Resting-State Functional Connectivity Changes in Older Adults with Sleep Disturbance and the Role of Amyloid Burden

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Article

Abstract

Sleep and related disorders could lead to changes in various brain networks, but little is known about the role of amyloid β (Aβ) burden—a key Alzheimer's disease (AD) biomarker—in the relationship between sleep disturbance and altered resting state functional connectivity (rsFC) in older adults. This cross-sectional study examined the association between sleep disturbance, Aβ burden, and rsFC using a large-scale dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Sample included 489 individuals (53.6% cognitively normal, 32.5% mild cognitive impairment, and 13.9% AD) who had completed sleep measures (Neuropsychiatric Inventory), PET Aβ data, and resting-state fMRI scans at baseline. Within and between rsFC of the Salience (SN), the Default Mode (DMN) and the Frontal Parietal network (FPN) were compared between participants with sleep disturbance versus without sleep disturbance. The interaction between Aβ positivity and sleep disturbance was evaluated using linear regressions, controlling for age, diagnosis status, gender, sedatives and hypnotics use, and hypertension. Although no significant main effect of sleep disturbance was found on rsFC, a significant interaction term emerged between sleep disturbance and Aβ burden on rsFC of SN (β=0.11, P=0.006). Specifically, sleep disturbance was associated with SN hyperconnectivity, only with the presence of Aβ burden. Sleep disturbance may lead to altered connectivity in the SN when Aβ is accumulated in the brain. Individuals with AD pathology may be at increased risk for sleep-related aberrant rsFC; therefore, identifying and treating sleep problems in these individuals may help prevent further disease progression.

Introduction

Alzheimer's disease (AD), a devastating neurodegenerative disease with a high mortality rate, is currently estimated to affect 6.07 million older adults in the United States, a number that is expected to increase 18% by 2025[1]. Elucidating underlying neural mechanisms of AD through brain-based biomarkers and their interactions may advance clinical trial design for AD treatments by informing sample selection and optimizing timeframes for early intervention.

Resting state functional connectivity (rsFC) (measured via resting-state functional magnetic resonance imaging (rs-fMRI) has been utilized to identify aberrant functional architecture of brain networks that are associated with AD pathology[2]. Network analyses allow identification of aberrant coactivation of brain regions within a large-scale network, which is believed to reflect the underlying neural mechanisms of various cognitive and affective processes[2–4]. Several networks are particularly relevant to processes affected in AD. The default mode network (DMN), including lateral parietal, precuneus, and medial prefrontal regions, has been studied extensively in AD literature[5, 6]. The DMN is implicated in autobiographical memory, episodic memory, and social cognition and has anatomical overlap with regions of early amyloid-beta (Aβ) accumulation, suggesting a strong association with AD pathology[7–9]. Recently, other key networks such as the frontal-parietal network (FPN; also referred to as central executive network) and the salience network (SN) also gained attention and have been shown to be altered in AD[10]. The FPN consists of the lateral prefrontal cortex and posterior parietal cortex and is

responsible for various aspects of cognitive control, such as working memory, attention, and decision making[11, 12]. The SN involves the anterior cingulate cortex, anterior insula, rostral prefrontal cortex, and supramarginal gyrus, which contributes to processing emotional information and modulating activities of the DMN and FPN[13–15]. While *hypo*activation in the DMN and FPN was indicative of worse progression of AD[10, 12, 16], other studies have shown AD-related *hyper*activation in SN, depending on the disease stages[9, 12]. Recent studies highlighted that there are periods of hyperactivity in DMN and SN in the very early stages of prodromal AD followed by hypoactive states in the later stages of AD pathology, indicating a non-linear association between rsFC and progression to AD[17–19].

Poor sleep disturbance and related sleep disorders are well-established risk factors for AD pathology and similarly are associated with dysfunctional neural networks[20, 21]. Insomnia, for instance, is associated with decreased rsFC within the DMN but increased connectivity in the SN, particularly in the insula[4, 21–23]. A recent study has also shown that improving sleep through light therapy decreased rsFC in the SN, indicating that SN hyperactivity is an aberrant neural activity that could stem from poor sleep and that treating sleep disturbance could "normalize" SN connectivity[24]. Together, these findings indicate that sleep disturbance is associated with AD-like changes in brain activity and provide further evidence to support that improving sleep could reduce these aberrant changes in the brain.

