ALZHEIMER'S DISEASE

Reduced non–rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease

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In Alzheimer's disease (AD), deposition of insoluble amyloid-β (Aβ) is followed by intracellular aggregation of tau in the neocortex and subsequent neuronal cell loss, synaptic loss, brain atrophy, and cognitive impairment. By the time even the earliest clinical symptoms are detectable, Aβ accumulation is close to reaching its peak and neocortical tau pathology is frequently already present. The period in which AD pathology is accumulating in the absence of cognitive symptoms represents a clinically relevant time window for therapeutic intervention. Sleep is increasingly recognized as a potential marker for AD pathology and future risk of cognitive impairment. Previous studies in animal models and humans have associated decreased non–rapid eye movement (NREM) sleep slow wave activity (SWA) with Aβ deposition. In this study, we analyzed cognitive performance, brain imaging, and cerebrospinal fluid (CSF) AD biomarkers in participants enrolled in longitudinal studies of aging. In addition, we monitored their sleep using a single-channel electroencephalography (EEG) device worn on the forehead. After adjusting for multiple covariates such as age and sex, we found that NREM SWA showed an inverse relationship with AD pathology, particularly tauopathy, and that this association was most evident at the lowest frequencies of NREM SWA. Given that our study participants were predominantly cognitively normal, this suggested that changes in NREM SWA, especially at 1 to 2 Hz, might be able to discriminate tau pathology and cognitive impairment either before or at the earliest stages of symptomatic AD.

INTRODUCTION

Aggregation of amyloid-β (Aβ) into oligomers and fibrils that are present in extracellular Aβ plaques in the brain is a key early step in Alzheimer's disease (AD) pathogenesis and begins to occur ~15 to 20 years before the onset of cognitive decline (*1*). The buildup of insoluble Aβ is followed by the intracellular aggregation of tau and its spread from the medial temporal lobe to different neocortical regions (*1, 2*). Localized tau aggregation in the medial temporal lobe during normal aging is probably independent of Aβ; however, in AD, its spread to the neocortex appears to be downstream from Aβ buildup and correlates strongly with neuronal cell loss, synaptic loss, brain atrophy, and cognitive impairment. These findings are strongly supported by genetic, pathological, and biomarker data in both sporadic and inherited AD (*1, 2*). By the time even the earliest clinical symptoms of AD are detectable, Aβ accumulation is close to reaching its peak, and there is almost always some neocortical tau pathology (*3*). Aβ42, the isoform of Aβ most prone to aggregate in insoluble plaques, decreases in cerebrospinal fluid (CSF) with brain amyloid deposition and correlates with amyloid positron emission tomography (PET) (*4*). The CSF tau/Aβ42 ratio is related to the dual effect of amyloid and tau pathology and predicts conversion to early symptomatic AD (*5*–*7*). There is also neuronal and synaptic loss in several brain regions relevant to memory and thinking (*3*). The period in which AD pathology is accumulating in the absence of cognitive symptoms has been termed "preclinical" AD (*8, 9*).

A bidirectional relationship between sleep and AD has been proposed on the basis of studies in animal models and humans (*10*–*12*). Numerous studies have shown that sleep-wake activity is disturbed in individuals with dementia due to AD (*13, 14*). Sleep disturbance has been measured via self-report, such as with questionnaires and sleep logs, as well as actigraphy and polysomnography. Increasing evidence also supports sleep disturbance as a marker for AD pathology and future risk of cognitive impairment (*15*–*22*). For instance, self-reported sleep disturbances, such as poor sleep quality and short sleep duration, have been associated with increased risk of cognitive impairment (*15*) and increased Aβ deposition on [^{11}C]Pittsburgh compound B (PiB) PET scans (*16*). Furthermore, excessive daytime sleepiness reported by a cohort of older adults was associated with increased longitudinal Aβ accumulation on PiB-PET scans (*17*). Sleep logs and actigraphy monitoring have found that reduced sleep efficiency and increased nap frequency in cognitively normal individuals were associated with Aβ deposition (*18*). Studies with polysomnography have associated increased risk of cognitive impairment in older adults with sleep-disordered breathing (*19*–*21*) and periodic limb movements during sleep (*22*).

In addition to sleep disturbance as a putative marker of AD pathology, evidence also supports the hypothesis that disturbed sleep increases AD risk, at least in part, via an Aβ mechanism (*11*). We have found that Aβ concentrations in CSF fluctuate with sleep-wake activity in both mice (*23*) and humans (*24*). This Aβ cycling pattern has been replicated in multiple studies (*25*) and assays (*26*). Aβ concentrations are directly regulated by neuronal activity (*27*–*31*) and evidence in mice suggests that decreased interstitial fluid (ISF) during sleep results, at least in part, from altered neuronal/metabolic activity decreasing Aβ production/release. In humans, we have recently

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shown that targeted slow wave sleep disruption (*32*) and sleep deprivation (*33*) will increase overnight CSF Aβ concentrations by 10 to 30% most likely due to increased Aβ production/release. There is also evidence that Aβ clearance is increased during sleep due to increased ISF bulk flow (for example, "glymphatic" clearance) (*34*).

Studies in animal models using electroencephalography (EEG) to monitor different sleep stages have found changes in sleep parameters and EEG power linked with both Aβ and tau pathology. For instance, Aβ deposition in APPswe/PS1δE9 mice led to disruption of the sleep-wake cycle (*35*), whereas increasing tauopathy in P301S tau transgenic mice was associated with decreased time in rapid eye movement (REM) and non-REM (NREM) sleep, increased wakefulness, and decreased NREM slow wave activity (SWA) (*36*). In humans, atrophy and Aβ accumulation in the medial prefrontal cortex (mPFC) were correlated with both decreased NREM SWA and impaired overnight hippocampus-dependent memory consolidation in cognitively normal older adults (*37, 38*). Although that cross-sectional study provides associative evidence between Aβ deposition, NREM sleep disruption, and memory impairment, tau pathology was not assessed. Longitudinal studies with AD biomarkers and cognitive evaluations are needed to establish both the sequential links between these events and causation (*39*), especially in relation to both Aβ and tau.

In this study, we monitored sleep-wake activity in 119 participants enrolled in longitudinal studies of aging at the Knight Alzheimer's Disease Research Center at Washington University. Sleep-wake activity was monitored over six nights with a single-channel EEG worn on the forehead (Sleep Profiler, Advanced Brain Monitoring), actigraphy (Actiwatch 2, Philips Respironics), and sleep logs. In addition, each participant was assessed for sleep-disordered breathing and periodic leg movements with a home sleep test (Alice PDx, Philips Respironics). Participants who underwent cognitive testing, apolipoprotein E (ApoE) genotyping, and assessment of AD biomarkers in CSF [Aβ42, tau, phosphorylated tau (p-tau)] or PET scans with [^{18}F]AV-45 (florbetapir) amyloid and [^{18}F]AV-1451 (flortaucipir) tau tracers were included in the analyses. Because tau pathology, but not Aβ pathology, is best associated with cognitive decline in AD, we hypothesized that decreased NREM SWA would be associated with increased tau pathology.

