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### Permalink

<https://escholarship.org/uc/item/7tk8x6sb>

### Journal

Current Psychiatry Reports, 19(11)

### ISSN

1523-3812

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### Publication Date

2017-11-01

### DOI

10.1007/s11920-017-0835-1

Peer reviewed



# HHS Public Access

Author manuscript

*Curr Psychiatry Rep.* Author manuscript; available in PMC 2018 February 05.

Published in final edited form as:

*Curr Psychiatry Rep.* ; 19(11): 89. doi:10.1007/s11920-017-0835-1.

## Dementia Risk in Posttraumatic Stress Disorder: the Relevance of Sleep-Related Abnormalities in Brain Structure, Amyloid, and Inflammation

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### Abstract

**Purpose of Review**—Posttraumatic stress disorder (PTSD) is associated with increased risk for dementia, yet mechanisms are poorly understood.

**Recent Findings**—Recent literature suggests several potential mechanisms by which sleep impairments might contribute to the increased risk of dementia observed in PTSD. First, molecular, animal, and imaging studies indicate that sleep problems lead to cellular damage in brain structures crucial to learning and memory. Second, recent studies have shown that lack of sleep might precipitate the accumulation of harmful amyloid proteins. Finally, sleep and PTSD are associated with elevated inflammation, which, in turn, is associated with dementia, possibly via cytokine-mediated neural toxicity and reduced neurogenesis.

**Summary**—A better understanding of these mechanisms may yield novel treatment approaches to reduce neurodegeneration in PTSD. The authors emphasize the importance of including sleep data in studies of PTSD and cognition and identify next steps.

### Keywords

Stress; Alzheimer's; Dementia; Veterans; Sleep; Inflammation; PTSD

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This article is part of the Topical Collection on *Disaster Psychiatry: Trauma, PTSD, and Related Disorders*

#### Compliance with Ethical Standards

**Conflict of Interest:** Thomas C. Neylan declares no conflict of interest.

**Human and Animal Rights and Informed Consent:** This article does not contain any studies with human or animal subjects performed by any of the authors.

## Introduction

Convergent lines of evidence suggest multiple possible mechanisms by which inflammation and sleep impairments may mediate the increased risk of dementia in posttraumatic stress disorder (PTSD). In this review, we consider three broad categories of sleep-related mechanisms that may mediate or moderate the relationship between PTSD and increased risk of dementia. First, we present evidence that the sleep impairments associated with PTSD may lead to cellular damage. Second, we discuss research suggesting that sleep impairment associated with PTSD causes the accumulation of amyloid beta (A $\beta$ ) and tau protein deposits associated with neurodegeneration in multiple forms of dementia. Thirdly, we consider the possibility that inflammation stemming from PTSD-related sleep impairments precipitates cognitive impairment via reduced neurogenesis and increased neurodegeneration. We conclude by outlining a research agenda that could clarify the role of sleep deficits in the development of dementia in individuals with PTSD.

## PTSD Is a Risk Factor for Dementia

In one large study of 181,093 male veterans enrolled at Veterans Affairs (VA) hospitals, 53,155 veterans diagnosed with PTSD had more than twice the risk for subsequent development of dementia compared to those without PTSD. Risk for incident dementia in the context of PTSD remained significantly elevated despite adjustment for sociodemographic variables, neuropsychiatric and medical comorbidities, and number of clinic visits [1]. In another VA study, receipt of the Purple Heart award was used as an indication that veterans had experienced psychologically traumatic events. Notably, dementia was more prevalent among veterans who had been diagnosed with PTSD compared to those without PTSD, regardless of Purple Heart status. These authors also controlled for a number of possible confounding variables, including number of clinic visits and psychiatric and medical comorbidities, including traumatic brain injury [2].