Nonetheless, only pair-wise associations among sleep, AD biomarkers, and rsFC have been examined rather than a comprehensive picture of their interactions. While sleep-induced changes in rsFC may be impacted by AD pathology, no previous study has examined how sleep disturbance in late-life interacts with AD pathology, measured by amyloid-beta (Aβ). Aβ burden is linked to altered rsFC in older adults[25, 26], and studies have shown that functional connectivity in the DMN is disturbed in preclinical adults with Aβ positivity even before the onset of clinical symptoms[25]. Additionally, sleep burden is bidirectionally associated with increased Aβ accumulation[27] and may moderate the relationship between Aβ and brain functions[27, 28]. Examining the interplay between sleep disturbance and Aβ would be important given their similar aversive impacts on brain aging and their potential synergistic effect in dysregulating brain network functioning. It is also crucial to examine this topic with epidemiologic data that represents older adult groups across various cognitive stages (preclinical to clinical AD).

Therefore, the current study aimed to examine the associations among sleep disturbance, Aβ accumulation based on positron emission tomography (PET) imaging, and rsFC in older adults in various stages of AD (cognitively normal, MCI, and AD) using a large-scale dataset from Alzheimer's Disease Neuroimaging Initiative (ADNI). We first tested the association between sleep disturbance and rsFC, then evaluated the association between

Aβ burden and rsFC, lastly, we assessed the interaction between sleep disturbance and Aβ on rsFC. Given previous findings on this similar topic, we hypothesized that 1) sleep disturbance will be strongly associated with altered rsFC and 2) the presence of Aβ burden in sleep disturbance will exacerbate these changes.

Materials And Methods

Participants:

Rs-fMRI data were acquired from 489 participants, 262 NC (53.6%), 159 MCI (32.5%), and 68 AD (13.9%) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (www.adni.loni.usc.edu) (Fig. 1). ADNI was launched in 2003 as a public-private partnership and examines the progression of MCI and AD through longitudinal assessments of MRI, PET, and other biomarkers, along with clinical and neuropsychological assessments. A detailed description of the ADNI cohort has been previously published[29]. Qualifying MCI subjects had: memory complaints, but no significant functional impairment; scored between 24 and 30 on the mini-mental status examination (MMSE); had a global clinical dementia rating (CDR) score of 0.5; a CDR memory score of 0.5 or greater; and objective memory impairment on the Wechsler Memory Scale – Logical Memory II test. Cognitively normal (CN) participants had: MMSE scores between 24 and 30; a global CDR of 0; and did not meet criteria for MCI or AD. Inclusion and diagnostic criteria, as well as procedures and protocols, for the ADNI studies can be found on http://www.adni-info.rg/Scientists/ADNIStudyProcedures.html.

For the current study, we included individuals with NC, MCI (both early and late MCI), and AD who had completed baseline sleep measures (Neuropsychiatric Inventory [30]/ NPI Questionnaire [NPI-Q]), PET-Aβ data, and rs-fMRI scans.

Standard Protocol Approvals, Registrations, and Patient Consents:

All procedures were approved by the Institutional Review Boards of all participating institutions. Written informed consent was obtained from every research participant according to the Declaration of Helsinki and the Belmont Report. For more up-to-date information, see www.adni-info.org.

Neuropsychiatric Inventory (NPI)/Neuropsychiatric Inventory Questionnaire (NPIQ):

The presence of sleep disturbance was rated by an informant (e.g., caregiver or partner) and was assessed using the NPI and the NPI-Q. ADNI-1 used the NPI-Q while ADNI-GO/2 used the NPI. Both versions assess 12 neuropsychiatric symptoms, and the main difference between them is that NPI is conducted as a caregiver/informant interview whereas the NPI-Q is conducted in a questionnaire format. Severity and frequency ratings are highly correlated between NPI and NPI-Q[31].

