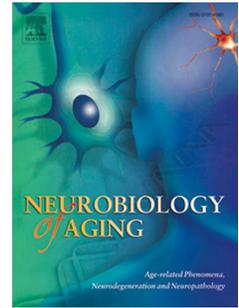


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**Sleep moderates the relationship between amyloid beta and memory recall**

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## Abstract

Amyloid- $\beta$  ( $A\beta$ ) accumulation is a hallmark of Alzheimer's disease (AD), though  $A\beta$  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  $A\beta$  and cognitive performance in 41 older adults, mean age 86. Sleep measures included actigraphy-assessed wake after sleep onset (WASO) and total sleep time (TST). 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 (TMT-B), and verbal fluency with FAS word generation.  $A\beta$  was assessed with a global measure of Pittsburgh Compound B (PiB). WASO moderated the relationship between  $A\beta$  and memory, with a stronger positive association for  $A\beta$  and forgetting in those with poorer sleep. These results suggest a possible protective role of sleep in preclinical AD.

Key Words: amyloid- $\beta$ , sleep, neuropsychological performance, mild cognitive impairment, preclinical Alzheimer's disease

### Competing Interests:

GE Healthcare holds a license agreement with the University of Pittsburgh. Drs. Klunk and Mathis are co-inventors 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 manuscript. All other authors have no conflicts of interest with this work.

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## 1.1 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 A $\beta$ , 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., 2018, Lucey, et al., 2017, 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 A $\beta$  (Spira, et al., 2013, Sprecher, et al., 2015). Further, the association between A $\beta$  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, A $\beta$ , and cognitive impairment.

The presence of aggregated A $\beta$  appears to be a necessary but insufficient criterion for cognitive decline (Aizenstein, et al., 2008a, Lucey and Bateman, 2014, Nebes, et al., 2013, Pietrzak, et al., 2015). Rather, health and lifestyle factors in late-life can moderate effects of A $\beta$  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 A $\beta$ , we posited that sleep may have a similarly protective relationship with A $\beta$  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 A $\beta$  burden and neurocognitive performance. As amyloid- $\beta$  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 A $\beta$  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 forty-four older adults ages 68-100 (mean = 86.32), 58% female recruited through two ongoing 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, DeKosky, et al., 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 Sub-Study, which included Pittsburgh Compound B positron emission tomography (PiB-PET) and magnetic resonance imaging (MRI). The GEMS imaging sub-study 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 Alzheimer's disease 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 five 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., benzodiazepines, narcotic analgesics, and cholinesterase inhibitors); contraindications to MRI 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., 2008b) out of the multi-domain 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 (SPGR) magnetic resonance (MR) scan was obtained for each subject for MR-PET image co-registration and anatomical region of interest (ROI) definition as previously described (Cohen, et al., 2009).

Positron emission tomography (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 [<sup>11</sup>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, Ziolkowski, et al., 2006). The PiB data were averaged over the interval 50-70 min post-injection. ROIs were separately hand-drawn on the co-registered 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 above, 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, since 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 multi-sensor 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 one-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 A $\beta$  accumulation (Blackwell, et al., 2006, Blackwell, et al., 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 of the night time 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*

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 & 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 A $\beta$  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 four cognitive domains assessed. To interpret significant interactions between sleep and A $\beta$ , 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**

### **Relationships among sleep variables**

Total sleep time and WASO were significantly inversely related to each other,  $r = -0.634$ ,  $p < 0.001$ . Time spent asleep outside of 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.

### 3.1 Group differences in sleep, A $\beta$ , 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 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,  $F(1, 34) = 0.226$ ,  $p = 0.637$ , or TST,  $F(1,34) = 0.001$ ,  $p = 0.978$ .

The cognitively healthy group were 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,  $F(1,35) = 4.46$ ,  $p = 0.042$ .

