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RESEARCH ARTICLE

Night-to-night variability in sleep and amyloid beta burden in normal aging

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Abstract

INTRODUCTION: Alzheimer's disease is associated with sleep disturbances and accumulation of cerebral amyloid beta. The objective was to examine whether actigraphy-detected sleep parameters might be biomarkers for early amyloid burden.

METHODS: Participants underwent a week of actigraphy and an amyloid positron emission tomography (PET) scan. Sleep duration and continuity disruption (sleep fragmentation and nocturnal awakenings) were extracted and compared between amyloid-positive and amyloid-negative participants. Then multiple linear regressions were used between mean or night-to-night intra-individual variability (standard deviation) of sleep parameters and brain amyloid burden in a voxel-wise analysis.

RESULTS: Eighty-six subjects were included (80.3 ± 5.4 years; 48.8% of women). Amyloid-positive participants had a higher variability of sleep fragmentation compared to amyloid-negative participants. This parameter was associated with a higher amyloid burden in the frontal and parietal regions, and in the precuneus, in the whole sample.

DISCUSSION: This study highlights the relevance of using variability in sleep continuity as a potential biomarker of early amyloid pathogenesis.

KEYWORDS
actigraphy, aging, amyloid, intra-individual variability of sleep, PET, sleep

1 | INTRODUCTION

An age-related change shared by a majority of older adults is the modification of sleep characteristics, which includes a decrease in sleep duration and continuity.[1] Sleep disruption is also observed in the symptomatology of Alzheimer's disease (AD),[2] and is associated with an increased risk of AD dementia,[3,4] supporting sleep disruption as a potential modifiable risk factor for AD.

Brain amyloid beta (Aβ) plaques and tau neurofibrillary tangles constitute the main hallmarks of AD pathology but are also observed in healthy older adults without any cognitive symptoms.[5] Different mechanisms have been proposed to explain the gradual accumulation of amyloid in the brain, and one of them is the amyloid cascade hypothesis.[6] More recent studies have linked the clearance of brain metabolites to the sleep/wake efficacy of the glymphatic system.[7–9] More precisely, it has been shown that the cerebrospinal fluid (CSF)

flow increases during slow-wave sleep (SWS) in rodents[10] and in humans.[11] Hence, deterioration of SWS could lead to a dysfunction of the glymphatic system and an accumulation of brain metabolites. In accordance, studies using polysomnography showed that reduced and fragmented SWS is correlated with decreased CSF Aβ levels[12] and that a decrease in slow-wave activity (SWA) was specifically related to brain Aβ burden[13] measured by positron emission tomography (PET).

Although studies based on sleep questionnaires also revealed a relationship between sleep and Aβ burden, conflicting results exist regarding which sleep parameters are involved. Indeed, either self-reported poor sleep quality,[14,15] short sleep duration,[14,16] sleep latency,[15,17] or daytime sleepiness[16,18,19] have been separately associated with Aβ burden. These different results could be partially due to the subjective feature of sleep questionnaires.[20] Although polysomnography is still the gold standard for objective sleep assessment, it is most of the time limited to one or two nights of sleep in a clinical environment. An alternative for objective sleep measurement is actigraphy, which allows recording of sleep over several days with its night-to-night variability in large samples and in a daily-life setting.[21] Two studies using actigraphy compared brain Aβ-positive (Aβ+) and Aβ-negative (Aβ−) older individuals and found that sleep latency, wake after sleep onset, and sleep efficiency were affected in Aβ+ cases.[22,23] One study[24] observed that actigraphy-derived sleep fragmentation variability in the first half of the sleep period, rich in SWS,[25] was associated with Aβ burden in a small area of the ventromedial prefrontal cortex. These differences in actigraphy results need to be readdressed in a population-based study in order to define which actigraphic parameters could be used as a biomarker for brain amyloid burden. Moreover, it has been shown that night-to-night intra-individual variability (IIV) of actigraphic data[26] should be an important factor to consider in sleep studies, and to this day it has not been clearly investigated in amyloid-burden analyses.

