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Research Report

Sleep and Tau Pathology in Vietnam War Veterans with Preclinical and Prodromal Alzheimer's Disease

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Abstract.

Background: The increasing prevalence of Alzheimer's disease (AD) and lack of effective medications has led to a need to identify modifiable risk factors as targets for interventions.

Objective: In this cross-sectional study, we sought to determine whether worse sleep quality is associated with increased pathological tau, and whether this relationship is affected by amyloid pathology.

Methods: 66 male participants underwent Florbetapir (AV45) positron emission tomography (PET) and Flortaucipir (FTP) PET and completed the Pittsburgh Sleep Quality Index questionnaire (PSQI) as part of the Department of Defense Alzheimer's Disease Neuroimaging Initiative, a multicenter study collecting data from Vietnam War veterans, some of whom have a history of post-traumatic stress disorder, or non-penetrating traumatic brain injury. AV45 PET was used to determine the presence of significant amyloid pathology. We used regression models to determine the effects of amyloid pathology and PSQI on tau deposition in brain regions associated with Braak stages.

Results: Among the 66 participants, 14 individuals were amyloid positive (21%) and 52 were amyloid negative (79%). In regions associated with Braak stages III-IV, there was a significant interaction of amyloid status on PSQI ($\beta = 0.04$, $p = 0.003$) with higher PSQI correlating with higher FTP SUVR in amyloid-positive individuals only ($\beta = 0.031$, $p = 0.005$).

Conclusion: Our study found that an AD profile of tau deposition was associated with an interaction between self-reported sleep quality and amyloid pathology such that worse self-reported sleep was related to higher tau in regions usually associated with AD progression, but only in individuals with high cerebral amyloid deposition.

Keywords: Amyloid, mild cognitive impairment, positron emission tomography, preclinical AD, sleep, tau

INTRODUCTION

Alzheimer's disease (AD) is a growing public health crisis due to an aging population and a lack of disease modifying medications. Importantly, it is now possible to identify a preclinical phase of AD, using biomarker identification of elevated amyloid- β ($A\beta$)

¹Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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deposits and to track the presence and location of pathological tau using positron emission tomography (tau PET). Potentially modifiable risk factors, including disordered sleep, are being increasingly sought as important targets to delay symptom onset and possible clinically detectable memory decline [1].

Poor sleep appears to be both a cause of, and a consequence of, AD [2]. Studies have displayed high prevalence of sleep disorders in people with AD [3–10]. Wide-ranging alterations in sleep physiology have been documented in patients with AD [11–13], and sleep disturbances are associated with the hallmark proteins of AD, A β and tau, both in rodents and in humans. These studies have linked subjective and objective measures of sleep quality to A β and tau in clinical populations of AD patients using cerebrospinal fluid (CSF) and PET. However, these studies have focused on cognitively impaired and/or demented populations, leaving questions about the relevance of this relationship in the earlier and pre-clinical stages of AD.

While pathological levels of amyloid are distributed widely in the brain a decade or more prior to symptom onset, pathological tau spreads in a topographically specific manner, with direct links between the regions involved and the cognitive function impaired. Pathological tau begins to accumulate prior to the onset of major cognitive impairment, and thus tau can be detectable in the preclinical stages, as well as in temporal lobe structures during normal aging [14]. Animal studies support the notion that sleep deprivation is related to increases in pathological tau [15] in models without amyloid manipulation, implying that this relationship between sleep and tau deposition may exist independent of amyloid. However, mice bred to be tau-deficient also demonstrate unusual sleep patterns [16], suggesting that the relationship between tau and sleep may be bidirectional. In a human cohort with no or mild cognitive impairment (MCI), about half of whom were amyloid negative (defined by an absence of cerebral amyloid deposition above a threshold indicative of AD dementia [17]), slow wave sleep activity (during non-rapid eye movement sleep) was associated with CSF tau elevations but not amyloid levels [18]. Furthermore, other human studies have reported increased CSF tau and amyloid levels as a result of acute sleep disruption [19, 20]. Thus, for now, it is unclear how sleep relates to the amyloid and tau and their combination.

