of trauma studied, rating scales, and comparison groups. Some studies have demonstrated impairment in attention and recall in veterans with PTSD compared with veterans without PTSD. Genetic factors influence the risk of cognitive impairment. Some studies, especially those with large sample sizes, did not find an independent association between cognitive impairment and lifetime PTSD. Several studies matched the comparison groups for trauma exposure, substance abuse, traumatic brain injury, compensation seeking behavior, general intelligence, and vascular risk factors. There has been no single study that controlled all covariates. The association between cognitive impairment and PTSD, observed in some studies, did not remain upon controlling the effect of depression, anxiety, and vascular risk score. The comorbidities in PTSD posed substantial difficulties in interpreting the findings. The cognitive impairment in PTSD was associated premorbid intelligence.

2.2.8. Neuroimaging studies in posttraumatic stress disorder

The neuroimaging studies are broadly divided into structural imaging and functional imaging studies. The commonly studied brain regions are the hippocampus, amygdala, and prefrontal cortex. Among the prefrontal structures, anterior cingulate cortex (ACC) has been the focus of PTSD research. Most data have been gathered in the past two decades, and they helped to delineate possible brain circuits involved in PTSD. Various neuroimaging modalities such as Magnetic Resonance Imaging (MRI), functional MRI (fMRI), Magnetic Resonance Spectroscopy (MRS), Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) have been used in the PTSD research.

2.2.8.1. Structural imaging

2.2.8.1.1. The Hippocampus

The hippocampus is situated in the medial part of the temporal lobe. It plays a vital role in short-term memory. Many studies have assessed hippocampal volumes in PTSD, and the results are mixed (Bonne et al., 2008; Bremner et al., 1995; Bremner et al., 2003; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; Golier et al., 2005; Jatzko et al., 2006; Pavic et al., 2007; Pederson et al., 2004; Villarreal et al., 2002; Wignall et al., 2004; Woon & Hedges, 2008). Some studies have shown reduced hippocampal volumes in PTSD (Bremner et al., 1995; Bremner et al., 2003; Gurvits et al., 1996; Villarreal et al., 2002; Wignall et al., 2004) while others failed to demonstrate such a volume reduction (Golier et al., 2005; Jatzko et al., 2006; Pederson et al., 2004). Magnetic Resonance Imaging studies have shown a reduced level of N-Acetyl Aspartic Acid (NAA) in the hippocampus of subjects with PTSD (Mohanakrishnan Menon, Nasrallah, Lyons, Scott, & Liberto, 2003; Schuff et al., 2008) . There is an inverse correlation between hippocampal volumes and verbal memory deficits and severity of combat exposure and depressive and PTSD symptoms (Bremner et al., 1995; Bremner et al., 2003; Gurvits et al., 1996; Villarreal et al., 2002). One study reported reduced hippocampal volumes in unexposed co-twins of veterans who had combat exposure and PSTD compared with unexposed co-twins of veterans without PTSD (Gilbertson et al., 2002). Further findings emerged along the line of genetic vulnerability for PTSD (Gilbertson et al., 2006). A case-control study that recruited veterans with PTSD (n=99) and a trauma-exposed control group (n=101) reported a reduced volume of the left hippocampus and no significant difference in the right hippocampal volume (Morey et al., 2012).

Despite the abundance of data suggesting reduced hippocampal volumes in PTSD, several other studies have failed to replicate the same finding (Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002; Pederson et al., 2004). Two prospective studies did not report a

significant decline in hippocampal volumes in subjects with PTSD over two years (Bonne et al., 2008; De Bellis et al., 2001). The variance in reliable and valid measures of PTSD, co-morbidities of PTSD, especially depression and alcohol, stages of PTSD viz., chronic vs. acute, and MRI volumetric methods may explain the discrepant results. There are meta-analyses of volumetric parameters of hippocampi in PTSD. An earlier meta-analysis has shown bilateral hippocampal volume reduction in PTSD but has not made firm conclusions because considerable heterogeneity existed among subjects and study methods (O'Doherty et al., 2015). For example, results varied depending on the whole brain volume correction and boundary definitions of hippocampi. A recent meta-analysis has identified smaller hippocampal volumes in PTSD compared with trauma-exposed controls (Bromis et al., 2018).

2.2.8.1.2. The Amygdala

In PTSD, no other brain structure is as extensively studied as the amygdala. Its role in fear response and processing, conditioning, and generalization of fear is well known (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011). Structural changes in the amygdala in PTSD have been investigated; the results are far from being consistent. Smaller and larger amygdala have been reported in PTSD compared with healthy controls (Kuo, Kaloupek, & Woodward, 2012; Rogers et al., 2009; Starcevic et al., 2014). A large US veteran study showed a significantly reduced volume of both amygdalae and the left hippocampus in the PTSD group compared with the trauma-exposed non-PTSD group after adjusted for alcohol use, depression, and medications. There was no correlation between trauma load or chronicity and amygdala volumes (Morey et al., 2012). In 49 male subjects with drug naïve PTSD, the left amygdala volume was smaller compared with the right amygdala, and volumes of both amygdale were significantly lower compared with those of healthy controls (Starcevic et al., 2014). These findings were replicated in a Japanese study, which also showed a correlation between the left amygdala volume and the symptom severity (Rogers et al., 2009). However, this study was limited by a small sample size, nine subjects with PTSD, and

16 control subjects. A meta-analysis did not show a significant difference in the amygdala volume between subjects with PTSD and trauma-exposed controls (Bromis et al., 2018).

2.2.8.1.3. The Anterior Cingulate Cortex

One of the widely accepted theories of PTSD is that there is an abnormally increased response to threatening stimuli because of the hyperactivity of the amygdala and failure of the ACC to send inhibitory signals to the amygdala (Kasai et al., 2008; O'Doherty et al., 2015; Shin et al., 2001; Yamasue et al., 2003). The ACC has been studied in PTSD because of its role in fear conditioning, and regulation of the hypothalamo-pituitary-axis (HPA) during emotional distress (Kitayama, Quinn, & Bremner, 2006). Manual tracing, voxel-based analysis, and automated segmentation have been employed to study volumetry of the ACC in PTSD. Unlike the findings related to the amygdala, studies of ACC have generated more consistent results. Manual tracing, Voxel-based morphometry (VBM), and segmentation method have shown a reduced volume of ACC in PTSD compared with trauma-exposed controls (Cohen et al., 2006; Rauch et al., 2003; Woodward et al., 2006).

2.2.8.2. Functional imaging

Enhanced activity of the amygdala, and a decreased activity of the hippocampus and frontal lobe structures characterize functional neuroimaging findings in PTSD (Hughes & Shin, 2011). The results are not uniform across the studies however; some have not shown a significant difference in amygdala activation between subjects with and without PTSD (Hughes & Shin, 2011). While the amygdala is involved in fear expressions, the frontal lobes serve the purpose of suppressing attention to the trauma-related stimuli. A fMRI study observed enhanced activity in the amygdala and diminished activity in the medial prefrontal cortex upon exposure to fearful faces compared with happy facial expression in patients with PTSD (Shin et al., 2005). Decreased hippocampal activity was seen in veterans with PTSD compared with veterans without PTSD during

rest as well as encoding and retrieval of word pairs (Geuze, Vermetten, Ruf, de Kloet, & Westenberg, 2008; Molina, Isoardi, Prado, & Bentolila, 2010). Reduced activation of hippocampus correlated with the severity of PTSD symptoms (Astur et al., 2006). A review of literature, however, showed contradictory findings such as increased activation of hippocampus in PTSD (Hughes & Shin, 2011).

Both fMRI and PET studies of rCBF have shown an exaggerated amygdala activity in veterans, including Vietnam veterans (Rauch et al., 2000; Shin et al., 2004). A meta-analysis of functional imaging studies has yielded insightful findings. Patients with PTSD exhibited increased activity in the amygdala and insula, but these patterns were also seen in patients with social phobia and social anxiety disorder. The unique feature of PTSD was deficient activity in the prefrontal cortex and rostral anterior cingulate cortex (ACC) and hyperactivity in the amygdala (Etkin & Wager, 2007).

While structural imaging studies of ACC have provided consistent results, functional imaging studies have not done so, and the findings are diffuse. Both hypoactivity and hyperactivity of ACC have been observed in patients with PTSD compared with controls. One study failed to demonstrate a significant difference in the ACC activity between subjects with PTSD and controls (Liberzon et al., 1999). Studies using PET imaging, SPECT, fMRI, and spectroscopy have demonstrated hyperactivity of the ACC (Rauch et al., 2003; Shin et al., 1997). These studies showed diversity in the imaging modalities, regions of the ACC studied, and symptom provocation methods used. For example, a study that used PET scan and visual images of combat-related pictures found increased regional cerebral blood flow (rCBF) in the ventral anterior cingulate cortex in the PTSD group (Shin et al., 1997) but a study using fMRI and Emotional Counting Stroop task, reported decreased activation in the rostral ACC (Shin et al., 2004). Another study that used PET scan showed an increase in rCBF in rostral ACC upon exposure to audiotaped traumatic scripts (Rauch et al., 1996).

Based on the emerging evidence and functional neuroimaging findings, a neurocircuitry model of PTSD involving the amygdala, medial prefrontal cortex and hippocampus has been proposed (Hughes & Shin, 2011). While this model has strong empirical data, it faces a few challenges. Functional imaging has limited spatial resolution and heterogeneity of findings warrants more studies in future. In addition, the findings are not suggestive of a specific neurodegenerative process.

2.2.8.3. Positron Emission Tomography

2-[18^{F}] fluoro-2-Deoxy-D-glucose (FDG) PET is an imaging modality that measures Cerebral Glucose Metabolic Rate in the brain as a proxy of neuronal activity. One of the well-validated biomarkers for AD that reflects the underlying neurodegeneration is the characteristic pattern of parietotemporal and posterior cingulate gyrus hypometabolism (Minoshima et al., 1997; Silverman et al., 2001). The addition of FDG PET to clinical diagnosis has improved diagnostic accuracy when measured against the final neuropathological diagnosis (Foster et al., 2007; Jagust, Reed, Mungas, Ellis, & Decarli, 2007).

2.2.8.3.1. Positron Emission Tomography studies in Posttraumatic Stress Disorder

The earliest PET study with ^{15}O-$H_{(2)}O$ showed an increased rCBF in the orbitofrontal cortex in the PTSD group compared with controls (Semple et al., 1993). This finding was replicated in a later study (Shin et al., 1999). One of the earlier studies used script driven provocation of symptoms and detected enhanced regional cerebral blood flow in the right amygdala, but this study did not have a control group (Rauch et al., 1996). Subsequent PET studies with control subjects have shown increased response in the amygdala (Bachman et al., 1993; Shin et al., 1997) and attenuated response in the medial prefrontal cortex upon symptom induction (Bremner et al., 1999), a pattern consistent with fMRI studies (Lanius et al., 2001; Osuch, Willis, Bluhm, Ursano, & Drevets, 2008). The findings are not without dissonance, however. Two studies that used script-driven

paradigm did not show increased activation in the amygdala (Bremner et al., 1999; Shin et al., 1999). While one study showed increased rCBF in the ACC in subjects with PTSD (Shin et al., 1999), another study demonstrated an increased rCBF in the ACC in subjects without PTSD (Bremner et al., 1999). Vietnam veterans with PTSD had a reduced rCBF in the medial prefrontal cortex (mPFC) compared with control veterans during recollection of non-traumatic stressful experiences in comparison with neutral events (Gold et al., 2011). A ^{15}O-$H_{(2)}O$ PET study compared survivors of motor vehicle collisions with non-traumatized subjects for cerebral perfusion during symptom provocation (Osuch et al., 2008). Subjects listened to traumatic and neutral scripts. While at rest, participants with a history of trauma exposure had hyperperfusion in the right mPFC and hypoperfusion in the right amygdala compared with control subjects. During symptoms provocation, hypoperfusion occurred in the left and right amygdala. In another study of male Vietnam veterans and female nurse veterans with PTSD and trauma-exposed control veterans, PET scan showed a reduced rCBF in the mPFC within the PTSD group during the exposure to traumatic scripts (Shin et al., 2004). Also, rCBF in the amygdala was inversely related to that in mPFC. Using ^{15}O-$H_{(2)}O$ PET, Pissiota et al. measured rCBF during symptom provocation with combat and neutral sounds in patients with PTSD (Pissiota et al., 2002). In this study, symptom provocation increased rCBF in the sensory-motor cortex and the right amygdala. The major limitation of the above studies is small sample sizes, ten or less in each group.

Inconsistent results could have been due to differences in the trauma and emotional responsiveness to personal narratives of the trauma. Rather than responding to general trauma-related images and pictures, patients react with an individualized account of trauma (Hull, 2002; Rauch et al., 1996). The amygdala is involved in encoding the emotional significance of an event rather than the event itself (Cahill et al., 1996).

2.2.8.4.2. ^{18}F-Fluorodeoxyglucose in Posttraumatic Stress Disorder

The above-described studies have examined brain activation during symptom provocation or cognitive tasks. There are only a few studies that measured resting cerebral glucose metabolism using the ^{18}F-Fluorodeoxyglucose **(**FDG) PET. One of the earlier studies measured brain metabolic activity using FDG PET after yohimbine administration (Bremner et al., 1997). Yohimbine is a presynaptic α-2 blocker. It has a dose-dependent effect on norepinephrine release. The elevated level of norepinephrine is associated with a decrease in brain metabolism while low levels with increased brain metabolism. In Vietnam veterans with PTSD, the rise in norepinephrine level after yohimbine administration was significantly more compared with control veterans and associated with anxiety symptoms. The metabolic rate was significantly lower in the hippocampus in subjects with PTSD than in the controls (Bremner et al., 1997). This study postulated an enhanced norepinephrine release in PTSD and subsequent reduction in metabolic activities in specific brain regions. The study was limited by a small sample size, ten veterans in each group, and a large number of brain regions were compared. A recent PET study estimated basal glucose metabolism and reported hypometabolism in multiple areas including the cingulate gyri, precuneus, insula, hippocampal, frontal, prefrontal and post-central regions in a small number of participants with PTSD (n=15) and controls (n=6) (Zandieh et al., 2016). None of the studies observed the characteristic AD type of hypometabolism in PTSD.

Summary

Magnetic resonance imaging techniques and PET imaging have been used to estimate regional brain volumes and proxy measures of metabolic activity in PTSD. In MRI, manual tracing, segmentation, and automated voxel-based morphometry were used for volumetric assessment. Structural and functional imaging studies of PTSD have yielded inconsistent results. Nonetheless, the results tend to show a reduced volume of the hippocampus and anterior

cingulate cortex, while findings of the amygdala are divided. Meta-analyses have demonstrated reduced volumes of hippocampi and anterior cingulate cortex in PTSD. There was an inverse correlation between the severity of trauma and hippocampal volume. Similar to the cognitive outcomes in PTSD, genetic factors influenced hippocampal volume in PTSD, and the findings questioned the independent role of PTSD in causing hippocampal atrophy. The anterior cingulate cortex has a role in the regulation of fear and the HPA axis during emotional distress. Several studies consistently showed the reduced volume of the anterior cingulate cortex in PTSD in comparison with trauma-exposed controls. The functional imaging studies used symptom provocation paradigm in PTSD. Subjects underwent functional imaging while exposed to trauma-related cues. Both hyperactivity and hypoactivity of the amygdala were seen in PTSD. Similarly, the medial prefrontal lobe showed both decreased and increased blood flow. Inconsistent findings may be explained by variation in the type of trauma, age of participants, the method of assessments and the currency of PTSD symptoms. A PET imaging study using ^{18}F-fluorodeoxyglucose in PTSD is in the preliminary stage and has not provided data useful for the evaluation of dementia risk.

2.2.9. Association between Posttraumatic Stress Disorder and dementia

The mounting evidence for cognitive impairment, along with neuroimaging findings in veterans with PTSD, paved the way for researchers to probe the scope and nature of the relationship between PTSD and cognitive decline. Subsequent epidemiological studies performed a prospective follow-up of the retrospective data. In most studies, subjects were Vietnam veterans, and in a few studies, subjects from the general community participated. The research in this area has witnessed an accelerated momentum with increasing number of studies in the past decade.

The first study by Yaffe et al. screened the records of 53155 veterans with PTSD and 127938 veterans without PTSD (Yaffe et al., 2010). The data was collected from the Veterans

Affairs (VA) National Patient Center database. The baseline PTSD diagnosis was based on the ICD-9 code, and diagnosis on at least two visits was required for inclusion to the PTSD group. The incident dementia for the next seven years was taken as the outcome. Incident dementia included Alzheimer's dementia, vascular dementia, Lewy Body dementia, frontotemporal dementia, and dementia not otherwise specified. The baseline characteristics of participants showed that substance abuse, clinical depression, and head injury were overrepresented in the PTSD group. The incident rate of dementia was significantly higher in the PTSD group (10.6%) compared with the non-PTSD group (6.6%) over seven years of follow-up. This difference persisted after adjusting for demographic variables, substance abuse, head injury, and depression. The increased risk was seen across all subtypes of dementia.

In the second retrospective cohort study, Qureshi et al. investigated the incidence and prevalence of dementia in veterans aged above 65 years who received the Purple Heart (PH). The Purple Heart is a U.S. combat decoration awarded to members of the U.S. Armed Forces who were killed or wounded while serving. The PH status was used to address combat exposure and combat trauma. The study involved veterans with PTSD and age-matched control group who belonged to four groups: PTSD and no PH (n=53,660); PH and no PTSD (n=1,503); PTSD and PH (n =5153); and no PTSD or PH (n=55,165). The number of clinic visits was adjusted for in the analysis. It was found that veterans with PTSD had significantly higher incidence and prevalence of dementia compared with those without PTSD with or without PH (Qureshi et al., 2010).

A retrospective cohort study included veterans aged 55 years and older and assessed PTSD at the baseline and incident dementia during the next nine-year period after adjusting for demographic variables, medical and psychiatric comorbidities, period of service, and the competing risk of death (Meziab et al., 2014). This study reported an increased risk of dementia in prisoners of war (POW) and patients with PTSD and additive effects from both PTSD and POW status. A population-based cohort study recruited participants from the Taiwan Health Insurance program (Wang et al., 2016). The risk of dementia was assessed in patients with PTSD from the general

population against a control group matched for demographic variables and psychiatric and medical morbidities. This study revealed a four times higher risk of dementia in subjects with PTSD than in the general population. The heightened risk remained after adjusting for depressive disorder and TBI. Also, there was a correlation between the severity of PTSD and the likelihood of the incidence of dementia. Unlike previous studies of male predominant veterans population, women outnumbered men in this study population. The findings of this study extended the risk of dementia associated with PTSD to both genders, non-combat trauma, and the general population.

In another retrospective cohort study of U.S veterans, the follow-up data was collected during 2004 to 2012 (Mawanda et al., 2017). The risk for dementia increased with PTSD diagnosis. The use of serotonin specific reuptake inhibitors (SSRI) and second-generation antipsychotics was associated with an increased risk of dementia diagnosis in veterans with PTSD, in addition to the independent association of PTSD with incident dementia. The most recent study of this series assessed the incidence of dementia over 13 years in a large civilian population (Flatt et al., 2018). The study involved 499,884 subjects, both men and women aged above 60 years. During the follow-up period 11.8% of the cohort developed dementia. The cumulative incidence of dementia was higher in both men and women with PTSD than in those without PTSD. Adjustment for TBI or vascular risk factors did not eliminate this association. Still, with depression, the increased risk of dementia in women was no longer present while it persisted in men.

In contrast to the above studies, Roughead et al. found no greater risk of dementia in veterans with PTSD in comparison with control veterans when psychiatric and medical comorbidities were controlled (Roughead et al., 2017). In a retrospective follow-up of the Vietnam veterans cohort, all dementia diagnoses in the first two years of the study were excluded to avoid the impact of prodromal dementia symptoms. The use of antipsychotics was associated with an increased risk of dementia in both groups.

The only prospective follow-up study included a small cohort of patients with PTSD (n=46) and assessed dementia incidence every six months (Bonanni et al., 2018). The study used MRI scan and assessed proteins ($A\beta_{42}$, and tau) in the cerebrospinal fluid. During a 6-10 years follow-up, eight patients developed dementia, Alzheimer's dementia in one patient, Lewy Body Dementia in one and semantic frontotemporal (FTD) dementia in six. The incidence of semantic FTD was 13%, much higher than in the general population. This study was limited by a small number of patients and absence of a control population. The increased incidence of semantic FTD may suggest the manifestation of prodromal symptoms of FTD as the symptoms of PTSD raising the possibility of a reverse causality.

Summary

Overall, eight studies assessed the risk of dementia in PTSD. Except one prospective study others employed a prospective follow-up of the retrospective data and involved huge sample sizes, sometimes above a hundred thousand. Seven out of eight studies reported an increased incidence of dementia, including Alzheimer's dementia in patients with PTSD. The follow-up period varied from seven years to 13 years. The risk of dementia rose with the use of an SSRI and antipsychotic and remained after accounting for vascular risk factors, traumatic brain injury, and education. None of the studies controlled for premorbid intelligence, however, although this factor influences the onset of dementia. There was little information on the methods and criteria for diagnosis of dementia or on the use of biomarkers of AD or post-mortem confirmation of clinical diagnosis in these studies leaving questions on the validity of dementia diagnosis unanswered in these large epidemiological studies. Overall, eight studies assessed the risk of dementia in PTSD. Except one prospective study others employed a prospective follow-up of the retrospective data and involved huge sample sizes, sometimes above a hundred thousand. Seven out of eight studies reported an increased incidence of dementia, including Alzheimer's dementia in patients with PTSD. The follow-up period varied from seven years to 13 years. The risk of dementia rose with the use of an SSRI and antipsychotic and remained after

accounting for vascular risk factors, traumatic brain injury, and education. None of the studies controlled for premorbid intelligence, however, although this factor influences the onset of dementia. There was little information on the methods and criteria for diagnosis of dementia or on the use of biomarkers of AD or post-mortem confirmation of clinical diagnosis in these studies leaving questions on the validity of dementia diagnosis unanswered in these large epidemiological studies.

2.3. Brain Amyloid and Tau Imaging

2.3.1. Introduction

The accuracy of clinical diagnostic criteria for probable AD is limited with a sensitivity of 81% and specificity of 70% compared with neuropathological diagnosis and the criteria require the presence of dementia syndrome (Beach, Monsell, Phillips, & Kukull, 2012; Knopman et al., 2001; McKhann et al., 1984). An early and more accurate diagnosis brings medical, social, and economic benefits (Birks, Chong, & Grimley Evans, 2015; Silverman et al., 2002; Small, Donohue, & Brooks, 1998). The early diagnosis helps clinicians to make judicious use of limited resources. Also, a diagnosis early in the course of the illness may inform patients and families of the prognosis and help them to plan for the remaining life. Moreover, it provides an opportunity for researchers for the trial of novel therapeutic agents that have the potential for disease modification. Therapy is more likely to be of benefit in the early stage of the disease before there is substantial neuronal loss, and this may be before symptoms manifest. The currently accepted method of early diagnosis is the *in vivo* detection of biomarkers of AD. Two well validated methods of *in vivo* detection include PET imaging of A-β or tau and the assay of cerebrospinal fluid A-β_{42} and pTau. Examples of a biomarker of AD specific neuronal damage are hypometabolism and atrophy of specific brain regions

visualized on structural and functional imaging modalities. As a general principle, pathological biomarkers precede the biomarkers of neuronal damage.

2.3.2. β-Amyloid tracers

Chet Mathis and William Klunk developed the first PET tracer specific for A-β at the University of Pittsburgh. This tracer was labelled with ^{11}C, and it was later named as the Pittsburgh B compound (^{11}C -PIB) by investigators at the Uppsala University in Sweden. The actual chemical is N-methyl [^{11}C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazole. This compound is a derivative of Thioflavin T, a fluorescent dye used to stain amyloid during pathological examination of the peptide. ^{11}C -PIB demonstrated rapid diffusion through the blood-brain barrier and high affinity for fibrillar A-β permitting *in-vivo* detection of amyloid in the brain. The first human study of ^{11}C -PIB was published in 2004. This study, with a relatively modest sample size, showed significantly higher retention of ^{11}C-PIB in specific brain regions that are known to contain a large amount of amyloid in patients with Alzheimer's dementia (Klunk et al., 2004). ^{11}C-PIB was most prominent in the frontal region. A considerable amount was observed in the parietal, temporal, and occipital cortices and the striatum. There was no significant difference in ^{11}C-PIB between patients with AD and the controls in the areas that are known to be spared in AD viz., subcortical white matter, sensory and motor cortices, cerebellum, and pons. The binding did not significantly differ in the key brain regions between young individuals aged 21-years and healthy older controls. This study also demonstrated reduced glucose metabolism as measured by ^{18}F-fluorodeoxyglucose PET in the areas of high ^{11}C -PIB intake. For the first time, this study provided evidence for the quantitative estimation of amyloid in living subjects.

Future studies replicated the above findings (Engler et al., 2006; Mintun et al., 2006; Rowe et al., 2007). Follow-up data showed the stability of ^{11}C-PIB retention in patients with Alzheimer's dementia over a two-year period whereas glucose metabolism was found to decline on ^{18}F -fluorodeoxyglucose PET (Engler et al., 2006). While PIB retention changed very little over two

years, a significant reduction (20%) in regional cerebral metabolic rate for glucose was observed in cortical regions. Moreover, a negative correlation was seen between regional metabolism and PIB retention in the parietal cortex of patients with Alzheimer's dementia. There was a negative correlation between ^{11}C -PIB retention in the parietal cortex and the Rey Auditory Verbal Learning test score. These results suggested that the amyloid deposit reached a plateau by the dementia stage of AD and preceded regional brain hypometabolism and cognitive decline (Engler et al., 2006). ^{11}C -PIB retention was found to be elevated in some non-demented individuals with the highest retention in the precuneus, a region that showed maximum retention in subjects with dementia (Mintun et al., 2006). Another study measured ^{11}C-PIB retention in cognitively asymptomatic controls and subjects with MCI, Alzheimer's dementia, frontotemporal dementia, and Lewy body dementia (Rowe et al., 2007). ^{11}C-PIB binding was high in Alzheimer's dementia, low and variable in Lewy body dementia, and absent in frontotemporal dementia. The pattern of ^{11}C -PIB binding mirrored the known histopathological distribution of amyloid. Mild cognitive impairment showed both an AD-like pattern and normal distribution. There was no correlation between ^{11}C-PIB retention and severity of dementia in AD. ^{11}C-PIB retention was higher in APOE e 4 carriers than in non-carriers. These findings supported the ability of ^{11}C-PIB PET to detect amyloid deposition in the preclinical stage. A Cochrane meta-analysis estimated 83% -100% sensitivity and 46%-88% specificity of ^{11}C-PIB PET in identifying MCI that progressed to Alzheimer's dementia (Zhang et al., 2014). However, the review found significant heterogeneity in the methods and interpretation of the test and lack of well-defined thresholds for the determination of test positivity. It is noticeable that the follow-up period varied with most studies reporting only 1-2-year outcome, but some extended to five years and were associated with greater specificity. Other studies found a correlation between cerebral amyloid burden as measured by ^{11}C-PIB PET scan and the rate of memory decline in MCI and the severity of memory impairment in healthy controls (Pike et al., 2007; Villemagne et al., 2008). Such a correlation was not seen in patients with AD. In a comparison study, PET imaging with ^{11}C-PIB discriminated subjects with AD from those with frontotemporal dementia (Rabinovici et al., 2007).

After the introduction of ^{11}C-PIB various ^{18}F labelled radio-ligands have been developed. They have the advantage of longer half-life (110 minutes), a property that allows their distribution to centers without on-site cyclotron production and thereby increased imaging accessibility. They, however, suffer from non-specific white matter retention, and on visual inspection, cortical to white matter differentiation is less appreciable compared with the ^{11}C-PIB compound. ^{18}F-florbetapir, ^{18}F-florbetaben and ^{18}F-flutemetamol are FDA and EMA approved PET tracers for the assessment of brain amyloid.

2.3.3 Tau tracers

Early attempts at developing *tau* tracers showed binding in AD that was indistinguishable from healthy controls despite promising *in-vitro* results (James, Doraiswamy, & Borges-Neto, 2015; Villemagne et al., 2012). However, [F-18]-T807 (now known as ^{18}F-AV1451) has an affinity for tau protein and high target selectivity. The first human brain imaging using [F-18]-T807 was published in 2013 (Chien et al., 2013). The investigation was on a small scale involving six human subjects, three healthy controls, one MCI, and two patients with AD. Available data showed high retention in the cortical regions of patients with MCI. In severe AD, the highest retention was seen in the parietal and lateral temporal lobes. The uptake in healthy controls was low. The white matter uptake was relatively small in all subjects. The tracer did not show binding to A-β. Above all, there was a trend towards an increased uptake as the severity of dementia progressed. It is expected that the combination of tau and amyloid imaging, along with clinical presentation, will move closer to the definite diagnosis of AD.

2.3.4. Assessment of amyloid and tau PET scans

Evaluation of ^{11}C-PIB PET scan is performed by both visual inspection and quantitative estimation of ^{11}C-PIB PET binding using the cerebellar cortex as the reference. Upon visual

inspection, the highest binding is seen in the frontal cortex, posterior cingulate gyrus, precuneus, striatum, parietal cortex, and lateral temporal cortex, sparing the occipital cortex, sensorimotor cortex, and mesial temporal cortex. A moderate degree of non-specific uptake of ^{11}C-PIB is seen in white matter in healthy controls. Because amyloid plaques are sparse in the cerebellum, it is often used as the reference region for calculating the ratio of specific to non-specific binding. This ratio is known as the Specific Uptake Value (SUV) ratio. In conditions where there are dense cerebellar amyloid deposits, viz., familial AD, and very advanced late-stage AD, the pons may be used as the reference region. While SUVR can be calculated for ^{18}F -AV-1451 PET scans, the visual inspection of ^{18}F-AV1451 tracer images has not been standardized yet. The Specific Uptake Value Ratio (SUVR) for ^{18}F-AV1451 was calculated using cerebellar uptake as the reference.

Summary

The measurement of biomarkers of AD has several advantages over traditional clinical diagnosis. They include early and accurate diagnosis, which can lead to risk reduction strategies, recruitment for therapeutic trials, and planning for the future should the biomarker evaluation shows positive results. ^{11}C-PIB, a compound developed at the Pittsburgh University, was the first radioactive ligand with an affinity for β-amyloid. It is a derivative of Thioflavin T, a compound used to stain A-β in the pathological examination. ^{11}C -PIB studies have shown an increased binding of the tracer in the areas that pathological examination showed presence of A-β, namely orbitofrontal, precuneus, lateral temporal, and posterior cingulate gyrus and little binding in the subcortical regions, cerebellum or pons, areas that are spared in the disease. The tracer binding reached a plateau by the time dementia developed and showed no correlation with the severity of dementia. The binding, however, showed correlation with cognitive decline in both patients with MCI and healthy controls, suggesting accumulation along with an acceleration of the cognitive decline in the pre-symptomatic phase of the disease. ^{11}C-PIB binding was increased in Alzheimer's dementia, variable in Lewy Body Dementia, and absent in frontotemporal

dementia. Since the introduction of ^{11}C-PIB, fluoride labelled radiotracers have been developed, and these compounds have longer half-life enabling their transport to sites remote from the cyclotron production. ^{18}F-AV1451 is a ligand that has a high affinity for tau. The cortical binding of ^{18}F-AV1451 showed a correlation with the cognitive decline in Alzheimer's dementia.

2.4. A Critical Evaluation of the Literature

2.4.1. Alzheimer's disease

Alzheimer's disease is not a disease that is categorically absent or present (Snowdon et al., 1997). Instead, it lies on a continuum of neurocognitive changes ushered by a continuum of neuropathology (Bennett, Schneider, Arvanitakis, & Wilson, 2012). It is a heterogeneous entity with diverse aetiology and different clinical manifestations. The aetiological mechanisms, the extent of brain lesions, and the relationship between biomarkers, and clinical expression of the disease vary among individuals. In spite of the heterogeneity, A-β and NFT are the defining lesions of the disease, seen in both early-onset genetically driven disease and the late-onset multifactorial disease.

There are two caveats in the pathological diagnosis of AD: one is the absence of dementia in the presence of plaques, and the other is the presence of dementia in the absence of the classical lesions. The amyloid hypothesis of AD faces several challenges. Senile plaques (SP) have been observed in brains of elderly individuals with intact cognitive functions (Davis, Schmitt, Wekstein, & Markesbery, 1999a; Knopman et al., 2003; Price & Morris, 1999). The density of SP in this population is the same, as seen in AD. Moreover, autopsy studies have failed to demonstrate a correlation between the number of SP and neuronal loss and duration of clinical illness (Bennett, Schneider, Wilson, Bienias, & Arnold, 2004b; Gomez-Isla et al., 1997). At the same time, neuronal degeneration and tangles correlated with the severity and duration of cognitive dysfunction

(Bennett, Schneider, Wilson, Bienias, & Arnold, 2004a; Gómez-Isla et al., 1997). A relationship with cognitive impairment was established with NFT, not with amyloid plaques. Although NFT are also seen in the brains of otherwise healthy people, the density is less, and distribution is limited compared with AD.

Nevertheless, several observations support the amyloid hypothesis of Alzheimer's dementia. First, the gene coding the amyloid precursor protein (APP) is localized on chromosome 21 and trisomy 21 (Down's syndrome) is invariably associated with AD pathology (Olson & Shaw, 1969). Second, altered presenilin, the catalytic subunit of the gamma-secretase enzyme is implicated in the preferential generation of A-β_{42}, which is more likely to aggregate and form neurotoxic plaques (Citron et al., 1997). Individuals born with mutations involving genes coding for APP and presenilin I manifest complete penetrance, meaning that all of them will suffer from Alzheimer's disease if they live expected lifespan (Goldman et al., 2011). The mutation of presenilin II shows near-complete penetrance (95%). In general, SP are more specific than tangles in the diagnosis of AD. Mutations in the gene encoding the tau protein lead to frontotemporal dementia, a neurodegenerative disease characterized by severe deposition of tau in NFT in the brain without amyloid deposits (Hutton et al., 1998; Spillantini, Bird, & Ghetti, 1998). Available evidence oscillates towards the possibility that amyloid plaque formation predates the production of NFT (Lemere et al., 1996; Mann, Yates, Marcyniuk, & Ravindra, 1986; Smith et al., 2001).

Three hypotheses have been proposed to explain the incongruence between pathological markers and clinical status. The first one is that brain lesions without dementia may represent situations in which individuals died during the pre-clinical disease. Second, the amyloid plaque seen in cognitively intact individuals is predominantly of the diffuse form, which is less clearly associated with neuronal damage. The third postulate is that the protective factors create high cognitive reserve delaying the expression of dementia in some individuals with increased amyloid load.

The second lacuna in the understanding of Alzheimer's disease is the absence of A-β plaque and the presence of NFT in a small subset of patients who otherwise present with characteristic symptoms of AD (Bancher & Jellinger, 1994; Itoh et al., 1996). Although CERAD and NIA criteria do not recognize these lesions as AD pathology, according to NIA/RI criteria these changes contribute to AD. Such AD cases are known as tangle dominant dementia, atypical AD or amyloid negative Alzheimer's like dementia, (Jellinger & Attems, 2007; Nelson et al., 2009). Recently primary age-related tauopathy (PART) has been proposed as a mechanism of cognitive impairment including loss of episodic memory but without dementia.

2.4.2. Post-Traumatic Stress Disorder and cognitive impairment

The concept of cognitive impairment in PTSD is central to the association between PTSD and dementia. Notwithstanding a plethora of studies, the association between cognitive impairment and PTSD is still not convincingly proven. First, the largest studies that tested specific cognitive functions in PTSD found no association between this disorder and various cognitive functions (Barrett et al., 1996; Zalewski et al., 1994). This may be explained by the fact that lifetime rather than current PTSD was investigated in these studies. Although other studies revealed a significant association they are not without questions. The sample sizes of studies that reported a positive association were relatively small. Where there were associations, psychiatric comorbidities of PTSD such as depression were confounding factors in some instances. For example, Brandes et al. found impaired attention and immediate recall for figural information and lower IQ in survivors with PTSD, but these findings lost significance when the effect of depression was controlled (Brandes et al., 2002). In another study, subjects with PTSD performed poorly on several neuropsychological tests when compared with healthy controls, but the performance of the PTSD group and that of other psychiatric patients matched for psychopathology severity were very similar (Gil, Calev, Greenberg, Kugelmass, & Lerer, 1990). These findings may be read in conjunction with the observation of a high rate of alcohol abuse (24-84%) and depression (28-84%) co-morbidity in PTSD (Keane & Kaloupek, 1997). It may be noted that 99% of Vietnam veterans with chronic PTSD

had other psychiatric morbidities, notably substance abuse disorder, another anxiety disorder and depressive disorder (Hamner, 1992).

A few studies have established cognitive deficits in PTSD and ruled out the confounding effects of alcohol use, depression, trauma exposure severity and pre-morbid learning problems (Gilbertson et al., 2001; Samuelson et al., 2006; Vasterling et al., 2006). The confounding effects of war and physical trauma on cognitive functions need to be considered. Vasterling et al. studied sustained attention, working memory/executive functions, fine motor speed, verbal and visual learning, and reaction time in 654 Iraqi veterans who were deployed and 307 soldiers who were not deployed in war zones. Impairment was found in sustained attention, verbal learning, and visual-spatial memory in association with deployment and these findings were independent of depression and stress symptoms (Vasterling et al., 2006). Nonetheless, a well-designed study that controlled for combat exposure, intellectual functions, and substance abuse suggested that cognitive deficits found in Vietnam veterans were independent of the above commonly occurring confounders (Vasterling et al., 2002).

2.4.3. Posttraumatic stress disorder and dementia

The epidemiological studies that suggested an increased risk of dementia in veterans with PTSD have methodological limitations. First, these studies, except a small prospective study, employed retrospective designs and the diagnoses were dependent on entry into medical records, not structured tools or any other specific screening method. Second, even in the best centers the accuracy of a clinical diagnosis of dementia is limited. The third limitation is the lack of information about the biomarkers specific to AD in PTSD. A mechanistic interpretation of the association between an increased risk of dementia and PTSD is lacking in these studies. The only prospective study had a very small sample size and the conclusions were limited by potential reverse causality.

2.4.4. Cognitive impairment in PTSD: pre-trauma vulnerability or post-trauma consequence?

Another challenge in interpreting the findings of cognitive function in PTSD is the influence of premorbid intelligence on cognitive performance. Pre-trauma neuropsychological function has a role in moderating the influence of trauma on PTSD symptoms (Marx, Doron-Lamarca, Proctor, & Vasterling, 2009). From a large epidemiological study involving 1599 students who suffered a catastrophic natural disaster, Parslow and Jorm have shown that the development of PTSD symptoms was associated with lower scores on word recall, digit span, coding speed, and verbal intelligence three years before trauma (Parslow & Jorm, 2007). The authors suggested that rather than a consequence of PTSD, the cognitive deficit was a risk factor for PTSD. Consistent with the above findings, Marx et al. have demonstrated that post-deployment PTSD symptom severity was inversely correlated with the pre-deployment visual memory performance even after controlling for PTSD symptom levels, combat intensity, test-retest interval, age and gender (Marx et al., 2009). Pre-trauma cognitive vulnerabilities may be exacerbated by trauma exposure and subsequent development of PTSD symptoms (Aupperle, Melrose, Stein, & Paulus, 2012). This implies that PTSD may lead to accelerated cognitive decline, but in a subset of individuals with low pre-existing cognitive performance.

Summary

Alzheimer's disease lies along a continuum and the extent of both pathological lesions and corresponding clinical manifestations vary among individuals. There is no single mechanism that explains the disease process or clinical symptoms in all individuals. There are several gaps in the existing knowledge of AD pathology. On one side there are individuals with A-β retention in the brain at a pathological level but without dementia and on the other side individuals without significant A-β burden develop dementia. NFT are better correlated with cognitive symptoms than A-β. The latter, however, precedes NFT which is considered as the downstream effect of

A-β. The observation of pathological brain lesions without dementia may be explained by three possibilities. People harbouring AD pathology may die before the onset of dementia. The implication is that individuals with pathological levels of A-β and tau develop dementia if they live long enough. Secondly, A-β seen in cognitively asymptomatic individuals is the diffuse form whereas A-β that causes the disease is in the form of the neurite. Thirdly, individuals with pathological deposition of A-β and NFT may have a high cognitive reserve which buffers the impact of pathology and delay the onset of dementia. Inconsistent findings, as well as methodological issues, place constraints over the association between PTSD and cognitive impairment. The studies that assessed cognitive function in PTSD have provided mixed results, some showed an association and others did not. Where there was an association the relationship between PTSD and cognitive impairment was either attenuated or eliminated by comorbid depression, anxiety, and premorbid IQ. The association between PTSD and clinical dementia also confronts questions. The outcome assessed in these studies was a clinical diagnosis, the accuracy of which is limited. The studies did not control for premorbid IQ which was previously shown to delay the onset of dementia. Lower premorbid IQ is a vulnerability factor for dementia, PTSD and cognitive impairment in PTSD.

2.4.5. Relevance of the current study

The pathophysiology of AD resists a uniform acceptance, despite voluminous research and generation of a massive amount of data. The existing literature on the relationship between PTSD and dementia is burgeoning and opening the path for further research. The current body of knowledge is largely derived from epidemiological research that relied on a clinical diagnosis of dementia with limited accuracy. Basic science research and investigation of biomarkers of AD, which have the potential for improved specificity and sensitivity for the detection of AD pathology, are the next steps forward.

Previous studies in this field involved combat PTSD. However, most papers reporting on cognitive deficits in PTSD have not examined brain volumes and vice versa or their interaction. Little is known of the impact of PTSD on cognition with aging when brain cognitive reserve is likely to be declining. To address these gaps, the present study measured biomarkers of AD in older Vietnam veterans prior to the development of MCI. The study aimed at a quantitative estimation of A-β and tau and regional metabolism and volumetry in Vietnam veterans while controlling for a wider range of likely confounders than most previous studies. Vietnam veterans are likely to be in their late 60s or early 70s implying that they are in an age group suitable for the study of AD biomarkers.

Chapter 3

Methods

3.1. Hypotheses

The study aimed at testing the following hypotheses

1. There is increased retention of A-β and tau in veterans with PTSD in comparison with veteran controls as measured by ^{18}F-florbetaben and ^{18}F-AV-1451 PET imaging, respectively.
2. Veterans with PTSD have reduced regional brain metabolism compared with veteran controls as measured by ^{18}F-fluorodeoxyglucose PET scan.
3. The volumes of the hippocampus, the amygdala, and the prefrontal cortex as measured by MRI are lower in veterans with PTSD than in controls.
4. Veterans with PTSD have impaired cognitive function as measured by neuropsychological battery compared with veteran controls.

3.2. Ethics

The research protocol adhered to the principles of the Helsinki Declaration of Human Research, the seventh edition ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). The Austin Human Health Ethics Committee provided approval for the study. Ethics approval was also obtained from the Department of Veterans Affairs and the US Department of Defence (DoD). A special application was submitted to the Australian Defence Department for the release of military aptitude test results, but this was eventually unsuccessful.

The Consent Form and the Participant Information Form (PIF) were mailed out to potentially eligible veterans who contacted the research centre over the phone in response to publicity for the study. The PIF contained information regarding the background of the study, procedures, anticipated adverse effects, radiation exposure, and provisions for compensation in case of injury. Veterans who were interested in the study had a consent session where information about the study was discussed. All participants provided written informed consent for the study participation and accessing data from health services. Informed consent was witnessed by an independent third person who was not involved in the study.

3.3. Participants and Recruitment

The current study utilized the Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL) infrastructure and resources. The PET imaging resources and the long-term involvement of Vietnam veterans with Austin Health provided the ideal environment for this research project to test the hypothesis of an association between PTSD and AD pathological biomarkers. The Vietnam Veterans Association of Australia has been actively involved in PTSD programs, and a PTSD clinic has been established in the Heidelberg Repatriation Hospital of Austin Health. The study protocol was formulated in October 2013 and then submitted to the Austin Ethics Committee (the Institutional Review Board). The study was based at the Department of Molecular Imaging and Therapy of Austin Health, one of the major metropolitan hospitals in Melbourne. The acquisition of amyloid and tau scans was performed at the Florey Institute of Neuroscience and Mental Health in Melbourne, and ^{18}F-fluorodeoxyglucose PET and MRI scans were acquired at Austin Health.

Veterans were recruited via an advertisement in the magazines and newsletters of the Older Veterans Psychiatric Program at Repatriation Hospital in Melbourne, Retired Service League (RSL), and Vietnam Veterans Association of Australia (VVAA). The investigators attended various meetings of veterans, including ANZAC day which is conducted every year at War Memorial in

Melbourne and Long Tan Remembrance Day. The research team worked closely with the office-bearers of VVAA.

Interested veterans underwent preliminary screening for exclusion criteria (see below). Upon passing the initial screening, the consent and PIF were mailed out to potentially eligible veterans. A research coordinator made appointments for psychiatric assessment, neuropsychological tests, and scans. According to the published literature, the effect size for discriminating between AD and controls with ^{18}F-florbetaben varied from 1.37 to 3. Using ^{18}F-florbetapir PET imaging results from the healthy controls in the US Alzheimer's Disease Neuroimaging Initiative (ADNI study), power analysis estimated that the study required 29 subjects in each group to detect a group difference with an effect size of 0.75 or more, with 80% power at α=0.05.

3.3.1. Inclusion criteria for the PTSD group.

1. Posttraumatic Stress Disorder as defined by the Clinician-Administered PTSD Scale (CAPS) and a minimum CAPS score of 40 as determined by a face-to-face assessment.
2. Combat exposure.

3.2.2. Inclusion criteria for the control group

1. Absence of PTSD as defined by CAPS and a CAPS score of 30 or less.
2. Combat exposure.

3.3.3. Exclusion criteria

The following exclusion criteria applied to the cases and controls

1. Substance abuse current or in the past six months.

2. Traumatic brain injury according to the criteria set by the U.S Department of Defense (DoD) (Management of Concussion/m, 2009).
3. Psychiatric disorders: any psychotic disorder, bipolar affective disorder, dementia, or existing diagnosis of MCI.
4. Any unstable medical condition that could have made participation difficult or have a significant impact on cognitive function.
5. All subjects who had scores between 30 and 40 were excluded from the analysis based on the presumption that they may have had fluctuating and sub-threshold symptoms of PTSD.

3.4 Instruments and Measurements

3.4.1 Brain imaging

3.4.1.1. β-Amyloid and tau imaging acquisition and analysis

All participants underwent a 20-minute PET scan (4 x 5-minute frames of emission data collected) acquired 90 minutes after a slow IV bolus administration of 250 MBq (± 10%) of ^{18}F-florbetaben and 70 minutes after the injection of 370 MBq of ^{18}F- AV-1451. Scans were acquired on a Siemens mCT PET/CT scanner, and CT attenuation correction was applied. Image reconstruction used the Ordered Subset Expectation Maximization (OSEM) algorithm. There was no correction for partial volume effect.

^{18}F-florbetaben and ^{18}F-AV-1451 PET were analysed with Computational Analysis of PET using CapAIBL software, which was developed by AIBL investigators and the Commonwealth for Scientific and Industrial Research Organization (CSRO) (Bourgeat et al., 2015; Zhou et al., 2014). The CapAIBL allows quantitative PET measurements without relying on Magnetic Resonance Imaging. Global β -Amyloid and regional tau burden were calculated by Standardized Uptake Value Ratio (SUVR) using the cerebellar grey matter uptake as the reference. ^{18}F-Florbetaben scan was

read visually by three readers, and the classification into a negative or positive scan was based on majority results. The visual inspection was based on Brain Amyloid Plaque Load (BAPL), which was derived from the Regional Cortical Tracer Uptake (RCTU) in four regions: lateral temporal cortex, frontal cortex, posterior cingulate cortex/precuneus, and parietal cortex. Typical transverse PET slices were judged as negative if the tracer uptake in the grey matter was lower than that of the white matter and positive if the uptake in the grey matter was equal to or more than that in the white matter in one or more lobes. ^{18}F- AV-1451 regional uptake in three regions was calculated: mesial temporal region consisting of amygdala, hippocampus, entorhinal cortex and parahippocampus; temporoparietal region composed of inferior and middle temporal lobes, fusiform gyrus, posterior cingulate/precuneus, superior and inferior parietal lobes, lateral occipital and orbitofrontal regions, gyrus rectus, supramarginalis and angularis; rest of the neocortex consisting of dorsolateral and ventrolateral prefrontal lobes, superior temporal lobe and anterior cingulate cortex.

A part of the data analysed in the preparation of this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.Ioni.usc.edu). The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, 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. For up-to-date information, please see www.adni.info.org.

3.4.1.2. ^{18}F-fluorodeoxyglucose PET scan

Subjects fasted for 4 hours and then had an injection of 250-300 MBq of ^{18}F-FDG. They remained in a quiet, darkened room with eyes open for 30 minutes to keep the occipital lobe metabolism consistent. The acquisition was commenced 30-45 minutes post-injection. A post-injection transmission scan for attenuation correction was performed. The acquisition time was 20 minutes. Reconstruction was performed with a RAMLA filter. The SUVR was calculated for the

frontal, mesial temporal, posterior cortical index (consisting of lateral temporal, parietal and posterior cingulate cortex) and rest of the neocortex.

3.4.1.3. Magnetic resonance imaging

The MRI scan was acquired at the Brain Research Institute, Austin Health. The investigators obtained the surgical history of all participants and thoroughly screened for metal implants. Participants underwent a 3-Tesla Siemens Trio whole-brain MRI scan. A three-dimensional (3D) T1 magnetization-prepared rapid gradient-echo (MPRAGE) was acquired with the following parameters: FoV = 260 x 256, Matrix = 240 x 256, 160 slices, 1.0 x 1.0 x 1.2 mm voxels, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°. The T1 weighted images were rigidly registered to the Montreal Neurological Institute (MNI) average brain and segmented into gray and white matter and CSF space with Expectation Maximisation Segmentation algorithm. Partial tissue classification and cortical thickness were then estimated using a software called Computational Quantification of MRI from AIBL (CurAIBL) (Bourgeat et al., 2015). Volumetry was adjusted for the Total Intracranial Volume (TICV) by dividing the regional volume by the TICV. Volumetry of the hippocampus, amygdala and pre-frontal cortex were performed. The following regions of the prefrontal cortex were included in the analysis: anterior cingulate cortex, orbitofrontal cortex, and middle frontal cortex.

3.4.2. Clinical and neuropsychological assessment

The Clinician's Administered PTSD Scale (CAPS- DSM-IV version) is a clinician-rated instrument designed to produce a DSM-IV diagnosis of PTSD. It has excellent test-retest reliability and internal consistency (Weathers et al., 2001). As mentioned above, a score of 40 and above defined PTSD. This score was based on the diagnostic utility data from an older version of CAPS for a range of selected cut-off scores, which indicated that a score of 40 had 93% sensitivity and 80% specificity (Shalev et al., 1998). A CAPS score of 30 or less and military experience formed

the inclusion criteria for the control group. These scores were chosen to ensure a clear separation between the diagnostic group and controls. The DSM-V criteria were used to exclude substance abuse and dependence (Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed, 2013). A panel of experts reviewed the substance consumption history before a participant was excluded based on substance abuse.

For depression rating, the Geriatric Depression Scale (GDS) 15-item short-form was used (Sheikh & Yesavage, 1986; Yesavage et al., 1982). The scale contains 15 questions that elicit yes, or no response based on the mood in the past one-week. Various cut off scores have been analysed; for instance, a cut-off score of 5 on the GDS 15-item scale gives 71.8%, sensitivity, and 78.2% specificity in identifying Structured Clinical Interview for DSM (SCID) diagnosis of depression (Marc, Raue, & Bruce, 2008). The Combat Exposure Scale (CES) measured the severity of combat exposure (Keane et al., 1989). The CES is supposed to measure the subjective experience of stress during exposure to combat roles. It has excellent test-retest reliability and acceptable internal consistency (Keane et al., 1989). The Pittsburgh Sleep Quality Index (PSQI) was the instrument to measure sleep quality. The PSQI is a self-rated questionnaire to assess sleep quality in the past month (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) . It has an acceptable internal homogeneity, test-retest reliability, and validity. A score >5 indicates severe sleep difficulties in two areas or moderate sleep difficulties in three areas.

The neuropsychological test battery consisted of the Logical Memory subset test 1 and 2 of the Wechsler Memory Scale-Revised edition (WMS-R) – Anna Thompson story only (Wechsler 1987), Rey Auditory Verbal Learning Test (Bean, 2011), the digit span from the Wechsler Adult Intelligence Scale third edition (Wechsler 1997), the Categorical Fluency Test from the Delis-Kaplan Executive Function System (Butters, Granholm, Salmon, Grant, & Wolfe, 1987), Rey-Osterrieth Complex Figure Test (ROCFT) (Rey & Osterrieth, 1993), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Trail Making Test parts A and B (Reitan, 1958). The following tests

measured memory: the delayed paragraph recall from the Logical Memory Test II (story A only), Rey Auditory Verbal Learning Test (RAVLT) learning trials, and the ROCFT, 3-minute delay, and 30-minute delay. Executive function was measured by the Trail Making Test, part B. The WAIS-III Digit Span measured attention and working memory whereas Trail Making Test, part A, assessed the visual attention and processing speed. The ROCFT measured visuospatial orientation. The MMSE and the MoCA were the measures of global cognitive performance. The study used the Wechsler's Test of Adult Reading (WTAR) to estimate premorbid intellectual function (Wechsler 2001). The reading skills, particularly reading words with atypical graphemes to phonemes translations, have been shown to be less susceptible to brain injury and effectively estimate premorbid intelligence in a range of clinical and non-clinical populations (Dykiert & Deary, 2013; Green, Malaspinas, et al., 2008). The WTAR was adjusted for age and then predicted Intelligence Quotient (IQ) was calculated using published criteria.

A cardiovascular risk factor score was calculated by giving one point to each of the following: hypertension, ischemic heart disease, previous history of stroke, atrial fibrillation, current smoking, diabetes, Body Mass Index (BMI) over 30, and hypercholesterolemia. The risk assessment was modelled on the original Framingham study of the probability of stroke (Wolf, D'Agostino, Belanger, & Kannel, 1991), which predicted significant cognitive dysfunction (Unverzagt et al., 2011). The assessment of vascular risk was based on clinical history, which was corroborated with the health records provided by the general practitioners of participants. A sum of all points gave a cumulative vascular risk factor score. The study recorded any previous polysomnographic diagnosis of obstructive sleep apnoea, as reported by patients and from the health records. Participants had a blood test for apolipoprotein E e4 (APOE e4).

3.5 Study Design

This cross-sectional study compared veterans with PTSD against veterans without PTSD as controls for biomarkers of AD along with cognitive function. The exposure variable was PTSD,

and the outcome variables were biomarkers of AD: amyloid and tau burden, regional brain metabolism and atrophy and cognitive function. After providing informed consent, veterans underwent medical and psychiatric assessments during the first visit. The same psychiatrist conducted face to face assessments for all participants. After passing the study criteria, participants completed a comprehensive neuropsychological battery during the second visit. Mild cognitive impairment was screened at this stage and excluded, and eligible veterans proceeded to the PET scans. Mild cognitive impairment was excluded to reduce recruitment bias and avoid confounding of the diagnosis of PTSD. After rigorous metal safety screening, the participants underwent the MRI scan.

This study was modelled on the U.S. Alzheimer's Disease Neuroimaging Initiative (ADNI)-Department of Defense Veterans study. The work that formed the basis of the thesis represented one arm of a collaborative study of Alzheimer's disease risk in dementia. The other arm was part of Alzheimer's Disease Neuroimaging Initiative (ADNI). The ADNI is a consortium of universities and medical centres in the United States and Canada established to develop standardized imaging techniques and biomarker procedures in normal subjects, subjects with MCI, and subjects with mild AD (Mueller et al., 2005). The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, 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. A part of the data analysed in the preparation of this study was obtained from the ADNI database (adni.loni.usc.edu). For up-to-date information, please see www.adni.info.org

3.6. Data Analysis

The PTSD group and controls were compared for the outcome variables. The normality test was performed first, and wherever the measures showed normal distribution independent t-test

was applied for the continuous variables to compare the means. Independent t-tests were 2-sided with 95% confidence intervals. The effect size based on standardized mean differences between the two groups was calculated and expressed as Cohen's d. For variables that did not show a normal distribution, the Mann-Whitney U test, a non-parametric test was used. The two-tailed results were corrected for multiple comparisons using the Benjamini-Hochberg procedure. Both groups were compared for the following continuous outcomes variables.

1. ^{18}F-florbetaben global SUVR.
2. ^{18}F- AV-1451 SUVR, global and regional.
3. ^{18}F-fluorodeoxyglucose regional SUVRs.
4. MRI volumetry of hippocampi, amygdala, anterior cingulate cortex, middle frontal cortex, and orbitofrontal cortex corrected for the total intracranial volume.
5. Cognitive test scores.

The demographic variables, viz., age, premorbid IQ, and the years of education and the potential co-variates, namely depression rating score and vascular risk factor score, were also analysed. The groups were compared for categorical variables using Chi-square ($\chi 2$) test. Positive or negative status of the ^{18}F-florbetaben scan, obstructive sleep apnoea, and APOE e4 status were treated as categorical variables. Pearson correlation test was applied to measure the correlation between the CAPS score and scores on the outcome variables. Co-morbidities were controlled in the regression analysis. The confounding factors that individually correlated or were associated with the outcome variables were adjusted in multiple linear regression models. The data were securely stored in FileMaker Pro. The analyses were performed with SPSS statistics version 24. For the purpose of this study, current PTSD was the outcome variable included in the primary analysis with *a priori* that it was the perpetual morbidity that could be associated with the risk of AD. Lifetime PTSD was, however, analysed later.