The aim of the present study was to compare actigraphy-derived sleep characteristics of conventionally defined Aβ+ and Aβ− individuals based on PET imaging and to investigate the association between sleep characteristics and Aβ burden in a population-based cohort of 86 healthy older adults presenting a large spectrum of Aβ burden. We included the mean and the night-to-night IIV of actigraphy-derived sleep characteristics in our analyses.

RESEARCH IN CONTEXT

1. **Systematic Review**: Cerebral amyloid beta (Aβ) accumulation is a hallmark of Alzheimer's disease (AD) but evidence indicates that healthy older individuals can have a pathological level of Aβ accumulation without any cognitive symptoms. Recent studies propose a link between sleep and the clearance of metabolites such as Aβ. An aspect of sleep has been neglected, its night-to-night intra-individual variability (IIV). Therefore, assessment of amyloid–positron emission tomography (PET) levels and objective sleep parameters including IIV, could help in determining a possible link between age-related sleep deterioration and amyloidopathy in cognitively healthy individuals.
2. **Interpretations**: Our findings indicate that night-to-night IIV of sleep fragmentation is positively associated with frontal and parietal brain Aβ accumulation in healthy elderly.
3. **Future Directions**: Findings support the inclusion of night-to-night IIV in sleep and AD research. Future studies should investigate the longitudinal aspect of this association and the utility of sleep fragmentation IIV in predicting Aβ accumulation.

2 | MATERIALS AND METHODS

2.1 | Participants

This study is based on a cross-sectional research protocol called EDUMA (Éducation et Maladie d'Alzheimer), including older individuals 65 years of age or older from two epidemiological prospective studies: the Aging Multidisciplinary Investigation (AMI)[27] and the Bordeaux site of the Three-City study (3C).[28] These study procedures were approved by a regional human research review board (University Hospital of Bordeaux for AMI and University Hospital of Kremlin-Bicêtre and Sud-Mediterranée III for 3C) and all participants provided written informed consent. All participants were right-handed and had no neurological or psychiatric disorders or any contraindications for magnetic resonance imaging (MRI) and PET scans.

A PET scan examination was proposed to 120 subjects in addition to MRI between 2012 and 2015. Among them, 92 also agreed to wear an actigraphy device. We excluded two subjects with significant brain abnormalities (frontal trauma, cavernoma), one with frontotemporal dementia and three with a Mini-Mental Status Examination (MMSE)[29] score below the standards established by age, sex, and education level,[30] leaving 86 subjects for the present analysis (Figure 1). The final sample is composed of cognitively unimpaired elderly without any neurological or psychological disorders.

2.2 | Sleep assessment

Sleep was measured with two models of wrist-worn actigraphs (Cambridge Neurotechnology, Cambridge, UK), ActiWatch 7 and MotionWatch 8, both validated against polysomnography.[31,32] The devices were placed on the nondominant wrist and were kept continuously for a week in the home environment. A minimum of four nights was required to be included (range: 4–9 nights; mean ± SD: 7.86 ± 0.59). MotionWare, v1.2.26 (Cambridge Neurotechnology, Cambridge, UK) with a sensitivity threshold of 20 counts was used. A sleep diary informing about bedtime and rise time was completed by each participant during the protocol. Information about sleep

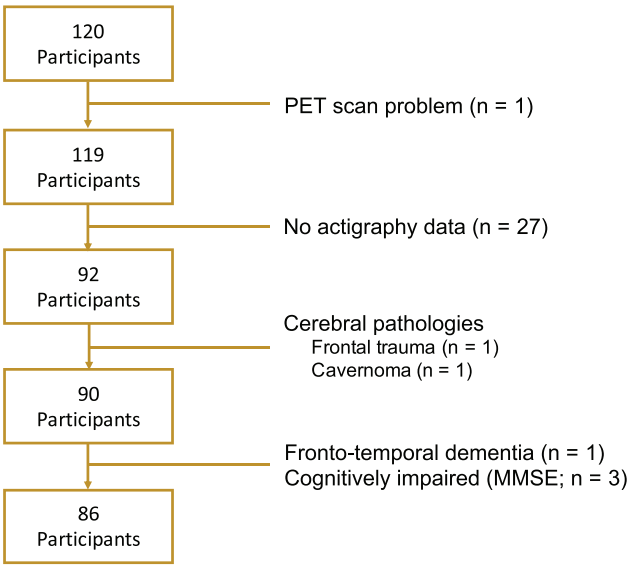

FIGURE 1 Flow chart of the study participants. MMSE, Mini-Mental State Examination; PET, positron emission tomography.

disturbances such as possible sleep apnea or sleep partners with dementia was collected during a pre-scan interview.

