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 b,f, Rebecca L. Koscik b, 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

A R T I C L E   I N F O

Article history:
Received 12 February 2015
Received in revised form 3 May 2015
Accepted 10 May 2015
Available online 14 May 2015

Keywords:
Sleep
Amyloid
Alzheimer’s disease
PET
Midlife
Self-report

A B S T R A C T

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 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.

© 2015 Elsevier Inc. All rights reserved.

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 Aβ 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 plaque 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
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) abnormalities. The T1-weighted volume was segmented into tissue classes 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.filion.ucl.ac.uk/spm).

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.

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, postero rior 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 correlation with other measures of sleep propensity and daytime sleepiness (Johns, 1991).
consistency (Cronbach’s alpha = 0.73–0.88) and test-retest reliability (correlation of measures across a 5-month interval = 0.82) (Johns, 1992).

The Sleep Scale from the Medical Outcomes Study (MOS) (Hays and Stewart, 1992) is summarized in Table 2. It comprises 12 questions about the past 4 weeks, from which 8 scores were computed. The first question asks how long it takes to fall asleep, with possible responses in 15-minute increments ranging from 1 = “0–15 minutes” to 5 = “more than 60 minutes”. The second question asks the average number of hours slept each night, which is entered freely. Responses to the remaining 10 questions are on a 6-point scale ranging from 1 = “all of the time” to 6 = “none of the time”. Responses were converted to a 0–100 scale, with higher values indicating more of the concept being measured, then summed to give scores for 6 sleep domains: sleep disturbance, somnolence, sleep adequacy, snoring, waking short of breath, or with a headache and sleep quantity, and 2 indices of sleep problems summarizing 6 (index I) or 9 (index II) items (Spritzer and Hays, 2003). Multi-item scores show good internal consistency (Cronbach’s alpha 0.71–0.81) (Viala-Danten et al., 2008). Table 2 indicates which items contribute to each score, with some items contributing to >1 score.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sleep scales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESS</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (ESS)</td>
<td>How likely are you to doze off or fall asleep in the following 8 situations?[^a^]</td>
</tr>
<tr>
<td>MOS Sleep Scale</td>
<td>During the past 4 wk...</td>
</tr>
<tr>
<td>1. How long did it usually take for you to fall asleep?[^b^]</td>
<td></td>
</tr>
<tr>
<td>2. On the average, how many hours did you sleep each night?[^c^]</td>
<td></td>
</tr>
<tr>
<td>How often did you...[^d^]</td>
<td></td>
</tr>
<tr>
<td>3. Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, and so forth, while sleeping)?</td>
<td></td>
</tr>
<tr>
<td>4. Get enough sleep to feel rested upon waking in the morning?</td>
<td></td>
</tr>
<tr>
<td>5. Awaken short of breath or with a headache?</td>
<td></td>
</tr>
<tr>
<td>6. Feel drowsy or sleepy during the day?</td>
<td></td>
</tr>
<tr>
<td>7. Have trouble falling asleep?</td>
<td></td>
</tr>
<tr>
<td>8. Awaken during your sleep time and have trouble falling asleep again?</td>
<td></td>
</tr>
<tr>
<td>9. Have trouble staying awake during the day?</td>
<td></td>
</tr>
<tr>
<td>10. Snore during your sleep?</td>
<td></td>
</tr>
<tr>
<td>11. Take naps (5 min or longer) during the day?</td>
<td></td>
</tr>
<tr>
<td>12. Get the amount of sleep you needed?</td>
<td></td>
</tr>
</tbody>
</table>

Responses (b, c, d) were converted to a 0–100 scale, then summed to give scores. ○ indicates item included in scale and □ indicates that item was reversed before computing scale.

[^a^]: Responses were on a 4-point scale ranging from 0 = “would never doze” to 3 = “high chance of dozing”: Responses were summed to produce a total score ranging from 0 to 24, with higher scores indicating greater daytime sleepiness.

[^b^]: Possible responses were 15-minute increments from 1 = “0–15 min” to 5 = “more than 60 min”.

[^c^]: Responses were free entry.

[^d^]: Responses were on a 6-point scale ranging from 1 = “all of the time” to 6 = “none of the time”.

Fig. 1. Automated Anatomical Labeling regions of interest. Abbreviations: Ang, angular gyrus; CingA, anterior cingulate; CingP, posterior cingulate; FMO, frontal middle orbital gyrus; P, precuneus; SM, supramarginal gyrus; TM, middle temporal gyrus; TS, superior temporal gyrus.
2.6. APOE, family history, and cognitive data

APOE genotype was expressed as a binary categorical variable, with participants classified as carriers (1 or more ε4 alleles present) or noncarriers (no ε4 allele present). Family history of AD was determined by a multidisciplinary diagnostic consensus panel, as previously described (Sager et al., 2005). Positive family history of AD was defined as having 1 or both parents with autopsy-confirmed or probable AD according to the criteria of the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (McKhann et al., 1984, 2011).