Summary

The study was compliant with the principles of the Helsinki Declaration of Human Research. Following a power analysis based on the effect size from the published literature and the ADNI data, the sample sizes were determined. Veterans who passed the initial screening had a face-to-face evaluation with a psychiatrist. Participants proceeded to assessments after providing an informed, written consent. All participants underwent 20-minute PET scans acquired 90 minutes after administration of 250 MBq (± 10%) of ^{18}F-florbetaben and 70 minutes after the injection of 370 MBq of ^{18}F-AV-1451. The study analysed the PET scans with the Computational Analysis of PET from AIBL (CapAIBL) software and calculated the Standardized Uptake Value Ratio (SUVR) of ^{18}F-florbetaben using the cerebellar grey matter uptake as the reference to quantify global A-β burden. The SUVR of ^{18}F-AV-1451, with the cerebellar uptake as the reference, estimated global and regional tau deposition in the following regions: mesialtemporal; temporoparietal; and rest of the neocortex. For the acquisition of ^{18}F-FDG PET scan, participants fasted for four hours and then had an injection of 250-300 MBq of ^{18}F-FDG. The FDG SUVR was calculated for the frontal, mesialtemporal, and posterior cortical regions and the rest of the neocortex. Participants underwent 3-Tesla brain MRI for the measurement of regional cortical volumes (hippocampi, anterior cingulate cortex, orbitofrontal cortex, and middle frontal cortex) and the total intracranial volume. The study used Clinician's Administered PTSD Scale (CAPS)- DSM-IV version to assess PTSD. A score of 40 or more and a history of combat exposure constituted the inclusion criteria for the PTSD group. A CAPS score of 30 or less and military experience formed the inclusion criteria for the control group. Subjects who scored between 30 and 40 were excluded. All subjects underwent an extensive neuropsychological test battery that included Wechsler's Test of Adult Reading (WTAR) to estimate premorbid Intelligent Quotient (IQ). A cardiovascular risk factor score was calculated and testing for ApoE-e4 was performed. After the test of normality independent t-test compared the current PTSD group with

controls for the normally distributed data and Mann-Whitney U test compared the groups for the data that did not follow a normal distribution. The continuous variables included in the analysis were the age of participants, cognitive test scores, ^{18}F-florbetaben, ^{18}F-AV-1451, and ^{18}F-fluorodeoxyglucose SUVRs, years of education, the TICV, GDS score, vascular risk factor score, and predicted IQ. The two-tailed results were corrected for multiple comparisons using the Benjamini-Hochberg procedure. The analyses were performed on SPSS version 24.

Chapter 4

Results

4.1. Introduction

The study began in March 2014, and the last participant was recruited in June 2017. During this period, 169 male veterans completed the initial medical and psychiatric assessments. One veteran served in the American Army, and the rest served in the Australian Army. Except for one veteran who was a resident of New South Wales, all were residents of the state of Victoria. There were no adverse incidents or injuries attributable to the study. Twenty veterans later withdrew from the study for reasons of inconvenience or perceived distress. After excluding 66 veterans, including three veterans who had CAPS score between 30 and 40, the analysis included neuropsychological and PET data from the remaining 83 veterans (reasons for exclusions are shown in a detailed flow chart-Figure 5). A diagnosis of lifetime PTSD was present in 53 veterans, and 30 veterans were controls. Among veterans with lifetime PTSD, a diagnosis of current PTSD was present in 30. All veterans experienced PTSD symptoms either during or soon after military service.

4.1.1. Distribution of variables

The age ranged from 62 years to 85 years. The mean age of the whole cohort was 69.13 ± 4.57 years. There were no female veterans. The following continuous variables did not show normal distribution: lifetime and the current CAPS scores, volume of the right amygdala and the left middle frontal lobe, premorbid IQ, depression rating score, years of education, vascular risk score, the ROCFT score, the MMSE and the MoCA total scores and SUVRs of ^{18}F-AV-1451 in all regions and ^{18}F-florbetaben. For these variables, the Mann-Whitney U test was performed. Other variables followed a normal distribution, and the independent t-test was applied to these variables.

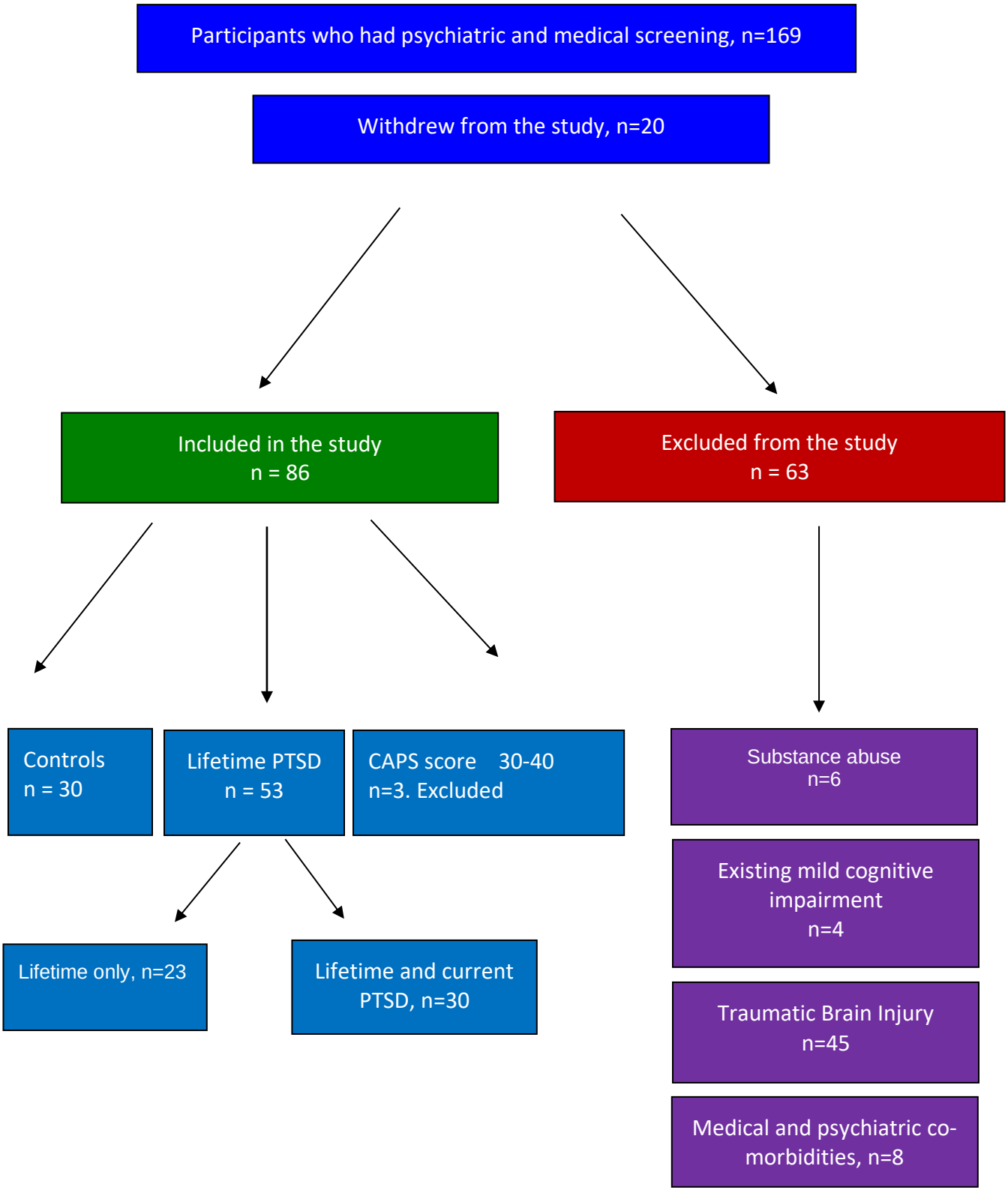

Figure. 5. Participants recruitment and exclusion

4.1.2. Participants' characteristics

4.1.2.1. Current PTSD vs. controls

The participants' characteristics are shown in table 1. The median current CAPS score for the PTSD group was 52.50 compared with 4.0 for the control group (Mann-Whitney U=0.000, p<.001). Veterans with current PTSD were slightly younger than those without PTSD (the PTSD group mean age: 67.80±2.48 vs. the control group mean age: 70.23 ± 5.46; p=0.043; CI= 0.220-4.64; Cohen's d=0.57). Median predicted premorbid IQ (104 vs. 114; U=201.00; p<.001) and years of education (11 vs. 12; U=305.00; p=0.043) were significantly lower whereas the median GDS score (5.50 vs. 1, U=130.00, p<.001) was significantly higher in the PTSD group than in the controls. The total intracranial volume was significantly lower in the PTSD group than in the control group (1565.2±1114.31 cm3 vs. 1674.12 ±1474.64 cm3; p=0.010; CI=33.6-184.3; Cohen's d=0.40). The median vascular risk factor score did not differ significantly between the groups (1 vs. 2, U=384.50, p=0.318). Apolipoprotein e4 carrier status was available for 55 (92%) participants, and at least one allele was present in 7 (24%) veterans with PTSD and 2 (9%) controls ($\chi 2$= 2.70, p=0.10). The Pittsburgh Sleep Quality Index (PSQI) score was significantly higher in the PTSD group than in controls (8.31 ± 3.86 vs. 4.38 ± 4.10. CI=-6.49- -1.374, p=0.003, Cohen's d=0.98). More veterans in the PTSD group had a diagnosis of obstructive sleep apnoea syndrome than in controls (2 vs. 13, $\chi 2$=10.33, p=0.001).

Table 1. Participant Characteristics.

Variables	Controls (n=30) Mean ± SD/ Median (Interquartile Range)	Current PTSD (n=30) Mean ± SD)/ Median (Interquartile Range)	p value (corrected)
Age	70.23 ± 5.46	67.80±2.48	0.043
Predicted IQ	114 (5)	104 (12)	<.001
Years of education	12.0 (5)	11 (4)	0.043
Total Intracranial Volume (cm^3)	1674.12 ± 1474.64	1565.17 ± 1114.31	0.01
GDS Score	1 (2)	5.50 (5)	<0.001
PSQI	4.38±3.86	8.31±4.10	0.003
Vascular Risk Factor Score	1	2	0.318

IQ=Intelligent quotient
PTSD=posttraumatic stress disorder
SD=Standard Deviation.
GDS=Geriatric Depression Scale.
PSQI=Pittsburgh Sleep Quality Index.
PSQI=Pittsburgh Sleep Quality Index
OSA=Obstructive Sleep Apnoea.

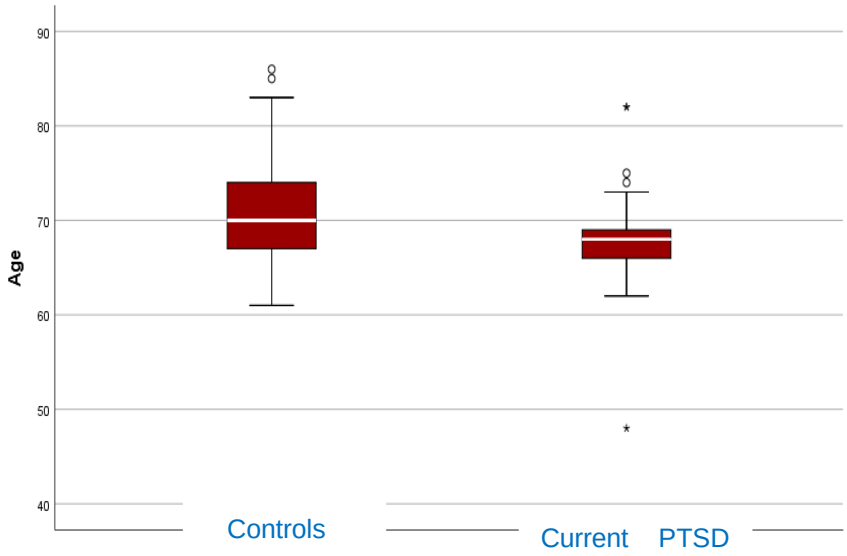

Figure 6. Age of participants.

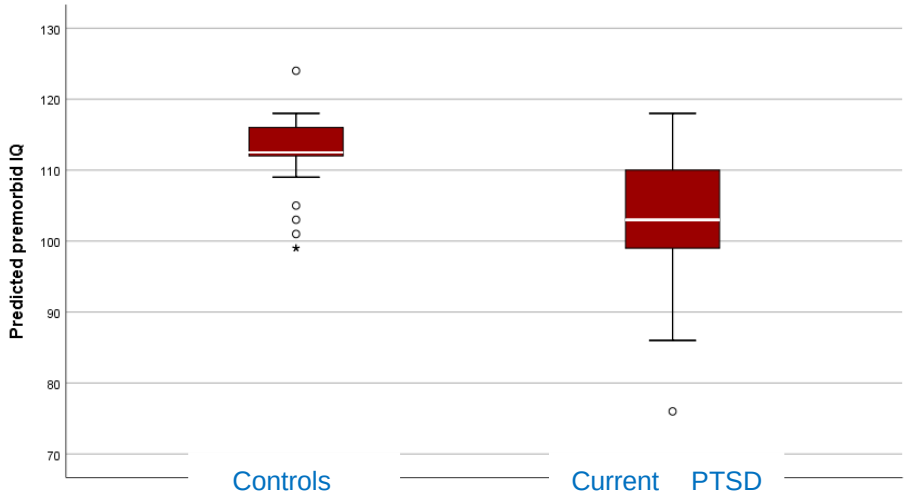

Figure 7. Predicted premorbid IQ.

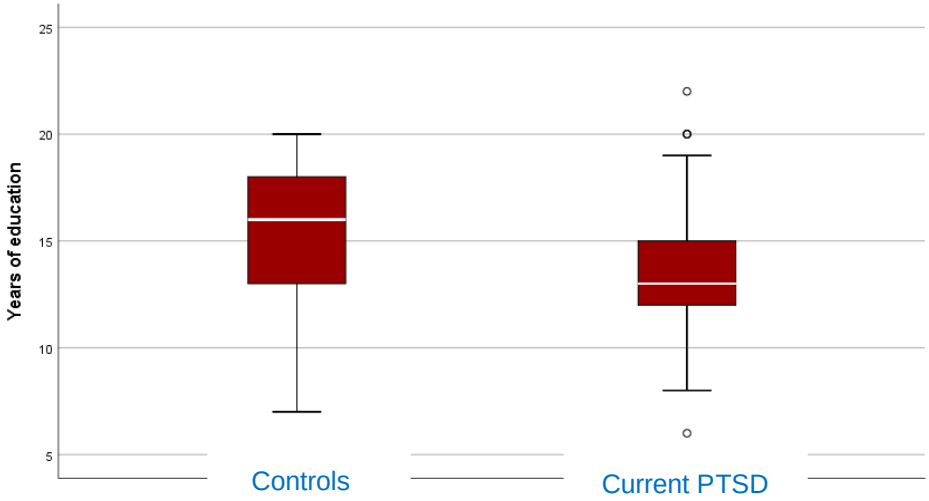

Figure 8. Years of education

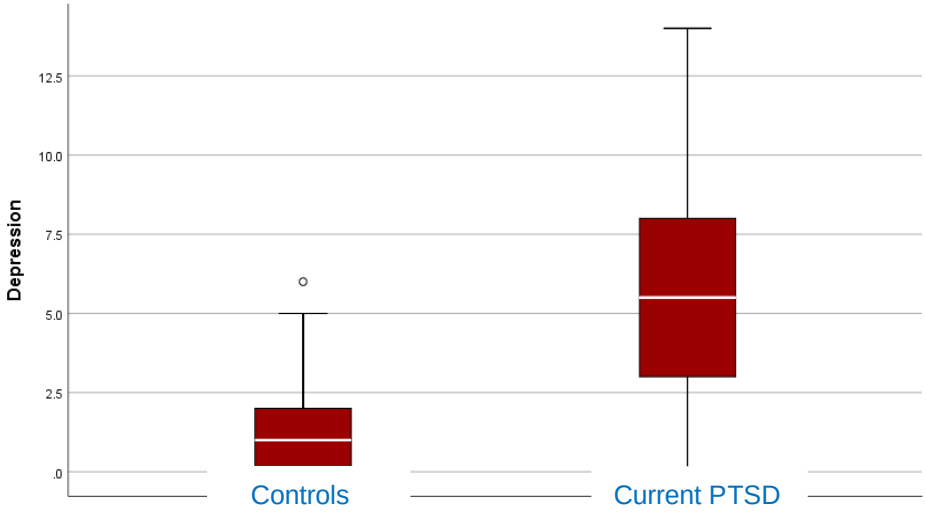

Figure 9. Geriatric Depression Score

4.1.2.2. Lifetime PTSD (with or without current PTSD) vs. control

The analysis was repeated after including all participants with PTSD (total number=53; current PTSD, n=30, and lifetime PTSD, but not current, n=23). The PTSD and control groups did not differ significantly in age **(**p=0.073) or vascular risk factor score (p=0.065). The mean lifetime CAPS score was 73.95 ± 17.09 in the PTSD group and 9.33 ± 9.33 in the control group (p<0.001, Cohen's d=4.69). The predicted IQ based on the WTAR and years of education were significantly

lower in the PTSD group compared with the control group (p<0.001, Cohen's d=0.94; p=0.045, Cohen's d=0.47, respectively). Compared with the control group, veterans with PTSD had a significantly higher score on the depression rating scale (p <0.001, Cohen's d=0.96) and a higher rate of previously diagnosed obstructive sleep apnoea (χ2=12.87, p<0.001). Veterans with lifetime PTSD scored significantly higher on the PSQI compared with controls (7.76 ± 3.81 vs. 4.38 ± 3.80, p=0.004, Cohen's d=0.88). Also, lifetime CAPS score positively correlated with PSQI total score (r=0.418, p=0.002). The APOE e4 status was not significantly different between the groups (χ2=2.14, p=0.143).

4.1.3. Combat exposure

Veterans with and without current PTSD did not differ in the CES score, but there was a non-significant trend towards increased combat exposure in the PTSD group. (15.12 ± 9.6 vs. 10.68 ± 8.15, p=0.07, Cohen's d=0.49). Similarly, the correlation between the mean CES score and mean current CAPS score did not reach statistical significance (r=0.226, p=0.088). There was no significant correlation between the CES score and cognitive test scores.

The analysis was performed with lifetime PTSD with and without current PTSD. In the lifetime PTSD group, seven veterans could not complete CES because of distress upon responding to the questionnaire items. Veterans with lifetime PTSD had significantly more trauma exposure as measured by the CES compared with the controls (16.06 ± 9.18 vs. 10.68 ± 8.15, p=0.013, Cohen's d=0.61). The mean CES score positively correlated with the mean lifetime CAPS score (r=0.252, p=0.030). There was no significant correlation between the mean CES score and any cognitive test scores.

4.2. Brain Imaging

4.2.1. B-Amyloid, tau and ^{18}F-Fluorodeoxyglucose PET imaging.

There was no significant difference between the current PTSD group and the controls in the median SUVR of the beta-amyloid tracer, ^{18}F-florbetaben (1.22 vs. 1.21, p=0.610). According to the visual inspection of ^{18}F-florbetaben scans, 7 (21.8%) veterans with current PTSD, and 4 (10.5%) veterans without PTSD had a positive scan. This difference was not significant ($\chi 2$ =0.57, p=0.48). In the multivariable regression analysis with ^{18}F-florbetaben SUVR as the dependent variable and current PTSD, age, APOE e4 and vascular risk factors as the independent variables, current PTSD did not predict ^{18}F-florbetaben SUVR (standardized coefficient β=-0.093, p=0.513) whereas APOE e4 was a significant predictor of the SUVR (R^2=0.126, standardized coefficient β=0.185, p=0.043). The SUVR of ^{18}F-florbetaben did not significantly correlate with the severity of PTSD, as measured by the CAPS. There was no significant correlation between the severity of war trauma as measured by the CES and ^{18}F-florbetaben SUVR.

As was the case with ^{18}F-florbetaben, the regional and global uptake of the tau tracer, ^{18}F-AV-1451, did not differ between the PTSD and control groups (Table 2). ^{18}F-AV-1451 SUVR did not correlate with any cognitive score or the total CES score. There was no significant correlation between the severity of PTSD as measured by the CAPS score and global or regional ^{18}F-AV-1451 SUVRs. There were no differences in the ^{18}F-FDG SUVRs between the groups (Table 2). There was no correlation between the severity of PTSD as measured by the CAPS and ^{18}F-FDG SUVR in any region. Similarly, ^{18}F-FDG SUVR did not significantly correlate with the total CES score, a measure of trauma severity. The analyses were repeated for subjects with lifetime PTSD with and without current PTSD (n=53) against the same control group (n=30). There was no significant difference in the uptake of any tracer globally or regionally between the two groups.

Adding the U.S. ADNI-DOD study amyloid PET data expanded the sample size to a total of 97 Vietnam veterans with PTSD and 85 controls. Centiloid units were calculated to allow the merging of scans obtained with the different beta-amyloid PET tracers, florbetapir, and florbetaben. The combined data has not revealed a significant difference between the two groups in the Centiloid values (PTSD Mean: 9.01 ± 20.73; versus Control Mean 14.37 ± 26.12, Cohen's d = 0.22; Median rank: 89.85 versus 93.39, p = 0.651; Mann-Whitney U = 3962.00). More veterans in the control group than in the PTSD group had a positive amyloid scan based on the Centiloid cut off score of 25 or more (13 vs. 7, $\chi 2=7.47$, p=0.024, uncorrected). With the additional ADNI data, APOE e4 was present in 23 veterans with PTSD and 17 veterans without PTSD ($\chi 2=0.567$, P=0.451, uncorrected).

Table 2. PET Tracer binding expressed in SUVR.

Tracers	Controls (n=30) Median/mean	Current PTSD (n=30) Median/mean	p value
^{18}F-florbetaben	1.21 (0.13)	1.22 (0.16)	0.610
^{18}F-AV-1451 (mesial temporal)	1.16 (0.12)	1.21 (0.20)	0.804
^{18}F-AV-1451 (temporoparietal)	1.17 (0.11)	1.16 (0.18)	0.610
^{18}F-AV-1451 (rest of neocortex)	1.17 (0.11)	1.14 (0.16)	0.610
Global ^{18}F-AV-1451	1.13 (0.14)	1.10 (0.13)	0.620
^{18}F-fluorodeoxyglucose (mesial temporal)	0.75 ± 0.05	0.74 ± 0.04	0.344
^{18}F-fluorodeoxyglucose (frontal)	1.05 ± 0.08	1. 03 ± 0.05	0.384
^{18}F-fluorodeoxyglucose (rest of neocortex)	1.06 ± 0.07	1.04 ± 0.06	0.303
^{18}F-fluorodeoxyglucose (Posterior Cortical Index)	1.056±0.06	1.03±0.06	0.231

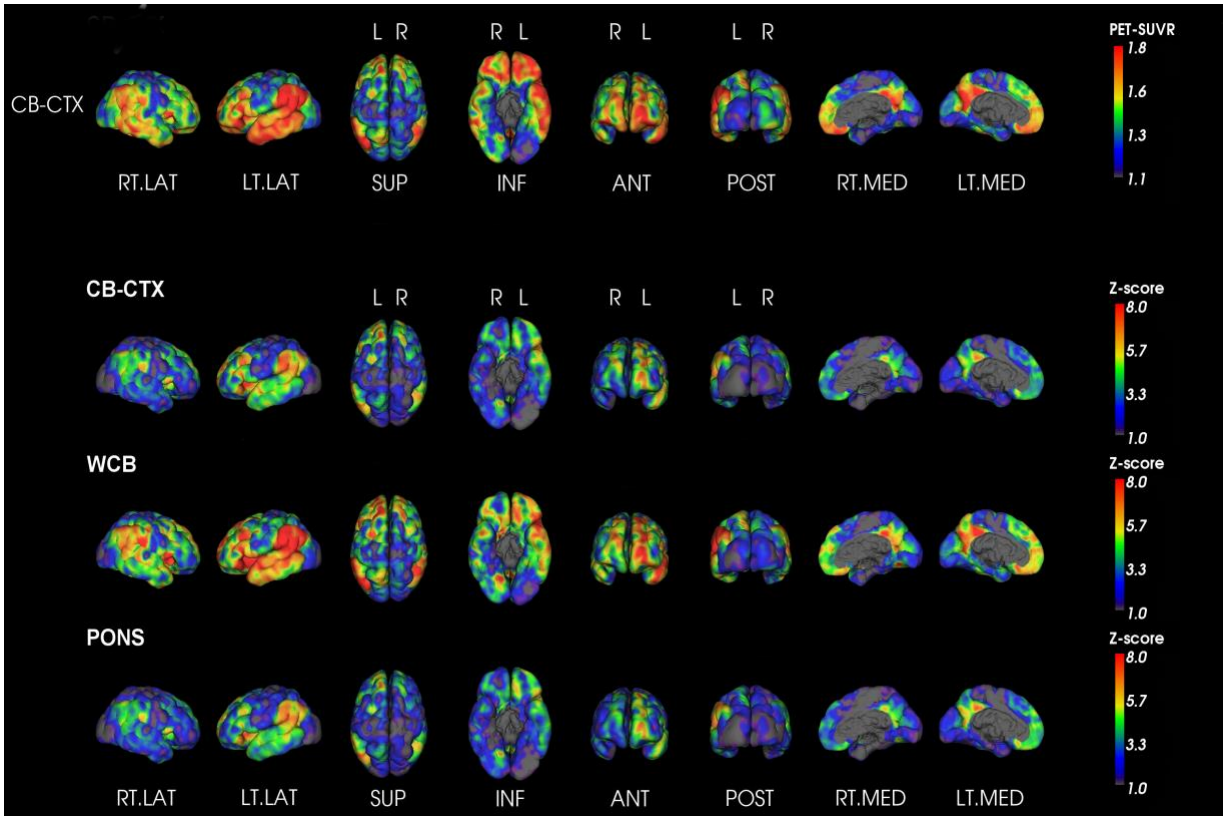

Figure 10. Stereotactic surface projection display of ^{18}F-florbetaben retention verses a normal age matched database from one study participant showing areas of elevated β-amyloid deposition in a Z-score graded colour scale of the SUVR for cortical voxels with cerebellar cortex, whole cerebellum and pons as reference regions.

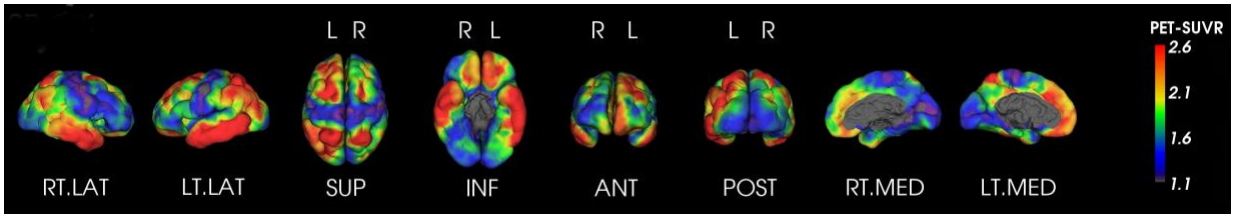

Figure 11. A positive ^{18}F-AV1451 scan displayed as stereotactic surface projection of SUVR using cerebellar grey matter as reference region.

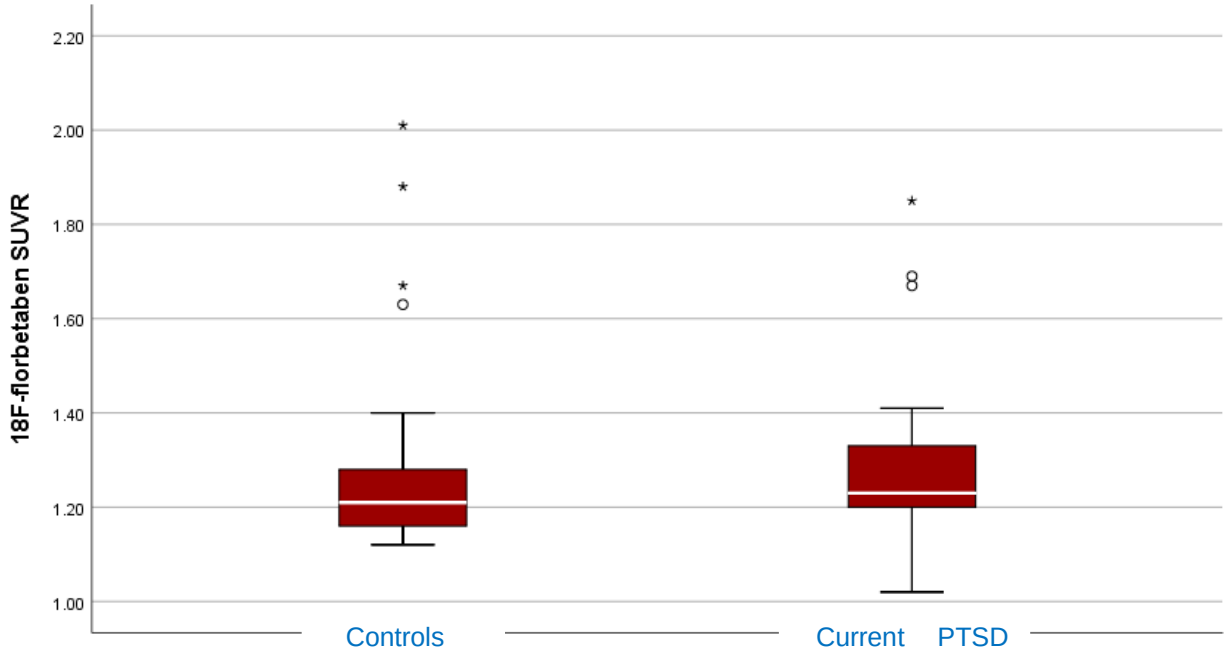

Figure 12. ^{18}F- florbetaben SUVR.

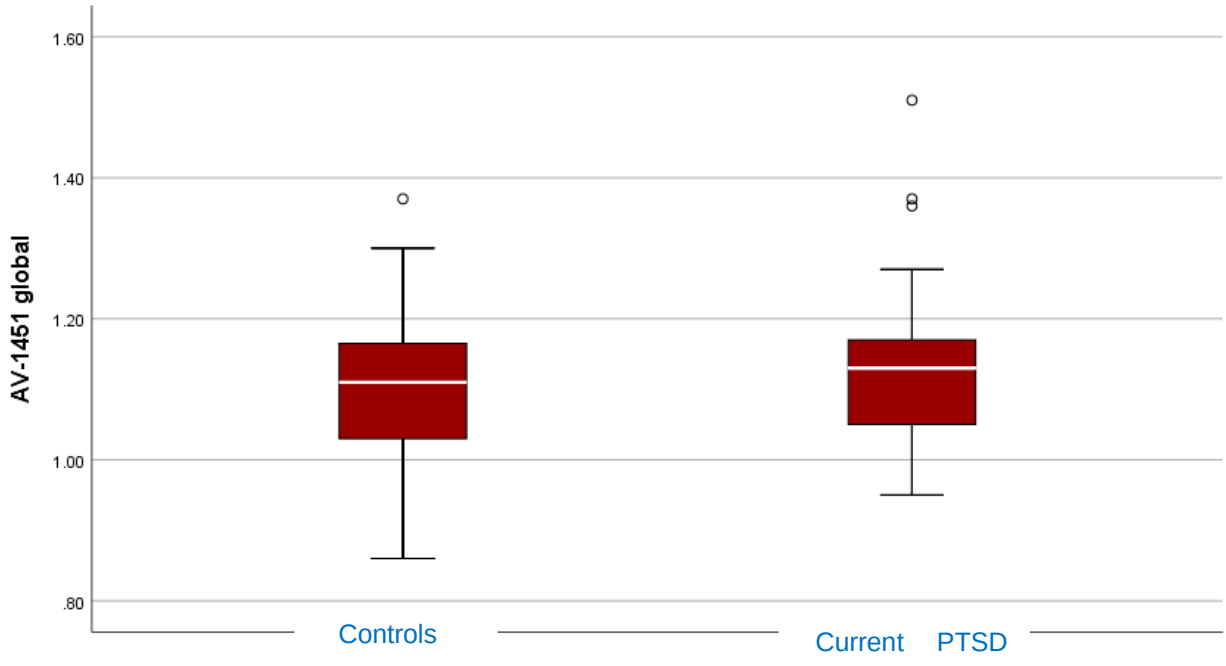

Figure 13 ^{18}F-AV-1451 global

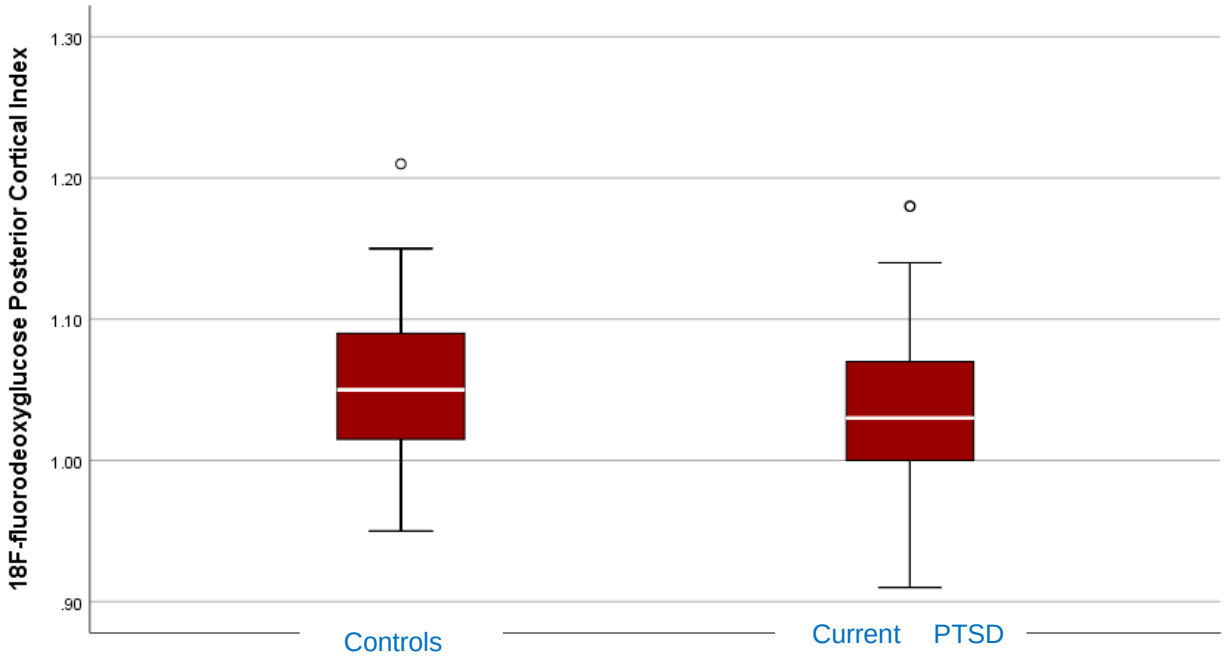

Figure 14 ^{18}F-fluorodeoxyglucose SUVR (Posterior Cortical

4.2.2. Magnetic resonance imaging

Forty veterans of the lifetime PTSD group, including 30 veterans with ongoing or current PTSD, and 25 controls underwent MRI. Others did not have MRI for reasons of inconvenience and metal safety. The total intracranial volume (TICV) was significantly lower in the current PTSD group than in the control group (1565.173±1114.31 cm3 vs. 1674.12 ±1474.64 cm3; p=0.01; CI=33.59-184.307; Cohen's d=0.40). There was no significant difference between veterans with and without current PTSD in the adjusted volumes of the hippocampus, the amygdala, the ACC, the middle frontal, or orbitofrontal cortex on either side (Table 3). The analysis was repeated with subjects who had a lifetime diagnosis of PTSD. The TICV was significantly lower in the lifetime PTSD group compared with the control group, but volumetric grey matter measures did not significantly differ between the groups. There was no significant correlation between volumetric measure and severity of current PTSD as quantified by the CAPS score.

Table 3. Magnetic Resonance Imaging Volumetry

Variables	Controls (n=25) Mean ± Standard Deviation	Current PTSD (n=24) Mean± Standard Deviation	p value
Total Intracranial Volume (in cm^3)	1674.12 ±1474.64	1565.173±1114.31	0.01
Regional volumetry in percentage			
Left hippocampus	0.18±0.01	0.19±0.01	0.676
Right hippocampus	0.19±0.01	0.19±0.01	0.640
Left amygdala	0.08±.01	0.08±0.01	0.640
Right amygdala	0.08±0.01	0.08±0.008	0.676
Left middle frontal cortex	0.17±0.02	0.17±0.01	0.846
Right middle frontal cortex	0.69±0.06	0.68±0.07	0.676
Left orbitofrontal cortex	0.17±0.02	0.17±0.02	0.676
Right orbitofrontal cortex	0.17±0.02	0.17±0.02	0.874
Left anterior Cingulate cortex	0.33±0.03	0.32±0.04	0.801
Right anterior Cingulate cortex	0.28±0.04	0.27±0.04	0.640

4.3. Cognitive Test Scores

There were no significant differences between the groups in the mean scores of cognitive tests that measured specific cognitive domains, such as episodic memory or attention, while the global cognitive performance, conversely, was impaired in the PTSD group (Table 4). The

performance of both groups was within the normal range of age-adjusted published norms of the neuropsychological tests except in the MoCA, where the mean score for the PTSD group (25.27) was fractionally below the conventional cut-off score of 26. In comparison with the controls, veterans with current PTSD scored lower on global cognitive function as measured by the MoCA (Median: 26 vs. 28; U=250.00; p=0.027). Multivariable regression analysis was performed with the total MoCA score as the dependent variable. The predicted premorbid IQ and the Geriatric Depression Score (GDS) score significantly correlated with the total MoCA score and also differed between the groups. Therefore, these variables were included in the model with current PTSD as explanatory (independent) variables. The regression analysis met all assumptions. In the regression analysis (adjusted R^2 = 0.249) the difference in the performance between the PTSD group and controls on the MoCA did not retain significance (β= -0.252, p=0.081) when predicted premorbid IQ (β=- 0.341, P=0.009) and the GDS score (β=0.006; p=0.611) were adjusted. The cognitive scores are summarized in table 3. There was no significant difference between the PTSD groups and the controls in the other cognitive measures. The correlation between predicted premorbid IQ and TICV was significant (r=0.351, p=0.013).

Table 4. Cognitive functions in PTSD and controls.

Variables	Controls (n=30) Mean ± SD/ Median (interquartile range)	Current PTSD (n=30) Mean ± SD/ Median (interquartile range)	p value
Digit Span	17.73±3.99	15.40±4.10	.135
Categorical fluency	38.97±9.91	38.13±11.44	.860
Trail making test A (time to completion in seconds)	37 (15)	34 (17)	.882
Trail making test B (time to completion in seconds)	90 (42)	97.50 (65)	.182
Rey Osterrieth complex figure copy test	29.43±2.97	30.40±5.99	.555
RAVLT Learning trials	47.17±10.56	44.70±9.22	.535
Composite memory score	0.02 ±0.74	-0.15 ± 0.69	0.535
MMSE	29 (1)	28 (2)	.182
MoCA	28 (4)	26 (4)	.027

Chapter 5

Discussion

5.1. Introduction

The present study has measured biomarkers of AD in PTSD. There is abundant literature on cognitive function, structural brain imaging, and incidence of dementia in Vietnam veterans with PTSD, but there is a paucity of information about specific biomarkers of AD in PTSD. The cognitive impairment, epidemiological data, and biomarkers should, in an ideal world, have formed an unbroken chain linking all aspects of Alzheimer's disease. But such a comprehensive investigation can turn out to be far more logistically challenging than what resources can support. There is very little data on AD biomarkers in PTSD. This study, therefore, focused on Aβ and tau along with regional brain metabolism and cortical volumes in patients with PTSD. In the present study recruitment of veterans ensured a homogenous population with military experience in both groups. In the PTSD cohort, a majority of veterans had ongoing PTSD symptoms meeting the criteria for current PTSD. Persistence of PTSD symptoms is in line with the previous data that showed no signs of abatement of symptoms in one-third of patients (Kessler et al., 1995). It is in the context of this perpetual morbidity to late life that the investigation of AD pathology, a process that takes decades, becomes relevant in PTSD.

5.1.2. Participants and demographics

5.1.2.1. Age and gender

The age of participants ranged from 63 years to 85 years, with a mean of 69 years. This age is consistent with the chronology of the Vietnam War. Age is the strongest risk factor for late-onset Alzheimer's disease (Jorm & Jolley, 1998). Age can also influence the performance of

cognitive functions. In this study, veterans with current PTSD were slightly younger than the control veterans (67 years vs. 70 years) with a medium effect size (Cohen's d=0.54). The PTSD group was still in the age range relevant to the preclinical phase of AD with the mean age of diagnosis of AD dementia being 78 years while the mean time before dementia that an amyloid PET scan becomes abnormal is 20 years. Had PTSD caused or accelerated the accumulation of amyloid, it should have been reflected on an ^{18}F-florbetaben scan by this age as veterans with PTSD had lived with PTSD for 40 or more years. The mean ^{18}F-florbetaben SUVR in the PTSD group was in the normal range. Moreover, a prospective cohort study has shown an estimated 12 years to increase amyloid plaque from none to where it first becomes detectable on PET and then another 20 years to reach the level found in the average AD patient with mild to moderate dementia (Villemagne et al., 2013). These findings suggest a prolonged accumulation of A-β over years, and therefore an age difference that has been observed in the present study between the current PTSD group and controls is unlikely to explain the absence of a significant difference in ^{18}F-florbetaben SUVR between two groups. When the analysis was repeated with the data of lifetime PTSD with and without current PTSD, age between the groups did not differ significantly, and there was still no significant difference in ^{18}F-florbetaben SUVR between the groups.

All participants were men. The study did not follow *a priori* that cognitive impairment and the risk of Alzheimer's disease were gender specific. Selective gender participation may reflect the fact that Australian servicewomen in the Vietnam War served the role of nurses, embassy staff, and journalists rather than duties in the combat field. Australia began to open combat roles for women in 2011 (CNN 2016). The roles that Australian women are now able to occupy include ground defence guards, infantry, artillery, and armoured units. During the time of the Vietnam War, only men served in combat roles in the Australian army.

5.1.2.2. Education

The findings derived from the present study are quite resonant with previous studies. The years of education in the current sample showed a wide range, 6 to 22, with a mean of 12. Subjects with PTSD had a significantly lower level of education compared with the controls. The relationship between education and PTSD warrants a careful interpretation. Low level of education is a risk factor for exposure to the trauma itself (Breslau et al., 1991). Previous studies found an increased incidence of PTSD among undereducated trauma-exposed individuals compared with highly educated individuals with trauma exposure. A meta-analysis concluded that a low level of education was a risk factor for the development of PTSD more in the military population than in the civilian population (Brewin et al., 2007). Another meta-analysis of the risk factors of combat-related PTSD replicated this finding (Xue et al., 2015). The finding of the present study is also in tune with the National Vietnam Veterans Readjustment Study, which found a lower level of education as one of the predictors of persistence of PTSD symptoms sufficient to meet a current PTSD diagnosis, 40 years after the War (Steenkamp et al., 2017). Above all, the recent ADNI-DoD veterans study that used similar methodology to this study also found a significantly lower level of education in the PTSD group compared with the controls (Weiner et al., 2017). These results imply impaired coping ability to catastrophic trauma in individuals with limited education. Low level of education may also adversely affect the ability to access care and remain in treatment programs with a risk for a protracted course of symptoms.

5.1.2.3. Premorbid intelligence

The range of predicted premorbid IQ was also wide-ranging from 74 to 124 with a mean of 107, which is nearly the current average age-adjusted IQ (110) in the general Australian population. The predicted premorbid IQ was significantly lower in the PTSD groups compared with the controls. Previous studies have shown lower premorbid IQ in combat-related PTSD than in healthy controls (Gilbertson et al., 2006; Scott et al., 2015a). Macklin et al. have demonstrated that the association

between PTSD and impaired performance on cognitive assessment was no longer significant when premorbid IQ, as measured by the military aptitude test, was controlled (Macklin et al., 1998). Low IQ at the age of 5 years predicted future PTSD after trauma exposure (Koenen, Stellman, Dohrenwend, Sommer, & Stellman, 2007). Pre-deployment Armed Forces Qualification Test, a measure of premorbid cognitive ability, was associated with the future development of PTSD in a co-twin control study of Vietnam veterans (Kremen et al., 2007). In the same vein, Breslau, et al. found that high childhood IQ reduced future exposure to trauma and the conditional risk of PTSD (Breslau et al., 2006). Gate et al. reproduced similar results and demonstrated a 39% increase in the future risk of PTSD in male Vietnam veterans with a one-standard-deviation reduction in early childhood cognitive ability (Gale et al., 2008). These findings merge towards a developmental origin of PTSD rather than a mere response to trauma.

Posttraumatic stress disorder is a unique psychiatric disorder in which the aetiological agent-exposure to catastrophic trauma-is specified. After combat exposure, most victims do not develop PTSD, however (Blake et al., 1990; Breslau et al., 1991; Lewis et al., 2019). The rate of PTSD among those who were exposed to catastrophic trauma was estimated at 23.6% in young civilians and 34.8% in veterans (Breslau et al., 1991; Xue et al., 2015). Factors that predispose to PTSD in veterans have been investigated. Increased combat exposure, relatively low level of education, and poor premorbid intelligence were previously reported as the risk factors for PTSD after trauma exposure (Brewin, Andrews, & Valentine, 2000b; Gilbertson et al., 2006; Scott et al., 2015a). The findings of the present study-i.e. a relatively low level of education and predicted premorbid IQ in the PTSD cohort -travel well with such a premorbid predisposition to PTSD.

5.1.2.4. Combat exposure and Posttraumatic Stress Disorder

Military trauma is unique in posing the highest risk of PTSD, especially with delayed onset and longer duration (Prigerson, Maciejewski, & Rosenheck, 2001). Additionally, combat-related PTSD is sometimes reported as more severe than non-combat PTSD (Brinker, Westermeyer,

Thuras, & Canive, 2007). As in the case of education and premorbid IQ, the severity of trauma exposure is a risk factor for PTSD, particularly in the military population (Brinker et al., 2007; Xue et al., 2015). In the current study, a diagnosis of lifetime PTSD was associated with increased exposure to combat trauma.

In a study of Vietnam veterans, the duration of combat exposure and combat rating were found to be associated with both the development and persistence of PTSD (Buydens-Branchey, Noumair, & Branchey, 1990), but an Australian study of Vietnam veterans did not replicate this finding (Hennessy & Oei, 1991). Recall bias needs to be considered in interpreting these results as trauma severity was assessed years after exposure. To address this methodological limitation, one study assessed the reliability of trauma severity reporting. The study has proven consistency in reporting combat severity over time, although it was affected by a change in PTSD symptoms, particularly re-experiencing of trauma (Koenen et al., 2007).

Summary

Numerous investigations have shown cognitive impairment and suggested an increased risk of Alzheimer's dementia in PTSD, but none utilized the biomarkers specific to Alzheimer's disease. This study involved veterans with PTSD with forty or more years of symptoms and compared against control veterans. The samples and the duration of symptoms were appropriate for the study of AD risk in PTSD. Moreover, this was a comprehensive assessment incorporating biomarkers of specific AD pathology, Aβ and tau, and for the imaging of neurodegeneration along with a detailed neuropsychological and psychiatric assessment. In the past, studies have provided evidence supporting the role of low education and premorbid IQ as a predisposing factor for PTSD symptoms following trauma exposure. The current study replicated these previous findings.

5.2. Brain Imaging

5.2.1. β -Amyloid and tau and ^{18}F-fluorodeoxyglucose PET

The findings of the current study did not show a significant association between PTSD and increased amyloid or tau deposition in the brain. This finding is consistent with the results from the U.S. ADNI-DoD study of the risk of AD in PTSD that also did not reveal a significant association between PSTD and increased A-β deposition (Weiner et al., 2017). This is the first study to report all four imaging biomarkers for AD in a study of PTSD, i.e. A-β and tau PET for the specific pathology of AD and ^{18}F-fluorodeoxyglucose PET and MRI measures of brain metabolism and volume respectively for the neurodegenerative pattern of AD.

In PTSD, chronically elevated stress was previously hypothesized as an aetiological mechanism for increased deposition of A-β, tau hyperphosphorylation, and neurodegeneration with subsequent risk of Alzheimer's disease (Carroll et al., 2011; Dong et al., 2004). Stress studies were undertaken in transgenic mice, and the stress was induced by isolation and repeated restraint. Increased activation of the β2-adrenergic receptor resulted in the stimulation of gamma-secretase activity (Ni et al., 2006). Moreover, regular treatment with β2-adrenergic receptor agonists led to increased production of Aβ in the mouse model of AD (Ni et al., 2006). Alterations in the hypothalamic-pituitary axis (HPA) have been noted in PTSD (Ehlert, Gaab, & Heinrichs, 2001; Morris, Compas, & Garber, 2012). Dysregulation of the HPA axis has been hypothesized to occur in the early stages of AD. (Green, Billings, Roozendaal, McGaugh, & LaFerla, 2006). In line with this, glucocorticoid administration augmented both Aβ and tau accumulation in animal models. Justice et al. demonstrated that genetically induced AD pathology has the potential to induce a stress response and PTSD symptoms (Justice et al., 2015). The exposure to trauma may trigger a common pathway that depends on corticotrophin-releasing factor (CRF) receptor 1 signalling and

this is postulated to drive AD pathology and PTSD symptoms. The authors also found a rise in the CSF level of A-β after trauma exposure, both short-term and long-term (12 months).

Notwithstanding the extensive data derived from animal studies, the results obtained from the current study do not support PTSD as an inducer or accelerator of AD pathology in humans or support the hypothesis of a vicious cycle set by PTSD and A-β. Neither the CAPS score, nor the Combat Exposure Scale score correlated with amyloid or tau tracer retention. Veterans in this study suffered from trauma exposure and subsequent PTSD symptoms at an early age, mostly in their 20s and the veterans with current PTSD in this study suffered from chronic stress for more than 40 years. If enduring stress caused or accelerated the pathology of AD, then it is reasonable to hypothesize that chronic PTSD should have resulted in an increased burden of A-β and tau in veterans as they enter the age range in which AD pathology is frequently developing. At age 70 years, approximately 15-20% of the general population have a positive amyloid PET scan (Chételat et al., 2013). But there was no such evidence of increased prevalence or amount of amyloid in those with PTSD in this current study.

Existing neuropathological literature indicates the accumulation of tau frequently occurs in healthy aging in the medial temporal lobes, even in the absence of A-β (Braak, Thal, Ghebremedhin, & Del Tredici, 2011). Increased tau in the medial temporal lobe may represent primary age -related tauopathy (PART), not necessarily AD. Tau retention outside of this region is usually associated with increased cortical A-β, APOE e4, and brain atrophy even in cognitively normal individuals and hence signifies a very high risk for development of symptomatic AD (Scholl et al., 2016). In the current study, it was also seen that amyloid load significantly and positively correlated with tau tracer retention in all regions. However, this association was present in both the PTSD and control cohorts and there was no increased A-β or tau tracer retention in veterans with PTSD compared with controls suggesting this process was not related to PTSD.

Commensurate with the absence of a difference between the PTSD and the control cohorts in amyloid and tau burden, the present study did not show evidence of a pattern of hypometabolism suggestive of AD in PTSD. Hypometabolism in posterior cingulate and cinguloparietal transitional areas, being a characteristic feature of AD, precedes the onset of dementia for several years (Bateman et al., 2012; Minoshima et al., 1997; Mosconi et al., 2008). In this way, ^{18}F-fluorodeoxyglucose is a powerful tool to investigate the shorter-term risk of AD in PTSD. The results of the present study contradicted past studies that used ^{18}F-fluorodeoxyglucose PET in PTSD. These studies are different from the current study in the methodology, regions studied, the age of participants, and sample size. In the first study, Bremner et al. measured regional metabolic rate after yohimbine administration: there was no report of basal metabolic rate (Bremner et al., 1997). Another study investigated changes in glucose metabolic rate in response to both placebo and hydrocortisone administration. With placebo resting glucose metabolic rate (rGMR) was lower in the right hippocampus and ventral amygdala, and higher rGMR in the left ventral amygdala in patients with PTSD in comparison with control group. Upon administration of hydrocortisone, this difference was eliminated (Yehuda et al., 2009). Another study in veterans measured ^{18}F-fluorodeoxyglucose uptake and documented hypometabolism in several regions: the cingulate gyri, insula, right precuneus, hippocampus, frontal, prefrontal and post-central regions, right lingual gyrus, calcarine, and inferior parietal areas (Molina et al., 2010). The amygdala showed normal metabolism. Hypermetabolism was observed in the fusiform gyri, temporal pole, and left precuneus, medial and inferior temporal gyri, and cerebellum. Metabolic alterations in such a large number of areas were derived from a small number of veterans, 15 with PTSD, and six without PTSD. The assessment was performed 20 years after the trauma. These findings could not be confirmed in the present study with a larger sample. Veterans in the previous study were younger, with an age range of 39-41 years, whereas the participants were much older in the current study. A recent study that recruited subjects with PTSD and mild TBI could delineate the metabolic changes in TBI from the controls, but the differentiation between TBI and PTSD was unclear (Buchsbaum, Simmons, DeCastro, Farid, & Matthews, 2015). Patients with mild TBI and TBI plus PTSD had similar findings indicating no features specific to PTSD. The current study excluded TBI, and the samples were

more homogeneous than the previous study. Another study used ^{18}F-fluorodeoxyglucose in the rat model of PTSD (Zhu et al., 2016). The animal model is not conducive to study the long-term impact of PTSD on brain metabolism.

A recent study investigated basal glucose metabolism in different types of traumas: danger and non-danger-based traumas in soldiers with PTSD in comparison with soldiers without PTSD (combat controls) and civilian controls (Ramage et al., 2016). There was hypermetabolism in the right amygdala in association with danger trauma. The mean age of participants in this study was 37 years, whereas, in the present study, it was 68.7 years. Another report on ^{18}F-fluorodeoxyglucose PET in PTSD was more like a case series with nine patients in the PTSD group and 10 healthy volunteers. No definite conclusions could be deduced from this report (Zandieh et al., 2016).

The present study measured brain metabolism in the regions characteristically affected in AD, whereas the areas investigated by the previous studies were not specific to AD. Also, metabolism in brain regions involved in other neurodegenerative diseases was measured. There was no significant difference in brain metabolism between the PTSD group and controls in any region, suggesting a lack of evidence for an association between PTSD and neurodegeneration seen in other dementia syndromes. In this study, neither the severity of PTSD as measured by CAPS nor the severity of trauma exposure significantly correlated with regional brain metabolism on ^{18}F-fluorodeoxyglucose PET. Given that the subjects in this study were in their 60s and 70s, the cumulative effect of PTSD should have produced a more severe degree of hypometabolism in the key brain regions unless long-term adaptations occur. However, this study did not make such observations. These results indicate that PTSD is not associated with neurodegeneration or early neuroimaging signs of dementia as assessed by FDG PET.

Summary

The present study did not show a significant association between PTSD and increased Aβ deposition in the brain. The finding of the current study is consistent with the results from the US-based ADNI veterans study that also did not find an association between PTSD and an increased Aβ deposition. This is the first study to report tau imaging in PTSD. There was no increase in binding of the tau tracer ^{18}F-AV-1451 in PTSD. Although animal studies have suggested accelerated production of Aβ and tau, the results of the present study do not support the hypothesis of a stress-induced Aβ and tau production. Had enduring stress induced pathology of AD, PTSD should have resulted in an increased burden of A-β and tau in veterans at the age of those in this study, but there was no such evidence from this study. Similarly, there was no difference between the PTSD group and the controls in regional brain metabolism. If PTSD caused neurodegeneration associated with various dementia syndromes, then it would be likely that some change would be evident after having PTSD symptoms for 40 or more years. ^{18}F-fluorodeoxyglucose PET scan has been reported as showing abnormality several years before the onset of Alzheimer's dementia. These results indicate that PTSD is not associated with progressive neurodegeneration or early neuroimaging signs of dementia as typically seen with FDG PET.

5.2.2 Posttraumatic Stress Disorder and structures involved in cognitive function: MRI findings

The present study measured volumes of key brain structures involved in disturbance of cognitive function in psychological and psychiatric disorders: the hippocampus, amygdala, anterior cingulate cortex, orbitofrontal cortex, and middle frontal cortex. The regional volumes were adjusted

for the total intracranial volume (TICV). Regional atrophy of structures specific to Alzheimer's dementia and other neurodegenerative syndromes precedes clinical manifestations (Moscoso et al., 2019). From the PTSD group and controls, many veterans did not undergo MRI because of metal safety. Such attrition is consistent with the finding of the ADNI study that revealed a large number of veterans excluded because of ferromagnetic metal in the body (Weiner et al., 2017).

5.2.2.1. The total intracranial volume

The PTSD cohort had a lower TICV compared with the controls. Relatively low intracranial volume has been previously reported in PTSD (Bromis et al., 2018; Woodward et al., 2007) notwithstanding absence of a significant difference between veterans with PTSD and without PTSD in another study (Gurvits et al., 1996). The findings of this study do not match with a meta-analysis that reported no significant difference in the TICV between the subjects with PTSD and trauma-exposed controls (Hedges & Woon, 2010). This meta-analysis did not include the study from Woodward, et al. Moreover, only two studies were included in the meta-analysis raising questions about its power to detect an actual difference. A more recent meta-analysis of 86 structural brain studies concluded that patients with PTSD had lower intracranial volume compared with controls (Bromis et al., 2018).

