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Sleep moderates the relationship between amyloid beta and memory recall

Kristine A. Wilckens [a,*], Dana L. Tudorascu [b], Beth E. Snitz [c], Julie C. Price [d,e], Howard J. Aizenstein [a], Oscar L. Lopez [c], Kirk I. Erickson [f], Brian J. Lopresti [d], Charles M. Laymon [d,g], Davneet Minhas [d], Chester A. Mathis [d], Daniel J. Buysse [a], William E. Klunk [a,b], Ann D. Cohen [a]

[a] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[b] Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[c] Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[d] Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[e] A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA
[f] Department of Psychology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[g] Department of Bioengineering, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

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ABSTRACT

Amyloid-β (Aβ) accumulation is a hallmark of Alzheimer's disease, although Aβ alone may be insufficient to cause impairments. Modifiable health factors, including sleep, may mitigate functional symptoms of neurodegeneration. We assessed whether sleep moderated the relationship between Aβ and cognitive performance in 41 older adults, mean age 83 years. Sleep measures included actigraphy-assessed wake after sleep onset and total sleep time. Cognitive performance was assessed with memory recall, cognitive flexibility, and verbal fluency. Memory recall was assessed with the Rey-Osterrieth Complex Figure task, cognitive flexibility with the Trail Making test, and verbal fluency with FAS word generation. Aβ was assessed with a global measure of Pittsburgh Compound B. Wake after sleep onset moderated the relationship between Aβ and memory, with a stronger positive association for Aβ and forgetting in those with poorer sleep. These results suggest a possible protective role of sleep in preclinical Alzheimer's disease.

1. Introduction

Decline in sleep and cognitive health is common with normal aging (Carrier et al., 2001), and there is increasing evidence that changes in the former may influence the latter. For instance, improvements in sleep in older adults have been associated with overnight improvements in memory consolidation (Papalambros et al., 2017; Westerberg et al., 2015), and longitudinal studies suggest that poorer sleep in middle age predicts later cognitive decline (Scullin and Bliwise, 2015). Sleep may also be involved in slowing neurodegenerative processes (Lucey and Bateman, 2014). Levels of amyloid-β (Aβ), a precursor of Alzheimer's Disease (AD) plaque pathology, in the interstitial space are reduced during sleep and increased with sleep deprivation (Kang et al., 2009; Lucey et al., 2017, 2018; Ooms et al., 2014; Xie et al., 2013). Cross-sectional human studies have shown that poorer self-reported sleep, including shorter sleep duration is associated with greater presence of Aβ (Spira et al., 2013; Sprecher et al., 2015). Furthermore, the association between Aβ burden in the medial prefrontal cortex and memory performance was found to be mediated by slow-wave activity during non-rapid eye movement sleep (Mander et al., 2015). These findings provide motivation to further understand the link between sleep, Aβ, and cognitive impairment.

The presence of aggregated Aβ appears to be a necessary but insufficient criterion for cognitive decline (Aizenstein et al., 2008; Lucey and Bateman, 2014; Nebes et al., 2013; Pietrzak et al., 2015). Rather, health and lifestyle factors in late life can moderate effects of Aβ on cognition (Stern, 2012). Factors such as education and occupational attainment (Stern, 2012) and physical activity (Wolf et al., 2006) have been shown to minimize the influence of amyloid accumulation on performance of cognitive tasks, reflecting "cognitive reserve" (Stern, 2012). Given reported associations between sleep and cognition in older adults, as well as sleep with Aβ,

* Corresponding author at: Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA. Tel.: +1 7044258603; fax: (412) 246-5300.
E-mail address: wilckenska@upmc.edu (K.A. Wilckens).

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we posited that sleep may have a similarly protective relationship with Aβ and cognitive function.

In a group of community-dwelling older adults, we assessed whether two measures of sleep, wake after sleep onset (WASO), and total sleep time (TST), moderated the association between Aβ burden and neurocognitive performance. As Aβ accumulation has been shown to (1) have a negative relationship with cognitive performance, particularly with measures of forgetting and across a wide range of cognitive status (Hedden et al., 2013; Jack et al., 2008), as is the case here, and (2) have a negative relationship with sleep (Mander et al., 2015; Spira et al., 2013), we hypothesized that the negative association between Aβ and cognitive performance would be weaker among individuals with better sleep (lower WASO and longer TST).