In this retrospective, cross-sectional, observational study, we used reported sleep data as well as PET data on both tau and A β imaging collected in the Depart-

ment of Defense Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI). While our study was mainly focused on the role of sleep quality in the AD continuum, we secondarily assessed potential differences in tau PET between individuals with traumatic brain injury (TBI) and those with post-traumatic stress disorder (PTSD), since PTSD is often characterized by disrupted sleep [21] and TBI has relationships with both sleep [22] and tau [23]. We hypothesized that elevated Pittsburgh Sleep Quality Index (PSQI), indicative of decreased sleep quality, would be associated with higher tau pathology, regardless of PTSD and TBI diagnoses. We further sought to establish if disrupted sleep was dependent on the presence of pathological levels of amyloid in this population.

MATERIALS AND METHODS

Study participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). For up-to-date information, see <http://www.adni-info.org>. The DoD-ADNI is a multisite study of the effects of mild to moderate non-penetrating TBI and PTSD on AD in a cohort of Vietnam war veterans with and without MCI. We examined the relationship between the PSQI, a self-report measure of sleep quality, and flortaucipir (AV1451, or FTP) tau PET in amyloid positive (A β +) and amyloid negative (A β -) veterans. The DoD-ADNI recruits participants with normal or mildly impaired cognition, some of whom had diagnoses of mild to moderate non-penetrating TBI, PTSD, or both.

Individuals who had undergone FTP tau PET, florbetapir (AV45) A β PET and completed the PSQI were included in these analyses. Amyloid positivity was determined based on the standard threshold of 1.11 cortical summary Standard Uptake Value ratio (SUVR) in each participant's AV45 scan available via processed data available on the ADNI database (<http://adni.loni.usc.edu>). From this, we identified all A β + individuals that had FTP PET data available ($N = 16$). One of these individuals was excluded due to abnormally high FTP SUVR (3.175 standard deviations above the mean), and one was excluded due to missing PSQI data. Of the A β - individuals with FTP PET data ($n = 60$), seven were excluded due to missing or incomplete PSQI data. In the remaining sample there was one woman who was excluded to eliminate potential sex effects [24].

Of the resulting dataset, 7 participants had an MCI diagnosis at the time of their FTP PET scan, 2 of whom were A β + (i.e., prodromal) and 5 of whom were A β -. ADNI criteria for MCI were: 1) Memory complaint by subject or study partner that is verified by a study partner; 2) Abnormal memory function documented by scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale – Revised (score ≤ 8 for those with ≥ 16 years of education; score ≤ 4 for those with 8–15 years of education; score ≤ 2 for those with 0–7 years of education); 3) Mini-Mental State Exam score between 24 and 30 (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director); 4) global CDR score of 0.5, with Memory Box score at least 0.5; and 5) general cognitive and functional performance sufficiently preserved such that a diagnosis of AD could not be made by the site physician at the time of screening. The remaining participants were cognitively unimpaired (CU) and thus represented either preclinical AD if A β + ($n = 12$) or were considered to be non-AD ($n = 47$). The A β + group had a mean (SD) Montreal Cognitive Assessment (MoCA) of 24.79 (2.33) while the A β - group had a mean (SD) MoCA of 24.04 (3.19). Participant data is summarized in Table 1.

In the subgroup of participants with a PTSD diagnosis ($n = 39$), 14 were taking medication for depression, 3 were taking medication for PTSD, and 1 was taking an antipsychotic medication.

All individuals in the DoD-ADNI are veterans. Because of this, for the purposes of this study, there was no possibility for a non-veteran control group.