RESULTS

One hundred nineteen participants aged >60 years old enrolled in longitudinal studies of aging at the Knight Alzheimer's Disease Research Center at Washington University in St. Louis, MO, were recruited for the study. Cognitive performance was evaluated by the Clinical Dementia Rating (CDR) (*40, 41*). Participants also underwent AV-45 amyloid and AV-1451 tau PET imaging and/or lumbar puncture to measure CSF Aβ42, tau, and p-tau concentrations. Sleep monitoring was performed for up to six nights with sleep logs, actigraphy, and a single-channel EEG. Average sleep parameters for participants with PET imaging and CSF biomarkers were not substantially different between amyloid negative versus amyloid positive, tau negative versus tau positive, and CDR 0 versus CDR 0.5 groups regardless of modality used to measure sleep-wake activity (tables S1 and S2). In participants with PET imaging, REM latency was lower in amyloid-positive participants (t_{36} = 2.98, P = 0.005) but longer in CDR 0.5 individuals (t_{36} = −2.49, P = 0.018). Amyloid-positive participants had lower wake after sleep onset (WASO)

Table 1. Participant characteristics.

	PET imaging	CSF
	Mean (SD)/*n* (%) (*N* = 38)	Mean (SD)/*n* (%) (*N* = 104)
Age (years)	73.8 (5.3)	74.57 (5.20)
Sex		
Men	18 (47.4)	59 (56.7)
Women	20 (52.6)	45 (43.3)
Race		
African-American	3 (7.9)	11 (10.6)
Caucasian	35 (92.1)	92 (88.5)
Asian	0 (0.0)	0 (0.0)
More than one	0 (0.0)	1 (1.0)
CDR		
0	29 (76.3)	83 (79.8)
0.5	9 (23.7)	21 (20.2)
ApoE4		
Negative	25 (65.8)	58 (55.8)
Positive	13 (34.2)	45 (43.3)
Sleep medications		
Yes	4 (10.5)	12 (11.5)
No	34 (89.5)	92 (88.5)
AHI (respiratory events/hour)*		
Negative (AHI < 5)	20 (52.6)	38 (36.5)
Mild (AHI 5–15)	13 (34.2)	43 (41.4)
Moderate (AHI 15–30)	5 (13.2)	18 (17.3)
Severe (AHI > 30)	0 (0)	5 (4.8)
PLMI (leg movements/hour)		
Negative (PLMI < 15)	21 (55.3)	49 (47.1)
Low (PLMI 15–45)	7 (18.4)	33 (31.7)
High (PLMI > 45)	10 (26.3)	22 (21.2)
AV-45 PET SUVR	1.44 (0.61)	—
AV-1451 PET SUVR	1.40 (0.49)	—
Aβ42 (pg/ml)	—	1012.59 (367.94)
t-tau (pg/ml)	—	245.46 (119.69)
p-tau (pg/ml)	—	23.66 (13.46)
AD pathology		
Amyloid negative/tau negative	20 (52.6)	31 (29.8)
Amyloid positive/tau negative	9 (23.7)	35 (33.7)
Amyloid positive/tau positive	8 (21.1)	27 (25.9)
Amyloid negative/tau positive	1 (2.6)	11 (10.6)
Time interval from scan/lumbar puncture to sleep study (years)		
AV-45 PET	0.29 (0.48)	1.00 (2.60)
AV-1451 PET	0.29 (0.40)	

*For the participants who underwent PET imaging (*N* = 38), 4 of 38 participants used continuous positive airway pressure therapy during sleep monitoring. For participants with CSF (*N* = 104), 12 of 104 participants used continuous positive airway pressure therapy and 1 participant used lateral position therapy device during sleep monitoring.

measured by actigraphy (t_{35} = 2.07, P = 0.046), whereas sleep-onset latency measured by actigraphy was prolonged in CDR 0.5 individuals (t_{35} = −2.33, P = 0.026). For participants with CSF, CDR 0.5 individuals were found to have longer REM latency measured by EEG (t_{104} = −2.91, P = 0.0044) and longer self-reported total sleep time (TST) (t_{104} = −2.27, P = 0.025). When measured by actigraphy, sleep efficiency was decreased (t_{106} = 3.40, P = 0.0009), sleep-onset latency was prolonged (t_{106} = −3.86, P = 0.0002), and WASO was greater (t_{106} = −2.68, P = 0.0086) in CDR 0.5 participants compared to CDR 0.

Thirty-eight participants with AV-45 amyloid and AV-1451 tau PET imaging and 104 participants with CSF Aβ42, tau, and p-tau underwent monitoring with the single-channel EEG device. Twenty-seven participants had both PET imaging and lumbar punctures. Characteristics for all participants are provided in Table 1. Of the participants with PET imaging, 52.6% (20 of 38) of participants were amyloid and tau negative, with 9 participants amyloid positive but tau negative and 8 participants positive for both amyloid and tau (Table 1). One participant was found to be tau positive but amyloid negative. Amyloid-negative/positive status was set at a standardized uptake value ratio (SUVR) of 1.19 (*42, 43*), and tau-negative/positive status was set at an SUVR of 1.22 (*44*). Average amyloid and tau burden on PET are shown in Figs. 1 and 2. For participants with CSF, previously published cutoffs for amyloid positive (CSF Aβ42 < 1098 pg/ml) and tau positive (CSF tau > 242 pg/ml) were used to define AD pathology (*45*). Of the participants with CSF, 29.8% were negative for amyloid and tau, 33.7% were amyloid positive but tau negative, 25.9% were positive for both amyloid and tau, and 10.6% were amyloid negative but tau positive (Table 1).

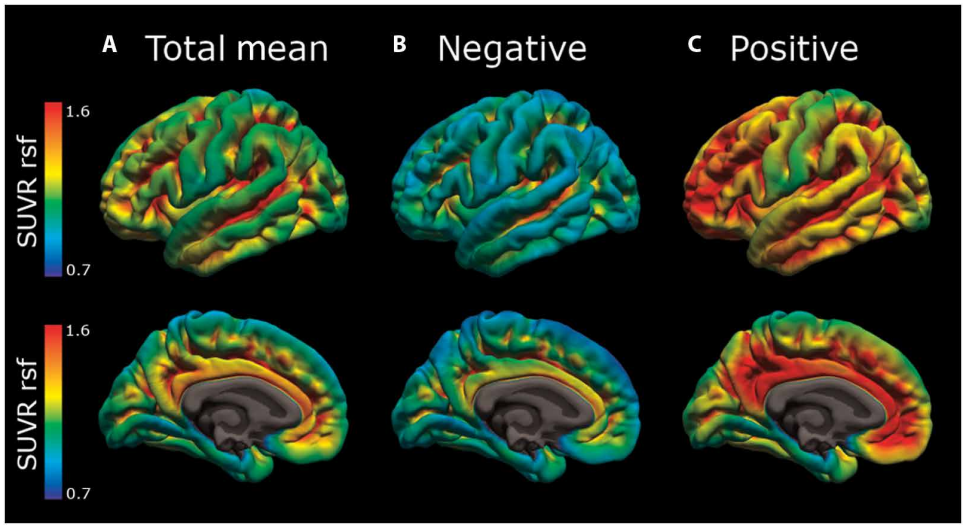

Fig. 1. Mean amyloid pathology for the 38 participants with PET imaging. Mean AV-45 amyloid pathology in (**A**) all, (**B**) amyloid-negative, and (**C**) amyloid-positive subjects as measured in SUVR units after partial volume correction using a regional spread function (rsf).

