Heterogeneity in spontaneous sleep arousals: positive and negative links with early amyloid-beta and cognition

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Abstract

Recent literature is pointing towards a tight relationship between sleep quality and amyloid-beta (Aβ) accumulation, a hallmark of Alzheimer’s disease (AD). Sleep arousals are considered to induce sleep disruption, and though their heterogeneity has been suggested, their correlates remain to be established. We classified arousals in sleep of 100 healthy older individuals according to their association with muscular tone increase (E+/E-) and sleep stage transition (T+/T-), and show differences in EEG oscillatory compositions across arousal types. We found that T+E- arousals, which interrupt sleep stability, were positively correlated with Aβ burden in brain regions earliest affected by AD neuropathology. By contrast, more prevalent T-E+ arousals, upholding sleep continuity, were associated with lower cortical Aβ burden, and better cognition. We provide empirical evidence that spontaneous arousals are diverse and differently associated with brain integrity and cognition. Sleep arousals may offer opportunities to transiently synchronise distant brain areas, akin to sleep spindles.

Introduction

Sleep is central to health and cognition\(^1\), and deteriorates with ageing\(^2,3\). In addition, sleep disruption is associated with Alzheimer’s disease (AD), as assessed by tau and amyloid-beta (Aβ) brain accumulation, most likely in a bidirectional manner\(^4,5\). Poorer sleep quality\(^6–8\), daytime sleepiness\(^8,9\), reduced slow-wave sleep\(^10–13\), and sleep deprivation\(^14,15\) have been linked to higher Aβ levels, but also to poorer cognitive performance\(^11,16\).

Sleep arousals, defined as transient accelerations in sleep electroencephalogram (EEG) rhythms, are usually considered as brain reactions to internal (e.g., apnoea) or external (e.g., auditory stimulus) perturbations\(^17\). Although key elements of sleep microstructure, they can also shape its macrostructure and lead to a shallower sleep stage\(^18\). They are most often considered as markers of sleep disruption, thereby a detrimental and harmful sleep feature. Several conceptual definitions classified them almost exclusively in the context of sleep disorders (e.g. sleep disordered breathing – SDB, and to a smaller extent periodic limb movements syndrome – PLMS), or in experimental protocols inducing arousals through external - mainly using auditory – stimulation\(^19–22\). These types of studies yielded mixed results. A negative link between arousal prevalence during sleep and cognitive performance was revealed in SDB, particularly in attention, and sometimes the executive and memory domains\(^23\). By contrast, other investigations did not find such a relationship, and imputed alterations in cognition in SDB to brain hypoxia (see\(^23\) for a review). In individuals devoid of sleep pathologies, arousals evoked by auditory stimuli were reported to impact subsequent daytime alertness\(^20\). In addition, sleep fragmentation induced by auditory stimulation is associated with higher Aβ cerebrospinal fluid (CSF) content the following day\(^10\).

Importantly, spontaneous arousals, i.e. not elicited by any identifiable internal or external stimuli, also constitute an authentic element of undisturbed sleep in healthy individuals. Their mechanisms, cerebral
correlates and functional consequences remain largely unknown\textsuperscript{17} with some authors suggesting that there may be physiologic and pathologic arousals. Understanding their respective roles might shed light on the adaptive properties of the sleeping brain and provide insight into pathological mechanisms associated with sleep disturbances\textsuperscript{17}.

Here, we assessed whether different types of spontaneous arousals during sleep were differentially associated with A\textsubscript{\beta} cortical deposition and cognitive performance in a cohort of healthy individuals in late midlife. We were able to tease apart different types of arousals, based on their temporal relationships with increased muscular tone and sleep stage transitions. In line with the hypothesis that arousals perturb sleep, we anticipated that arousals fragmenting sleep structure would be associated with both worse cognitive performance and A\textsubscript{\beta} deposition in brain areas that are first affected by AD neuropathology.

**Results**

**EEG oscillations differ across arousal types**

We recorded undisturbed sleep at habitual sleep times under EEG in 101 healthy individuals aged 50 to 70 y (59 ± 5y; 68 women), following one week of regular sleep-wake schedule. In order to evaluate the potential heterogeneity of arousals, we split them according to two criteria, which we considered as relevant in research settings as well as clinical practice. Firstly, whether arousals did trigger a sleep stage transition (T+) (when they occurred within 15s of a stage change) or not (T-); and secondly, their salience, reflected by the concomitant increase in EMG tone (E+) or its absence (E-).