Participants completed a comprehensive battery of standard psychometric tests and health and lifestyle questionnaires (Sager et al., 2005). Here, we report measures known to be associated with AD and/or sleep function. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), global cognitive function was assessed with the Mini-Mental State Exam (MMSE) (Folstein et al., 1975), episodic memory was assessed with the Rey Auditory Verbal

### Table 3

<table>
<thead>
<tr>
<th>ROI</th>
<th>Sleep adequacy</th>
<th>Sleep problems index I</th>
<th>Somnolence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>t</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>−0.002</td>
<td>0.001</td>
<td>−1.948</td>
</tr>
<tr>
<td>R</td>
<td>−0.003</td>
<td>0.001</td>
<td>−2.910</td>
</tr>
<tr>
<td>Cingulum anterior</td>
<td>−0.003</td>
<td>0.001</td>
<td>−2.565</td>
</tr>
<tr>
<td>R</td>
<td>−0.004</td>
<td>0.001</td>
<td>−2.819</td>
</tr>
<tr>
<td>Cingulum posterior</td>
<td>−0.003</td>
<td>0.001</td>
<td>−2.536</td>
</tr>
<tr>
<td>R</td>
<td>−0.002</td>
<td>0.001</td>
<td>−2.373</td>
</tr>
<tr>
<td>Frontal medial orbital</td>
<td>−0.003</td>
<td>0.001</td>
<td>−2.843</td>
</tr>
<tr>
<td>R</td>
<td>−0.004</td>
<td>0.001</td>
<td>−2.896</td>
</tr>
<tr>
<td>Precuneus</td>
<td>−0.003</td>
<td>0.001</td>
<td>−2.461</td>
</tr>
<tr>
<td>R</td>
<td>−0.003</td>
<td>0.001</td>
<td>−2.823</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>−0.001</td>
<td>0.001</td>
<td>−1.472</td>
</tr>
<tr>
<td>R</td>
<td>−0.002</td>
<td>0.001</td>
<td>−2.473</td>
</tr>
<tr>
<td>Temporal middle</td>
<td>−0.001</td>
<td>0.001</td>
<td>−1.542</td>
</tr>
<tr>
<td>R</td>
<td>−0.002</td>
<td>0.001</td>
<td>−2.067</td>
</tr>
<tr>
<td>Temporal superior</td>
<td>−0.001</td>
<td>0.001</td>
<td>−0.830</td>
</tr>
<tr>
<td>R</td>
<td>−0.002</td>
<td>0.001</td>
<td>−1.998</td>
</tr>
<tr>
<td>Mean</td>
<td>−0.002</td>
<td>0.001</td>
<td>−2.503</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All models were adjusted for age, sex, APOE4, family history of Alzheimer’s disease, and body mass index. Statistically significant associations are in bold and trends in italics.

Key: APOE4, the epsilon 4 allele of the apolipoprotein E gene; B, unstandardized regression coefficient; η²_p, partial eta squared; ROI, regions of interest; SE, standard error of the coefficient.

Fig. 2. Association between sleep scores and mean PiB DVR. Raw data is plotted, regression line is adjusted for age, sex, the epsilon 4 allele of the apolipoprotein E gene, family history of Alzheimer’s disease and body mass index. Abbreviations: DVR, distribution volume ratio; PiB, Pittsburgh Compound B.
Learning Task (Spreen and Strauss, 1998), and executive function was assessed with the Trail Making Tests A and B (Reitan and Wolfson, 1993) and the Digit Symbol Substitution subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997).

2.7. Statistical analysis

We used multiple regression to assess the relationship between self-reported sleep and regional amyloid load, quantified as PiB DVR. Separate models were tested for each possible sleep score and ROI combination, with sleep as the predictor of interest and PiB DVR as the outcome, using SPSS version 22 (IBM Corporation, Armonk, NY, USA). Because sleep and amyloid can be affected by age, sex, APOE4 genotype, family history of AD and body mass index these were included as covariates. Age was taken from the PET scan. It has previously been shown that the effect of sleep-disordered breathing on cognition depends on APOE genotype (Nikodemova et al., 2013), therefore, for each possible combination of sleep score and ROI, we tested a regression model that included a term for the interaction between sleep score and binary APOE4 status. Case analyses identified no outliers in need of removal. To explore the difference between ESS and MOS somnolence scores, we used Pearson’s correlation to test the relationship between ESS and the 3 sub-items of the MOS somnolence score. Results were considered statistically significant when p < 0.05.