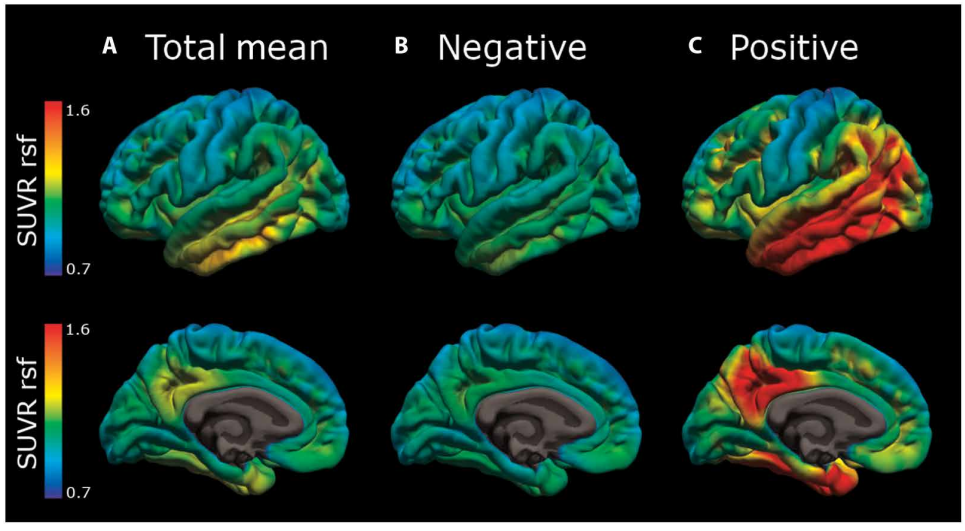

Fig. 2. Mean tau pathology for the 38 participants with PET imaging. Mean AV-1451 tau pathology in (**A**) all, (**B**) tau-negative, and (**C**) tau-positive subjects as measured in SUVR units after partial volume correction using a regional spread function.

Decreased NREM SWA with increased tauopathy

Multiple factors may affect sleep and/or AD pathology including age, sex, and sleep disorders. To assess the relationship between NREM SWA and tau pathology, we performed general linear mixed models of NREM SWA with a mean AV-1451 tau PET composite, age, sex, race, ApoE4 status, CDR, apnea-hypopnea index (AHI), periodic limb movement index (PLMI), and sleep medications. The composite of the mean AV-1451 tau SUVR was determined from the average SUVR of the entorhinal cortex, amygdala, lateral occipital, and lateral temporal regions.

As AV-1451 tau SUVR increased, all-night 1- to 4.5-Hz SWA was decreased (Table 2). Because previous work found an inverse relationship between the slowest frequencies and amyloid deposition in the mPFC (*38*), we tested different frequency ranges (1 to 2 Hz, 2 to 3 Hz, and 3 to 4 Hz) in this model and found that this inverse relationship between NREM SWA and tau was maximal in the 1- to 2-Hz range (Table 2). In our model, time represents longitudinal sleep monitoring over multiple nights. Time was not significant in the model (P > 0.05), supporting previous reports that the EEG power measures are stable with small within-subject night-to-night variability (*46, 47*). Age and sex were also inversely associated with NREM SWA. These findings are not surprising given the well-described decline in NREM SWA with increased age and male sex (*48, 49*). CDR showed negative association with 1- to 2-Hz NREM SWA, indicating that 1- to 2-Hz NREM SWA decreased with worsening tau pathology and cognitive impairment.

To investigate how regional differences in AV-1451 tau PET were associated with NREM SWA, we performed general linear mixed

Table 2. Relationship of NREM SWA to AV-1451 tau PET composite after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time. Linear mixed models were used to calculate the estimates and *P* values for the 38 participants with PET imaging. Time, longitudinal sleep monitoring.

Dependent variable	Covariate	Estimate	SE	*F* statistic (df)	*P*
1–4.5 Hz SWA	Mean AV-1451 tau composite	−8.889	2.625	11.46 (1,27)	0.002
	Age	−0.670	0.243	7.59 (1,28)	0.010
	Sex	−7.850	2.636	8.87 (1,28)	0.006
	CDR	−6.882	3.312	4.32 (1,29)	0.047
	Race	−9.299	4.950	3.53 (1,27)	0.071
	ApoE4 status	+4.002	2.891	1.92 (1,27)	0.178
	Sleep medications	+3.225	4.468	0.52 (1,27)	0.476
	AHI	+0.141	0.166	0.73 (1,28)	0.401
	PLMI	+0.121	0.0537	5.09 (1,28)	0.032
	Time	+0.0001	0.142	0.00 (1,145)	0.999
1–2 Hz SWA	Mean AV-1451 tau composite	−21.477	6.123	12.30 (1,28)	0.002
	Age	−1.539	0.567	7.36 (1,28)	0.011
	Sex	−18.542	6.148	9.10 (1,28)	0.005
	CDR	−18.339	7.750	5.60 (1,29)	0.025
	Race	−21.620	11.537	3.51 (1,27)	0.072
	ApoE4 status	+9.044	6.732	1.80 (1,27)	0.190
	Sleep medications	+8.298	10.410	0.64 (1,27)	0.432
	AHI	0.346	0.387	0.80 (1,28)	0.379
	PLMI	0.273	0.125	4.76 (1,28)	0.038
	Time	0.013	0.355	0.00 (1,146)	0.970
2–3 Hz SWA	Mean AV-1451 tau composite	−5.919	1.998	8.78 (1,28)	0.006
	Age	−0.509	0.186	7.51 (1,28)	0.011
	Sex	−5.577	2.009	7.71 (1,28)	0.010
	CDR	−3.654	2.500	2.14 (1,28)	0.155
	Race	−6.496	3.773	2.96 (1,28)	0.096
	ApoE4 status	+2.925	2.210	1.75 (1,28)	0.197
	Sleep medications	+1.731	3.410	0.26 (1,28)	0.616
	AHI	+0.085	0.126	0.46 (1,28)	0.504
	PLMI	+0.092	0.041	5.02 (1,28)	0.033
	Time	−0.013	0.095	0.02 (1,29)	0.891
3–4 Hz SWA	Mean AV-1451 tau composite	−2.186	0.766	8.16 (1,27)	0.008
	Age	−0.181	0.071	6.44 (1,28)	0.017
	Sex	−2.028	0.772	6.90 (1,28)	0.014
	CDR	−1.150	0.957	1.44 (1,27)	0.240
	Race	−2.406	1.447	2.76 (1,27)	0.108
	ApoE4 status	+1.004	0.849	1.40 (1,28)	0.247
	Sleep medications	+0.420	1.308	0.10 (1,27)	0.750
	AHI	+0.027	0.048	0.32 (1,28)	0.577
	PLMI	+0.035	0.016	4.84 (1,28)	0.036
	Time	−0.004	0.038	0.01 (1,28)	0.914

modeling for NREM SWA in frequency ranges of 1 to 4.5 Hz, 1 to 2 Hz, 2 to 3 Hz, and 3 to 4 Hz with each region of interest (ROI).