It remains unclear whether PTSD increases risk for some forms of dementia more than others. In the study by Yaffe et al., the dementia subtype associated with PTSD with the highest adjusted hazard ratio (HR) was frontotemporal dementia (FTD; a dementia associated with the deposition of intracellular tau protein aggregates) [3], with a HR of 2.19, after adjustment for demographic variables as well as medical and psychiatric comorbidity. Vascular dementia (VD) had the lowest adjusted HR at 1.69, but the effect was nonetheless statistically significant [1]. However, in a smaller study of 93 Holocaust survivors, all of whom had PTSD; the incidence of dementia was 16%. The incidence of dementia, by subtype, was highest for VD (60%) and 20% for both Alzheimer's disease (AD) and "Other Dementia Subtypes". [4] In a retrospective observational study of war veterans with dementia, almost all of whom had been diagnosed with PTSD, patients with disruptive nighttime behavior relative to matched subjects without disruptive nighttime behavior were more likely to be diagnosed with subcortical dementia subtypes (i.e., dementia with Lewy bodies [DLB] and Parkinson's dementia) and less likely to be diagnosed with AD [5]. Though this last study does not help to differentiate the causes of dementia in subjects with PTSD versus without PTSD, it does suggest that dementia in subjects with PTSD might more often be attributable to subcortical causes when it is accompanied by disruptive or

agitated nighttime behavior. In sum, based on available evidence, PTSD appears to increase risk for different types of dementia.

## **Sleep Impairment May Mediate the Relationship Between PTSD and Dementia**

Poor sleep is strongly associated with risk of multiple types of dementia [5–9, 10•, 11–13], and as discussed by Germain et al. elsewhere in this special issue, sleep impairment is an extremely common and modifiable symptom of PTSD [14]. Briefly, subjective sleep impairments, including trauma-related nightmares and “sleep disturbance” are listed among the diagnostic criteria for PTSD [1, 15]. Sleep impairments are also among the most commonly reported symptoms of the disorder [2, 16–21]. Nightmares are a common and especially distressing symptom. [22]

With a few notable exceptions [7, 14, 23–27], most studies have found objective sleep differences in subjects with PTSD versus healthy controls, though it should be noted that the sleep impairments associated with PTSD may be different from those observed in chronic short sleep duration and insomnia, two other conditions that have been studied in some detail [21]. A meta-analysis of sleep characteristics associated with PTSD found that, when controlling for age, sex, comorbid depression, and substance use, subjects with PTSD had greater rapid eye movement (REM) sleep density and reduced slow wave sleep. Lower total sleep time was associated with PTSD status only among younger subjects [3, 28–31]. However, overall, the particular sleep differences associated with PTSD have been found inconsistently [32]. Furthermore, the sleep differences seen after a trauma may be different from those seen at later time points, with sleep in the period of time closer to the trauma being characterized by fragmented and decreased REM [32, 33]. Posttraumatic stress disorder is additionally associated with motor disturbances in REM sleep [34]. Though some work suggests that sleep problems are a risk factor for PTSD [1, 35], most work suggests that exposure to trauma and development of PTSD leads to significant sleep problems [4, 14]. Taken together, the literature indicates that PTSD is associated with a variety of sleep differences and that the relationship of sleep disturbances with PTSD is bidirectional.

The sleep problems observed in PTSD may also contribute to dementia risk [7, 24, 26, 27]. One possible mechanism by which this occurs could involve damage to the hippocampus. The hippocampus is one of the few sites in the brain associated with adult neurogenesis and is an essential component of the circuitry of learning and memory and contextual fear conditioning [36]. Damage to the hippocampus by any mechanism could lower the threshold at which cognitive deficits stemming from any mechanism become clinically significant. Numerous studies have determined through imaging that hippocampal volume is reduced in PTSD [37–40]. Although some studies have found no difference in hippocampal volumes in PTSD versus controls [41–44], several recent meta-analyses have reported reduced hippocampal volume in PTSD [43, 45–47]. The causal relationship between hippocampal size and PTSD remains obscure, with some suggesting that smaller hippocampal sizes precede and constitute a risk for PTSD [48–50] and others suggesting that smaller hippocampal size is more likely to be a consequence of the disorder [50]. Studies by

Cardenes-Nicholsen et al. [51] and Apfel et al. [37] suggest that hippocampal size in PTSD may increase in subjects who go into remission or decrease among those with worsening of symptoms over time.