The intracranial volume reaches its maximum size in adolescence, and it does not change with age. Although the TICV was lower in the PTSD group than in controls, it was within the normal range of the published data (1469±102 cm) from men (Matsumae et al., 1996). The TICV positively correlated with predicted premorbid IQ, a finding consistent with previous meta-analyses, which suggested a correlation between intracranial volume and intelligence. (Gignac & Bates, 2017; Pietschnig, Penke, Wicherts, Zeiler, & Voracek, 2015). Previously published findings showed a correlation between the TICV and cognitive function in the elderly population (MacLullich et al., 2002). The findings of the present study suggest relatively low measures of premorbid brain reserve in PTSD.

5.2.2.2. The hippocampus: Given the crucial role of the hippocampus in memory processing and reports that hippocampal volume may be influenced by regulation of the hypothalamo-pituitary axis, the hippocampal volume has been extensively studied in PTSD. Findings from this study suggested no significant difference in the adjusted hippocampal volumes between the PTSD group and controls. A meta-analysis of imaging studies in PTSD observed a significant reduction in both right and left hippocampal volumes, greater on the left side, in subjects with PTSD in comparison with healthy as well as trauma-exposed controls (Bromis et al., 2018; O'Doherty et al., 2015). But the heterogeneity among the included studies was significant, and several studies included in the meta-analysis had major depressive disorder as a comorbidity with PTSD. Depression is associated with hippocampal atrophy (Bremner et al., 2000; Caetano et al., 2004; Sheline, Wang, Gado, Csernansky, & Vannier, 1996). Apart from the confounding effect of depressive disorder, substance abuse, bipolar affective disorder, and generalized anxiety disorder were also comorbid with PTSD in the studies included in the meta-analysis. Therefore, heterogeneity and confounding effects of comorbidities limit the interpretation of meta-analyses.

The findings of the present study are not consistent with the meta-analysis and several previous studies that showed hippocampal volume reduction in PTSD, but there was variability in hippocampal volume among studies. In one study, the volume of the left hippocampus was found to be significantly lower in the PTSD group compared with the trauma-exposed controls (Morey et al., 2012). In another study, PTSD was associated with a smaller right hippocampus, not the left hippocampus (Wignall et al., 2004). Such inconsistent findings, often connoting lack of reproducibility, do not allow a definite conclusion of hippocampal atrophy in PTSD. Another important consideration is the impact of the duration of symptoms on the hippocampal volume. Flemingham et al. observed a correlation between the duration of PTSD and hippocampal atrophy (Felmingham et al., 2009). From such a finding, one would expect a greater extent of atrophy in older veterans who have endured symptoms for decades. The findings of the current study that included older veterans do not show significantly increased hippocampal atrophy in PTSD and,

therefore, do not support the hypothesis of the cumulative effect of post trauma symptoms on the hippocampus. The observations made by the current study are in line with the findings in Holocaust survivors. In a study of 14 elderly Holocaust survivors with PTSD and 13 survivors without PTSD, there was no association between PTSD and smaller hippocampal volume (Golier et al., 2005). The ADNI-DoD study of older veterans did not find significant volume loss of brain structures previously shown to be atrophied in PTSD (Weiner et al., 2017). These results raise a possibility that alterations in hippocampal and regional cortical volumes could be temporary, or the mild volume reductions may be masked by the atrophy that occurs with healthy aging. The participants of this study were in the 60s and 70s, and the effect of aging may have more impact on volumetric changes than PTSD itself, in cortical as well as hippocampal regions. Moreover, multimodal psychological interventions, and Eye Movement and Desensitization and Reprocessing (EMDR) have been reported to increase the volume of the hippocampus and amygdala in PTSD (Butler et al., 2018; Laugharne et al., 2016). Long-term antidepressant treatment has also been associated with an increase in hippocampal volume in patients with PTSD (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003). Such findings suggest that the hippocampal and amygdala volume changes in PTSD are not static or progressive, but potentially reversible. Future longitudinal studies are required to address these possibilities.

5.2.2.3. The amygdala: Emotions, especially fear, have been historically wired into the limbic system of the brain. A compartmentalized view of the limbic system as a substrate for emotions is not without debate (LeDoux, 2000). Fear processing is hypothesized to be mediated through circuits that have the amygdala as a hub. The amygdala has a role in the acquisition and expression of conditioned fear (LeDoux, 2000). Functional imaging studies have shown activation of the amygdala upon the perception of threats. Data from the structural analysis did not show a correlation between the amygdala volume and the magnitude of fear acquisition (Hartley, Fischl, & Phelps, 2011). Structural imaging studies of the amygdala in PTSD have varied in methodological approach. Most studies used a 1.5-Tesla MRI scan, and other studies reported findings with 2-Tesla and 3-Tesla scans (Bonne et al., 2008; Morey et al., 2012). The slice thickness varied from

1 mm to 4 mm. The studies have assessed PTSD using different tools such as CAPS, and Structured Clinical Interview for DSM (SCID*).* The heterogeneity was also present in the type of trauma: amygdala volume was studied in PTSD arising from combat exposure and civilian trauma. Variability in these factors has resulted in inconsistent results in the volumetric studies of the amygdala.

Both larger (Kuo et al., 2012) and smaller amygdala (Karl et al., 2006; Morey et al., 2012) were found to be associated with PTSD. Other studies did not show a decreased amygdala volume in PTSD (Gurvits et al., 1996; Lindauer et al., 2004; Wignall et al., 2004). In some studies, where there was a significant difference, the amygdala was smaller in PTSD in comparison with a healthy population, but not compared with trauma-exposed controls (Karl et al., 2006; Woon & Hedges, 2008). A meta-analysis showed no significant difference in its volume between the subjects with PTSD and trauma-exposed controls (O'Doherty et al., 2015). The present study is consistent with this meta-analysis and had sample sizes larger than the previous studies. The severity of trauma or chronicity of trauma had inconsistent relation with amygdala volume in previous studies; no significant correlation was observed with volume of amygdala in one study (Morey et al., 2012) whereas another study suggested a negative correlation between the severity of PTSD and volumes of left amygdala and anterior cingulate cortex (Rogers et al., 2009). The present study did not show a significant correlation between the severity of PTSD and the volume of these structures.

5.2.2.4. Anterior cingulate cortex and other frontal lobe structures: Volumetric analysis of the data from the present study found no significant difference in anterior cingulate cortex volume between veterans with PTSD and controls. The volumes of the middle frontal cortex and orbitofrontal cortex also did not differ significantly between the groups. Previous studies were consistent in showing a reduced ACC volume in PTSD compared with trauma-exposed controls (Kitayama et al., 2006; O'Doherty et al., 2015; Rauch et al., 2003). Like in the case of the hippocampus and amygdala, a systematic review of structural imaging studies of ACC in PTSD has, however, revealed significant heterogeneity among studies (O'Doherty et al., 2015). The

heterogeneity originated from differences in the age of participants, type of trauma (combat vs. civilian life), duration of symptoms, and methods of assessment. There have been differences in tools that were used to define PTSD, imaging modalities, and techniques of measurements. The age of participants in this study was much older compared with previous studies. The discrepancies in the methodology, age of participants, and the type of trauma studied may explain the disparities in results. In line with ^{18}F-fluorodeoxyglucose PET findings, the MRI results from the present study do not support a pattern of AD atrophy or regional brain atrophy associated with other neurodegenerative diseases such frontotemporal lobar degeneration. These observations do not suggest an increased risk of brain pathology associated with various dementia syndromes in PTSD.

Summary

Consistent with the results of Aβ, tau, and ^{18}F-fluorodeoxyglucose PET, there was no significant difference between the PTSD groups and controls in the adjusted volumes of regions that were previously shown to be involved in PTSD. The study found a slightly lower intracranial volume in PTSD compared with controls, as has been previously reported, but within the published normal range. As regards the hippocampal volume, the normal findings of this study are inconsistent with previous studies and meta-analyses that have shown a reduced hippocampal volume in PTSD. Previous studies have nonuniformly reported a correlation between the duration of PTSD and hippocampal atrophy. The findings of this study do not show a significantly increased hippocampal atrophy after 40 years of PTSD and do not support the hypothesis of a cumulative effect of PTSD symptoms on the hippocampus. The present study has not shown a decreased amygdala volume in PTSD or a correlation between the severity of PTSD and the brain volumes. Similarly, in contrast to some previous reports, there was no association between PTSD and anterior cingulate cortex volume. There are several potential explanations for the discrepancy between earlier reports on brain volumes in PTSD and negative findings from the current study. Alterations in hippocampal and regional cortical volumes could

be temporary, or the mild volume reductions, as previously described, may be masked by the atrophy that occurs with healthy aging. Participants in this study were in their 60s and 70s, and the effect of aging may have had more impact on the volumetric changes than PTSD itself, in cortical as well as hippocampal regions. Existing evidence suggests that multimodal psychological interventions have resulted in an increased volume of hippocampus and amygdala in PTSD, indicating a potential reversal of volume changes with therapy. Alternatively, this study excluded or corrected for comorbidity frequently associated with PTSD that may affect cognition and brain volume. Depression has been associated with hippocampal atrophy. Systematic reviews of structural imaging studies in PTSD revealed significant heterogeneity among studies. The heterogeneity originated from the differences in the age of participants, type of trauma (combat vs. civilian life), duration of symptoms, and methods of assessments. In summary, there were no MRI signs that could support a pattern of AD atrophy in PTSD.

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reductions, as previously described, may be masked by the atrophy that occurs with healthy aging. Participants in this study were in their 60s and 70s, and the effect of aging may have had more impact on the volumetric changes than PTSD itself, in cortical as well as hippocampal regions. Existing evidence suggests that multimodal psychological interventions have resulted in an increased volume of hippocampus and amygdala in PTSD, indicating a potential reversal of volume changes with therapy. Alternatively, this study excluded or corrected for comorbidity frequently associated with PTSD that may affect cognition and brain volume. Depression has been associated with hippocampal atrophy. Systematic reviews of structural imaging studies in PTSD revealed significant heterogeneity among studies. The heterogeneity originated from the differences in the age of participants, type of trauma (combat vs. civilian life), duration of symptoms, and methods of assessments. In summary, there were no MRI signs that could support a pattern of AD atrophy in PTSD.

5.3. Posttraumatic Stress Disorder and Cognitive Impairment

The present study is one of the few investigations to examine cognitive function in PTSD in Vietnam veterans aged above 65 years. In the prior studies, deficit in working memory, processing speed, new learning, and attention was the most frequently reported finding in PTSD (Cohen et al., 2013; Geuze et al., 2009; Gilbertson et al., 2001; Vasterling et al., 2002; Yehuda et al., 2005a). The present study has assessed these cognitive domains in Vietnam veterans with PTSD and compared against control veterans. The results indicated that compared with veterans without PTSD, those with PTSD had significantly lower scores on the measure of global cognitive function, as reflected in the impaired performance on the MoCA. Nonetheless, the difference was mild, and there was no difference in the MoCA once the results were adjusted for depression or predicted IQ. Therefore, the cognitive findings in this study can be accounted for by the recruitment bias with the Vietnam veteran controls having an above-average predicted IQ. The study, therefore, found no evidence of significantly impaired cognitive performance independently associated with PTSD.

There are not many studies that investigated cognitive performance in older veterans with PTSD. After adjusting for IQ, available but limited data have suggested impairment in delayed free recall in combat PTSD (Yehuda et al., 2005a). The present study could not replicate this result. The disparity may be due to stringent exclusion criteria. Yehuda et al. controlled for substance abuse, depression, and IQ, but other factors such as head injury, vascular risk, and obstructive sleep apnoea were not taken into account (Yehuda et al., 2005a). The present study excluded head injury and mild cognitive impairment. In the current study, depression also affected the relationship between PTSD and cognitive performance, but it was premorbid intelligence that had the most substantial effect on the association between PTSD and cognitive scores.

The course of cognitive deficits in PTSD, as reported in previous studies, is worth considering in this context. Different cognitive tasks followed diverse outcomes: the performance on California Verbal Learning Test (CVLT) improved over time while paired-associate learning declined with aging (Yehuda et al., 2006). In the participants of the present study, PTSD symptoms were present for four decades. Therefore, cognitive deficits that could be present earlier might have improved or resolved over time. Treatment response is another factor that predicts the persistence of impairment. A previous study has documented improved cognitive function in PTSD after long-term antidepressant treatment (Vermetten et al., 2003). Like in the case of the hippocampal and amygdala volume, cognitive deficits in PTSD responded favourably to trauma-focused psychotherapy (Kessler et al., 2005). Poor performance on cognitive function has been described in treatment non-responders compared with patients who responded to cognitive-behavioural therapy (Wild & Gur, 2008). The implication is that cognitive impairment in PTSD is not necessarily permanent or progressive. These factors may explain discrepant results among studies that investigated cognitive function in PTSD.

Summary

The present study is one of the few investigations to assess cognitive function in PTSD in Vietnam veterans aged above 65 years. The present study demonstrated that the test scores for individual cognitive domains were within the age-adjusted published norms in both the PTSD group and controls. Compared with control veterans, those with PTSD had significantly lower scores on the MoCA, a measure of global cognitive function. The difference was mild, and there was no difference in the MoCA total score once the results were adjusted for depression or predicted IQ derived from the WTAR. Cognitive findings in this study can be accounted for by the Vietnam veteran controls having above-average predicted IQ. The study, therefore, found no evidence of significantly impaired cognitive performance in older veterans independently associated with PTSD. Depression also affected the relationship between PTSD and cognitive performance, but it was premorbid IQ that had the most substantial effect on the association between PTSD and cognitive scores.

5.4. Posttraumatic Stress Disorder and Dementia

The above multilayered findings reject the hypotheses tested in this study. It can be concluded that there is no evidence to suggest increased prevalence of biomarkers of AD in veterans with PTSD compared with control veterans. In the context of negative results regarding the biomarkers of AD, it is worth exploring other factors that may explain the previously reported association between PTSD and dementia. The increased risk of dementia in PTSD was derived from two sets of information: epidemiological data and basic science research in animal models.

5.4.1. Epidemiological studies

The findings of the present study are inconsistent with the hypothesis of increased risk of Alzheimer's disease in PTSD, as suggested by the epidemiological studies (Table 5). Epidemiological studies have a few advantages (Flatt et al., 2018; Mawanda et al., 2017; Meziab et al., 2014; Qureshi et al., 2010; Wang et al., 2016; Yaffe et al., 2010). They were long-term studies that followed up a large number of veterans over many years, up to 14 years in one study (Flatt et al., 2018). They have adjusted confounders, such as TBI, vascular risk factors, and substance abuse (Qureshi et al., 2010; Wang et al., 2016; Yaffe et al., 2010). Yaffe et al. controlled the effect of education in the analysis. These studies, however, face a few limitations. First, the outcome measured was entry into a medical record of a clinical diagnosis of dementia, the accuracy of which is limited (Beach et al., 2012; Knopman et al., 2001). Pooled data from 13 studies showed 81% sensitivity and 70% specificity of a clinical diagnosis of dementia (Knopman et al., 2001). The criteria for clinical diagnoses evolved over time. The epidemiological studies used the International Classification of Diseases 9'th edition (ICD-9) criteria for dementia, which was replaced by ICD-10 (World Health, 2004). When diagnostic code was unavailable from records, the status of cognitive medications such as cholinesterase inhibitors or memantine was taken as a proxy for diagnosis (Qureshi et al., 2010). These studies did not use modern diagnostic criteria such as NINCDS-ADRDA criteria.

Second, the increased risk of dementia found in the above epidemiological studies applied to all types of dementia, including Alzheimer's dementia. Each type of dementia is associated with characteristic pathology, and it is difficult to concede that PTSD increases the risk of each of the diverse pathophysiological processes. The link between pathological alterations in PTSD and the aetiology of dementia is nebulous. One of the well-studied biological alterations in PTSD is the HPA axis dysfunction. Downregulated HPA axis and enhanced cortisol negative feedback inhibition of ACTH secretion have been documented in PTSD (Cooper, Bonert, Moser, Mirocha, & Melmed, 2017; Yehuda, Golier, Halligan, Meaney, & Bierer, 2004). These findings are inconsistent with the

results provided by other studies, and a meta-analysis did not show a significant difference in cortisol levels between trauma-exposed control subjects and patients with PTSD or signs of HPA axis dysfunction in PTSD (Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012). Even if it is argued that altered HPA axis exerts deleterious effects on neurocognitive structures such as the hippocampus, an increased risk of all types of dementia in PTSD is difficult to explain. For example, the HPA axis dysfunction is not part of pathological processes in frontotemporal dementia or Lewy Body Dementia. The epidemiological studies that suggested the risk of dementia in PTSD lacked data for neurocognitive structure, for instance, the hippocampal volume.

Thirdly, the presence of A-β, tau, regional hypometabolism in the precuneus, and posterior cingulate cortex and to lesser extent, the atrophy in medial temporal lobe structures, are relatively specific to AD, and these biomarkers were not studied in the previous investigations. In the epidemiological studies, there was no information on APOE e4, one of the strongest risk factors of sporadic AD. The present study did not find an association between PTSD and APOE e4, although the existing data suggest an increased risk of combat PTSD in APOE e4 carriers (Roby, 2017). The focus of epidemiological studies was dementia syndrome; the interest of the present study was pathological processes of dementia which precede the manifestation of dementia. In a very recent systematic review, it was found that the heterogeneity in epidemiological studies was significant (Desmarais et al., 2020). Therefore, a meta-analysis of risk of dementia in PTSD was not conducted. Except in the prospective study of Bonanni et al. the long intervals between the development of PTSD and the later onset of dementia in other studies suggest low probability of dementia prodrome manifesting as PTSD (Bonanni et al., 2018). At the same time, the symptoms of PTSD could be representing the prodrome of dementia, if the dementia diagnosis was made in the early part of the study. This possibility is raised by the only negative study of Roughead et al. that excluded all diagnoses of dementia in the first two years of follow-up and showed no increased risk of dementia with PTSD (Roughead et al., 2017). A recent study found lower plasma Aβ load and higher $A\beta_{42}/A\beta_{40}$ ratios in World Trade Centre responders with PTSD, but this study had no neuroimaging data (Clouston et al., 2019)

Table 5. Epidemiological studies of the risk of dementia in Posttraumatic Stress Disorder.

Studies (author, year)	**Participants Study method**	**Findings**	**Comments**
Yaffe et al. (Yaffe et al., 2010)	Vietnam veterans; stratified, retrospective cohort study. Compared veterans with PTSD against veterans without PTSD PTSD, n=53,155 Controls, n=127,938	Outcome: incident dementia over 7-years. Veterans with PTSD were more than twice as likely to develop incident dementia	Excluded head injury, substance abuse and clinical depression. Other factors adjusted: sex, race/ethnicity, educational level, income and medical comorbidities.
Qureshi et al. (Qureshi et al., 2010)	Veterans PTSD (with and without Purple Heart * Recipients) against veterans without PTSD Review of medical records. PTSD+/PH-, n=3,660 PTSD-/PH+, n=1,503 PTSD+/PH+, n=153 PTSD-/PH-, n=5,165	Outcome: Veterans with PTSD had twice the incidence and prevalence of dementia regardless of Purple Heart status.	Since more clinic visits may be associated with an increased rate of dementia diagnosis, the study controlled for the number of clinic visits

Studies (author, year)	Participants Study method	Findings	Comments
Meziab et al. (Meziab et al., 2014)	Data collected from Veterans Health Administrations National Patient Center Database. Retrospective cohort study. Studied the risk of dementia in prisoners of war (POW) and PTSD Total sample, n=182,879 PTSD, n=6114. POW+PTSD =150	Cumulative incidence of dementia according to Cox's proportional hazard model. Risk was increased for POW alone, PTSD alone and the greatest for both compared with none.	Demographics, medical and psychiatric comorbidities, period of service, and the competing risk of death were adjusted.
Wang et al. (Wang et al., 2016)	Study of general population based on a Health Insurance Research database. 1750 patients diagnosed with PTSD between 2001 and 2009 and 7000 age-/sex-matched individuals without PTSD. PTSD, n= 1750 Controls, n= 7000	Cox's regression model. PTSD was an independent risk factor for the risk for dementia in a dose (severity of PTSD) dependent fashion.	Demographic data and medical and psychiatric comorbidities were adjusted. Results extended to general population.

Studies (author, year)	Participants Study method	Findings	Comments
Mawanda et al. (Mawanda et al., 2017)	Nationwide sample of US veterans. PTSD, n=22,674 Controls, n=394,498	Cox's regression model. PTSD diagnosis increased the risk for dementia diagnosis. Benzodiazepines and SSRI medications were also associated with risk of dementia independent of PTSD.	Risk of dementia in PTSD varied with psychotropic medication.
Flatt et al. (Flatt et al., 2018)	Study based on medical records. PTSD, n=5,1147 Controls, n=498,697)	Dementia incidence; Cox's hazard model. PTSD was a risk factor for dementia in both sexes, with a heightened risk in those with comorbid depression.	Age, demographics, and comorbidities were adjusted. Results extended to general population and female gender.

Studies (author, year)	Participants Study method	Findings	Comments
Roughead et al. (Roughead et al., 2017)	Retrospective study based on Department of Veterans Affairs administrative claim data. PTSD, n=10767 Controls, n=4845	Dementia incidence. Patients with PTSD who had hospital admission and antipsychotics had higher incidence than controls. No significant association between PTSD and dementia when medical and psychiatric comorbidities and antipsychotic use were adjusted.	All dementia diagnoses within the first two years of enrolment were excluded.

5.4.2. Animal studies

Increased formation of A-β and hyperphosphorylation of tau after stress have been demonstrated in animals. According to Willner, an animal model of disease should satisfy three criteria: 1. Face validity: the constructed model must have a phenomenological resemblance to the condition studied. 2. Construct validity: the underlying disease mechanism must be the same as that in humans. 3. Predictive validity: the model must allow correct predictions about treatment outcomes (Willner, 1984). The symptoms of PTSD can be modelled using behavioral tests with

face, construct, and predictive validity (Flandreau & Toth, 2018). Because traumatic experience can induce PTSD, animal models can simulate the induction of PTSD. Therefore, animal models of physical and psychological trauma have been established. The neural circuit of fear has been highly conserved across species during the evolutionary process (Flandreau & Toth, 2018). Researchers have developed several validated models of PTSD with physical, social, and psychological stressors (Borghans & Homberg, 2015).

Animal studies have certain advantages. In human studies, participants cannot be randomly assigned to trauma exposure, whereas in animal experiments, researchers can control trauma type, intensity, timing, and duration. Because of the enhanced control, pre-existing factors can be separated from the consequences of trauma. Another advantage is that more invasive procedures can be performed in animals than what is possible in humans. Animal models thus play an important role in understanding disease pathogenesis and act as preclinical tools for investigations.

Animal models have limitations. A Chronic Stress Model (CSM) could not be reproduced reliably. Due to the differences in anatomical, physiological, and genetic differences, the results from animal research have limited applications in humans. Considering the heterogeneity of types of trauma that can induce PTSD and the wide range of its symptoms, it is unlikely that a single animal model will reproduce the complexity of the human disorder. The natural history of both dementia and PTSD in animals is different from humans. For example, the time required for the accumulation of A-β is too long to be reproduced in animals. Even though A-β in transgenic mice is morphologically similar to human amyloid, it fails to recapitulate AD cellular pathology and has different biophysical and biochemical properties (Kokjohn & Roher, 2009). Genetically modified mice develop both diffuse and fibrillar A-β, and mild neuronal and synaptic losses can be observed in the zones adjacent to fibrillar deposits, but a severe degree of atrophy as seen in humans does not develop in mice (Jankowsky & Zheng, 2017). In humans, three-repeat (3R) and four-repeat (4R) isoforms of tau are seen, but only 4R develops in mice. Animal models are based on familial

AD, while most presentations of AD in humans are sporadic. It is more than 15 years since the first transgenic mice model of AD was developed. Ironically, no definite therapy for AD has emerged after that. Two currently approved drugs, acetylcholinesterase inhibitors and memantine were not derived from studies in transgenic mice. The stark reality is that many molecules showed benefits in animal models, but universally failed in human trials. These discrepancies may explain the dissonance in the findings between animal research and human studies of A-β and tau after trauma.

5.4.3. Confounding factors

Dementia is a syndrome, the clinical manifestation of a specific disease process, and factors different from the disease process may facilitate its clinical expression (Esiri et al., 1999; Gottesman et al., 2017; Lewis et al., 2006; Snowdon et al., 1997; Vemuri et al., 2015b; Zekry et al., 2002). In other words, increased incidence of dementia may occur from factors that precipitate the manifestation of the underlying disease process, for instance, vascular lesions or low cognitive brain reserve (Snowdon et al., 1997; Vemuri et al., 2015a; Zekry et al., 2002). Whether such factors are overrepresented in patients with PTSD is worth probing. The factors related to both PTSD and the onset of dementia include TBI, substance abuse, cognitive brain reserve, vascular lesions, sleep disorders, and depression. Among these factors, vascular burden, depressive disorders, substance use, and TBI were adjusted for in previous epidemiological studies that have demonstrated an increased risk of dementia in PTSD. Sleep disorders or indicators of brain reserve were seldom analysed, however (Flatt et al., 2018; Mawanda et al., 2017; Meziab et al., 2014; Qureshi et al., 2010; Wang et al., 2016; Yaffe et al., 2010). TBI and substance abuse were excluded from the current study. Depression, sleep disturbances, and low levels of education and premorbid intelligence, on the other hand, emerged as significant associations of PTSD in the current study. These factors are discussed below.

5.4.3.1. Intracranial volume and PTSD and dementia

A relatively low intracranial volume has been previously linked to both PTSD and dementia. The larger premorbid brain may have increased reserve. This hypothesis is supported by post-mortem data that showed senile plaques and NFT in sufficient quantity to meet the pathological diagnosis of dementia in individuals with a larger brain and no dementia before death (Katzman et al., 1988). According to an early study, there was no correlation between the TICV and the age of onset of dementia (Jenkins, Fox, Rossor, Harvey, & Rossor, 2000). The findings stood against the brain reserve hypothesis. Later studies that measured head circumference provided inconsistent results; one study has proven that smaller head circumference in the presence APOE e4 allele hastened the onset of dementia (Borenstein Graves et al., 2001) and similar results were replicated by a recent study (Wang et al., 2019) whereas another study did not observe head circumference as a significant predictor of progression to Alzheimer's dementia in longitudinal follow-up (Espinosa et al., 2006). The Nun Study demonstrated that large head size was a protective factor against the onset of dementia, but only among those with a high level of education (Mortimer et al., 2003). A very recent cross-sectional investigation of probable Alzheimer's disease and subjects with the preclinical disease has demonstrated that increased intracranial volume mitigated adverse effects of dementia pathology on cognitive function, particularly attention and executive function (Groot et al., 2018). There is evidence that the TICV is smaller in patients with Alzheimer's dementia and vascular dementia in comparison with the control subjects but with a small effect size (Wolf, Julin, Gertz, Winblad, & Wahlund, 2004). A low TICV in the presence of APOE e4 was associated with dementia (Tate et al., 2011). These findings implicate the role of the TICV and the interacting effect of the head circumference with other risk factors in influencing the risk of dementia.

5.4.3.2. Premorbid intelligence, Posttraumatic Stress Disorder and dementia

In the present study, predicted premorbid IQ, like the total intracranial volume, was lower in veterans with PTSD than in controls. Low premorbid IQ has been associated with both the

development of PTSD and a high level of premorbid IQ with a delayed onset. Previously Scarmeas et al. demonstrated that in patients with early AD, premorbid IQ correlated with reduced regional cerebral blood flow at a given level of disease severity indicating that a greater degree of brain damage would be required for symptom manifestation in patients with high premorbid IQ (Scarmeas & Stern, 2003).

In a landmark study, male twins were followed up for 50 years, and it was found that the scores of Army General Classification Test which was administered to the U.S. Armed Forces inductees in the 1940s accounted for 20.6% of variance in cognitive performance in the late age, less than the contribution of genetic factor (30%) and more than that of education (16.7%). The rest of the variance was explained by occupation, cultural experience, and general health (Plassman et al., 1995). A Swedish twin study has proven the influence of early intellectual development on dementia outcomes (Gatz et al., 2001). It was childhood intellectual level rather than education that predicted which twin would develop dementia. Premorbid cognitive performance was found to be a predictor of the onset of dementia independent of APOE e4 (Cervilla, Prince, Joels, Lovestone, & Mann, 2004). In another study, the National Adult Reading Test (NART) score significantly predicted the onset of dementia, but the significance was lost upon controlling the effect of education. A follow-up study showed that the baseline premorbid IQ rather than education influenced the rate of cognitive decline in patients with Alzheimer's disease (Pavlik, Doody, Massman, & Chan, 2006). In contrast to the above findings, a retrospective study found significantly lower premorbid cognitive ability in patients with vascular dementia than in the controls, but such a difference was not seen with Alzheimer's dementia (McGurn, Deary, & Starr, 2008).

5.4.3.3. Education and Alzheimer's disease

The present study demonstrated that years of education was significantly lower in veterans with PTSD than in controls. Low level of education is a risk factor for both PTSD and the onset of dementia. Education is one of the most commonly used proxy measures of cognitive reserve (CR).

Mounting evidence suggests that the risk of development of Alzheimer's dementia in the presence of increased A-β is possibly lower in highly educated individuals than in those with low education (Bennett et al. 2005; McDowell et al. 2007 (Sharp & Gatz, 2011). The greatest challenge in explaining the link between education and Alzheimer's dementia is the long interval between the completion of education and the onset of dementia. Nonetheless, education has relatively a central place in a wide causal web; it is connected to the innate intellectual level of a person, education of parents, healthy lifestyles, and socioeconomic status (Cobb et al., 1995). Education may influence future jobs, cognitive engagement, and exposure to hazardous objects. These factors may affect cognitive outcomes in late life; for example, childhood cognitive ability, level of education, and adult occupation had an independent impact on word recognition test results at the age of 53 years (Gatz et al., 2001; Richards & Sacker, 2003).

The relationship between education and dementia has been critically approached. Confounding elements, for instance, lifestyle, question the nature of the relationship between education and dementia. Additionally, education may be a surrogate for other unmeasured variables. There are potential mechanisms that may explain the reduced risk of dementia in individuals with a high level of education. The proposed mechanisms vary from selection biases in study designs and consequent artefact relationships to the neurobiological bedrock. The findings that support a spurious association between education and dementia include inconsistent results among studies of education and dementia, the bias in study designs, and attrition (Sharp & Gatz, 2011). For example, during the consenting process, educated subjects joining the control group may outnumber the educated individuals entering the dementia group. This may lead to the overrepresentation of highly educated individuals in the non-dementia group (Brenner et al., 1993). The loss to follow-up or the attrition rate declines with a high level of education (Richards & Sacker, 2003).

Indeed, the relationship between education and a reduced risk of dementia is valid and robust. Many authors have put forward theories explaining the relation. One category of explanation

focuses on the link between education and lifestyles that could reduce the risk of dementia. A high level of education may entail increased knowledge of exercise and sleep that may reduce cardiovascular risk and vascular dementia and possibly Alzheimer's dementia (Cobb et al., 1995). From the Rush Religious Order Study, it is known that frequent engagement in cognitive activity was associated with a reduced rate of cognitive decline (Wilson et al., 2002). This association was independent of age and gender. Another study has suggested the protective effect of vast social networks on cognition in older women (Crooks, Lubben, Petitti, Little, & Chiu, 2008).

Analysis of the data from the Canadian Study of Health and Aging showed that bias and artefacts in the assessment process might have contributed to the association between education and dementia, but they explained only a small part of the educational gradient (McDowell, Xi, Lindsay, & Tierney, 2007). The analysis also demonstrated that occupation, lifestyle factors, and socioeconomic status only partially explained the link between education and dementia. They did not erase the entire relationship between education and dementia. On the other hand, the early development of high intelligence accounted for almost one-fifth of the education-dementia relation. Individuals who had high educational attainment but had no careers that demanded increased mental activity showed no reduction in dementia risk. This observation suggests the strength of 'use it or lose it' theory. At the same time, low education, followed by an enhanced level of mental activity, did not lead to a significant benefit in reducing the dementia risk.

In conclusion, there was a real association between high education and reduced risk of dementia, and adjustment for lifestyle, occupation, socioeconomic factors, intelligence, and mental activity reduced the strength of this relationship but did not remove the link. Highly educated individuals developed dementia later in the disease course, but despite the delayed onset, they died relatively sooner than those with a low level of education (McDowell et al., 2007). The inference is that highly educated individuals manifest the clinical symptoms late in the course of the disease, and as the disease is advanced, the remaining lifespan becomes short.

Education does not alter A-β accumulation; it significantly attenuates the effect of amyloid deposition on cognition (Bennett, Schneider, Wilson, Bienias, & Arnold, 2005). Garibotto et al. demonstrated an inverse correlation between education and brain metabolism in the posterior temporoparietal region and precuneus in Alzheimer's dementia and MCI converters (Garibotto et al., 2008).. In MCI non-converters and healthy controls, no such correlation was observed. For an equivalent degree of cognitive impairment, highly educated subjects had a more severe reduction in cerebral metabolism compared with those who attained a low level of education. Like functional imaging findings, there was an inverse correlation between cortical thickness and level of education in the temporal and parietal cortices in AD when there was no such relation in the healthy controls (Julkunen et al., 2010). These findings imply that relatively more pathology is required to produce the same level of cognitive impairment in highly educated individuals. Later studies supported this inference; an ^{18}F-fluorodeoxyglucose PET study of cognitively normal controls and prodromal Alzheimer's dementia demonstrated more hypometabolism in highly educated subjects compared with poorly educated subjects in the medial and inferior temporal lobes and hypermetabolism in the dorsolateral frontal cortex which correlated with metabolism in the parahippocampal gyrus and precuneus (Morbelli et al., 2013). The pattern of hypermetabolism seen in educated subjects showed only partial overlap with the controls suggesting the recruitment of alternate circuits in these subjects. Highly educated individuals may be able to cope better with the disease process.

Amyloid PET imaging with ^{11}C-PiB and ^{18}F-fluorodeoxyglucose PET imaging of highly educated and undereducated individuals have provided further insight into the understanding of how education is related to the brain structural changes. For the equivalent level of cognitive decline, there was more retention of ^{11}C-PiB in individuals with a high level of education than in individuals with a low level of education in the lateral frontal lobe. From these observations, it is inferred that the neurocompensatory mechanism of education occurs at multiple levels. ^{18}F-fluorodeoxyglucose PET scan showed lower metabolism in temporoparietal regions in highly educated individuals compared with poorly educated individuals (Kemppainen et al., 2008). In a multimodal imaging study, education was linked to the functional connectivity between the anterior

cingulate cortex and the hippocampus as well as the inferior frontal lobe, posterior cingulate cortex, and angular gyrus (Arenaza-Urquijo et al., 2013). Increased connectivity was reflected in improved cognitive performances.

5.4.3.4. Impact of depression on the relationship between Posttraumatic Stress Disorder and cognition

The present study found that the depression-rating score was significantly higher in the PTSD group than in controls. The mean GDS score in the PTSD group (5.42) was above the cut off score of 5, indicating that veterans with PTSD could have depressive symptoms although GDS alone does not make a diagnosis of depressive disorder. This finding is consistent with the known frequent comorbidity of depression in PTSD that varied from 44.5% to 56% (Bleich, Koslowsky, Dolev, & Lerer, 1997). According to a meta-analysis, 52% of patients with current PTSD had a diagnosis of comorbid depression (Rytwinski, Scur, Feeny, & Youngstrom, 2013). Military trauma was associated with higher rates of comorbid depression in PTSD compared with civilian and natural disasters. In PTSD, comorbid depression is a predictor of chronicity of symptoms (Breslau et al., 1991; Marmar et al., 2015; McFarlane & Papay, 1992). Comorbid depression in PTSD was associated with increased trauma exposures, low social integration, health-related unemployment, and exposure to further traumatic events after the index trauma (Caramanica, Brackbill, Liao, & Stellman, 2014). A high level of neuroticism and low extraversion were other risk factors associated with the development of comorbidity (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). Two views explain the comorbidity of depression in PTSD: one proposes comorbidity as a result of the overlap of symptoms, and the other argues that comorbidity is a distinct phenotype, perhaps a different type of PTSD (Flory & Yehuda, 2015).

The association between PTSD and the impaired performance on MoCA in the current study did not remain when adjusted for depression. Previous studies demonstrated the impact of depression on cognitive performance in PTSD (Brandes et al., 2002; Dretsch et al., 2012). Existing

literature suggests that depression is independently linked to cognitive impairment (McAllister-Williams, Ferrier, & Young, 1998). In another study, veterans with PTSD performed poorly on processing speed, categorical fluency, verbal learning, and recognition, but these findings, except the impairment in processing speed, lost significance upon controlling the effect of depression (Cohen et al., 2013). Another study replicated this finding by showing that strength of the relationship between PTSD and the deficit in psychomotor speed, attention, learning, and working memory has attenuated in the presence of depression (Sumner et al., 2017).

In an epidemiological study, depression significantly modified the association between PTSD and dementia (Flatt et al., 2018). The increased risk of dementia in women was no longer observed upon controlling for depressive symptoms, although it remained for men. Such observations strengthen the previously known association between depression and the risk of dementia (Barnes et al., 2012; Diniz, Butters, Albert, Dew, & Reynolds, 2013). Pseudodementia that occurs in the severe form of depression has been shown to be a predecessor of dementia. Several prospective studies, two cross-sectional studies, and two meta-analyses examined the risk of dementia in late-onset depression (Byers & Yaffe, 2011). Most studies support an association between depression and dementia. Alexopoulos et al. proposed that (Alexopoulos et al., 1997) cerebrovascular diseases may predispose, precipitate, or perpetuate geriatric depressive syndromes. This is known as the ‘vascular depression hypothesis’ and an important step in explaining cognitive impairment in depression. In summary depressive symptoms contribute to cognitive impairment in PTSD and to the risk of dementia, possibly through the vascular pathology.

5.4.3.5. Posttraumatic Stress Disorder and sleep disorders

As in the case of premorbid IQ, education and depression, sleep disturbances are associated with both PTSD and dementia. In this study, the Pittsburgh Sleep Quality Index (PSQI) score was significantly higher in veterans with PTSD than in controls. This implies that veterans with PTSD had a poor quality of sleep in comparison with control subjects. Sleep disruption is one

of the hallmarks of PTSD. A vast majority of patients (70%-87%) with PTSD experienced various sleep disturbances (Foa et al., 2016; Leskin, Woodward, Young, & Sheikh, 2002; Ohayon & Shapiro, 2000). Compared with the general population and Vietnam veterans without PTSD, there was more considerable sleep disruption in veterans with PTSD (91%), particularly intermittent insomnia (Neylan et al., 1998; Roszell, McFall, & Malas, 1991). Nightmares have been reported by as many as 71% of patients (Leskin et al., 2002). The reported sleep problems in PTSD included recurrent awakenings, threatening dreams, thrashing movements during sleep, and awakenings with startle or panic features (Mellman, Kulick-Bell, Ashlock, & Nolan, 1995). Past studies showed that sleep disturbances in PTSD could not be explained by trauma severity (Maher, Rego, & Asnis, 2006). Shorter sleep duration and poor quality of sleep have been associated with increased Aβ retention (Spira et al., 2013). Older individuals with insomnia had an accelerated progression to dementia from normal cognitive functioning compared with those who did not report insomnia (Osorio et al., 2011). These findings support the hypothesis that sleep disturbances in PTSD may pose an increased risk of dementia.

Obstructive Sleep Apnoea (OSA) is characterized by cycles of hypoxia/hypercapnia/reoxygenation, transitory increases in the intrathoracic pressure, hemodynamic disruptions, and recurrent brain arousals with sleep fragmentation. Obstructive sleep apnoea syndrome is diagnosed in the presence of clinical symptoms, most commonly excess daytime sleepiness (Sanchez-de-la-Torre, Campos-Rodriguez, & Barbe, 2013). The present study found a significantly increased rate of obstructive sleep apnoea in veterans with PTSD compared with the controls. This is consistent with existing literature. Obstructive Sleep Apnoea has been found at a higher rate in both the veteran population and patients with PTSD compared with the general population (Colvonen et al., 2015; Ocasio-Tascon, Alicea-Colon, Torres-Palacios, & Rodriguez-Cintron, 2006; Yesavage et al., 2012). Yesavage, et al. found a very high prevalence (69%) of OSA in PTSD (Yesavage et al., 2012). The adverse impact of OSA on cognitive function is well known; recent findings suggest accelerated cognitive decline in the presence of OSA (Fulda & Schulz, 2001; Osorio et al., 2015). The cognitive domains reported to be impaired in OSA are

attention, procedural memory and episodic memory (Cosentino et al., 2008; Mazza et al., 2005; Naegele et al., 2006), processing speed and executive function (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Felver-Gant et al., 2007; Wallace & Bucks, 2013). Executive dysfunction has been reported in Vietnam veterans with OSA (Felver-Gant et al., 2007). Language ability and psychomotor functions remain relatively unaffected. The confounding effect of OSA was not adequately addressed in previous studies that reported cognitive impairment in PTSD.

Apart from cognitive impairment, existing data suggest an association between OSA and MCI and dementia (Emamian et al., 2016). A seminal longitudinal study found a two-fold risk for MCI and dementia in patients with OSA during a five-year follow-up (Osorio et al., 2015). After early observations of the association between OSA and dementia, further findings have accrued supporting a link between sleep-disordered breathing and both MCI and dementia (Mander et al., 2015; Osorio et al., 2015). A recent study demonstrated an annual decline in the level of cerebrospinal fluid (CSF) Aβ42 over two years in cognitively asymptomatic elderly patients with OSA, implying an increased risk of AD in this condition (Sharma et al., 2018). The change in CSF $A\beta_{42}$ correlated with the severity of OSA independent of APOE. However, Sharma et al. have not observed an association between OSA and an increased amyloid uptake on PET scans.

Summary

Given the negative findings regarding the biomarkers of AD in PTSD, an attempt has been made to discuss the possible explanations for the previously reported increase in dementia risk in PTSD. The findings that indicated such a risk came from epidemiological studies and basic science research. The epidemiological studies, though large and some were performed with long follow-up, met challenges because of the limited accuracy of a clinical diagnosis of dementia. Dementia diagnoses changed over time and depended on medical and military records, and sometimes just inferred the diagnosis from the use of cholinesterase inhibitors. The

epidemiological studies showed an increased risk of all types of dementia in PTSD but given that each type of dementia has a unique characteristic pathology, it is difficult to explain why PTSD would increase all dementias. Information about biomarkers specific to AD, evidence of neurodegeneration, and APOE e4 status is largely lacking in the epidemiological studies. Animal studies have shown increased Aβ and tau in PTSD. Animal models have advantages, and it is possible to induce PTSD features in an animal model of PTSD, but considering the anatomical, physiological, and genetic differences, no single animal model can reproduce human PTSD. The development of Aβ in humans is too long to be modelled in animals. Because of the different biophysical and biochemical properties of Aβ in humans, it is difficult to recapitulate AD cellular pathology in animals. In the determination of dementia incidence, factors other than the causative pathological process, but that have the potential to precipitate symptoms are worth considering. In individuals with increased Aβ and tau burden, these factors may account for an increased incidence of dementia by an early precipitation of symptoms. There are several such factors common to both PTSD and dementia, and an examination of these confounding factors is imperative in the approach towards an increased dementia incidence in PTSD. Increased vascular lesions, comorbid depressive symptoms, sleep disturbances and low cognitive reserve may influence the onset of dementia.

5.5.

Cognitive Reserve: Potential Explanation for the Association between Posttraumatic Stress Disorder and Dementia

The present study has yielded three layers of findings that point toward a relatively low brain and cognitive reserve in PTSD: (a) total intracranial volume (TICV), (b) premorbid intelligence, and (c) education. The indices of these three factors were significantly lower in the PTSD group than in the controls. These measures, both innate and acquired, are proxy for brain and cognitive reserve. The TICV and premorbid IQ are innate and were shown to be associated with PTSD in the literature, and the current study replicated previous findings. Education, an acquired factor that

contributes to CR, was also found to be lower in PTSD according to previous studies as well as the present study. Besides the variables measured in this study, there are other factors that are associated with both PTSD and relatively low CR according to existing literature. Such factors include a reduced activity level and impaired occupation in PTSD.

Cognitive reserve is a potential mechanism to buffer the impact of pathological processes associated with AD. The concept of CR originated from the dissonance between the degree of the neuropathology of AD and corresponding clinical manifestations. Approximately 20% of elderly individuals met the post-mortem criteria for AD without dementia (Bennett et al., 2006; Katzman et al., 1988). Additionally, there is a wide variation among individuals in the threshold for symptoms occurrence with the same level of brain pathology. In patients with higher CR, symptoms of AD may arise years later than in patients with lower CR. Several factors such as APOE e4, vascular lesions, physical and cognitive activity in middle life, education, and premorbid intelligence affect the translation of increased biomarkers to the clinical manifestation (Friedland et al., 2001; Stern et al., 1994).

According to the existing literature, CR is a hypothesis put forward to explain the capacity of an adult brain to cope with brain damage to minimize symptomatology, typically from a neurodegenerative disorder (Stern, 2002). In essence, it is represented by the difference between the actual cognitive performance and the cognitive performance expected from the level of biomarkers and the degree of neurodegeneration. Cognitive reserve is one of the factors that hamper the prognostic and clinical value of amyloid and tau PET imaging. Many authors have suggested a threshold model for CR. According to this, Brain Reserve Capacity (BRC) may be depleted as the pathological process sets in, and once the threshold of the damage is crossed, clinical symptoms manifest (Satz, 1993; Stern et al., 2005). The protection from cognitive reserve is thus not absolute. There are several proxy indices of cognitive reserve. The total brain size and synaptic connections are concrete examples of the brain cognitive reserve (BRC).

Another model of CR is known as the ‘active model’ (Stern et al., 2005). Rather than relying on physiological differences in brain size or similar parameters, this model is based on the use of a more efficient and flexible cognitive network upon increased demand for tasks. In this model, individuals who can use networks that are less susceptible to a disease process or an alternate network will have more CR and be able to maintain cognitive performance longer than those who have no access to such networks. For instance, increased metabolic activity has been demonstrated in the right inferior, middle, and superior frontal gyri in highly educated individuals compared with poorly educated individuals (Morbelli et al., 2013). In other words, these individuals process cognitive functions more efficiently.

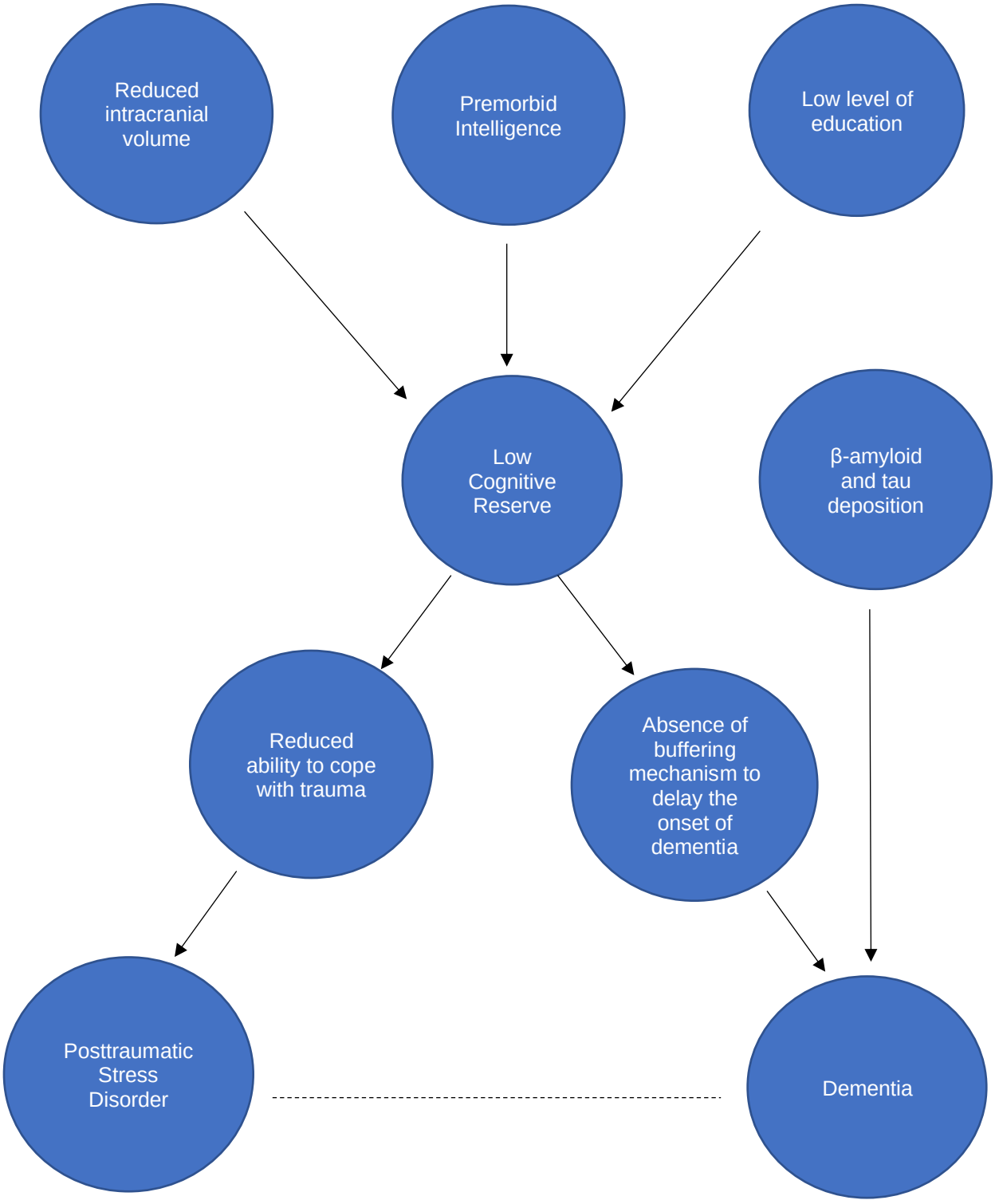

Figure 15. Hypothesized mechanism for increased risk of dementia in posttraumatic stress disorder.

Cognitive reserve is now conceptualized as a hypothetical construct represented by interlinked factors. According to this model, multiple factors contribute to CR, and they are linked. Cognitive reserve is not a fixed entity, but a changing phenomenon over time. Innate or genetic factors, education, occupation, and cognitive engagement contribute to CR (Katzman, 1993; Schmand et al., 1997). Premorbid intelligence is linked to the development of CR (Alexander et al., 1997; Caffò et al., 2016; Scarmeas & Stern, 2003). Cognitive Reserve Index (CRI)-as measured by a questionnaire that gathered information related to education level, working activity, and leisure time-correlated with premorbid IQ (Caffò et al., 2016). Participation in activities such as watching television, playing cards, reading books or magazines, going to lectures or concerts, going for walks, singing and volunteer work in the past six months was associated with advanced disease pathology in the brain as reflected in reduced cerebral blood flow at a given level of clinical disease severity in patients with early Alzheimer's dementia (Scarmeas & Stern, 2003). These findings signified increased cognitive brain reserve with physical and mental activities. The limitation of these findings is that the activities are non-specific, and an objective assessment of the activities is yet to be determined.

In previous studies that showed an association between PTSD and dementia, premorbid intelligence or level of education was not controlled (Flatt et al., 2018; Mawanda et al., 2017; Qureshi et al., 2010; Wang et al., 2016). Another study has controlled the level of education in assessing the risk of dementia, but premorbid intelligence was not analysed (Yaffe et al., 2010). According to one investigation, premorbid intelligence, rather than education, was associated with a delayed onset of dementia (Schmand et al., 1997). A recent longitudinal study of a cohort with originally intact cognition concluded that low physical activity increased the risk of dementia in individuals older than 75 years and non-carriers of APOE e4 (Tan et al., 2017). Furthermore, active lifestyle, social engagement, and diverse leisure activities appear to have a protective effect against cognitive decline and the onset of dementia (Marioni et al., 2015), but these factors were not investigated in previous studies. Posttraumatic stress disorder is likely to preclude a cognitively engaged lifestyle. Patients with PTSD often experience hyperarousal symptoms, and they often

avoid activities. Taylor et al. demonstrated that reliving trauma and hyperarousal predicted occupational impairment in PTSD (Taylor, Wald, & Asmundson, 2006). Also, PTSD interfered with work capacity (Stein, Walker, Hazen, & Forde, 1997). A recent meta-analysis found that patients with PTSD are 9% less likely to engage in physical activity (van den Berk-Clark et al., 2018).

In the face of illnesses, people confront changing roles in life. Patients with PTSD startle, see the world as a threat, wake up from sleep with nightmares, perceive intimate relations as cold and inanimate, and live in incessant turmoil. Consequently, cognitive and physical activities decline. Such a lifestyle in PTSD may imply a reduced cognitive reserve and, therefore, added risk for an earlier manifestation of dementia compared with individuals without PTSD.

5.5.1. The clinical implications

Factors that precede and follow PTSD reduce CR in this disorder (Stein & McAllister, 2009). The presence of PTSD signifies less resistance to the impact of dementia pathology so that the clinical manifestation of the disease process is accelerated. An important finding from the present study was that the TICV, predicted premorbid IQ or education did not fall below the normal range in the PTSD group. Instead, they were at a lower level in comparison with the veteran controls. The increased incidence of dementia reported by epidemiological studies was also in comparison with the healthy veteran controls. These findings denote that both low CR and the dementia risk in PTSD are relative, not absolute.

Not long after Alzheimer's description of neuritic plaques and tangles, Lorand remarked: "work of any kind, even mental work alone, is a means of preventing precocious senility" (Lorand, 1913). Given that CR is a dynamic construct, it can undergo modifications throughout life. Physical and mental activities contribute to CR in old age (Carvalho, Rea, Parimon, & Cusack, 2014; Yaffe et al., 2011). Apart from cognitive activities, non-cognitive leisure activities also improve cognitive reserve (Scarmeas & Stern, 2003). A randomized controlled trial showed that cognitive

interventions led to the improvement in targeted cognitive domains compared with the baseline (Ball et al., 2002). Benefits of cognitive training were found to be lasting for years and transferable to instrumental activities of daily life (Willis et al., 2006). Longitudinal studies have found a reduced risk of dementia with regular physical activities after adjusting for education and APOE e4 (Cheng, 2016). The Lancet Commission on dementia recommended physical activity and social engagement as prevention strategies (Livingston et al., 2017). It has been calculated that more than a third of dementia cases may be theoretically preventable (Livingston et al., 2017).

While the results obtained by the current study do not support an increased risk of Alzheimer's disease in PTSD, they do not invalidate the finding-an increased risk of dementia syndrome in general with PTSD- derived from the epidemiological studies. It can be inferred from these epidemiological studies that PTSD is associated with an increased risk of dementia syndrome, not a specific disease process causing dementia. As described above, the risk of dementia may be mediated through precipitation of dementia syndrome in individuals at risk because of already existing pathology and relatively low CR. Patients with PTSD may be able to enhance CR by engaging in cognitive and physical activities and thereby delay the onset of dementia. The recognition of a long preclinical phase indicates that there is time for therapeutic interventions that have the potential for risk reduction.

The dementia risk modification in PTSD is relevant both theoretically and therapeutically. Demonstrated in clinical trials, psychological interventions in PTSD have produced reversal of hippocampal and amygdala atrophy and yielded improvement in occupational impairment (Butler et al., 2018; Laugharne et al., 2016; Speicher, Walter, & Chard, 2014). Abnormalities in dendritic spines have been observed in depression and stress-related psychiatric disorders (Licznerski & Duman, 2013). Stressful experiences can produce profound changes in the morphology of neurons within mPFC, specifically dendritic spine architecture with a variety of behavioral consequences (Moench & Wellman, 2015). Such alterations have implications in PTSD because some of these changes may be amenable to treatment. For instance, increased expression of synaptic proteins

and trophic factors that lead to neurogenesis occur during antidepressant treatment (Licznerski & Duman, 2013). These observations accentuate the importance of brain plasticity in PTSD. Neuroplasticity is defined as the final common pathway of neurobiological processes, including structural, functional, or molecular mechanisms that result in stability or compensation for the age- or disease-related changes.

For a long time, it was assumed that neuroplasticity was a phenomenon of young brain. This traditional wisdom has been challenged by recent observations (Pauwels, Chalavi, & Swinnen, 2018; Porto et al., 2015). Functional neuroimaging data showed that task-related brain activity and training-induced brain activation did not differ significantly between young and older participants (Santos Monteiro et al., 2017). Although, certain age-related changes and a degree of cognitive decline are inevitable, the above findings have crucial significance given the pace of change in technological advances with which the older population may have to adapt successfully. In this context, lifelong brain plasticity provides a critical foundation for continued involvement of older individuals in various roles in society. Adequate treatment of PTSD must therefore aim at the restoration of physical and mental activities along with occupational function. The present study also suggests that the recruitment process to the military should focus on premorbid intellectual function. This may minimize the risk of PTSD as well as the future risk of dementia.

The relationship between cognitive reserve and functional connectivity network and its role in delaying dementia onset is worth exploring in future studies. Limited data suggests that high CR is associated with enhanced activity of brain functional network in both patients with Alzheimer's dementia and healthy controls (Weiler et al., 2018). The influence of network connectivity on cognitive decline in PTSD particularly in relation to various dementia pathological processes is a topic that requires further research in future.