Whereas decreased NREM SWA at all slow wave frequencies was associated with increased tau pathology measured by the AV-1451 tau PET composite, regional analyses, uncorrected for multiple comparisons, found that this relationship was most evident in the entorhinal, parahippocampal, inferior parietal, insula, isthmus cingulate, lingual, supramarginal, and orbitofrontal regions (table S3 and fig. S1). After correcting for multiple comparisons, multiple regions on AV-1451 tau PET remained significant for 1- to 4.5-Hz NREM SWA including the entorhinal, parahippocampal, orbital frontal, precuneus, inferior parietal, and inferior temporal regions (all $P < 0.05$; see Fig. 3 and table S3). This relationship was driven by 1- to 2-Hz NREM SWA, with only the lingual and medial orbital frontal regions on AV-1451 tau PET significantly associated with 2- to 3-Hz and 3- to 4-Hz NREM SWA (all $P < 0.05$). The significance map for 1- to 2-Hz NREM SWA (Fig. 3) shows a similar spatial pattern of tauopathy seen for other changes in AD, such as cortical thickness (*44, 50–52*).

Decreased 1- to 2-Hz NREM SWA with increased Aβ deposition

Using the same model as for AV-1451 tau PET, we assessed the relationship between NREM SWA and AV-45 amyloid PET. The mean cortical AV-45 amyloid composite was calculated as the average SUVR for the frontal, temporal, and parietal lobes. All-night 1- to 4.5-Hz SWA was not associated with AV-45 amyloid PET (Table 3). Then, we tested NREM SWA in frequency ranges of 1 to 2 Hz, 2 to 3 Hz, and 3 to 4 Hz. There was an inverse relationship between 1- to 2-Hz NREM SWA and the mean cortical AV-45 amyloid composite ($P = 0.043$; Table 3).

Uncorrected for multiple comparisons, decreased NREM SWA at 1 to 4.5 Hz and 1 to 2 Hz was associated with increased Aβ deposition in frontal, temporal, and inferior parietal regions, as well as the supramarginal and isthmus cingulate regions (table S4 and fig. S2). At 2 to 3 Hz and 3 to 4 Hz, however, this inverse association with Aβ deposition was seen in fewer regions including the inferior parietal, isthmus cingulate, transtemporal, supramarginal, middle frontal, and pars opercularis regions (table S4 and fig. S2). After correcting for multiple comparisons, there were no regions on AV-45 amyloid PET associated with NREM SWA (table S4).

Decreased NREM SWA linked with increased CSF tau/Aβ42 ratio but not CSF Aβ42

To further assess the relationship between NREM SWA and AD pathology, we analyzed 104 participants with CSF in the same model used in participants with PET imaging except CSF Aβ42 and tau/Aβ42 measurements were used as covariates in place of AV-45 amyloid PET and AV-1451 tau PET, respectively. NREM SWA did not correlate with Aβ42 after adjusting for all covariates, whereas CDR, race, ApoE4 status, and sleep medications showed correlation with Aβ42 (Table 4).

Previous work found that tau/Aβ42 ratio is sensitive to early stages of AD pathology and predicts cognitive decline from normal to impaired over several years (*5–7*). Furthermore, poor sleep has been associated with higher tau/Aβ42 ratio (*53*). Tau/Aβ42 ratio also controls for the relationship between Aβ42 and tau. In the same model used to investigate the relationship between NREM SWA and tau PET, there was a significant inverse association between NREM SWA and tau/Aβ42 ($P < 0.05$; Table 5), indicating that NREM SWA decreased as the tau/Aβ42 ratio increased (meaning greater AD pathology). CSF tau is a marker of neuronal injury, and CSF p-tau is a marker for neurofibrillary tangles (*54*); therefore, we also tested the same model with p-tau/Aβ42 ratio and found a similar inverse relationship with NREM SWA as tau/Aβ42 (table S5). Similar to our findings for tau PET, the relationships between NREM SWA and both tau/Aβ42 and p-tau/Aβ42 ratios were maximal at the lowest 1- to 2-Hz frequencies. CDR, race, ApoE4 status, and sleep medications were also significantly associated with NREM SWA in the model (all $P < 0.05$; Table 5).

Specific sleep parameters associated with AD pathology

Previous studies have shown a relationship between various sleep parameters and AD pathology (*16–18, 53*). To investigate the relationship between other sleep parameters in our model, we compared the relationship between sleep parameters measured by the single-channel EEG device, actigraphy, and sleep logs to the mean AV-45 amyloid and AV-1451 tau composites using the same linear mixed model as above (table S6). Sleep parameters tested in the models included TST, sleep efficiency, sleep latency, REM onset latency, WASO, time in each sleep stage, number of arousals, and time spent napping per day (table S6). No sleep parameters measured by sleep log or actigraphy were associated with AV-45 amyloid PET. For EEG-derived sleep parameters, REM latency ($F_{1,30} = 12.5$, $P = 0.001$) and sleep latency ($F_{1,29} = 4.4$, $P = 0.045$) had significant negative relationships with Aβ, suggesting that as Aβ deposition increased, the time to fall asleep and enter REM sleep decreased.