3. Results

3.1. Participant characteristics

Participant characteristics are summarized in Table 1. The mean age was 62.4 years (standard deviation = 5.7, range = 50–73) at the time of the PET scan. Mean interval between PET scan and questionnaire completion was 0.69 (standard deviation: 0.98) years, and the results did not change when interval was added as a covariate. The sample was enriched for AD risk factors: 34 (34.7%) were APOE4 carriers, 74 (75.5%) had 1 or both parents with AD. Four participants had MMSE scores between 23 and 26, within the range of possible mild cognitive impairment. The remaining 94 participants had MMSE scores ≥27. Six participants had a CES-D score of 15–21, indicating possible mild-moderate depressive symptoms. One participant had a CES-D score of 27, indicating possible major depressive symptoms.

3.2. Association of self-reported sleep characteristics with regional amyloid load

After adjusting for covariates, poorer sleep was significantly associated (p < 0.05) with greater amyloid burden in most of the ROIs examined, across multiple sleep measures, with effect sizes ranging from small to medium (partial η² = 0.04–0.09). Sleep scores that were significantly associated with PiB DVR are in Table 3, other scores are in Supplementary Table 2. Note that beta coefficients appear small because responses to the MOS questionnaire were converted from a 6-point to 100-point scale for scoring. Data for 3 representative sleep score—ROI combinations are plotted in Fig. 2.

3.2.1. Sleep adequacy

Sleep Adequacy is derived from 2 questions; 1 asks whether respondents are getting the amount of sleep they need and the other asks whether respondents are getting enough sleep to feel rested. Less adequate sleep was associated with greater amyloid burden in the angular gyrus, anterior and posterior cingulate, frontal medial orbital gyrus, precuneus, supramarginal gyrus, temporal middle gyrus, and temporal superior gyrus and averaged across all 8 ROIs (Table 3).

3.2.2. Sleep problems

MOS sleep problems index I is computed from 6 items probing a range of sleep issues including sleep-disordered breathing.
ences between ESS and MOS somnolence further by testing the relationship with Pearson correlation. ESS was significantly associated with greater amyloid burden in several regions (Table 4). We further examined the relationship between the ESS and MOS somnolence score but not a higher score on the ESS, which may underestimate daytime sleepiness in adults 65 years (Onen et al., 2013). Furthermore, the scales assess distinct constructs: feeling sleepy (MOS) versus propensity for falling asleep (ESS) (Kim and Young, 2005). The ESS asks about the propensity to fall asleep while performing other activities (e.g., talking to someone, reading, driving) whereas the MOS somnolence score assesses feeling sleepy without falling asleep, voluntary napping, and trouble staying awake during the day. Indeed, ESS did not correlate with the MOS sub-item “taking naps”. The MOS somnolence score may capture a broader definition of perceived sleepiness or sleep inadequacy that does not require falling asleep. Our findings suggest that greater amyloid burden is associated with drowsiness but not involuntary daytime sleep. It also highlights the importance of assessing a range of self-reported sleep characteristics, given that sleep is a complex, multidimensional concept.

4.2. Sleep quantity and amyloid

There was no association between self-reported sleep duration and amyloid burden. This is consistent with previous studies in older adults using objective measures of sleep duration (polysonmography and actigraphy) and amyloid (Al42) in CSF (Ju et al., 2013) or plaques (Spira et al., 2014). In contrast, Spira et al. (2013) found that, in an older age group, self-reported shorter sleep was correlated with greater amyloid burden in the precuneus and averaged across the cortex. Whereas Spira et al. measured sleep duration with a 4-category scale, we treated sleep duration as a continuous variable (number of hours slept) because criteria for optimal sleep quantity are widely debated in the literature. Furthermore, categorization of continuous variables in regression analyses reduces power and increases the likelihood of false-
positives (Royston et al., 2006). We recoded our data according to the categorical scale of Spira et al. (<5; >5–6; >6–7; >7 hours) and again found no association between sleep duration and amyloid in our sample (data not shown). However, we cannot discount the possibility that sleep duration may impact amyloid deposition differently in older versus middle-aged subjects.