The 12 symptoms in the NPI/NPI-Q include hallucinations, delusions, agitation/aggression, dysphoric/depression, anxiety, irritability, disinhibition, euphoria, apathy, and aberrant motor behavior. The informant is first asked to rate the presence of each symptom within the past 1 month with "yes" or "no", then if the answer is "yes," is asked to rate severity (range 0–3). For the current study, sleep disturbance (SD) at baseline was determined to be present if the study partner endorsed having sleep disturbance

(e.g., "Does the patient have difficulty sleeping? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?"). It was coded as absent if not endorsed by the partner, and individuals without SD were categorized as Good Sleepers. Additionally, the total severity score was calculated for both NPI and NPI-Q by summing up the severity ratings for all domains except for sleep and nighttime behaviors. NPI or NPI-Q data were obtained from the Laboratory of Neuroimaging Image Data Archive (LONI IDA).

Amyloid Positivity:

Florbetapir (AV45) PET images were processed by ADNI researchers (JAGUST LAB) as described in the previous publication[32]. Cortical summary regions were defined based on FreeSurfer v7.1.1. Florbetapir uptakes were calculated by dividing the cortical summary region by the whole cerebellum reference region. For cross-sectional florbetapir analyses, it is recommended to use a cutoff of 1.11 using the whole cerebellum reference region, which is equivalent to the upper 95% confidence interval above the mean of a group of young normal controls[33] and transformed to the ADNI FreeSurfer (FS) pipeline initially using FS v5.3.[34]. The threshold was validated in the independent study[35]. The PET data used in this study were obtained from the ADNI files 'UCBERKELEYAV45_04_26_22.csv'. A detailed description of PET acquisition, measurement, and quality control and preprocessing procedures were presented in http://adni.loni.usc.edu/methods/.

rs-fMRI data analysis:

Functional data was preprocessed using fMRIPrep [30]; RRID:SCR_016216). Specifically, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9)[36]. BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207[37](RRID:SCR_005927). The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration[38]. Co-registration was configured with six degrees of freedom. The BOLD time-series were resampled into standard MNI152NLin2009cAsym space. Several confounding time-series were calculated based on the preprocessed BOLD: Frame-wise displacement (FWD) was calculated from the six motion parameters and root-mean-square difference (RMSD) of the BOLD percentage signal in the consecutive volumes. Contaminated volumes were then detected and classified as outliers by the criteria FWD > 0.5 mm or RMSD > 0.3% and replaced with new volumes generated by linear interpolation of adjacent volumes. The three global signals are extracted within the cerebrospinal fluid (CSF), the white matter masks. A bandpass filter with cut-off frequencies of 0.01 and 0.09 Hz was used. Finally, the covariates corresponding to head motion (6 realignment parameters), outliers, and the BOLD time series from the subject-specific white matter and CSF masks were used in the connectivity analysis as predictors of no interest, and were removed from the BOLD functional time series using linear regression.

ROI-to-ROI connectivity analysis was performed in CONN toolbox using 11 CONN resting state network nodes composing 3 networks (Default Mode Network (DMN): medial pre-frontal cortex (MPFC), precuneus cortex (PCC), bilateral lateral parietal (LP); Salience Network (SN): anterior cingulate cortex (ACC), bilateral anterior insula (AI), rostral pre-frontal cortex (RPFC), and supramarginal gyrus (SMG); Fronto-parietal Network (FP): bilateral lateral pre-frontal cortex (LPFC) and posterior parietal cortex (PPC)[39]. The mean BOLD time series was computed across all voxels within each ROI. Bivariate regression analyses were used to determine the linear association of the BOLD time series between each pair of regions for each subject. Both positive and negative correlations were examined. The resultant correlation coefficients were transformed into z-scores using Fisher's transformation to satisfy normality assumptions. The within network-level FC was calculated as the average of the FCs within the networks of SN, DMN and FPN.