### 3.2 Moderation Analyses with Neuropsychological Performance

#### 3.2.1 Wake after Sleep Onset (WASO)

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, Figure 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,  $\beta = 0.35$ ,  $p = 0.022$  and  $\beta = 0.426$ ,  $p = 0.005$  for immediate and delayed, respectively. Sensitivity analyses accounting for daytime naps showed that this interaction remained significant,  $\beta = 0.40$ ,  $p = 0.017$  for immediate forgetting and  $\beta = 0.418$ ,  $p = 0.006$  for delayed forgetting. Further, accounting for daytime naps showed an additional

significant linear association between higher WASO and more delayed forgetting,  $\beta = 0.327$ ,  $p = 0.046$ . Consistent with our hypotheses, the relationship between A $\beta$  and forgetting was stronger for those with higher WASO as indicated by a significant positive slope for high WASO ( $m = 2.64$ ,  $t = 2.91$ ,  $p = 0.006$  for immediate forgetting,  $m = 3.29$ ,  $t = 3.57$ ,  $p = 0.001$  for delayed forgetting). The slope for low WASO was in the negative direction, but did not reach significance,  $p$ 's  $> .05$ . This moderating effect of WASO was robust to removal of three potentially influential cases with WASO  $> 125$  mins,  $\beta = 0.36$ ,  $p = 0.039$  for immediate, and  $\beta = 0.39$ ,  $p = 0.034$  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  $\beta = 0.42$ ,  $p = 0.047$ , with no significant simple slopes between age and memory performance at low or high levels of WASO,  $p$ 's  $> 0.40$ .

### 3.2.2 Total Sleep Time (TST)

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 A $\beta$  and delayed memory performance,  $m = 2.68$ ,  $t = 3.10$ ,  $p = 0.004$  for low TST,  $m = -2.23$ ,  $t = -2.23$ ,  $p = 0.126$  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,  $\beta = -0.33$ ,  $p = 0.045$  after controlling for daytime napping.

Further, 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  $\beta = -0.24$ ,  $p = 0.259$ , but the significance of the above interaction with WASO was unchanged,  $\beta = 0.461$ ,  $p = 0.007$ .

#### **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 A $\beta$  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 NIA-Alzheimer's Association research criteria for preclinical AD is A $\beta$  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 A $\beta$  and memory performance. Though 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 A $\beta$ . 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., 2015, Mander, et al., 2013). 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 A $\beta$ . Further, the cognitively normal group with higher A $\beta$  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 A $\beta$  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 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 total sleep time 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 total sleep time 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 above, i.e. sleep is protective against the biological aging processes that lead to cognitive impairments, including A $\beta$  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 A $\beta$ . 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 A $\beta$  (Hedden, et al., 2013). Further, 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.

#### *4.4 Strengths, Limitations, and Future Directions*

This study had several strengths, including robust in vivo measures of A $\beta$  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 mild cognitive impairment. Previous findings of significant linear associations between longer total sleep time and less A $\beta$  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 10 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 current study allowed us to examine a wide range of memory and executive function abilities and A $\beta$  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 A $\beta$  burden or the same time of onset of cognitive impairments.

#### **Conclusions**

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

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**Table 1: Demographics, MMSE, and sleep measures separated by PiB status (negative and positive). Main effect of PiB status represents F values based on MANOVA. \*p <0.05, \*\*p <0.01, \*\*\*p<0.001. Confidence interval for sex is based on 1=male and 2=female. Significant differences are in bold font.**

	PiB(-) (n=22) Mean/N (sd/%)	PiB(+) (n=19) Mean/N (sd/%)	Main effect of PiB Status F(1,39) value	95% Confidence Interval
<b>Age</b>	<b>83.45 (8.11)</b>	<b>89.63 (7.95)</b>	<b>6.03*</b>	<b>1.09:11.27</b>
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
<b>Global PiB SUVR</b>	<b>1.46 (0.12)</b>	<b>2.31 (0.40)</b>	<b>90.67***</b>	<b>0.67:1.03</b>
WASO	67.52 (39.56)	61.53 (38.16)	0.24	-30.65:18.66
TST (mins)	365.33 (86.16)	376.68 (72.06)	0.21	-39.31:62.00
Daytime Naps (mins)	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 (sec)	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

**Table 2: Demographics, MMSE, and sleep measures for controls and MCI. Main effect of patient type represents F values based on MANOVA. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001. Confidence interval for sex is based on 1=male and 2=female. Significant differences are in bold font.**