TST measured by single-channel EEG device ($F_{1,28} = 5.99$, $P = 0.021$) and sleep log ($F_{1,29} = 4.80$, $P = 0.037$) was positively associated with increased tauopathy in tau PET. That is, participants slept

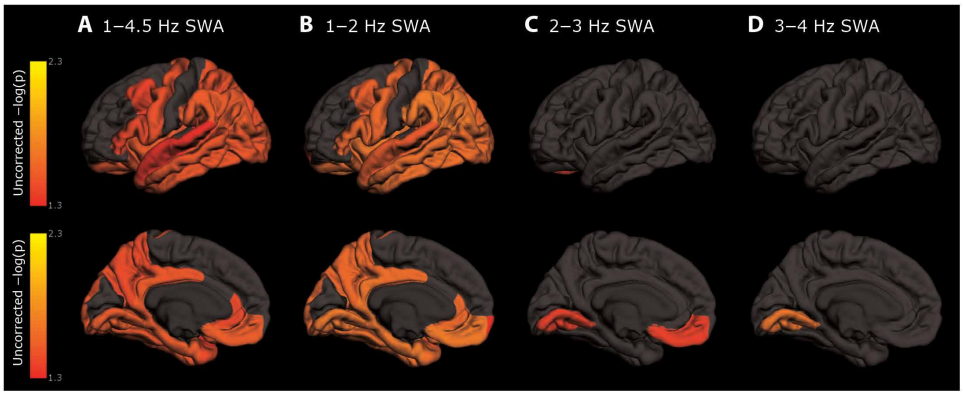

Fig. 3. Regional differences in the relationship between NREM SWA and tau PET. Regional differences in NREM SWA at 1 to 4.5 Hz (**A**), 1 to 2 Hz (**B**), 2 to 3 Hz (**C**), and 3 to 4 Hz (**D**) on AV-1451 tau PET after correction for multiple comparisons for the 38 participants with PET imaging. Linear mixed models were performed with NREM SWA as dependent variable and covariates age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time. Each AV-1451 tau PET region was included in the model individually and was corrected for multiple comparisons. The *P* value in the model from each region was mapped on a brain image and transformed to a logarithmic scale ($P < 0.05 = >1.30$).

Table 3. Relationship of NREM SWA to AV-45 amyloid PET composite after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time. Linear mixed models were used to calculate the estimates and *P* values for the 38 participants with PET imaging.

Dependent variable	Covariate	Estimate	SE	*F* statistic (df)	*P*
1–4.5 Hz SWA	Mean cortical AV-45 amyloid composite	−4.926	2.422	4.14 (1,28)	0.052
	Age	−0.680	0.270	6.36 (1,28)	0.018
	Sex	−8.590	2.948	8.49 (1,28)	0.007
	CDR	−3.489	3.463	1.02 (1,29)	0.322
	Race	−10.003	5.567	3.23 (1,27)	0.083
	ApoE4 status	+2.946	3.327	0.78 (1,27)	0.384
	Sleep medications	+3.124	4.963	0.40 (1,27)	0.534
	AHI	+0.123	0.183	0.45 (1,28)	0.507
	PLMI	+0.084	0.062	1.83 (1,28)	0.187
	Time	−0.003	0.142	0.00 (1,145)	0.982
1–2 Hz SWA	Mean cortical AV-45 amyloid composite	−12.017	5.676	4.48 (1,28)	0.043
	Age	−1.563	0.632	6.12 (1,28)	0.020
	Sex	−20.401	6.914	8.71 (1,28)	0.006
	CDR	−10.138	8.139	1.55 (1,29)	0.223
	Race	−23.326	13.041	3.20 (1,27)	0.085
	ApoE4 status	+6.427	7.786	0.68 (1,27)	0.416
	Sleep medications	−8.086	11.625	0.48 (1,27)	0.493
	AHI	+0.299	0.431	0.48 (1,28)	0.493
	PLMI	+0.184	0.146	1.59 (1,28)	0.218
	Time	+0.003	0.355	0.00 (1,146)	0.994
2–3 Hz SWA	Mean cortical AV-45 amyloid composite	−3.239	1.814	3.19 (1,28)	0.085
	Age	−0.514	0.202	6.48 (1,28)	0.017
	Sex	−6.066	2.205	7.57 (1,28)	0.010
	CDR	−1.472	2.568	0.33 (1,28)	0.571
	Race	−6.936	4.167	2.77 (1,28)	0.107
	ApoE4 status	+2.196	2.498	0.77 (1,28)	0.387
	Sleep medications	+1.613	3.716	0.19 (1,28)	0.668
	AHI	0.073	0.137	0.29 (1,28)	0.598
	PLMI	+0.067	0.046	2.09 (1,28)	0.159
	Time	−0.014	0.095	0.02 (1,29)	0.886
3–4 Hz SWA	Mean cortical AV-45 amyloid composite	−1.350	0.682	3.91 (1,28)	0.058
	Age	−0.183	0.076	5.80 (1,28)	0.023
	Sex	−2.229	0.830	7.21 (1,28)	0.012
	CDR	−0.339	0.963	0.12 (1,27)	0.727
	Race	−2.645	1.565	2.86 (1,27)	0.102
	ApoE4 status	+0.682	0.939	0.53 (1,28)	0.474
	Sleep medications	+0.425	1.396	0.09 (1,27)	0.763
	AHI	+0.024	0.051	0.21 (1,28)	0.647
	PLMI	+0.024	0.017	1.94 (1,28)	0.175
	Time	−0.003	0.038	0.01 (1,27)	0.928

Table 4. Relationship of NREM SWA to Aβ42 after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time. Linear mixed models were used to calculate the estimates and *P* values for the 104 participants with CSF.

Dependent variable	Covariate	Estimate	SE	*F* statistic (df)	*P*
1–4.5 Hz SWA	Aβ42	+0.004	0.003	1.44 (1,10)	0.257
	Age	+0.021	0.188	0.01 (1,12)	0.911
	Sex	+0.457	2.687	0.03 (1,12)	0.868
	CDR	+8.270	3.304	6.27 (1,15)	0.024
	Race	−10.031	3.910	6.58 (1,10)	0.029
	ApoE4 status	−6.597	2.897	5.18 (1,11)	0.044
	Sleep medications	−17.910	6.102	8.62 (1,12)	0.013
	AHI	−0.007	0.151	0.00 (1,11)	0.966
	PLMI	+0.055	0.041	1.83 (1,13)	0.199
	Time	−0.174	0.167	1.08 (1,76)	0.302
1–2 Hz SWA	Aβ42	+0.008	0.007	1.48 (1,11)	0.248
	Age	+0.077	0.447	0.03 (1,12)	0.866
	Sex	+0.900	6.394	0.02 (1,12)	0.890
	CDR	+18.082	7.873	5.28 (1,16)	0.036
	Race	−21.715	9.301	5.45 (1,11)	0.040
	ApoE4 status	−15.565	6.894	5.10 (1,12)	0.044
	Sleep medications	−44.695	14.524	9.47 (1,13)	0.009
	AHI	−0.056	0.360	0.02 (1,12)	0.879
	PLMI	+0.086	0.097	0.78 (1,14)	0.393
	Time	−0.489	0.401	1.49 (1,77)	0.226
2–3 Hz SWA	Aβ42	+0.003	0.002	2.44 (1,9)	0.153
	Age	+0.003	0.128	0.00 (1,11)	0.980
	Sex	+0.299	1.846	0.03 (1,11)	0.874
	CDR	+7.227	2.203	10.76 (1,14)	0.005
	Race	−8.654	2.739	9.98 (1,8)	0.013
	ApoE4 status	−5.372	2.009	7.15 (1,10)	0.024
	Sleep medications	−13.941	4.198	11.03 (1,11)	0.007
	AHI	+0.016	0.105	0.02 (1,10)	0.884
	PLMI	+0.059	0.028	4.52 (1,12)	0.054
	Time	−0.085	0.125	0.47 (1,16)	0.504
3–4 Hz SWA	Aβ42	+0.002	0.001	4.09 (1,12)	0.066
	Age	−0.023	0.072	0.10 (1,13)	0.759
	Sex	−0.216	1.027	0.04 (1,13)	0.837
	CDR	+2.623	1.074	5.97 (1,12)	0.032
	Race	−3.301	1.538	4.61 (1,12)	0.053
	ApoE4 status	−1.964	1.121	3.07 (1,13)	0.104
	Sleep medications	−6.387	2.267	7.94 (1,12)	0.016
	AHI	+0.018	0.058	0.10 (1,12)	0.763
	PLMI	+0.024	0.015	2.72 (1,13)	0.124
	Time	−0.012	0.052	0.06 (1,15)	0.815