Statistical Analysis:

Demographic characteristics between the control group and individuals with sleep disturbance were compared using the 2-sample independent T-tests (for continuous variables) and chi-square tests (for categorical variables). We first tested the association between sleep disturbance and rsFC using the linear regressions ("Main Effects"). Each linear regression includes each rsFC as the dependent variable and sleep disturbance as the independent variable after adjusting for age, sex, education, clinical status (CN, MCI, AD), sedatives hypnotics use, history of hypertension and total NPI as covariates. Then, Aβ was evaluated in the same model after replacing sleep disturbance with Aβ positivity. Finally, we evaluated the interactions between Aβ positivity and sleep disturbance by adding the Aβ x sleep disturbance interaction terms in the model ("Interaction Terms"). For the rsFC with significant Aβ positivity x sleep disturbance interaction ($p < .05$), we performed a post-hoc T-test to quantify the effect of sleep disturbance by Aβ positivity status. The multiple comparison corrections were performed within each hypothesis using False Discovery Rate (FDR) corrections. Regardless, the standardized beta coefficients and their 95% confidence intervals were reported in addition to p-values. All analyses were performed using R software (R Core Team, 2014, Vienna, Austria), and p-values < 0.05 were considered to indicate statistical significance.

Data Availability:

ADNI datasets are available to the research community upon request at www.adni.loni.usc.edu. The processed imaging data are available for the qualified investigators upon request at seonjoo.lee@nyspi.columbia.edu .

Results

The mean age of the entire study sample (N = 489) was 74.8 (SD 7.6) years, and 51% were females. Sleep disturbance was reported in 87 individuals (17.8% of the study sample). Comparisons of the study sample by sleep disturbance groups indicated that there was a significantly greater proportion of females in the sleep disturbed group, compared to controls (Ps ≤ 0.04) (Table 1). Total NPI/NPIQ score was also

greater in individuals with sleep disturbance, indicating greater neuropsychiatric symptoms (P < .001). Additionally, the sleep disturbance group had significantly less education and greater use of sleep medications (P ≤ 0.02). Other demographic characteristics, including age, clinical status, and Aβ positivity were not significantly different across groups, and both groups had comparable use of sedative/hypnotic medication use.

Table 1
Demographics of the study sample

	Control (N = 402)	Sleep Disturbance (N = 87)	Total (N = 489)	P Value
Age (Mean (SD))				0.66
Mean (SD)	74.73 (7.75)	75.05 (7.01)	74.78 (7.62)	
Sex (Women, n, %)	196 (48.8%)	53 (60.9%)	249 (50.9%)	0.04
Education (Mean (SD))	16.522 (2.550)	15.782 (2.522)	16.391 (2.558)	0.012
Ethnicity (n, %)				0.50
Hispanic	14 (3.5%)	5 (5.7%)	19 (3.9%)	
Not Hispanic	386 (96.0%)	82 (94.3%)	468 (95.7%)	
Unknown	2 (0.5%)	0 (0.0%)	2 (0.4%)	
Race (n, %)				0.42
White	358 (89.1%)	80 (92.0%)	438 (89.6%)	
Others	44 (10.9%)	7 (8.0%)	51 (10.4%)	
Sleep Medication Use (n, %)				0.02
No	363 (90.3%)	71 (81.6%)	434 (88.8%)	
Yes	39 (9.7%)	16 (18.4%)	55 (11.2%)	
Hypertension (n, %)	162 (40.3%)	43 (49.4%)	205 (41.9%)	0.12
Cognitive Statics (n, %)				0.19
Cognitively Normal	223 (55.5%)	39 (44.8%)	262 (53.6%)	
MCI	125 (31.1%)	34 (39.1%)	159 (32.5%)	
Dementia	54 (13.4%)	14 (16.1%)	68 (13.9%)	
Total NPI/NPIQ score (Mean (SD))	0.903 (1.801)	2.287 (3.053)	1.149 (2.143)	< 0.001
Aβ positivity (n, %)				0.14

MCI = Mild Cognitive Impairment; NPI = Neuropsychiatric Inventory; NPIQ = Neuropsychiatric Inventory Questionnaire; Aβ = Amyloid-beta; APOE, SN = Salience Network; DMN = Default Mode Network; FPN = Frontoparietal Network.

	Control (N = 402)	Sleep Disturbance (N = 87)	Total (N = 489)	P Value
Below Cutoff	206 (51.2%)	37 (42.5%)	243 (49.7%)	
Above Cutoff	196 (48.8%)	50 (57.5%)	246 (50.3%)	
MCI = Mild Cognitive Impairment; NPI = Neuropsychiatric Inventory; NPIQ = Neuropsychiatric Inventory Questionnaire; Aβ = Amyloid-beta; APOE, SN = Salience Network; DMN = Default Mode Network; FPN = Frontoparietal Network.				