In a first step, we assessed whether characterising sleep arousals by their association with sleep stage transition (T+ or T-), and the co-occurrence of an EMG tone increase (E+) or not (E-) differed by their oscillatory properties. We computed individual relative power in the different EEG frequency bands defining an arousal (theta – 4.5-7.5Hz, alpha – 8.5-11.5Hz, and beta – 16-30Hz). A GLMM, with relative power as dependent variable, first indicated that relative power changed across frequency bands ($F_{2,294.1}=403.84$, $p < 0.0001$, $R^2_{\beta^*}=0.73$). More importantly, it yielded a triple interaction between transition (T+ and T-), EMG status (E+ and E-) and frequency band ($F_{2,880}=3.39$, $p = 0.034$, $R^2_{\beta^*}=0.008$) implying that arousals differ in their spectral composition based on the presence or absence of EMG changes and sleep stage transition (Fig. 1). This was further reflected in main effects of EMG status ($F_{1,989.9}=75.97$, $p = 0.0001$, $R^2_{\beta^*}=0.07$) and transition ($F_{1,708.6}=39.17$, $p < 0.0001$, $R^2_{\beta^*}=0.05$), as well as in interactions between transition and frequency band ($F_{2,709.5}=34.62$, $p < 0.0001$, $R^2_{\beta^*}=0.09$), between EMG status and frequency band ($F_{2,979.2}=187.39$, $p < 0.0001$, $R^2_{\beta^*}=0.28$), and between EMG status and transition ($F_{1,879.3}=22.55$, $p < 0.0001$, $R^2_{\beta^*}=0.025$). Based on this first analysis, we therefore concluded that the factors of arousal heterogeneity eloquently define 4 types of arousals (T+ E+, T+ E-, T-E+, T-E-). We finally note that multiple post-hoc comparisons within each band yielded significant differences across arousal types over the theta and beta bands (see suppl. table S1).
**Arousals heterogeneity reflects different associations with Aβ burden**

Aβ burden was quantified over the regions previously reported as the earliest cortical aggregation sites in all but one participant. In a second GLMM, we tested whether associations between arousal density and early cortical Aβ burden depend on transition (T+, T-) and EMG (E+, E-) statuses, while regressing out age and sex effects. We observed a main effect of transition ($F_{1,196}=607.52, p<0.0001, R^2_{β^*}=0.76$) and EMG status ($F_{1,98}=70.63, p<0.0001, R^2_{β^*}=0.42$) as well as an interaction between EMG status and transition ($F_{1,196}=102.32, p<0.0001, R^2_{β^*}=0.34$), indicating that density of arousal types significantly varied. Interestingly, we did not find any significant main effect of early cortical Aβ burden ($F_{1,96}=0.26, p=0.61$), age ($F_{1,96}=2.44, p=0.12$) and sex ($F_{1,96}=0.12, p=0.73$). Critically, the GLMM yielded a significant triple interaction between early cortical Aβ burden, EMG status and transition ($F_{1,196}=7.16, p=0.008, R^2_{β^*}=0.035$) implying that the association between arousals and early cortical Aβ burden depends on the concomitant change in muscular tone and sleep stage transition. The heterogeneity in spontaneous arousals was further reflected by the significant interactions between early cortical Aβ burden and EMG status ($F_{1,98}=8.64, p=0.004, R^2_{β^*}=0.08$). Figure 2 decomposes the associations between each of the four type of arousal and early cortical Aβ burden. Pearson’s correlation revealed no significant link between early cortical Aβ burden and T-E- arousals ($r=0.13, p=0.19$; Fig. 2A), a significant negative association with T-E+ arousals ($r=-0.30, p=0.002$; Fig. 2B), a significant positive association with T+ E- arousals ($r=0.29, p=0.004$; Fig. 2C) and no significant relation to T+ E+ arousals ($r=0.07, p=0.5$; Fig. 2D).