Sleep onset and offset were first estimated by MotionWare based on activity levels and then verified by an examinator using the sleep diary and the light sensor data. In short, an abrupted disappearance of light and a lack of activity for more than 5 minutes determined sleep onset. An important movement after rest and continuity of activity after determined sleep offset. Total Sleep Time (TST) represents the sum in minutes of all epochs classified as sleep (<20 counts) between sleep onset and offset. Sleep continuity was estimated during the first half of the sleep period, calculated as half of the period between sleep onset and offset. Two sleep continuity parameters were investigated: sleep fragmentation index (SF) and the duration of wake after sleep onset (WASO). SF is a direct estimation of the percentage of sleep duration disturbed by fine movements (>0 counts) during the estimated sleep period and is calculated as the sum of the "Mobile time (%)" and the "Immobile bouts ≤1 min (%)." WASO is the duration of all epochs classified as wake (>20 counts) during the estimated sleep period and reflects an indirect estimation of nocturnal awakenings duration. The mean and SD of these parameters were calculated over the week (IIV-TST; IIV-SF; IIV-WASO).

2.3 | MRI

MRI scans were obtained with an ACHIEVA 3T scanner (Philips Medical System, The Netherlands) with a SENSE 8-channel head coil. Anatomic high-resolution MRI volumes were acquired in a transverse plan using a three-dimensional (3D) magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted sequence with the following parameters: repetition time (TR) = 8.2 ms, echo time (TE) = 3.5 ms, 7-degree flip angle, field of view (FOV) 256 × 256 mm^2, 180 slices, no gap and voxel size of 1 × 1 × 1 mm^3. Gray matter (GM), white matter, and CSF volumes were estimated for each subject using the Computational Analysis Toolbox v12 (https://neuro-jena.github.io/cat/) implemented in Statistical Parametric Mapping software v12 (SPM12, www.fil.ion.ucl.ac.uk/spm).

2.4 | Amyloid beta PET scan

A Discovery RX (General Electric) PET/computerized tomography (CT) system was used to acquire PET images 90 minutes after an intravenous bolus injection of 185 MBq ± 5% of ^{18}F-flutemetamol ligand, following a standardized acquisition protocol described elsewhere.[33] A 30 minute dynamic acquisition was performed after a CT scan used to provide an attenuation correction map. These images were reconstructed with the ordered subset expectation maximization method and corrected for the following: attenuation of annihilation radiation, scatter normalization, random events, decay, and deadtime. The PMOD software v3.5 (PMOD Technologies Ltd, Adliswil, Switzerland) was used to post-process PET images. A mean image for each subject was created and co-registered to the corresponding T1-weighted MR image. Partial volume effects were corrected with the Geometric Transfer Matrix method[34] using probability tissue maps obtained from the segmentation of the T1-weighted image by FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu). PET images were expressed in standardized uptake value (SUV) and converted in SUV ratio (SUVr) PET images, by dividing the SUV of each voxel by the mean SUV of the reference region, the cerebellar GM.

PET images were then warped to the Montreal Neurological Institute (MNI) space and masked to constrain voxel-based analysis to GM only.

A cortical mean value above 1.5 SUVr is considered as the ^{18}F-flutemetamol-positive threshold[35] (Aβ+) and a cortical mean value under 1.35 SUVr is considered as the ^{18}F-flutemetamol-negative threshold (Aβ–). Participants with a cortical mean value between 1.35 and 1.5 were considered as undetermined.

2.5 | Other variables

Educational level was categorized in five levels (primary school or less; primary school diploma; middle school; high school; and university). The MMSE was used to evaluate global cognitive status. Consumption of psycholeptic drugs was assessed, such as anxiolytics, hypnotics and/or sedatives, and antipsychotics for anxiety. The presence of at least one ε4 allele of the apolipoprotein E (*APOE*) gene was derived from blood samples available for 72 participants.