2. Material and methods

2.1. Participants

Participants were 44 older adults aged 64–96 y (mean = 83.37), 58% female recruited through two ongoing Pittsburgh Compound B positron emission tomography (PiB-PET) imaging studies at the University of Pittsburgh, one of normal aging and amyloid (n = 20) and the other focused on vascular-amyloid interactions in oldest-old normal aging (n = 21). For the first parent study, participants were a subgroup of the Ginkgo Evaluation of Memory (GEM) study (DeKosky et al., 2006, 2008). Subjects in the parent study were 75 years of age and older, initially recruited from the Pittsburgh community through voter registration and mailing lists from 2000 to 2002 (DeKosky et al., 2008). Of the 966 participants from the original GEM study at the Pittsburgh, Pennsylvania, site, 197 continued in 2009 with the "GEMS" imaging substudy, which included PiB-PET and magnetic resonance (MR) imaging. The GEMS imaging substudy inclusion criterion was completion of the GEM parent study. Exclusion criteria were contraindications for neuroimaging (Snitz et al., 2013) and dementia at the completion of the GEM parent study, based on consensus cognitive diagnosis, which closely follows the approach and structure of the Alzheimer's Disease Research Center Consensus Conference (Lopez et al., 2000).

Participants from the second parent study were 65 years of age and older recruited from the community primarily from advertisements in a local seniors' newspaper, and others were recruited from previous studies on the effect of normal aging on cognitive performance (Nebes et al., 2006). They were not recruited from an AD research center and, therefore, had not sought treatment for dementia nor were they recruited as the spouses or family members of patients with dementia. However, a family history of dementia was not an exclusion criterion for this study.

Exclusion criteria for the two studies included the following: a diagnosis of dementia based on consensus cognitive diagnosis; a history of major psychiatric or neurological conditions (i.e., bipolar disorder, major depression in the last 5 years, stroke, Parkinson's disease, and substance abuse); an unstable medical condition that could affect cognition (i.e., chronic renal failure); visual, auditory, or motor deficits sufficient to impair performance on neuropsychological tasks; use of medications affecting neuropsychological performance (i.e., benzodiazapines, narcotic analgesics, and cholinesterase inhibitors); contraindications to MR imaging such as metal in the body or claustrophobia. Both studies had overlapping neuropsychological measures, amyloid imaging, and actigraphy, measured with the SenseWear armband. All participants provided written informed consent, and all study procedures were approved by the institutional review board of the University of Pittsburgh.

To maximize power, only measures that overlapped between the two studies were examined for the current analyses. Participants were excluded from the present analyses if they had less than 4 nights of SenseWear data (n = 2) or if their sleep consistently occurred during the day (n = 1). The final sample included 41 older adults. Twenty-eight participants were diagnosed as cognitively normal, defined as having no more than 1 or 2 tests, 1 standard deviation below age- and education-adjusted means (Aizenstein et al., 2008) out of the multidomain battery. Thirteen participants had a diagnosis of mild cognitive impairment (MCI) defined as 1 to 3 tests scored 1.5 standard deviations below age- and education-adjusted means (Albert et al., 2011). Participants were categorized as normal or MCI post hoc, not at the time of recruitment or study entry.

2.2. Measures

2.2.1. PET acquisition and quantitation

Before the PET imaging sessions, a spoiled gradient recalled MR scan was obtained for each subject for MR-PET image coregistration and anatomical region of interest (ROI) definition as previously described (Cohen et al., 2009).

PET imaging was conducted using a Siemens/CTI ECAT HR+ (three-dimensional mode, 15.2 cm field-of-view, 63 planes, reconstructed image resolution ~6 mm). High specific activity [^{11}C]PiB (PiB), produced as described by (Price et al., 2005), was synthesized by a standard method (Hamacher et al., 1986). The PiB-PET data were acquired as previously described (Price et al., 2005).

