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Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults

Kate E. Sprecher [a,b,c,*], Barbara B. Bendlin [d,e], Annie M. Racine [a,e], Ozioma C. Okonkwo [d,e], Bradley T. Christian [e,f], Rebecca L. Koscik [g], Mark A. Sager [e,g], Sanjay Asthana [d,e,g], Sterling C. Johnson [d,e,g], Ruth M. Benca [b,c]

[a] Neuroscience Training Program, University of Wisconsin-Madison, Madison, WI, USA
[b] Wisconsin Center for Sleep Medicine and Research, University of Wisconsin-Madison, Madison, WI, USA
[c] Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA
[d] Geriatric Research Education and Clinical Center, William S. Middleton Memorial VA Hospital, Madison, WI, USA
[e] Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[f] Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[g] Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

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ABSTRACT

Midlife may be an ideal window for intervention in Alzheimer's disease (AD). To determine whether sleep is associated with early signs of AD neuropathology (amyloid deposition) in late midlife, we imaged brain amyloid deposits using positron emission tomography with [C-11]Pittsburgh Compound B (PiB), and assessed sleep with the Epworth Sleepiness Scale and the Medical Outcomes Study Sleep Scale in 98 cognitively healthy adults (aged 62.4 ± 5.7 years) from the Wisconsin Registry for Alzheimer's Prevention. We used multiple regressions to test the extent to which sleep scores predicted regional amyloid burden. Participants reporting less adequate sleep, more sleep problems, and greater somnolence on the Medical Outcomes Study had greater amyloid burden in AD-sensitive brain regions (angular gyrus, frontal medial orbital cortex, cingulate gyrus, and precuneus). Amyloid was not associated with reported sleep amount, symptoms of sleep-disordered breathing, trouble falling asleep, or Epworth Sleepiness Scale. Poor sleep may be a risk factor for AD and a potential early marker of AD or target for preventative interventions in midlife.

1. Introduction

Amyloid plaques are a hallmark of Alzheimer's disease (AD). Accumulation and aggregation of the peptide β-amyloid (1–42) (Aβ42) into insoluble plaques is evident a decade or more before AD symptoms appear, during the preclinical phase of the disease (Jack et al., 2013; Sperling et al., 2011), and is thought to be a major cause of neural dysfunction and cognitive decline to dementia. Older adults (mean age 65.6 years) with pathological levels of Aβ42 in cerebrospinal fluid (CSF) had lower sleep efficiency as measured by actigraphy than those with normal Aβ42 levels (Ju et al., 2013). In humans, amyloid plaques can be imaged with positron emission tomography (PET) using radioligands such as [C-11]Pittsburgh Compound B (PiB). In older adults (mean age 78.2 years), greater amyloid burden was associated with self-report of poor sleep quality and shorter sleep duration (Spira et al., 2013).

The mechanism linking poor sleep with greater amyloid burden is not clear. In mice, sleep disruption increases amyloid generation (Shiota et al., 2013) and deposition (Kang et al., 2009). Amyloid levels in brain interstitial fluid follow a diurnal pattern (Kang et al., 2009; Roh et al., 2012), and clearance of exogenous amyloid is greatest during sleep (Xie et al., 2013). Aβ plaques arise from an imbalance between Aβ production and clearance (Yan et al., 2009). Thus, sleep problems may reduce Aβ clearance, leading to its accumulation and aggregation into plaques.

The association between sleep and amyloid burden has not been examined in late middle age. This age range is important because amyloid accumulation begins years before AD symptoms begin, and current AD treatments targeting later-stage disease have shown disappointing results (Schneider et al., 2014). Earlier intervention may be a more effective strategy to prevent or delay clinical

* Corresponding author at: Department of Psychiatry, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI 53719, USA. Tel.: 608 284 8422; fax: 608 236 4521.
E-mail address: ksprecher@wisc.edu (K.E. Sprecher).

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symptom onset due to AD pathology (Sperling et al., 2011). Sleep is an attractive therapeutic target because well-established methods already exist for improving sleep. Alternatively, if sleep is affected by amyloid deposition, sleep may harbor markers of early, preclinical AD useful for prognosis, and treatment monitoring.

The objective of this study was to determine whether sleep quality and quantity are related to amyloid burden in late midlife and to determine which aspects of sleep are associated with increased amyloid burden. We used PiB PET imaging and validated sleep questionnaires to test the hypothesis that in cognitively healthy middle-aged adults, poorer self-reported sleep quality would be associated with greater amyloid burden in brain regions typically affected by AD.

2. Methods

2.1. Participants and study design

Participants were drawn from the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal cohort of >1500 cognitively healthy adults, aged 40–65 years at study entry (Sager et al., 2005). Participants were included in the present analysis if they had completed the WRAP wave 4 visit, which included sleep assessment, and had completed a PiB PET scan; 98 individuals met inclusion criteria. Pertinent demographic and cognitive characteristics are summarized in Table 1; note that the sample was enriched with parental family history of AD and the epsilon 4 allele of the apolipoprotein E (APOE4) genotype, to a similar degree as the entire WRAP cohort.