2.6 | Statistical analyses

All statistical analyses were performed using R Studio v4.0.4 and SPM12. Demographics and sleep parameters were first compared between Aβ– and Aβ+ participants using Mann-Whitney U test

for non-normally distributed variables, Student's *t*-test for normally distributed variables, and chi-square test for qualitative variables. Statistical significance was set at $p < 0.05$.

In order to better understand the importance of IIV of sleep parameters and how they interact with each other, a correlation matrix using Spearman rho was created between all sleep parameters mean and variability. Statistical significance was set for $p < 0.05$ with a multiple comparison correction (false discovery rate).

A first analysis using multiple linear regressions with SPM12 was conducted with Aβ burden maps being the dependent variables and age as the independent variable in order to determine the statistical threshold adapted to our PET data. Expected age effect on brain amyloid distribution was obtained for $p < 0.001$, uncorrected for multiple comparisons with no association in the reverse contrast; no age effect was observed using a correction for multiple comparisons.

Whole-brain exploratory analyses were then performed with Aβ burden maps being the dependent variables and TST, SF, and WASO being the independent variables in three separate models including age, sex, and education level as covariates. In another set of analyses, IIV-TST, IIV-SF, and IIV-WASO were the independent variables in three separate models including age, sex, education level, and the corresponding mean sleep parameter as a covariate. In the case of a significant association, additional statistical models were performed and included first total GM volume, expressed as a percentage of the total intracranial volume, and then *APOE* ε4 status ($N = 72$) as covariates. A statistical threshold of $p < 0.001$, uncorrected for multiple comparisons, and a significant threshold cluster of 100 voxels were used for all voxel-wise analyses in the whole sample of 86 subjects.

Sensitivity analysis was conducted by excluding internally or externally disturbed sleepers from our sample. Two participants declared sleep apnea, two had sleep partners with dementia, and 13 took psycholeptic drugs, which left a group of 69 subjects. We verified the specificity of the first part of the sleep period by analyzing sleep continuity in the second part of the sleep period in a supplementary analysis.

3 | RESULTS

3.1 | Participants' characteristics

Demographic, clinical, and sleep parameters are presented in Table 1. The mean age in our sample was 80.3 years old (±5.4), with 48.8% women, and a mean MMSE score of 27.7 (±1.9); 15.1% took psycholeptic medication and 18.1% were *APOE* ε4 carriers. In total, 682 nights were analyzed with an average of 7.8 ± 0.59 nights per participant. Mean sleep duration was 7h01 with 43 min of night-to-night variation (IIV-TST). Regarding sleep continuity, mean SF was 29.4 and mean WASO was 30 minutes, with a night-to-night variation of 12.7 (IIV-SF), and 12 minutes (IIV-WASO), respectively.

Our population had an average cortical Aβ burden of 1.5 ± 0.4, with 23.3% of participants being Aβ+ and 59.3% Aβ−, whereas the remaining participants are undetermined.

TABLE 1 Subjects characteristics.

Variable	$N = 86$
Demographics	
Age, mean (SD), years	80.3 (5.4)
Sex, no. (%), women	42 (49)
Education level, no. (%)	
Primary school or less	16 (19)
Primary school diploma	22 (26)
Middle school	19 (22)
High school	15 (17)
University	14 (16)
Aβ burden, mean (SD), SUVr	1.5 (0.4)
APOE ε4 status[b], no. (%)	13 (18.1)
MMSE[a], mean (SD), score	27.7 (1.9)
Declared sleep apnea, no. (%)	2 (2)
Psycholeptic intake, no. (%)	13 (15)
Sleep parameters	
Whole sleep period	
Total sleep time, mean (SD), hour	7h01 (1h04)
Total sleep time—IIV, mean (SD), hour	0h43 (0h21)
First part of the sleep period	
WASO, mean (SD), hour	0h30 (0h16)
WASO—IIV, mean (SD), hour	0h12 (0h07)
Sleep fragmentation, mean (SD), %	29.4 (12.9)
Sleep fragmentation—IIV, mean (SD), %	12.7 (5.2)

Abbreviations: Aß, cortical amyloid beta; IIV, intra-individual variability; MMSE, Mini-Mental State Examination; SUVr, standard uptake value ratio; WASO, wake after sleep onset.
[a]Missing data for two subjects.
[b]At least one ε4 allele, missing data for 14 subjects.