Summary

The present study has yielded three layers of findings that point toward a relatively low brain and cognitive reserve in PTSD: (a) total intracranial volume (TICV), (b) premorbid intelligence, and (c) education. These indices represent proxy measures of cognitive reserve (CR). These measures were previously shown to be lower in PTSD compared with controls and associated with the onset of dementia. Cognitive reserve is a potential mechanism to buffer the impact of pathological processes associated with AD. The concept of CR originated from the dissonance between the degree of the neuropathology of AD and corresponding clinical manifestations. The total brain size and synaptic connections are concrete examples of the cognitive brain reserve. According to a dynamic model of CR, individuals who can use alternative networks that are less susceptible to a disease process will have more CR and be able to maintain cognitive performance longer. Physical activity and cognitive engagement, promote CR, but the symptoms of PTSD, such as hyperarousal and avoidance, may preclude such activities and further reduce the prospect of development of CR. Relatively low CR may explain the previously reported association between this disorder and dementia. An important finding from the present study was that the TICV, predicted premorbid IQ or education in the PTSD group did not fall below the normal range. Instead, they were at a lower level in comparison with the veteran controls. The increased incidence of dementia reported by epidemiological studies was also in comparison with the healthy veteran controls. These findings denote that both low CR and the dementia risk in PTSD are relative, not absolute. Treatment interventions for PTSD, particularly cognitive training, may restore optimal functioning and contribute to CR. The principle of brain plasticity supports rehabilitation and dementia risk modification in PTSD.

5.6. Methodological Considerations

5.6.1. Strengths of the study

This study highlights the need for careful evaluation and comparison of disease cohorts and controls, especially when recruited by advertisement. Although the PTSD and control cohorts served in the Vietnam War and the same advertising methods recruited all, the controls had significantly higher education and premorbid IQ. Consequently, on cognitive tests, the PTSD cohort appeared impaired relative to the controls, but they were performing normally without evidence of brain atrophy. Studies that fail to correct for premorbid intelligence or adjust volumetry for intracranial volume could give erroneous conclusions. The present study has excluded other confounding factors, as much as possible, that could influence cognitive outcomes: traumatic brain injury, substance abuse, major psychiatric disorders, and unstable medical conditions. The study analysed relevant covariates: age, vascular risk factors, depression, obstructive sleep apnoea, as well as years of education and predicted premorbid intelligence and found no evidence of cognitive impairment or brain atrophy independently associated with PTSD even after many decades of symptoms. In the past, research focused on cognitive function in PTSD in cohorts of relatively young age or middle age, not the usual age of onset of dementia. Previous studies, therefore, have not evaluated the risk of early signs of Alzheimer's dementia. Since PTSD is a chronic disease it is vital to select the older population to study the progressive impact of PTSD on cognition and brain structures.

In the current study, three types of PET and an MRI have been combined in the same cohort. Such an approach helps a comprehensive assessment of AD risk. Even if one measurement failed to demonstrate the actual difference between the PTSD and control groups due to type II error, it is unlikely that all measurements failed. AD risk evaluation must, therefore, cover a gamut of preclinical abnormalities of dementia, ranging from subtle cognitive deficits to A-

β burden through regional volume changes, brain metabolism, and tau deposition. Whereas the pathological markers are specific to each type of dementia, the markers of neuronal damage are common to all types of neurodegenerative dementia. Known that increased risk of dementia in PTSD was not attached to a particular type of dementia, measures general to all types of dementia such as cognitive evaluation, MRI volumetry, and ^{18}F-fluorodeoxyglucose PET are critical in the assessment of dementia risk notwithstanding the additional benefit that a specific pattern of hypometabolism on ^{18}F-flurodeoxyglucose PET is seen with most types of dementia. At the same time, amyloid and tau scans are specific to AD, and the fact that A-β precedes other changes in dementia for many years necessitates the use of amyloid PET in the evaluation of AD risk.

The present study included only combat PTSD and veteran controls. Meta-analyses of cognitive performance and brain volumetry showed considerable heterogeneity of results. Differences in trauma type and control groups` contributed to heterogeneity. It is, therefore, pivotal to ensure that the same type of trauma is studied in both PTSD and control groups. There was uniformity in the method of assessments, as well. The scanner, radioactive ligands, the neuropsychologist, the psychiatrist, and the investigators that evaluated PET scans were the same for all subjects.

5.6.2. Limitations

The diagnosis of PTSD is a challenge because of the subjective nature of symptoms. A study that investigated corroboration between the diagnosis of PTSD and the level of trauma exposure as entered into military records, as well as the level of impairment, found no evidence of falsification (Dohrenwend et al., 2006). If veterans reported PTSD symptoms by outright lying or exaggerated symptoms by retrospective distortions, then it is natural to expect that these veterans should be overrepresented among veterans who reported the experience of high war-zone stress, but their record-based military historical exposure rate indicated the contrary. Using measures of dissembling and self-reported symptoms, Dohrenwend et al. found no indication of dissembling.

The current study ensured clear separation between the cases and controls; this is reflected in the mean CAPS scores of cases and controls, which were wide apart and highly significantly different. However, the assignment of participants to the inclusion group was based on the self-report and combat exposure was assessed by Combat Exposure Scale which contains items that seek responses based on self-report. Self-reports carry recollection and reporting bias. The difference in age between the groups may limit the interpretation of comparability of cognitive function.

Although several comorbidities were excluded, the study did not exclude anxiety disorders, which could impact cognitive performance. One study found no difference in the cognitive performance between PTSD and generalized anxiety disorder (Zalewski et al., 1994), and another one concluded that the cognitive deficits in PTSD were not attributable to anxiety (Brandes et al., 2002). Anxiety symptoms were not excluded because of the overlap between the components of anxiety disorders and posttraumatic stress disorder (autonomous and physiological arousal symptoms such as sweating, and palpitation and avoidance reaction). Exclusion of anxiety symptoms could have resulted in the exclusion of a large number of participants who would have otherwise been eligible for the evaluation of AD risk in PTSD. A recent study linked loneliness to increased amyloid burden regardless of age, gender, socioeconomic status, depression, anxiety, and APOE e4 status (Donovan et al., 2016). The UCLA Loneliness scale assessed loneliness. The present study did not assess loneliness and, therefore, could not take this factor into consideration in the analysis of amyloid burden. Loneliness may be a symptom in the early stage of AD, perhaps arising as a consequence of amyloid accumulation rather than a cause of it. Another limitation of the study was that large numbers of veterans met the exclusion criteria. Among the excluded veterans, some declined participation because of perceived stress. Whether they had an intense form of PTSD or they would have altered the results if included is unknown. The large proportion of excluded veterans was also seen in the ADNI study (Weiner et al., 2017). This disproportionate rate of exclusion was higher in the PTSD cohort than in the civilian population (Weiner et al., 2017). Head injury, substance abuse, and medical illnesses are comorbid with PTSD, and such factors

may lead to restricted inclusion of veterans. Exclusion of several comorbidities impacted the generalizability of findings.

Type II error is a more relevant consideration given the findings of this study. For the amyloid imaging, adding the ADNI data did give improved power sufficient to detect an effect size of 0.43. It is relevant to note that there were more APOE e4 carriers in the PTSD group than in the control group, although the difference was statistically insignificant. Despite the relatively greater presence of this strong risk factor for AD, there was no increase in A-β or tau in the PTSD group.

The premorbid level of intelligence was assessed with the WTAR and education, which are indirect measures. Best efforts were made to access military entry aptitude tests, but for logistics reasons related to the retrieval of old records, this attempt was unsuccessful. The WTAR has been validated as a measurement of premorbid intelligence in patients with traumatic brain injury, and WTAR was used in previous research that measured premorbid intelligence in PTSD (Green, Melo, et al., 2008; Larson, Zollman, Kondiles, & Starr, 2013). Other authors have used the WTAR to estimate predicted IQ in PTSD and demonstrated that impairment in memory was moderated by premorbid intelligence (Larson et al., 2013). The influence of PTSD treatment status on cognitive function has not been evaluated in the current study. A meta-analysis suggested that the treatment-seeking PTSD samples had more cognitive impairment compared with the community-based samples (Scott, et al 2015). This may be due to the possibility that treatment-seeking samples would have severe symptoms and, therefore, cognitive deficits.

The area of cognitive reserve is in the developing phase. It is known that cognitive reserve may delay the onset of dementia, but a clear picture of the mechanism is elusive. The hypothesis of relatively low CR as an explanation for increased dementia incidence in PTSD was based on *the post hoc* approach. *Post hoc* analysis is a limitation in scientific inquiry. Hypotheses suggested by a given dataset, when tested with the same dataset that suggested them, are likely to be accepted even when they are not true (Curran-Everett & Milgrom, 2013). Generating hypotheses based on data already observed, in the absence of testing them on new data, is referred to as *post hoc* bias.

The paradigm of hypothesis-generating research complements hypothesis-testing studies. Although *post hoc* analysis is of limited value, unplanned *post hoc* analyses of data provide means by which studies can generate hypotheses that can be tested in future studies with a different dataset and design. With *post hoc* analysis no hypothesis was tested in the current study.

6.0 Conclusions

Against mounting evidence of an association between PTSD and dementia, the present study makes a significant contribution to the existing literature and advances knowledge related to AD biomarkers in PTSD. The findings of the current study do not support a hypothesis that veterans with PTSD have an increased prevalence of AD biomarkers. While an ominous relationship-i.e. a causative influence of PTSD on AD biomarkers-was not observed, results of the present study do not invalidate an epidemiological association between PTSD and dementia. The association between PTSD and dementia is likely to be general to the syndrome of dementia, not specific to any dementia pathology. This study suggests hypotheses that could be tested in future studies. The association between PTSD and dementia may be mediated through accompanying features of PTSD, such as a relatively low cognitive reserve and common comorbidities, particularly depression and sleep disorders, all of which are known to affect the onset of dementia. Patients with PTSD often suffer from hyperarousal symptoms, avoidant behavior, and impaired occupational function. Therapy may do more than mend a broken mind; therapy may rehabilitate patients sequestered in homes and bring them to cognitive engagement and productive activities with subsequent reduction of risk of dementia in PTSD. A replenished mind is a resilient mind.

Bibliography

2018 Alzheimer's disease facts and figures. (2018). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 14*(3), 367-429. doi:10.1016/j.jalz.2018.02.001

2019 Alzheimer's disease facts and figures. (2019). *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 15*(3), 321-387. doi:10.1016/j.jalz.2019.01.010

Abikoff, H., Alvir, J., Hong, G., Sukoff, R., Orazio, J., Solomon, S., & Saravay, S. (1987). Logical memory subtest of the Wechsler Memory Scale: age and education norms and alternate-form reliability of two scoring systems. *J Clin Exp Neuropsychol, 9*(4), 435-448. doi:10.1080/01688638708405063

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Alexander, G. E., Furey, M. L., Grady, C. L., Pietrini, P., Brady, D. R., Mentis, M. J., & Schapiro, M. B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *The American journal of psychiatry, 154*(2), 165-172. doi:10.1176/ajp.154.2.165

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Arch Gen Psychiatry, 54*(10), 915-922. doi:10.1001/archpsyc.1997.01830220033006

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Mattis, S., & Kakuma, T. (1993). The course of geriatric depression with "reversible dementia": a controlled study. *The American journal of psychiatry, 150*(11), 1693-1699. doi:10.1176/ajp.150.11.1693

Alladi, S., Bak, T. H., Duggirala, V., Surampudi, B., Shailaja, M., Shukla, A. K., . . . Kaul, S. (2013). Bilingualism delays age at onset of dementia, independent of education and immigration status. *Neurology, 81*(22), 1938-1944. doi:10.1212/01.wnl.0000436620.33155.a4

Alzheimer, A. (1906). Uber einen eigenartigen schweren Erkrankungsprozess der Hirninde. *Neurologisches Centralblatt, 25*, 1134. Retrieved from https://ci.nii.ac.jp/naid/10029748179/en/

Archibald, H. C., & Tuddenham, R. D. (1965). Persistent stress reaction after combat. *Archives of General Psychiatry, 12*(5), 475-481. doi:10.1001/archpsyc.1965.01720350043006

Arenaza-Urquijo, E. M., Landeau, B., La Joie, R., Mevel, K., Mézenge, F., Perrotin, A., . . . Chételat, G. (2013). Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *NeuroImage, 83*, 450-457. doi:10.1016/j.neuroimage.2013.06.053

Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T., & Hyman, B. T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology, 42*(3 Pt 1), 631-639. doi:10.1212/wnl.42.3.631

Astur, R. S., St Germain, S. A., Tolin, D., Ford, J., Russell, D., & Stevens, M. (2006). Hippocampus function predicts severity of post-traumatic stress disorder. *Cyberpsychology & behavior : the impact of the Internet, multimedia and virtual reality on behavior and society, 9*(2), 234-240. doi:10.1089/cpb.2006.9.234

Aupperle, R. L., Melrose, A. J., Stein, M. B., & Paulus, M. P. (2012). Executive function and PTSD: disengaging from trauma. *Neuropharmacology, 62*(2), 686-694. doi:10.1016/j.neuropharm.2011.02.008

Bachman, D. L., Wolf, P. A., Linn, R. T., Knoefel, J. E., Cobb, J. L., Belanger, A. J., . . . D'Agostino, R. B. (1993). Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology, 43*(3 Pt 1), 515-519. doi:10.1212/wnl.43.3_part_1.515

Bacigalupo, I., Mayer, F., Lacorte, E., Di Pucchio, A., Marzolini, F., Canevelli, M., . . . Vanacore, N. (2018). A Systematic Review and Meta-Analysis on the Prevalence of Dementia in Europe: Estimates from the Highest-Quality Studies Adopting the DSM IV Diagnostic Criteria. *Journal of Alzheimer's disease : JAD, 66*(4), 1471-1481. doi:10.3233/JAD-180416

Baddeley, A. D., & Hitch, G. (1974). Working Memory. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (Vol. 8, pp. 47-89): Academic Press.

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., . . . Vital Elderly Study, G. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA, 288*(18), 2271-2281. doi:10.1001/jama.288.18.2271

Ballatore, C., Lee, V. M., & Trojanowski, J. Q. (2007). Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci, 8*(9), 663-672. doi:10.1038/nrn2194

Bancher, C., Brunner, C., Lassmann, H., Budka, H., Jellinger, K., Wiche, G., . . . Wisniewski, H. M. (1989). Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. *Brain Res, 477*(1-2), 90-99. doi:10.1016/0006-8993(89)91396-6

Bancher, C., & Jellinger, K. A. (1994). Neurofibrillary tangle predominant form of senile dementia of Alzheimer type: a rare subtype in very old subjects. *Acta Neuropathol, 88*(6), 565-570.

Barbagallo, M., & Dominguez, L. J. (2014). Type 2 diabetes mellitus and Alzheimer's disease. *World J Diabetes, 5*(6), 889-893. doi:10.4239/wjd.v5.i6.889

Barnes, D. E., Kaup, A., Kirby, K. A., Byers, A. L., Diaz-Arrastia, R., & Yaffe, K. (2014). Traumatic brain injury and risk of dementia in older veterans. *Neurology, 83*(4), 312-319. doi:10.1212/WNL.0000000000000616

Barnes, D. E., Yaffe, K., Byers, A. L., McCormick, M., Schaefer, C., & Whitmer, R. A. (2012). Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry, 69*(5), 493-498. doi:10.1001/archgenpsychiatry.2011.1481

Barrett, D. H., Green, M. L., Morris, R., Giles, W. H., & Croft, J. B. (1996). Cognitive functioning and posttraumatic stress disorder. *Am J Psychiatry, 153*(11), 1492-1494. doi:10.1176/ajp.153.11.1492

Barthel, H., Gertz, H. J., Dresel, S., Peters, O., Bartenstein, P., Buerger, K., . . . Sabri, O. (2011). Cerebral amyloid-beta PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neurol, 10*(5), 424-435. doi:10.1016/s1474-4422(11)70077-1

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., . . . Morris, J. C. (2012). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *367*(9), 795-804. doi:10.1056/NEJMoa1202753

Beach, T. G., Monsell, S. E., Phillips, L. E., & Kukull, W. (2012). Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol, 71*(4), 266-273. doi:10.1097/NEN.0b013e31824b211b

Bean, J. (2011). Rey Auditory Verbal Learning Test, Rey AVLT. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 2174-2175). New York, NY: Springer New York.

Beckham, J. C., Crawford, A. L., & Feldman, M. E. (1998). Trail making test performance in Vietnam combat veterans with and without posttraumatic stress disorder. *J Trauma Stress, 11*(4), 811-819. doi:10.1023/a:1024409903617

Beebe, D. W., Groesz, L., Wells, C., Nichols, A., & McGee, K. (2003). The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. *Sleep, 26*(3), 298-307. doi:10.1093/sleep/26.3.298

Bello, V. M. E., & Schultz, R. R. (2011). Prevalence of treatable and reversible dementias: A study in a dementia outpatient clinic. *Dementia & neuropsychologia, 5*(1), 44-47. doi:10.1590/S1980-57642011DN05010008

Bennett, D. A., Schneider, J. A., Arvanitakis, Z., Kelly, J. F., Aggarwal, N. T., Shah, R. C., & Wilson, R. S. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology, 66*(12), 1837-1844. doi:10.1212/01.wnl.0000219668.47116.e6

Bennett, D. A., Schneider, J. A., Arvanitakis, Z., & Wilson, R. S. (2012). Overview and findings from the religious orders study. *Curr Alzheimer Res, 9*(6), 628-645.

Bennett, D. A., Schneider, J. A., Wilson, R. S., Bienias, J. L., & Arnold, S. E. (2004a). Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. *Arch Neurol, 61*(3), 378-384. doi:10.1001/archneur.61.3.378

Bennett, D. A., Schneider, J. A., Wilson, R. S., Bienias, J. L., & Arnold, S. E. (2004b). Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. *Archives of neurology, 61*(3), 378-384. doi:10.1001/archneur.61.3.378

Bennett, D. A., Schneider, J. A., Wilson, R. S., Bienias, J. L., & Arnold, S. E. (2005). Education modifies the association of amyloid but not tangles with cognitive function. *Neurology, 65*(6), 953-955. doi:10.1212/01.wnl.0000176286.17192.69

Berrios, G. E. (1987). Dementia during the seventeenth and eighteenth centuries: a conceptual history. *Psychol Med, 17*(4), 829-837. doi:10.1017/s0033291700000623

Berry, D. T. R., Allen, R. S., & Schmitt, F. A. (1991). Rey-Osterrieth complex figure: Psychometric characteristics in a geriatric sample. *Clinical Neuropsychologist, 5*(2), 143-153. doi:10.1080/13854049108403298

Birks, J. S., Chong, L. Y., & Grimley Evans, J. (2015). Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev, 9*, Cd001191. doi:10.1002/14651858.CD001191.pub4

Blacker, D., Haines, J. L., Rodes, L., Terwedow, H., Go, R. C., Harrell, L. E., . . . Tanzi, R. (1997). ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. *Neurology, 48*(1), 139-147. doi:10.1212/wnl.48.1.139

Blake, D. D., Keane, T. M., Wine, P. R., Mora, C., Taylor, K. L., & Lyons, J. A. (1990). Prevalence of PTSD symptoms in combat veterans seeking medical treatment. *Journal of Traumatic Stress, 3*(1), 15-27. doi:10.1007/BF00975133

Bleich, A., Koslowsky, M., Dolev, A., & Lerer, B. (1997). Post-traumatic stress disorder and depression. An analysis of comorbidity. *Br J Psychiatry, 170*, 479-482. doi:10.1192/bjp.170.5.479

Boller, F., & Forbes, M. M. (1998). History of dementia and dementia in history: an overview. *J Neurol Sci, 158*(2), 125-133. doi:10.1016/s0022-510x(98)00128-2

Bonanni, L., Franciotti, R., Martinotti, G., Vellante, F., Flacco, M. E., Di Giannantonio, M., . . . Onofrj, M. (2018). Post Traumatic Stress Disorder Heralding the Onset of Semantic Frontotemporal Dementia. *J Alzheimers Dis, 63*(1), 203-215. doi:10.3233/jad-171134

Bonne, O., Vythilingam, M., Inagaki, M., Wood, S., Neumeister, A., Nugent, A. C., . . . Charney, D. S. (2008). Reduced posterior hippocampal volume in posttraumatic stress disorder. *J Clin Psychiatry, 69*(7), 1087-1091. doi:10.4088/jcp.v69n0707

Bora, E., Fornito, A., Pantelis, C., & Yucel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord, 138*(1-2), 9-18. doi:10.1016/j.jad.2011.03.049

Borenstein Graves, A., Mortimer, J. A., Bowen, J. D., McCormick, W. C., McCurry, S. M., Schellenberg, G. D., & Larson, E. B. (2001). Head circumference and incident Alzheimer's disease: modification by apolipoprotein E. *Neurology, 57*(8), 1453-1460. doi:10.1212/wnl.57.8.1453

Borghans, B., & Homberg, J. R. (2015). Animal models for posttraumatic stress disorder: An overview of what is used in research. *World journal of psychiatry, 5*(4), 387-396. doi:10.5498/wjp.v5.i4.387

Bourgeat, P., Villemagne, V. L., Dore, V., Brown, B., Macaulay, S. L., Martins, R., . . . Fripp, J. (2015). Comparison of MR-less PiB SUVR quantification methods. *Neurobiol Aging, 36 Suppl 1*, S159-166. doi:10.1016/j.neurobiolaging.2014.04.033

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica, 112*(4), 389-404. doi:10.1007/s00401-006-0127-z

Braak, H., & Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging, 16*(3), 271-278; discussion 278-284. doi:10.1016/0197-4580(95)00021-6

Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol, 70*(11), 960-969. doi:10.1097/NEN.0b013e318232a379

Brandes, D., Ben-Schachar, G., Gilboa, A., Bonne, O., Freedman, S., & Shalev, A. Y. (2002). PTSD symptoms and cognitive performance in recent trauma survivors. *Psychiatry Res, 110*(3), 231-238.

Brayne, C., Ince, P. G., Keage, H. A., McKeith, I. G., Matthews, F. E., Polvikoski, T., & Sulkava, R. (2010). Education, the brain and dementia: neuroprotection or compensation? *Brain, 133*(Pt 8), 2210-2216. doi:10.1093/brain/awq185

Bremner, J. D., Innis, R. B., Ng, C. K., Staib, L. H., Salomon, R. M., Bronen, R. A., . . . Charney, D. S. (1997). Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. *Arch Gen Psychiatry, 54*(3), 246-254. doi:10.1001/archpsyc.1997.01830150070011

Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., & Charney, D. S. (2000). Hippocampal volume reduction in major depression. *Am J Psychiatry, 157*(1), 115-118. doi:10.1176/ajp.157.1.115

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., . . . Innis, R. B. (1995). MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry, 152*(7), 973-981. doi:10.1176/ajp.152.7.973

Bremner, J. D., Scott, T. M., Delaney, R. C., Southwick, S. M., Mason, J. W., Johnson, D. R., . . . Charney, D. S. (1993). Deficits in short-term memory in posttraumatic stress disorder. *Am J Psychiatry, 150*(7), 1015-1019. doi:10.1176/ajp.150.7.1015

Bremner, J. D., Staib, L. H., Kaloupek, D., Southwick, S. M., Soufer, R., & Charney, D. S. (1999). Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry, 45*(7), 806-816.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., . . . Charney, D. S. (2003). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry, 160*(5), 924-932. doi:10.1176/appi.ajp.160.5.924

Brenner, D. E., Kukull, W. A., van Belle, G., Bowen, J. D., McCormick, W. C., Teri, L., & Larson, E. B. (1993). Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study. *Neurology, 43*(2), 293-293. doi:10.1212/wnl.43.2.293

Breslau, N., Davis, G. C., Andreski, P., & Peterson, E. (1991). Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch Gen Psychiatry, 48*(3), 216-222. doi:10.1001/archpsyc.1991.01810270028003

Breslau, N., Lucia, V. C., & Alvarado, G. F. (2006). Intelligence and other predisposing factors in exposure to trauma and posttraumatic stress disorder: a follow-up

study at age 17 years. *Arch Gen Psychiatry, 63*(11), 1238-1245. doi:10.1001/archpsyc.63.11.1238

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000a). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol, 68*(5), 748-766. doi:10.1037//0022-006x.68.5.748

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000b). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of consulting and clinical psychology, 68*(5), 748-766. doi:10.1037//0022-006x.68.5.748

Brewin, C. R., Kleiner, J. S., Vasterling, J. J., & Field, A. P. (2007). Memory for emotionally neutral information in posttraumatic stress disorder: A meta-analytic investigation. *Journal of Abnormal Psychology, 116*(3), 448-463. doi:10.1037/0021-843X.116.3.448

Brinker, M., Westermeyer, J., Thuras, P., & Canive, J. (2007). Severity of combat-related posttraumatic stress disorder versus noncombat-related posttraumatic stress disorder: a community-based study in American Indian and Hispanic veterans. *J Nerv Ment Dis, 195*(8), 655-661. doi:10.1097/NMD.0b013e31811f4076

Brodaty, H., Connors, M. H., Ames, D., & Woodward, M. (2014). Progression from mild cognitive impairment to dementia: A 3-year longitudinal study. *Australian & New Zealand Journal of Psychiatry, 48*(12), 1137-1142. doi:10.1177/0004867414536237

Bromis, K., Calem, M., Reinders, A. A. T. S., Williams, S. C. R., & Kempton, M. J. (2018). Meta-Analysis of 89 Structural MRI Studies in Posttraumatic Stress Disorder and Comparison With Major Depressive Disorder. *Am J Psychiatry, 175*(10), 989-998. doi:10.1176/appi.ajp.2018.17111199

Bryant, R. A., & Harvey, A. G. (1997). Attentional bias in posttraumatic stress disorder. *J Trauma Stress, 10*(4), 635-644. doi:10.1023/a:1024849920494

Buchsbaum, M. S., Simmons, A. N., DeCastro, A., Farid, N., & Matthews, S. C. (2015). Clusters of Low (18)F-Fluorodeoxyglucose Uptake Voxels in Combat Veterans with Traumatic Brain Injury and Post-Traumatic Stress Disorder. *J Neurotrauma, 32*(22), 1736-1750. doi:10.1089/neu.2014.3660

Busse, A., Hensel, A., Guhne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology, 67*(12), 2176-2185. doi:10.1212/01.wnl.0000249117.23318.e1

Butler, O., Willmund, G., Gleich, T., Gallinat, J., Kühn, S., & Zimmermann, P. (2018). Hippocampal gray matter increases following multimodal psychological treatment for combat-related post-traumatic stress disorder. *Brain and behavior, 8*(5), e00956-e00956. doi:10.1002/brb3.956

Butters, N., Granholm, E., Salmon, D. P., Grant, I., & Wolfe, J. (1987). Episodic and semantic memory: a comparison of amnesic and demented patients. *J Clin Exp Neuropsychol, 9*(5), 479-497. doi:10.1080/01688638708410764

Buydens-Branchey, L., Noumair, D., & Branchey, M. (1990). Duration and intensity of combat exposure and posttraumatic stress disorder in Vietnam veterans. *J Nerv Ment Dis, 178*(9), 582-587. doi:10.1097/00005053-199009000-00005

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research, 28*(2), 193-213. doi:10.1016/0165-1781(89)90047-4

Byers, A. L., & Yaffe, K. (2011). Depression and risk of developing dementia. *Nat Rev Neurol, 7*(6), 323-331. doi:10.1038/nrneurol.2011.60

Byrne, G. J., & Pachana, N. A. (2010). Anxiety and depression in the elderly: do we know any more? *Curr Opin Psychiatry, 23*(6), 504-509. doi:10.1097/YCO.0b013e32833f305f

Caetano, S. C., Hatch, J. P., Brambilla, P., Sassi, R. B., Nicoletti, M., Mallinger, A. G., . . . Soares, J. C. (2004). Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry Res, 132*(2), 141-147. doi:10.1016/j.pscychresns.2004.08.002

Caffò, A. O., Lopez, A., Spano, G., Saracino, G., Stasolla, F., Ciriello, G., . . . Bosco, A. (2016). The role of pre-morbid intelligence and cognitive reserve in predicting cognitive efficiency in a sample of Italian elderly. *Aging clinical and experimental research, 28*(6), 1203-1210. doi:10.1007/s40520-016-0580-z

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., . . . McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences of the United States of America, 93*(15), 8016-8021. doi:10.1073/pnas.93.15.8016

Calvo, F., Karras, B. T., Phillips, R., Kimball, A. M., & Wolf, F. (2003). Diagnoses, syndromes, and diseases: a knowledge representation problem. *AMIA ... Annual Symposium proceedings. AMIA Symposium, 2003*, 802-802. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14728307

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1480257/

Cameron, K., Sturdivant, R., & Baker, S. (2019). Trends in the incidence of physician-diagnosed posttraumatic stress disorder among active-duty U.S. military personnel between 1999 and 2008. *Military Medical Research, 6*, 8. doi:10.1186/s40779-019-0198-5

Capitani, E., Rosci, C., Saetti, M. C., & Laiacona, M. (2009). Mirror asymmetry of Category and Letter fluency in traumatic brain injury and Alzheimer's patients. *Neuropsychologia, 47*(2), 423-429. doi:10.1016/j.neuropsychologia.2008.09.016

Caramanica, K., Brackbill, R. M., Liao, T., & Stellman, S. D. (2014). Comorbidity of 9/11-related PTSD and depression in the World Trade Center Health Registry 10-11 years postdisaster. *J Trauma Stress, 27*(6), 680-688. doi:10.1002/jts.21972

Carroll, J. C., Iba, M., Bangasser, D. A., Valentino, R. J., James, M. J., Brunden, K. R., . . . Trojanowski, J. Q. (2011). Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. *J Neurosci, 31*(40), 14436-14449. doi:10.1523/jneurosci.3836-11.2011

Carvalho, A., Rea, I. M., Parimon, T., & Cusack, B. J. (2014). Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clinical interventions in aging, 9*, 661-682. doi:10.2147/CIA.S55520

Caselli, R. J., Dueck, A. C., Locke, D. E., Hoffman-Snyder, C. R., Woodruff, B. K., Rapcsak, S. Z., & Reiman, E. M. (2011). Longitudinal modeling of frontal cognition in APOE epsilon4 homozygotes, heterozygotes, and noncarriers. *Neurology, 76*(16), 1383-1388. doi:10.1212/WNL.0b013e3182167147

Caselli, R. J., Reiman, E. M., Locke, D. E., Hutton, M. L., Hentz, J. G., Hoffman-Snyder, C., . . . Osborne, D. (2007). Cognitive domain decline in healthy apolipoprotein E epsilon4 homozygotes before the diagnosis of mild cognitive impairment. *Arch Neurol, 64*(9), 1306-1311. doi:10.1001/archneur.64.9.1306

Castellano, J. M., Kim, J., Stewart, F. R., Jiang, H., DeMattos, R. B., Patterson, B. W., . . . Holtzman, D. M. (2011). Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci Transl Med, 3*(89), 89ra57. doi:10.1126/scitranslmed.3002156

Cerami, C., Della Rosa, P. A., Magnani, G., Santangelo, R., Marcone, A., Cappa, S. F., & Perani, D. (2014). Brain metabolic maps in Mild Cognitive Impairment predict heterogeneity of progression to dementia. *NeuroImage. Clinical, 7*, 187-194. doi:10.1016/j.nicl.2014.12.004

Cervilla, J., Prince, M., Joels, S., Lovestone, S., & Mann, A. (2004). Premorbid cognitive testing predicts the onset of dementia and Alzheimer's disease better than and independently of APOE genotype. *J Neurol Neurosurg Psychiatry, 75*(8), 1100-1106. doi:10.1136/jnnp.2003.028076

Chang-Quan, H., Bi-Rong, D., & Yan, Z. (2012). Association between sleep quality and cognitive impairment among Chinese nonagenarians/centenarians. *J Clin Neurophysiol, 29*(3), 250-255. doi:10.1097/WNP.0b013e3182570f2e

Cheng, S.-T. (2016). Cognitive Reserve and the Prevention of Dementia: the Role of Physical and Cognitive Activities. *Current psychiatry reports, 18*(9), 85-85. doi:10.1007/s11920-016-0721-2

Chételat, G., La Joie, R., Villain, N., Perrotin, A., de La Sayette, V., Eustache, F., & Vandenberghe, R. (2013). Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *NeuroImage: Clinical, 2*, 356-365. doi:https://doi.org/10.1016/j.nicl.2013.02.006

Chien, D. T., Bahri, S., Szardenings, A. K., Walsh, J. C., Mu, F., Su, M. Y., . . . Kolb, H. C. (2013). Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J Alzheimers Dis, 34*(2), 457-468. doi:10.3233/jad-122059

Cipriani, G., Dolciotti, C., Picchi, L., & Bonuccelli, U. (2011). Alzheimer and his disease: a brief history. *Neurol Sci, 32*(2), 275-279. doi:10.1007/s10072-010-0454-7

Citron, M., Westaway, D., Xia, W., Carlson, G., Diehl, T., Levesque, G., . . . Selkoe, D. J. (1997). Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. *Nat Med, 3*(1), 67-72.

Clarfield, A. M. (2003). The decreasing prevalence of reversible dementias: an updated meta-analysis. *Arch Intern Med, 163*(18), 2219-2229. doi:10.1001/archinte.163.18.2219

Clouston, S. A. P., Deri, Y., Diminich, E., Kew, R., Kotov, R., Stewart, C., . . . Luft, B. J. (2019). Posttraumatic stress disorder and total amyloid burden and amyloid-beta

42/40 ratios in plasma: Results from a pilot study of World Trade Center responders. *Alzheimers Dement (Amst), 11*, 216-220. doi:10.1016/j.dadm.2019.01.003

Cobb, J. L., Wolf, P. A., Au, R., White, R., & D'Agostino, R. B. (1995). The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. *Neurology, 45*(9), 1707-1712. doi:10.1212/wnl.45.9.1707

Cohen, B. E., Neylan, T. C., Yaffe, K., Samuelson, K. W., Li, Y., & Barnes, D. E. (2013). Posttraumatic stress disorder and cognitive function: findings from the mind your heart study. *J Clin Psychiatry, 74*(11), 1063-1070. doi:10.4088/JCP.12m08291

Cohen, R. A., Grieve, S., Hoth, K. F., Paul, R. H., Sweet, L., Tate, D., . . . Williams, L. M. (2006). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry, 59*(10), 975-982. doi:10.1016/j.biopsych.2005.12.016

Colvonen, P. J., Masino, T., Drummond, S. P. A., Myers, U. S., Angkaw, A. C., & Norman, S. B. (2015). Obstructive Sleep Apnea and Posttraumatic Stress Disorder among OEF/OIF/OND Veterans. *J Clin Sleep Med, 11*(5), 513-518. doi:10.5664/jcsm.4692

Cooper, O., Bonert, V., Moser, F., Mirocha, J., & Melmed, S. (2017). Altered Pituitary Gland Structure and Function in Posttraumatic Stress Disorder. *Journal of the Endocrine Society, 1*(6), 577-587. doi:10.1210/js.2017-00069

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., . . . Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261*(5123), 921-923. doi:10.1126/science.8346443

Corrada, M. M., Brookmeyer, R., Paganini-Hill, A., Berlau, D., & Kawas, C. H. (2010). Dementia incidence continues to increase with age in the oldest old: the 90+ study. *Annals of neurology, 67*(1), 114-121. doi:10.1002/ana.21915

Cosentino, F. I. I., Bosco, P., Drago, V., Prestianni, G., Lanuzza, B., Iero, I., . . . Ferri, R. (2008). The APOE ε4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. *Sleep Medicine, 9*(8), 831-839. doi:https://doi.org/10.1016/j.sleep.2007.10.015

Crary, J. F., Trojanowski, J. Q., Schneider, J. A., Abisambra, J. F., Abner, E. L., Alafuzoff, I., . . . Nelson, P. T. (2014). Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol, 128*(6), 755-766. doi:10.1007/s00401-014-1349-0

Crocq, M.-A., Macher, J.-P., Barros-Beck, J., Rosenberg, S. J., & Duval, F. (1993). Posttraumatic Stress Disorder in World War II Prisoners of War from Alsace-Lorraine Who Survived Captivity in the USSR. In J. P. Wilson & B. Raphael (Eds.), *International Handbook of Traumatic Stress Syndromes* (pp. 253-261). Boston, MA: Springer US.

Crocq, M. A., & Crocq, L. (2000). From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. *Dialogues in clinical neuroscience, 2*(1), 47-55. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22033462

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181586/
Crooks, V. C., Lubben, J., Petitti, D. B., Little, D., & Chiu, V. (2008). Social network, cognitive function, and dementia incidence among elderly women. *American journal of public health, 98*(7), 1221-1227. doi:10.2105/AJPH.2007.115923
Cummings, J. L., Vinters, H. V., Cole, G. M., & Khachaturian, Z. S. (1998). Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology, 51*(1 Suppl 1), S2-17; discussion S65-17. doi:10.1212/wnl.51.1_suppl_1.s2
Curran-Everett, D., & Milgrom, H. (2013). Post-hoc data analysis: benefits and limitations. *13*(3), 223-224. doi:10.1097/ACI.0b013e3283609831
Dahm, R. (2006). Alzheimer's discovery. *Curr Biol, 16*(21), R906-910. doi:10.1016/j.cub.2006.09.056
Dams-O'Connor, K., Spielman, L., Singh, A., Gordon, W. A., Lingsma, H. F., Maas, A. I., . . . Yuh, E. L. (2013). The impact of previous traumatic brain injury on health and functioning: a TRACK-TBI study. *J Neurotrauma, 30*(24), 2014-2020. doi:10.1089/neu.2013.3049
Davis, D. G., Schmitt, F. A., Wekstein, D. R., & Markesbery, W. R. (1999a). Alzheimer neuropathologic alterations in aged cognitively normal subjects. *Journal of neuropathology and experimental neurology, 58*(4), 376-388. doi:10.1097/00005072-199904000-00008
Davis, D. G., Schmitt, F. A., Wekstein, D. R., & Markesbery, W. R. (1999b). Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol, 58*(4), 376-388. doi:10.1097/00005072-199904000-00008
De Bellis, M. D., Hall, J., Boring, A. M., Frustaci, K., & Moritz, G. (2001). A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry, 50*(4), 305-309. doi:10.1016/s0006-3223(01)01105-2
de Bruijn, R. F., & Ikram, M. A. (2014). Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med, 12*, 130. doi:10.1186/s12916-014-0130-5
DeCarli, C., Mungas, D., Harvey, D., Reed, B., Weiner, M., Chui, H., & Jagust, W. (2004). Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology, 63*(2), 220-227. doi:10.1212/01.wnl.0000130531.90205.ef
Desmarais, P., Weidman, D., Wassef, A., Bruneau, M. A., Friedland, J., Bajsarowicz, P., . . . Nguyen, Q. D. (2020). The Interplay Between Post-traumatic Stress Disorder and Dementia: A Systematic Review. *Am J Geriatr Psychiatry, 28*(1), 48-60. doi:10.1016/j.jagp.2019.08.006
Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. (2013). Arlington, VA, US: American Psychiatric Publishing, Inc.
Dileo, J. F., Brewer, W. J., Hopwood, M., Anderson, V., & Creamer, M. (2008). Olfactory identification dysfunction, aggression and impulsivity in war veterans with post-traumatic stress disorder. *Psychological Medicine, 38*(4), 523-531. doi:10.1017/S0033291707001456

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F., 3rd. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry, 202*(5), 329-335. doi:10.1192/bjp.bp.112.118307

Dohrenwend, B. P., Turner, J. B., Turse, N. A., Adams, B. G., Koenen, K. C., & Marshall, R. (2006). The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. *Science, 313*(5789), 979-982. doi:10.1126/science.1128944

Dolan, D., Troncoso, J., Resnick, S. M., Crain, B. J., Zonderman, A. B., & O'Brien, R. J. (2010). Age, Alzheimer's disease and dementia in the Baltimore Longitudinal Study of Ageing. *Brain, 133*(Pt 8), 2225-2231. doi:10.1093/brain/awq141

Dong, H., Goico, B., Martin, M., Csernansky, C. A., Bertchume, A., & Csernansky, J. G. (2004). Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. *Neuroscience, 127*(3), 601-609. doi:10.1016/j.neuroscience.2004.05.040

Donovan, N. J., Okereke, O. I., Vannini, P., Amariglio, R. E., Rentz, D. M., Marshall, G. A., . . . Sperling, R. A. (2016). Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults. *JAMA Psychiatry, 73*(12), 1230-1237. doi:10.1001/jamapsychiatry.2016.2657

Dretsch, M. N., Thiel, K. J., Athy, J. R., Irvin, C. R., Sirmon-Fjordbak, B., & Salvatore, A. (2012). Mood symptoms contribute to working memory decrement in active-duty soldiers being treated for posttraumatic stress disorder. *Brain and behavior, 2*(4), 357-364. doi:10.1002/brb3.53

Driscoll, I., Resnick, S. M., Troncoso, J. C., An, Y., O'Brien, R., & Zonderman, A. B. (2006). Impact of Alzheimer's pathology on cognitive trajectories in nondemented elderly. *Ann Neurol, 60*(6), 688-695. doi:10.1002/ana.21031

Dunsmoor, J. E., Prince, S. E., Murty, V. P., Kragel, P. A., & LaBar, K. S. (2011). Neurobehavioral mechanisms of human fear generalization. *Neuroimage, 55*(4), 1878-1888. doi:10.1016/j.neuroimage.2011.01.041

Dykiert, D., & Deary, I. J. (2013). Retrospective validation of WTAR and NART scores as estimators of prior cognitive ability using the Lothian Birth Cohort 1936. *Psychol Assess, 25*(4), 1361-1366. doi:10.1037/a0033623

Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behav Res Ther, 38*(4), 319-345. doi:10.1016/s0005-7967(99)00123-0

Ehlert, U., Gaab, J., & Heinrichs, M. (2001). Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. *Biol Psychol, 57*(1-3), 141-152.

Eisen, S. A., Griffith, K. H., Xian, H., Scherrer, J. F., Fischer, I. D., Chantarujikapong, S., . . . Tsuang, M. T. (2004). Lifetime and 12-month prevalence of psychiatric disorders in 8,169 male Vietnam War era veterans. *Mil Med, 169*(11), 896-902. doi:10.7205/milmed.169.11.896

Elzinga, B. M., & Bremner, J. D. (2002). Are the neural substrates of memory the final common pathway in posttraumatic stress disorder (PTSD)? *J Affect Disord, 70*(1), 1-17. doi:10.1016/s0165-0327(01)00351-2

Emamian, F., Khazaie, H., Tahmasian, M., Leschziner, G. D., Morrell, M. J., Hsiung, G. Y., . . . Sepehry, A. A. (2016). The Association Between Obstructive Sleep Apnea and Alzheimer's Disease: A Meta-Analysis Perspective. *Front Aging Neurosci, 8*, 78. doi:10.3389/fnagi.2016.00078

Engler, H., Forsberg, A., Almkvist, O., Blomquist, G., Larsson, E., Savitcheva, I., . . . Nordberg, A. (2006). Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. *Brain, 129*(Pt 11), 2856-2866. doi:10.1093/brain/awl178

Eren-Kocak, E., Kilic, C., Aydin, I., & Hizli, F. G. (2009). Memory and prefrontal functions in earthquake survivors: differences between current and past post-traumatic stress disorder patients. *Acta Psychiatr Scand, 119*(1), 35-44. doi:10.1111/j.1600-0447.2008.01281.x

Esiri, M. M., Nagy, Z., Smith, M. Z., Barnetson, L., & Smith, A. D. (1999). Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet, 354*(9182), 919-920. doi:10.1016/s0140-6736(99)02355-7

Espinosa, P. S., Kryscio, R. J., Mendiondo, M. S., Schmitt, F. A., Wekstein, D. R., Markesbery, W. R., & Smith, C. D. (2006). Alzheimer's disease and head circumference. *Journal of Alzheimer's disease : JAD, 9*(1), 77-80. doi:10.3233/jad-2006-9108

Farlow, M. R., He, Y., Tekin, S., Xu, J., Lane, R., & Charles, H. C. (2004). Impact of APOE in mild cognitive impairment. *Neurology, 63*(10), 1898-1901. doi:10.1212/01.wnl.0000144279.21502.b7

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., . . . van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Jama, 278*(16), 1349-1356.

Felmingham, K., Williams, L. M., Whitford, T. J., Falconer, E., Kemp, A. H., Peduto, A., & Bryant, R. A. (2009). Duration of posttraumatic stress disorder predicts hippocampal grey matter loss. *Neuroreport, 20*(16), 1402-1406. doi:10.1097/WNR.0b013e3283300fbc

Felver-Gant, J. C., Bruce, A. S., Zimmerman, M., Sweet, L. H., Millman, R. P., & Aloia, M. S. (2007). Working memory in obstructive sleep apnea: construct validity and treatment effects. *J Clin Sleep Med, 3*(6), 589-594.

Fennema-Notestine, C., Stein, M. B., Kennedy, C. M., Archibald, S. L., & Jernigan, T. L. (2002). Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol Psychiatry, 52*(11), 1089-1101. doi:10.1016/s0006-3223(02)01413-0

Ferman, T. J., Smith, G. E., Kantarci, K., Boeve, B. F., Pankratz, V. S., Dickson, D. W., . . . Petersen, R. C. (2013). Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. *Neurology, 81*(23), 2032-2038. doi:10.1212/01.wnl.0000436942.55281.47

Fiest, K. M., Roberts, J. I., Maxwell, C. J., Hogan, D. B., Smith, E. E., Frolkis, A., . . . Jette, N. (2016). The Prevalence and Incidence of Dementia Due to Alzheimer's Disease: a Systematic Review and Meta-Analysis. *Can J Neurol Sci, 43 Suppl 1*, S51-82. doi:10.1017/cjn.2016.36

Figley, C. R., & Boscarino, J. A. (2012). The traumatology of life. *The Journal of Nervous and Mental Disease, 200*(12), 1113-1120. doi:10.1097/NMD.0b013e318275d559

Flandreau, E. I., & Toth, M. (2018). Animal Models of PTSD: A Critical Review. *Curr Top Behav Neurosci, 38*, 47-68. doi:10.1007/7854_2016_65

Flatt, J. D., Gilsanz, P., Quesenberry, C. P., Jr., Albers, K. B., & Whitmer, R. A. (2018). Post-traumatic stress disorder and risk of dementia among members of a health care delivery system. *Alzheimers Dement, 14*(1), 28-34. doi:10.1016/j.jalz.2017.04.014

Fleminger, S., Oliver, D. L., Lovestone, S., Rabe-Hesketh, S., & Giora, A. (2003). Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J Neurol Neurosurg Psychiatry, 74*(7), 857-862. doi:10.1136/jnnp.74.7.857

Flory, J. D., & Yehuda, R. (2015). Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues in clinical neuroscience, 17*(2), 141-150. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26246789

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4518698/

Foa, E. B., McLean, C. P., Zang, Y., Zhong, J., Powers, M. B., Kauffman, B. Y., . . . Knowles, K. (2016). Psychometric properties of the Posttraumatic Diagnostic Scale for DSM-5 (PDS-5). *Psychol Assess, 28*(10), 1166-1171. doi:10.1037/pas0000258

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Foster, N. L., Heidebrink, J. L., Clark, C. M., Jagust, W. J., Arnold, S. E., Barbas, N. R., . . . Minoshima, S. (2007). FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain, 130*(Pt 10), 2616-2635. doi:10.1093/brain/awm177

Fratiglioni, L., Ahlbom, A., Viitanen, M., & Winblad, B. (1993). Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. *Ann Neurol, 33*(3), 258-266. doi:10.1002/ana.410330306

Fratiglioni, L., Launer, L. J., Andersen, K., Breteler, M. M., Copeland, J. R., Dartigues, J. F., . . . Hofman, A. (2000). Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology, 54*(11 Suppl 5), S10-15.

Fratiglioni, L., Viitanen, M., von Strauss, E., Tontodonati, V., Herlitz, A., & Winblad, B. (1997). Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology, 48*(1), 132-138. doi:10.1212/wnl.48.1.132

Freeman, K. J. (1927). The Work and Life of Solon. *Journal of Hellenic Studies, 47*, 139.

Friedland, R. P., Fritsch, T., Smyth, K. A., Koss, E., Lerner, A. J., Chen, C. H., . . . Debanne, S. M. (2001). Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proceedings of the National Academy of Sciences of the United States of America, 98*(6), 3440-3445. doi:10.1073/pnas.061002998

Fritsch, T., Smyth, K. A., Debanne, S. M., Petot, G. J., & Friedland, R. P. (2005). Participation in Novelty-Seeking Leisure Activities and Alzheimer's Disease. *Journal of Geriatric Psychiatry and Neurology, 18*(3), 134-141. doi:10.1177/0891988705277537

Fulda, S., & Schulz, H. (2001). Cognitive dysfunction in sleep disorders. *Sleep Med Rev, 5*(6), 423-445. doi:10.1053/smrv.2001.0157

Gale, C. R., Deary, I. J., Boyle, S. H., Barefoot, J., Mortensen, L. H., & Batty, G. D. (2008). Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age: the Vietnam experience study. *Arch Gen Psychiatry, 65*(12), 1410-1418. doi:10.1001/archpsyc.65.12.1410

Gao, S., Hendrie, H. C., Hall, K. S., & Hui, S. (1998). The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry, 55*(9), 809-815. doi:10.1001/archpsyc.55.9.809

Gardner, R. C., Burke, J. F., Nettiksimmons, J., Kaup, A., Barnes, D. E., & Yaffe, K. (2014). Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol, 71*(12), 1490-1497. doi:10.1001/jamaneurol.2014.2668

Garibotto, V., Borroni, B., Kalbe, E., Herholz, K., Salmon, E., Holtoff, V., . . . Perani, D. (2008). Education and occupation as proxies for reserve in aMCI converters and AD: FDG-PET evidence. *Neurology, 71*(17), 1342-1349. doi:10.1212/01.wnl.0000327670.62378.c0

Gatz, M., Svedberg, P., Pedersen, N. L., Mortimer, J. A., Berg, S., & Johansson, B. (2001). Education and the Risk of Alzheimer's Disease: Findings From the Study of Dementia in Swedish Twins. *The Journals of Gerontology: Series B, 56*(5), P292-P300. doi:10.1093/geronb/56.5.P292

Gersons, B. P., & Carlier, I. V. (1992). Post-traumatic stress disorder: the history of a recent concept. *Br J Psychiatry, 161*, 742-748. doi:10.1192/bjp.161.6.742

Geuze, E., Vermetten, E., de Kloet, C. S., Hijman, R., & Westenberg, H. G. (2009). Neuropsychological performance is related to current social and occupational functioning in veterans with posttraumatic stress disorder. *Depress Anxiety, 26*(1), 7-15. doi:10.1002/da.20476

Geuze, E., Vermetten, E., Ruf, M., de Kloet, C. S., & Westenberg, H. G. M. (2008). Neural correlates of associative learning and memory in veterans with posttraumatic stress disorder. *Journal of psychiatric research, 42*(8), 659-669. doi:10.1016/j.jpsychires.2007.06.007

Gignac, G. E., & Bates, T. C. (2017). Brain volume and intelligence: The moderating role of intelligence measurement quality. *Intelligence, 64*, 18-29. doi:https://doi.org/10.1016/j.intell.2017.06.004

Gil, T., Calev, A., Greenberg, D., Kugelmass, S., & Lerer, B. J. J. o. T. S. (1990). Cognitive functioning in Post-Traumatic Stress Disorder. *3*(1), 29-45. doi:10.1007/bf00975134

Gilbertson, M. W., Gurvits, T. V., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2001). Multivariate assessment of explicit memory function in combat veterans with

posttraumatic stress disorder. *J Trauma Stress, 14*(2), 413-432. doi:10.1023/a:1011181305501

Gilbertson, M. W., Paulus, L. A., Williston, S. K., Gurvits, T. V., Lasko, N. B., Pitman, R. K., & Orr, S. P. (2006). Neurocognitive function in monozygotic twins discordant for combat exposure: Relationship to posttraumatic stress disorder. *Journal of Abnormal Psychology, 115*(3), 484-495. doi:10.1037/0021-843X.115.3.484

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature neuroscience, 5*(11), 1242-1247. doi:10.1038/nn958

Glenner, G. G., & Wong, C. W. (1984). Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun, 120*(3), 885-890. doi:10.1016/s0006-291x(84)80190-4

Godbolt, A. K., Cancelliere, C., Hincapie, C. A., Marras, C., Boyle, E., Kristman, V. L., . . . Cassidy, J. D. (2014). Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil, 95*(3 Suppl), S245-256. doi:10.1016/j.apmr.2013.06.036

Gold, A. L., Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., . . . Pitman, R. K. (2011). Decreased regional cerebral blood flow in medial prefrontal cortex during trauma-unrelated stressful imagery in Vietnam veterans with post-traumatic stress disorder. *Psychol Med, 41*(12), 2563-2572. doi:10.1017/s0033291711000730

Goldman, J. S., Hahn, S. E., Catania, J. W., LaRusse-Eckert, S., Butson, M. B., Rumbaugh, M., . . . Bird, T. (2011). Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med, 13*(6), 597-605. doi:10.1097/GIM.0b013e31821d69b8

Golier, J., Yehuda, R., Cornblatt, B., Harvey, P., Gerber, D., & Levengood, R. (1997). Sustained attention in combat-related posttraumatic stress disorder. *Integrative Physiological and Behavioral Science, 32*(1), 52-61. doi:10.1007/bf02688613

Golier, J. A., Yehuda, R., De Santi, S., Segal, S., Dolan, S., & de Leon, M. J. (2005). Absence of hippocampal volume differences in survivors of the Nazi Holocaust with and without posttraumatic stress disorder. *Psychiatry Research: Neuroimaging, 139*(1), 53-64. doi:https://doi.org/10.1016/j.pscychresns.2005.02.007

Golier, J. A., Yehuda, R., Lupien, S. J., Harvey, P. D., Grossman, R., & Elkin, A. (2002). Memory performance in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry, 159*(10), 1682-1688. doi:10.1176/appi.ajp.159.10.1682

Gomez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J. H., Petersen, R. C., . . . Hyman, B. T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol, 41*(1), 17-24. doi:10.1002/ana.410410106

Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J. H., Petersen, R. C., . . . Hyman, B. T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in

Alzheimer's disease. *Annals of neurology, 41*(1), 17-24. doi:10.1002/ana.410410106

Gottesman, R. F., Albert, M. S., Alonso, A., Coker, L. H., Coresh, J., Davis, S. M., . . . Knopman, D. S. (2017). Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurol, 74*(10), 1246-1254. doi:10.1001/jamaneurol.2017.1658

Graeber, M. B., & Mehraein, P. (1999). Reanalysis of the first case of Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci, 249 Suppl 3*, 10-13. doi:10.1007/pl00014167

Graves, A. B., van Duijn, C. M., Chandra, V., Fratiglioni, L., Heyman, A., Jorm, A. F., . . . et al. (1991). Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol, 20 Suppl 2*, S48-57. doi:10.1093/ije/20.supplement_2.s48

Green, B. L., & Lindy, J. D. (1994). Post-traumatic stress disorder in victims of disasters. *Psychiatr Clin North Am, 17*(2), 301-309.