	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	84.75 (7.39)	89.69 (10.07)	3.14	-0.70:10.58
<b>Sex (% Female)</b>	<b>20 (71.4%)</b>	<b>4 (30.8%)</b>	<b>6.75*</b>	<b>0.09:0.72</b>
Education	14.57 (2.60)	14.23 (3.54)	0.12	-2.32:1.64
<b>MMSE (n=40)</b>	<b>28.44 (1.45)</b>	<b>26.77 (2.01)</b>	<b>9.09**</b>	<b>-2.8:-0.55</b>
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 (mins)	382.75 (73.77)	344.41 (86.93)	2.18	-14.65:91.33
Daytime Naps (mins)	26.83 (36.11)	40.89 (38.64)	1.29	-39.11:11.00
<b>Immediate Forgetting</b>	<b>2.82 (2.47)</b>	<b>5.12 (3.57)</b>	<b>5.73*</b>	<b>0.36:4.23</b>
Delayed Forgetting	3.07 (2.76)	4.73 (4.40)	2.71	-0.61:3.93
<b>Cognitive Flexibility (sec)</b>	<b>45.97 (17.46)</b>	<b>103.62 (70.21)</b>	<b>17.07***</b>	<b>29.42:85.86</b>
Verbal Fluency Total	43.96 (13.43)	36.54 (13.50)	2.71	-16.56:1.71

**Table 3. Regression coefficients for each of the cognitive domains with WASO as a factor; Bold font denotes uncorrected significance. \* $p < 0.05$  corrected.**

	WASO		Global PiB SUVR		Model 2 R <sup>2</sup> change	WASO × Global PiB SUVR		Model 3 R <sup>2</sup> change
	$\beta$	$p$	$\beta$	$p$		$\beta$	$p$	
<b>Immediate Memory</b>	0.197	0.243	0.134	0.464	0.05	<b>0.415</b>	<b>0.01*</b>	<b>0.17</b>
<b>Delayed Memory</b>	0.25	0.133	0.144	0.421	0.07	<b>0.472</b>	<b>0.002*</b>	<b>0.22</b>
Cognitive Flexibility	-0.160	0.246	0.055	0.712	0.03	0.120	0.388	0.01
Verbal Fluency	-0.053	0.726	-0.003	0.984	0.003	0.063	0.683	0.004

**Table 4. Regression coefficients for each of the cognitive domains with TST as a factor; Bold font denotes uncorrected significance.**

	TST		Global PiB SUVR			TST × Global PiB SUVR		
	$\beta$	$p$	$\beta$	$p$	Model 2 R <sup>2</sup> Change	$\beta$	$p$	Model 3 R <sup>2</sup> Change
Immediate Memory	-0.238	0.155	0.143	0.431	0.07	-0.194	0.263	0.03
<b>Delayed Memory</b>	-0.119	0.48	0.138	0.451	0.03	<b>-0.368</b>	<b>0.031</b>	<b>0.12</b>
Cognitive Flexibility	-0.102	0.460	0.075	0.620	0.01	-0.149	0.303	0.02
Verbal Fluency	0.003	0.982	0.00	0.999	<0.001	0.027	0.867	0.001

**Figure Captions:**

**Figure 1: WASO moderates the relationship between global PiB SUVR and forgetting immediate (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) Scatterplot 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.**