Chronic sleep deprivation might lead to changes in the hippocampus as well. Imaging studies have found smaller hippocampal volumes in rodents deprived of sleep [52] and in humans with insomnia or environmental sleep restrictions [53, 54]. Other studies have not found a correlation between the diagnosis of primary insomnia (PI) and hippocampal size, but have found negative correlations between wake time after sleep onset (WASO) and hippocampal volume among those with PI [55, 56]. In what has been called the glucocorticoid vulnerability hypothesis, changes in hippocampal cellular structure or function render the region especially susceptible to permanent damage from acute physiological stressors. In this setting, the hippocampus is less able to regulate the hypothalamic-pituitary-adrenal axis and baseline glucocorticoid levels go up. This situation leads to neuronal cell death under conditions of chronic stress when such stress is punctuated by an additional metabolic challenge (e.g., stroke, ischemia, hyperglycemia, or hypoxia) and damage accumulates over time [57]. An extensive discussion of this topic as it relates to PTSD is beyond the scope of this article.

Few studies have systematically examined the role of sleep in the relationship between PTSD and hippocampal volume [24, 58, 59]. However, there are important reasons to suspect that it could play a key role. Sleep restriction in rats promotes changes in cellular and molecular structures that are crucial to the process of memory formation through long-term potentiation [60]. These include decreases in actin-binding cortactin [61], reduced  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor phosphorylation [62], diminished cell proliferation [63–66], impaired calcium signaling [67, 68], and reduced hippocampal *N*-methyl-D-aspartate (NMDA) receptor quantity [67, 69]. Sleep disruption in rodents leads to decreased long-term potentiation and impaired learning and memory [62, 66, 70–75], processes that clearly depend on the hippocampus [76]. Evidence from humans is mixed. With important exceptions, the bulk of studies of insomnia show decreased performance compared to healthy controls on measures of learning and memory [77]. Long and short sleep duration has likewise been associated with impaired learning, with an inverted U shape relationship [78]. PTSD is also associated with decreased verbal and visual memory [79], attributable to impairments in encoding [80, 81]. In sum, both PTSD and impaired sleep are related to impairments in learning and memory and all of these entities are related to decreased hippocampal volume. The cognitive reserve model holds that damage to the hippocampus from any cause could elevate the risk of dementia [82]. Thus, available evidence raises the distinct possibility that the sleep problems associated with PTSD damage the hippocampus, leading to impairments in learning and memory and increased risk of dementia.

Sleep impairment in PTSD may also lead to abnormal protein processing and the buildup of amyloid beta ( $A\beta$ ), tau, and phosphorylated tau (p-tau). These proteins are highly associated with AD [83] and other neurodegenerative diseases [84]. Based on histopathological findings and the fact that genetic disorders that increased amyloid precursor protein (APP)

cleavage conferred an increased risk of AD, the amyloid cascade hypothesis holds that the buildup of A $\beta$  is an essential causal step in the development of AD [83].

In healthy volunteers of various ages, Huang et al. found decreases in diurnal variations of cerebrospinal fluid (CSF) A $\beta$  levels in older age, regardless of various activities performed during wakefulness, possibly indicating impaired sleep-dependent A $\beta$  clearance in older age [85]. Other data from humans indicate that more frequent nighttime awakenings are associated with increased amyloid pathology in CSF and positron emission tomography (PET) imaging [13]. One study of 23 participants found that amyloid burden, as assessed by CSF Ab42 levels, and sleep efficiency interacted in their effects on memory performance [86].

Alternatively, sleep may promote clearance of A $\beta$  by increasing the transfer of fluid to the interstitial space in the brain parenchyma, thereby facilitating CSF flow across neurons [87]. Thus, decreased sleep may lead to buildup of brain A $\beta$  by decreasing its rate of clearance from the brain. Consistent with this hypothesis, self-reported shorter sleep duration is associated with greater brain A $\beta$  burden in older adults [88]. Evidence for this is limited and needs to be extended to human experiments.