We further computed a GLMM with early cortical Aβ burden as dependent variable to assess whether its association with T-E+ and T+ E- arousal were truly significant and different from one another in a more complex model, regressing out age and sex. Both associations were significant with a negative link between Aβ and T-E+ arousals ($F_{1,95}=14.15, p=0.0003, R^2_{β^*}=0.13$) and a positive association between Aβ and T+ E- arousals ($F_{1,95}=8.16, p=0.0053, R^2_{β^*}=0.08$) – together with a main effect of age ($F_{1,95}=13.02, p=0.0005, R^2_{β^*}=0.12$), and no main effect of sex ($F_{1,95}=2.54, p=0.11$). Critically, a post-hoc contrast showed that the links between the two types of arousals and early cortical Aβ burden were significantly different ($t_{93}=3.73, p=0.0003$). In addition, T-E+ and T+ E- arousals are not correlated (suppl. fig. S1). Supplementary analysis showed the same statistical picture in a GLMM including all four arousal types together, with a significant post-hoc contrast when considering T-E+ and T+ E- arousals vs. early cortical Aβ burden (suppl. table S2).

**Arousals linked with better Aβ status are associated with better cognitive performance**

We then tested whether cognition, as assessed through an extensive neuropsychological test battery, was differentially associated with the two arousal types showing opposite association with early cortical Aβ burden. Pearson’s correlation revealed a significant positive correlation between global cognitive performance and T-E+ arousal index ($r=0.22, p=0.026$), but not between T+ E- arousal index and global cognition ($r=-0.15, p=0.14$). In a GLMM, the association between global cognition and T-E+ arousal index remained significant ($p=0.048, R^2_{β^*}=0.04$), on top of the education effect, but no relation with T+ E- arousals index ($p=0.25$), age, or sex (Table 1; Fig. 3).
We assessed the specificity of the findings for T-E+ arousals and considered the potential link between number of full awakenings during sleep and WASO and the different cognitive measures in separate exploratory GLMMs. We found no link between cognition and number of awakenings, while a significant negative association was detected between WASO and global cognition (F(1,95) = 4.66, p = .03) which was driven by the executive domain (F(1,95) = 7.58, p = .007) (suppl. fig. S2 & S3). Furthermore neither WASO nor number of awakening were associated with early cortical Aβ burden (suppl. fig. S4).

**Discussion**

Brain dynamics which buttress cerebral functions entail stationary and non-stationary interactions between neuronal populations. Sleep stages, which can be seen as enduring and widespread oscillatory modes sculpting brain activity, allow recurrent brief faster oscillatory activity, which sometimes lead to stage transitions. Here, we focused on spontaneous arousals because their functional correlates remain undetermined. They are usually considered to induce sleep disruption and its detrimental functional consequences. However, spontaneous sleep arousals might also carry positive effects on brain function.
functions. We quantified the prevalence of spontaneous arousals during undisturbed sleep in healthy individuals in late midlife (N = 101), and assessed whether it was associated with early cortical Aβ deposition and cognitive performance. Based on the theoretical concept that sleep arousals are diverse, we classified them according to their temporal association with a change in muscular tone and a sleep stage transition. Based on this straightforward phenotyping in a large data sample we provide the first empirical evidence that different types of sleep arousals have distinct correlates in terms of cognition and brain amyloid burden. Indeed, we found that arousals associated with sleep transitions (T + E-) are associated with higher cortical Aβ deposition in brain regions affected early on by AD neuropathology, suggesting their association with sleep fragmentation and worse brain status. By contrast and unexpectedly, the more prevalent T-E + arousals, which do not result in sleep transitions, are all the more frequent as Aβ deposition is low and cognitive performance superior, particularly in the attentional domain. This arousal type is therefore associated to a more favourable brain and cognitive status. This is of particular importance since arousals have been reported to increase with age, and age represents the most important risk factor for cognitive decline and AD.

Our analyses show that the main characteristic differentiating the two types of arousals is whether or not they lead to a sleep stage transition. A second important criterion consisted of the concomitant increase in EMG tone. Aside from their different links with Aβ burden and cognition, T + E- and T-E + arousals are not correlated with each other and differ in their spectral composition: T + E- bear a larger proportion of theta and alpha power while T-E + arousal are composed of a higher proportion of beta power. The reason why T-E- and T + E+ arousals are not significantly associated with Aβ and cognition is unclear and might reside in diverging effects of sleep transitions and EMG bursts, which would obscure the relationship. Future studies are warranted to further investigate this issue.