longer with increased tauopathy. Self-reported time napping on sleep logs was increased with greater tau pathology ($F_{1,27} = 9.28$, $P = 0.005$) (table S6). This suggests that participants with greater tau pathology experienced daytime sleepiness despite increased TST. All other sleep parameters measured by EEG, actigraphy, and sleep log did not show correlation with tauopathy. Using the same model, no

Table 5. Relationship of NREM SWA to tau/Aβ42 ratio after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time. Linear mixed models were used to calculate the estimates and *P* values for the 104 participants with CSF.

Dependent variable	Covariate	Estimate	SE	*F* statistic (df)	*P*
1–4.5 Hz SWA	Tau/Aβ42	−10.788	4.673	5.33 (1,12)	0.040
	Age	+0.034	0.170	0.04 (1,12)	0.846
	Sex	+0.838	2.350	0.13 (1,12)	0.728
	CDR	+7.567	2.880	6.90 (1,14)	0.020
	Race	−13.860	3.818	13.18 (1,9)	0.006
	ApoE4 status	−6.961	2.645	6.92 (1,11)	0.024
	Sleep medications	−19.697	5.565	12.53 (1,12)	0.004
	AHI	+0.056	0.141	0.16 (1,11)	0.699
	PLMI	+0.060	0.037	2.59 (1,13)	0.132
	Time	−0.154	0.169	0.83 (1,70)	0.365
1–2 Hz SWA	Tau/Aβ42	−25.757	11.078	5.41 (1,13)	0.038
	Age	+0.106	0.403	0.07 (1,12)	0.797
	Sex	+1.571	5.571	0.08 (1,12)	0.783
	CDR	+16.425	6.807	5.82 (1,14)	0.030
	Race	−31.133	9.074	11.77 (1,10)	0.007
	ApoE4 status	−16.216	6.278	6.67 (1,12)	0.025
	Sleep medications	−49.386	13.196	14.01 (1,13)	0.003
	AHI	+0.103	0.333	0.10 (1,12)	0.762
	PLMI	+0.100	0.0875	1.31 (1,13)	0.272
	Time	−0.435	0.406	1.15 (1,74)	0.288
2–3 Hz SWA	Tau/Aβ42	−11.594	3.251	12.72 (1,11)	0.004
	Age	+0.008	0.122	0.00 (1,12)	0.952
	Sex	+0.343	1.680	0.04 (1,12)	0.842
	CDR	+6.431	1.765	13.27 (1,8)	0.006
	Race	−12.567	2.739	21.06 (1,9)	0.001
	ApoE4 status	−5.995	1.889	10.07 (1,11)	0.009
	Sleep medications	−19.944	3.810	27.40 (1,10)	0.0004
	AHI	+0.069	0.097	0.50 (1,10)	0.496
	PLMI	+0.058	0.025	5.28 (1,11)	0.042
	Time	−0.082	0.129	0.41 (1,17)	0.533
3–4 Hz SWA	Tau/Aβ42	−5.549	1.687	10.82 (1,10)	0.008
	Age	−0.019	0.064	0.09 (1,11)	0.773
	Sex	−0.001	0.878	0.00 (1,11)	0.999
	CDR	+2.223	0.911	5.95 (1,10)	0.036
	Race	−5.076	1.403	13.08 (1,8)	0.006
	ApoE4 status	−2.104	0.978	4.63 (1,10)	0.057
	Sleep medications	−6.784	1.965	11.92 (1,9)	0.007
	AHI	+0.040	0.050	0.64 (1,10)	0.444
	PLMI	+0.029	0.013	4.78 (1,10)	0.053
	Time	−0.019	0.053	0.13 (1,15)	0.719

sleep parameters measured by EEG, actigraphy, or sleep log were associated with CSF tau/Aβ42 (table S7).

DISCUSSION

Our study showed that NREM SWA has an inverse relationship with AD pathology measured by PET imaging and CSF biomarkers. That is, NREM SWA decreased with increased evidence of Aβ deposition and tau accumulation. For PET, this relationship was stronger with tau than with Aβ pathology. We also showed that increased CSF tau/Aβ42 ratio, another marker of AD pathology, was inversely associated with NREM SWA. We observed these associations after adjustment for multiple potential confounders, particularly age, sex, and CDR, supporting a strong relationship independent of these factors. Although AV-45 amyloid PET showed a similar inverse relationship with NREM SWA as AV-1451 tau PET, the estimated magnitude of this association was greater for tau and the findings with CSF tau/Aβ42 suggest that tau is critical for this relationship. Because the study participants were predominantly cognitively normal with the remaining showing only very mild impairment, this suggests that decreased NREM SWA, especially at the lowest 1- to 2-Hz frequencies, might be associated with tau pathology either before or at the earliest stages of cognitive decline.

Regional analyses of the PET images found that decreases in NREM SWA were most pronounced with Aβ deposition in areas of the frontal, temporal, and parietal lobes. There was no association in our models between NREM SWA and CSF Aβ42. Previous findings associated decreased NREM SWA, particularly at the lowest 0.6- to 1-Hz frequencies, with Aβ deposition in the mPFC on PiB-PET imaging (*38*). Because we recorded a single-channel EEG from the forehead, we were unable to localize the NREM SWA more specifically than to the frontal lobes. This location of electrode placement likely contributes to the robust relationship between NREM SWA and tau pathology in the frontal regions. We were also unable to test frequencies in the 0.6- to 1-Hz range due to hardware limitation of the single-channel EEG device (*55, 56*). Another recent study reported associations between baseline excessive daytime sleepiness and longitudinal Aβ deposition in the anterior cingulate, posterior cingulate-precuneus, and parietal regions (*17*). After correcting for multiple comparisons, our study found no association between 1- to 2-Hz SWA and Aβ deposition in all brain regions analyzed.

For AV-1451 tau PET, regions known to be involved with AD progression showed associations with decreased NREM SWA including the orbitofrontal, entorhinal, parahippocampal, lingual, and inferior parietal regions. These relationships were most evident in the 1- to 2-Hz range, and the association remained valid after correcting for multiple comparisons. This spatial pattern is similar to other imaging changes in AD, such as cortical thickness (*50–52*). Decreased cortical thickness, however, does not explain our findings because the PET ROIs were volume-corrected.