Green, K. N., Billings, L. M., Roozendaal, B., McGaugh, J. L., & LaFerla, F. M. (2006). Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci, 26*(35), 9047-9056. doi:10.1523/jneurosci.2797-06.2006

Green, R. C., Cupples, L. A., Go, R., Benke, K. S., Edeki, T., Griffith, P. A., . . . Farrer, L. A. (2002). Risk of dementia among white and African American relatives of patients with Alzheimer disease. *Jama, 287*(3), 329-336. doi:10.1001/jama.287.3.329

Green, R. E., Malaspinas, A. S., Krause, J., Briggs, A. W., Johnson, P. L., Uhler, C., . . . Paabo, S. (2008). A complete Neandertal mitochondrial genome sequence determined by high-throughput sequencing. *Cell, 134*(3), 416-426. doi:10.1016/j.cell.2008.06.021

Green, R. E., Melo, B., Christensen, B., Ngo, L. A., Monette, G., & Bradbury, C. (2008). Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). *J Clin Exp Neuropsychol, 30*(2), 163-172. doi:10.1080/13803390701300524

Grober, E., Lipton, R. B., Hall, C., & Crystal, H. (2000). Memory impairment on free and cued selective reminding predicts dementia. *Neurology, 54*(4), 827-832. doi:10.1212/wnl.54.4.827

Gronroos, P., Raitakari, O. T., Kahonen, M., Hutri-Kahonen, N., Marniemi, J., Viikari, J., & Lehtimaki, T. (2007). Influence of apolipoprotein E polymorphism on serum lipid and lipoprotein changes: a 21-year follow-up study from childhood to adulthood. The Cardiovascular Risk in Young Finns Study. *Clin Chem Lab Med, 45*(5), 592-598. doi:10.1515/cclm.2007.116

Groot, C., van Loenhoud, A. C., Barkhof, F., van Berckel, B. N. M., Koene, T., Teunissen, C. C., . . . Ossenkoppele, R. (2018). Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. *Neurology, 90*(2), e149-e156. doi:10.1212/wnl.0000000000004802

Grundke-Iqbal, I., Iqbal, K., Tung, Y. C., Quinlan, M., Wisniewski, H. M., & Binder, L. I. (1986). Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc Natl Acad Sci U S A, 83*(13), 4913-4917. doi:10.1073/pnas.83.13.4913

Guillozet, A. L., Weintraub, S., Mash, D. C., & Mesulam, M. M. (2003). Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol, 60*(5), 729-736. doi:10.1001/archneur.60.5.729

Gupta, A., & Iadecola, C. (2015). Impaired Aβ clearance: a potential link between atherosclerosis and Alzheimer's disease. *Frontiers in aging neuroscience, 7*, 115-115. doi:10.3389/fnagi.2015.00115

Gurvits, T. V., Lasko, N. B., Schachter, S. C., Kuhne, A. A., Orr, S. P., & Pitman, R. K. (1993). Neurological status of Vietnam veterans with chronic posttraumatic stress disorder. *J Neuropsychiatry Clin Neurosci, 5*(2), 183-188. doi:10.1176/jnp.5.2.183

Gurvits, T. V., Shenton, M. E., Hokama, H., Ohta, H., Lasko, N. B., Gilbertson, M. W., . . . Pitman, R. K. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological psychiatry, 40*(11), 1091-1099. doi:10.1016/S0006-3223(96)00229-6

Gussekloo, J., Heeren, T. J., Izaks, G. J., Ligthart, G. J., & Rooijmans, H. G. (1995). A community based study of the incidence of dementia in subjects aged 85 years and over. *J Neurol Neurosurg Psychiatry, 59*(5), 507-510. doi:10.1136/jnnp.59.5.507

Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., & Skoog, I. (2003). An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med, 163*(13), 1524-1528. doi:10.1001/archinte.163.13.1524

Hamner, M. B. (1992). Trauma and the Vietnam War Generation: Report of Findings from the National Vietnam Veterans Readjustment Study. Edited by Richard A. Kulka Ph.D., William E. Schlenger, Ph.D., John A. Fairbank, Ph.D., Richard L. Hough, Ph.D., B. Kathleen Jordan, Ph.D., Charles R. Marmar, M.D., Daniel S. Weiss, Ph.D., David A. Grady, Psy.D., New York: Brunner/Mazel, Publishers, 1990, 322 pages, $19.95. *Journal of Traumatic Stress, 5*(2), 321-322. doi:10.1002/jts.2490050217

Hardy, J. (1997). Amyloid, the presenilins and Alzheimer's disease. *Trends Neurosci, 20*(4), 154-159. doi:10.1016/s0166-2236(96)01030-2

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356. doi:10.1126/science.1072994

Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., . . . Williams, J. (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet, 41*(10), 1088-1093. doi:10.1038/ng.440

Haroutunian, V., Schnaider-Beeri, M., Schmeidler, J., Wysocki, M., Purohit, D. P., Perl, D. P., . . . Grossman, H. T. (2008). Role of the neuropathology of Alzheimer disease

in dementia in the oldest-old. *Arch Neurol, 65*(9), 1211-1217. doi:10.1001/archneur.65.9.1211

Hartley, C. A., Fischl, B., & Phelps, E. A. (2011). Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cereb Cortex, 21*(9), 1954-1962. doi:10.1093/cercor/bhq253

Hashimoto, T., Serrano-Pozo, A., Hori, Y., Adams, K. W., Takeda, S., Banerji, A. O., . . . Hyman, B. T. (2012). Apolipoprotein E, especially apolipoprotein E4, increases the oligomerization of amyloid beta peptide. *J Neurosci, 32*(43), 15181-15192. doi:10.1523/jneurosci.1542-12.2012

Hasselmo, M. E., Wyble, B. P., & Wallenstein, G. V. (1996). Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. *Hippocampus, 6*(6), 693-708. doi:10.1002/(sici)1098-1063(1996)6:6<693::Aid-hipo12>3.0.Co;2-w

Hatashita, S., & Wakebe, D. (2017). Amyloid-beta Deposition and Long-Term Progression in Mild Cognitive Impairment due to Alzheimer's Disease Defined with Amyloid PET Imaging. *J Alzheimers Dis, 57*(3), 765-773. doi:10.3233/jad-161074

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology, 80*(19), 1778-1783. doi:10.1212/WNL.0b013e31828726f5

Hedges, D. W., & Woon, F. L. (2010). Premorbid brain volume estimates and reduced total brain volume in adults exposed to trauma with or without posttraumatic stress disorder: a meta-analysis. *Cogn Behav Neurol, 23*(2), 124-129. doi:10.1097/WNN.0b013e3181e1cbe1

Hennessy, B., & Oei, T. P. (1991). The relationship between severity of combat exposure and army status on post-traumatic stress disorder among Australian Vietnam war veterans. *Behaviour Change, 8*(3), 136-144.

Hickie, I., Naismith, S., Ward, P. B., Turner, K., Scott, E., Mitchell, P., . . . Parker, G. (2005). Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br J Psychiatry, 186*, 197-202. doi:10.1192/bjp.186.3.197

Hirschman, C., Preston, S., & Loi, V. M. (1995). Vietnamese Casualties During the American War: A New Estimate. *Population and Development Review, 21*(4), 783-812. doi:10.2307/2137774

Hoch, C. C., Reynolds, C. F., 3rd, Kupfer, D. J., Houck, P. R., Berman, S. R., & Stack, J. A. (1986). Sleep-disordered breathing in normal and pathologic aging. *J Clin Psychiatry, 47*(10), 499-503.

Hoge, C. W., Auchterlonie, J. L., & Milliken, C. S. (2006). Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *Jama, 295*(9), 1023-1032. doi:10.1001/jama.295.9.1023

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2004). Combat Duty in Iraq and Afghanistan, Mental Health Problems, and Barriers to Care. *New England Journal of Medicine, 351*(1), 13-22. doi:10.1056/NEJMoa040603

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *Br J Psychiatry, 140*, 566-572. doi:10.1192/bjp.140.6.566

Hughes, K. C., & Shin, L. M. (2011). Functional neuroimaging studies of post-traumatic stress disorder. *Expert review of neurotherapeutics, 11*(2), 275-285. doi:10.1586/ern.10.198

Hull, A. M. (2002). Neuroimaging findings in post-traumatic stress disorder. Systematic review. *Br J Psychiatry, 181*, 102-110.

Hurd, M. D., Martorell, P., Delavande, A., Mullen, K. J., & Langa, K. M. (2013). Monetary costs of dementia in the United States. *N Engl J Med, 368*(14), 1326-1334. doi:10.1056/NEJMsa1204629

Hutton, M., Lendon, C. L., Rizzu, P., Baker, M., Froelich, S., Houlden, H., . . . Heutink, P. (1998). Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature, 393*(6686), 702-705. doi:10.1038/31508

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., . . . Montine, T. J. (2012). National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement, 8*(1), 1-13. doi:10.1016/j.jalz.2011.10.007

Itoh, A., Nitta, A., Nadai, M., Nishimura, K., Hirose, M., Hasegawa, T., & Nabeshima, T. (1996). Dysfunction of Cholinergic and Dopaminergic Neuronal Systems in β-Amyloid Protein-Infused Rats. *Journal of Neurochemistry, 66*(3), 1113-1117. doi:10.1046/j.1471-4159.1996.66031113.x

Jack, C. R., Jr., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., . . . Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 257-262. doi:10.1016/j.jalz.2011.03.004

Jack, C. R., Jr., Lowe, V. J., Weigand, S. D., Wiste, H. J., Senjem, M. L., Knopman, D. S., . . . Petersen, R. C. (2009). Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain, 132*(Pt 5), 1355-1365. doi:10.1093/brain/awp062

Jagust, W., Reed, B., Mungas, D., Ellis, W., & Decarli, C. (2007). What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology, 69*(9), 871-877. doi:10.1212/01.wnl.0000269790.05105.16

Jahn, H. (2013). Memory loss in Alzheimer's disease. *Dialogues in clinical neuroscience, 15*(4), 445-454. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24459411
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898682/

James, B. D., Leurgans, S. E., Hebert, L. E., Scherr, P. A., Yaffe, K., & Bennett, D. A. (2014). Contribution of Alzheimer disease to mortality in the United States. *Neurology, 82*(12), 1045-1050. doi:10.1212/wnl.0000000000000240

James, O. G., Doraiswamy, P. M., & Borges-Neto, S. (2015). PET Imaging of Tau Pathology in Alzheimer's Disease and Tauopathies. *Frontiers in neurology, 6*, 38-38. doi:10.3389/fneur.2015.00038

Jankowsky, J. L., & Zheng, H. (2017). Practical considerations for choosing a mouse model of Alzheimer's disease. *Mol Neurodegener, 12*(1), 89. doi:10.1186/s13024-017-0231-7

Jatzko, A., Rothenhofer, S., Schmitt, A., Gaser, C., Demirakca, T., Weber-Fahr, W., . . . Braus, D. F. (2006). Hippocampal volume in chronic posttraumatic stress disorder (PTSD): MRI study using two different evaluation methods. *J Affect Disord, 94*(1-3), 121-126. doi:10.1016/j.jad.2006.03.010

Jellinger, K. A., & Attems, J. (2007). Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. *Acta Neuropathol, 113*(2), 107-117. doi:10.1007/s00401-006-0156-7

Jenkins, M. A., Langlais, P. J., Delis, D., & Cohen, R. (1998). Learning and memory in rape victims with posttraumatic stress disorder. *Am J Psychiatry, 155*(2), 278-279. doi:10.1176/ajp.155.2.278

Jenkins, R., Fox, N. C., Rossor, A. M., Harvey, R. J., & Rossor, M. N. (2000). Intracranial volume and Alzheimer disease: evidence against the cerebral reserve hypothesis. *Arch Neurol, 57*(2), 220-224. doi:10.1001/archneur.57.2.220

Johnsen, G. E., Kanagaratnam, P., & Asbjornsen, A. E. (2008). Memory impairments in posttraumatic stress disorder are related to depression. *J Anxiety Disord, 22*(3), 464-474. doi:10.1016/j.janxdis.2007.04.007

Johnsen, G. E., Kanagaratnam, P., & Asbjørnsen, A. E. (2008). Memory impairments in posttraumatic stress disorder are related to depression. *Journal of Anxiety Disorders, 22*(3), 464-474. doi:10.1016/j.janxdis.2007.04.007

Jones, E., & Wessely, S. (2001). The origins of British military psychiatry before the First World War. *War Soc, 19*(2), 91-108. doi:10.1179/072924701791201512

Jones, G. M., Sahakian, B. J., Levy, R., Warburton, D. M., & Gray, J. A. (1992). Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology (Berl), 108*(4), 485-494. doi:10.1007/bf02247426

Jorm, A. F. (2001). History of depression as a risk factor for dementia: an updated review. *Aust N Z J Psychiatry, 35*(6), 776-781. doi:10.1046/j.1440-1614.2001.00967.x

Jorm, A. F., Dear, K. B., & Burgess, N. M. (2005). Projections of future numbers of dementia cases in Australia with and without prevention. *Aust N Z J Psychiatry, 39*(11-12), 959-963. doi:10.1080/j.1440-1614.2005.01713.x

Jorm, A. F., & Jolley, D. (1998). The incidence of dementia: a meta-analysis. *Neurology, 51*(3), 728-733. doi:10.1212/wnl.51.3.728

Jorm, A. F., Korten, A. E., & Henderson, A. S. (1987). The prevalence of dementia: a quantitative integration of the literature. *Acta Psychiatr Scand, 76*(5), 465-479. doi:10.1111/j.1600-0447.1987.tb02906.x

Josephs, K. A., Murray, M. E., Tosakulwong, N., Whitwell, J. L., Knopman, D. S., Machulda, M. M., . . . Dickson, D. W. (2017). Tau aggregation influences cognition and hippocampal atrophy in the absence of beta-amyloid: a clinico-imaging-pathological study of primary age-related tauopathy (PART). *Acta neuropathologica, 133*(5), 705-715. doi:10.1007/s00401-017-1681-2

Julkunen, V., Niskanen, E., Koikkalainen, J., Herukka, S.-K., Pihlajamäki, M., Hallikainen, M., . . . Hilkka, S. (2010). Differences in cortical thickness in healthy controls, subjects with mild cognitive impairment, and Alzheimer's disease patients: a longitudinal study. *Journal of Alzheimer's disease : JAD, 21*(4), 1141-1151. doi:10.3233/jad-2010-100114

Justice, N. J., Huang, L., Tian, J. B., Cole, A., Pruski, M., Hunt, A. J., Jr., . . . Zheng, H. (2015). Posttraumatic stress disorder-like induction elevates beta-amyloid levels, which directly activates corticotropin-releasing factor neurons to exacerbate stress responses. *J Neurosci, 35*(6), 2612-2623. doi:10.1523/jneurosci.3333-14.2015

Karl, A., Schaefer, M., Malta, L. S., Dorfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev, 30*(7), 1004-1031. doi:10.1016/j.neubiorev.2006.03.004

Kasai, K., Yamasue, H., Gilbertson, M. W., Shenton, M. E., Rauch, S. L., & Pitman, R. K. (2008). Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biol Psychiatry, 63*(6), 550-556. doi:10.1016/j.biopsych.2007.06.022

Katzman, R. (1986). Alzheimer's disease. *N Engl J Med, 314*(15), 964-973. doi:10.1056/nejm198604103141506

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology, 43*(1 Part 1), 13-13. doi:10.1212/WNL.43.1_Part_1.13

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., . . . Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of neurology, 23*(2), 138-144. doi:10.1002/ana.410230206

Keane, T. M., Fairbank, J. A., Caddell, J. M., Zimering, R. T., Taylor, K. L., & Mora, C. A. (1989). Clinical evaluation of a measure to assess combat exposure. *Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1*(1), 53-55. doi:10.1037/1040-3590.1.1.53

Keane, T. M., & Kaloupek, D. G. (1997). Comorbid psychiatric disorders in PTSD. Implications for research. *Ann N Y Acad Sci, 821*, 24-34. doi:10.1111/j.1749-6632.1997.tb48266.x

Kemppainen, N. M., Aalto, S., Karrasch, M., Någren, K., Savisto, N., Oikonen, V., . . . Rinne, J. O. (2008). Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. *Annals of neurology, 63*(1), 112-118. doi:10.1002/ana.21212

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry, 62*(6), 617-627. doi:10.1001/archpsyc.62.6.617

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., . . . Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric

disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry, 51*(1), 8-19. doi:10.1001/archpsyc.1994.03950010008002

Kessler, R. C., Mickelson, K. D., & Williams, D. R. (1999). The prevalence, distribution, and mental health correlates of perceived discrimination in the United States. *J Health Soc Behav, 40*(3), 208-230.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry, 52*(12), 1048-1060. doi:10.1001/archpsyc.1995.03950240066012

Khachaturian, Z. S. (1985). Diagnosis of Alzheimer's disease. *Arch Neurol, 42*(11), 1097-1105. doi:10.1001/archneur.1985.04060100083029

Kiloh, L. G. (1961). PSEUDO-DEMENTIA. *Acta Psychiatrica Scandinavica, 37*(4), 336-351. doi:10.1111/j.1600-0447.1961.tb07367.x

Kitayama, N., Quinn, S., & Bremner, J. D. (2006). Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *Journal of Affective Disorders, 90*(2-3), 171-174. doi:10.1016/j.jad.2005.11.006

Kivipelto, M., Helkala, E. L., Laakso, M. P., Hanninen, T., Hallikainen, M., Alhainen, K., . . . Nissinen, A. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ (Clinical research ed.), 322*(7300), 1447-1451. doi:10.1136/bmj.322.7300.1447

Kivling-Boden, G., & Sundbom, E. (2003). Cognitive abilities related to post-traumatic symptoms among refugees from the former Yugoslavia in psychiatric treatment. *Nord J Psychiatry, 57*(3), 191-198. doi:10.1080/08039480310001346

Klaassens, E. R., Giltay, E. J., Cuijpers, P., van Veen, T., & Zitman, F. G. (2012). Adulthood trauma and HPA-axis functioning in healthy subjects and PTSD patients: a meta-analysis. *Psychoneuroendocrinology, 37*(3), 317-331. doi:10.1016/j.psyneuen.2011.07.003

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., . . . Langstrom, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol, 55*(3), 306-319. doi:10.1002/ana.20009

Knopman, D. S., DeKosky, S. T., Cummings, J. L., Chui, H., Corey-Bloom, J., Relkin, N., . . . Stevens, J. C. (2001). Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*(9), 1143-1153. doi:10.1212/wnl.56.9.1143

Knopman, D. S., Parisi, J. E., Salviati, A., Floriach-Robert, M., Boeve, B. F., Ivnik, R. J., . . . Petersen, R. C. (2003). Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol, 62*(11), 1087-1095. doi:10.1093/jnen/62.11.1087

Koenen, K. C., Harley, R., Lyons, M. J., Wolfe, J., Simpson, J. C., Goldberg, J., . . . Tsuang, M. (2002). A TWIN REGISTRY STUDY OF FAMILIAL AND INDIVIDUAL RISK FACTORS FOR TRAUMA EXPOSURE AND POSTTRAUMATIC STRESS DISORDER. *The Journal of Nervous and Mental Disease, 190*(4). Retrieved from https://journals.lww.com/jonmd/Fulltext/2002/04000/A_TWIN_REGISTRY_STUDY_OF_FAMILIAL_AND_INDIVIDUAL.1.aspx

Koenen, K. C., Stellman, S. D., Dohrenwend, B. P., Sommer, J. F., Jr., & Stellman, J. M. (2007). The consistency of combat exposure reporting and course of PTSD in Vietnam War veterans. *J Trauma Stress, 20*(1), 3-13. doi:10.1002/jts.20191

Kokjohn, T. A., & Roher, A. E. (2009). Amyloid precursor protein transgenic mouse models and Alzheimer's disease: understanding the paradigms, limitations, and contributions. *Alzheimers Dement, 5*(4), 340-347. doi:10.1016/j.jalz.2009.03.002

Kokmen, E., Beard, C. M., Offord, K. P., & Kurland, L. T. (1989). Prevalence of medically diagnosed dementia in a defined United States population: Rochester, Minnesota, January 1, 1975. *Neurology, 39*(6), 773-776. doi:10.1212/WNL.39.6.773

Koso, M., & Hansen, S. (2006). Executive function and memory in posttraumatic stress disorder: a study of Bosnian war veterans. *Eur Psychiatry, 21*(3), 167-173. doi:10.1016/j.eurpsy.2005.06.004

Kral, V. A., & Emery, O. B. (1989). Long-Term Follow-up of Depressive Pseudodementia of the Aged. *The Canadian Journal of Psychiatry, 34*(5), 445-446. doi:10.1177/070674378903400515

Kremen, W. S., Koenen, K. C., Boake, C., Purcell, S., Eisen, S. A., Franz, C. E., . . . Lyons, M. J. (2007). Pretrauma cognitive ability and risk for posttraumatic stress disorder: a twin study. *Arch Gen Psychiatry, 64*(3), 361-368. doi:10.1001/archpsyc.64.3.361

Kuo, J. R., Kaloupek, D. G., & Woodward, S. H. (2012). Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. *Arch Gen Psychiatry, 69*(10), 1080-1086. doi:10.1001/archgenpsychiatry.2012.73

Langa, K. M., Larson, E. B., Karlawish, J. H., Cutler, D. M., Kabeto, M. U., Kim, S. Y., & Rosen, A. B. (2008). Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimers Dement, 4*(2), 134-144. doi:10.1016/j.jalz.2008.01.001

Langa, K. M., & Levine, D. A. (2014). The diagnosis and management of mild cognitive impairment: a clinical review. *Jama, 312*(23), 2551-2561. doi:10.1001/jama.2014.13806

Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Gupta, M. A., Neufeld, R. W., . . . Menon, R. S. (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *Am J Psychiatry, 158*(11), 1920-1922. doi:10.1176/appi.ajp.158.11.1920

Larson, E., Zollman, F., Kondiles, B., & Starr, C. (2013). Memory deficits, postconcussive complaints, and posttraumatic stress disorder in a volunteer sample of veterans. *Rehabil Psychol, 58*(3), 245-252. doi:10.1037/a0032953

Laugharne, J., Kullack, C., Lee, C. W., McGuire, T., Brockman, S., Drummond, P. D., & Starkstein, S. (2016). Amygdala Volumetric Change Following Psychotherapy for Posttraumatic Stress Disorder. *J Neuropsychiatry Clin Neurosci, 28*(4), 312-318. doi:10.1176/appi.neuropsych.16010006

Launer, L. J., Andersen, K., Dewey, M. E., Letenneur, L., Ott, A., Amaducci, L. A., . . . Hofman, A. (1999). Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group

and Work Groups. European Studies of Dementia. *Neurology, 52*(1), 78-84. doi:10.1212/wnl.52.1.78

Lautenschlager, N. T., Cupples, L. A., Rao, V. S., Auerbach, S. A., Becker, R., Burke, J., . . . Farrer, L. A. (1996). Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? *Neurology, 46*(3), 641-650. doi:10.1212/wnl.46.3.641

LeDoux, J. E. (2000). Emotion Circuits in the Brain. *23*(1), 155-184. doi:10.1146/annurev.neuro.23.1.155

Lehto, J. E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: Evidence from children. *British Journal of Developmental Psychology, 21*(1), 59-80. doi:10.1348/026151003321164627

Lehtovirta, M., Helisalmi, S., Mannermaa, A., Soininen, H., Koivisto, K., Ryynanen, M., & Riekkinen, P., Sr. (1995). Apolipoprotein E polymorphism and Alzheimer's disease in eastern Finland. *Neurosci Lett, 185*(1), 13-15. doi:10.1016/0304-3940(94)11213-3

Leland, A., Oboroceanu, M.-J., Library of, C., & Congressional Research, S. (2010). *American War and Military Operations Casualties: Lists and Statistics*.

Lemere, C. A., Blusztajn, J. K., Yamaguchi, H., Wisniewski, T., Saido, T. C., & Selkoe, D. J. (1996). Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. *Neurobiol Dis, 3*(1), 16-32. doi:10.1006/nbdi.1996.0003

Leskin, G. A., Woodward, S. H., Young, H. E., & Sheikh, J. I. (2002). Effects of comorbid diagnoses on sleep disturbance in PTSD. *Journal of psychiatric research, 36*(6), 449-452. doi:10.1016/s0022-3956(02)00025-0

Letenneur, L., Gilleron, V., Commenges, D., Helmer, C., Orgogozo, J. M., & Dartigues, J. F. (1999). Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry, 66*(2), 177-183. doi:10.1136/jnnp.66.2.177

Lewis, H., Beher, D., Cookson, N., Oakley, A., Piggott, M., Morris, C. M., . . . Kalaria, R. N. (2006). Quantification of Alzheimer pathology in ageing and dementia: age-related accumulation of amyloid-beta(42) peptide in vascular dementia. *Neuropathol Appl Neurobiol, 32*(2), 103-118. doi:10.1111/j.1365-2990.2006.00696.x

Lewis, S. J., Arseneault, L., Caspi, A., Fisher, H. L., Matthews, T., Moffitt, T. E., . . . Danese, A. (2019). The epidemiology of trauma and post-traumatic stress disorder in a representative cohort of young people in England and Wales. *Lancet Psychiatry, 6*(3), 247-256. doi:10.1016/s2215-0366(19)30031-8

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004). *Neuropsychological assessment, 4th ed*. New York, NY, US: Oxford University Press.

Liberzon, I., Taylor, S. F., Amdur, R., Jung, T. D., Chamberlain, K. R., Minoshima, S., . . . Fig, L. M. (1999). Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry, 45*(7), 817-826. doi:10.1016/s0006-3223(98)00246-7

Licznerski, P., & Duman, R. S. (2013). Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. *Neuroscience, 251*, 33-50. doi:10.1016/j.neuroscience.2012.09.057

Lim, A. S., Yu, L., Kowgier, M., Schneider, J. A., Buchman, A. S., & Bennett, D. A. (2013). Modification of the relationship of the apolipoprotein E epsilon4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol, 70*(12), 1544-1551. doi:10.1001/jamaneurol.2013.4215

Lindauer, R. J., Vlieger, E. J., Jalink, M., Olff, M., Carlier, I. V., Majoie, C. B., . . . Gersons, B. P. (2004). Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. *Biol Psychiatry, 56*(5), 356-363. doi:10.1016/j.biopsych.2004.05.021

Lindsay, J., Laurin, D., Verreault, R., Hébert, R., Helliwell, B., Hill, G. B., & McDowell, I. (2002). Risk Factors for Alzheimer's Disease: A Prospective Analysis from the Canadian Study of Health and Aging. *American Journal of Epidemiology, 156*(5), 445-453. doi:10.1093/aje/kwf074

Lissek, S., & Grillon, C. (2010). Overgeneralization of conditioned fear in the anxiety disorders: Putative memorial mechanisms. *Zeitschrift für Psychologie/Journal of Psychology, 218*(2), 146-148. doi:10.1027/0044-3409/a000022

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., . . . Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet, 396*(10248), 413-446. doi:10.1016/S0140-6736(20)30367-6

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., . . . Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet, 390*(10113), 2673-2734. doi:10.1016/S0140-6736(17)31363-6

Lloyd, A. J., Ferrier, I. N., Barber, R., Gholkar, A., Young, A. H., & O'Brien, J. T. (2004). Hippocampal volume change in depression: Late- and early-onset illness compared. *British Journal of Psychiatry, 184*(6), 488-495. doi:10.1192/bjp.184.6.488

Lobo, A., Launer, L. J., Fratiglioni, L., Andersen, K., Di Carlo, A., Breteler, M. M., . . . Hofman, A. (2000). Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology, 54*(11 Suppl 5), S4-9.

Lorand, A. (1913). Old age deferred / by Arnold Lorand. Retrieved from http://catalog.hathitrust.org/api/volumes/oclc/501418983.html

Ma, Y., Zhang, S., Li, J., Zheng, D.-M., Guo, Y., Feng, J., & Ren, W.-D. (2014). Predictive accuracy of amyloid imaging for progression from mild cognitive impairment to Alzheimer disease with different lengths of follow-up: a meta-analysis. [Corrected]. *Medicine, 93*(27), e150-e150. doi:10.1097/MD.0000000000000150

Maass, A., Lockhart, S. N., Harrison, T. M., Bell, R. K., Mellinger, T., Swinnerton, K., . . . Jagust, W. J. (2018). Entorhinal Tau Pathology, Episodic Memory Decline, and Neurodegeneration in Aging. *J Neurosci, 38*(3), 530-543. doi:10.1523/jneurosci.2028-17.2017

MacGregor, A. J., Clouser, M. C., Mayo, J. A., & Galarneau, M. R. (2017). Gender Differences in Posttraumatic Stress Disorder Among U.S. Navy Healthcare Personnel. *J Womens Health (Larchmt), 26*(4), 338-344. doi:10.1089/jwh.2014.5130

Macklin, M. L., Metzger, L. J., Litz, B. T., McNally, R. J., Lasko, N. B., Orr, S. P., & Pitman, R. K. (1998). Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychol, 66*(2), 323-326. doi:10.1037//0022-006x.66.2.323

MacLullich, A. M., Ferguson, K. J., Deary, I. J., Seckl, J. R., Starr, J. M., & Wardlaw, J. M. (2002). Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. *Neurology, 59*(2), 169-174. doi:10.1212/wnl.59.2.169

Maher, M. J., Rego, S. A., & Asnis, G. M. (2006). Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. *CNS drugs, 20*(7), 567-590. doi:10.2165/00023210-200620070-00003

Management of Concussion/m, T. B. I. W. G. (2009). VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. *J Rehabil Res Dev, 46*(6), CP1-CP68. Retrieved from https://pubmed.ncbi.nlm.nih.gov/20108447

Mander, B. A., Marks, S. M., Vogel, J. W., Rao, V., Lu, B., Saletin, J. M., . . . Walker, M. P. (2015). β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nature neuroscience, 18*(7), 1051-1057. doi:10.1038/nn.4035

Mander, B. A., Winer, J. R., Jagust, W. J., & Walker, M. P. (2016). Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease? *Trends in neurosciences, 39*(8), 552-566. doi:10.1016/j.tins.2016.05.002

Mann, D. M., Yates, P. O., Marcyniuk, B., & Ravindra, C. R. (1986). The topography of plaques and tangles in Down's syndrome patients of different ages. *Neuropathol Appl Neurobiol, 12*(5), 447-457.

Marc, L. G., Raue, P. J., & Bruce, M. L. (2008). Screening performance of the 15-item geriatric depression scale in a diverse elderly home care population. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 16*(11), 914-921. doi:10.1097/JGP.0b013e318186bd67

Marioni, R. E., Proust-Lima, C., Amieva, H., Brayne, C., Matthews, F. E., Dartigues, J.-F., & Jacqmin-Gadda, H. (2015). Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. *BMC Public Health, 15*(1), 1089. doi:10.1186/s12889-015-2426-6

Markesbery, W. R., Schmitt, F. A., Kryscio, R. J., Davis, D. G., Smith, C. D., & Wekstein, D. R. (2006). Neuropathologic substrate of mild cognitive impairment. *Arch Neurol, 63*(1), 38-46. doi:10.1001/archneur.63.1.38

Marmar, C. R., Schlenger, W., Henn-Haase, C., Qian, M., Purchia, E., Li, M., . . . Kulka, R. A. (2015). Course of Posttraumatic Stress Disorder 40 Years After the Vietnam

War: Findings From the National Vietnam Veterans Longitudinal Study. *JAMA Psychiatry, 72*(9), 875-881. doi:10.1001/jamapsychiatry.2015.0803

Marx, B. P., Doron-Lamarca, S., Proctor, S. P., & Vasterling, J. J. (2009). The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes among Iraq-deployed Army soldiers. *J Int Neuropsychol Soc, 15*(6), 840-852. doi:10.1017/s1355617709990488

Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., . . . Gagnepain, P. (2020). Resilience after trauma: The role of memory suppression. *Science, 367*(6479), eaay8477. doi:10.1126/science.aay8477

Masters, C. L., Simms, G., Weinman, N. A., Multhaup, G., McDonald, B. L., & Beyreuther, K. (1985). Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci U S A, 82*(12), 4245-4249. doi:10.1073/pnas.82.12.4245

Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition and Emotion, 16*(3), 331-354. doi:10.1080/02699930143000518

Matsumae, M., Kikinis, R., Morocz, I. A., Lorenzo, A. V., Sandor, T., Albert, M. S., . . . Jolesz, F. A. (1996). Age-related changes in intracranial compartment volumes in normal adults assessed by magnetic resonance imaging. *J Neurosurg, 84*(6), 982-991. doi:10.3171/jns.1996.84.6.0982

Matthews, F. E., Arthur, A., Barnes, L. E., Bond, J., Jagger, C., Robinson, L., . . . Ageing, C. (2013). A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet (London, England), 382*(9902), 1405-1412. doi:10.1016/S0140-6736(13)61570-6

Mawanda, F., Wallace, R. B., McCoy, K., & Abrams, T. E. (2017). PTSD, Psychotropic Medication Use, and the Risk of Dementia Among US Veterans: A Retrospective Cohort Study. *J Am Geriatr Soc, 65*(5), 1043-1050. doi:10.1111/jgs.14756

Mawuenyega, K. G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J. C., . . . Bateman, R. J. (2010). Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science, 330*(6012), 1774. doi:10.1126/science.1197623

Mayeux, R., Sano, M., Chen, J., Tatemichi, T., & Stern, Y. (1991). Risk of dementia in first-degree relatives of patients with Alzheimer's disease and related disorders. *Arch Neurol, 48*(3), 269-273. doi:10.1001/archneur.1991.00530150037014

Mazza, S., Pépin, J.-L., Naëgelé, B., Plante, J., Deschaux, C., & Lévy, P. (2005). Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. *European Respiratory Journal, 25*(1), 75-80. doi:10.1183/09031936.04.00011204

McAllister-Williams, R. H., Ferrier, I. N., & Young, A. H. (1998). Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. *Psychological Medicine, 28*(3), 573-584. doi:10.1017/S0033291798006680

McDowell, I., Xi, G., Lindsay, J., & Tierney, M. (2007). Mapping the connections between education and dementia. *Journal of clinical and experimental neuropsychology, 29*(2), 127-141. doi:10.1080/13803390600582420

McFarlane, A. C., & Papay, P. (1992). Multiple diagnoses in posttraumatic stress disorder in the victims of a natural disaster. *J Nerv Ment Dis, 180*(8), 498-504. doi:10.1097/00005053-199208000-00004

McGurn, B., Deary, I. J., & Starr, J. M. (2008). Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. *Neurology, 71*(14), 1051-1056. doi:10.1212/01.wnl.0000319692.20283.10

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939-944. doi:10.1212/wnl.34.7.939

Mehta, K. M., Ott, A., Kalmijn, S., Slooter, A. J., van Duijn, C. M., Hofman, A., & Breteler, M. M. (1999). Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. *Neurology, 53*(9), 1959-1962. doi:10.1212/wnl.53.9.1959

Mellman, T. A., Kulick-Bell, R., Ashlock, L. E., & Nolan, B. (1995). Sleep events among veterans with combat-related posttraumatic stress disorder. *The American journal of psychiatry, 152*(1), 110-115. doi:10.1176/ajp.152.1.110

Mervis, C. B., Robinson, B. F., & Pani, J. R. (1999). Visuospatial construction. *Am J Hum Genet, 65*(5), 1222-1229. doi:10.1086/302633

Mezey, G., & Robbins, I. (2001). Usefulness and validity of post-traumatic stress disorder as a psychiatric category. *BMJ (Clinical research ed.), 323*(7312), 561-563. doi:10.1136/bmj.323.7312.561

Meziab, O., Kirby, K. A., Williams, B., Yaffe, K., Byers, A. L., & Barnes, D. E. (2014). Prisoner of war status, posttraumatic stress disorder, and dementia in older veterans. *Alzheimer's & Dementia, 10*(3, Supplement), S236-S241. doi:https://doi.org/10.1016/j.jalz.2014.04.004

Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L., & Kuhl, D. E. (1997). Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol, 42*(1), 85-94. doi:10.1002/ana.410420114

Mintun, M. A., Larossa, G. N., Sheline, Y. I., Dence, C. S., Lee, S. Y., Mach, R. H., . . . Morris, J. C. (2006). [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology, 67*(3), 446-452. doi:10.1212/01.wnl.0000228230.26044.a4

Mitchell, A. J., & Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand, 119*(4), 252-265. doi:10.1111/j.1600-0447.2008.01326.x

Mitchell, T. W., Mufson, E. J., Schneider, J. A., Cochran, E. J., Nissanov, J., Han, L. Y., . . . Arnold, S. E. (2002). Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. *Ann Neurol, 51*(2), 182-189. doi:10.1002/ana.10086

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Moench, K. M., & Wellman, C. L. (2015). Stress-induced alterations in prefrontal dendritic spines: Implications for post-traumatic stress disorder. *Neuroscience letters, 601*, 41-45. doi:10.1016/j.neulet.2014.12.035

Mohanakrishnan Menon, P., Nasrallah, H. A., Lyons, J. A., Scott, M. F., & Liberto, V. (2003). Single-voxel proton MR spectroscopy of right versus left hippocampi in PTSD. *Psychiatry Res, 123*(2), 101-108. doi:10.1016/s0925-4927(03)00044-1

Molina, M. E., Isoardi, R., Prado, M. N., & Bentolila, S. (2010). Basal cerebral glucose distribution in long-term post-traumatic stress disorder. *World J Biol Psychiatry, 11*(2 Pt 2), 493-501. doi:10.3109/15622970701472094

Morales, J. M., Gonzalez-Montalvo, J. I., Bermejo, F., & Del-Ser, T. (1995). The screening of mild dementia with a shortened Spanish version of the "Informant Questionnaire on Cognitive Decline in the Elderly". *Alzheimer Dis Assoc Disord, 9*(2), 105-111. doi:10.1097/00002093-199509020-00008

Morbelli, S., Perneczky, R., Drzezga, A., Frisoni, G. B., Caroli, A., van Berckel, B. N. M., . . . Nobili, F. (2013). Metabolic networks underlying cognitive reserve in prodromal Alzheimer disease: a European Alzheimer disease consortium project. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 54*(6), 894-902. doi:10.2967/jnumed.112.113928

Morey, R. A., Gold, A. L., LaBar, K. S., Beall, S. K., Brown, V. M., Haswell, C. C., . . . McCarthy, G. (2012). Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Arch Gen Psychiatry, 69*(11), 1169-1178. doi:10.1001/archgenpsychiatry.2012.50

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol, 58*(3), 397-405. doi:10.1001/archneur.58.3.397

Morris, M. C., Compas, B. E., & Garber, J. (2012). Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. *Clin Psychol Rev, 32*(4), 301-315. doi:10.1016/j.cpr.2012.02.002

Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2003). Head circumference, education and risk of dementia: findings from the Nun Study. *J Clin Exp Neuropsychol, 25*(5), 671-679. doi:10.1076/jcen.25.5.671.14584

Mortimer, J. A., van Duijn, C. M., Chandra, V., Fratiglioni, L., Graves, A. B., Heyman, A., . . . et al. (1991). Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol, 20 Suppl 2*, S28-35. doi:10.1093/ije/20.supplement_2.s28

Mosconi, L., Tsui, W. H., Herholz, K., Pupi, A., Drzezga, A., Lucignani, G., . . . de Leon, M. J. (2008). Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med, 49*(3), 390-398. doi:10.2967/jnumed.107.045385

Moscoso, A., Silva-Rodríguez, J., Aldrey, J. M., Cortés, J., Fernández-Ferreiro, A., Gómez-Lado, N., . . . Alzheimer's Disease Neuroimaging, I. (2019). Prediction of Alzheimer's disease dementia with MRI beyond the short-term: Implications for the design of predictive models. *NeuroImage. Clinical, 23*, 101837-101837. doi:10.1016/j.nicl.2019.101837

Mueller, S. G., Weiner, M. W., Thal, L. J., Petersen, R. C., Jack, C., Jagust, W., . . . Beckett, L. (2005). The Alzheimer's Disease Neuroimaging Initiative. *Neuroimaging Clinics, 15*(4), 869-877. doi:10.1016/j.nic.2005.09.008

Naegele, B., Launois, S. H., Mazza, S., Feuerstein, C., Pepin, J. L., & Levy, P. (2006). Which memory processes are affected in patients with obstructive sleep apnea? An evaluation of 3 types of memory. *Sleep, 29*(4), 533-544. doi:10.1093/sleep/29.4.533

Namba, Y., Tomonaga, M., Kawasaki, H., Otomo, E., & Ikeda, K. (1991). Apolipoprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. *Brain Res, 541*(1), 163-166. doi:10.1016/0006-8993(91)91092-f

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc, 53*(4), 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Nelson, P. T., Abner, E. L., Schmitt, F. A., Kryscio, R. J., Jicha, G. A., Santacruz, K., . . . Markesbery, W. R. (2009). Brains with medial temporal lobe neurofibrillary tangles but no neuritic amyloid plaques are a diagnostic dilemma but may have pathogenetic aspects distinct from Alzheimer disease. *J Neuropathol Exp Neurol, 68*(7), 774-784. doi:10.1097/NEN.0b013e3181aacbe9

Neylan, T. C., Marmar, C. R., Metzler, T. J., Weiss, D. S., Zatzick, D. F., Delucchi, K. L., . . . Schoenfeld, F. B. (1998). Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *The American journal of psychiatry, 155*(7), 929-933. doi:10.1176/ajp.155.7.929

Ni, Y., Zhao, X., Bao, G., Zou, L., Teng, L., Wang, Z., . . . Pei, G. (2006). Activation of beta2-adrenergic receptor stimulates gamma-secretase activity and accelerates amyloid plaque formation. *Nat Med, 12*(12), 1390-1396. doi:10.1038/nm1485

Nichols, E., Szoeke, C. E. I., Vollset, S. E., Abbasi, N., Abd-Allah, F., Abdela, J., . . . Murray, C. J. L. (2019). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology, 18*(1), 88-106. doi:https://doi.org/10.1016/S1474-4422(18)30403-4

Nisbet, R. M., Polanco, J. C., Ittner, L. M., & Gotz, J. (2015). Tau aggregation and its interplay with amyloid-beta. *Acta Neuropathol, 129*(2), 207-220. doi:10.1007/s00401-014-1371-2

O'Doherty, D. C., Chitty, K. M., Saddiqui, S., Bennett, M. R., & Lagopoulos, J. (2015). A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Res, 232*(1), 1-33. doi:10.1016/j.pscychresns.2015.01.002

O'Toole, B. I., Marshall, R. P., Grayson, D. A., Schureck, R. J., Dobson, M., Ffrench, M., . . . Vennard, J. (1996). The Australian Vietnam Veterans Health Study: III. psychological health of Australian Vietnam veterans and its relationship to combat. *Int J Epidemiol, 25*(2), 331-340. doi:10.1093/ije/25.2.331

Ocasio-Tascon, M. E., Alicea-Colon, E., Torres-Palacios, A., & Rodriguez-Cintron, W. (2006). The veteran population: one at high risk for sleep-disordered breathing. *Sleep Breath, 10*(2), 70-75. doi:10.1007/s11325-005-0043-9

Ohayon, M. M., & Shapiro, C. M. (2000). Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Comprehensive psychiatry, 41*(6), 469-478. doi:10.1053/comp.2000.16568

Okello, A., Koivunen, J., Edison, P., Archer, H. A., Turkheimer, F. E., Nagren, K., . . . Brooks, D. J. (2009). Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology, 73*(10), 754-760. doi:10.1212/WNL.0b013e3181b23564

Olff, M., Langeland, W., Draijer, N., & Gersons, B. P. (2007). Gender differences in posttraumatic stress disorder. *Psychol Bull, 133*(2), 183-204. doi:10.1037/0033-2909.133.2.183

Olson, M. I., & Shaw, C. M. (1969). Presenile dementia and Alzheimer's disease in mongolism. *Brain, 92*(1), 147-156. doi:10.1093/brain/92.1.147

Osorio, R. S., Gumb, T., Pirraglia, E., Varga, A. W., Lu, S.-E., Lim, J., . . . Alzheimer's Disease Neuroimaging, I. (2015). Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology, 84*(19), 1964-1971. doi:10.1212/WNL.0000000000001566

Osorio, R. S., Pirraglia, E., Agüera-Ortiz, L. F., During, E. H., Sacks, H., Ayappa, I., . . . de Leon, M. J. (2011). Greater risk of Alzheimer's disease in older adults with insomnia. *Journal of the American Geriatrics Society, 59*(3), 559-562. doi:10.1111/j.1532-5415.2010.03288.x

Osterrieth, P. A. (1944). Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure; contribution to the study of perception and memory.]. *Archives de Psychologie, 30*, 206-356.

Osuch, E. A., Willis, M. W., Bluhm, R., Ursano, R. J., & Drevets, W. C. (2008). Neurophysiological responses to traumatic reminders in the acute aftermath of serious motor vehicle collisions using [15O]-H2O positron emission tomography. *Biol Psychiatry, 64*(4), 327-335. doi:10.1016/j.biopsych.2008.03.010

Ott, A., Breteler, M. M., van Harskamp, F., Claus, J. J., van der Cammen, T. J., Grobbee, D. E., & Hofman, A. (1995). Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *Bmj, 310*(6985), 970-973. doi:10.1136/bmj.310.6985.970

Parslow, R. A., & Jorm, A. F. (2007). Pretrauma and posttrauma neurocognitive functioning and PTSD symptoms in a community sample of young adults. *Am J Psychiatry, 164*(3), 509-515. doi:10.1176/ajp.2007.164.3.509

Partington, J. E., & Leiter, R. G. (1949). *Partington Pathways Test*. Oxford, England: Psychological Service Center.

Pauwels, L., Chalavi, S., & Swinnen, S. P. (2018). Aging and brain plasticity. *Aging, 10*(8), 1789-1790. doi:10.18632/aging.101514

Pavic, L., Gregurek, R., Rados, M., Brkljacic, B., Brajkovic, L., Simetin-Pavic, I., . . . Kalousek, V. (2007). Smaller right hippocampus in war veterans with posttraumatic stress disorder. *Psychiatry Res, 154*(2), 191-198. doi:10.1016/j.pscychresns.2006.08.005

Pavlik, V. N., Doody, R. S., Massman, P. J., & Chan, W. (2006). Influence of Premorbid IQ and Education on Progression of Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders, 22*(4), 367-377. doi:10.1159/000095640

Pederson, C. L., Maurer, S. H., Kaminski, P. L., Zander, K. A., Peters, C. M., Stokes-Crowe, L. A., & Osborn, R. E. (2004). Hippocampal volume and memory performance in a community-based sample of women with posttraumatic stress disorder secondary to child abuse. *J Trauma Stress, 17*(1), 37-40. doi:10.1023/b:Jots.0000014674.84517.46

Perani, D., Farsad, M., Ballarini, T., Lubian, F., Malpetti, M., Fracchetti, A., . . . Abutalebi, J. (2017). The impact of bilingualism on brain reserve and metabolic connectivity in Alzheimer's dementia. *Proc Natl Acad Sci U S A, 114*(7), 1690-1695. doi:10.1073/pnas.1610909114

Perl, D. P. (2010). Neuropathology of Alzheimer's disease. *The Mount Sinai journal of medicine, New York, 77*(1), 32-42. doi:10.1002/msj.20157

Petersen, R. C., Smith, G. E., Ivnik, R. J., Tangalos, E. G., Schaid, D. J., Thibodeau, S. N., . . . Kurland, L. T. (1995). Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *Jama, 273*(16), 1274-1278.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308. doi:10.1001/archneur.56.3.303

Pietschnig, J., Penke, L., Wicherts, J. M., Zeiler, M., & Voracek, M. (2015). Meta-analysis of associations between human brain volume and intelligence differences: How strong are they and what do they mean? *Neurosci Biobehav Rev, 57*, 411-432. doi:10.1016/j.neubiorev.2015.09.017

Pike, K. E., Savage, G., Villemagne, V. L., Ng, S., Moss, S. A., Maruff, P., . . . Rowe, C. C. (2007). Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain, 130*(Pt 11), 2837-2844. doi:10.1093/brain/awm238

Pissiota, A., Frans, O., Fernandez, M., von Knorring, L., Fischer, H., & Fredrikson, M. (2002). Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. *Eur Arch Psychiatry Clin Neurosci, 252*(2), 68-75. doi:10.1007/s004060200014

Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., . . . Breitner, J. C. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology, 55*(8), 1158-1166. doi:10.1212/wnl.55.8.1158

Plassman, B. L., Welsh, K. A., Helms, M., Brandt, J., Page, W. F., & Breitner, J. C. (1995). Intelligence and education as predictors of cognitive state in late life: a 50-year follow-up. *Neurology, 45*(8), 1446-1450. doi:10.1212/wnl.45.8.1446

Polvikoski, T., Sulkava, R., Haltia, M., Kainulainen, K., Vuorio, A., Verkkoniemi, A., . . . Kontula, K. (1995). Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. *N Engl J Med, 333*(19), 1242-1247. doi:10.1056/nejm199511093331902

Porto, F. H. d. G., Fox, A. M., Tusch, E. S., Sorond, F., Mohammed, A. H., & Daffner, K. R. (2015). In vivo evidence for neuroplasticity in older adults. *Brain Research Bulletin, 114*, 56-61. doi:https://doi.org/10.1016/j.brainresbull.2015.03.004

Price, J. L., & Morris, J. C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Annals of neurology, 45*(3), 358-368. doi:10.1002/1531-8249(199903)45:3<358::aid-ana12>3.0.co;2-x

Prigerson, H. G., Maciejewski, P. K., & Rosenheck, R. A. (2001). Combat trauma: trauma with highest risk of delayed onset and unresolved posttraumatic stress disorder symptoms, unemployment, and abuse among men. *J Nerv Ment Dis, 189*(2), 99-108. doi:10.1097/00005053-200102000-00005

Prince, M., Ali, G.-C., Guerchet, M., Prina, A. M., Albanese, E., & Wu, Y.-T. (2016). Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimer's research & therapy, 8*(1), 23-23. doi:10.1186/s13195-016-0188-8

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement, 9*(1), 63-75.e62. doi:10.1016/j.jalz.2012.11.007

Prins, N. D., van der Flier, W. M., Brashear, H. R., Knol, D. L., van de Pol, L. A., Barkhof, F., & Scheltens, P. (2013). Predictors of progression from mild cognitive impairment to dementia in the placebo-arm of a clinical trial population. *J Alzheimers Dis, 36*(1), 79-85. doi:10.3233/jad-122233

Qureshi, S. U., Kimbrell, T., Pyne, J. M., Magruder, K. M., Hudson, T. J., Petersen, N. J., . . . Kunik, M. E. (2010). Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder. *J Am Geriatr Soc, 58*(9), 1627-1633. doi:10.1111/j.1532-5415.2010.02977.x

Rabinovici, G. D., Furst, A. J., O'Neil, J. P., Racine, C. A., Mormino, E. C., Baker, S. L., . . . Jagust, W. J. (2007). 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology, 68*(15), 1205-1212. doi:10.1212/01.wnl.0000259035.98480.ed

Rajan, K. B., Weuve, J., Barnes, L. L., Wilson, R. S., & Evans, D. A. (2019). Prevalence and incidence of clinically diagnosed Alzheimer's disease dementia from 1994 to 2012 in a population study. *Alzheimers Dement, 15*(1), 1-7. doi:10.1016/j.jalz.2018.07.216

Raji, C. A., Lopez, O. L., Kuller, L. H., Carmichael, O. T., & Becker, J. T. (2009). Age, Alzheimer disease, and brain structure. *Neurology, 73*(22), 1899-1905. doi:10.1212/WNL.0b013e3181c3f293

Ramage, A. E., Litz, B. T., Resick, P. A., Woolsey, M. D., Dondanville, K. A., Young-McCaughan, S., . . . Consortium, S. S. (2016). Regional cerebral glucose metabolism differentiates danger- and non-danger-based traumas in post-traumatic stress disorder. *Social cognitive and affective neuroscience, 11*(2), 234-242. doi:10.1093/scan/nsv102

Rauch, S. L., Shin, L. M., Segal, E., Pitman, R. K., Carson, M. A., McMullin, K., . . . Makris, N. (2003). Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport, 14*(7), 913-916. doi:10.1097/01.wnr.0000071767.24455.10

Rauch, S. L., van der Kolk, B. A., Fisler, R. E., Alpert, N. M., Orr, S. P., Savage, C. R., . . . Pitman, R. K. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry, 53*(5), 380-387. doi:10.1001/archpsyc.1996.01830050014003

Rawle, M. J., Davis, D., Bendayan, R., Wong, A., Kuh, D., & Richards, M. (2018). Apolipoprotein-E (Apoe) ε4 and cognitive decline over the adult life course. *Translational Psychiatry, 8*(1), 18. doi:10.1038/s41398-017-0064-8

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *8*(3), 271-276. doi:10.2466/pms.1958.8.3.271

Rey, A. (1964). *L'examen clinique en psychologie*. Paris: Presses universitaires de France.

Rey, A., & Osterrieth, P. A. (1993). Translations of excerpts from Andre Rey"s Psychological examination of traumatic encephalopathy and P. A. Osterrieth"s The Complex Figure Copy Test. *Clinical Neuropsychologist, 7*(1), 4-21.

Reynolds, C. F., 3rd, Kupfer, D. J., Taska, L. S., Hoch, C. C., Sewitch, D. E., Restifo, K., . . . et al. (1985). Sleep apnea in Alzheimer's dementia: correlation with mental deterioration. *J Clin Psychiatry, 46*(7), 257-261.

Richards, M., & Sacker, A. (2003). Lifetime Antecedents of Cognitive Reserve. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 614-624. doi:10.1076/jcen.25.5.614.14581

Riley, K. P., Snowdon, D. A., & Markesbery, W. R. (2002). Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Ann Neurol, 51*(5), 567-577. doi:10.1002/ana.10161

Ritchie, K., Artero, S., & Touchon, J. (2001). Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology, 56*(1), 37-42. doi:10.1212/wnl.56.1.37

Roberts, K. F., Elbert, D. L., Kasten, T. P., Patterson, B. W., Sigurdson, W. C., Connors, R. E., . . . Bateman, R. J. (2014). Amyloid-beta efflux from the central nervous system into the plasma. *Ann Neurol, 76*(6), 837-844. doi:10.1002/ana.24270

Roby, Y. (2017). Apolipoprotein E variants and genetic susceptibility to combat-related post-traumatic stress disorder: a meta-analysis. *Psychiatr Genet, 27*(4), 121-130. doi:10.1097/ypg.0000000000000174

Rocca, W. A., Amaducci, L. A., & Schoenberg, B. S. (1986). Epidemiology of clinically diagnosed Alzheimer's disease. *Ann Neurol, 19*(5), 415-424. doi:10.1002/ana.410190502

Rocca, W. A., Hofman, A., Brayne, C., Breteler, M. M., Clarke, M., Copeland, J. R., . . . et al. (1991). Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980-1990 prevalence findings. The EURODEM-Prevalence Research Group. *Ann Neurol, 30*(3), 381-390. doi:10.1002/ana.410300310

Roe, C. M., Xiong, C., Miller, J. P., & Morris, J. C. (2007). Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology, 68*(3), 223-228. doi:10.1212/01.wnl.0000251303.50459.8a

Roehr, S., Pabst, A., Luck, T., & Riedel-Heller, S. G. (2018). Is dementia incidence declining in high-income countries? A systematic review and meta-analysis. *Clinical epidemiology, 10*, 1233-1247. doi:10.2147/CLEP.S163649

Rogers, M. A., Yamasue, H., Abe, O., Yamada, H., Ohtani, T., Iwanami, A., . . . Kasai, K. (2009). Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. *Psychiatry Res, 174*(3), 210-216. doi:10.1016/j.pscychresns.2009.06.001

Rosenberg, S. J., Ryan, J. J., & Prifitera, A. (1984). Rey Auditory-Verbal Learning Test performance of patients with and without memory impairment. *Journal of Clinical Psychology, 40*(3), 785-787. doi:10.1002/1097-4679(198405)40:3<785::AID-JCLP2270400325>3.0.CO;2-4

Rosenman, S. (2002). Trauma and posttraumatic stress disorder in Australia: findings in the population sample of the Australian National Survey of Mental Health and Wellbeing. *Aust N Z J Psychiatry, 36*(4), 515-520. doi:10.1046/j.1440-1614.2002.01039.x

Roszell, D. K., McFall, M. E., & Malas, K. L. (1991). Frequency of symptoms and concurrent psychiatric disorder in Vietnam veterans with chronic PTSD. *Hospital & Community Psychiatry, 42*(3), 293-296.

Rothman, K. J. (2012). *Epidemiology : an introduction*. New York, NY: Oxford University Press.

Roughead, E. E., Pratt, N. L., Kalisch Ellett, L. M., Ramsay, E. N., Barratt, J. D., Morris, P., & Killer, G. (2017). Posttraumatic Stress Disorder, Antipsychotic Use and Risk of Dementia in Veterans. *J Am Geriatr Soc, 65*(7), 1521-1526. doi:10.1111/jgs.14837

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., . . . Villemagne, V. L. (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology, 68*(20), 1718-1725. doi:10.1212/01.wnl.0000261919.22630.ea

Rowe, C. C., & Villemagne, V. L. (2011). Brain amyloid imaging. *J Nucl Med, 52*(11), 1733-1740. doi:10.2967/jnumed.110.076315

Russ, T. C., Hannah, J., Batty, G. D., Booth, C. C., Deary, I. J., & Starr, J. M. (2017). Childhood Cognitive Ability and Incident Dementia: The 1932 Scottish Mental Survey Cohort into their 10th Decade. *Epidemiology (Cambridge, Mass.), 28*(3), 361-364. doi:10.1097/EDE.0000000000000626

Rytwinski, N. K., Scur, M. D., Feeny, N. C., & Youngstrom, E. A. (2013). The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress, 26*(3), 299-309. doi:10.1002/jts.21814

Saez-Fonseca, J. A., Lee, L., & Walker, Z. (2007). Long-term outcome of depressive pseudodementia in the elderly. *J Affect Disord, 101*(1-3), 123-129. doi:10.1016/j.jad.2006.11.004

Salthouse, T. A. (2011). What cognitive abilities are involved in trail-making performance? *Intelligence, 39*(4), 222-232. doi:10.1016/j.intell.2011.03.001

Samuelson, K. W. (2011). Post-traumatic stress disorder and declarative memory functioning: a review. *Dialogues in clinical neuroscience, 13*(3), 346-351. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22033732 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3182004/

Samuelson, K. W., Neylan, T. C., Metzler, T. J., Lenoci, M., Rothlind, J., Henn-Haase, C., . . . Marmar, C. R. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology, 20*(6), 716-726. doi:10.1037/0894-4105.20.6.716

Sanchez-de-la-Torre, M., Campos-Rodriguez, F., & Barbe, F. (2013). Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med, 1*(1), 61-72. doi:10.1016/s2213-2600(12)70051-6

Sando, S. B., Melquist, S., Cannon, A., Hutton, M., Sletvold, O., Saltvedt, I., . . . Aasly, J. (2008a). Risk-reducing effect of education in Alzheimer's disease. *Int J Geriatr Psychiatry, 23*(11), 1156-1162. doi:10.1002/gps.2043

Sando, S. B., Melquist, S., Cannon, A., Hutton, M. L., Sletvold, O., Saltvedt, I., . . . Aasly, J. O. (2008b). APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from central Norway. *BMC neurology, 8*, 9-9. doi:10.1186/1471-2377-8-9

Santos Monteiro, T., Beets, I. A. M., Boisgontier, M. P., Gooijers, J., Pauwels, L., Chalavi, S., . . . Swinnen, S. P. (2017). Relative cortico-subcortical shift in brain activity but preserved training-induced neural modulation in older adults during bimanual motor learning. *Neurobiol Aging, 58*, 54-67. doi:10.1016/j.neurobiolaging.2017.06.004

Sarac-Hadzihalilović, A., Kulenović, A., & Kucukalić, A. (2008). Stress, memory and Bosnian war veterans. *Bosnian journal of basic medical sciences, 8*(2), 135-140. doi:10.17305/bjbms.2008.2968

Sareen, J. (2014). Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. *Canadian journal of psychiatry. Revue canadienne de psychiatrie, 59*(9), 460-467. doi:10.1177/070674371405900902

Satizabal, C. L., Beiser, A. S., Chouraki, V., Chene, G., Dufouil, C., & Seshadri, S. (2016). Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med, 374*(6), 523-532. doi:10.1056/NEJMoa1504327

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273-295. doi:10.1037/0894-4105.7.3.273

Savva, G. M., Wharton, S. B., Ince, P. G., Forster, G., Matthews, F. E., & Brayne, C. (2009). Age, neuropathology, and dementia. *N Engl J Med, 360*(22), 2302-2309. doi:10.1056/NEJMoa0806142

Scarmeas, N., & Stern, Y. (2003). Cognitive reserve and lifestyle. *Journal of clinical and experimental neuropsychology, 25*(5), 625-633. doi:10.1076/jcen.25.5.625.14576

Schmand, B., Smit, J., Lindeboom, J., Smits, C., Hooijer, C., Jonker, C., & Deelman, B. (1997). Low education is a genuine risk factor for accelerated memory decline and dementia. *Journal of clinical epidemiology, 50*(9), 1025-1033. doi:10.1016/s0895-4356(97)00121-2

Schoenberg, B. S. (1986). Epidemiology of Alzheimer's disease and other dementing illnesses. *Journal of Chronic Diseases, 39*(12), 1095-1104. doi:10.1016/0021-9681(86)90142-6

Schoenberg, B. S., Anderson, D. W., & Haerer, A. F. (1985). Severe dementia. Prevalence and clinical features in a biracial US population. *Arch Neurol, 42*(8), 740-743. doi:10.1001/archneur.1985.04210090004002

Scholl, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., . . . Jagust, W. J. (2016). PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron, 89*(5), 971-982. doi:10.1016/j.neuron.2016.01.028

Schrijvers, E. M., Verhaaren, B. F., Koudstaal, P. J., Hofman, A., Ikram, M. A., & Breteler, M. M. (2012). Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology, 78*(19), 1456-1463. doi:10.1212/WNL.0b013e3182553be6

Schuff, N., Neylan, T. C., Fox-Bosetti, S., Lenoci, M., Samuelson, K. W., Studholme, C., . . . Weiner, M. W. (2008). Abnormal N-acetylaspartate in hippocampus and anterior cingulate in posttraumatic stress disorder. *Psychiatry research, 162*(2), 147-157. doi:10.1016/j.pscychresns.2007.04.011

Scott, J. C., Matt, G. E., Wrocklage, K. M., Crnich, C., Jordan, J., Southwick, S. M., . . . Schweinsburg, B. C. (2015a). A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull, 141*(1), 105-140. doi:10.1037/a0038039

Scott, J. C., Matt, G. E., Wrocklage, K. M., Crnich, C., Jordan, J., Southwick, S. M., . . . Schweinsburg, B. C. (2015b). A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull, 141*(1), 105-140. doi:10.1037/a0038039

Seal, K. H., Bertenthal, D., Miner, C. R., Sen, S., & Marmar, C. (2007). Bringing the war back home: mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs facilities. *Arch Intern Med, 167*(5), 476-482. doi:10.1001/archinte.167.5.476

Semple, W. E., Goyer, P., McCormick, R., Morris, E., Compton, B., Muswick, G., . . . et al. (1993). Preliminary report: brain blood flow using PET in patients with posttraumatic stress disorder and substance-abuse histories. *Biol Psychiatry, 34*(1-2), 115-118.