Presence of sleep disturbance was not significantly associated with any of the three intrinsic networks, after adjusting for covariates (Ps ≥ 0.18) (Table 2). Aβ positivity was not significantly associated with rsFC, but did have a negative association with the DMN at the trend-level significance (β=-0.03, P = 0.07). When the interaction term between sleep disturbance and Aβ was included, a significant interaction was found for the rsFC of the SN (β = 0.11, P = 0.006 [P = 0.018 after FDR corrections]) but not that of DMN or FPN, after adjusting for covariates (Table 2). Further examination revealed that sleep disturbance, in the presence of Aβ positivity, was associated with increased rsFC in the SN (Fig. 1), compared with the group without Aβ positivity.

Table 2
Main and Interaction Effects of Sleep Disturbance and Aβ

Independent variables*	SN			DMN			FPN		
	β	CI	P	β	CI	P	β	CI	P
Model 1:									
Sleep Disturbance	0.03	-0.01–0.07	0.18	0.01	-0.04–0.05	0.75	0.01	-0.04–0.06	0.66
Model 2:									
PET Aβ	0.0009	-0.03–0.03	0.96	-0.03	-0.07–0.0025	0.07	0.01	-0.03–0.05	0.79
Model 3:									
Sleep Disturbance	-0.03	-0.09–0.03	0.28	0.01	-0.06–0.07	0.86	-0.02	-0.10–0.05	0.56
PET Aβ	-0.02	-0.05–0.01	0.28	-0.03	-0.07 – 0.0045	0.08	-0.01	-0.05–0.04	0.81
Sleep Disturbance x Aβ	0.11	0.03–0.18	**0.006**	0.01	-0.08–0.09	0.90	0.06	-0.04–0.16	0.23
SN = Salience Network; DMN = Default Mode Network; FPN = frontoparietal network; PET = positron emission tomography; Aβ = Amyloid-beta									

Note: Separate models were employed to test the main effects of sleep disturbance and PET Aβ and the interaction term of the two variables (Model 1: main effect of sleep disturbance; Model 2: main effect of Aβ; Model 3: interactive effects of sleep disturbance and Aβ).

Sensitivity Analyses

We conducted separate analyses without individuals with dementia, given the potential role of AD pathology on the association between sleep disturbance, Aβ positivity, and rsFC. In a sample with only CN and MCI (N = 407), our findings indicated that there was a significant interaction between sleep disturbance and Aβ positivity on the SN connectivity (β = 0.13, P = 0.002) but not on DMN or FPN, which are consistent with our main finding in all sample. This indicates that our main findings are not driven by unique characteristics of the AD group (i.e., neurodegenerative process) (**Supplemental Table 1**).

Discussion

The present study examined the association between sleep disturbance, Aβ positivity, and resting-state functional connectivity within the SN, DMN and FPN. While we did not observe a significant direct association between sleep disturbance and rsFC within those three networks, there was a significant interaction between sleep disturbance and Aβ positivity on rsFC within the SN, suggesting that sleep disturbance was associated with aberrant salience network connectivity only when there was a presence of Aβ positivity.

Increased activation in SN is a well-established phenomenon related to AD pathology and sleep disorders. Hyperconnectivity in the SN is dependent on the stage of AD and has been particularly relevant to the preclinical stages of AD (e.g., presymptomatic or amnestic MCI)[9, 19, 40]. Interestingly, hyperactivity tends to wane during later stages of the disease and transition to a hypoconnectivity state[18, 19]. this paradoxically increased rsFC pattern has been noted in the DMN[17–19] and also separately in the hippocampus[18]. SN hyperactivity is also noted with Aβ positivity[17] and has been associated with Aβ-related increases in emotional sensitivity[41]. Clinically, elevated SN activation in AD manifest as neuropsychiatric symptoms, such as irritability, restlessness, anxiety, agitation, and suspiciousness, which are commonly seen in the progression of AD[9].