Thus, the buildup of A $\beta$  has been associated with lower sleep time and increased awakenings. Therefore, it may be that these features of sleep impairment seen in PTSD lead to increased A $\beta$  buildup in individuals with the disorder. However, a recent interim analysis of a large ongoing multisite study showed that military veterans with lifetime history of PTSD resulting from service in the Vietnam War had a higher prevalence of mild cognitive impairment (MCI), but lower brain amyloid PET levels and a much lower prevalence of amyloid positivity on PET scans [89]. These results support the hypothesis that in many cases, MCI and possibly future dementia that is associated with PTSD may not involve amyloid deposition. On the other hand, another recent study found self-reported poor sleep to be associated with lower levels of cerebrospinal fluid A $\beta$ , a state that is paradoxically associated with increased amyloid in the brain [90]. More work needs to be done in this area.

## The Role of the Immune System and Inflammation

The inflammatory response of the immune system could also play an important role in the development of dementia in individuals with PTSD. Several lines of evidence now indicate that trauma exposure and PTSD are associated with elevated inflammation as indexed by higher levels of peripheral systemic inflammatory markers such as high sensitivity C-reactive protein and the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [91–93] and by elevated pro-inflammatory signaling to immune cells through the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B) [94–96]. Notably, however, not all individuals with PTSD display elevated inflammation [97, 98, 99]. A recent meta-analysis including 20 studies of inflammatory markers in PTSD found that PTSD was associated with higher levels of IL-6, IL-1 $\beta$ , and interferon  $\gamma$ , whereas TNF- $\alpha$  was higher in subjects with PTSD only in a subgroup analysis of patients who were not on psychotropic medications. Univariate meta-regression analyses showed IL-6 to be associated with illness

severity as assessed by the Clinician-Administered PTSD Scale (CAPS) score but not with illness duration. Illness duration was associated with IL-1 $\beta$  levels, though available studies of IL-1 $\beta$  could have been affected by publication bias, as determined by a separate linear regression test [100••].

The relationship between PTSD and inflammation is likely bidirectional. On the one hand, elevated CRP levels have been linked to the development of PTSD [101]. Additionally, elevated inflammation can manifest as symptoms of PTSD [102–106]. On the other hand, chronic stress is associated with sustained levels of inflammation and acute stressors with increases in inflammatory activity [91, 107–111]. Remitted PTSD does not appear to be associated with above-normal levels of inflammation, though data on this topic is very sparse [112].

Elevated inflammation may in turn be a direct mechanism of increased dementia risk in PTSD. There are at least two lines of clinical evidence linking inflammation with dementia. First, elevated inflammation, as indexed by circulating levels of systemic inflammatory proteins or spontaneous production of pro-inflammatory cytokines, is a risk factor for the development of dementia [113, 114]. Second, there is some evidence that long-term use of some non-steroidal anti-inflammatory drugs (NSAIDs) actually protects against the development of Alzheimer's and Parkinson's disease [115, 116] and that administration of the TNF- $\alpha$  antagonist etanercept improves functioning in patients with Alzheimer's disease [117]. This clinical evidence is bolstered by a large body of basic science research showing that inflammation can promote neurotoxicity across multiple neurodegenerative disorders [118, 119].

Researchers are also now beginning to uncover the mechanistic pathway underlying the association between inflammation and neurodegeneration. Accumulating evidence points to inflammatory proteins called cytokines as key players in this relationship. Cytokines are typically too large to pass through the blood-brain barrier (BBB). However, they can nonetheless influence brain function and structure by transmitting signals through interactions between brain endothelial cells and perivascular macrophages, activating afferent vagal fibers, passing through the BBB when it loses structural integrity due to sepsis, entering brain areas without BBB, and actively transporting circulating cytokines into brain parenchyma via cytokine-specific saturable transporters [103, 119, 120].