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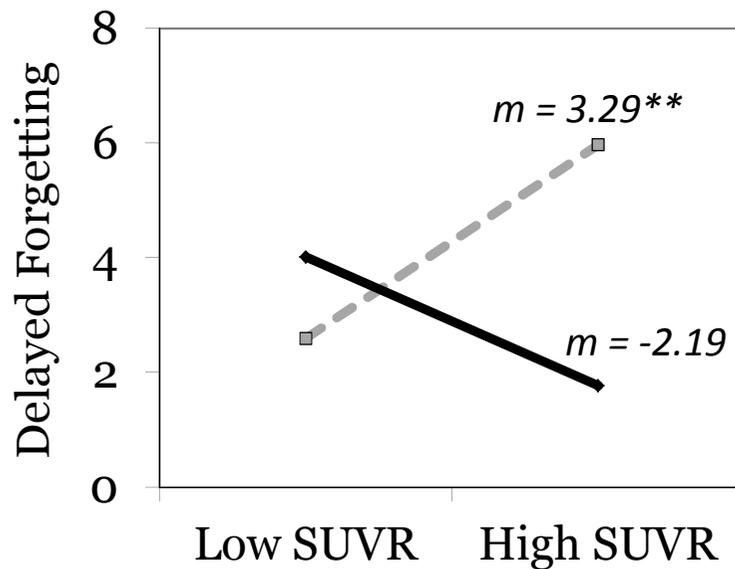
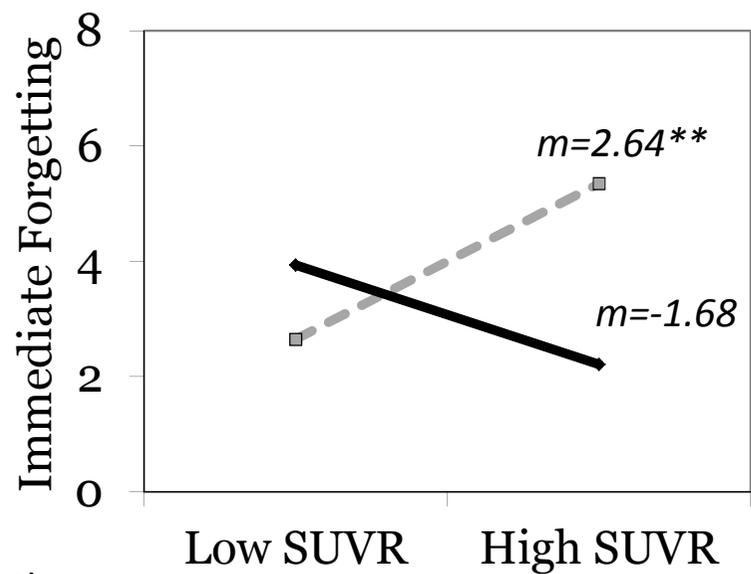
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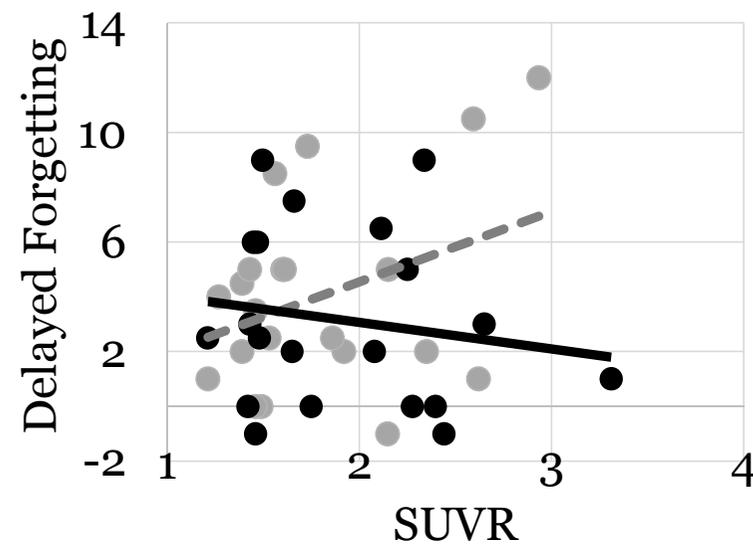
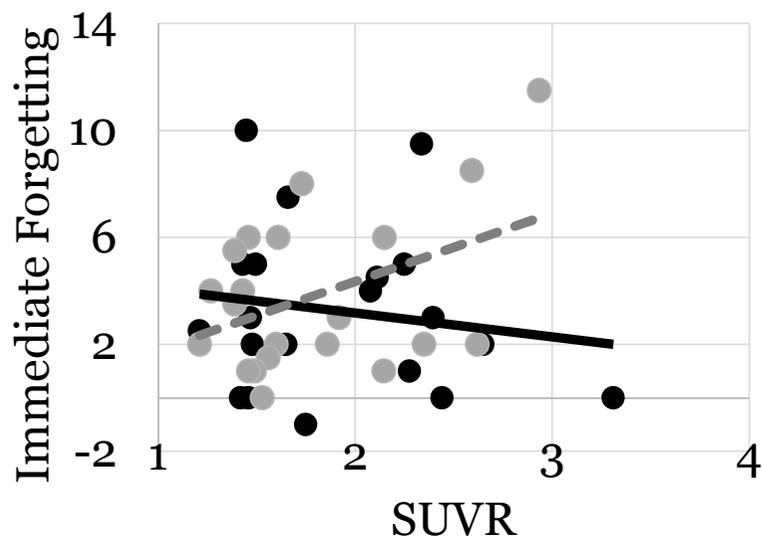
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A)



□ High  
WASO  
● Low  
WASO

B)



● High  
WASO  
● Low  
WASO

## Highlights

- Sleep continuity moderated the relationship between amyloid and memory retention.
- Individuals with more wake time after sleep onset showed a stronger relationship between amyloid deposition and memory retention.
- The moderating relationship between sleep and amyloid did not apply to executive function tasks, suggesting specificity to memory retention.
- Findings suggest a potential protective role of sleep in the relationship between amyloid and memory performance.