WRAP participants underwent comprehensive neurocognitive and medical history assessment at baseline, 4 years later, and every 2 years thereafter at the University of Wisconsin (Sager et al., 2005). Participants were recruited to PiB PET imaging sub-studies by telephone, letter, or in person at their WRAP visit. The scan closest to the time of the sleep questionnaires was used in this analysis. Exclusion criteria included magnetic resonance imaging (MRI) contraindications, abnormal structural MRI, and diagnosis of significant neurological disease, medical illness, or major psychiatric disorders (determined by patient self-report). All study procedures were approved by the University of Wisconsin Institutional Review Board and each participant provided signed informed consent before participation.

Table 1
Participant characteristics (n = 98)

Variable	Data (n = 98)
Age at PiB PET scan, y	62.4 (5.7; 50–73)
Age at sleep assessment, y	63.0 (5.6; 51–73)
Interval between PiB PET scan and sleep assessment, y	0.69 (0.98; 0–3.7)
Female, %	67.3
APOE4 positive, %	34.7
FH positive, %	75.5
Maternal FH positive, %	52
BMI, kg/m^2	28.7 (5.7)
Education, y	16.582 (2.832; 12–25)
CES-D	5.78 (5.48; 0–27)
MMSE	29.31 (1.22; 23–30)
AVLT total	50.21 (8.66; 30–67)
AVLT delayed recall	10.36 (2.96; 0–15)
Trails A time[a]	10.11 (2.18; 5–17)
Trails B time[a]	10.26 (2.51; 6–17)
Digit symbol[a]	13.35 (2.1; 9–19)

All values are mean (SD; range) except where indicated.
Key: APOE4, the epsilon 4 allele of the apolipoprotein E gene; AVLT, Auditory Verbal Learning Test; BMI, Body Mass Index, CES-D, Center for Epidemiological Studies Depression Scale; FH, family history of Alzheimer's disease; MMSE, Mini-Mental State Exam; PET, positron emmision tomography; PiB, Pittsburgh Compound B; SD, standard deviation.
[a] Scaled for age and gender.

2.2. MRI acquisition and processing

All participants were scanned on a GE 3.0 Tesla MR750 (Waukesha, WI, USA) using an 8 channel head coil. A T1-weighted brain volume was acquired in the axial plane with a 3D inversion recovery prepared fast spoiled gradient-echo (3D) sequence using the following parameters: inversion time = 450 ms; repetition time = 8.1 ms; echo time = 3.2 ms; flip angle = 12°; acquisition matrix = 256 × 256 × 156 mm, field of view = 256 mm; slice thickness = 1.0 mm. Voxels were 1 mm isotropic. The image acquisition protocol also included T2-weighted and fluid-attenuated inversion recovery anatomical scans, which were reviewed by a neuroradiologist for exclusionary abnormalities. The T1-weighted volume was segmented into tissue classes using the updated segmentation feature in SPM12 (www.fil.ion.ucl.ac.uk/spm).

2.3. PiB PET imaging

[C-11] PiB PET radiochemical synthesis, acquisition parameters, and generation of distribution volume ratio (DVR) maps were detailed previously (Johnson et al., 2014). Briefly, after a 70-minute dynamic [C-11]PiB PET acquisition, PET data were reconstructed using a filtered back-projection algorithm Direct inverse Fourier Transformation (DIFT) and were corrected for random events, attenuation of annihilation radiation, deadtime, scanner normalization, and scatter radiation and were realigned and coregistered in SPM12. The data were then transformed into voxelwise DVR maps of [C-11]PiB binding using the time activity curve in the gray matter (GM) of the cerebellum as the reference region (Logan et al., 1996).

2.4. Cortical amyloid burden quantification

To reduce the number of statistical tests, amyloid binding was averaged within 8 bilateral regions of interest (ROIs), selected on the basis of AD sensitivity and known amyloid binding. The 8 ROIs from the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) were angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus (Fig. 1). The inverse deformation field resulting from unified segmentation on each subject image was applied to each Automated Anatomical Labeling ROI to produce ROI masks in native space. To constrain ROI analyses to GM only, each ROI mask was next multiplied by the binarized GM probability map thresholded at 0.3. A summary measure of amyloid burden was calculated by averaging all ROI means.

2.5. Sleep assessment

Two validated questionnaires assessing sleep were completed as part of a larger standardized neuropsychological assessment, proximal to the time of the PET scan. The Epworth Sleepiness Scale (ESS) (Johns, 1991) assesses sleep propensity and daytime sleepiness. Participants rate how likely they are to doze off or fall asleep in 8 common situations that vary in their soporific qualities, such as watching TV, talking to someone, or lying down. Responses are on a 4-point scale ranging from 0 = "would never doze" to 3 = "high chance of dozing". Responses are summed to produce a total score ranging from 0 to 24, with higher scores indicating greater daytime sleepiness. The ESS has been shown to have good internal