3.2 | IIV of sleep parameters

The correlation matrix is shown in Figure 2. Considering each parameter mean and variability, WASO and IIV-WASO are highly correlated ($r = 0.62$; $p < 0.001$); SF and IIV-SF are moderately correlated ($r = 0.39$; $p < 0.001$); but TST and IIV-TST are not ($r = -0.13$; $p = 0.257$).

IIV-WASO is negatively correlated to TST ($r = -0.46$; $p < 0.001$) and positively correlated to SF ($r = 0.50$; $p < 0.001$). IIV-SF is negatively correlated to TST ($r = -0.28$; $p = 0.012$).

3.3 | Aβ± versus Aβ− participants

Demographic, clinical, and sleep parameters for Aβ+ and Aβ− participants are presented in Table 2. There was no difference in sex, level of education, MMSE, reported sleep apnea, medication intake, TST, IIV-TST, WASO, IIV-WASO, and SF. As expected, the Aβ+ group displayed a significantly higher mean cortical amyloid SUVr (2.2 ± 0.4 vs 1.3 ± 0.1; $p < 0.001$) and included a higher proportion of *APOE* ε4 carriers (40% vs

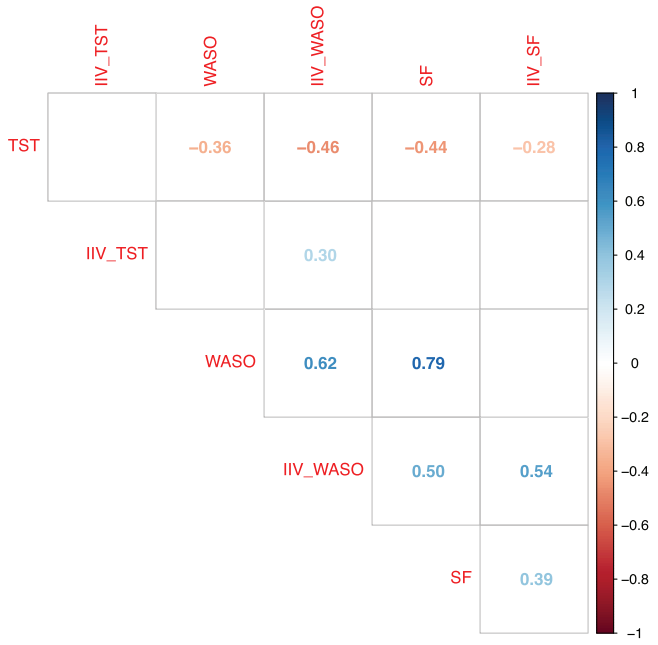

FIGURE 2 Correlation matrix between sleep parameters. Spearman rho is indicated for each significant correlation with a color-coded scale. Results are presented at $p < 0.05$ corrected for false discovery rate. IIV, intra-individual variability; SF, sleep fragmentation; TST, total sleep time; WASO, wake after sleep onset.

7.8%; $p = 0.004$). Participants included in the Aβ+ group were significantly older (83.1 ± 5.3 vs 79.0 ± 5.3; $p = 0.003$) and had a higher IIV-SF (15.7 ± 6.6 vs 11.5 ± 4.0; $p = 0.016$) than those in the Aβ− group.

3.4 | Associations between sleep parameters and Aβ burden

In regression models including either TST, SF, or WASO, no significant association with amyloid burden was observed.

High IIV-SF of the first half of the night was related significantly to an elevated Aβ burden, controlled for age, sex, level of education, and SF ($p < 0.001$ uncorrected, cluster size of 100 voxels, Figure 3A). This association was observed mostly in the frontal regions (left [L] and right [R] orbital gyrus, L/R inferior gyrus, R middle gyrus, and L/R precentral gyrus), as well as in the insular gyrus (L/R), cingulate gyrus (R), medioventral occipital cortex(R), superior temporal gyrus (L/R), and in parietal regions (L/R postcentral gyrus, L/R inferior lobule, and L/R precuneus; Figure 2). Adding GM volume or *APOE* ε4 status in the statistical model did not change the results but the concerned regions were less spatially extended.