Two hypotheses can be put forward to explain the heterogeneity in arousals. On the one hand, all arousals, triggered by a common set of brain areas, might be part of a continuum in which each arousal is characterised by the intensity in its driving neural activity, its spectral composition, its associated muscular tone and its probability of sleep stage transition. Alternatively, the two arousal types are distinct physiological events prompted by different triggering brain structures and propagation cerebral networks. Oddly enough, the origin of spontaneous arousals remains elusive. Recent fMRI data showed that subcortical regions (including the thalamus, midbrain, basal ganglia and cerebellum) were activated during non-REM (NREM) arousals while cortical regions were deactivated. A recent yet-to-be-reviewed study in rodents provides evidence that arousals leading to sleep state transition are, at least partly driven by the locus coeruleus (LC), brainstem source of norepinephrine with strong and ubiquitous influence on distant cortical brain regions, including during sleep. In addition, optogenetic stimulation of the LC causes immediate sleep-to-wake transitions, from both NREM and REM sleep and results in high-frequency EEG activity. Hence, subcortical activity, for instance in the LC, could underlie transition-arousals while no-transition arousals could also merely be the reflection of cortico-cortical or thalamo-cortical interplay. Identifying the brain sources of the two types of arousals would require invasive
animal testing, coupling EEG to fMRI recordings in humans, or source reconstruction of high density EEG signals. The cellular and molecular underpinnings of the distinct relationship between the two types of arousals, Aβ burden, and cognition are currently unknown. We can reasonably speculate that T+E- arousals have potentially deleterious impacts. Firstly, they interrupt a sleep stage and consequently all its associated cellular phenomena, like plasticity. Secondly, it seems possible that they considerably increase cellular activity in diffused cerebral regions, a condition conducive to increase Aβ release. By contrast, T-E+ arousals might promote Aβ clearance, hypothetically by increasing the pulsatility of cortical penetrating arteries. Additionally, T-E+ arousals might offer recurring opportunities to transiently synchronise distant brain areas, in frequency bands otherwise related to cognition (beta oscillations) without enduringly disrupting the underlying brain oscillations (i.e. sleep state), similarly to what sleep spindles allow over sigma band (12-16Hz) oscillations. In complex dynamics wordings, T-E+ arousals can be seen as distinct dynamics generated when the oscillatory trajectory is trapped in a local submanifold of an attractor. These transient oscillations give rise to dynamic instability despite the fact that the global manifold does not change. Dynamic instability is a form of complexity in neuronal systems, which is critical for adaptive brain functions such as selection in self-organising systems, learning or memory. On the other hand, T+E- arousals would represent a distinct type of complexity, where the involvement of the brainstem would lead to a change in oscillatory regime through a change in the attractor manifold. Similar transient oscillations have been previously reported during wakefulness and related to cognition. Further studies are needed to unravel whether higher T+E-/lower T-E+ arousal indexes are facilitating Aβ aggregation or if, conversely, accumulating Aβ burden is disrupting sleep processes. Data in young individuals, in which current Aβ detection is typically negative, as well as longitudinal studies are needed to address this issue.

We emphasise that (1) our cohort only comprised healthy individuals, devoid of SDB, and (2) we focused on spontaneous arousals, which are not generated in response to an endogenous or exogenous perturbation (e.g. apnoea or noise). Therefore, our findings probably do not apply to perturbation-induced arousals and their negative behavioural and neurodegenerative aftermaths. It is tantalising to suggest, and empirically testable, that arousals found in SDB mostly consist in transition-arousals which would contribute in part to the higher risk for AD reported in SDB. We further found no significant link between early Aβ burden and the number of full night-time awakenings during sleep or with time spent awake after sleep onset, two markers related to the fragmentation of sleep macrostructure defining in part sleep quality. The associations we find with Aβ burden in healthy late midlife appear therefore to be stronger with, if not specific to, sleep arousals, as compared to other indices of wakefulness during sleep or fragmentation of sleep. This contrast with a previous actigraphy study that reported correlations between WASO and Aβ burden in participants older than those included here (mean: 76.7 ± 3.5y). Our findings may therefore suggest that, at a younger age (~59y), the detrimental association between sleep quality and AD neuropathology initially concerns transition-arousals leading to sleep macrostructure fragmentation, before being subsequently detected over other markers of sleep fragmentation.
Sleep arousals may connect the sleeper’s brain with the surrounding endogenous and exogenous relevant incoming information and contribute to elements of cortico-cortical information processing\textsuperscript{17,34}. as done through sleep spindles, another fundamental feature of sleep microstructure\textsuperscript{33}. Our findings constitute the first empirical evidence of the conceptual existence of different arousal types differently associated to important parameters of cognitive and brain health\textsuperscript{17}. Sleep micro-fragmentation, as easily indexed by automatic detection of spontaneous arousals, could therefore constitute a marker of favourable brain and cognitive trajectory in clinical practice, at least in late midlife adults and/or in individuals with still early AD neuropathology.