Cytokines are critical for almost all aspects of brain function, and they play an important facilitative role in learning and memory [121]. However, when markedly elevated, they may also reduce neurogenesis and have toxic effects on neurons [119]. Such effects may explain the inverse relationship between inflammation and hippocampal volume observed in some studies [97•, 122••]. In fact, neuroinflammation has been proposed as a mechanism of dementia, including vascular dementia, Alzheimer's disease, and all dementias combined [119, 123–125].



## Collective Impact of Sleep and Inflammation

Sleep and inflammation are intricately interlinked. While inflammation plays a key role in regulating sleep (in some cases promoting and in others disturbing it), depriving humans and other animals of sleep also profoundly enhances inflammation [126, 127]. In particular, experimentally induced sleep deprivation is associated with increased pro-inflammatory signaling through NF- $\kappa$ B and heightened levels of inflammatory proteins, including IL-6 and TNF- $\alpha$  [128–130]. Moreover, in a sample of 70 military veterans with TBI receiving care for sleep disturbance, improvements in sleep quality were accompanied by reductions in PTSD, depressive symptoms, and improvements in quality of life. Those improvements in turn associated with reductions in levels of the systemic inflammatory marker C-reactive protein (CRP) [131]. Given the causal effects of sleep loss on inflammation, sleep impairments could contribute to the elevated inflammation observed in patients with PTSD.

## Conclusions and Future Directions

Given evidence from animal models and the observed associations among PTSD, sleep, inflammation, and dementia in humans, sleep disturbance and inflammatory factors may play a key role in the relationship between PTSD and dementia. In this review, we have identified multiple possible sleep-related mechanisms that might explain this relationship. Firstly, PTSD and sleep impairments are associated with macrostructural changes in the hippocampus as well as microstructural and functional degradation within the limbic system. Thus, the sleep impairments associated with PTSD may cause damage to structures critical for maintaining cognitive reserve and protecting against dementia. Secondly, recent studies have demonstrated that sleep impairment in rodents leads to the accumulation of A $\beta$  and tau. If this relationship holds true in humans as well, and if such accumulation contributes to the development of dementia, then this represents another mechanism by which sleep impairment associated with PTSD would increase the risk of dementia. Finally, PTSD and sleep are also both associated with elevated inflammation, as indicated by increased levels of inflammatory cytokines and pro-inflammatory signaling. Such changes have also been implicated in neurodegeneration and could similarly increase the likelihood of dementia.

These mechanisms are not specific to PTSD, per se. It may be, for example, that decreased total sleep time (discussed above as being inconsistently observed in PTSD) allows for the buildup of A $\beta$  and that this occurs in individuals who have decreased sleep time regardless of PTSD status. In this model, decreased sleep time could either predate PTSD or be caused by it. Similarly, individuals with PTSD have a high rate of high risk health-related behaviors such as smoking [132] and heavy alcohol use [133] and a high prevalence of obstructive sleep apnea (OSA) [134, 135]. These factors could elevate risk of dementia in PTSD via mechanisms separate from or complimentary to those discussed above [94, 136], as described by the glucocorticoid vulnerability hypothesis referenced above [57].

The relationship between PTSD, sleep impairment, and dementia is likely multidirectional, with sleep impairments playing some role in the development of PTSD and PTSD itself precipitating sleep impairments [137]. It is also likely multifactorial, as the mechanisms discussed are not mutually exclusive. An impaired BBB may allow for the inflammatory



mediators to inflict damage upon hippocampal cellular circuitry, lowering the threshold at which clinically significant cognitive impairment is observed. Concurrent abnormalities in protein processing could exacerbate this effect and further accelerate cognitive decline. Finally, the mechanisms discussed in this review do not preclude the possibility that, in some cases, mechanisms that lead to dementia predate both PTSD and sleep problems. Since REM behavior disorder has been associated with increased risk of dementia [138] (especially dementia associated with Lewy body pathology) [139, 140] and may even represent the earliest manifestations of dementia in individuals without PTSD [141], it is possible that REM disturbances in PTSD comprise a common early sign of neurodegeneration in this disorder.