High IIV-WASO was also associated significantly with Aβ burden in frontal lobes (Figure 3B), including the orbital gyrus (L/R), the inferior frontal gyrus (L) and the precentral gyrus (L), as well as in parietal lobes including the postcentral gyrus (L/R) and the inferior parietal lobule (L/R; $p < 0.001$ uncorrected, cluster size of 100 voxels).

In the sensitivity analysis considering only self-reported undisturbed sleepers, we observed the same association between IIV-SF and Aβ burden ($p < 0.001$ uncorrected, cluster size of 100 voxels), albeit less spatially extended (Supplementary Figure). However, the association between IIV-WASO and Aβ burden was only observed at a subthreshold level ($p < 0.005$, uncorrected, 100 voxels).

Sleep parameters of the second part of the sleep period were not associated with Aβ burden.

4 | DISCUSSION

In this study, we observed that 23.3% of cognitively unimpaired older adults had a pathological level of Aβ accumulation, a hallmark of AD pathogenesis in the brain. This is in line with a recent meta-analysis including 1849 healthy older individuals (68 years old on average) without cognitive impairment. Ossenkoppele et al.[36] reported that 24.2% of these individuals are considered as being Aβ+. Previous studies have tried to investigate whether actigraphy-derived sleep parameters differ between Aβ+ and Aβ− groups, with some data indicating no difference (PET imaging),[37,38] whereas other reported worse sleep quality in Aβ+ participants (PET imaging,[23] and CSF measures of amyloid burden[22]). Our analyses did not reveal any difference in sleep duration, WASO, or sleep fragmentation between Aβ+ and Aβ− participants. However, we observed a higher night-to-night variability in sleep fragmentation in the Aβ+ group compared to the Aβ− group. To the best of our knowledge, no other study compared night-to-night variability of actigraphy-derived sleep parameters between Aβ+ and Aβ− groups. Aβ+ individuals are more at risk of developing AD, and studies have shown that high sleep fragmentation is a risk factor for AD.[3] Thus night-to-night variability of sleep fragmentation could be another aspect of a lack of sleep continuity linked to AD pathogenesis and looking only at the mean of this parameter could omit an important part of it.

Accordingly, voxel-wise analyses revealed that a high IIV-SF in the first half of the sleep period was positively related to a high Aβ burden in several cortical brain regions, mostly located over the frontal and parietal lobes. Additional analyses indicated that these results were not affected by GM volume, *APOE* status, or sleep medication. This voxel-wise analysis allowed us to precisely describe the brain regions affected by amyloid in relation to a high IIV-SF in the first half of the sleep period. The observation in this relatively cognitively preserved population of an association between night-to-night IIV-SF and brain Aβ burden adds to the results of a previous study.[24] This study reinforces the hypothesis associating sleep characteristics and brain Aβ burden not only in AD[39] or other dementia[40] but also in cognitively healthy older individuals. These results considering sleep characteristics of the first half of the sleep period, rich in SWS, are consistent with previous studies linking Aβ burden and specific sleep parameters derived from polysomnography.[12,13,41,42] It has been found that frontal Aβ burden in older adults was linked to a diminished amplitude and a lower proportion of <1 Hz SWA.[41,42] This is particularly interesting because certain brain regions we observed to be linked to IIV-SF (i.e., frontal lobes, insular gyrus, and cingulate gyrus) are implicated in slow-wave generation during sleep.[43]

TABLE 2 Groups comparison.