The involvement of SN in sleep disorders has been commonly studied together with its role in emotion processing and regulation, such as detecting and perceiving emotionally salient information and initiating resources for appropriate behavioral response[42–44]. Sleep disturbance in the form of insomnia has been linked with increased activation in global functional connectivity, including the SN, FPN, DMN, and other cognitive control networks (dorsal attention network and visual network)[45, 46]. Hyperactivation in the SN may be conceptualized as a transdiagnostic marker of insomnia severity[47], as it has been associated with common co-morbid psychiatric symptoms, such as depression[43, 48, 49] and anxiety[50]. Within the SN, activity of the insula is particularly elevated in individuals with insomnia[51]. The insula's

role in SN is especially notable for detection of emotionally salient stimuli and could contribute to increased subjective alertness and negative affect in sleep disturbance. Additionally, the insula has been identified as a source of slow-wave activity measured by electroencephalogram (EEG) during sleep[52], and the increased coactivation of the left insula with SN could disrupt generation of low-frequency EEG waves as part of sleep initiation[50]. The anterior cingulate cortex within the SN is associated with processing negative emotional stimuli[53] and has been implicated in depressive symptoms associated with poor sleep[54].

While sleep disturbance has been identified to cause significant damage to the brain (i.e., atrophy, neurotoxin build-up), hyperactivity in rsFC may represent "compensatory" connectivity in response to limit the clinical consequences of tissue damage in progress[55, 56]. Previous literature has indicated that hyperconnectivity in sleep disturbance is the brain's hyperarousal state as a response to compensate for loss of energy[45]. In an insomnia model, it may also be true that somatic hyperarousal could lead to further cortical arousal and problems with sleep initiation and maintenance[57].

Taken together, hyperconnectivity in the SN appears to represent insult to the brain that may be induced by both AD pathology and sleep disturbance. While sleep disturbance is being increasingly recognized as a modifiable risk factor for AD and its cognitive symptoms[58–60], the current study clarified underlying neurobiological mechanisms and indicated that sleep disturbance may be associated with disrupted SN connectivity only when it interacts with established Aβ pathology. Based on this key finding, our data suggest that Aβ could induce AD-like rsFC profile in sleep disturbance. Functional connectivity of different brain networks (e.g., SN or DMN) has been shown to first increase with Aβ accumulation in the non-clinical stages while maintaining normal cognitive function, but eventually decreases as Aβ accumulates to abnormal (pathologic) levels[17]. This phenomenon is thought to reflect the earliest manifestation of cognitive reserve, the brain's effort to compensate for emerging pathological processes[61]. Although our study did not assess other AD biomarkers or behavioral symptoms along with rsFC biomarkers, previous studies have found that Aβ augments AD processes (cognition and cortical thinning) that are associated with aberrant rsFC[62, 63]. Interestingly, our previous study also found that the presence of both sleep disturbance and Aβ burden was predictive of reduced cortical volume in AD regions and cognitive decline during a 5-year follow-up period, indicating that their interaction may help identifying individuals at an increased risk for AD (e.g., Aβ-positive individuals who also have sleep disorders)[64].

The role of Aβ on the relationship between sleep disturbance and rsFC is an understudied area, and the current study used a large dataset from ADNI to demonstrate that Aβ plays a significant moderating role in brain activity that is induced by sleep disturbance. Based on our knowledge, this is the first study to examine this topic using a large dataset from ADNI that comprises individuals at various clinical stages. Nonetheless, there are also methodological limitations to this study that warrant careful interpretation. One major limitation is a lack of objective and standard sleep measure. Sleep disturbance was defined broadly (using the NPI/NPI-Q), regardless of its etiology (e.g., sleep apnea, insomnia, or other sleep disorders), and was based on informants' observations. While only presence/absence of sleep

disturbance was determined, we believe that such a dichotomous format may reflect the reality of screening conducted in the primary care setting and indicate that even quick and brief screening for sleep disturbance may provide insight into the risk of developing abnormal brain functioning. Previous studies from ADNI, NACC, and Harvard Aging Brain Study have also demonstrated clinical implications of poor/insufficient sleep in the community-based setting using a single-item subjective measure[65-67]. The cross-sectional design of this study is also a notable limitation that makes causal inferences difficult. Certainly, there is evidence supporting the impact of AD pathology on poor sleep[68] and this makes the association between sleep disturbance and AD characteristics bi-directional; however, large-scale studies that utilized Mendelian randomization analyses demonstrated the impact of sleep on dementia risk[60, 69], shedding more light on the hypothesis that sleep disturbance could cause AD-like brain changes and thus is a modifiable risk factor for AD. Future studies with longitudinal analyses may further elucidate the causal relationship between sleep disturbance and rsFC alterations.