We were also able to compare the relationship between PET imaging with AV-45 amyloid and AV-1451 tau tracers, as well as CSF Aβ42 and tau/Aβ42, to sleep parameters measured with different methods such as sleep logs. Although NREM SWA was associated with AD pathology, traditional sleep parameters measured by single-channel EEG-based sleep scoring, actigraphy, or sleep logs generally did not show association in our study. SWA is a measure of sleep homeostasis and may be altered even when other sleep parameters are unchanged (*57*). Increased TST measured by the single-channel EEG and sleep log were associated with increasing tau pathology on PET, as was self-reported increased time napping. These results, coupled with the NREM SWA findings, suggest that the quality of sleep decreases with increasing tau despite increased sleep time. Furthermore, self-reported napping time per day may be an important question to screen individuals for tauopathy.

A strength of our study is the multiple modalities of both sleep monitoring and biomarkers for AD pathology available from all of our participants. In addition to PET imaging, CSF biomarkers, and different sleep measures, we were able to adjust for multiple variables that affect sleep and AD pathology. Model covariates, such as sex, race, ApoE4, and sleep medications, need further study in other larger cohorts and longitudinal studies. A weakness of this study, however, is that we cannot establish whether or not sleep disturbances preceded or followed the development of AD pathology. Furthermore, this study included only 38 participants in the imaging analyses, and therefore, a limitation of these analyses is overfitting a model with 10 covariates. Another limitation of our study is that stages of AD pathology (for example, amyloid negative/tau negative) differed between participants with PET imaging and CSF. These limitations are offset by the complementary findings between NREM SWA and AD pathology with both PET imaging and CSF biomarkers. Previous work that reported these associations between sleep parameters and AD pathology generally included larger numbers of participants than our study. However, the fact that we could see robust differences in NREM SWA in relation to tau pathology measured on tau PET and CSF tau/Aβ42 suggests strong relationships between the variables analyzed.

With the rising incidence of AD in an aging population, our findings have potential application in both clinical trials and patient screening for AD to noninvasively monitor for progression of AD pathology. For instance, periodically measuring NREM SWA, in conjunction with other biomarkers, may have utility monitoring AD risk or response to an AD treatment. To apply our findings in these settings, further longitudinal studies are needed to confirm the timing of when NREM SWA decreases in relation to increased Aβ deposition and tauopathy.

MATERIALS AND METHODS

Study design

This is an ongoing longitudinal observational study to assess the association between sleep parameters and the AD biomarkers in which sleep-wake activity was observed over six nights. All sleep data collected by 3 April 2018 were included in the analysis. One hundred nineteen participants enrolled in longitudinal studies at the Knight Alzheimer's Disease Research Center at Washington University in St. Louis, MO, were recruited thus far to participate in this study. All participants were >60 years old and assessed clinically with a standard protocol that included obtaining a CDR, which ranged from 0 (no impairment) to 3 (maximal impairment) (*40, 41*). Participants who completed all assessments were included in the analysis. Of the 38 participants who completed PET imaging, 29 participants (76.3%) had a score of 0 and 9 participants (23.7%) had a score of 0.5. These percentages were similar to 104 participants who underwent lumbar puncture for CSF collection with 79.8% CDR 0 and 20.2% CDR 0.5. ApoE genotype was obtained from the Knight Alzheimer's Disease Research Center Genetics Core. Participants also reported if they were taking any of the following

medications that could affect sleep: benzodiazepine receptor agonists (zolpidem, zaleplon, eszopiclone), benzodiazepines (triazolam, temazepam, alprazolam), ramelteon, gabapentin, dopamine agonists (ropinirole, pramipexole, rotigotine), doxepin, antihistamines, antidepressants, and narcotics. Participants were listed as on a sleep medication if they were taking at least one medication from this list. Participant demographic information is shown in Table 1. The study protocol was approved by the Washington University Institutional Review Board. All participants provided written informed consent and were compensated for their participation in the study.

Sleep monitoring

Sleep was assessed longitudinally in all participants using three separate measures over six nights at home: (i) sleep logs, (ii) actigraphy (Actiwatch 2, Philips Respironics), and (iii) a single-channel EEG device worn on the forehead (Sleep Profiler, Advanced Brain Monitoring). Sleep logs and actigraphy were scored as previously reported (*18*). Single-channel EEG sleep studies were visually scored by registered polysomnographic technologists using criteria adapted from the standard American Academy of Sleep Medicine (AASM) criteria (*56*). Sleep parameters for time in each sleep stage, sleep latency, sleep efficiency, WASO, and TST were calculated. Nights were excluded if >10% of the recording was artifactual or if the bed and rise times did not match the sleep log and/or actigraphy. All participants needed at least two nights from the single-channel EEG device that met these criteria to be included in this analysis.

Because of the increased prevalence of sleep apnea and periodic leg movements during sleep with age, all participants were monitored for one night with a home sleep test (Alice PDx, Philips Respironics). Bed and rise times were confirmed with sleep logs and actigraphy. A minimum of 4 hours artifact-free recording was obtained for all participants. Respiratory events and periodic leg movements were scored by registered polysomnographic technologists using AASM criteria; hypopneas were scored using 4% oxygen desaturation (*58*). AHI and PLMI were calculated per hour of monitoring time for each participant.

Spectral power analysis

SWA during NREM sleep was calculated from each single-channel EEG study using Matlab (MathWorks, Natick, MA), as previously described (*56, 59, 60*). To briefly summarize, the EEG signal was down-sampled to 128 Hz for analysis to eliminate processing error. The single-channel EEG device filtered the signal during acquisition with a 0.1– to 0.6–band-stop filter. We then applied a band-pass (two-way least-squares finite impulse response) filter between 0.5 and 40 Hz. Spectral analysis was performed in consecutive 6-s epochs (Welch method, Hamming window, no overlap). Artifacts were excluded in a semiautomatic method. Power in the 20- to 30-Hz and 1- to 4.5-Hz bands for each electrode across all epochs of a recording was displayed. The operator (B.P.L.) then selected a threshold between the 95th and 99.5% threshold of power to remove artifactual epochs. This resulted in fewer than 4% of all epochs being rejected as artifactual.

Magnetic resonance imaging

T1-weighted images were acquired using a magnetization-prepared rapid gradient-echo sequence on a Siemens Biograph mMR or Tim Trio 3T scanner. Scans had a resolution of either 1 × 1 × 1 mm or 1 × 1 × 1.25 mm. Parcellations of the T1-weighted image into cortical and subcortical regions were performed with FreeSurfer v5.3-HCP (*61*) for use in the processing of PET data.