Variable	Aβ− (*n* = 51)	Aβ+ (*n* = 20)	*p* value
Demographics			
Age, mean (SD), years	79.0 (5.3)	83.1 (5.3)	0.003
Sex, no. (%), women	37 (52)	34 (48)	NS
Education level, no. (%)			NS
Primary school or less	13 (25)	1 (5)	
Primary school diploma	12 (24)	4 (20)	
Middle school	13 (25)	3 (15)	
High school	6 (12)	6 (30)	
University	7 (14)	6 (30)	
Aβ burden, mean (SD), SUVr	1.3 (0.1)	2.2 (0.4)	< .001
APOE ε4 status[a], no. (%)	4 (7.8)	8 (40)	0.004
MMSE[b], mean (SD), score	27.6 (1.8)	27.7 (1.9)	NS
Declared sleep apnea, no. (%)	1 (2)	0 (0)	NS
Psycholeptic intake, no. (%)	9 (21)	4 (9)	NS
Sleep parameters			
Whole sleep period			
Total sleep time, mean (SD), hour	7h10 (1h05)	6h50 (1h11)	NS
Total sleep time—IIV, mean (SD), hour	0h44 (0h22)	0h42 (0h25)	NS
First part of the sleep period			
WASO, mean (SD), hour	0h31 (0h20)	0h28 (0h12)	NS
WASO—IIV, mean (SD), hour	0h11 (0h06)	0h14 (0h10)	NS
Sleep fragmentation, mean (SD), %	29.3 (14.5)	30.7 (10.1)	NS
Sleep fragmentation—IIV, mean (SD), %	11.5 (4.0)	15.7 (6.6)	0.016

Abbreviations: Aß, cortical amyloid beta; IIV, intra-individual variability; MMSE, Mini-Mental State Examination; SUVr, standard uptake value ratio; WASO, wake after sleep onset.

[a]At least one ε4 allele, missing data for 14 subjects.

[b]Missing data for two subjects.

This can contribute to the bidirectional effect of the sleep–amyloid relationship described previously.[9,44] Aβ aggregation and sleep disturbances occur early during the preclinical phase of AD.[3,22] Thus, during this phase, older people with not only a bad sleep continuity as suggested in the literature but also a lack of stability in this sleep continuity could have an ineffective glymphatic system, leading to a greater risk of heavy accumulation of amyloid. As of today, IIV is not widely used in sleep clinics and in research even though it could be easily integrated.[26] We observed that IIV of sleep continuity (SF and WASO) is correlated negatively with sleep duration and positively correlated with mean sleep discontinuity, suggesting that a high variability of sleep continuity reflects poor sleep quality. A study by Westerberg et al.[45] found that higher night-to-night IIV of actigraphic sleep was associated to lower story recall in the healthy elderly and individuals with amnestic mild cognitive impairment. They proposed that inconsistent sleep across nights could impair neural systems involved in memory processes. Another study from Mezick et al.[46] found that actigraphic IIV-SF was related to a higher number of stressful life events and higher norepinephrine levels in healthy middle-aged and elderly. Hence, an inability to maintain a proper sleep state in the elderly could impact the brain's ability to maintain appropriate homeostasis.

We did not find a difference in WASO between our groups unlike Ju et al.[22] and Ettore et al.[23] This could be due to a methodological difference—Ju et al.[22] used a CSF measure of amyloid burden—or due to a higher proportion of women in the case of Ettore et al.[23] (70.6%), with women being at higher risk of developing AD and presenting different age-related sleep characteristics.[47] In addition, Ettore et al.[23] did not control for external sleep disturbances or for sleep medication. We also found a positive association between IIV-WASO and Aβ burden but it did not remain significant when we excluded disturbed sleepers and sleep medication intake.

The strength of this study resides in the use of actigraphy and PET scan in healthy older adults. Actigraphy is a more reliable tool to measure sleep in real life compared to subjective sleep assessment.[20,48] Amyloid PET scan allows a direct in vivo measure of the spatial brain localization of Aβ burden, compared to CSF measures, for example. Limitations should also be considered in our study. First, the cross-sectional design precludes any causal interpretation. Another