Semple, W. E., Goyer, P. F., McCormick, R., Donovan, B., Muzic, R. F., Jr., Rugle, L., . . . Schulz, S. C. (2000). Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry, 63*(1), 65-74.

Shalev, A. Y., Freedman, S., Peri, T., Brandes, D., Sahar, T., Orr, S. P., & Pitman, R. K. (1998). Prospective study of posttraumatic stress disorder and depression following trauma. *Am J Psychiatry, 155*(5), 630-637. doi:10.1176/ajp.155.5.630

Sharma, R. A., Varga, A. W., Bubu, O. M., Pirraglia, E., Kam, K., Parekh, A., . . . Osorio, R. S. (2018). Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly. A Longitudinal Study. *American journal of respiratory and critical care medicine, 197*(7), 933-943. doi:10.1164/rccm.201704-0704OC

Sharp, E. S., & Gatz, M. (2011). Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord, 25*(4), 289-304. doi:10.1097/WAD.0b013e318211c83c

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health, 5*(1-2), 165-173. doi:10.1300/J018v05n01_09

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the United States of America, 93*(9), 3908-3913. doi:10.1073/pnas.93.9.3908

Shin, L. M., Kosslyn, S. M., McNally, R. J., Alpert, N. M., Thompson, W. L., Rauch, S. L., . . . Pitman, R. K. (1997). Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. *Arch Gen Psychiatry, 54*(3), 233-241. doi:10.1001/archpsyc.1997.01830150057010

Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., . . . Pitman, R. K. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *Am J Psychiatry, 156*(4), 575-584. doi:10.1176/ajp.156.4.575

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., . . . Pitman, R. K. (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry, 61*(2), 168-176. doi:10.1001/archpsyc.61.2.168

Shin, L. M., Whalen, P. J., Pitman, R. K., Bush, G., Macklin, M. L., Lasko, N. B., . . . Rauch, S. L. (2001). An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry, 50*(12), 932-942. doi:10.1016/s0006-3223(01)01215-x

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., . . . Rauch, S. L. (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Archives of general psychiatry, 62*(3), 273-281. doi:10.1001/archpsyc.62.3.273

Shipherd, J. C., & Beck, J. G. (2005). The role of thought suppression in posttraumatic stress disorder. *Behavior Therapy, 36*(3), 277-287. doi:https://doi.org/10.1016/S0005-7894(05)80076-0

Silverman, D. H., Gambhir, S. S., Huang, H. W., Schwimmer, J., Kim, S., Small, G. W., . . . Phelps, M. E. (2002). Evaluating early dementia with and without assessment of regional cerebral metabolism by PET: a comparison of predicted costs and benefits. *J Nucl Med, 43*(2), 253-266.

Silverman, D. H., Small, G. W., Chang, C. Y., Lu, C. S., Kung De Aburto, M. A., Chen, W., . . . Phelps, M. E. (2001). Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome. *Jama, 286*(17), 2120-2127. doi:10.1001/jama.286.17.2120

Small, G. W., Donohue, J. A., & Brooks, R. L. (1998). An economic evaluation of donepezil in the treatment of Alzheimer's disease. *Clin Ther, 20*(4), 838-850.

Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011). A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nat Rev Neurosci, 12*(10), 585-601. doi:10.1038/nrn3085

Smallwood, R. G., Vitiello, M. V., Giblin, E. C., & Prinz, P. N. (1983). Sleep apnea: relationship to age, sex, and Alzheimer's dementia. *Sleep, 6*(1), 16-22. doi:10.1093/sleep/6.1.16

Smith, J. S., & Kiloh, L. G. (1981). The investigation of dementia: results in 200 consecutive admissions. *Lancet, 1*(8224), 824-827. doi:10.1016/s0140-6736(81)92692-1

Smith, M. J., Kwok, J. B., McLean, C. A., Kril, J. J., Broe, G. A., Nicholson, G. A., . . . Brooks, W. S. (2001). Variable phenotype of Alzheimer's disease with spastic paraparesis. *Ann Neurol, 49*(1), 125-129.

Smith, R. (2002). In search of "non-disease". *BMJ (Clinical research ed.), 324*(7342), 883-885. doi:10.1136/bmj.324.7342.883

Smith, T., Gildeh, N., & Holmes, C. (2007). The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Canadian journal of psychiatry. Revue canadienne de psychiatrie, 52*(5), 329-332. doi:10.1177/070674370705200508

Snowdon, D. A. (1997). Aging and Alzheimer's Disease: Lessons From the Nun Study1. *The Gerontologist, 37*(2), 150-156. doi:10.1093/geront/37.2.150 %J The Gerontologist

Snowdon, D. A. (2003). Healthy aging and dementia: findings from the Nun Study. *Ann Intern Med, 139*(5 Pt 2), 450-454. doi:10.7326/0003-4819-139-5_part_2-200309021-00014

Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *Jama, 277*(10), 813-817.

Snowdon, D. A., Kemper, S. J., Mortimer, J. A., Greiner, L. H., Wekstein, D. R., & Markesbery, W. R. (1996). Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *Jama, 275*(7), 528-532.

Soldan, A., Pettigrew, C., Lu, Y., Wang, M. C., Selnes, O., Albert, M., . . . Miller, M. I. (2015). Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical Alzheimer's disease. *Hum Brain Mapp, 36*(7), 2826-2841. doi:10.1002/hbm.22810

Speicher, S. M., Walter, K. H., & Chard, K. M. (2014). Interdisciplinary residential treatment of posttraumatic stress disorder and traumatic brain injury: effects on symptom severity and occupational performance and satisfaction. *The American journal of occupational therapy : official publication of the American*

Occupational Therapy Association, 68(4), 412-421. doi:10.5014/ajot.2014.011304

Spillantini, M. G., Bird, T. D., & Ghetti, B. (1998). Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies. *Brain Pathol, 8*(2), 387-402.

Spinhoven, P., Penninx, B. W., van Hemert, A. M., de Rooij, M., & Elzinga, B. M. (2014). Comorbidity of PTSD in anxiety and depressive disorders: prevalence and shared risk factors. *Child Abuse Negl, 38*(8), 1320-1330. doi:10.1016/j.chiabu.2014.01.017

Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M., . . . Resnick, S. M. (2013). Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol, 70*(12), 1537-1543. doi:10.1001/jamaneurol.2013.4258

Stancu, I. C., Vasconcelos, B., Terwel, D., & Dewachter, I. (2014). Models of beta-amyloid induced Tau-pathology: the long and "folded" road to understand the mechanism. *Mol Neurodegener, 9*, 51. doi:10.1186/1750-1326-9-51

Starcevic, A., Postic, S., Radojicic, Z., Starcevic, B., Milovanovic, S., Ilankovic, A., . . . Radonjic, V. (2014). Volumetric analysis of amygdala, hippocampus, and prefrontal cortex in therapy-naive PTSD participants. *BioMed research international, 2014*, 968495-968495. doi:10.1155/2014/968495

Steenkamp, M. M., Schlenger, W. E., Corry, N., Henn-Haase, C., Qian, M., Li, M., . . . Marmar, C. (2017). Predictors of PTSD 40 years after combat: Findings from the National Vietnam Veterans longitudinal study. *Depression and Anxiety, 34*(8), 711-722. doi:10.1002/da.22628

Stein, M. B., & McAllister, T. W. (2009). Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *The American journal of psychiatry, 166*(7), 768-776. doi:10.1176/appi.ajp.2009.08101604

Stein, M. B., Walker, J. R., Hazen, A. L., & Forde, D. R. (1997). Full and partial posttraumatic stress disorder: findings from a community survey. *The American journal of psychiatry, 154*(8), 1114-1119. doi:10.1176/ajp.154.8.1114

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society : JINS, 8*(3), 448-460. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11939702

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *Jama, 271*(13), 1004-1010.

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., . . . van Heertum, R. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral cortex (New York, N.Y. : 1991), 15*(4), 394-402. doi:10.1093/cercor/bhh142

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed*. New York, NY, US: Oxford University Press.

Summerfield, D. (2001). The invention of post-traumatic stress disorder and the social usefulness of a psychiatric category. *BMJ, 322*(7278), 95-98. doi:10.1136/bmj.322.7278.95

Sumner, J. A., Hagan, K., Grodstein, F., Roberts, A. L., Harel, B., & Koenen, K. C. (2017). Posttraumatic stress disorder symptoms and cognitive function in a large cohort of middle-aged women. *Depress Anxiety, 34*(4), 356-366. doi:10.1002/da.22600

Tan, Z. S., Spartano, N. L., Beiser, A. S., DeCarli, C., Auerbach, S. H., Vasan, R. S., & Seshadri, S. (2017). Physical Activity, Brain Volume, and Dementia Risk: The Framingham Study. *The journals of gerontology. Series A, Biological sciences and medical sciences, 72*(6), 789-795. doi:10.1093/gerona/glw130

Tang, B., Deng, Q., Glik, D., Dong, J., & Zhang, L. (2017). A Meta-Analysis of Risk Factors for Post-Traumatic Stress Disorder (PTSD) in Adults and Children after Earthquakes. *International journal of environmental research and public health, 14*(12), 1537. doi:10.3390/ijerph14121537

Tate, D. F., Neeley, E. S., Norton, M. C., Tschanz, J. T., Miller, M. J., Wolfson, L., . . . Bigler, E. D. (2011). Intracranial volume and dementia: some evidence in support of the cerebral reserve hypothesis. *Brain research, 1385*, 151-162. doi:10.1016/j.brainres.2010.12.038

Taylor, S., Wald, J., & Asmundson, G. J. G. (2006). Factors Associated with Occupational Impairment in People Seeking Treatment for Posttraumatic Stress Disorder. *Canadian Journal of Community Mental Health, 25*(2), 289-301. doi:10.7870/cjcmh-2006-0026

Terry, R. D. (1986). Interrelations among the lesions of normal and abnormal aging of the brain. *Prog Brain Res, 70*, 41-48. doi:10.1016/s0079-6123(08)64296-x

Thal, D. R., Rub, U., Orantes, M., & Braak, H. (2002). Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology, 58*(12), 1791-1800. doi:10.1212/wnl.58.12.1791

Thompson, W. W., Gottesman, I. I., & Zalewski, C. (2006). Reconciling disparate prevalence rates of PTSD in large samples of US male Vietnam veterans and their controls. *BMC psychiatry, 6*, 19-19. doi:10.1186/1471-244X-6-19

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol, 14*(2), 167-177.

Tortella-Feliu, M., Fullana, M. A., Pérez-Vigil, A., Torres, X., Chamorro, J., Littarelli, S. A., . . . Fernández de la Cruz, L. (2019). Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. *Neuroscience & Biobehavioral Reviews, 107*, 154-165. doi:https://doi.org/10.1016/j.neubiorev.2019.09.013

Tulving, E. (1985). Memory and consciousness. *Canadian Psychology/Psychologie canadienne, 26*(1), 1-12. doi:10.1037/h0080017

Uddo, M., Vasterling, J. J., Brailey, K., & Sutker, P. B. (1993). Memory and attention in combat-related post-traumatic stress disorder (PTSD). *Journal of Psychopathology and Behavioral Assessment, 15*(1), 43-52. doi:10.1007/BF00964322

Ullman, M. T. (2004). Contributions of memory circuits to language: the declarative/procedural model. *Cognition, 92*(1-2), 231-270. doi:10.1016/j.cognition.2003.10.008

Unverzagt, F. W., McClure, L. A., Wadley, V. G., Jenny, N. S., Go, R. C., Cushman, M., . . . Howard, G. (2011). Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology, 77*(19), 1729-1736. doi:10.1212/WNL.0b013e318236ef23

van den Berk-Clark, C., Secrest, S., Walls, J., Hallberg, E., Lustman, P. J., Schneider, F. D., & Scherrer, J. F. (2018). Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity, and co-occuring smoking: A systematic review and meta-analysis. *Health Psychol, 37*(5), 407-416. doi:10.1037/hea0000593

van Zelst, W. H., de Beurs, E., Beekman, A. T., Deeg, D. J., & van Dyck, R. (2003). Prevalence and risk factors of posttraumatic stress disorder in older adults. *Psychother Psychosom, 72*(6), 333-342. doi:10.1159/000073030

Vasterling, J. J., & Arditte Hall, K. A. (2018). Neurocognitive and Information Processing Biases in Posttraumatic Stress Disorder. *Curr Psychiatry Rep, 20*(11), 99. doi:10.1007/s11920-018-0964-1

Vasterling, J. J., Brailey, K., Constans, J. I., & Sutker, P. B. (1998). Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology, 12*(1), 125-133. doi:10.1037//0894-4105.12.1.125

Vasterling, J. J., Brailey, K., & Sutker, P. B. (2000). Olfactory Identification in Combat-Related Posttraumatic Stress Disorder. *Journal of Traumatic Stress, 13*(2), 241-253. doi:10.1023/A:1007754611030

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A. N., Jr., & Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology, 16*(1), 5-14.

Vasterling, J. J., Proctor, S. P., Amoroso, P., Kane, R., Heeren, T., & White, R. F. (2006). Neuropsychological outcomes of army personnel following deployment to the Iraq war. *Jama, 296*(5), 519-529. doi:10.1001/jama.296.5.519

Vemuri, P., Lesnick, T. G., Przybelski, S. A., Knopman, D. S., Preboske, G. M., Kantarci, K., . . . Jack, C. R., Jr. (2015a). Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain, 138*(3), 761-771. doi:10.1093/brain/awu393 %J Brain

Vemuri, P., Lesnick, T. G., Przybelski, S. A., Knopman, D. S., Preboske, G. M., Kantarci, K., . . . Jack, C. R., Jr. (2015b). Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain, 138*(Pt 3), 761-771. doi:10.1093/brain/awu393

Venegas, J., & Clark, E. (2011). Wechsler Test of Adult Reading. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 2693-2694). New York, NY: Springer New York.

Vermetten, E., Vythilingam, M., Southwick, S. M., Charney, D. S., & Bremner, J. D. (2003). Long-term treatment with paroxetine increases verbal declarative

memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry, 54*(7), 693-702. doi:10.1016/s0006-3223(03)00634-6

Villarreal, G., Hamilton, D. A., Petropoulos, H., Driscoll, I., Rowland, L. M., Griego, J. A., . . . Brooks, W. M. (2002). Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. *Biol Psychiatry, 52*(2), 119-125. doi:10.1016/s0006-3223(02)01359-8

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., . . . Masters, C. L. (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol, 12*(4), 357-367. doi:10.1016/s1474-4422(13)70044-9

Villemagne, V. L., Furumoto, S., Fodero-Tavoletti, M., Harada, R., Mulligan, R. S., Kudo, Y., . . . Okamura, N. (2012). The challenges of tau imaging. *7*(4), 409-421. doi:10.2217/fnl.12.34

Villemagne, V. L., Pike, K. E., Chetelat, G., Ellis, K. A., Mulligan, R. S., Bourgeat, P., . . . Rowe, C. C. (2011). Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. *Ann Neurol, 69*(1), 181-192. doi:10.1002/ana.22248

Villemagne, V. L., Pike, K. E., Darby, D., Maruff, P., Savage, G., Ng, S., . . . Rowe, C. C. (2008). Abeta deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. *Neuropsychologia, 46*(6), 1688-1697. doi:10.1016/j.neuropsychologia.2008.02.008

Viticchi, G., Falsetti, L., Buratti, L., Sajeva, G., Luzzi, S., Bartolini, M., . . . Silvestrini, M. (2017). Framingham Risk Score and the Risk of Progression from Mild Cognitive Impairment to Dementia. *J Alzheimers Dis, 59*(1), 67-75. doi:10.3233/jad-170160

Wahba, H. (2004). The antipyretic effect of ibuprofen and acetaminophen in children. *Pharmacotherapy, 24*(2), 280-284. doi:10.1592/phco.24.2.280.33138

Wallace, A., & Bucks, R. S. (2013). Memory and obstructive sleep apnea: a meta-analysis. *Sleep, 36*(2), 203-220. doi:10.5665/sleep.2374

Wang, F., Mortimer, J. A., Ding, D., Luo, J., Zhao, Q., Liang, X., . . . Hong, Z. (2019). Smaller Head Circumference Combined with Lower Education Predicts High Risk of Incident Dementia: The Shanghai Aging Study. *Neuroepidemiology, 53*(3-4), 152-161. doi:10.1159/000501103

Wang, T. Y., Wei, H. T., Liou, Y. J., Su, T. P., Bai, Y. M., Tsai, S. J., . . . Chen, M. H. (2016). Risk for developing dementia among patients with posttraumatic stress disorder: A nationwide longitudinal study. *J Affect Disord, 205*, 306-310. doi:10.1016/j.jad.2016.08.013

Ward, A., Arrighi, H. M., Michels, S., & Cedarbaum, J. M. (2012). Mild cognitive impairment: disparity of incidence and prevalence estimates. *Alzheimers Dement, 8*(1), 14-21. doi:10.1016/j.jalz.2011.01.002

Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician-administered PTSD scale: a review of the first ten years of research. *Depress Anxiety, 13*(3), 132-156.

Wechsler, D. (1987). Wechsler Memory Scale-Revised. *Psychological Corporation*. Retrieved from https://ci.nii.ac.jp/naid/10008745172/en/

Weiler, M., Casseb, R. F., de Campos, B. M., de Ligo Teixeira, C. V., Carletti-Cassani, A. F. M. K., Vicentini, J. E., . . . Castellano, G. (2018). Cognitive Reserve Relates to

Functional Network Efficiency in Alzheimer's Disease. *Frontiers in aging neuroscience, 10*, 255-255. doi:10.3389/fnagi.2018.00255

Weiner, M. W., Harvey, D., Hayes, J., Landau, S. M., Aisen, P. S., Petersen, R. C., . . . Neylan, T. C. (2017). Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary Report. *Alzheimers Dement (N Y), 3*(2), 177-188. doi:10.1016/j.trci.2017.02.005

Welberry, H. J., Brodaty, H., Hsu, B., Barbieri, S., & Jorm, L. R. (2020). Measuring dementia incidence within a cohort of 267,153 older Australians using routinely collected linked administrative data. *Scientific Reports, 10*(1), 8781. doi:10.1038/s41598-020-65273-w

Whalley, L. J., Starr, J. M., Athawes, R., Hunter, D., Pattie, A., & Deary, I. J. (2000). Childhood mental ability and dementia. *Neurology, 55*(10), 1455-1459. doi:10.1212/wnl.55.10.1455

Whitmer, R. A., Gustafson, D. R., Barrett-Connor, E., Haan, M. N., Gunderson, E. P., & Yaffe, K. (2008). Central obesity and increased risk of dementia more than three decades later. *Neurology, 71*(14), 1057-1064. doi:10.1212/01.wnl.0000306313.89165.ef

Wignall, E. L., Dickson, J. M., Vaughan, P., Farrow, T. F., Wilkinson, I. D., Hunter, M. D., & Woodruff, P. W. (2004). Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. *Biol Psychiatry, 56*(11), 832-836. doi:10.1016/j.biopsych.2004.09.015

Wild, J., & Gur, R. C. (2008). Verbal memory and treatment response in post-traumatic stress disorder. *Br J Psychiatry, 193*(3), 254-255. doi:10.1192/bjp.bp.107.045922

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., . . . Group, A. S. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA, 296*(23), 2805-2814. doi:10.1001/jama.296.23.2805

Willner, P. (1984). The validity of animal models of depression. *Psychopharmacology (Berl), 83*(1), 1-16. doi:10.1007/bf00427414

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., . . . Bennett, D. A. (2007). Loneliness and Risk of Alzheimer Disease. *Archives of General Psychiatry, 64*(2), 234-240. doi:10.1001/archpsyc.64.2.234

Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *Jama, 287*(6), 742-748. doi:10.1001/jama.287.6.742

Wisniewski, K. E., Wisniewski, H. M., & Wen, G. Y. (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol, 17*(3), 278-282. doi:10.1002/ana.410170310

Witvliet, C. v. O., Ludwig, T. E., & Laan, K. L. V. (2001). Granting Forgiveness or Harboring Grudges: Implications for Emotion, Physiology, and Health. *Psychological Science, 12*(2), 117-123. doi:10.1111/1467-9280.00320

Wolf, H., Ecke, G. M., Bettin, S., Dietrich, J., & Gertz, H.-J. (2000). Do white matter changes contribute to the subsequent development of dementia in patients with mild cognitive impairment? A longitudinal study. *International Journal of Geriatric Psychiatry, 15*(9), 803-812. doi:10.1002/1099-1166(200009)15:9<803::AID-GPS190>3.0.CO;2-W

Wolf, H., Julin, P., Gertz, H.-J., Winblad, B., & Wahlund, L.-O. (2004). Intracranial volume in mild cognitive impairment, Alzheimer's disease and vascular dementia: evidence for brain reserve? *International journal of geriatric psychiatry, 19*(10), 995-1007. doi:10.1002/gps.1205

Wolf, P. A., D'Agostino, R. B., Belanger, A. J., & Kannel, W. B. (1991). Probability of stroke: a risk profile from the Framingham Study. *Stroke, 22*(3), 312-318. doi:10.1161/01.str.22.3.312

Woodward, S. H., Kaloupek, D. G., Streeter, C. C., Kimble, M. O., Reiss, A. L., Eliez, S., . . . Arsenault, N. J. (2007). Brain, skull, and cerebrospinal fluid volumes in adult posttraumatic stress disorder. *J Trauma Stress, 20*(5), 763-774. doi:10.1002/jts.20241

Woodward, S. H., Kaloupek, D. G., Streeter, C. C., Martinez, C., Schaer, M., & Eliez, S. (2006). Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry, 59*(7), 582-587. doi:10.1016/j.biopsych.2005.07.033

Woon, F. L., & Hedges, D. W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus, 18*(8), 729-736. doi:10.1002/hipo.20437

World Health, O. (2004). *ICD-10 : international statistical classification of diseases and related health problems / World Health Organization*. Geneva: World Health Organization.

World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. (2013). *Jama, 310*(20), 2191-2194. doi:10.1001/jama.2013.281053

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013a). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373-377. doi:10.1126/science.1241224

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013b). Sleep drives metabolite clearance from the adult brain. *Science (New York, N.Y.), 342*(6156), 373-377. doi:10.1126/science.1241224

Xu, W., Tan, L., Wang, H. F., Tan, M. S., Tan, L., Li, J. Q., . . . Yu, J. T. (2016). Education and Risk of Dementia: Dose-Response Meta-Analysis of Prospective Cohort Studies. *Mol Neurobiol, 53*(5), 3113-3123. doi:10.1007/s12035-015-9211-5

Xue, C., Ge, Y., Tang, B., Liu, Y., Kang, P., Wang, M., & Zhang, L. (2015). A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans. *PLoS One, 10*(3), e0120270. doi:10.1371/journal.pone.0120270

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K. E., Neylan, T., . . . Marmar, C. (2010). Posttraumatic stress disorder and risk of dementia among US veterans. *Arch Gen Psychiatry, 67*(6), 608-613. doi:10.1001/archgenpsychiatry.2010.61

Yaffe, K., Weston, A., Graff-Radford, N. R., Satterfield, S., Simonsick, E. M., Younkin, S. G., . . . Harris, T. B. (2011). Association of Plasma β-Amyloid Level and Cognitive Reserve With Subsequent Cognitive Decline. *JAMA, 305*(3), 261-266. doi:10.1001/jama.2010.1995

Yamasue, H., Kasai, K., Iwanami, A., Ohtani, T., Yamada, H., Abe, O., . . . Kato, N. (2003). Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci U S A, 100*(15), 9039-9043. doi:10.1073/pnas.1530467100

Yehuda, R., Golier, J. A., Halligan, S. L., Meaney, M., & Bierer, L. M. (2004). The ACTH response to dexamethasone in PTSD. *Am J Psychiatry, 161*(8), 1397-1403. doi:10.1176/appi.ajp.161.8.1397

Yehuda, R., Golier, J. A., Tischler, L., Stavitsky, K., & Harvey, P. D. (2005a). Learning and memory in aging combat veterans with PTSD. *J Clin Exp Neuropsychol, 27*(4), 504-515. doi:10.1080/138033990520223

Yehuda, R., Golier, J. A., Tischler, L., Stavitsky, K., & Harvey, P. D. (2005b). Learning and Memory in Aging Combat Veterans with PTSD. *Journal of Clinical and Experimental Neuropsychology, 27*(4), 504-515. doi:10.1080/138033990520223

Yehuda, R., Harvey, P. D., Golier, J. A., Newmark, R. E., Bowie, C. R., Wohltmann, J. J., . . . Buchsbaum, M. S. (2009). Changes in relative glucose metabolic rate following cortisol administration in aging veterans with posttraumatic stress disorder: an FDG-PET neuroimaging study. *J Neuropsychiatry Clin Neurosci, 21*(2), 132-143. doi:10.1176/appi.neuropsych.21.2.132

10.1176/jnp.2009.21.2.132

Yehuda, R., Keefe, R. S., Harvey, P. D., Levengood, R. A., Gerber, D. K., Geni, J., & Siever, L. J. (1995). Learning and memory in combat veterans with posttraumatic stress disorder. *Am J Psychiatry, 152*(1), 137-139. doi:10.1176/ajp.152.1.137

Yehuda, R., Southwick, S. M., & Giller, E. L. (1992). Exposure to atrocities and severity of chronic posttraumatic stress disorder in Vietnam combat veterans. *The American Journal of Psychiatry, 149*(3), 333-336. doi:10.1176/ajp.149.3.333

Yehuda, R., Tischler, L., Golier, J. A., Grossman, R., Brand, S. R., Kaufman, S., & Harvey, P. D. (2006). Longitudinal assessment of cognitive performance in Holocaust survivors with and without PTSD. *Biol Psychiatry, 60*(7), 714-721. doi:10.1016/j.biopsych.2006.03.069

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res, 17*(1), 37-49.

Yesavage, J. A., Kinoshita, L. M., Kimball, T., Zeitzer, J., Friedman, L., Noda, A., . . . O'Hara, R. (2012). Sleep-Disordered Breathing in Vietnam Veterans with Posttraumatic Stress Disorder. *The American Journal of Geriatric Psychiatry, 20*(3), 199-204. doi:https://doi.org/10.1097/JGP.0b013e3181e446ea

Zalewski, C., Thompson, W., & Gottesman, I. I. (1994). Comparison of Neuropsychological Test Performance in PTSD, Generalized Anxiety Disorder, and Control Vietnam Veterans. *Assessment, 1*(2), 133-142. doi:10.1177/1073191194001002003

Zandieh, S., Bernt, R., Knoll, P., Wenzel, T., Hittmair, K., Haller, J., . . . Mirzaei, S. (2016). Analysis of the Metabolic and Structural Brain Changes in Patients With Torture-Related Post-Traumatic Stress Disorder (TR-PTSD) Using (1)(8)F-FDG PET and MRI. *Medicine (Baltimore), 95*(15), e3387. doi:10.1097/md.0000000000003387

Zeitlin, S. B., & McNally, R. J. (1991). Implicit and explicit memory bias for threat in post-traumatic stress disorder. *Behaviour Research and Therapy, 29*(5), 451-457. doi:10.1016/0005-7967(91)90129-Q

Zekry, D., Duyckaerts, C., Moulias, R., Belmin, J., Geoffre, C., Herrmann, F., & Hauw, J. J. (2002). Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. *Acta Neuropathol, 103*(5), 481-487. doi:10.1007/s00401-001-0493-5

Zhang, S., Smailagic, N., Hyde, C., Noel-Storr, A. H., Takwoingi, Y., McShane, R., & Feng, J. (2014). (11)C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*(7), Cd010386. doi:10.1002/14651858.CD010386.pub2

Zhu, Y., Du, R., Zhu, Y., Shen, Y., Zhang, K., Chen, Y., . . . Tian, M. (2016). PET Mapping of Neurofunctional Changes in a Posttraumatic Stress Disorder Model. *J Nucl Med, 57*(9), 1474-1477. doi:10.2967/jnumed.116.173443

Other references

Australian Government. Australian Institute of Health and Welfare. Cardiovascular disease. July 15, 2020.

Australian War Memorial. Vietnam War (1962-1975). Retrieved from https://www.awm.gov.au/articles/event/vietnam

Health status of Vietnam veterans volume IV Psychological and neuropsychological evaluation. U.S. Department of Health and Human Services. (1989). Retrieved from the Centers for Disease Control Center for Environmental Health and Injury Control Atlanta, Georgia. https://www.cdc.gov/nceh/veterans/default1c.htm

Australia lifts restrictions for women in combat roles. CNN (2016). Retrieved from https://edition.cnn.com/2011/09/27/world/asia/australia-women-combat/index.html.

Grinker, R. R. Spiegel, J. P. (1946). Men under stress. Philadelphia: Blakiston.

Kardiner, A., Spiegel, H. (1947). War Stress and Neurotic Illness. New York, NY: Paul B. Hoeber, Inc.

Richards, S., Sweet, R. (2009). Dementia. In Sadock BJ, Sadock VA, Ruiz P (Editors). Kaplan and Sadock's Comprehensive Textbook of Psychiatry. Pp 1191-1221. Philadelphia. Wolters Kluwer.

Shalev, A.Y, Marmar, C.R. (2017). Posttraumatic stress disorder. In Sadock BJ, Sadock VA, Ruiz P (Editors). Kaplan and Sadock's Comprehensive Textbook of Psychiatry, pp. 1817. Philadelphia. Wolters Kluwer.

Wechsler (2001). Wechsler test of adult reading. San Antonio, TX: Harcourt Assessment. The Psychological Corporation.

Wechsler, D. (1997). WAIS-III Administration and scoring manual. San Antonio, TX: The Psychological Association.

Wechsler, D. (1987). Wechsler Memory Scale-Revised. New York: Psychological Corporation.

Appendix

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Amyloid-β, Tau, and ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in Posttraumatic Stress Disorder

Alby Elias[a,b,*], Tia Cummins[a,c], Fiona Lamb[a], Regan Tyrrell[a], Vincent Dore[d], Rob Williams[c], Jeffrey V. Rosenfeld[e,f], Malcolm Hopwood[b], Victor L. Villemagne[a] and Christopher C. Rowe[a]
[a]*Department of Molecular Imaging and Therapy, Austin Health, The University of Melbourne, Melbourne, VIC, Australia*
[b]*Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia*
[c]*Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia*
[d]*Commonwealth Scientific and Industrial Research Organization (CSIRO), Australia*
[e]*Department of Surgery, Monash University, VIC, Australia*
[f]*Department of Neurosurgery, Alfred Hospital, Melbourne, VIC, Australia*

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Abstract.
Background: Epidemiological studies suggest a relationship between posttraumatic stress disorder (PTSD) and dementia.
Objective: This study assessed whether Alzheimer's disease (AD) imaging biomarkers were elevated in Vietnam veterans with PTSD.
Methods: The study compared cognition, amyloid-β, tau, regional brain metabolism and volumes, and the effect of *APOE* in 83 veterans with and without PTSD defined by the Clinician-Administered PTSD Scale.
Results: The PTSD group had significantly lower education, predicted premorbid IQ, total intracranial volume, and Montreal Cognitive Assessment score compared with the controls. There was no difference between the two groups in the imaging or genetic biomarkers for AD.
Conclusion: Our findings do not support an association between AD pathology and PTSD of up to 50 years duration. Measures to assess cognitive reserve, a factor that may delay the onset of dementia, were lower in the PTSD group compared with the controls and this may account for the previously observed higher incidence of dementia with PTSD.

Keywords: Alzheimer's disease, amyloid, biomarkers, dementia, positron emission tomography, posttraumatic stress disorder, tau

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a chronic and disabling condition with a lifetime prevalence of 1–9% in the general population and an increased prevalence in military veterans [1, 2]. Previous studies that provided compelling evidence for cognitive impairment in combat-related PTSD sparked a series of investigations that examined the association between PTSD and dementia in Vietnam veterans [3, 4]. Several epidemiological studies have recently demonstrated an increased incidence of dementia including Alzheimer's disease (AD) on clinical criteria in older veterans with PTSD com-

*Correspondence to: Alby Elias, 145 Studley St, Heidelberg, VIC, Australia. Tel.: +61 417325223; E-mail: alby.elias@unimelb.edu.au.

pared with those without PTSD [5–9]. Furthermore, structural and functional magnetic resonance imaging (MRI) studies have shown reduced volumes of structures involved in cognition such as hippocampi, amygdala, and anterior cingulate cortex along with reduced activity in the anterior cingulate cortex in PTSD [10, 11]. Metabolic imaging studies with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) have produced inconsistent findings in PTSD with a tendency to hypometabolism in anterior cingulate, limbic, and temporal regions [12]. These studies had small, middle aged cohorts. In contrast, more specific patterns of brain hypometabolism occur in most dementia syndromes [13]. Brain hypometabolism reflects synaptic dysfunction and loss and is regarded as a measure of neurodegeneration that may precede the onset of symptoms by several years [14, 15]. The hypometabolic findings characteristic of AD relate to posterior brain regions, in particular the posterior cingulate gyrus and parietotemporal cortex.

The previous studies did not examine the specific pathological biomarkers of AD, amyloid-β (Aβ) and tau, in PTSD. Deposition of extracellular neuritic plaques and intracellular neurofibrillary tangles is the pathological hallmark of AD [16]. Enabling *in vivo* and early detection of Aβ and tau using specific radioactive ligands, amyloid and tau PET represents a breakthrough in AD research. The uptake of these radioactive tracers is a proxy measure of Aβ and tau although not the same as the autopsy, which is the gold standard for AD diagnosis. Aβ plaques can be detected on PET up to 20 years before the onset of dementia due to AD [17, 18]. Compared with Aβ plaques, the progression of neurofibrillary tangles is believed to occur closer to the development of symptoms and consequently has shown a better correlation with neuronal damage and cognitive deterioration in patients with AD [19]. Current knowledge of the role of Aβ and tau in the pathogenesis of AD, although not fully understood, is expanding and the relationship may be best described as synergistic [20]. Animal studies have observed elevated Aβ in PTSD [21]. Exposure to psychological trauma and corticotrophin-releasing factor have been reported to enhance both Aβ plaque formation and tau phosphorylation [22].

A recent study by the Alzheimer's Disease Neuroimaging Initiative (ADNI) group in Vietnam veterans (ADNI-DOD study) did not find an increased risk of AD with PTSD according to the global Aβ burden estimated from ^{18}F-florbetapir PET [23]. Whether tau accumulation or other types of neurodegeneration explain the elevated incidence of dementia in PTSD remains unknown. The aim of this study was to use ^{18}F-florbetaben and ^{18}F-AV-1451 to quantify Aβ and tau burden, respectively, ^{18}F-FDG to estimate regional brain metabolism, and MRI to measure regional brain volume in Vietnam veterans with and without PTSD. Our hypothesis is that veterans with PTSD have increased AD pathology as detected by neuroimaging biomarkers for AD, and neurodegeneration prior to a diagnosis of mild cognitive impairment or dementia.

METHODS

Participant recruitment

The institutional review board of Austin Health, one of the major metropolitan hospitals in Melbourne, provided ethics approval and written informed consent was obtained from all participants.

Participants were Australian male Vietnam veterans recruited from the community via advertisement. Interested veterans went through preliminary screening. We applied the following exclusion criteria: substance abuse in the past six months, traumatic brain injury, psychosis, bipolar affective disorder, dementia, existing diagnosis of mild cognitive impairment (MCI), and any unstable medical condition that could have made participation difficult or have a significant impact on cognitive assessment. MCI and dementia were excluded to reduce recruitment bias and avoid confounding of the diagnosis of PTSD. Veterans who passed the initial screening had a face-to-face evaluation with a psychiatrist.

Brain imaging

All participants underwent 20-min PET scans acquired 90 min after a slow IV bolus administration of 250 MBq (±10%) of ^{18}F-florbetaben and 70 min after the injection of 370 MBq of ^{18}F-AV-1451. Scans were acquired on a Siemens PET/CT mCT128 and CT attenuation correction was applied. Image reconstruction used the Ordered Subset Expectation Maximization algorithm. There was no correction for partial volume effect. We analyzed the PET scans with the Computational Analysis of PET from AIBL and calculated standardized uptake value ratio (SUVR) of ^{18}F-florbetaben using cerebellar grey matter uptake as the reference to quantify global Aβ burden [24]. Amyloid burden was also calculated in

Centiloid units using the standard Centiloid method cortical region of interest normalized to whole cerebellum as previously described [25]. ^{18}Florbetaben scan was read visually by three readers and the classification into negative or positive scan was based on majority results. The visual inspection was based on brain amyloid plaque load, which was derived from the regional cortical tracer uptake in the four regions: lateral temporal cortex, frontal cortex, posterior cingulate cortex/precuneus, and parietal cortex. Typical transverse PET slices were judged as negative if the tracer uptake in the grey matter was lower than that of the white matter and positive if the uptake in the grey matter was equal to or more than that in the white matter. The SUVR of ^{18}F-AV-1451, using cerebellar grey matter uptake as the reference region, estimated global and regional tau deposition. We measured tau in the following regions: mesial temporal; temporoparietal; and rest of the neocortex.

A part of the data analyzed in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni.info.org.

For the acquisition of ^{18}F-FDG PET scan, participants fasted for four hours and then had an injection of 200 MBq of ^{18}F-FDG. As per standard practice, they remained in a quiet, darkened room for 30 min with eyes open in order to keep the occipital metabolism consistent. Acquisition was commenced 30 min after the injection on a Philips Allegro PET camera. A post-injection transmission scan for attenuation correction was performed. Acquisition time was 20 min. Reconstruction was performed with a RAMLA filter. SUVR was calculated for frontal, mesial temporal, and rest of the neocortex. Participants underwent 3-Tesla Siemens Trio brain MRI for the measurement of hippocampal volume and the total intracranial volume (TICV). A three-dimensional (3D) T1 magnetization-prepared rapid gradient echo (MPRAGE) was acquired with the following parameters: FoV = 260 × 256, Matrix = 240 × 256, 160 slices, 1.0 × 1.0 × 1.2 mm voxels, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°. The T1 weighted images were rigidly registered to the Montreal Neurological Institute (MNI) average brain and segmented into grey and white matter and cerebrospinal fluid space with Expectation Maximisation Segmentation algorithm. Partial tissue classification and cortical thickness were then estimated using a software Computational Quantification program [24]. The Harmonized Hippocampus protocol was used to define the hippocampus region of interest. Volumetry was adjusted for the TICV by dividing the regional volume by TICV.

Clinical and cognitive assessment

We used Clinician-Administered PTSD Scale (CAPS) - DSM-IV version to assess PTSD [26]. A score of 40 or more and a history of combat exposure constituted the inclusion criteria for the PTSD group. This score was based on the existing diagnostic utility data for a range of selected cut-off scores which indicated that a CAPS score of 40 had 93% sensitivity and 80% specificity for dichotomous classification of PTSD [27]. A CAPS score of 30 or less and military experience formed the inclusion criteria for the control group. We have chosen these scores to ensure a clear separation between the diagnostic groups and controls. Subjects who scored between 30 and 40 were excluded from the analysis based on the presumption that they had fluctuating and sub-threshold symptoms. The Geriatric Depression Scale (GDS) measured depressive symptoms [28]. Participants underwent *APOE* ε4 genotyping. A vascular risk factor score was calculated by giving one point to each of the following: hypertension, ischemic heart disease, previous history of stroke, atrial fibrillation, current smoking, diabetes mellitus, body mass index over 30, and hypercholesterolemia. Sum of all points gave cumulative vascular risk score. Veterans with mild, moderate, or severe traumatic brain injury according to the criteria set by the U.S Department of Defense (DoD) were excluded.

A standardized neuropsychological test battery assessed cognitive functions [29–35]. The following tests measured memory component: the delayed paragraph recall from the Logical Memory Test II, Rey Auditory Verbal Learning Test 30-min delay, and the Rey-Osterrieth Complex Figure Test (ROCFT) 30-min delay. We calculated a composite memory score from these three tests using standard deviation and mean scores from the control population. We used Trail Making Test part A to assess the visual orientation and processing speed, part B to measure executive function, Wechsler Adult Intelligence Scale to measure attention, categorical fluency test to assess semantic fluency, and ROCFT to assess visuospatial orientation and constructional skills. The Mini-Mental State Examination and the Montreal

Cognitive Assessment (MoCA) measured global cognitive function [36, 37]. Along with the measurement of attention, delayed recall, and visuospatial abilities, MOCA assesses executive function using an alternation task adapted from the Trail Making Test Part B, phonemic fluency task and two-item verbal abstraction task. Wechsler's Test of Adult Reading (WTAR) estimated premorbid Intelligent Quotient (IQ) [35]. WTAR was adjusted for age and then predicted IQ was calculated using published criteria.

Statistical analysis

The PTSD and the control groups were compared for the following outcome variables: ^{18}F-florbetaben SUVR and Centiloid units, ^{18}F-AV-1451 and ^{18}F-FDG SUVRs, MRI regional volumes, and cognitive test scores. Age, *APOE* ε4, and vascular risk factors were analyzed as covariates in a multivariable regression analysis because of their known association with amyloid retention. For this study, current PTSD was the explanatory variable for the primary analysis given *a priori* that it is the persistence of symptoms that is related to the risk of AD in late life. Life-time history of PTSD was also examined. The two-tailed results were corrected for multiple comparisons using the Benjamini-Hochberg procedure. Chi-square (χ^2) was used to analyze categorical variables, such as positive or negative ^{18}F-florbetaben scan, and *APOE* ε4 status. Pearson correlation test was performed for the whole sample to test correlation between the tracer SUVRs and CAPS scores. The analyses were performed on SPSS version 21. Using florbetapir Aβ PET results from normal controls in the ADNI study, we calculated that to detect a group difference with an effect size of 0.75, with 80% power at $\alpha = 0.05$, required 29 subjects in each group.

RESULTS

From 2014 March to May 2017, 169 male Vietnam veterans expressed interest in the study. 20 veterans later withdrew from the study for reasons of inconvenience and perceived distress. After excluding 66 veterans (including three veterans who had CAPS score between 30 and 40) for the reasons shown in Fig. 1, we collected the neuropsychological and PET data from the remaining 83 veterans. A diagnosis of lifetime PTSD was present in 53 veterans, and 30 vet-

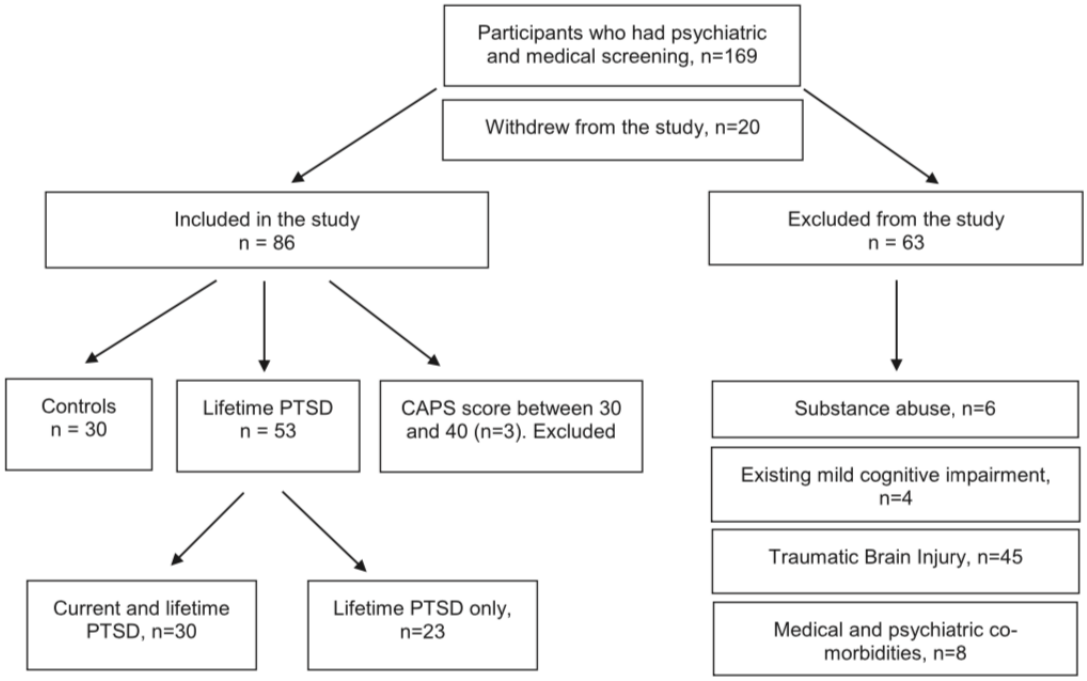

Fig. 1. Participants recruitment.

erans were controls. Among veterans with lifetime PTSD, a diagnosis of current PTSD was present in 30. All veterans experienced PTSD symptoms either during or soon after military service.

The participants' characteristics are shown in Table 1. The median current CAPS score for the PTSD group was 52.50 compared with 4 for the control group (Mann-Whitney U = 0.000, $p < 0.001$). Veterans with current PTSD were slightly younger than those without PTSD (PTSD group mean age: 67.80 ± 2.48 versus the control group mean age: 70.23 ± 5.46; $p = 0.043$; CI = 0.220–4.64; Cohen's d = 0.57). Median predicted premorbid IQ (104 versus 114; U = 201.00; $p < .001$) and years of education (11 versus 12; U = 305.00; $p = 0.043$) were significantly lower whereas the median GDS score (5.50 versus 1, U = 130.00, $p < .001$) was significantly higher in the PTSD group than in the controls. The TICV was significantly lower in the PTSD group than in the control group (1565.173 ± 1114.31 cm^3 versus 1674.12 ± 1474.64 cm^3; $p = 0.010$; CI = 33.59–184.307; Cohen's d = 0.40). The median vascular risk factor score did not differ significantly between the groups (1 versus 2, U = 384.50, $p = 0.318$). APOE ε4 carrier status was available for 55 (92%) participants, and at least one allele was present in 7 (24%) veterans with PTSD and 2 (9%) controls ($\chi^2 = 2.70$, $p = 0.10$).

PET imaging

There was no significant difference between the PTSD group and the controls in the mean SUVR of the Aβ tracer, ^{18}F-florbetaben ($p = 0.927$, Cohen's d = 0.02). According to the visual inspection of ^{18}F-florbetaben scans, 7 (21.8%) veterans with current PTSD and 4 (10.5%) veterans without PTSD had a positive scan. This difference was not significant ($\chi^2 = 0.57$, $p = 0.48$). In the multivariable regression analysis with ^{18}F-florbetaben SUVR as the dependent variable and current PTSD, age, *APOE* ε4, and vascular risk factors as the independent variables, current PTSD did not predict ^{18}F-florbetaben SUVR (standardized coefficient β = –0.093, $p = 0.513$), whereas *APOE* ε4 did ($R^2 = 0.126$, standardized coefficient β = 0.185, $p = 0.043$). The regional and global uptake of the tau tracer, ^{18}F-AV-1451 did not differ between the PTSD and control groups (Table 2). ^{18}F-AV1451 SUVR did not correlate with any cognitive score. There was no significant correlation between the severity of PTSD as measured by CAPS score and global or regional ^{18}F-AV-1451 SUVRs. There were no differences in the ^{18}F-FDG SUVRs between the groups (Table 2). There was no correlation between the severity of PTSD as measured by CAPS and ^{18}F-FDG SUVR in any region. We repeated the analysis for subjects with lifetime PTSD with and without cur-

Table 1
Participant characteristics

Variables	Controls ($n = 30$) Mean ± SD/Median (Interquartile Range)	Current PTSD ($n = 30$) Mean ± SD)/Median (Interquartile Range)	p (corrected)
Age	70.23 ± 5.46	67.80 ± 2.48	0.043
Predicted IQ	114 (5)	104 (12)	<0.001
Years of education	12.0 (5)	11 (4)	0.043
Total Intracranial Volume (cm^3)	1674.12 ± 1474.64	1565.17 ± 1114.31	0.01
GDS Score	1 (2)	5.50 (5)	<0.001

Table 2
PET Tracer binding expressed in SUVR

Tracers	Controls ($n = 30$) Median/mean (interquartile range)	Current PTSD ($n = 30$) Median/mean (interquartile range)	p
^{18}F-florbetaben	1.21 (0.13)	1.22 (0.16)	0.610
^{18}F-AV-1451 (mesial temporal)	1.16 (0.12)	1.21 (0.20)	0.804
^{18}F-AV-1451 (temporoparietal)	1.17 (0.11)	1.16 (0.18)	0.610
^{18}F-AV-1451 (rest of neocortex)	1.17 (0.11)	1.14 (0.16)	0.610
Global ^{18}F-AV-1451	1.13 (0.14)	1.10 (0.13)	0.620
^{18}F-fludeoxyglucose (mesial temporal)	0.75 ± 0.05	0.74 ± 0.04	0.344
^{18}F-fludeoxyglucose (frontal)	1.05 ± 0.08	1.03 ± 0.05	0.384
^{18}F-fludeoxyglucose (rest of neocortex)	1.06 ± 0.07	1.04 ± 0.06	0.303

rent PTSD ($n = 53$) against the same control group ($n = 30$). There was no significant difference in the uptake of any tracer globally or regionally between the two groups.

Adding the U.S. ADNI-DOD study amyloid PET data expanded the sample size to a total of 97 Vietnam veterans with PTSD and 85 controls. Centiloid units were calculated to allow the merging of scans obtained with the different Aβ PET tracers, florbetapir and florbetaben. The combined data did not reveal a significant difference between the two groups in the Centiloid values (PTSD Mean: 9.01 ± 20.73; versus Control Mean 14.37 ± 26.12 Cohen's d = 0.22; Median rank: 89.85 versus 93.39, $p = 0.651$; Mann-Whitney U = 3962.00). More veterans in the control group than in the PTSD group had a positive amyloid scan based on Centiloid score of 25 or more (13 versus 7, $\chi^2 = 7.47$, $p = 0.024$, uncorrected). With the additional ADNI data *APOE* ε4 was present in 23 veterans with PTSD and 17 veterans without PTSD ($\chi^2 = 0.567$, $p = 0.451$, uncorrected).

MRI results

Forty of the lifetime PTSD group including 30 with ongoing or current PTSD, and 25 controls underwent MRI. Others did not have MRI for reasons of inconvenience and metal safety. The TICV was slightly but significantly lower in the current PTSD group than in the control group (1565.173 ± 1114.31 cm^3 versus 1674.12 ± 1474.64 cm^3; $p = 0.01$; CI = 33.59–184.307; Cohen's d = 0.40). There was no significant difference between veterans with and without current PTSD in the adjusted volumes of the hippocampus, amygdala, anterior cingulate cortex, middle frontal, or orbitofrontal cortex on either side (Table 3). The analysis was repeated with subjects who had a lifetime diagnosis of PTSD. The TICV was significantly lower in the lifetime PTSD group compared with the control group, but volumetric grey matter measures did not significantly differ between the groups. There was no significant correlation between volumetric measure and severity of current PTSD as quantified by the CAPS score.

Cognitive functions

The performance of both groups was within the normal range of age-adjusted published norms of the neuropsychological tests except on the MoCA where the mean score for the PTSD group (25.27) was fractionally below the conventional cut-off score of 26. In comparison with the controls, veterans with current PTSD scored lower on global cognitive function as measured by the MoCA (Median: 26 versus 28; U = 250.00; $p = 0.027$). We performed a multivariable regression analysis after log-transformation of the total MoCA score. The predicted premorbid IQ and the GDS score significantly correlated with the total MoCA score and also differed between the groups. Therefore, these variables were included in the model along with current PTSD as explanatory (independent) variables with the MoCA as the dependent variable. The regression analysis met all assumptions. In the regression analysis (adjusted $R^2 = 0.249$), the difference in the performance on the MoCA (β = –0.252, $p = 0.081$) did not retain significance when predicted premorbid lQ (β = –0.341, $p = 0.009$) and depression score (β = 0.006; $p = 0.611$) were adjusted. The cognitive scores are summarized in Table 4. There was no significant difference between the PTSD groups and the controls in the other cognitive measures. The correlation between predicted premorbid IQ and the TICV was significant ($r = 0.351$, $p = 0.013$).

Table 3
MRI volumes in PTSD and controls, adjusted for total intracranial volume

Variables	Controls ($n = 25$) Mean	Current PTSD ($n = 24$)	p
Left hippocampus	0.18 ± 0.01	0.19 ± 0.01	0.116
Right hippocampus	0.19 ± 0.01	0.19 ± 0.01	0.131
Left amygdala	0.08 ± 0.01	0.08 ± 0.01	0.492
Right amygdala	0.08 ± 0.01	0.08 ± 0.008	0.571
Left middle frontal cortex	0.75 ± 0.08	0.72 ± 0.08	0.332
Right middle frontal cortex	0.69 ± 0.06	0.68 ± 0.07	0.468
Left orbitofrontal cortex	0.17 ± 0.02	0.17 ± 0.01	0.774
Right orbitofrontal cortex	0.17 ± 0.02	0.17 ± 0.02	0.660
Left anterior cingulate cortex	0.33 ± 0.03	0.32 ± 0.04	0.670
Right anterior cingulate cortex	0.28 ± 0.04	0.27 ± 0.04	0.574

Table 4
Cognitive functions in PTSD and controls

Variables	Controls ($n = 30$) Mean ± SD/ Median (interquartile range)	Current PTSD ($n = 30$) Mean ± SD/ Median (interquartile range)	p
Digit Span	17.73 ± 3.99	15.40 ± 4.10	0.135
Categorical fluency	38.97 ± 9.91	38.13 ± 11.44	0.860
Trail making test A (time to completion, s)	37 (15)	34 (17)	0.882
Trail making test B (time to completion, s)	90 (42)	97.50 (65)	0.182
Rey Osterrieth complex figure copy test	29.43 ± 2.97	30.40 ± 5.99	0.555
RAVLT Learning trials	47.17 ± 10.56	44.70 ± 9.22	0.535
Composite Memory score	0.02 ± 0.74	–0.15 ± 0.69	0.535
MMSE	29 (1)	28 (2)	0.182
MoCA	28 (4)	26 (4)	0.027

RAVLT, Rey Auditory Verbal Learning Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

DISCUSSION

There is abundant literature on cognitive function, structural brain imaging, and incidence of dementia in Vietnam veterans with PTSD, but little is known about the AD pathological biomarkers in PTSD. This study measured Aβ and tau *in vivo* in Vietnam veterans with PTSD against veterans without PTSD. This ensured a homogenous population with military experience in both groups and an age range in which preclinical AD pathology is developing and detectable in the general population. The present study did not show a significant association between PTSD and increased amyloid deposition in the brain as measured by ^{18}F-florbetaben. Global amyloid burden or regional amyloid as reflected in the visual inspection was not significantly different between the PTSD and the control groups. Amyloid deposition is the earliest detectable marker of AD and amyloid PET scans become abnormal up to 20 years before the clinical diagnosis of AD dementia [17, 18]. Our finding is consistent with the results from the US-based ADNI Veterans study that also did not find an association between PTSD and increased Aβ deposition [23]. Like our findings, the PTSD cohort in the ADNI-DOD veterans study had worse global cognition than controls. The ADNI-DOD data revealed a significantly lower level of education in the PTSD group, and our study showed the same.