Conclusion

Findings from the current study imply that the presence of sleep disturbance is associated with rsFC alterations in the salience network when Aβ burden is present. Given that this aberrant brain connectivity may be signs of progression of Alzheimer's pathology, sleep screening should be conducted routinely in older adults, particularly in those at risk of Aβ accumulation (e.g., individuals with mild cognitive impairment) to reduce sleep difficulties and slow the progression of AD.

Declarations

CONFLICT OF INTEREST:

Hyun Kim

Nothing to Disclose

Xi Zhu

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Yiming Zhao

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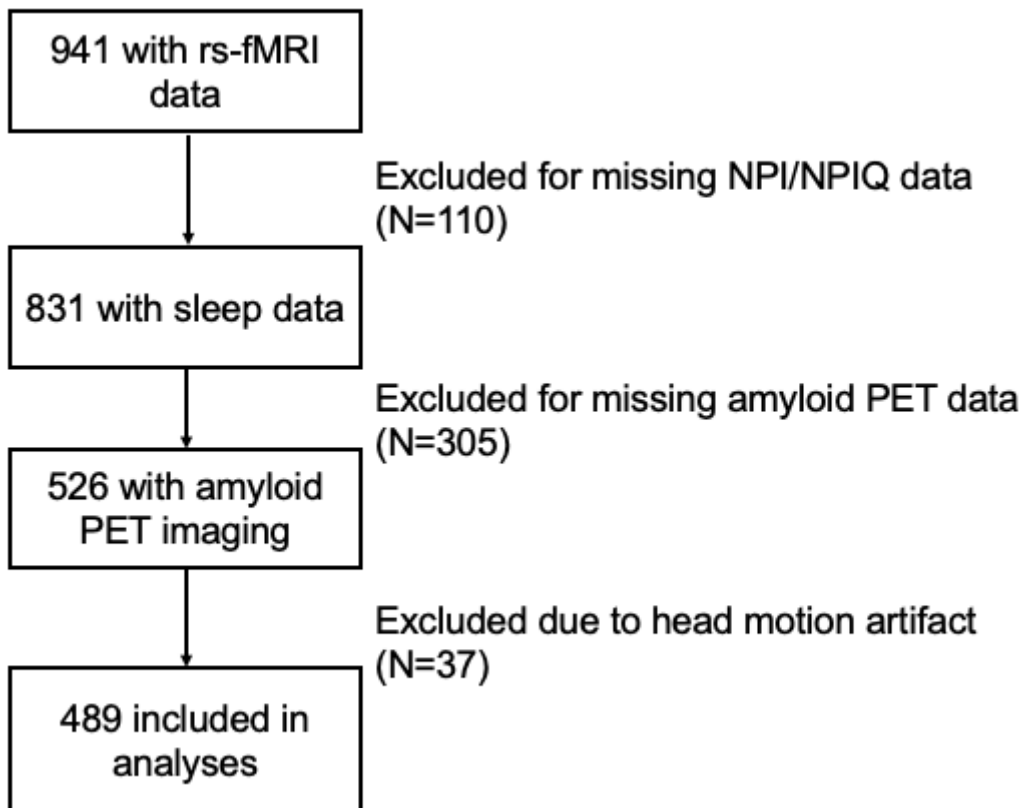
Figures