Analysis of the PiB-PET data was performed on time-averaged images in a manner consistent with established methods (Herholz et al., 2002; Minoshima et al., 1995; Ziolko et al., 2006). The PiB data were averaged over the interval 50–70 minutes after injection. ROIs were separately hand drawn on the coregistered MR image and included the following: frontal cortex, anterior cingulate cortex, striatum (caudate and anterior putamen), precuneus/posterior cingulate cortex, parietal cortex, lateral temporal cortex, and cerebellum (along the anterior plane near the top of the fourth ventricle) (Rosario et al., 2011). Regions were drawn by a single individual at the PET center blind to all clinical factors and hypotheses, as a course of the standard PiB-PET pipeline, in line with prior studies (Cohen et al., 2009; Rosario et al., 2011). The ROIs were transferred to the coregistered, frame-averaged PET images and used to extract mean tracer concentrations for each of the regions. A global tracer concentration value (GBL6) was determined by calculating a voxel-weighted average of the regions listed previously, excluding the cerebellum. The cerebellum, which is largely devoid of amyloid deposition and therefore exhibits mainly nonspecific PiB binding, was used as a reference region. Thus, each regional concentration was normalized by dividing by the cerebellar concentration. This yields tissue ratios, also known as standardized uptake value ratios (SUVR) for each ROI.

The present analyses used the global measure of PiB, GBL6, because the regions included are those typically involved in the pathophysiology of AD and active in tasks represented by those tested here including memory recall, verbal fluency, and cognitive flexibility. Limiting analyses to GBL6 further limited the number of tests and thereby the type I error rate. PiB positivity was determined using an established cutoff of 1.51 SUVR (Cohen et al., 2013).

2.2.2. Neurocognitive performance

Cognition was assessed with a neuropsychological battery with overlapping assessments between the two studies. Overlapping tasks were with the Rey-Osterrieth Complex Figure task (ROCF), Trail-Making Tasks A and B, and Semantic Verbal Fluency (FAS). Immediate and delayed memory forgetting were calculated by subtracting the ROCF immediate recall condition from the copy condition and the ROCF delayed recall condition from the copy

condition, respectively. Cognitive flexibility assessed with the Trail-Making tasks was calculated by subtracting Trails A from Trails B time. Verbal fluency was assessed with sum of words correctly generated across F, A, and S conditions.

2.2.3. Physiological data collection

A multisensor wearable device (SenseWear armband) was used to assess participants' sleep. Participants wore the armband for one week between the two experiment sessions. Participants were not assessed for sleep disorders or sleepiness. The device's propriety algorithm estimated every 60 seconds whether participants were active, lying down, or asleep based on body axis, heat flux, activity, galvanic skin response, body temperature, and near-body ambient temperature (Sunseri et al., 2009). Sleep and lying down estimates were visually inspected to define the lying down and sleep period for each night including sleep onset, final awakening, and time in bed. Participants did not complete a sleep diary for the present study, thus the sleep bout was not guided by self-report sleep times. The nighttime sleep bout was defined after 10 consecutive 1-minute epochs defined as "sleep" by the SenseWear algorithm. A research assistant blind to study hypotheses and all other clinical variables performed all SenseWear data reduction. Minutes spent awake between sleep onset and final awakening were used to calculate WASO for each night. Minutes spent asleep between sleep onset and final awakening were used to calculate TST for each night. Averages across all nights were then calculated for WASO (average minutes spent awake following sleep onset) and TST (average time spent sleeping each night). WASO and TST were chosen because these measures have been most consistently implicated in cognitive performance and Aβ accumulation (Blackwell et al., 2006, 2014; Diem et al., 2016; Spira et al., 2013; Wilckens et al., 2014) and can be measured actigraphically with SenseWear (Sunseri et al., 2009; Wilckens et al., 2014). To capture time spent sleeping outside the nighttime sleep bout, we calculated daytime naps (average minutes spent asleep outside of the nighttime sleep bout). Average WASO, TST, and daytime naps for controls and MCI are presented in Table 1.