4.3. Sleep disorders and amyloid

We found no association between reports of symptoms of sleep-disordered breathing and amyloid burden, consistent with a prior finding of no relation of amyloid to reports of waking several times during the night in an elderly cohort (Spira et al., 2013). This is surprising, given that several lines of evidence link sleep-disordered breathing with AD. Sleep-disordered breathing is more prevalent in dementia than the general population (Frohnhofen and Roffe, 2012), increases risk of developing AD (Yaffe et al., 2011), and is correlated with AD markers in human CSF (amyloid and tau) (Osorio et al., 2013, 2014). In rodents, sleep disruption and intermittent hypoxia (features of sleep-disordered breathing) increase amyloid production and deposition (Kang et al., 2009; Shiota et al., 2013). We chose not to consider diagnosis of sleep disorders in this analysis because obstructive sleep apnea is underdiagnosed (Kapur et al., 2002). We measured self-reported symptoms; however, sleep-disordered breathing can be present without awareness or endorsement of symptoms (Gooneratne and Vitiello, 2014; Halász et al., 2004). Therefore, it is likely that some participants who did not report symptoms of sleep-disordered breathing actually did suffer from the disorder. Similarly, we found no association between brain amyloid and reports of insomnia-type symptoms (trouble falling and staying asleep). This is consistent with a study using a similar measure (self-report of trouble falling asleep, trouble staying asleep, and use of sleep medications), which found no association between disturbed sleep and Aβ42 in plasma, although those reporting troubled sleep had an ~1.5 higher risk of developing AD (Benedict et al., 2014). In contrast, behavioral measurement of sleep continuity (actigraphy) found that those with pathological CSF Aβ42 levels had significantly lower sleep efficiency. Although sleep-disordered breathing and insomnia were not individually associated with amyloid, both contributed to the sleep problems index, which was positively associated with greater amyloid burden. These findings highlight the need for further studies using physiological measures of sleep, breathing, and hypoxia to clarify their relationship with amyloid deposition. Self-reported sleep measures remain important, given that perceptions of disturbed sleep are what drive patients to seek clinical evaluation for sleep disorders.

4.4. Possible mechanisms linking sleep and amyloid

Because this study was cross-sectional, we cannot determine whether poor sleep drives amyloid deposition or vice versa. Studies in mice suggest the relationship may be bidirectional. Sleep restriction increased amyloid plaque burden (Kang et al., 2009), and chronic intermittent hypoxia during sleep (a feature of obstructive sleep apnea) increased CSF Aβ42 (Shiota et al., 2013). Conversely, rising plaque burden was accompanied by disrupted sleep, and immunization against plaque formation preserved sleep (Roh et al., 2012).

Aβ accumulation arises from an imbalance between Aβ production and clearance, and plaque formation is dependent on regional Aβ concentrations (Thal et al., 2006). Sleep disruption may affect several steps in the process of amyloid plaque formation. Amyloid is released during synaptic activity (Cirrito et al., 2005), and brain regions with greater neuronal activity show greater Aβ concentrations in interstitial fluid, and subsequently more plaque formation (Bero et al., 2011). Synaptic activity and synaptic strength are progressively decreased during sleep (Tononi and Cirelli, 2012; Vyazovskiy et al., 2009). Therefore, sleep disruption could chronically elevate neuronal activity, thereby increasing amyloid release. The resulting accumulation of extracellular amyloid would result in greater aggregation and plaque formation.

Aβ levels in CSF follow a diurnal pattern (Kang et al., 2009), with clearance greatest during sleep (Xie et al., 2013). In healthy men (40–60 years), 1 night of sleep deprivation abolished the overnight decline in CSF Aβ42 (Ooms et al., 2014). More wakefulness during the sleep period (i.e., lower sleep efficiency) may reduce Aβ clearance, leading to its accumulation and then aggregation into plaques. Consistent with this hypothesis, a study of older adults (mean 65.6 years) found lower sleep efficiency (measured objectively with actigraphy) and more napping (measured by sleep diary) in the group with lower CSF Aβ42, indicative of Aβ sequestration into plaques (Ju et al., 2013).

In addition to sleep disruption promoting amyloid deposition, amyloid may affect sleep by impairing the function of sleep-active brain regions and networks. Sleep is characterized by electrical oscillations in corticocortical and thalamocortical neural assemblies that directly contribute to neural plasticity and daytime cognitive function (Poe et al., 2010). Aβ disrupts synaptic transmission (Wang et al., 2009), network oscillations (Palop and Mucke, 2010) and functional connectivity (Bero et al., 2012; Sheline et al., 2010). Amyloid may impair the restorative functions of sleep oscillations, leading to perceptions of inadequate sleep and impaired daytime cognitive function.