There is little direct evidence for a causal mechanism by which the diagnosis of PTSD confers an increased risk of dementia. However, we believe that enough circumstantial evidence exists to merit greater attention to sleep and inflammation in published studies of cognition in PTSD.

Future studies investigating the relationship between PTSD and cellular damage, A $\beta$  and tau processing, and inflammation should include sleep impairments and inflammatory markers as possible mediators. Also, more longitudinal research is needed on the relationship between PTSD and sleep impairments, and among PTSD, inflammatory markers and specific indicators of dementia risk such as brain and cerebrospinal fluid levels of A $\beta$ , tau, and p-tau. More specifically, the field of dementia research awaits confirmation that sleep impairments lead to altered protein processing in humans as well as rodents, and the mechanisms by which inflammation remain incompletely understood. At the behavioral level, it would be extremely valuable to know whether interventions targeted at improving sleep in individuals with PTSD could lower long-term risk of dementia. Such studies should be undertaken in ways that test certain mechanistic possibilities. For instance, it would be crucial to know whether aspects of A $\beta$  processing or immune system functioning fluctuated with the severity of PTSD and whether they normalized with treatment of the disorder or with treatment of associated sleep problems. Finally, studying subjects with and without PTSD who have the same sleep problems and health-related behaviors would help to determine whether PTSD confers unique risks for dementia beyond those other factors.

## Acknowledgments

Brian S. Mohlenhoff received salary support from the Department of Veterans Affairs Office of Academic Affiliations Advanced Fellowship Program in Mental Illness Research and Treatment at the San Francisco Veterans Affairs Medical Center and the Department of Veterans Affairs Sierra-Pacific Region Mental Illness Research, Education and Clinical Center (MIRECC).

Aoife O'Donovan received salary support from Society in Science – The Branco Weiss Fellowship and a NIMH Career Development Award (K01-MH109871). This study was supported by the NIH/NIA/National Institute of Mental Health (BSM: R25MH060482; TCN: 5R01MH073978-04, 5R34MH077667-03, 1R56MH107042-01A1; MWW: R01AG10897, 2U01AG024904, 1P41 EB015904, P01 AG19724, R01 AG032306, R01A G03879) and by funding from the US Veterans Health Administration for the Mental Illness Research, Education and Clinical Center, VISN 21 and grant DAMD17-01-1-0764.

Michael W. Weiner has served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, and Eli Lilly. He has provided consulting to Synarc, Pfizer, Janssen, KLJ Associates, Easton Associates, Harvard University, University of California, Los Angeles (UCLA), Alzheimer's Drug Discovery Foundation (ADDF), Avid Radiopharmaceuticals, Clearview Healthcare Partners, Perceptive Informatics, Smartfish

AS, Decision Resources, Inc., Araclon, Merck, Defined Health, and Genentech. The following entities have provided funding for travel: Pfizer, Paul Sabatier University, MCI Group France, Travel eDreams, Inc., Neuroscience School of Advanced Studies (NSAS), Danone Trading, BV, CTAD Ant Congres, Kenes, Intl., ADRC, UCLA, UCSD, Sanofi-Aventis Groupe, University Center Hospital, Toulouse, Araclon, AC Immune, Eli Lilly, New York Academy of Sciences (NYAS), and National Brain Research Center, India for Johns Hopkins Medicine. He served on the Editorial Boards for Alzheimer's & Dementia and MRI. He received honoraria from Pfizer, Tohoku University, and Danone Trading, BV. He received research support from Merck, Avid, the Veterans Administration (VA) and Department of Defense (DOD). Dr. Weiner additionally received support for his work from the following grants: W81XWH-13-1-0259, W81XWH-12-2-0012, ADNI 2-12-233,036, 20,110,506 and R01 MH098062-01 from the following sources; DOD, Alzheimer's Association, Alzheimer's Drug Discovery Foundation.

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