2.3. Analytic techniques

2.3.1. Group differences

Mulitvariate analysis of variance (MANOVA) was used to assess group differences in terms of MCI status and PiB status as well as interactions between MCI and PiB status. Variables presented in Tables 1 and 2 were included as dependent variables in the MANOVA. The MANOVA was tested with age, sex, and education included among the dependent variables and then again as covariates.

2.3.2. Moderation analyses

2.3.2.1. Neurocognitive performance. Hierarchical regression analyses were conducted on each of the 4 cognitive domains as the dependent variable with each mean-centered sleep measure, mean-centered global PiB SUVR, and their interaction as independent variables. Each regression included 3 hierarchical models. Age, sex, and education were included in model 1 as covariates. Model 2 included the mean-centered sleep variable (WASO or TST) and mean-centered global PiB SUVR. Model 3 included an interaction term between the centered sleep variable and centered global PiB SUVR to test whether WASO and TST moderate the relationship between Aβ and neuropsychological performance. Separate regressions were performed for WASO and TST. Holm Sidak family-wise error correction was used to adjust p values for each of the 4 cognitive domains assessed. To interpret significant interactions between sleep and Aβ, we followed up significant interactions with a simple slope analysis at high (+1 SD) and low (−1 SD) levels of WASO and TST.

3. Results

3.1. Relationships among sleep variables

TST and WASO were significantly inversely related to each other, $r = -0.634$, $p < 0.001$. Time spent asleep outside the defined nighttime sleep bout (daytime naps) was negatively correlated with TST, $r = -0.354$, $p = 0.023$, such that individuals with more time spent napping had less nighttime TST. A positive association between WASO and daytime naps did not reach significance, $r = 0.233$, $p = 0.142$. To account for these associations between sleep variables of interest and daytime naps and their potential influence, we included follow-up sensitivity analyses with daytime naps as a covariate.

3.2. Group differences in sleep, Aβ, and neuropsychological performance

Differences between PiB(−) and PiB(+) groups are displayed in Table 1, and differences between control and MCI groups are displayed in Table 2. PiB positivity was associated only with older age. Controlling for age, sex, and education in PiB status comparisons led

Table 1
Demographics, MMSE, and sleep measures separated by PiB status (negative and positive)

Measure	PiB(−) (n = 22) mean/N (sd/%)	PiB(+) (n = 19) mean/N (sd/%)	Main effect of PiB status F(1,39) value	95% Confidence interval
Age	**80.73 (7.99)**	**86.77 (7.80)**	**5.95**[a]	**1.03:11.05**
Sex (% Female)	14 (63.6%)	10 (52.6%)	0.49	−0.42:0.23
Education	14.09 (2.88)	14.89 (2.92)	0.78	−1.03:2.64
MMSE (n = 40)	27.81 (1.75)	28.00 (1.92)	0.11	−0.98:1.36
Global PiB SUVR	**1.46 (0.12)**	**2.31 (0.40)**	**90.67**[b]	**0.67:1.03**
WASO	67.52 (39.56)	61.53 (38.16)	0.24	−30.65:18.66
TST (min)	365.33 (86.16)	376.68 (72.06)	0.21	−39.31:62.00
Daytime naps (min)	33.83 (44.72)	28.36 (26.44)	0.22	−18.23:29.17
Immediate forgetting	3.34 (2.61)	3.80 (3.50)	0.22	−1.48:2.38
Delayed forgetting	3.57 (2.78)	3.63 (4.07)	0.003	−2.11:2.24
Cognitive flexibility (s)	58.57 (42.64)	70.83 (56.36)	0.63	−19.06:43.59
Verbal fluency total	42.27 (14.85)	40.84 (12.68)	0.11	−10.23:7.37

Main effect of PiB status represents F values based on MANOVA.
Confidence interval for sex is based on 1 = male and 2 = female. Significant differences are in bold font.
Key: MMSE, mini-mental state examination; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratios; TST, total sleep time; WASO, wake after sleep onset.
[a] $p < 0.05$.
[b] $p < 0.001$.