4.5. Limitations

Strengths of this study include the assessment of multiple aspects of sleep, regional amyloid binding, and a well-characterized cohort in midlife, an age range that may be optimal for interventions. Limitations discussed above include the use of self-report, which decreased our ability to detect sleep disorders such as sleep-disordered breathing. There were multiple comparisons; however, the likelihood of type I error was minimized by restricting analyses to ROIs chosen a priori based on published literature. The consistent relationship of mean PiB DVR (averaged across all 8 ROIs) to sleep factors adds confidence to the findings. Although the PET scan and questionnaire were completed on separate days, sleep disorders are typically chronic, and the sleep questionnaire asked for symptoms over the previous 4 weeks. Indeed, results did not change when interval was included as a covariate (data not shown). The study was cross-sectional and observational, therefore, we cannot determine causality. However, this study establishes a link between sleep and amyloid in midlife, before the onset of AD symptoms.

4.6. Implications

No adequate treatments exist to reverse or prevent AD (Schneider et al., 2014). Effective treatments already exist for optimizing sleep, and treating sleep disorders in AD patients improves cognition, although dementia is not resolved (Ancoli-Israel et al., 2008). Our findings suggest that earlier interventions to improve sleep quality and to treat sleep disorders could potentially impact AD progression by reducing amyloid pathology. Additionally, sleep characteristics that are modified by amyloid may provide early biomarkers of preclinical AD and may be useful for diagnosis, prognosis, and for monitoring effectiveness of treatments. Prospective longitudinal studies and randomized control trials in...
cohorts at risk for AD are needed to determine which aspects of sleep are the most useful as treatment targets or disease markers. Greater amyloid burden was associated with perceptions of inadequate sleep, daytime sleepiness, and napping, but not with reported sleep amount or symptoms of sleep-disordered breathing or insomnia. It will be important for future studies to include physiological measures of the signs and symptoms of sleep disorders. However, healthy sleep is more than the absence of sleep disorders; it can be broadly defined as patterns of sleep-wakefulness that produce physical, mental, and social well-being (Buysse, 2014). Healthy sleep may take different forms across individuals and cultures. For example, sleep duration and cognitive vulnerability to sleep restriction vary between individuals in a trait-like manner (Rupp et al., 2012; Van Dongen et al., 2004), and across cultures sleep patterns vary from highly consolidated western schedules to siestas or biphasic schedules (Ekirch, 2005; Worthman and Melby, 2002). Although it is essential to identify mechanisms to effectively target interventions, it is also important to recognize that our understanding of sleep function and regulation continues to evolve. For example, it has become increasingly clear in recent years that, rather than being a global state, sleep can be considered a localized phenomenon, taking place independently in discrete neural circuits and even individual cells (Fisher and Vyazovskiy, 2014; Nir et al., 2011). Therefore, perceptions of inadequate sleep may capture defective sleep processes that we have yet to identify on a physiological level. Our finding that neuropathology is associated with perceptions of inadequate sleep but not with reported sleep duration or symptoms of sleep disorders highlight the importance of maintaining a broader view of sleep health at this time, when sleep’s role in AD pathology is only beginning to be uncovered. For example, rather than considering absolute amounts of sleep, it may be more informative to assess whether individuals are getting less sleep than they need, which is captured by questions addressing sleep adequacy.

5. Conclusion

We found that self-reported sleep quality, but not quantity, was associated with amyloid plaques in brain regions typically affected in AD. These relationships were present in middle-aged adults who are currently cognitively healthy, therefore, sleep may be useful during the preclinical phase of AD as a biomarker or modifiable risk factor to prevent or delay AD. Future work will need to clarify which aspects of sleep are most strongly related to amyloid and other markers of AD pathology, and the mechanisms linking sleep and AD progression.

Disclosure statement

Ruth M. Benca has served as a consultant to Merck and Jazz and receives grant support from Merck. The remaining authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

This research was supported by National Research Service Award (NRSA) T32 GM07507 (Kate E. Sprecher), CTSA award UL1TR000427 (Kate E. Sprecher), and by the National Institute on Aging grants R01 AG027161 (Sterling C. Johnson), AHRQ P30 AG033514 (Sanjay Asthana), R01 AG021155 (Sterling C. Johnson), and R01 AG037639 (Barbara B. Bendlin). The authors thank Caitlin A. Cleary, BSc, Sandra Harding, MS, Jennifer Bond, BA, and the WRAP psychometrists for assistance with study data collection. The authors gratefully acknowledge support of researchers and staff of the Waisman Center, University of Wisconsin-Madison where the brain scans took place. Finally, the authors thank participants in the Wisconsin Registry for Alzheimer’s Prevention for their ongoing dedication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, http://dx.doi.org/10.1016/j.neurobiolaging.2015.05.004.

References


2576

K.E. Sprecher et al. / Neurobiology of Aging 36 (2015) 2568–2576