To the best of our knowledge, this is the first study to report tau deposition in PTSD along with Aβ, regional brain metabolism and brain volumetry along with neuropsychological data. This is perhaps the most comprehensive assessment of biomarkers of AD in PTSD. We found no increase in binding of the tau tracer ^{18}F-AV-1451 in PTSD. Similarly, there was no difference between the PTSD group and the controls in regional brain metabolism or regional brain volumetry. If PTSD causes neurodegeneration associated with various dementia syndromes, then it would be likely that after 40 or more years of symptoms in the age group under study, some change would be present. ^{18}F-FDG PET scan has been reported as showing abnormality several years before the onset of AD dementia [14, 15]. Similarly, alterations in hippocampal and regional cortical volumes in PTSD could be temporary, or the mild volume reductions as previously described may be masked by the atrophy that occurs with normal aging. Our participants were in their 60 s and 70 s, and the effect of aging may have had more impact on volumetric changes than PTSD itself, in cortical as well as hippocampal regions. A longitudinal study is required to address these possibilities.

Commensurate with the finding of no difference between PTSD and the control status regarding Aβ, tau, and regional brain metabolism and volumes, there was no evidence of an independent association between PTSD and cognitive impairment. Although previous studies, mostly done in younger veterans, have shown impaired cognitive function in PTSD, our findings suggest that cognitive functions are mostly intact in older veterans with PTSD and the mild impairment we found in the global cognitive performance was reflective of predicted premorbid IQ and the affective state. Our finding is in line with previous data that suggested lower premorbid IQ as a vulnerability factor for the development of PTSD upon trauma exposure and associated cognitive impairment [38, 39]. A co-twin-control study of veterans

found that premorbid cognitive ability, as measured by Armed Forces Qualification Test, predicted the future risk of PTSD in a dose dependent manner indicating the role premorbid intellectual function in the adaptive coping ability after trauma [39]. It should be noted that patients with PTSD do not form a low IQ group because the premorbid IQ in the PTSD group was consistent with the expected general population average, but the veteran controls were above average.

The findings of the present study and those of the ADNI-DOD veterans study do not lend support to a direct link between PTSD and AD pathology. Therefore, it is worth exploring the potential explanatory factors behind the previously reported association between PTSD and dementia including AD [5–9]. The present study suggests a low cognitive reserve (CR) in PTSD. Cognitive reserve is a potential mechanism to buffer the impact of the pathological process associated with AD [40]. With high CR more pathological load is required to produce the same degree of cognitive impairment than with low CR possibly because of recruitment of alternate functional circuits particularly in the dorsolateral prefrontal cortex [41]. High CR affords protection against the onset of dementia, not the neuropathological markers of AD suggesting the role of CR as neurocompensation rather than neuroprotection [42].

According to our findings, predicted premorbid intelligence and education, the proxy measures of CR and TICV which is a measure of brain reserve (BR) were the significantly lower in the PTSD group than in the controls. A recent study demonstrated that increased intracranial volume mitigated adverse effects of dementia pathology on cognitive function, particularly attention and executive function [43]. Likewise, premorbid cognitive performance predicted the onset of dementia independent of the potent genetic risk factor for AD, *APOE* ε4 [44]. Furthermore, physical and cognitive engagement and leisure activities contribute to CR, but evidence suggests that avoidant behavior and hyperarousal symptoms of PTSD may preclude such activities [45, 46]. We postulate that the relatively low CR and other dementia risk factors associated with PTSD may account for previously observed higher incidence of dementia with PTSD. It may be noted, however, that it is not the abnormally low CR or BR that may explain the association of PTSD and dementia. It is a relative concept in comparison with the controls that is worth considering and the previously reported increased risk of dementia with PTSD was also in comparison with the controls. This may suggest that while subjects with PTSD may have the same risk as that of general population, those without PTSD may have additional protection against the onset of dementia from increased CR or BR and the previous epidemiological studies may be reflective of this difference. The clinical implication is that treatments that aim to restore physical and cognitive activities in patients with PTSD may increase CR and lead to dementia risk reduction. In this context, reverse causation hypothesis is also valid: i.e., people with higher reserve may more frequently choose to engage in these types of activities.

This study has several limitations. We could not access direct measurements of pre-military IQ; premorbid IQ in our study was an indirect measure based on the WTAR. Nonetheless, WTAR was validated and used in the cognitive assessment of traumatic brain injury studies [47]. Secondly, given the negative findings, type II error is an important consideration. Although there were small numbers of veterans with a positive amyloid scan and the samples were underpowered for Chi-square test, the analysis for the global burden of amyloid by SUVR had 80% power to detect a difference with effect size of 0.75 or more. For the amyloid imaging, adding the ADNI data did give improved power sufficient to detect an effect size of 0.43. Another limitation of the study was that large numbers of veterans met the exclusion criteria. Among the excluded veterans some declined participation because of perceived stress. Whether they had more severe PTSD or would have altered the results is unknown. The ADNI-DOD study also reported a large number of excluded veterans. Head injury, substance abuse, and medical illnesses are comorbid with PTSD and such factors may lead to restricted inclusion of veterans. Limited inclusion could impact the generalizability of findings. The literature of CR and BR is complex and still evolving, and an explanation of the relationship between PTSD and dementia, being far from conclusive, needs more research.

In conclusion, our findings indicate that PTSD is not associated with an increased prevalence of the biomarkers for the specific pathology of AD or other forms of progressive neurodegeneration. Compared with the controls, veterans with PTSD had a relatively low cognitive reserve. Given that high cognitive reserve may delay the onset of dementia, low cognitive reserve in PTSD may explain its previous association with dementia.

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REFERENCES

[1] Eisen SA, Griffith KH, Xian H, Scherrer JF, Fischer ID, Chantarujikapong S, Hunter J, True WR, Lyons MJ, Tsuang MT (2004) Lifetime and 12-month prevalence of psychiatric disorders in 8,169 male Vietnam War era veterans. *Mil Med* **169**, 896-902.

[2] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **62**, 593-602.

[3] Vasterling JJ, Duke LM, Brailey K, Constance JI, Allain AN Jr, Sutker PB (2002) Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology* **16**, 5-14.

[4] Scott JC, Matt GE, Wrocklage KM, Crnich C, Jordan J, Southwick SM, Krystal JH, Schweinsburg BC (2015) A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull* **141**, 105-140.

[5] Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, Kluse M, Marmar C (2010) Post-traumatic stress disorder and risk of dementia among U.S. Veterans. *Arch Gen Psychiatry* **67**, 608-613.

[6] Qureshi SU, Kimbrell T, Pyne JM, Magruder KM, Hudson TJ, Petersen NJ, Yu HJ, Schulz PE, Kunik ME (2010) Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder. *J Am Geriatr Soc* **58**, 1627-1633.

[7] Mawanda F, Wallace RB, McCoy K, Abrams TE (2017) PTSD, psychotropic medication use and the risk of dementia among US veterans: A retrospective cohort study. *J Am Geriatr Soc* **65**, 1043-1050.

[8] Flatt JD, Gilsanz P, Quesenberry CP, Albers KB, Whitmer RA (2018) Post-traumatic stress disorder and risk of dementia among members of a health care delivery system. *Alzheimers Dement* **14**, 28-34.

[9] Wang TY, Wei HT, Liou YJ, Su TP, Bai YM, Tsai SJ, Yang AC, Chen TJ, Tsai CF, Chen MH (2016) Risk of developing dementia among patients with posttraumatic stress disorder: A nationwide longitudinal study. *J Affect Disord* **205**, 306-310.

[10] Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW (2001) Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. *Am J Psychiatry* **158**, 1920-1922.

[11] Bromis K, Calem M, Reinders AATS, Williams SCR, Kempton MJ (2018) Meta-analysis of 89 structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *Am J Psychiatry* **175**, 989-998.

[12] Zandieh S, Bernt R, Knoll P, Wenzel T, Hittmair K, Haller J, Hergan K, Mirzaei S (2016) Analysis of the metabolic and structural brain changes in patients with torture-related

post-traumatic stress disorder (TR-PTSD) using ^{18}F-FDG PET and MRI. *Medicine (Baltimore)* **95**, e3387.

[13] Teune LK, Bartels AL, de Jong BM, Willemsen AT, Eshuis SA, de Vries JJ, van Oostrom JC, Leenders KL (2010) Typical cerebral metabolic patterns in neurodegenerative brain diseases. *Mov Disord* **25**, 2395-2404.

[14] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC; Dominantly Inherited Alzheimer Network (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Eng J Med* **367**, 795-804.

[15] Chételat G, Desgranges B, Landeau B, Mézenge F, Poline JB, de la Sayette V, Viader F, Eustache F, Baron JC (2008) Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. *Brain* **131**, 60-71.

[16] Wilcock GK, Esiri MM (1982), Plaques, tangles and dementia. *J Neurol Sci* **56**, 343-356.

[17] Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, Fripp J, Tochon-Danguy H, Morandeau L, O'Keefe G, Price R, Raniga P, Robins P, Acosta O, Lenzo N, Szoeke C, Salvado O, Head R, Martins R, Masters CL, Ames D, Villemagne VL (2010) Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* **31**, 1275-1283.

[18] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szoeke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL; Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group (2013) Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol* **12**, 357-367.

[19] Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* **42**, 631-639.

[20] Nisbet RM, Polanco JC, Ittner LM, Gotz J (2015), Tau aggregation and its interplay with amyloid-β. *Acta Neuropathol* **129**, 207-220.

[21] Justice NJ, Huang L, Tian JB, Cole A, Pruski M, Hunt AJ Jr, Flores R, Zhu MX, Arenkiel BR, Zheng H (2015) Post-traumatic stress disorder-like induction elevates β-amyloid levels, which directly activates corticotropin-releasing factor neurons to exacerbate stress responses. *J Neurosci* **35**, 2612-2623.

[22] Carroll JC, Iba M, Bangasser DA, Valentino RJ, James MJ, Brunden KR, Lee VM, Trojanowski JQ (2011) Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. *J Neurosci* **31**, 14436-14449.

[23] Weiner MW, Harvey D, Hayes J, Landau SM, Aisen PS, Petersen RC, Tosun D, Veitch DP, Jack CR Jr, Decarli C, Saykin AJ, Grafman J, Neylan TC; Department of Defense Alzheimer's Disease Neuroimaging Initiative (2017) Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary report. *Alzheimers Dement* **3**, 177-188.

[24] Bourgeat P, Villemagne VL, Dore V, Brown B, Macaulay SL, Martins R, Masters CL, Ames D, Ellis K, Rowe CC, Salvado O, Fripp J; AIBL Research Group (2015) Comparison of MR-less PiB SUVR quantification methods. *Neurobiol Aging* **36**, S159-S166.

[25] Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD Sr, Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, Rowe CC, Skovronsky DM, Mintun MA (2015) The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement* **15**, 1-15.

[26] Weathers FW, Keane TM, Davidson JR (2001) Clinician-Administered PTSD Scale: A review of the first ten years of research. *Depress Anxiety* **13**, 132-156.

[27] Shalev AY, Freedman SA, Peri T, Brandes D, Sahar T (1997) Predicting PTSD in trauma survivors: Prospective evaluation of self-report and clinician-administered instruments. *Br J Psychiatry* **170**, 558-564.

[28] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1983) Development and validation of a geriatric depression screening scale: A preliminary report. *J Psychiatr Res* **17**, 37-49.

[29] Wechsler D (1997) *Wechsler Memory Scale-Revised*. The Psychological Corporation, San Antonio, TX.

[30] Wechsler D (1987) *Wechsler Adult Intelligence Scale - Third Edition*. The Psychological Corporation, San Antonio, TX.

[31] Delis DC, Kaplan E, Kramer JH (2001) *Delis-Kaplan Executive Function System*. The Psychological Corporation, San Antonio, TX.

[32] Rey A, Osterrieth PA (1993) Translations of excerpts from Rey's 'Psychological Examination of Traumatic Encephalopathy'and Osterrieth's 'The Complex Figure Test'. *Clin Neuropsychol* **7**, 2-21.

[33] Rey A (1964) L'examen Clinique en psychologie. Presses Universitaires de France, Paris.

[34] Reitan RM (1958) Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* **8**, 271-276.

[35] Wechsler D (2001) *Wechsler Test of Adult Reading: WTAR*. The Psychological Corporation, San Antonio, TX.

[36] Folstein MF, Folstein SE, McHugh PR (1975) Mini-Mental State, A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **2**, 189-198.

[37] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[38] Macklin ML, Metzger LJ, Litz BT, McNally RJ, Lasko NB, Orr SP, Pitman RK (1998) Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychol* **66**, 323-326.

[39] Kremen WS, Koenen KC, Boake C, Purcell S, Eisen SA, Franz CE, Tsuang MT, Lyons MJ (2007) Pretrauma cognitive ability and risk for posttraumatic stress disorder: A twin study. *Arch Gen Psychiatry* **64**, 361-368.

[40] Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* **11**, 1006-1012.

[41] Morbelli S, Perneczky R, Drzezga A, Frisoni GB, Caroli A, van Berckel BN, Ossenkoppele R, Guedj E, Didic M, Brugnolo A, Naseri M, Sambuceti G, Pagani M, Nobili F (2013), Metabolic networks underlying cognitive reserve in prodromal Alzheimer disease: A European Alzheimer disease consortium project. *J Nucl Med* **54**, 894-902.

[42] Brayne C, Ince PG, Keage HAD, McKeith IG, Matthews FE, Polvikoski T. EClipSE Collaborative Members (2010) Education, the brain and dementia: Neuroprotection or compensation? EClipSE Collaborative Members. *Brain* **133**, 2210-2216.

[43] Groot C, van Loenhoud AC, Barkhof F, van Berckel BNM, Koene T, Teunissen CC, Scheltens P, van der Flier WM, Ossenkoppele R (2018) Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. *Neurology* **90**, e149-e156.

[44] Cervilla J, Prince M, Joels S, Lovestone S, Mann A (2004), Premorbid cognitive testing predicts the onset of dementia and Alzheimer's disease better than and independently of APOE genotype. *J Neurol Neurosurg Psychiatry* **75**, 1100-1106.

[45] Cheng S-T (2016) Cognitive reserve and the prevention of dementia: The role of physical and cognitive activities. *Curr Psychiatry Rep* **18**, 85.

[46] van den Berk-Clark C, Secrest S, Walls J, Hallberg E, Lustman PJ, Schneider FD, Scherrer JF (2018) Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity and co-occuring smoking: A systematic review and meta-analysis. *Health Psychol* **37**, 407-416.

[47] Green RE, Melo B, Christensen B, Ngo LA, Monette G, Bradbury C (2008) Measuring premorbid IQ in traumatic brain injury: An examination of the validity of the Wechsler Test of Adult Reading (WTAR). *J Clin Exp Neuropsychol* **30**, 163-172.

The following paper has been published from the dataset of Vietnam Veterans study of Alzheimer's Disease. A part of the data was derived from Vietnam veterans with posttraumatic stress disorder, but it also has data from veterans with Traumatic Brain Injury (TBI).

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Risk of Alzheimer's Disease in Obstructive Sleep Apnea Syndrome: Amyloid-β and Tau Imaging

Alby Elias[a,e,*], Tia Cummins[f], Regan Tyrrell[a], Fiona Lamb[a], Vincent Dore[b], Robert Williams[c], J.V. Rosenfeld[d], Malcolm Hopwood[e], Victor L. Villemagne[a] and Christopher C. Rowe[a]
[a]*Department of Molecular Imaging and Therapy, Austin Health, The University of Melbourne, Victoria, Australia*
[b]*CSIRO Brisbane, Queensland, Australia*
[c]*Melbourne Brain Centre, Parkville, Victoria, Australia*
[d]*Department of Neurosurgery, Monash University, Victoria, Australia*
[e]*Department of Psychiatry, The University of Melbourne, Victoria, Australia*
[f]*The Florey Institute of Neuroscience and Mental Health*

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Abstract.
Background: An association between obstructive sleep apnea (OSA) and Alzheimer's disease has been suggested but little is known about amyloid-β and tau deposition in this syndrome.
Objective: To determine amyloid and tau burden and cognitive function in OSA in comparison with those without a diagnosis of OSA.
Methods: The status of OSA was determined by asking participants about history of polysomnographic diagnosis of OSA and the use of Continuous Positive Airway Pressure (CPAP). A comprehensive neuropsychological battery measured cognitive function. Positron emission tomography (PET) was used to measure standardized uptake value ratio (SUVR) of ^{18}F-florbetaben and ^{18}F-AV1451, to quantify amyloid and tau burden.
Results: 119 male Vietnam veterans completed assessment. Impairment in visual attention and processing speed and increased body mass index (BMI) were seen in subjects with OSA compared with those without a diagnosis OSA. The cortical uptake of ^{18}F-florbetaben was higher in the OSA group than in the control group (SUVR: 1.35 ± 0.21 versus 1.27 ± 0.16, $p = 0.04$). There were more apolipoprotein E ε4 allele (APOE ε4) carriers in the OSA group than in the control group. In multilinear regression analysis, the significance of OSA in predicting ^{18}F-florbetaben uptake remained independent of age and vascular risk factors but not when BMI or APOE ε4 was adjusted. The reported use of CPAP ($n = 14$) had no effect on cognitive or amyloid PET findings. There was no significant difference in ^{18}F-AV1451 uptake between the two groups.
Conclusions: Obstructive sleep apnea is associated with Alzheimer's disease pathology, but this relationship is moderated by APOE ε4 and BMI.

Keywords: Alzheimer's disease, amyloid PET, dementia, obstructive sleep apnea, tau PET

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1, 2]. The precise mechanism of the disease is still unknown, but investigations over the past several decades have identified numerous risk factors for AD [3–9]. Age is the strongest risk factor for AD and genetic factors posit substantial risk [5, 7, 8]. Neuritic plaques and neurofibrillary tangles (NFT) are the two cardinal lesions of AD. The plaque contains a central core of amyloid-β (Aβ) and NFT are intracytoplasmic fibrillar structures composed of

*Correspondence to: Alby Elias, 343 Burwood Hwy, East Burwood, 3151 Victoria, Australia. Tel.: +61 417325223; Fax: +61 3 98725964; E-mail: alby.elias@unimelb.edu.au.

abnormally phosphorylated tau proteins [10, 11]. Given that amyloid plaques and NFT are cardinal lesions in AD, positron emission tomographic (PET) imaging using specific radioactive ligands that bind to amyloid and tau is a useful technique to evaluate the risk factors of AD. ^{18}F-florbetaben and ^{18}F-AV1451 are radio-ligands that have specific affinity for Aβ and 3R4 R tau aggregates, respectively [12, 13].

Sleep disorders have been investigated as potential risk factors for AD. Obstructive sleep apnea (OSA) is a syndrome that is diagnosed in the presence of clinical symptoms, most commonly excess daytime sleepiness in conjunction with an apnea-hypopnea index (AHI) greater than 5 events per hour [14]. The prevalence of OSA in the community-based cohorts has been estimated as 2%–8% and it increases with age [15, 16]. Early studies demonstrated an association between AD and sleep apnea and a correlation between the severity of apnea and dementia [17, 18]. Recent investigations have demonstrated a link between Aβ deposition and sleep disturbances [19]. OSA is associated with earlier onset of both mild cognitive impairment (MCI) and dementia compared with subjects without OSA [20]. In a small sample of five patients with MCI, higher AHI and oxygen desaturation index were associated with greater amyloid deposition [21]. However, little is known about Aβ and tau imaging in cognitively asymptomatic individuals with OSA. In the present study, we report cognitive function and Aβ and tau imaging findings in cognitively asymptomatic patients with OSA.

METHODS

Participants recruitment

This was a cross-sectional study evaluating AD risk in the community-based Vietnam Veterans. Veterans were recruited via the Older Veterans Psychiatric Program of the Repatriation Hospital, Austin Health and advertisement in magazines and newsletters of Retired Service League and the Vietnam Veterans Association of Australia. The institutional review board of Austin Health, a major metropolitan health service in Melbourne provided ethical approval for the study. Presence of dementia, existing diagnosis of MCI, psychotic and bipolar affective disorder, current substance abuse, and any unstable medical condition that could have impacted cognitive performance or made participation difficult were exclusions. Assessment consisted of medical history, Pittsburgh Sleep Quality Index (PSQI) [22], neuropsychological examination, apolipoprotein E (APOE) ε4 status, vascular risk factors, and Aβ and tau imaging. For the analysis of cognitive functions, subjects with traumatic brain injury (TBI) were excluded given its impact on cognitive outcomes. All subjects were screened for a history of polysomnographic diagnosis of OSA and the use of Continuous Positive Airway Pressure (CPAP) mask. This history was corroborated by documentation from the primary care doctor of participants whenever possible. Those with no polysomnographic diagnosis of OSA or symptoms of OSA were the controls. Considering the poor sensitivity of the global score of PSQI in detecting OSA [23], the global score was not used to diagnose OSA but positive responses to the individual items-cessation of breathing during sleep and excess daytime sleepiness-were exclusion criteria for the controls.

Assessment of cognitive functions and vascular risk factors

The neuropsychological examination included Logical Memory subset test 1 and 2 of Wechsler Memory Scale (WMS) – Anna Thompson story only [24], digit span forward and backwards from the Wechsler Adult Intelligence Scale third edition [25], categorical fluency test from the Delis-Kaplan Executive Function System [26], Rey Osterrieth Complex Figure Test (ROCFT) [27] and Trail Making Test parts A and B [28]. Vascular risk factor score was calculated by giving one point to each of the following: Diabetes mellitus, hypertension, coronary artery disease, hypercholesterolemia, body mass index (BMI) above 30, current smoking status, previous history of stroke, and atrial fibrillation. Sum of all points gave cumulative vascular risk.

PET imaging

The participants underwent a 20-min PET scan (4 x 5-min frames of emission data collected) acquired 90 min after a slow IV bolus administration of 250 MBq (±10%) of ^{18}F-florbetaben and 70 min after the injection of 370 MBq of ^{18}F-AV1451. Acquisition was performed with a Siemens PET/CT mCT128 and CT attenuation correction was applied. Image reconstruction used the Ordered Subset Expected Maximization (OSEM) algorithm. There was no correction for partial volume effect. ^{18}F-florbetaben and ^{18}F-AV1451 PET were both analyzed with Computational Analysis of PET from AIBL (CapAIBL)

Table 1
Patients characteristics in OSA

Variables	OSA group ($n=42$)	Non-OSA group ($n=77$)	p
Age	67.69 ± 5.37	68.30 ± 3.86	0.47
Gender	Males = 42 Females = 0	Males = 77 Females = 0	
Education in years	11.43 ± 2.78	11.70 ± 2.85	0.62
Apolipoprotein E ε4	34.2% (n = 35)	15.9% (n = 69)	$\chi^2 = 4.53$, $p = 0.03$
Vascular risk factor score	2.37 ± 1.18	1.43 ± 1.16	$p < 0.001$
BMI	32.56 ± 4.05	27.82 ± 4.03	$p < 0.001$

software developed by the Commonwealth Scientific and Industrial Research Organization (CSIRO) [29]. CapAIBL allows quantitative PET measurements without relying on magnetic resonance imaging [30]. Global Aβ and regional tau burden were calculated by standardized uptake value ratio (SUVR) using cerebellar grey matter uptake as the reference. ^{18}F-Florbetaben scans were also read visually according to the manufacturer's instructions by three readers and the classification into negative or positive scan was based on majority results. ^{18}F-AV1451 regional uptake in three regions was calculated by CapAIBL software: Mesial temporal (amygdala, hippocampus, entorhinal cortex, and parahippocampus); temporoparietal (inferior and middle temporal lobe, fusiform gyrus, posterior cingulate/precuneus, superior and inferior parietal and lateral occipital cortex); and rest of the neocortex. A visual read of ^{18}F-AV1451 images was not performed as a standard method has yet to be developed.

Statistical analyses

The continuous variables viz., ^{18}F-florbetaben and ^{18}F-AV1451 SUVRs and neuropsychological test scores were analyzed using independent t test while the categorical variables, OSA and APOE ε4 status, were analyzed by Chi-square test. All tests were two-tailed with 95% confidence interval. Pearson correlation was used to find correlates of both ^{18}F-florbetaben and ^{18}F-AV1451 SUVRs and cognitive test scores. Multilinear regression analysis was then performed with explanatory variables found to be correlated and associated with ^{18}F-florbetaben or ^{18}F-AV1451 SUVRs and cognitive scores. ^{18}F-florbetaben and ^{18}F-AV1451 SUVRs and cognitive scores were treated as the dependent variables. General linear model was used to test the interaction between OSA and amyloid and tau tracer SUVRs and a visually positive amyloid scan in predicting cognitive function.

RESULTS

Between March 2014 and June 2017, 170 veterans underwent screening after providing informed consent. From the consecutive sample, 44 veterans were excluded: 11 veterans had medical morbidities making participation difficult; seven met criteria for alcohol abuse; five had existing diagnosis of MCI; five could not cope with psychiatric assessment because of post-traumatic stress disorder and perceived stress; one had bipolar affective disorder; one had claustrophobia; and 14 withdrew from the study because of inconvenience. After exclusion 126 male veterans completed neuropsychological assessments and scans. Seven veterans reported symptoms of OSA according to PSQI but they did not have polysomnographic evaluation and they were therefore excluded from the analyses. The data from the remaining 119 veterans were analyzed. A polysomnographically confirmed diagnosis of OSA was present in 42 (35.2%) subjects. The characteristics of participants are shown in Table 1. Twenty-four patients reported regular use of CPAP; 14 veterans did not use CPAP; and use was indeterminate in four subjects. The mean duration between the diagnosis of OSA and the study assessment was 74.35 ± 27.06 months. Veterans with OSA had significantly higher vascular risk factor score compared with those without OSA (2.37 ± 1.18 versus 1.43 ± 1.16, $p < 0.001$, CI = –1.45 to –0.42). BMI was significantly higher in the OSA group than in the controls (32.56 ± 4.05 versus 27.82 ± 4.03, $p < 0.001$). There was no significant difference in age or years of education between the OSA and the control group (Table 1). The characteristics of OSA has been shown in Table 2.

Veterans with OSA and controls did not differ significantly in the following cognitive functions: Digit span, categorical fluency, Logical Memory Test 1 and 2, ROCFT, ROCFT 3-min and 30-min delayed recall. However, subjects with OSA scored significantly higher on Trail Making Test A

Table 2
Characteristics of OSA

Variables	
Mean duration of diagnosis	6 years
Regular CPAP users	24
Mean nadir oxygen saturation	85.5% (74%–93%)
Apnea-hypopnea Index	33.0 (6–89)

(time to completion in seconds: 41.81 ± 12.54 versus 35.63 ± 11.69, $p = 0.03$, CI = –11.80, to –0.544) and B (time to completion in seconds: 126.70 ± 82.47 versus 97.95 ± 33.79, $p = 0.03$, CI = –54.29 to –3.22) (Table 3). Both test scores positively correlated with vascular risk factor score ($r = 0.24$, $p = 0.03$; $r = 0.22$, $p = 0.04$, respectively). The significant relation between OSA and Trail Making Test B did not stay when Trail Making Test A, a measure of visual attention and processing speed was controlled ($R^2 = 0.23$, $p = 0.12$). The significance of OSA in predicting Trail Making Tests A ($R^2 = 0.118$, $p = 0.04$) remained upon controlling the effects of age, education and APOE ε4, but not when vascular risk factor score was adjusted for ($R^2 = 0.07$, $p = 0.16$). In the general linear model analysis, there was no significant interaction between ^{18}F-florbetaben SUVR and OSA or visually positive ^{18}F-florbetaben scan and OSA in predicting either Trail Making Test A or B.

The boxplots for the distribution of ^{18}F-florbetaben SUVR are given in Fig. 1. Independent t test showed that the SUVR of ^{18}F-florbetaben was significantly higher in the OSA group than in the control group (1.35 ± 0.21 versus 1.27 ± 0.16, $p = .04$, CI = –0.14 to –0.003). A greater number of subjects with a visually positive ^{18}F-florbetaben scan in the OSA group did not reach significance between the OSA and the control group (29.7% versus 17.3%, $\chi^2 = 2.26$, $p = 0.13$). There was no significant increase in ^{18}F-AV1451 SUVR in OSA in any regions studied (Table 3). BMI significantly and positively correlated with ^{18}F-florbetaben SUVR ($r = 0.341$, $p < 0.001$) which was significantly higher in those with obesity (BMI more than 30, $n = 48$) compared with those who were non-obese (1.37 ± 0.22 versus 1.25 ± 0.13, $p < 0.001$). Vascular risk score showed significant positive correlation with global SUVR of ^{18}F-florbetaben ($r = 0.206$, $p = 0.049$) and regional SUVRs of ^{18}F-AV1451 in mesial temporal ($r = 0.327$, $p = 0.004$) and temporoparietal ($r = 0.26$, $p = 0.03$) regions. When separate analysis was done for the OSA group there was no significant difference between veterans who were regularly using CPAP and the non-users of CPAP in global ^{18}F-florbetaben (1.36 ± 0.23 versus 1.35 ± 0.22, $p = 0.82$) or regional ^{18}F-AV1451 SUVRs. Baseline sleep diagnostic reports were available for 14 subjects. The

Table 3
Cognitive tests scores in OSA

Cognitive tests	OSA group ($n = 27$)	Non-OSA group ($n = 56$)	p
Digit span	15.78 ± 3.50	17.09 ± 4.17	0.16
3-min delayed visual recall	17.21 ± 4.98	16.28 ± 6.73	0.53
30-min delayed visual recall	17.32 ± 4.91	16.28 ± 6.73	0.21
Categorical fluency	19.44 ± 5.59	21.41 ± 4.82	0.10
Trial Making Test A test, time to completion	41.81 ± 12.54	35.63 ± 11.69	0.03
Trail Making Test B test time to completion (s)	126.70 ± 82.47	97.95 ± 33.79	0.03
Recognition	20.03 ± 2.21	20.50 ± 1.67	0.30
Logical Memory Test 1	11.85 ± 4.65	13.30 ± 4.29	0.16
Logical Memory test 2	10.85 ± 4.37	11.37 ± 4.37	0.61
Rey Copy Figure Test	29.74 ± 6.39	29.88 ± 2.66	0.88

Table 4
^{18}F-florbetaben and ^{18}F-AV1451 SUVR

Tracer SVURs	OSA ($n = 36$)	Non-OSA ($n = 70$)	p (95% CI)
^{18}F-florbetaben	1.35 ± 0.21	1.27 ± 0.16	0.04
^{18}F-AV1451 Mesial temporal	1.24 ± 0.14	1.19 ± 0.12	0.09
^{18}F-AV1451 Neocortical	1.18 ± 0.10	1.15 ± 0.08	0.14
^{18}F-AV1451 Temporoparietal	1.20 ± 0.10	1.17 ± 0.09	0.11

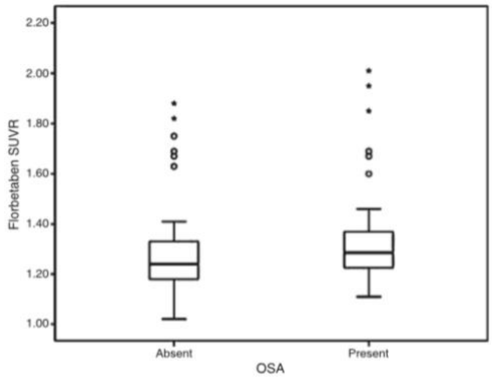

Fig. 1. ^{18}F-florbetaben SUVR in OSA and controls.

negative correlation between nadir oxygen saturation and ^{18}F-florbetaben SUVR did not reach statistical significance ($r = -0.563$, $p = 0.140$). There was no significant correlation between AHI and ^{18}F-florbetaben SUVR ($r = -0.316$, $p = 0.317$).

APOE ε4 carrier status was available for 104 veterans. There was increased rate of APOE ε4 allele in the OSA group compared with the controls (34.2% versus 15.9%, $\chi^2 = 4.53$, $p = 0.03$). The SUVR for ^{18}F-florbetaben was significantly higher in the APOE ε4 carriers than in the non-carriers (1.41 ± 0.21 versus 1.27 ± 0.17, $p = 0.02$). There were more visually positive ^{18}F-florbetaben scans in APOE ε4 carriers than in non-carriers (50% versus 13.2%, $\chi^2 = 14.17$, $p < 0.001$). The SUVR of ^{18}F-AV1451 did not show a significant difference between APOE ε4 carriers and non-carriers in any regions. In the multilinear regression analysis with ^{18}F-florbetaben SUVR as the dependent variable, vascular risk factor score and APOE ε4 were added to OSA because these variables showed association and correlation with ^{18}F-florbetaben SUVR. Age was also added in view of its well-known correlation with amyloid deposition. The significance of OSA in predicting ^{18}F-florbetaben SUVR remained significant upon controlling for vascular risk score ($R^2 = 0.10$, $p = 0.04$) and age ($R^2 = 0.07$, $p = 0.03$). Similarly, APOE e4 continued to be a significant predictor of ^{18}F-florbetaben SUVR when age ($R^2 = 0.08$, $p = 0.02$) and vascular risk score ($R^2 = 0.10$, $p = 0.04$) were adjusted. OSA did not retain its significance in predicting a visually positive ^{18}F-florbetaben scan ($R^2 = 0.11$, $p = 0.12$) or ^{18}F-florbetaben SUVR ($R^2 = 0.145$, $p = 0.971$) when APOE ε4 or BMI was added while APOE ε4 ($p = 0.037$) and BMI remained significant ($p = 0.010$). In the general linear model there was no significant interaction ($F = 0.11$, $p = 0.73$) between APOE ε4 and OSA in predicting ^{18}F-florbetaben SUVR (Fig. 2).

DISCUSSION

Cognitive functions

The cognitive functions previously reported to be impaired in OSA include attention, procedural memory and episodic memory [31–33], processing speed [34], spatial memory [33], and executive function [35, 36]. Executive dysfunction has been reported in Vietnam veterans with OSA [35]. Language ability and psychomotor functions remain relatively unaffected. In the present study, subjects with OSA performed poorly on Trail Making Tests A and B. The Trail Making Test A measures visual attention and processing speed whereas Trail Making Test B assesses executive function. Felver-Gant et al. reported impaired performance on Trail Making Test B in OSA [35]. We have replicated this finding in subjects with OSA, but when we controlled for the score of Trail Making Test A, the effect of visual attention and processing speed the significance of Trail Making Test B did not remain indicating that the deficit was actually in the processing speed rather than executive function. The association between OSA and impairment in these cognitive domains was independent of age, APOE ε4, and education of the subjects, but not vascular risk burden, which was associated with OSA. The confounding effect of vascular burden was not adequately addressed in previous studies. A review of cognitive deficits in OSA has revealed varying

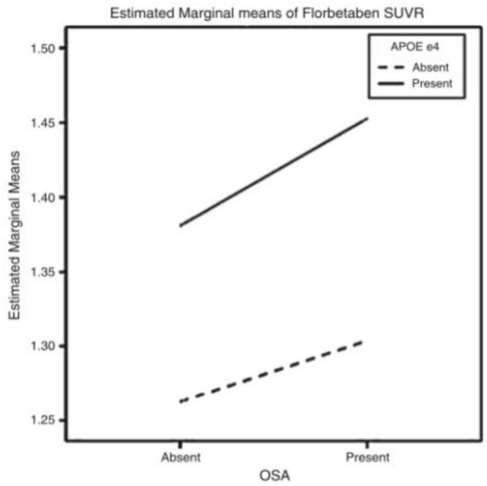

Fig. 2. Interaction between OSA and APOE ε4: In the presence of APOE ε4, amyloid burden was more greatly increased in OSA.

cognitive deficits across studies [37]. The pattern of cognitive deficits varied according to the assessment settings (community cohorts against sleep medicine clinic), treatment with CPAP and age [38, 39]. A study that compared cognitive functions between young and older individuals found more attentional deficits in the older patients, a pattern supported by our study [37].

Sleep apnea and Alzheimer's disease

Apart from cognitive impairment, existing data suggest an association between OSA and MCI and dementia. A seminal longitudinal study found a two-fold risk for MCI or dementia in patients with OSA over five-year follow-up [20]. Following early observations of association between OSA and dementia further findings have accrued recently supporting the link between sleep disordered breathing and both MCI and dementia [18–20]. A recent study demonstrated annual decline in the level of cerebrospinal fluid (CSF) $A\beta_{42}$ over a two-year period in cognitively asymptomatic elderly patients with OSA, implying increased risk of AD in this condition [40]. The change in CSF $A\beta_{42}$ correlated with the severity of OSA independent of APOE. However, there was no association between OSA and increased amyloid uptake on PET scan. The results of the present study show that patients with a polysomnographic diagnosis of OSA have slight but significantly higher global uptake of ^{18}F-florbetaben compared with subjects without a diagnosis OSA. This association was independent of age and vascular risk factors, but not APOE ε4 or BMI. Both BMI and APOE ε4 were associated with ^{18}F-florbetaben SUVR. Previous studies have suggested a negative correlation between BMI and amyloid load [41, 42]. The relationship between dementia and BMI is two-phased, increased risk of dementia was seen with BMI when weight was measured 20 years or more prior to dementia diagnosis and this association was reversed when weight was measured in 10 years or less before dementia diagnosis [43]. The first phase may represent a causal effect of obesity on dementia and the second phase is due to weight loss from metabolic changes arising from damage to medial temporal lobe during long preclinical stage of AD. The mean age of our subjects was 68.36 years suggesting that the participants have not yet reached the stage of declining weight which may commence with increasing amyloid accumulation at any stage later.

There was no significant difference in regional uptakes of ^{18}F-AV-1451 between the groups. Recently a small study found increased amyloid deposition in elderly patients with MCI and OSA in correlation with oxygen desaturation index [21]. Such a correlation was not found in cognitively normal individuals with OSA [21], but the sample sizes of this study were very small, eight patients with normal cognitive function and five patients with MCI. Our subjects were elderly without an existing diagnosis of MCI.

Interaction between sleep apnea and APOE ε4

The mechanism through which OSA is associated with dementia and Aβ deposits is not precisely known. Aβ binding to APOE ε4 results in Aβ-APOE ε4 complex which is internalized by Very Low-Density Lipoprotein (VLDL) receptor more slowly than Aβ-APOE ε2 and Aβ-APOE ε3 complexes leading to decreased clearance of Aβ with APOE ε4 [44]. In the general population and clinical samples, OSA was found to be associated with the APOE ε4 allele [45–47] but other studies and a meta-analysis did not find such an association [48]. We found a significantly increased rate of APOE ε4 in OSA in our sample but the significantly increased Aβ tracer retention in OSA was no longer observed when the effect of APOE ε4 was controlled. APOE ε4 had stronger association with Aβ burden than OSA. The influence of OSA on ^{18}F-florbetaben SUVR was higher in the presence of APOE ε4, than in its absence (Fig. 2). We did not find a significant difference in tau retention between the OSA group and controls but considering that cortical tau deposition follows Aβ accumulation and may be more closely associated with cognitive deficits, or dementia, this is not unexpected as our sample excluded subjects with MCI.

Limitations

While the diagnosis of OSA was made with polysomnographic studies, subjects without a diagnosis of OSA did not have laboratory sleep evaluation. The corollary is that some of the control subjects may have undiagnosed OSA. Therefore, the control group is not really a group without OSA; rather it is a group without symptoms of OSA. In our study we used PSQI, a sleep questionnaire that elicits symptoms of arrested breathing during sleep and daytime sleepiness. One study has reported that PSQI has poor sensitivity (38%) in screening for OSA, but this study used global PSQI score, not the responses to individual questions that are most relevant to OSA [23]. We excluded the participants who reported symptoms of OSA on PSQI. The rate of OSA in our sample (35.2%) is higher than the prevalence of OSA reported in the older general community (17%–24%) suggesting that Australian Vietnam veterans are well monitored for this condition and at low risk for missed diagnosis [49]. Our sample was primarily veterans with military deployment. This may limit generalizability of the above findings. The correlational analysis between nadir oxygen saturation and ^{18}F-florbetaben SUVR involved a small sample and type II error needs to be considered in this context. It is noteworthy that the subject with highest ^{18}F-florbetaben SUVR (2.01) had the lowest oxygen saturation (74%). Therefore, an association between oxygen desaturation and Aβ in OSA cannot be ruled out.

CONCLUSION

We identify an association between obstructive sleep apnea and increased Aβ deposition. However, the association with Aβ deposition was moderated by APOE ε4 and BMI. Overall the study does not support a direct association between OSA and increased Aβ deposition. Likewise, an association between obstructive sleep apnea and increased tau retention was not established in this study.

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REFERENCES

[1] Fratiglioni L, Grut M, Forsell Y, Viitanen M, Grafström M, Holmén K, Ericsson K, Bäckman L, Ahlbom A, Winblad B (1991) Prevalence of Alzheimer's disease and other dementias in an elderly urban population: Relationship with age, sex, and education. *Neurology* **41**, 1886-1892.

[2] Shoenberg BS, Kokmen E, Okazaki H (1987) Alzheimer's disease and other dementing illnesses in a defined United States population: Incidence rates and clinical features. *Ann Neurol* **22**, 724-772.

[3] Jorm AF (2005) Risk factors for Alzheimer's disease. In *Dementia*, 3rd Edn, Burns A, O'Brien J, Ames D, eds. Hodder Arnold, Boca Raton.

[4] Launer LJ, Anderson K, Dewey ME, Letenneur L, Ott, A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A (1999) Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. *Neurology* **52**, 78-84.

[5] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I (2002) Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* **56**, 445-453.

[6] Kivipelto M, Ngandu T, Fratiglioni L Viitanen M, Kåreholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A (2005) Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* **62**, 1556-1560.

[7] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux RH, Pericak-Vance MA, Risch N, van Dujin CM (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer

disease. A meta-analysis. APOE and Alzheimer Disease Meta-Analysis Consortium. *JAMA* **278**, 1349-1356.

[8] Mayeux R, Sano M, Chen J, Tatemichi T, Stern Y (1991) Risk of dementia in first-degree relatives of patients with Alzheimer's disease and related disorders. *Arch Neurol* **48**, 269-73.

[9] Jorm AF, Jolley D (1998) The incidence of dementia: A meta-analysis. *Neurology* **51**, 728-733.

[10] Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K (1985) Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci U S A* **82**, 4245-4249.

[11] Bancher C, Brunner C, Lassmann H, Budka H, Jellinger K, Wiche G, Seitelberger F, Grundke-Iqbal I, Wisniewski HM (1989) Accumulation of abnormally phosphorylated x precedes the formation of neurofibrillary tangles in Alzheimer's disease. *Brain Res* **477**, 90-99.

[12] Sabri O, Seibyl J, Rowe C, Barthel H (2015) Beta-amyloid imaging with florbetaben. *Clin Transal Imaging* **3**, 13-26.

[13] Lowe VJ, Curran G, Fang P, Liesinger AM, Josephs KA, Parisi JE, Kantarci K, Boeve BF, Pandey MK, Bruinsma T, Knopman DS, Jones DT, Petrucelli L, Cook CN, Graff-Radford NR, Dickson DW, Petersen RC, Jack CR Jr, Murray ME (2016) An autoradiographic evaluation of AV-1451 Tau PET in dementia. *Acta Neuropathol Commun* **4**, 58.

[14] Kryger MF, Roth T, Dement WC (editors) (2015) *Principles and practice of sleep medicine*. Expert Consult premium edition. Elsevier Saunders.

[15] Punjabi NM (2008) The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* **5**, 136-143.

[16] Peppard PE, Young T, Barnet JH Palta M, Hagen EW, Hla KM (2013) Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* **177**, 1006-1014.

[17] Hoch CC, Reynolds CF, Houck PR Houck PR, Berman SR, Stack JA (1986) Sleep-disordered breathing in normal and pathologic aging. *J Clin Psychiatry* **47**, 499-503.

[18] Reynolds CF, Kupfer DJ, Taska LS Hoch CC, Sewitch DE, Restifo K, Spiker DG, Zimmer B, Marin RS, Nelson J, et al. (1985) Sleep apnea in Alzheimer's dementia: Correlation with mental deterioration. *J Clin Psychiatry* **46**, 257-261.

[19] Mander BA, Marks SM, Vogel JW, Rao V, Lu B, Saletin JM, Ancoli-Israel S, Jagust, WJ, Walker MP (2015) β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci* **18**, 1051-1057.

[20] Osorio RS, Gumb T, Pirraglia T, Varga AW, Lu S, Lim J, Wohlleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, de Leon MJ (2015) Sleep disordered breathing advances cognitive decline in the elderly. *Neurology* **84**, 1964-1971.

[21] Spira AP, Yager C, Brandt J, Smith GS, Zhou Y, Mathur A, Kumar A, Braăić JR, Wong DF, Wu MN (2014) Objectively measured sleep and β-amyloid burden in older adults: A pilot study. *SAGE Open Med* **2**, 2050312114546520.

[22] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* **28**, 193-213.

[23] Scarlata S, Pedone C, Curcio G, Cortese L, Chiurco D, Fontana D, Calabrese M, Fusiello R, Abbruzzese G, Santangelo S, Zito A, Incalzi RA (2013) Pre-polysomnographic assessment using the Pittsburgh Sleep Quality Index questionnaire is not useful in identifying people at higher risk for obstructive sleep apnea *J Med Screen* **20**, 220-226.

[24] Wechsler D (1987) *Wechsler Memory Scale-Revised*. The Psychological Corporation, San Antonio, TX.

[25] Wechsler D (1997) *Wechsler Adult Intelligence Scale - Third Edition*. The Psychological Corporation, San Antonio, TX.

[26] Butters, N, Granholm E, Salmon DP, Grant I, Wolfe J (1987) Episodic and semantic memory: A comparison of amnesic and demented patients. *J Clin Exp Neuropsychol* **9**, 479-497.

[27] Rey A, Osterrieth PA (1993) Translations of excerpts from Rey's 'Psychological Examination of Traumatic Encephalopathy' and Osterrieth's 'The Complex Figure Test'. *Clin Neuropsychol* **7**, 2-21.

[28] Reitan RM (1958) Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* **8**, 271-276.

[29] Zhou L, Salvado O, Dore V, Bourgeat P, Raning P, Macaulay SL, Ames D, Masters CL, Ellis KA, Villemagne VL, Rowe CC, Fripp J, AIBL Research Group (2014) MR-Less surface-based amyloid assessment based on ^{11}C PiB PET. *PLoS* **9**, e84777.

[30] Bourgeat P, Villemagne VL, Dore V, Brown B, Macaulay SL, Martins R, Masters CL, Ames D, Ellis K, Rowe CC, Salvado O, Fripp J, AIBL Research Group (2015) Comparison of MR-Less PiB SUVR quantification methods *Neurobiol Aging* **36**, S159-166.

[31] Cosentino FII, Bosco P, Drago V, Prestianni G, Lanuzza B, Iero I, Tripodi M, Spada RS, Toscano G, Caraci F, Ferri R. (2008) The APOE ε4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. *Sleep Med* **9**, 831-839.

[32] Mazza S, Pepin JL, Naëgelé B, Plante J, Deschaux C, Lévy P (2005) Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. *Eur Respir J* **25**, 75-80.

[33] Naegele B, Launois SH, Mazza S, Feuerstein C, Pepin J-L, Levy P (2006) Which memory processes are affected in patients with obstructive sleep apnea? *Sleep* **29**, 533-544.

[34] Kilpinen R, Saunamaki T, Jehkonen M (2014) Information processing speed in obstructive sleep apnea syndrome: A review. *Acta Neurol Scand* **129**, 209-218.

[35] Felver-Gant JC, Bruce AS, Zimmerman M, Sweet LH, Milmman RP, Aloia MS (2007) Working memory in obstructive sleep apnea: Construct validity and treatment affects. *J Clin Sleep Med* **6**, 589-594.

[36] Andreou G, Vlachos F, Makanikas K (2012) Neurocognitive Deficits in Patients with Obstructive Sleep Apnea Syndrome (OSAS), Neuroscience, Dr. Thomas Heinbockel (Ed.), ISBN: 978-95351-0617-3, In Tech, Available from: http://www.intechopen.com/books/neuroscience/neurocognitive-deficits-inpatients-with-obstructive-sleep-apnea-syndrome-osas.

[37] Alchanatis M, Zias N, Deligiorgis N, Liappas I, Chroneou A, Soldatos C, Roussos C (2008) Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. *Sleep Breath* **12**, 17-24.

[38] Naegele B, Pepin JL, Levy P, Bonnet C, Pellat J, Feuerstein C (1998) Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. *Sleep* **21**, 392-397.

[39] Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL (2011) Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* **306**, 613-619.

[40] Sharma RA, Varga AW, Bubu AM, Pirraglia E, Kam K, Parekh A, Wohlleber M, Miller MD, Andrade A, Lewis C, Tweardy S, Buj M, Yau PL, Sadda R, Mosconi L, Li Y, Butler T, Glodzik L, Fieremans E, Babb JS, Blennow K, Zetterberg H, Lu SE, Badia SG, Romero S, Rosenzweig I, Gosselin N, Jean-Louis G, Rapoport DM, de Leon MJ, Ayappa I, Osorio RS (2017) Obstructive sleep apnoea severity affects amyloid burden in cognitively normal elderly: A longitudinal study. *Am J Respir Crit Care Med* **197**, 933-943.

[41] Vidoni ED, Townley RA, Honea RA, Burns JM (2011) Alzheimer's Disease Neuroimaging Initiative. Alzheimer disease biomarkers are associated with body mass index. *Neurology* **77**, 1913-1920.

[42] Hsu DC, Mormino EC, Schultz AP, Amariglio RE, Donovan NJ, Rentz DM, Johnson KA, Sperling RA, Marshall GA Harvard Aging Brain Study (2016) Lower late-life body-mass index is associated with higher cortical amyloid burden in clinically normal elderly. *J Alzheimers Dis* **53**, 1097-1105.

[43] Kivimaki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, Knutsson A, Koskenvuo M, Kuosma E, Nordin M, Suominen SB, Theorell T, Vuoksimaa E, Westerholm P, Westerlund H, Zins M, Kivipelto M, Vahtera J, Kaprio J, Singh-Manoux A, Jokela M (2018) Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer Dement* **14**, 601-609.

[44] Deane R1, Sagare A, Hamm K, Parisi M, Lane S, Finn MB, Holtzman DM, Zlokovic BV (2008) apoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. *J Clin Invest* **118**, 4002-4013.

[45] Kadotani H, Kadotani T, Young T, Peppard PE, Finn L, Colrain IM, Murphy GM Jr, Mignot E (2001) Association between apolipoprotein E epsilon4 and sleep disordered breathing in adults. *JAMA* **285**, 2888-2890.

[46] Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, Young T (2004) APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: The Sleep Heart Health Study. *Neurology* **63**, 664-668.

[47] Lemoine P, Sassolas A, Lestra C, Laforest L, Chamba G (2004) Is there an interaction between sleep-disordered breathing, depression and apolipoprotein E phenotype? *L'Encephale* **30**, 360-362.

[48] Thakre TP, Mamtani MR, Kulkarni H (2009) Lack of association of the APOE epsilon 4 allele with the risk of obstructive sleep apnea: Meta-analysis and meta-regression. *Sleep* **32**, 1507-1511.

[49] Ancoli-Israel S, Kripke DF, Ancoli-Israel S, Klauber MR, Mason WJ, Fell R, Kaplan O (1991) Sleep-Disordered Breathing in community-dwelling elderly. *Sleep* **14**, 486-495.

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Risk of Dementia in Posttraumatic Stress Disorder

Alby Elias[1,2], Christopher Rowe[1], and Malcolm Hopwood[2]

Abstract

Several studies have investigated the risk of dementia in posttraumatic stress disorder (PTSD) using a varying methodology. Epidemiological studies have found an increased risk of dementia with PTSD in Vietnam veterans as well as the general population. Laboratory studies reported the accelerated formation of β-amyloid and tau, which represent the primary pathology of Alzheimer's dementia in animal models of PTSD. These investigations were conducted against a background of cognitive impairment and atrophy of the hippocampus and certain cortical areas in patients with PTSD. Very few studies have investigated the pathological basis in humans for the reported association of PTSD with dementia. This important gap in the literature has recently been partly addressed by very few studies that estimated the burden of β-amyloid and tau. The PET studies did not show an association between PTSD and the specific pathology of Alzheimer's disease or signs of neurodegenerative diseases underlying other dementia syndromes. Another study demonstrated decreased plasma β-amyloid load and increased plasma β-amyloid 42/40 ratio in PTSD without PET evaluation. While PTSD is associated with an increased risk of dementia syndrome in general, there is no convincing evidence that it causes or accelerates the pathology of Alzheimer's disease, which causes the most common type of dementia. Factors that may account for the association between PTSD and a clinical diagnosis of dementia are discussed in this review.

Keywords

Alzheimer's disease, dementia, posttraumatic stress disorder, PTSD

Introduction

The relationship between posttraumatic stress disorder (PTSD) and dementia has recently become a flourishing field of research. It originated with clinical studies that demonstrated cognitive impairment in association with PTSD, mostly in persons with combat-related PTSD.[1,2] Concurrent with this research, structural neuroimaging studies reported atrophy of the medial temporal lobe and certain cortical areas in PTSD.[3] Such findings naturally generated the next research question: is PTSD associated with an increased risk of dementia? Epidemiological studies have found an increased risk of dementia with PTSD in Vietnam veterans, as well as with PTSD in the general population.[4-9] Further research assessing the key pathological features specific to Alzheimer's disease (AD) showed an accelerated formation of β-amyloid and tau in the animal models of PTSD.[10,11] Subsequent human studies with comprehensive measurements, including an array of biomarkers of AD contributed to this growing area of research.[12-14] This paper reviews the risk of dementia in PTSD in the light of the latest research findings. This review was conducted based on articles published on MEDLINE, EMBASE, and SCOPUS from January 1990 to December 2019. We used the following keywords: "posttraumatic stress disorder," "PTSD," "cognitive impairment," "neuroimaging," "dementia," and "Alzheimer's disease."

Association Between Posttraumatic Stress Disorder and Dementia

According to the International Classification of Diseases 10'th edition (ICD-10), dementia is defined as a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. The focus of this paper is on the progressive forms of dementia.

Seven epidemiological studies assessed the risk of incident dementia in PTSD with control populations (Table 1). The first study by Yaffe et al. was a retrospective cohort study.[5] The incident dementia diagnosed using ICD-9 for the next seven years was taken as the outcome. The baseline characteristics of

[1] Department of Molecular Imaging and Therapy, Austin Health, The University of Melbourne, Victoria, Australia
[2] Department of Psychiatry, The University of Melbourne, Victoria, Australia

Corresponding Author:
Alby Elias, Department of Molecular Imaging and Therapy, Austin Health, The University of Melbourne, 145 Studley Road, Heidelberg, Victoria 3082, Australia.
Email: alby.elias@unimelb.edu.au

Table 1. Retrospective Cohort Studies of Dementia Risk in PTSD.

Studies (author, year)	Participants and study method	Mean or median age of participants in years at the time of enrolment	Findings	Comments
Yaffe, et al. 2010 [5]	Vietnam veterans; stratified. Compared veterans with PTSD against veterans without PTSD PTSD, n = 53,155 Controls, n = 127,938	68.8 ± 8.6	Outcome: incident dementia over 7-years. Veterans with PTSD were more than twice as likely to develop incident dementia	Excluded head injury, substance abuse and clinical depression. Other factors adjusted: sex, race/ethnicity, educational level, income and medical comorbidities.
Qureshi, et al 2010 [6]	Veterans PTSD (with and without Purple Heart * Recipients) against veterans without PTSD Review of medical records. PTSD+/PH-, n = 3,660 PTSD-/PH+, n = 1,503 PTSD+/PH+, n = 153 PTSD-/PH-, n = 5,165 Almost all were men (99.9%)	PTSD+/PH- = 73.9 ±5.3 PTSD-/PH+ = 73.7±5.0 PTSD+/PH+ = 73.3 ± 4.7 PTSD-/PH- = 73.8 ±5.2	Outcome: Veterans with PTSD had twice the incidence and prevalence of dementia regardless of Purple Heart status.	Since more clinic visits may be associated with an increased rate of dementia diagnosis, the study controlled for the number of clinic visits.
Meziab, et al 2014. [7]	Data collected from Veterans Health Administrations National Patient Center Database. Studied the risk of dementia in prisoners of war (POW) and PTSD Total sample, n = 182,879 PTSD, n = 6114. POW+PTSD = 150	Mean age of the POW group: 76.51 ± 4.66 Mean Age of non-POW group: 68.40 ± 7.85	Cumulative incidence of dementia according to Cox's proportional hazard model. Risk was increased for POW alone, PTSD alone and the greatest for both compared with none.	Demographics, medical and psychiatric comorbidities, period of service, and the competing risk of death were adjusted.
Wang et al 2016[9]	Study of general population based on a Health Insurance Research database. 1750 patients diagnosed with PTSD between 2001 and 2009 and 7000 age-/sex-matched individuals without PTSD. PTSD, n = 1750 Controls, n = 7000	PTSD = 55.44 ±9.20 Controls = 55.42 ± 9.22	Cox's regression model. PTSD was an independent risk factor for the risk for dementia in a dose (severity of PTSD) dependent fashion.	Demographic data and medical and psychiatric comorbidities were adjusted. Results extended to general population.
Mawanda et al. 2017[8]	Nationwide sample of US veterans . PTSD, n = 22,674 Controls, n = 394,498	PTSD = 60.93 ± 7.50 Controls = 68.09 ± 7.96	Cox's regression model. PTSD diagnosis increased the risk for dementia diagnosis. Benzodiazepines and SSRI medications were also associated with risk of dementia independent of PTSD.	Risk of dementia in PTSD varied with psychotropic medication.
Flatt et al 2018 [4]	Study based on medical records. PTSD, n = 5,1147 Controls, n = 498,697)	PTSD = 71.1 ±7.9 Controls = 67.7 ±6.9	Dementia incidence; Cox's hazard model. PTSD was a risk factor for dementia in both sexes, with a heightened risk in those with comorbid depression.	Age, demographics, and comorbidities were adjusted. Results extended to general population and female gender.
Roughead et al. 2017[15]	Department of Veterans Affairs administrative claim data. PTSD, n = 10767 Controls, n = 4845	Age range = 55 to 65 Median (interquartile range) = 57 (56–60)	Dementia incidence. Patients with PTSD who had hospital admission and antipsychotics had higher incidence than controls. No significant association between PTSD and dementia when medical and psychiatric comorbidities and antipsychotic use were adjusted.	All dementia diagnoses within the first 2 years of enrolment were excluded.