Table 2
Demographics, MMSE, and sleep measures for controls and MCI

Measure	Control (n = 28) mean/N (sd/%)	MCI (n = 13) mean/N (sd/%)	Main effect of patient type F(1,39) value	95% Confidence interval
Age	82.07 (7.16)	86.67 (10.17)	2.79	−0.97:10.17
Sex (% Female)	**20 (71.4%)**	**4 (30.8%)**	**6.75**[a]	**0.09:0.72**
Education	14.57 (2.60)	14.23 (3.54)	0.12	−2.32:1.64
MMSE (n = 40)	**28.44 (1.45)**	**26.77 (2.01)**	**9.09**[b]	**−2.8:−0.55**
Global PiB SUVR	1.80 (0.49)	1.96 (0.57)	0.84	−0.19:0.51
WASO	63.53 (32.61)	67.36 (50.49)	0.09	−22.64:30.31
TST (min)	382.75 (73.77)	344.41 (86.93)	2.18	−14.65:91.33
Daytime naps (min)	26.83 (36.11)	40.89 (38.64)	1.29	−39.11:11.00
Immediate forgetting	**2.82 (2.47)**	**5.12 (3.57)**	**5.73**[a]	**0.36:4.23**
Delayed forgetting	3.07 (2.76)	4.73 (4.40)	2.71	−0.61:3.93
Cognitive flexibility (s)	**45.97 (17.46)**	**103.62 (70.21)**	**17.07**[c]	**29.42:85.86**
Verbal fluency total	43.96 (13.43)	36.54 (13.50)	2.71	−16.56:1.71

Main effect of patient type represents F values based on MANOVA.
Confidence interval for sex is based on 1 = male and 2 = female. Significant differences are in bold font.
Key: MCI, mild cognitive impairment; MMSE, mini-mental state examination; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratios; TST, total sleep time; WASO, wake after sleep onset.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

to no other significant differences in participant characteristics displayed in Table 1. MANOVA revealed no significant interactions between patient type and PiB status for WASO, $F(1, 34) = 0.23$, $p = 0.634$, or TST, $F(1,34) = 0.001$, $p = 0.979$.

The cognitively healthy group was younger and had a greater proportion of female participants. MANOVA across all participant characteristics confirmed significantly poorer performance in the MCI group for immediate forgetting and cognitive flexibility. After controlling for age, sex, and education, delayed forgetting was also significantly poorer in the MCI group, $F(1,35) = 4.61$, $p = 0.039$.

3.3. Moderation analyses with neuropsychological performance

3.3.1. Wake after sleep onset

For all cognitive domains, after controlling for covariates in model 1, model 2 showed that WASO and global PiB SUVR were not linearly associated with performance (Table 3). Model 3 demonstrated that WASO and global PiB SUVR significantly interacted in their association with both immediate and delayed forgetting (Table 3, Fig. 1). Sensitivity analyses revealed the same interactions for WASO with the dichotomous PiB status variable. These associations were significant after Holm Sidak correction and remained significant when patient type (MCI vs. control) was included as a covariate, $\beta = 0.35$, $p = 0.021$ and $\beta = 0.43$, $p = 0.005$ for immediate and delayed, respectively. Sensitivity analyses accounting for daytime naps showed that this interaction remained significant, $\beta = 0.45$, $p = 0.012$ for immediate forgetting and $\beta = 0.46$, $p = 0.004$ for delayed forgetting. Furthermore, accounting for daytime naps showed an additional significant linear association between higher WASO and more delayed forgetting, $\beta = 0.32$, $p = 0.049$. Consistent with our hypotheses, the relationship between Aβ and forgetting was stronger for those with higher WASO as indicated by a significant positive slope for high WASO (m = 2.65, $t = 2.92$, $p = 0.006$ for immediate forgetting, m = 3.29, $t = 3.56$, $p = 0.001$ for delayed forgetting). The slope for low WASO was in the negative direction but did not reach significance, p's > 0.05. This moderating effect of WASO was robust to removal of three potentially influential cases with WASO >125 minutes, $\beta = 0.39$, $p = 0.033$ for immediate, and $\beta = 0.37$, $p = 0.038$ for delayed.