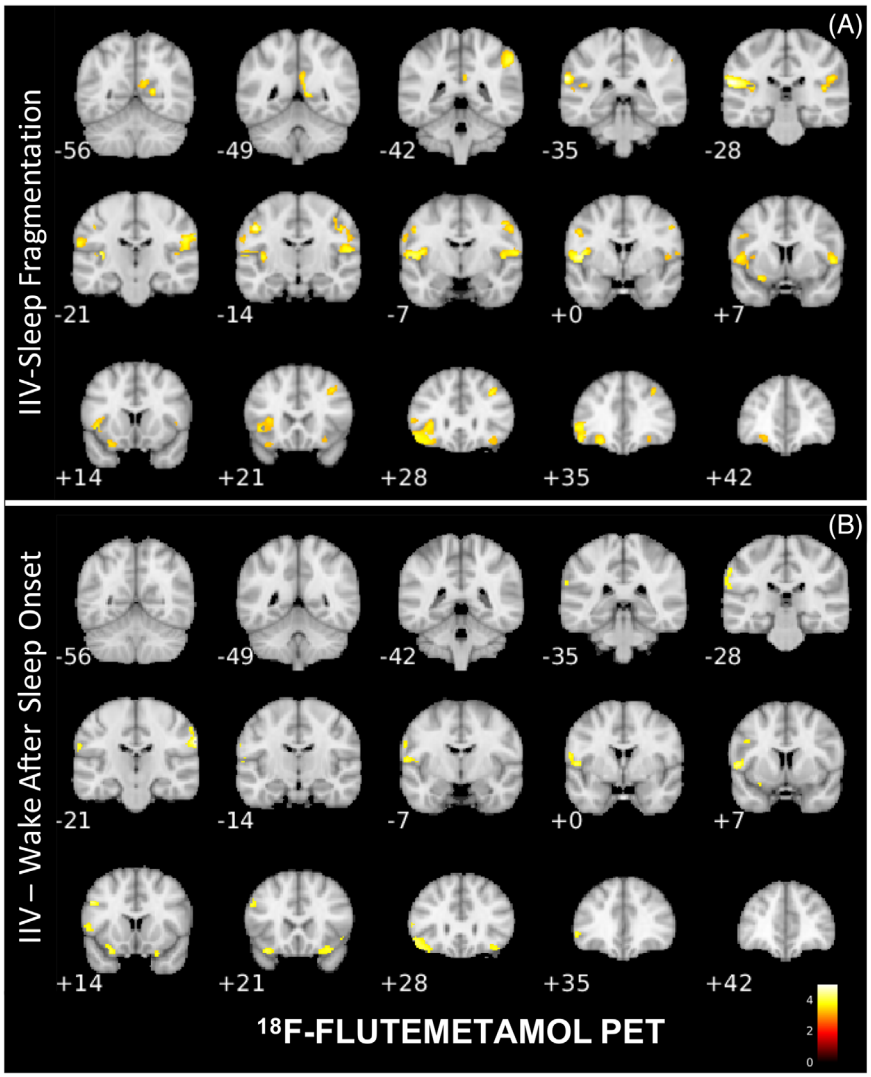

FIGURE 3 Multiple regressions between sleep parameters of the first part of the sleep period and amyloid burden in the whole sample ($n = 86$). IIV—sleep fragmentation (A) and IIV—wake after sleep onset (B) are positively associated with amyloid burden. Results are presented at $p < 0.001$ (uncorrected), cluster size > 100 voxels and shown on coronal slices in MNI152 space. Analyses are adjusted by age, sex, education, and the corresponding mean parameter. IIV, intra-individual variability; PET, positron emission tomography.

limitation lies in our statistical method, as an uncorrected statistical threshold was used in whole-brain voxel-wise analyses. However, at this threshold, no significant association was observed in the reverse contrast (i.e. there was no negative correlation) which strengthens our findings and expected age effect on brain amyloid distribution was obtained. We did not assess tau deposition within the brain, considering that tau metabolism is also sleep related[42] and more directly related to cognitive disturbances in older individuals.[49] Finally, although sex difference has been described previously in sleep literature[50] and in pathophysiology of AD,[47] in the actigraphy/amyloid literature, possible sex interactions have not been clearly investigated yet. Thus there is a need for additional studies on this field directly addressing the sex difference.

In conclusion, we reported a positive association between the night-to-night IIV-SF in the first half of the sleep period and higher Aβ burden mainly in the frontal lobes in cognitively normal older adults. These results can help with the early detection of individuals at risk for AD and to implement preventive strategies based on sleep health promotion.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

CONSENT STATEMENT

All human subjects provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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