Purple Heart is the highest US military decoration awarded to veterans who were injured while serving.

participants showed that substance abuse, clinical depression, and head injury were overrepresented in the PTSD group. In veterans with PTSD relative to those without PTSD, the incident rate of dementia was significantly higher. This difference persisted after adjusting for demographic variables, substance abuse, head injury, and depression. The increased risk was seen across all subtypes of dementia. In the second retrospective cohort study, Qureshi et al. found that veterans with PTSD had a significantly higher incidence and prevalence of dementia compared with those without PTSD.[6] The third study was a retrospective cohort study of U.S. veterans, and it reported an increased risk of dementia in prisoners of war (POW) and PTSD and additive effects from both.[7] Another study followed up U.S. veterans aged over 55 from 2004 to 2012.[8] The risk for dementia was increased with PTSD diagnosis. The use of serotonin specific reuptake inhibitors (SSRI) and second-generation antipsychotics was associated with a further increase in the risk of dementia in veterans with PTSD, although PTSD was independently associated with incident dementia.

Apart from the studies in veterans, the risk of dementia in PTSD has been investigated in the general population. In a population-based cohort study, the risk of dementia was assessed in patients with PTSD against a control group matched for demographic data and psychiatric and medical morbidities.[9] This study signified a higher risk of dementia in patients with PTSD as high as 4 times that in the general population. The heightened risk remained after depressive disorder, and TBI were adjusted. There was a correlation between the incidence of dementia and the severity of PTSD, but the severity was unconventionally defined as the number of visits to the PTSD clinic rather than by a rating scale. The findings of this study extended the risk of dementia in PTSD to the female gender, non-combat traumas, and the general population. The most recent epidemiological study assessed the incidence of dementia over 13 years in a civilian population, both men and women aged above 60 years.[4] The cumulative incidence of dementia was higher in both men and women with PTSD than in those without PTSD. Adjustment for traumatic brain injury (TBI) or vascular risk factors did not eliminate this association, but with depression, the increased risk of dementia in women was no longer present while it persisted in men.

In contrast to the above studies, Roughead et al. found no significant risk of dementia in veterans with PTSD in comparison with control veterans when psychiatric and medical comorbidities were controlled.[15] During a retrospective follow-up of the veterans cohort, all dementia diagnoses in the first 2 years of the study were excluded to avoid the impact of prodromal dementia symptoms. Although the risk of dementia was higher with PTSD, the association was insignificant with an adjusted Hazard Ratio 1.2, (95% Confidence Interval = 0.77 -1.89). The use of antipsychotics was associated with an increased risk of dementia in both groups.

Apart from the retrospective studies, the only prospective follow-up study included a small cohort of patients with PTSD (n = 46) and assessed dementia incidence every 6 months.[16] The study used an MRI scan and assessed proteins ($A\beta_{42}$ and tau) in the cerebrospinal fluid. During a 6-10-year follow-up, 8 patients developed dementia, Alzheimer's dementia in 1 patient, Lewy Body Dementia in 1 and semantic frontotemporal (FTD) dementia in 6. The incidence of semantic FTD was 13%, much higher than in the general population. This study was limited by a small number of patients and the absence of a control population. The increased incidence of semantic FTD may suggest the manifestation of prodromal symptoms of FTD as the symptoms of PTSD, raising the possibility of reverse causality. This is consistent with another report that suggested the onset of dementia heralded by PTSD symptoms.[17]

The increased risk of dementia in PTSD has been studied mostly in relation to Alzheimer's disease, but such a risk is observed across other types of dementia arising from neurodegenerative diseases. In a study of Holocaust survivors (n = 93) with PTSD, vascular dementia (66% of all dementias, n = 15) was the most common type.[18] This is consistent with the increased prevalence of cardiovascular diseases, especially hypertension and stroke in PTSD.[18-20] According to anecdotal reports, Lewy Body Dementia developed in patients with PTSD, a finding which is consistent with a longitudinal study that showed an increased risk of Parkinson's disease in patients with PTSD compared with those without PTSD.[16,21,22] Common genetic loci between rapid eye movement (REM) sleep disorder and Parkinson's disease have been reported in relation to the development of synucleinopathies.[23] Whether nightmares-disturbing dreams with awakening from REM sleep-in PTSD represent the prodrome of Parkinson's disease and other synucleinopathies such as Lewy Body Dementia is worth investigating. As described above, Bonanni et al. reported an increased incidence of frontotemporal dementia in PTSD.[16] Epigenetic changes that represent the process of attachment of certain chemicals to the genome and gene expression modification have been described in PTSD.[24] One such mechanism, known as histone acetylation, has also been implicated in memory function and brain diseases including Alzheimer's disease.[25]

Biomarkers of Alzheimer's Disease in Posttraumatic Stress Disorder

Biomarkers of Alzheimer's disease (AD) are broadly divided into those that measure the specific pathological features and those that measure the neurodegeneration consequent to the pathology. Amyloid plaques and neurofibrillary tangles are the defining lesions of Alzheimer's disease, and neurodegeneration manifests as regional brain hypometabolism and atrophy.[26] Both animal and human studies have provided information about the biomarkers of AD in PTSD. Animal studies preceded human investigations and showed an increased accumulation of β-amyloid in PTSD like states.[10,11] In PTSD, chronically elevated stress was previously hypothesized as an etiological mechanism for increased deposition of A-β, tau hyperphosphorylation, and neurodegeneration with subsequent risk of

Table 2. Cross-Sectional Studies of Alzheimer's Disease Biomarkers in Persons With PTSD.

Study	Participants and study method	Mean age of participants in years	Findings	Comments
Weiner, et al. 2017[12]	PTSD, n = 63 Controls, n = 63 The ADNI study of Vietnam veterans with and without PTSD. Only men. 18F-florbetapir PET imaging, MRI and neuropsychological tests.	PTSD = 67.8 ± 3.6 Controls = 71.1 ± 5.9	Veterans without PTSD had increased odds of positive 18F-florbetapir PET scan. The PTSD cohort had lower cognitive scores and education level.	No evidence of increased amyloid burden in veterans with PTSD.
Elias, et al. 2019. [14]	PTSD, n = 30 Controls, n = 30 Veterans with PTSD compared against those without PTSD using 18F-florbetaben, 18F-AV-1451, and 18F-flurodeoxyglucose PET, MRI volumetry and neuropsychological tests. Only men.	PTSD = 67.80 ± 2.48 Controls = 70.23 ± 5.46	Veterans with PTSD had lower total intracranial volume, predicted premorbid intelligence, education level.	No evidence of increased amyloid or tau burden. No significant difference in regional brain metabolism or volumetry.
Clouston et al.[13] 2019	PTSD, n = 17 Controls, n = 17 9/11 World Trade Center responders with PTSD. Plasma measures of amyloid-β (Aβ) 42/40 ratios, total Aβ, total tau, and neurofilament light.	Age at 09/11/2001 PTSD = 38.63 ± 6.94 Controls = 37.75 ± 9.03 Age at outcome evaluation PTSD = 52.75 ± 6.97 Controls = 52.29 ± 9.18	PTSD was associated with lower plasma Aβ load and higher Aβ42/Aβ40 ratios.	PTSD associated with potential alterations in blood markers of AD, but technique requires further validation. No neuroimaging or CSF analysis performed.

Alzheimer's disease.[11,27] Stress studies were undertaken in transgenic mice, and the stress was induced by isolation and repeated restraint. Alterations in the hypothalamic-pituitary axis (HPA) have been noted in PTSD.[28,29] Dysregulation of the HPA axis has been hypothesized to occur in the early stages of AD.[30] In line with this, glucocorticoid administration augmented both Aβ and tau accumulation. Justice et al. demonstrated that genetically induced AD pathology has the potential to induce a stress response and PTSD symptoms.[10] The exposure to trauma may trigger a common pathway that depends on the corticotrophin-releasing factor (CRF) receptor 1 signaling and drives AD pathology and PTSD symptoms.

Human studies of β-amyloid and tau and neurodegeneration in PTSD are limited (Table 2). The U.S. based Alzheimer's Disease Neuroimaging Initiative (ADNI), and Australian Imaging Biomarkers and Lifestyle study of aging (AIBL) used PET imaging to estimate the uptake of radioactive tracers that bind to β-amyloid and tau in Vietnam veterans with and without PTSD.[12,14] The uptake of these tracers represents a proxy measure of amyloid and tau burden. In contrast to the epidemiological studies, these studies did not lend credence to the hypothesis of an increased risk of Alzheimer's disease pathology in PTSD, as suggested by previous structural neuroimaging studies. The ADNI and AIBL investigations measured regional brain volumetry and metabolism and APOE e4 in addition to the estimation of β-amyloid and tau. These studies found no evidence of neurodegeneration in PTSD or a significant difference between the PTSD and control cohorts in any of these biomarkers. A recent study found decreased plasma β-amyloid load and increased plasma β-amyloid 42/40 ratios in World Trade Centre responders with PTSD, but this study did not use PET imaging.[13] The ADNI and AIBL Vietnam veterans biomarker studies had limitations. Firstly, they focused on the detection of AD pathology, not a clinical diagnosis of dementia. AD accounts for about 60% of cases of dementia, so it is possible that PTSD is associated with another neurodegenerative process. Another limitation is the sample sizes of the PET studies. In total, only 93 veterans with PTSD were compared to 93 veteran controls. The studies were underpowered to detect a difference with a small effect size. Moreover, these studies had a large number of excluded veterans because the PTSD symptoms in some veterans made the assessments intolerable. Whether the inclusion of veterans with more severe PTSD would have altered the results is unknown. To conclude, human PET studies that investigated specific neuroimaging biomarkers of AD did not find evidence to support the increased dementia risk due to AD in PTSD, as suggested by the epidemiological studies or the accelerated development of β-amyloid and tau as shown by animal studies.

Confounding Factors: Potential Explanations for Increased Risk of Dementia in PTSD

From the epidemiological studies, it may be inferred that PTSD is associated with dementia syndrome in general, not specific dementia pathology. This may be a confounding relationship, if not causative. In the absence of conclusive evidence linking PTSD with Alzheimer's disease pathology, it is worth

exploring other potential explanatory factors behind the relation between PTSD and the general risk of dementia syndrome.

Cognitive Reserve

Relatively, a low level of premorbid intelligence and education has been associated with both PTSD and dementia. Proxy measures of cognitive and brain reserve such as total intracranial volume, the premorbid intellectual quotient (IQ), and level of education were found to be lower in veterans with PTSD than in the control veterans.[3,12,31,32] Cognitive reserve is a potential mechanism to buffer the impact of the pathological process associated with Alzheimer's disease.[33] A recent study demonstrated that increased intracranial volume mitigated adverse effects of dementia pathology on cognitive function, particularly attention and executive function.[34] Premorbid intelligence and education may delay the onset of dementia.[35,36] Low education is a risk factor for both trauma exposure as well as PTSD after trauma. Furthermore, occupational activity, as well as cognitive engagement, increase cognitive reserve, but these activities are impaired in PTSD.[37,38] High cognitive reserve (CR) affords protection against the onset of dementia, not the neuropathological markers of AD, suggesting the role of CR as neurocompensation rather than neuroprotection.[39] So, the association of PTSD with dementia may be due to individuals with PTSD being less able to compensate for an already existing neurodegenerative pathology and so develop dementia at an earlier age than controls, rather than PTSD inducing Alzheimer's disease. This hypothesis may be tested in future prospective studies.

Resilience

Resilience is the ability to maintain a state of normal equilibrium in the face of extremely unfavorable circumstances.[40] Resilience and perceived social support were found to be protective against traumatic symptoms.[41] Social isolation was found to be associated with an increased risk of incident dementia.[42] These findings imply that like high cognitive reserve, certain psychosocial factors are protective against both PTSD and the onset of dementia.

Depressive Disorder

Existing literature suggests heavy comorbidity of depression in PTSD, which was estimated at 52%, according to a meta-analysis.[43] Two views explain the comorbidity of depression in PTSD: one proposes comorbidity as a result of the overlap of symptoms particularly in the context of dysphoric symptoms which are integral to the concept of PTSD, and the other argues that comorbidity is a distinct phenotype, perhaps a different type of PTSD.[44] Military trauma was associated with higher rates of comorbid depression in PTSD compared with civilian and natural disasters. Depression is independently linked to cognitive impairment.[45] In a study, veterans with PTSD performed poorly on processing speed, categorical fluency, verbal learning, and recognition, but these findings, except the impairment in processing speed, lost significance upon controlling the effect of depression.[46] Another study replicated this finding by showing that strength of the relationship between PTSD and the deficit in psychomotor speed, attention, learning, and working memory has attenuated in the presence of depression.[47]

In an epidemiological study, depression significantly modified the association between PTSD and dementia.[4] The increased risk of dementia in women was no longer observed upon controlling for depressive symptoms, although it remained for men. Such observations strengthen the previously known association between depression and the risk of dementia.[48,49] Cognitive impairment that occurs in the severe form of depression has been shown to be a predecessor of dementia. Several prospective studies, two cross-sectional studies, and two meta-analyses examined the risk of dementia in late-onset depression.[50] Most studies support an association between depression and dementia. Alexopoulos et al. proposed that cerebrovascular diseases may predispose, precipitate, or perpetuate geriatric depressive syndromes.[51] This is known as the "vascular depression hypothesis" and an important step in explaining cognitive impairment in depression. In summary, depressive symptoms are associated with cognitive impairment and the risk of dementia in PTSD, possibly through the vascular pathology.

Besides depressive disorder, psychotropic medications are associated with an increased risk of dementia in PTSD. Both Serotonin Specific Reuptake Inhibitors (SSRI) and antipsychotics are found to be associated with dementia in veterans with PTSD.[8,15]

Sleep Disorders

As in the case of premorbid IQ, education, and depression, sleep disturbances are associated with both PTSD and dementia. A vast majority of patients (70%-87%) with PTSD experienced various sleep disturbances.[52-54] Compared with the general population and Vietnam veterans without PTSD, there was more considerable sleep disruption in veterans with PTSD (91%), particularly intermittent insomnia.[55,56] Nightmares have been reported by as many as 71% of patients.[52] The reported sleep problems in PTSD included recurrent awakenings, threatening dreams, thrashing movements during sleep, and awakenings with startle or panic features.[57] Yesavage, et al. found a very high prevalence (69%) of obstructive sleep apnoea (OSA) in PTSD.[58]

Sleep-dependent memory enhancement has been demonstrated in human experiments.[59] In a study of Iraqi Freedom veterans, it was found that cognitive impairment in PTSD was found to be mediated by self-reported sleep disturbances.[60] The adverse impact of OSA on cognitive function is well known; recent findings suggest accelerated cognitive decline in the presence of OSA.[61,62] The cognitive domains reported to be impaired in OSA are attention, procedural memory, and episodic memory,[63-65] processing speed, and executive function.[66-68] Executive dysfunction has been reported in Vietnam veterans

with OSA.[67] The confounding effect of OSA was not adequately addressed in previous studies that addressed the relation between PTSD and dementia.

Shorter sleep duration and poor quality of sleep have been associated with increased Aβ retention.[69] Older individuals with insomnia had an accelerated progression to dementia from normal cognitive functioning compared with those who did not report insomnia.[70] These findings support the hypothesis that sleep disturbances in PTSD may pose an increased risk of dementia. Apart from cognitive impairment, existing data suggest an association between obstructive sleep apnoea and mild cognitive impairment (MCI) and dementia.[71] A seminal longitudinal study found a 2-fold risk for MCI and dementia in patients with OSA during a five-year follow-up.[62] After early observations of the association between OSA and dementia, further findings have accrued supporting a link between sleep-disordered breathing and both MCI and dementia.[62,72] A recent study demonstrated an annual decline in the level of cerebrospinal fluid (CSF) $A\beta_{42}$ over two years in cognitively asymptomatic elderly patients with OSA, implying an increased risk of AD in this condition.[73] The change in CSF $A\beta_{42}$ correlated with the severity of OSA independent of APOE.

Metabolic and Vascular Diseases

A prospective twin study demonstrated a 40% increase in the age-adjusted incidence of onset of type 2 diabetes mellitus in twins with PTSD compared with those without PTSD.[74] It is also known that diabetes increases the risk of vascular dementia, almost double in one study.[75] Patients with PTSD had a higher incidence of hypertension and overweight,[74] factors that imply an increased risk of both Alzheimer's and vascular dementia.[76,77]

Clinical Implications

Not long after Alzheimer's description of neuritic plaques and tangles, Lorand remarked: "work of any kind, even mental work alone, is a means of preventing precocious senility."[78] Given that cognitive reserve is a dynamic construct, it can undergo modifications throughout life. Physical and mental activities contribute to CR in old age.[79,80] A randomized controlled trial showed that cognitive interventions led to the improvement in targeted cognitive domains compared with the baseline.[81] Moreover, Yang et al. have demonstrated enhanced activation of cognitive control regions after cognitive-behavioral therapy.[82] The Benefits of cognitive training were found to be lasting for years and transferable to instrumental activities of daily life.[83] Apart from cognitive activities, non-cognitive leisure activities also improve cognitive reserve.[84] Longitudinal studies have found a reduced risk of dementia with regular physical activities after adjusting for education and APOE e4.[38] As described above, increased incidence of diabetes and overweight in PTSD implies the importance of behavioral and lifestyle factors in dementia risk modification, independent of their relation to psychiatric disorders.[74] Patients with PTSD may be able to enhance cognitive reserve by engaging in cognitive and physical activities and thereby delay the onset of dementia. The recognition of a long preclinical phase indicates that there is time for therapeutic interventions that have the potential for risk reduction.

The dementia risk modification in PTSD is relevant both theoretically and therapeutically. Demonstrated in clinical trials, psychological interventions in PTSD have produced a reversal of hippocampal and amygdala atrophy and yielded improvement in occupational impairment.[85-87] Abnormalities in dendritic spines have been observed in depression and stress-related psychiatric disorders.[88] Stressful experiences can produce profound changes in the morphology of neurons within mPFC, specifically dendritic spine architecture with a variety of behavioral consequences.[89] Such alterations have implications in PTSD because some of these changes may be amenable to treatment. For instance, increased expression of synaptic proteins and trophic factors that lead to neurogenesis occur during antidepressant treatment.[88] The long-term antidepressant treatment has resulted in an increase in hippocampal volume in patients with PTSD.[90] These observations accentuate the importance of brain plasticity in PTSD. These findings are contradictory to an increased risk of dementia with use of SSRI in PTSD as shown by Mawanda et al. Such contrasting observations may be due to the possibility that patients in the study of Mawanda et al. were older (mean age = 61 years) and representing a more chronic or severe form of the disorder whereas the increase in hippocampal volume was demonstrated in relatively young individuals (mean age = 47 years). This may imply that the beneficial effects of SSRI are relevant in the early stages of PTSD. The epigenetics of PTSD, as well as dementia, is a growing field of research. A detailed account of the epigenetic mechanism is beyond the scope of this review. Nonetheless, an association between increased DNA methylation of the brain-derived neurotrophic factor (BDNF) promotor region and PTSD is worth considering in this context given that BDNF is a key mediator of brain plasticity and its levels were found to be lower in patients with dementia and cognitive impairment in comparison with healthy controls but known to be elevated after antidepressant treatment.[91-93] Adequate treatment of PTSD must aim at the restoration of physical and mental activities along with occupational function.

Limitations

This is a narrative review and is limited by the absence of a systematic review and meta-analyses. Potential selection bias in study inclusion is a limitation of narrative review The concept of cognitive reserve is still in a developing phase. Whether interventions in PTSD and improvement in cognitive reserve reduce the risk of dementia warrants testing in future prospective studies.

Conclusion

A robust amount of data suggests an increased risk of dementia in PTSD. The epidemiological studies have, however, not unraveled different types of dementia based on the characteristic pathology. Recent studies that investigated the pathological basis of dementia have been a few and mostly included biomarkers of Alzheimer's disease. There is a dearth of studies to conclude whether PTSD is associated with increased pathology of Alzheimer's disease, and more future studies are warranted. At the same time, an increased risk of dementia in PTSD may be mediated by confounding factors, which may include a relatively low cognitive reserve, psychiatric and medical comorbidities, especially metabolic and vascular diseases, sleep disorders, or an increased occurrence of other neuropathology.

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ORCID iD

Alby Elias https://orcid.org/0000-0002-7494-1028

References

1. Uddo M, Vasterling JJ, Brailey K, et al. Memory and attention in combat-related post-traumatic stress disorder (PTSD). *J Psychopathol Behav Assess*. 1993;15(1):43-52. doi:10.1007/BF00964322
2. Vasterling JJ, Duke LM, Brailey K, Joseph IC, Allain NA Jr, Patricia BS. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology*. 2002;16(1):5-14.
3. Bromis K, Calem M, Reinders AATS, Steven Williams CR, Matthew JK. Meta-analysis of 89 structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *Amer J Psych*. 2018;175(10):989-998. doi:10.1176/appi.ajp.2018.17111199
4. Flatt JD, Gilsanz P, Quesenberry CP Jr, Kathleen BA, Rachel AW. Post-traumatic stress disorder and risk of dementia among members of a health care delivery system. *Alzheimers Dement*. 2018;14(1):28-34. doi:10.1016/j.jalz.2017.04.014
5. Yaffe K, Vittinghoff E, Lindquist K, et al. Posttraumatic stress disorder and risk of dementia among US veterans. *Arch Gene Psych*. 2010;67(6):608-613. doi:10.1001/archgenpsychiatry.2010.61
6. Qureshi SU, Kimbrell T, Pyne JM, et al. Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder. *J Ame Geriat Soci*. 2010;58(9):1627-1633. doi:10.1111/j.1532-5415.2010.02977.x
7. Meziab O, Kirby KA, Williams B, et al. Prisoner of war status, posttraumatic stress disorder, and dementia in older veterans. *Alzheim Dement*. 2014;10(3 suppl):S236-S241. doi:10.1016/j.jalz.2014.04.004
8. Mawanda F, Wallace RB, McCoy K, Thad EA. PTSD, psychotropic medication use, and the risk of dementia among US veterans: a retrospective cohort study. *J Amer Geriat Soci*. 2017;65(5):1043-1050. doi:10.1111/jgs.14756
9. Wang TY, Wei HT, Liou YJ, et al. Risk for developing dementia among patients with posttraumatic stress disorder: a nationwide longitudinal study. *J Affec Disord*. 2016;205:306-310. doi: 10.1016/j.jad.2016.08.013
10. Justice NJ, Huang L, Tian JB, et al. Posttraumatic stress disorder-like induction elevates beta-amyloid levels, which directly activates corticotropin-releasing factor neurons to exacerbate stress responses. *J Neurosci*. 2015;35(6):2612-2623. doi:10.1523/jneurosci.3333-14.2015
11. Carroll JC, Iba M, Bangasser DA, et al. Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. *J Neurosci*. 2011;31(40):14436-14449. doi:10.1523/jneurosci.3836-11.2011
12. Weiner MW, Harvey D, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam veterans using the Alzheimer's Disease Neuroimaging Initiative: preliminary report. *Alzheim Dement (New York, N Y)*. 2017;3(2):177-188. doi:10.1016/j.trci.2017.02.005
13. Clouston SAP, Deri Y, Diminich E, et al. Posttraumatic stress disorder and total amyloid burden and amyloid-beta 42/40 ratios in plasma: results from a pilot study of world trade center responders. *Alzheim Dement (Amsterdam, Netherlands)* 2019;11:216-220. doi:10.1016/j.dadm.2019.01.003
14. Elias A, Cummins T, Lamb F, et al. Amyloid-beta, tau, and 18F-fluorodeoxyglucose positron emission tomography in posttraumatic stress disorder. *J Alzheimer's Dis*. 2020;73(1):163-173. doi:10.3233/jad-190913
15. Roughead EE, Pratt NL, Kalisch Ellett LM, et al. Posttraumatic stress disorder, antipsychotic use and risk of dementia in Veterans. *J Amer Geriat Soci*. 2017;65(7):1521-1526. doi:10.1111/jgs.14837
16. Bonanni L, Franciotti R, Martinotti G, et al. Post traumatic stress disorder heralding the onset of semantic frontotemporal dementia. *JAD*. 2018;63(1):203-215. doi:10.3233/jad-171134
17. Johnston D. A series of cases of dementia presenting with PTSD symptoms in World War II combat veterans. *J Amer Geriat Soci*. 2000;48(1):70-72. doi:10.1111/j.1532-5415.2000.tb03032.x
18. Sperling W, Kreil SK, Biermann T. Posttraumatic stress disorder and dementia in Holocaust survivors. *J Nerv Ment Dis*. 2011;199(3):196-198. doi:10.1097/NMD.0b013e31820c71e0
19. O'Toole BI, Catts SV. Trauma, PTSD, and physical health: an epidemiological study of Australian Vietnam veterans. *J Psychosom Res*. 2008;64(1):33-40. doi:10.1016/j.jpsychores.2007.07.006
20. Brass LM, Page WF. Stroke in former prisoners of war. *J Stroke Cerebrovasc Dis*. 1996;6(2):72-78. doi:10.1016/s1052-3057(96)80006-1

21. Ahearn E, Walaszek A. When post-traumatic stress disorder and Charles Bonnet syndrome become Lewy body dementia. *Am J Geriatr Psychiatry*. 2018;26(8):911. doi:10.1016/j.jagp.2018.02.007
22. Chan YE, Bai YM, Hsu JW, et al. Post-traumatic stress disorder and risk of Parkinson disease: a nationwide longitudinal study. *Am J Geriatr Psychiatry*. 2017;25(8):917-923. doi: 10.1016/j.jagp.2017.03.012
23. Gan-Or Z, Girard SL, Noreau A, et al. Parkinson's disease genetic loci in rapid eye movement sleep behavior disorder. *J Mol Neurosci*. 2015;56(3):617-622. doi:10.1007/s12031-015-0569-7
24. Rusiecki JA, Chen L, Srikantan V, et al. DNA methylation in repetitive elements and post-traumatic stress disorder: a case-control study of US military service members. *Epigenomics*. 2012;4(1):29-40. doi:10.2217/epi.11.116
25. Bahari-Javan S, Sananbenesi F, Fischer A. Histone-acetylation: a link between Alzheimer's disease and post-traumatic stress disorder? *Front Neurosci*. 2014;8(160):3 doi:10.3389/fnins.2014.00160
26. Wilcock GK, Esiri MM. Plaques, tangles and dementia. A quantitative study. *J Neurol Sci*. 1982;56(2-3):343-356. doi:10.1016/0022-510x(82)90155-1
27. Dong H, Goico B, Martin M, et al. Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. *Neuroscience*. 2004;127(3):601-609. doi:10.1016/j.neuroscience.2004.05.040
28. Ehlert U, Gaab J, Heinrichs M. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. *Biol Psychol*. 2001;57(1-3):141-152.
29. Morris MC, Compas BE, Garber J. Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. *Clin Psychol Rev*. 2012;32(4):301-315. doi:10.1016/j.cpr.2012.02.002
30. Green KN, Billings LM, Roozendaal B, James LM, Frank ML. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci*. 2006;26(35):9047-9056. doi:10.1523/jneurosci.2797-06.2006
31. Macklin ML, Metzger LJ, Litz BT, et al. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychol*. 1998;66(2):323-326. doi:10.1037//0022-006x.66.2.323
32. Kremen WS, Koenen KC, Boake C, et al. Pretrauma cognitive ability and risk for posttraumatic stress disorder: a twin study. *Arch Gene Psych*. 2007;64(3):361-368. doi:10.1001/archpsyc.64.3.361
33. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006-1012. doi:10.1016/s1474-4422(12)70191-6
34. Groot C, van Loenhoud AC, Barkhof F, et al. Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. *Neurology*. 2018;90(2):e149-e56. doi:10.1212/wnl.0000000000004802
35. Cervilla J, Prince M, Joels S, Lovestone S, Mann A. Premorbid cognitive testing predicts the onset of dementia and Alzheimer's disease better than and independently of APOE genotype. *J Neurol Neurosurg Psych*. 2004;75(8):1100-1106. doi:10.1136/jnnp.2003.028076
36. Sando SB, Melquist S, Cannon A, et al. Risk-reducing effect of education in Alzheimer's disease. *Intl J Geriat Psych*. 2008;23(11):1156-1162. doi:10.1002/gps.2043
37. Den Berk Clark CV, Secrest S, Walls J, et al. Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity, and co-occuring smoking: a systematic review and meta-analysis. *Health Psychol*. 2018;37(5):407-416. doi:10.1037/hea0000593
38. Cheng ST. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. *Curr Psych Rep*. 2016;18(9):85. doi:10.1007/s11920-016-0721-2
39. Brayne C, Ince PG, Keage HA, et al. Education, the brain and dementia: neuroprotection or compensation? *Brain*. 2010;133(Pt 8):2210-2216. doi:10.1093/brain/awq185
40. Bonanno GA. Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? *Am Psychol* 2004;59(1):20-28. doi:10.1037/0003-066x.59.1.20
41. Pietrzak RH, Johnson DC, Goldstein MB, James CM, Steven MS. Psychological resilience and postdeployment social support protect against traumatic stress and depressive symptoms in soldiers returning from operations enduring freedom and Iraqi freedom. *Depress Anx*. 2009;26(8):745-751. doi:10.1002/da.20558
42. Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. *Arch Gene Psych*. 2007;64(2):234-240. doi:10.1001/archpsyc.64.2.234
43. Rytwinski NK, Scur MD, Feeny NC, Eric AY. The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. *J Trauma Stress*. 2013;26(3):299-309. doi:10.1002/jts.21814
44. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues Clin Neurosci*. 2015;17(2):141-150.
45. McAllister-Williams RH, Ferrier IN, Young AH. Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. *Psychol Med*. 1998;28(3):573-584. doi:10.1017/S0033291798006680
46. Cohen BE, Neylan TC, Yaffe K, Kristin WS, Yongmei L, Deborah EB. Posttraumatic stress disorder and cognitive function: findings from the mind your heart study. *J Clin Psychiat*. 2013;74(11):1063-1070. doi:10.4088/JCP.12m08291
47. Sumner JA, Hagan K, Grodstein F, Andrea LR, Brian H, Karestan CK. Posttraumatic stress disorder symptoms and cognitive function in a large cohort of middle-aged women. *Depres Anx*. 2017;34(4):356-366. doi:10.1002/da.22600
48. Barnes DE, Yaffe K, Byers AL, McCormick M, Catherine S, Rachel AW. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gene Psych*. 2012;69(5):493-498. doi:10.1001/archgenpsychiatry.2011.1481
49. Diniz BS, Butters MA, Albert SM, Mary AD, Charles FR III. Late-life depression and risk of vascular dementia and

Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*. 2013;202(5): 329-335. doi:10.1192/bjp.bp.112.118307

50. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol*. 2011;7(6):323-331. doi:10.1038/nrneurol.2011.60
51. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gene Psych*. 1997;54(10):915-922. doi:10.1001/archpsyc.1997.01830220033006
52. Leskin GA, Woodward SH, Young HE, Javaid IS. Effects of comorbid diagnoses on sleep disturbance in PTSD. *J Psych Res*. 2002;36(6):449-452. doi:10.1016/s0022-3956(02)00025-0
53. Foa EB, McLean CP, Zang Y, et al. Psychometric properties of the posttraumatic diagnostic scale for DSM-5 (PDS-5). *Psychol Assess*. 2016;28(10):1166-1171. doi:10.1037/pas0000258
54. Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr Psych*. 2000;41(6):469-478. doi:10.1053/comp.2000.16568
55. Roszell DK, McFall ME, Malas KL. Frequency of symptoms and concurrent psychiatric disorder in Vietnam veterans with chronic PTSD. *Hosp Comm Psych*. 1991;42(3):293-296.
56. Neylan TC, Marmar CR, Metzler TJ, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *Amer J Psych*. 1998;155(7): 929-933. doi:10.1176/ajp.155.7.929
57. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. *Amer J Psych*. 1995;152(1):110-115. doi:10.1176/ajp.152.1.110
58. Yesavage JA, Kinoshita LM, Kimball T, et al. Sleep-disordered breathing in Vietnam veterans with posttraumatic stress disorder. *Ame J Geriat Psych*. 2012;20(3):199-204. doi:10.1097/JGP.0b013e3181e446ea
59. Stickgold R. Sleep-dependent memory consolidation. *Nature*. 2005;437(7063):1272-1278. doi:10.1038/nature04286
60. Verfaellie M, Lee LO, Lafleche G, Avron S. Self-reported sleep disturbance mediates the relationship between PTSD and cognitive outcome in blast-exposed OEF/OIF veterans. *J Head Trauma Rehabil*. 2016;31(5):309-319. doi:10.1097/HTR.0000000000000197
61. Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev*. 2001;5(6):423-445. doi:10.1053/smrv.2001.0157
62. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. 2015;84(19):1964-1971. doi:10.1212/WNL.0000000000001566
63. Naegele B, Launois SH, Mazza S, Claude F, Jean-Louis P, Patrick L. Which memory processes are affected in patients with obstructive sleep apnea? An evaluation of 3 types of memory. *Sleep*. 2006;29(4):533-544. doi:10.1093/sleep/29.4.533
64. Cosentino FII, Bosco P, Drago V, et al. The APOE ε4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. *Sleep Med*. 2008;9(8):831-839. doi:10.1016/j.sleep.2007.10.015
65. Mazza S, Pépin J-L, Naëgelé B, Plante J, Deschaux C, Lévy P. Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. *Euro Resp J*. 2005;25(1):75-80. doi:10.1183/09031936.04.00011204
66. Beebe DW, Groesz L, Wells C, Alisha N, Kevin M. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. *Sleep* 2003;26(3): 298-307. doi:10.1093/sleep/26.3.298
67. Felver-Gant JC, Bruce AS, Zimmerman M, Lawrence HS, Richard PM, Mark SA. Working memory in obstructive sleep apnea: construct validity and treatment effects. *J Clin Sleep Med*. 2007;3(6):589-594.
68. Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. *Sleep* 2013;36(2):203-220. doi:10.5665/sleep.2374
69. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol*. 2013;70(12):1537-1543. doi:10.1001/jamaneurol.2013.4258
70. Osorio RS, Pirraglia E, Agüera-Ortiz LF, et al. Greater risk of Alzheimer's disease in older adults with insomnia. *J Ame Geriat Soci*. 2011;59(3):559-562. doi:10.1111/j.1532-5415.2010.03288.x
71. Emamian F, Khazaie H, Tahmasian M, et al. The association between obstructive sleep apnea and Alzheimer's disease: a meta-analysis perspective. *Front Aging Neurosci*. 2016;8:78. doi:10.3389/fnagi.2016.00078
72. Mander BA, Marks SM, Vogel JW, et al. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci*. 2015;18(7):1051-1057. doi:10.1038/nn.4035
73. Sharma RA, Varga AW, Bubu OM, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. a longitudinal study. *Am J Respir Crit Care Med*. 2018;197(7): 933-943. doi:10.1164/rccm.201704-0704OC
74. Vaccarino V, Goldberg J, Magruder KM, et al. Posttraumatic stress disorder and incidence of type-2 diabetes: a prospective twin study. *J Psych Res*. 2014;56:158-164. doi:10.1016/j.jpsychires.2014.05.019
75. Ahtiluoto S, Polvikoski T, Peltonen M, et al. Diabetes, Alzheimer disease, and vascular dementia. a population-based neuropathologic study. *Neurology*. 2010;75(13):1195-1202. doi:10.1212/WNL.0b013e3181f4d7f8
76. Hassing LB, Dahl AK, Thorvaldsson V, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. *Int J Obes (Lond)*. 2009;33(8):893-898. doi:10.1038/ijo.2009.104
77. Nagai M, Hoshide S, Kario K. Hypertension and dementia. *Ame J Hyper*. 2010;23(2):116-124. doi:10.1038/ajh.2009.212
78. Lorand A. *Old Age Deferred*. 1913. Philadelphia: F.A. Davis Company.
79. Carvalho A, Rea IM, Parimon T, Barry JC. Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clin Interv Aging*. 2014;9:661-682. doi:10.2147/CIA.S55520
80. Yaffe K, Weston A, Graff-Radford NR, et al. Association of plasma β-amyloid level and cognitive reserve with subsequent cognitive decline. *JAMA*. 2011;305(3):261-266. doi:10.1001/jama.2010.1995

81. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288(18):2271-2281. doi:10.1001/jama.288.18.2271
82. Yang Z, Oathes DJ, Linn KA, et al. Cognitive behavioral therapy is associated with enhanced cognitive control network activity in major depression and posttraumatic stress disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(4):311-319. doi:10.1016/j.bpsc.2017.12.006
83. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*. 2006;296(23):2805-2814. doi:10.1001/jama.296.23.2805
84. Scarmeas N, Stern Y. Cognitive reserve and lifestyle. *J Clin Exp Neuropsych*. 2003;25(5):625-633. doi:10.1076/jcen.25.5.625.14576
85. Speicher SM, Walter KH, Chard KM. Interdisciplinary residential treatment of posttraumatic stress disorder and traumatic brain injury: effects on symptom severity and occupational performance and satisfaction. *Am J Occup Ther*. 2014;68(4):412-421. doi:10.5014/ajot.2014.011304
86. Butler O, Willmund G, Gleich T, Jürgen G, Simone K, Peter Z. Hippocampal gray matter increases following multimodal psychological treatment for combat-related post-traumatic stress disorder. *Brain Behav*. 2018;8(5):e00956-e01056. doi:10.1002/brb3.956
87. Laugharne J, Kullack C, Lee CW, et al. Amygdala volumetric change following psychotherapy for posttraumatic stress disorder. *J Neuropsych Clin Neurosci*. 2016;28(4):312-318. doi:10.1176/appi.neuropsych.16010006
88. Licznerski P, Duman RS. Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. *Neuroscience*. 2013;251:33-50. doi:10.1016/j.neuroscience.2012.09.057
89. Moench KM, Wellman CL. Stress-induced alterations in prefrontal dendritic spines: implications for post-traumatic stress disorder. *Neurosci Lett*. 2015;601:41-45. doi:10.1016/j.neulet.2014.12.035
90. Vermetten E, Vythilingam M, Southwick SM, Charney SD, Douglas Bremner J. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psych*. 2003;54(7):693-702. doi:10.1016/s0006-3223(03)00634-6
91. Kim TY, Kim SJ, Chung HG, Choi JH, Kim SH, Kang JI. Epigenetic alterations of the BDNF gene in combat-related posttraumatic stress disorder. *Acta Psych Scand*. 2017;135(2):170-179. doi:10.1111/acps.12675
92. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psych*. 2008;64(6):527-532. doi:10.1016/j.biopsych.2008.05.005
93. Siuda J, Patalong-Ogiewa M, Żmuda W, et al. Cognitive impairment and BDNF serum levels. *Neurol Neurochir Pol*. 2017;51(1):24-32. doi:10.1016/j.pjnns.2016.10.001

Austin Health

AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL FOR AMENDMENT

Prof Chris Rowe
Nuclear Medicine /PET Centre
Level 1 HSB Austin Campus

20 April 2016

Dear Prof Chris Rowe

AU RED HREC Reference Number: 04947

Austin Health Project Number: 04947

Project Title: Effects of traumatic brain injury and post traumatic stress disorder on Alzheimerâ€™s Disease in Australian war veterans

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I am pleased to advise that the above project amendment has **received ethical approval** from the Austin Health Human Research Ethics Committee (HREC). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Research Involving Humans (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

Original HREC Approval Date: 13/06/2013

Approved Documents:

The following documents have been reviewed and approved:

Document	Version	Date
Protocol	6	27/07/2015
Austin Health PICF	6	07/07/2015
Austin Health PICF (Alternative)	6B	07/07/2015

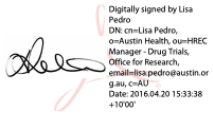
Conditions of Ethics Approval:

- You are required to submit to the HREC:
  - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
  - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.

- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: ***Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009***.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters which may impact the conduct of the project.
- If your project involves radiation, you are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice 'Exposure of Humans to Ionizing Radiation for Research Purposes' Radiation Protection series Publication No.8 (May 2005)(ARPANSA Code).

The HREC may conduct an audit of the project at any time.

Yours sincerely



Lisa Pedro
HREC Manager – Drug Trials

Austin Health

Place Patient Label Here

FAH018170

Version 6 Date: 7th July 2015

PARTICIPANT INFORMATION /CONSENT FORM

Interventional Study - *Adult providing own consent*

Full Project Title: Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer's disease in Australian war veterans.

Site Name: Austin Health

Principal Investigator: Prof. Christopher Rowe
Director of Nuclear Medicine and the Centre for PET
Austin Health

Associate Investigators: Malcolm John Hopwood
Associate Professor
Department of Psychiatry at the University of Melbourne

Victor Villemagne
Associate Professor
Department of Medicine at the University of Melbourne

Jeffrey Rosenfeld
Professor
Department of Neurosurgery at Alfred Health

Michael Weiner
Professor
School of Medicine at the University of California, San Francisco

Robert Williams
Research Fellow/Technologist
Melbourne Brain Centre at the University of Melbourne

Part 1 What does my participation involve?

1.1. Introduction

You are invited to take part in a study entitled 'Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer's Disease in Australian war veterans' that will be conducted by Professor Christopher Rowe of Austin Health.

The aim of this research is to identify, prevent and target treatment of Alzheimer's disease in combat veterans.

You have been asked to join the study because you are an Australian war veteran:

☐ A: with combat associated traumatic brain injury (TBI)

☐ B: with post traumatic stress disorder (PTSD)

☐ C: a veteran control without TBI or PTSD

This Participant Information and Consent Form tells you about the research project and explains the tests involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this project is entirely voluntary, and you are free to withdraw at any time without your decision to withdraw impacting in any way upon the future treatment you may receive from Austin Health.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to have the tests that are described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

1.2. What is the purpose of this research?

The purpose of this research project is to help identify risk factors for development of Alzheimer's Disease (AD) in military veterans. Alzheimer's disease is the most common cause of dementia. The scale of this chronic disease is enormous. Worldwide, nearly 35.6 million people live with dementia. This number is expected to double by 2030 (65.7 million) and more than triple by 2050 (115.4 million); (WHO report April 2012).

Evidence suggests that both traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) increase risk for cognitive decline, AD, and dementia. However, currently no study using imaging and biomarkers, which directly measure changes in the brain and AD pathology, have been performed to study the effects of TBI and PTSD.

Positron Emission Tomography (PET) imaging, cerebrospinal fluid collection, MRI imaging and other tools will be used to identify veterans at risk. These tools can then be used to establish links between veterans' experience and Alzheimer's disease to identify those at risk and develop preventive strategies for those groups.

The information collected from this research would assist in the future care of veterans and help to identify those at high risk of AD and who may benefit from early intervention trials.

The outcomes will have direct implications for recently returned service men and women by providing them with more effective treatment sooner and guiding new acute treatments.

This research has been funded by Piramal Pharmaceuticals and the USA Department of Defence.

1.3. What does participation in this research involve?

An appointment will be organised for you to attend the Florey Institute of Neuroscience and Mental Health at Parkville or the Austin Health Heidelberg campus, where written consent will be obtained and you will undergo a series of clinical and cognitive (memory and thinking) tests. Appointments will then be made for you to have a lumbar puncture, blood draw, 1-2 MRI scans and three PET scans, as explained below. The lumbar puncture is optional .

Visit Schedule:

Procedure	Pre-Screening	Screening	Baseline	18 mth FU
Website/Telephone questionnaire	x			
PICF sent to interested volunteers	x			
Informed consent		x		
Demographics Medical/Medication History		x		
Psychometrics			x	x
Biomarkers assessment CSF, Bloods			x	
MRI			x	x
PET FBB			x	
MRI 7T			x	
PET TAU			x	
PET FDG			x	

Screening

The screening visit will take about 2 hours. You will be asked to attend for an interview. A senior study investigator will ensure that you have fully understood the Participant Information and Consent Form and then obtain your written consent to participate in the study. (The consent form is located at the end of this document).

The investigator or his delegate will ask questions about your past medical history and any current medical problems.

Baseline

This visit is actually several visits to different locations such as the Florey Institute of Neuroscience and Mental Health Clinic (Parkville or Heidelberg), Austin Health (Heidelberg), St. Vincent's Hospital (Fitzroy) and Royal Melbourne Hospital (Parkville). (Note: Taxi vouchers may be provided)

Neuropsychological Assessment:
You will be asked to complete some memory and attention tasks. These will help the investigators understand how well your memory and other areas of thinking are working. Allow 1-2 hours for these assessments.

MRI:

You will be asked to have an MRI scan, and a subset of participants will be asked to have a second MRI scan. This involves lying still in the MRI scanner for about 40 minutes. This will be done at the Florey Institute of Neuroscience and Mental Health Clinic in Heidelberg/Parkville, Swinburne University of Technology or the Royal Melbourne Hospital. There are no injections and no side-effects. MRI is painless but you will hear loud noises like a drumbeat. Headphones are provided. There are also some reasons why people cannot undergo an MRI; for example, if you have a permanent pacemaker, or an inner ear implant. These will be discussed with you beforehand.

Blood sample:

An 80ml blood sample (which is equivalent to about 16 teaspoons) will also be taken from you during this visit for routine tests and Apolipoprotein E (ApoE). ApoE is not a routine clinical blood test. This blood sample will only be identified by a coded number to make sure that the analysed information remains strictly confidential. ApoE may have a role in the formation of brain amyloid with certain types associated with increased risk of developing Alzheimer's disease. This blood sample will be coded so that it can be correlated with clinical information. The results of the ApoE test will not be released to you. The remainder of the blood sample will be stored at the Florey Institute of Neurosciences and Mental Health (FINMH), Parkville, for future testing. It may also be made available to other research groups, worldwide, for use in Ethics Committee approved research in related areas of medicine.

Cerebrospinal fluid collection (optional & dependent upon further funding):

Collection of cerebral spinal fluid (CSF) via lumbar puncture will be conducted by a specialist anaesthetist at St Vincent's Hospital. This will be later analyzed for Alzheimer's disease related biomarkers. As per the blood samples, CSF will be stored at the FINMH for further research and may be shared with other research groups working in similar fields.

A lumbar puncture involves a needle being inserted at the base of the spine and a sample of cerebrospinal fluid (CSF) taken in order to measure the levels of certain proteins linked to Alzheimer's disease. This procedure is performed under local anaesthesia. After each lumbar puncture you MUST rest for at least two hours and you are encouraged to drink at least 2 litres of fluids within the next 15 hours. The actual procedure only takes approximately 10 minutes, however, from your arrival at the Anaesthetics' Department, and including an observation period after the procedure, please allow 2 ½ hours.

PET Scans:

You will be asked to return to either FINMH in Parkville or to the Centre for PET at Austin Health for another visit for the ^{18}F-Florbetaben PET scan to measure amyloid in the brain, and again on another day for the ^{18}F-FDG PET scan to measure brain activity and metabolism. You will be asked to attend another appointment for the ^{18}F-T807 scan, to measure tau in the brain. On the day of your FDG scan, you will be asked to fast from 8am.

An intravenous cannula will be inserted into a vein in your arm for the injection of a small amount (less than 5 micrograms, 200 MBq) of ^{18}F-Florbetaben and ^{18}F-T807 (less than 5 micrograms, 185MBq).

The ^{18}F-Florbetaben scan will commence 90 minutes after the injection and will last for 20-30 minutes. For the FDG PET scan you will be injected with a small amount (less than 5 micrograms, 185 MBq) of ^{18}F-FDG. You will be asked to remain in a darkened, quiet room for 30 minutes, followed by a 20-30 minute scan. After the scan you will be provided with a meal. The ^{18}F-T807 scan will commence 80 minutes post injection, and will last 30 minutes. You are then free to leave, however, you should avoid close contact with pregnant women and you should not cuddle children for 2 hours after the injection, as both tracers only have a 2 hour half-life. This is to be

completely certain there can be no effect whatsoever on others from the tiny amount of radiation you received. Please allow about 3 hours for each scan appointment. All 3 scans will need to be performed on separate days.

18 Month Follow-up

Memory testing, an MRI scan and blood sample collection will be repeated after 18 months (subject to further funding)

Reimbursements

Taxi vouchers will be provided for participants living within a 1 hour drive of the visit site, for each visit, when required. If you live further away than a 1 hour drive from the visit site, we are unable to provide taxi vouchers but can offer you a free parking space if you drive in to FINMH in Parkville or the Centre for PET at Austin Health. A lunch box can also be provided for participants for each visit.

1.4. Other relevant information about the research project.

Overall, 150 participants over 60 years of age will take part in the study.
This will consist of 50 participants with a history of TBI, 50 participants with ongoing PTSD and 50 veteran controls without TBI or PTSD.

If after three months recruitment for the different groups becomes difficult to fill, TBI participants with PTSD will be included.

Your coded data will be shared with researchers world-wide through 2 research websites. The first is run by the University of California and it is called LONI (Laboratory of Neuroimaging). The second is run by the U.S. National Institute of Health and the Department of Defense, and is called FITBIR (Federal Interagency of Traumatic Brain Injury Research). In addition, portions of your blood and CSF may be sent to other research groups working in the same or related areas of medical research and the results from this study will be used in the PhD projects of Tia Cummins and Dr. Alby Elias.

1.5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Austin Health. If you decide to withdraw from the research project, the researchers may still use the information and results collected to that point, unless you specifically request them not to.

1.6. What are the alternatives to participation?

You do not have to participate in this study.

1.7. What are the possible benefits of taking part?

There will be no clear benefit to you from your participation in this research. However, data from this study could potentially be used to develop preventative measures and potential cures for Alzheimer's disease, which would benefit society in the future.

1.8. What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

18F-Florbetaben has been administered to over 500 patients with various dementias and healthy volunteers worldwide and has been well tolerated. In addition, animal testing has shown no toxic effects of ^{18}F-T807, however, neither ^{18}F-Florbetaben nor ^{18}F-T807 has been approved by the Therapeutic Goods Administration (TGA) in Australia and their use as a scanning agent is therefore considered experimental. The risks and discomforts associated with this study are listed below:

Blood Sampling
Approximately 80 mls of blood will be removed for tests at the scan visit. This equates to about 16 tablespoons. This should have no adverse effect. In comparison, blood donors give 500 mls.

MRI
MRI stands for magnetic resonance imaging. An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

We will ask you to lie on a table inside the MRI scanner. The scanner will record information about your brain. It is very important that you keep very still during the scanning. When you lie on the table, we will make sure you are in a comfortable position so that you can keep still. The scanner is very noisy and we can give you some earphones to reduce the noise. Some people may experience symptoms of claustrophobia from lying in a confined space. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to you.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

We will thoroughly examine you to make sure there is no reason for you not to have the scan. You must tell us if you have metal implanted in your body, such as a pacemaker or metal pins.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat or manage a particular condition. A specialist will look at your MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features.

Positron Emission Tomography (PET) Scans

You may find the PET table to be uncomfortable to lie on during the scans. The PET technologist will do their best to make you comfortable.

There is a slight risk of discomfort, bruising, fainting, or infection with the catheter used for injecting the tracer compounds and taking blood. Some people may become anxious during the PET scan. You will be able to communicate with the study staff during the scan and ask that the scan be stopped if you feel anxious.
There have been no reported adverse reactions to the ^{18}F-Florbetaben or ^{18}F-T807 compounds. Despite this, there is still the possibility of a rare allergic reaction.

Neither ^{18}F –Florbetaben nor ^{18}F-T807 has been registered by the Therapeutic Goods Administration (TGA), therefore their use as a scanning agent is experimental and unexpected adverse effects are possible.

18F-FDG is registered with the TGA and is widely used for clinical purposes. There have been no adverse reactions reported to the TGA that were due to 18F-FDG.

Radiation Exposure

This research project involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 11.1 mSv. The dose from this research project is comparable to that received from many diagnostic medical x-ray and nuclear medicine procedures. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. In order to limit radiation exposure, you should not take part in any other study involving the use of ionising radiation for 5 years following this project.

Contraception

The effects of ^{18}F-Florbetaben and ^{18}F-T807 on an unborn child and on a newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are male, you should not father a child for 3 months after the scan.

CSF Sampling

The lumbar puncture will be performed by a highly trained and experienced anesthetist. The majority of individuals who undergo a lumbar puncture experience slight pain and discomfort from the needle at the time of insertion; this goes away when the needle is removed. The doctor will attempt to reduce the pain by using a local anaesthetic. Some individuals continue to experience pain for a short time, however the pain is very mild and there is very little risk of serious injury. Some individuals feel tired and have a slight backache the day after the test. This may result in difficulty sleeping for 1 to 2 days following the procedure. Lumbar punctures may cause a headache, which can be severe. Symptoms should improve when lying down. Participants will be advised to take over-the counter pain relief and ensure that fluid intake is adequate. However, if the headache persists beyond 48 hours you should contact the study team and inform them of your condition for monitoring.
Overall, CSF sampling is generally considered to be a safe procedure to collect cerebrospinal fluid; however this procedure is not without its share of complications and side effects, including:

- Nerve damage
- Back pain
- Cerebrospinal fluid leakage

Nevertheless, if properly carried out, serious side effects are very rare.

Please notify the study team if you are taking any anticoagulant medications.
If you are on any anticoagulant medications, you will be excluded from the lumbar puncture procedure.

Please be aware that there may be additional unforeseen or unknown risks associated with this research project. The risks outlined above can occur in the veteran control volunteers and as well as participants with traumatic brain injury and post traumatic stress disorder. Any concerns you may have should be discussed with one of the study team members.

1.9. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the study drug that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

In the event that an unexpected abnormality is found (eg. stroke or brain tumor), you will be informed and appropriate treatment arranged in consultation with your usual doctor.

The results of the ^{18}F-Florbetaben & ^{18}F-T807 PET scan will not be released to you as we do not yet know the significance of finding amyloid and tau in the brain of someone with PTSD or TBI. It is only by undertaking such research that we will be

able to learn the significance and implications of a positive 18F –Florbetaben or ^{18}F-T807 scan in all circumstances.

1.10. Can I have other treatments during this research project?

There is no restriction on taking existing medications or starting new ones during this study.

1.11. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

If you decide to leave the project, the researchers would like to keep the personal and health information about you and your blood samples that have already been collected. This is to help them make sure that the results of the research can be measured properly. However no further information will be collected. If you do not want them to do this, you must tell them before you join the research project.

1.12. Could this research project be stopped unexpectedly?

This research project may be stopped for a variety of reasons such as loss of funding or unexpected adverse events.

1.13. What will happen when my participation in this research project ends?

Once you have completed the study, no further follow-up is required with the study doctor.

Part 2 How is the research project being conducted?

2.1. What will happen to information about me?

By signing the consent form you consent to the study investigators and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. It will be disclosed only with your permission, or as permitted by law.

Information about you may be obtained from your health records held at this, and other, health services for the purposes of this research. All data collected about you will be coded with a study number. All records at the study site will be stored in a secure location. All records will be stored for at least 15 years from the completion of the study.

Your health records and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and the organisations relevant to this Austin Health Participant Information and Consent Form or as required by law. Representatives of the U.S. Army Medical

Research and Materiel Command are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of your information. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

It is desirable that your local doctor be advised of your decision to participate in this research project. By signing the consent section, you agree to your local doctor being notified of your decision to participate in this research project.

Information about your participation in this research project may be recorded in your health records.

2.2. Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

2.3. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Austin Health.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

2.4. Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 03 9496 5183 or any of the following people:

Clinical contact person
Name: Professor Christopher Rowe
Position: Principal Investigator
Telephone: (03) 9496 5183
Email: Christopher.rowe@austin.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person
Name: Professor Christopher Rowe
Position: Principal Investigator
Telephone: (03) 9496 5183
Email: Christopher.rowe@austin.org.au

For further information or appointments:
Name: Tia Cummins
Position: Research Assistant
Telephone: (03) 9496 5748
Email: tia.cummins@austin.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Local HREC Office contact
Name: Dr Sianna Panagiotopoulos
Position: Manager Office for Research, Austin Health
Telephone: (03) 9496 5088
Email: ethics@austin.org.au

Consent Form - *Adult providing own consent*

Project Title: Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer's disease in Australian war veterans.

Site Name: Austin Health

Protocol No.:

Principal Investigator: Prof. Christopher Rowe

Associate Investigators: Malcolm John Hopwood
Victor Villemagne
Jeffrey Rosenfeld
Michael Weiner
Robert Williams

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language I understand.

I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher‡

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

FAH018170

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

☐ I consent for my blood and CSF sample to be stored at the Florey Institute of Neurosciences and Mental Health (FINMH), Parkville, for future testing as described under Section 1.3 of this document. My stored blood and CSF sample may also be made available to other research groups worldwide for use in Ethics Committee approved research in related areas of medicine.

☐ I **do not** consent for my blood and CSF sample to be stored at the Florey Institute of Neurosciences and Mental Health (FINMH), Parkville, for future testing as described under Section 1.3 of this document. My stored blood and CSF sample may also be made available to other research groups worldwide for use in Ethics Committee approved research in related areas of medicine.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.