Although these analyses controlled for age, given that the PiB positive group was significantly older (Table 1), we tested the same models with age in place of PiB SUVR as a post hoc sensitivity analysis. This analysis revealed a weaker interaction that was significant only for immediate memory $\beta = 0.44$, $p = 0.037$, with no significant simple slopes between age and memory performance at low or high levels of WASO, p's > 0.05.

3.3.2. Total sleep time

For all cognitive domains, model 2 showed that TST and global PiB SUVR were not linearly associated with performance (Table 4). Model 3 demonstrated that TST and global PiB SUVR interacted in their association with delayed recall only (Table 4). Simple slope analysis suggested that shorter TST was associated with a stronger positive relationship between Aβ and delayed memory performance, m = 2.72, $t = 3.15$, $p = 0.003$ for low TST, m = −2.19, $t = -1.54$, $p = 0.132$ for high TST. This interaction was significant for both the interaction between TST and the continuous global PiB SUVR measure as well as the dichotomous PiB status measure but only passed multiple comparisons correction when tested with PiB status (Table 4). Sensitivity analyses with naps showed that the interaction between TST and amyloid in relation to delayed forgetting remained significant, $\beta = -0.36$, $p = 0.03$ after

Table 3
Regression coefficients for each of the cognitive domains with WASO as a factor

Cognitive domain	WASO		Global PiB SUVR			WASO × Global PiB SUVR		
	β	*p*	*β*	*P*	Model 2 R^2 change	*β*	*p*	Model 3 R^2 change
Immediate memory	0.20	0.243	0.14	0.463	0.05	**0.42**	**0.01**[a]	**0.17**
Delayed memory	0.25	0.133	0.14	0.426	0.07	**0.47**	**0.002**[a]	**0.22**
Cognitive flexibility	−0.16	0.244	0.05	0.710	0.03	0.12	0.400	0.01
Verbal fluency	−0.06	0.713	−0.005	0.975	0.003	0.07	0.665	0.004

Bold font denotes uncorrected significance.
Key: PiB, Pittsburgh compound B; SUVR, standardized uptake value ratios; WASO, wake after sleep onset.
[a] $p<0.05$ corrected.

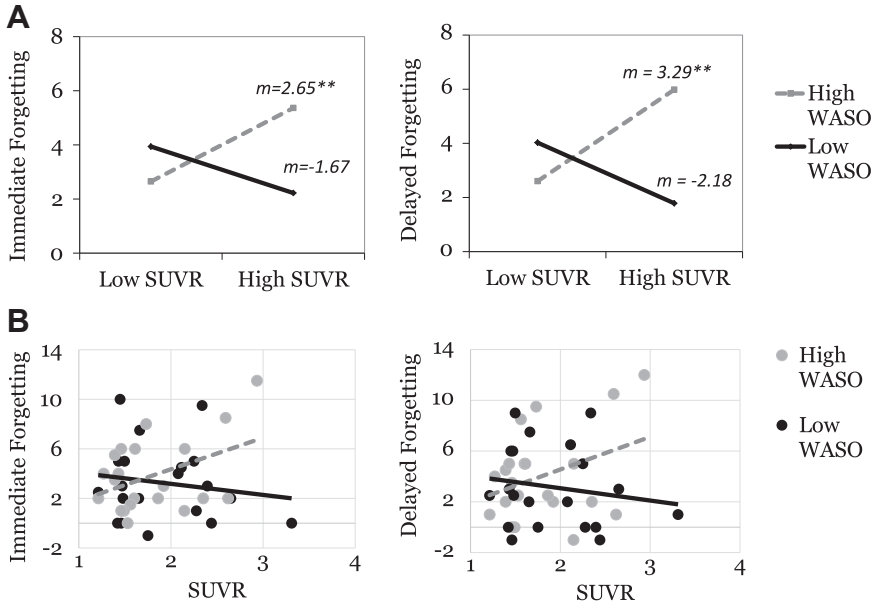

Fig. 1. WASO moderates the relationship between global PiB SUVR and immediate forgetting (left) and delayed forgetting (right). (A) Simple slopes for the relationship between global PiB SUVR and forgetting at high and low levels of WASO. (B) Scatter plot of the association between global PiB SUVR for the half of the sample with high (gray) versus low (black) WASO. Forgetting represents the difference between Rey-O copy performance and immediate or delayed performance. **Denotes significance $p < 0.01$. Abbreviations: PiB, Pittsburgh compound B; SUVR, standardized uptake value ratios; WASO, wake after sleep onset.