Figure 1

Flow chart of the study sample

rs-fMRI=resting-state functional magnetic resonance imaging; NPI/NPIQ=Neuropsychiatric Inventory/Neuropsychiatric Inventory Questionnaire; PET=positron emission tomography
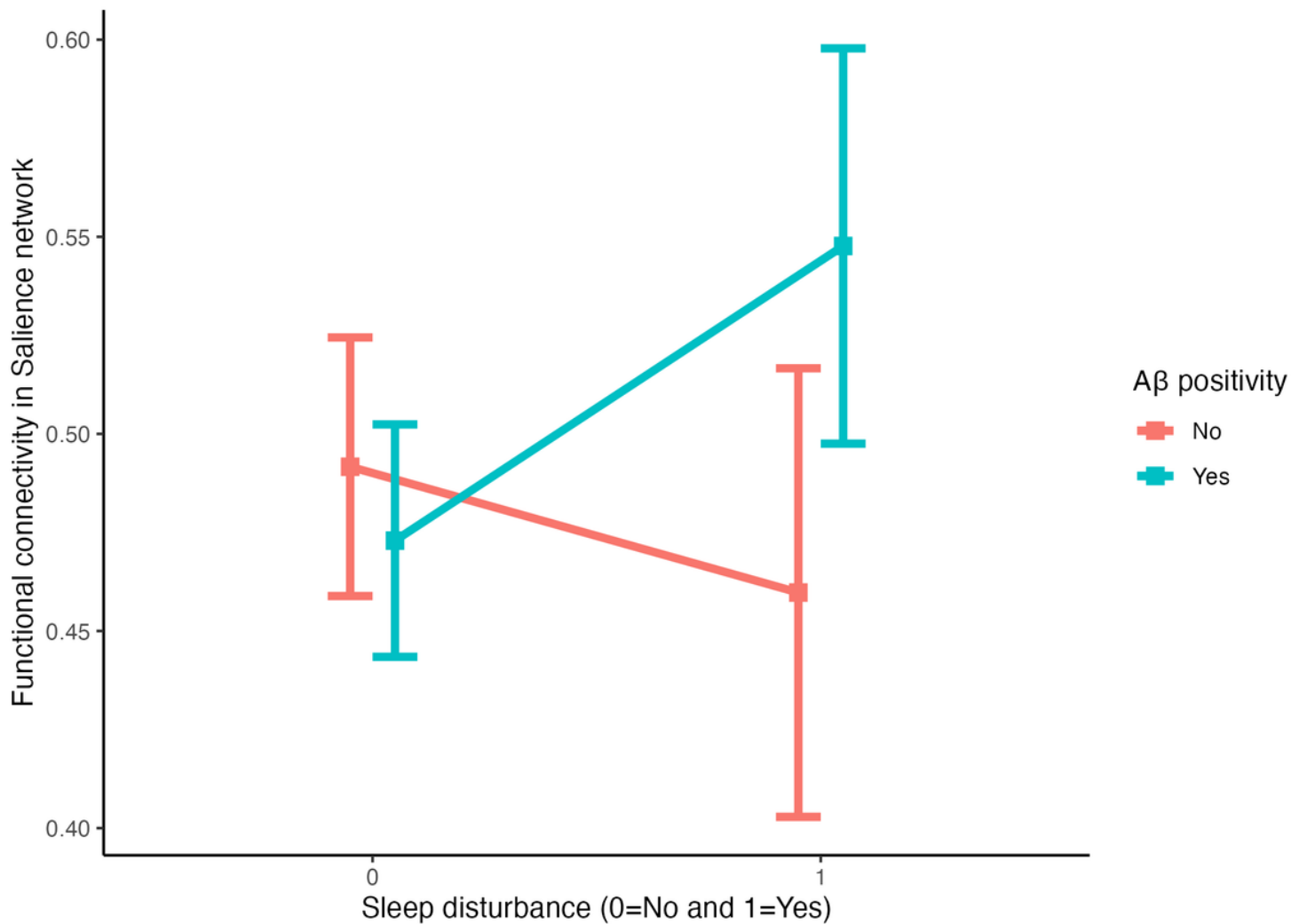
Figure 2

Interaction between sleep disturbance and amyloid beta positivity on the salience network connectivity

Aβ=Amyloid-beta

Note: Error bars represent the range of 95% Confidence Interval.

Supplementary Files

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- SupplementalTableADNIsleeprsFCpaper02.02.2023.docx