Imaging data

We downloaded regional summary AV45 SUVR data and partial volume corrected regional summary FTP SUVR data from the LONI database. Methods for the calculation and partial volume correction of these data have been described elsewhere [25, 26]. Given the relatively small sample size, we limited our analyses to regions relevant to each of the Braak stages [14] where tau is expected in each pathological stage of AD. Braak SUVR data from ADNI are grouped into three pairs (I-II, III-IV, and V-VI), so relationships are reported here as such. In the context of this paper, Braak regions refer not to the Braak stage that each participant is in, but rather refers to regions where we would expect to see tau in relation to AD progression. Briefly, the regions covered in stages I-II are entorhinal and hippocampus, III-IV extend to the amygdala and other subcortical regions as well as the cortex of the inferior temporal lobe and parahippocampal gyrus, V-VI extends isocortically beyond the temporal lobe into the frontal, parietal and occipital cortex. For a full listing of regions see the FTP processing methods available on the ADNI database [27].

PSQI

The PSQI is a self-report questionnaire that determines sleep quality by evaluating seven components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction [28]. We downloaded PSQI data from the ADNI database and calculated a total score for each

Table 1
Average Age, Years of Education (YOE), Pittsburgh Sleep Quality Index (PSQI), and Montreal Cognitive Assessment (MoCA)s by Amyloid Status and Diagnosis

Characteristic	A β +(CU = 12, MCI = 2)	A β - (CU = 47, MCI = 5)	p
Age (SD)	72.39 (6.95)	70.64 (3.80)	0.21
YOE (SD)	15.79 (2.67)	15.09 (2.44)	0.36
PSQI (SD)	8.07 (2.56)	8.25 (3.13)	0.85
MoCA (SD)	24.79 (2.33)	24.04 (3.19)	0.41
SUVr in Regions Associated with Braak Stages I-II (SD)	1.28 (0.17)	1.17 (0.14)	0.02
SUVr in Regions Associated with Braak Stages III-IV (SD)	1.39 (0.13)	1.33 (0.11)	0.07
SUVr in Regions Associated with Braak Stages V-VI (SD)	1.45 (0.13)	1.42 (0.11)	0.41
Clinical Diagnosis (%)			ANOVA n.s.
Neither TBI nor PTSD	6	14	
TBI	2	5	
PTSD	3	23	
PTSD & TBI	3	10	

participant from 0 to 21, with scores higher than 5 suggesting worse sleep quality.

Statistical analysis

We used *t*-tests to determine if there were differences in age, education, overall PSQI or MoCA, or tau PET uptake within each Braak-combined-region between the A β + and A β - groups, and chi square to analyze for differences of frequency in the exposure (PTSD, TBI, PTSD&TBI) categories between the A β + and A β - groups. We then conducted three regression models, one for each of the Braak-combined-regions assessing main effects of amyloid status and PSQI on FTP SUVR. In each model, we included the interaction term of interest, amyloid status x PSQI. Each model covaried for age. We corrected for multiple comparisons using the Bonferroni method. In models where the interaction term was significant after correction, we then conducted a further pair of regression models for each of the amyloid-status groups, to understand the interaction. We reran our analyses excluding MCI individuals in order to ensure that our results were not driven by this small group. Finally, given the mixture of exposure to TBI and PTSD in this cohort, we used ANOVA to determine whether FTP SUVR in each of the Braak-combined regions, as well as PSQI, differed between veterans with each kind of exposure. We used pairwise comparisons to investigate significant differences between groups where necessary.

In order to investigate the specific sleep components driving the relationships represented in our

study, we repeated our analyses, using the seven components of the PSQI to further understand the relationship between sleep and tau.

Ethics approval and consent

Written informed consent was provided by all study participants in accordance with the Institutional Review Boards of the respective ADNI sites.

RESULTS

The A β + group had significantly higher FTP SUVR in regions associated with Braak stages I-II, but not in either of the other Braak-combined regions (Table 1). In the regression models (Table 2), there were no significant main effects of amyloid status or PSQI on FTP SUVR in any of the three Braak-combined regions.