controlling for daytime napping. Furthermore, visual inspection of the data suggested that this result was influenced by an outlier. After removal of this outlier, the TST association was not significant $\beta = -0.24$, $p = 0.264$, but the significance of the above interaction with WASO was unchanged, $\beta = 0.46$, $p = 0.007$.

4. Discussion

Sleep may play a protective role in cognitive impairment and progression of AD. Here we found that WASO, and to a lesser extent TST, moderated the relationship between Aβ and memory performance. Associations between WASO and immediate and delayed memory were robust after accounting for MCI status and daytime napping.

4.1. Higher amyloid is associated with worse memory recall in individuals with poor sleep

The National Institute of Aging–Alzheimer's Association research criteria for preclinical AD is Aβ burden without cognitive impairment (Cohen, 2016; Lucey and Bateman, 2014; Sperling et al., 2011). In this study, individuals with better sleep in terms of less WASO exhibited a weaker association between Aβ and memory performance. Although these data are cross-sectional, and poorer sleep may be a result of AD pathology, this finding may suggest that greater sleep continuity is protective against cognitive impairments despite the presence of Aβ. The moderating effect of sleep on amyloid is consistent with a study of drosophila, which showed that enhancing sleep reversed memory deficits in flies expressing amyloid precursor protein (Dissel et al., 2017). Possible mechanisms through which sleep could be protective for memory function include increasing attention, and thereby compensating for hippocampal amyloid accumulation, mitigating neurotoxicity, or increasing hippocampal function. For instance, hippocampal-prefrontal connectivity, a putative marker of systems-level memory consolidation, has been shown to be associated with sleep (Mander et al., 2013, 2015). Alternatively, cognitively healthy individuals with amyloid may be in an early phase of the disease progression, before deficits in sleep have taken place. However, cognitively normal participants with high amyloid in fact had numerically better sleep than their low-amyloid counterparts though this difference did not reach significance (see Table 5, Supplementary Material), favoring the idea that better sleep may be protective against Aβ. Furthermore, the cognitively normal group with higher Aβ was also significantly older than the cognitively normal group with low amyloid (see Table 5, Supplementary Material). Thus, better sleep in the high amyloid group was not due to their comparatively younger age. Nonetheless, the protective explanation versus early disease stage explanation may not be mutually exclusive. Cognitive reserve studies have shown that high functioning individuals with high levels of Aβ often show more dramatic disease progression once symptoms begin to appear (Stern, 2012) and the main effect of cognitive reserve is to stave off the onset of AD rather than slow the rate of decline once the

Table 4
Regression coefficients for each of the cognitive domains with TST as a factor

Cognitive domain	TST		Global PiB SUVR			TST × global PiB SUVR		
	β	*p*	*β*	*P*	Model 2 R^2 change	*β*	*P*	Model 3 R^2 change
Immediate memory	−0.24	0.156	0.14	0.432	0.07	−0.19	0.264	0.03
Delayed memory	−0.12	0.480	0.14	0.458	0.03	**−0.37**	**0.032**	**0.12**
Cognitive flexibility	−0.10	0.454	0.07	0.626	0.01	−0.15	0.289	0.02
Verbal fluency	0.003	0.982	0.002	0.993	<0.001	0.03	0.863	0.001

Bold font denotes uncorrected significance.
Key: PiB, Pittsburgh compound B; SUVR, standardized uptake value ratios; TST, total sleep time.

protective cognitive reserve factors have been overcome. Thus, future studies may examine whether cognitive reserve and brain reserve from better sleep is similarly associated with more rapid cognitive decline upon emergence of AD following a delayed disease onset.