PET imaging

Thirty-eight participants underwent PET imaging with both amyloid and tau tracers. Amyloid PET imaging was performed using [^{18}F]AV-45 (florbetapir). Data from the 50 to 70 post-injection window were analyzed with an in-house pipeline using FreeSurfer-derived ROIs (PET Unified Pipeline, https://github.com/ysu001/PUP) (*43, 61*). Tau PET imaging was completed using [^{18}F]AV-1451 (flortaucipir). Data from the 80- to 100-min post-injection window were analyzed. Unprocessed tau PET images were reviewed by a nuclear medicine–trained physician to evaluate for off-target tracer binding; before analysis, one potential participant with sleep monitoring and a tau PET scan was excluded because of high bone marrow uptake in the frontal cortex. Regional signal estimates for both tracers were transformed into SUVRs by using cerebellar cortex as the reference region. Data were partial volume–corrected using a regional spread function technique (*62, 63*). ROI PET data were presented as the average across hemispheres for statistical analysis. For global analyses, summary measures of SUVR 1.19 were used for amyloid negative/positive on AV-45 amyloid PET (*42, 43*), and summary measures of SUVR 1.22 were used for tau negative/positive on AV-1451 tau PET (*44*).

CSF biomarkers

CSF was collected under a standardized protocol (*45*). After fasting overnight, participants underwent a lumbar puncture at 8 a.m. CSF (20 to 30 ml) was collected by gravity drip into a 50-ml conical tube using a 22-gauge atraumatic Sprotte spinal needle, gently inverted to disrupt potential gradient effects, and centrifuged at low speed to pellet any cellular debris. Samples were aliquoted (500 μl) in polypropylene tubes and stored at −80°C until analysis. CSF Aβ42, total tau, and p-tau 181 were measured as previously described using an automated electrochemiluminescence immunoassay (Elecsys on the cobas e 601 analyzer, Roche) (*45, 64*).

Statistical analysis

All data were entered into a secure, web-based application designed to support data capture for research studies [Research Electronic Data Capture (REDCap)] (*65*). Statistical significance for all analyses was set at $P < 0.05$. No methods were used to predetermine sample sizes. All serial sleep monitoring nights were analyzed with general linear mixed models using an unstructured covariance structure to account for the dependencies among the longitudinal measurements (*66*). For analyses of the participants who completed PET imaging, AV-45 amyloid and AV-1451 tau PET SUVR, mean-centered age (mean age 74.8 years), sex, race, CDR, ApoE4 status (negative/positive), mean-centered AHI (mean AHI 9.8 respiratory events per hour of monitoring time), mean-centered PLMI (mean PLMI 23.2 leg movements per hour of monitoring time), and sleep medication (yes/no) were treated as fixed effects. Analyses of participants with CSF were the same as those with imaging biomarkers, and there were no differences in mean-centered age (mean age 74.5 years), mean-centered AHI (mean AHI 9.8 respiratory events per hour of monitoring time), and mean-centered PLMI (mean PLMI 23 leg movements per hour of monitoring time). The time covariate was longitudinal sleep monitoring over multiple nights and was treated as a random effect with random intercepts and slopes used to accommodate

individual variation. The normality assumption was verified through residual plots. Statistical analyses for mixed models were performed using Statistical Analysis Software (SAS). Regional analysis of AV-45 amyloid and AV-1451 tau PET was performed using R 3.3.2 (*67*) with the same model except for individual ROI rather than whole-brain composite indices. Bonferroni correction was used when comparing between multiple brain regions. Differences in sleep parameters between amyloid-negative/positive and tau-negative/positive groups were determined by unpaired two-tailed *t* test.

SUPPLEMENTARY MATERIALS

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Fig. S1. Relationship between NREM SWA and tau PET varies by region when uncorrected for multiple comparisons.

Fig. S2. Relationship between NREM SWA and amyloid PET varies by region when uncorrected for multiple comparisons.

Table S1. Group differences in average sleep parameters between amyloid negative/positive, tau negative/positive, and CDR 0/0.5 for participants with PET imaging.

Table S2. Group differences in average sleep parameters between amyloid negative/positive, tau negative/positive, and CDR 0/0.5 for participants with CSF.

Table S3. Relationship of NREM SWA power to AV-1451 tau PET regions after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time.

Table S4. Relationship of NREM SWA to AV-45 amyloid PET regions after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time.

Table S5. Relationship of NREM SWA to p-tau/Aβ42 ratio after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time.

Table S6. Relationship of sleep parameters to AV-45 amyloid and AV-1451 tau PET after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time.

Table S7. Relationship of sleep parameters to tau/Aβ42 ratio after adjusting for age, sex, race, CDR, ApoE4 status, AHI, PLMI, sleep medications, and time.

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Author contributions: B.P.L.: conception and design, acquisition of data, analysis and interpretation of data, and drafting of manuscript; A.M.: analysis and interpretation of data and revising of manuscript; E.C.L.: analysis and interpretation of data and revising of manuscript; C.D.T.: acquisition of data and revising of manuscript. J.S.M.: acquisition of data and revising of manuscript; A.M.Z.: analysis and interpretation of data and revising of manuscript; A.M.F.: acquisition of data, analysis and interpretation of data, and revising of manuscript; L.M.: analysis and interpretation of data and revising of manuscript; CX: analysis and interpretation of data and revising of manuscript; J.C.M.: acquisition of data, analysis and interpretation of data, and revising of manuscript; T.L.S.B.: acquisition of data, analysis and interpretation of data, and revising of manuscript; D.M.H.: conception and design, acquisition of data, analysis and interpretation of data, and drafting of manuscript. **Competing interests:** B.P.L., A.M., E.C.L., C.D.T., J.S.M., A.M.Z., L.M., and C.X. declare that they have no competing interests. D.M.H. co-founded and is on the scientific advisory board of C_2N Diagnostics. D.M.H. consults for Genentech, AbbVie, Proclara, and Denali. Washington University receives research grants to the laboratory of D.M.H. from C_2N Diagnostics, AbbVie, and Denali. Neither J.C.M. nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. J.C.M. is currently participating in clinical trials of antidementia drugs from Eli Lilly and Company and Biogen. He receives research support from Eli Lilly/Avid Radiopharmaceuticals and is funded by NIH grants P50AG005681, P01AG003991, P01AG026276, and UF01AG032438. T.L.S.B. is currently participating in clinical trials of antidementia drugs from Eli Lilly and Company, Biogen, Roche, and Janssen. She receives research support from Eli Lilly/Avid Radiopharmaceuticals (including support for AV-45 and AV-1451 in this work) and is

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Reduced non–rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease

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Losing sleep over Alzheimer's disease

In patients with Alzheimer's disease (AD), amyloid-β (Aβ) plaques and tau protein tangles accumulate in the brain long before the appearance of clinical symptoms. Early intervention is critical for slowing neurodegeneration and disease progression. Therefore, reliable markers of early AD are needed. Lucey *et al.* analyzed sleep patterns in aging cognitively normal subjects and showed that non–rapid eye movement (NREM) sleep negatively correlated with tau pathology and A β deposition in several brain areas. The results show that alterations in NREM sleep may be an early indicator of AD pathology and suggest that noninvasive sleep analysis might be useful for monitoring patients at risk for developing AD.