However, there was a significant interaction of amyloid status on PSQI in regions associated with Braak stage III-IV such that high PSQI was associated with elevated FTP SUVR in A β + participants only (Fig. 1). No such interactions were evident in the other Braak-combined regions. These results held when we excluded MCI individuals.

The different diagnoses (PTSD, TBI, both, or neither) did not differ significantly in FTP SUVR in any of the regions investigated, but, as expected, did differ significantly in average PSQI ($F = 7.402, p = 0.0003$), with higher average PSQI in the PTSD group compared with the normal group ($p = 0.001$), and the TBI group ($p < 0.05$), but not the PTSD & TBI group (Fig. 2).

Table 2
Results of Regression Models in the Whole Sample. Bolded *p*-values indicate significance at corrected α of 0.017

Whole Sample	β	<i>t</i>	<i>p</i>
FTP SUVR in Regions Associated with Braak Stages I & II			
Amyloid	-0.1225	-0.852	0.398
PSQI	-0.0006	-0.097	0.923
Amyloid*PSQI	0.0262	1.554	0.125
FTP SUVR in Regions Associated with Braak Stages III & IV			
Amyloid	-0.2627	-2.376	0.021
PSQI	-0.0076	-1.556	0.125
Amyloid*PSQI	0.0400	3.084	0.003
FTP SUVR in Regions Associated with Braak Stages V & VI			
Amyloid	-0.1623	-1.515	0.135
PSQI	-0.0046	-0.960	0.341
Amyloid*PSQI	0.0246	1.954	0.055

Fig. 1. Relationship between PSQI and FTP SUVR in Regions Associated with Braak Stages III & IV in Aβ+ and Aβ- groups.

Of the PSQI components, only subjective sleep quality ($\beta = 0.0988$, $p = 0.003$) and sleep efficiency ($\beta = 0.0902$, $p = 0.013$) demonstrated significant interactions with amyloid designation at $\alpha = 0.05$. Only subjective sleep quality survived multiple comparisons correction (Table 3, Fig. 3).

DISCUSSION

This study investigated the relationship between tau and sleep quality in cognitively intact Vietnam War veterans. We found that worse self-reported sleep quality was associated with higher levels of tau in

Table 3

Interactive effect of each PSQI subcomponent with amyloid status on tau SUVR in Regions Associated with Braak Stages III & IV. Bolded p -values indicate significance at corrected α of 0.007. While Habitual Sleep Efficiency was significant in the model, this did not survive correction

	Interaction Term	
	β	p
Subjective Sleep Quality	0.0988	0.003
Sleep Latency	0.0466	0.179
Sleep Duration	0.0591	0.077
Habitual Sleep Efficiency	0.0902	0.013
Sleep Disturbances	0.0250	0.670
Use of Sleeping Medication	-0.0667	0.126
Daytime Dysfunction	-0.0108	0.821

regions associated with Braak stages III & IV in Aβ+ individuals only. Thus, in these men who have preclinical or prodromal AD, worse sleep quality was associated with more tau. Our *post-hoc* analyses revealed that, of the PSQI components, subjective sleep quality appeared to be driving the overall effect, such that worse subjective sleep quality was associated with higher levels of tau in regions associated with Braak Stages III & IV in Aβ+ individuals only (Fig. 3). While total PSQI and regional FTP SUVR did not differ significantly between the Aβ+ and Aβ- subgroups, no relationship between self-reported sleep and tau was evident in these regions in Aβ- individuals. Given the small group of MCI individuals in our largely preclinical dataset, we reran our regressions excluding these individuals. We found that our results held, suggesting that our results were not driven by the small prodromal subgroup.

Preclinical AD can be defined by presence of pathological levels of amyloid in the absence of significant cognitive or functional loss [29]. Using a

Fig. 2. Boxplots of PSQI and FTP SUVR in Regions Associated with Braak Stages III & IV by Diagnosis.