Our findings with TST paralleled the moderating relationship found with WASO, but to a less consistent extent. These findings intuitively fit with the WASO results. However, it is worth noting that many studies of self-reported sleep duration show that longer sleep duration is associated with poorer cognitive performance (Scullin and Bliwise, 2015; Yaffe et al., 2014), and some studies show a U-shaped relationship (Scullin and Bliwise, 2015; Wilckens et al., 2014; Xu et al., 2011) suggesting that very short and very long sleep are associated with poorer performance. In the present study, it is notable that the range of total nighttime sleep was relatively short, mean = 6.18 hours, with an additional 31.29 minutes of daytime sleep on average, and a maximum of 8.29 hours. Thus, the range of TST in this sample falls below what is typically considered long sleep (>9 hours). This range of TST in the current sample may explain why a positive relationship was found here in which moderate sleep time as opposed to short sleep time is associated with better performance, particularly in the PiB positive group. Nonetheless, the results with TST here were not robust to removal of outliers or multiple comparisons correction. Thus, the results with TST should be interpreted with caution.

Our post hoc sensitivity analyses testing whether sleep moderated the relationship between age and performance (given that the PiB-positive group was older) revealed a significant (uncorrected) moderating relationship only for immediate memory: the relationship between WASO and forgetting was greater in the older half of the sample. This intriguing finding may in fact be driven by the PiB findings mentioned previously, that is, sleep is protective against the biological aging processes that lead to cognitive impairments, including Aβ accumulation. This question warrants further investigation in samples with wide ranges of PiB accumulation and limited age ranges.

4.2. Lack of moderating associations with WASO for executive function

Cognitive flexibility and verbal fluency domains did not exhibit the hypothesized interaction with sleep and Aβ. The absence of such findings may reflect low statistical power for a small effect size, or it may reflect specificity of sleep as a moderator of memory as opposed to a moderator of executive functions. Accelerated decline in memory function often occurs earlier than executive function in preclinical AD (Grober et al., 2008), memory more consistently than executive function is associated with Aβ (Hedden et al., 2013). Furthermore, AD pathology often accumulates earlier in brain structures that support memory such as the medial temporal lobes (Guillozet et al., 2003). If the current findings reflect differences between normal aging and preclinical AD, then associations should in fact be stronger in cognitive domains that are known to depend on the medial temporal lobes, as is the case here.

4.3. Strengths, limitations, and future directions

This study had several strengths, including robust in vivo measures of Aβ deposition in a relatively older geriatric sample, rigorous neuropsychological assessment and diagnosis, and objectively assessed habitual sleep. The main limitation of this study is the small sample size, particularly for individuals who are PiB positive or have MCI. Previous findings of significant linear associations between longer TST and less Aβ burden (Spira et al., 2013) were not found here. This could be explained by the sample size or the average age difference between samples (this sample being approximately 7 years older on average). Thus, it will be important to follow up these analyses with larger sample sizes across each of the participant groups presented here.

Although the heterogeneity of the present study allowed us to examine a wide range of memory and executive function abilities and Aβ burden, future work may benefit from examining moderating effects of sleep within a more homogenous sample with respect to disease progression or cognitive symptoms. Such a sample may provide greater power in assessing, for instance, the moderating role of sleep in memory performance among individuals with similar levels of Aβ burden or the same time of onset of cognitive impairments.

5. Conclusions

Among individuals with poorer sleep, there was a stronger positive relationship between Aβ and forgetting. These data broadly suggest a role for sleep in the association between Aβ accumulation and memory retention and provide further impetus for research into the possible protective role of sleep in memory impairment and AD.

Disclosure statement

GE Healthcare holds a license agreement with the University of Pittsburgh. WK and CM are coinventors of PiB and, as such, have a financial interest in this license agreement. GE Healthcare provided no grant support for this study and had no role in the design or interpretation of results or preparation of this article. All other authors have no conflicts of interest with this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.07.011.

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