Fig. 3. Relationship between PSQI Subcomponent 1 (Subjective Sleep Quality) and FTP SUVr in Regions Associated with Braak Stages III & IV in Aβ+ and Aβ- groups.

more recently developed tau tracer, MK6240, which is known to have less off-target age related binding, Betthausen and colleagues demonstrated that elevated tau PET uptake in combination with elevated amyloid PET uptake was associated with more rapid later cognitive decline than is typical of aging [30]. Thus, we might expect the veterans in this study with the most tau to be more likely to show cognitive decline in their return DoD-ADNI visits.

We limited our regions of interest to those typical of the progression of tau described by Braak and Braak [14]. In this clinic-pathological correlation paper, all samples who were elevated at stages I and II only did not have clinically defined dementia, half of the 10 patients with each of stage III and IV tau had dementia, thus stages III and IV seem to represent a transitional zone between symptoms being evident or not, with stages V and VI representing regions where tau is found on autopsy in those with moderate to severe dementia. We believe that our findings are limited to regions associated with Braak stages III and IV because participants in our sample are relatively early in the progression of the disease, when tau is more limited to these regions and cognition is minimally impacted. The same relationship was not found in regions corresponding to Braak stages I and II, likely due to the fact that patients are too early in the progression of the disease to demonstrate specific AD-related pathology. Tau PET signal related to age and not amyloid sta-

tus has been reported, but the spatial patterns related to AD are seen much more commonly in Aβ+ participants [31]. Thus, we would expect those in our Aβ+ group with elevations in tau to decline, and we will analyze these longitudinal data once they become available.

Longitudinal and intervention studies are needed to identify whether tau leads to poor sleep, the reverse is true, or if an alternative or bidirectional model exists. Our study was not designed to unravel the causality or directionality in this relationship, but does suggest the possibility of sleep as a modifiable risk factor for AD. Thus, further study of sleep quality in the context of AD, particularly in these preclinical and prodromal periods, is of great importance. The elevation of PSQI in the PTSD cohort points to a potential comorbidity, although we did not see elevated tau in the PTSD group as a whole (Fig. 2). To an extent, this finding is contrary to a Mohamed et al. [32], which reported increased tau deposition in the brain of nondemented war veterans with TBI and/or PTSD decades after their trauma. However, Mohamed et al. focused mainly on topographical differences in tau and did not focus on the possible impact of sleep (PSQI) on tau or amyloid deposition. While overall patterns of tau deposition may differ between diagnostic groups, as reported by Mohamed, in our study, specific deposition in regions associated with AD progression is correlated to an interaction between PSQI and amyloid status, rather than PTSD/TBI diagnosis.

There are several limitations to our study. Primarily, this is a cross-sectional study that, at this time point, precludes a delayed verification of AD diagnosis for cases currently classified as preclinical or prodromal AD. The PSQI is a self-report measure of sleep quality, although a well validated indicator. As a result, our study could not ascertain whether any distinct type of sleep disturbance is driving the relationship with tau. Future research is needed to determine if sleep apnea, insomnia, or other disturbances have a particularly strong relationship with tau, as they have been shown to be associated with increased risk of MCI and AD [33–37]. Furthermore, our study is limited to men, though some research suggests that the relationship between sleep and other biomarkers of AD may be stronger in women [38]. Finally, our study is limited to a very small sample size, which limits our ability to make meaningful conclusions on the role of PTSD and TBI diagnoses in this relationship. Although our study did not find any differences between groups in terms of biomarker results, a control group of non-veterans would be use-

ful to confirm and generalize the results of our study. While sleep quality data do not currently exist in the ADNI study outside of the DoD-ADNI substudy, we hope that these data will become available in the future. Replication and extension of these findings in other datasets and with other methods of assessing sleep quality and tau accumulation in normal aging, preclinical and prodromal AD, and victims of psychological and physical trauma are warranted.

In summary, our results suggest a role of sleep quality in the preclinical and prodromal stages of AD. We found that tau deposition following an AD profile was associated with an interaction between self-reported sleep quality and amyloid status. While our results do not establish directionality in this association, they highlight the potential of sleep quality as a target for future AD research.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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