**Methods**

The study was registered with EudraCT 2016-001436-35. All procedures were approved by the Hospital-Faculty Ethic Committee of ULiège.

**Study design and participants**

Participants signed an informed consent prior to participating. In order to ensure the presence of at least some Aβ brain deposit\textsuperscript{24}, we targeted healthy older individuals aged 50-70y. 208 volunteers were recruited, of which 101 participated in the actual study (Table 1), the rest being excluded due to one of the following exclusion criteria: clinical symptoms of cognitive impairment (Dementia rating scale < 130; Mini Mental State Examination < 27); Body Mass Index (BMI) ≤ 18 and ≥ 29; recent psychiatric history or severe brain trauma; medication affecting the central nervous system; smoking; excessive alcohol (> 14 units/week) or caffeine (> 5 cups/day) consumption; shift work in the past 6 months; transmeridian travel in the last 2 months. Participants were screened for sleep apnoea/hypopnoea syndrome during an in-lab night of sleep under polysomnography; volunteers with apnoea/hypopnea index ≥ 15/h were excluded. One volunteer was excluded from analyses that included amyloid-beta data due to corrupted PET-scan data caused by technical issues during acquisition. Demographic characteristics of the study sample can be found in Table 2.
Table 2

**Sample characteristics of our dataset (mean ± SD)**

**N = 101.** T: arousals associated (T+) or not (T-) with a sleep stage transition; E: arousals associated (E+) or not (E-) with an increase in EMG signal; Indexes correspond to hourly density. Nd/hr: number detected per hour of sleep.

| Sex                      | 68 ♂ / 33 ♀ |
|--------------------------|-------------|
| Age (y)                  | 59.4 ± 5.3  |
| Education (y)            | 15.2 ± 3    |
| Dementia rating scale (N = 97) | 142.5 ± 1.9 |
| BMI (kg/m$^2$)           | 24.6 ± 2.9  |
| Apnoea/hypopnoea index (nd/hr) | 3.1 ± 2.9 |
| PLMS (nd/hr)             | 5.3 ± 15.4  |
| TST (min)                | 393.2 ± 45.9|
| WASO (min)               | 49.3 ± 37.2 |
| Awakenings index (nd/hr) | 1.7 ± 0.8   |
| % N1                     | 6.2 ± 2.7   |
| % N2                     | 51.6 ± 8.8  |
| % N3                     | 19.1 ± 6.4  |
| % REM                    | 23.1 ± 6.8  |
| Total arousal index (nd/hr) | 27.6 ± 9  |
| * T- arousals            | 22.9 ± 8    |
| * T-E-                   | 14.7 ± 6    |
| * T-E+                   | 8 ± 4       |
| * T + arousals           | 3 ± 1       |
| * T + E-                 | 1 ± 1       |
| * T + E+                 | 2 ± 1       |
| * E- arousals            | 16 ± 7      |
| * E+ arousals            | 10 ± 4      |

Sleep assessment
Participants were required to follow a regular sleep-wake schedule (± 30 min) for 1 week based on their preferred bed and wake-up times. Compliance was verified using sleep diaries and wrist actigraphy (Actiwatch©, Cambridge Neurotechnology, UK). Participants then joined the laboratory ~ 6.5h prior to habitual sleep time and were maintained in dim-light thereafter. Undisturbed habitual sleep was recorded with N7000 amplifiers (EMBLA, Natus, Planegg, Germany) using 11 EEG derivations placed according to the 10–20 system (F3, Fz, F4; C3, Cz, C4; P3, Pz, P4; O1, O2), 2 bipolar electrooculogram (EOGs), and 2 bipolar submental electromyogram (EMG) electrodes. Recordings were sampled at 200 Hz, and re-referenced to the mean of the two mastoids.

**Arousal detection**

Sleep stage scoring and arousal detection were carried out in separate steps by two independent algorithms. Sleep stage scoring was performed in 30s windows using a validated algorithm (ASEEGA, Physip, Paris, France)\(^3\). Automatic arousal detection was then computed as it is objective, reproducible and time-saving\(^3\). We used an individually tailored algorithm based on the American Academy of Sleep Medicine (AASM) definition\(^1\).

In brief, arousal detection is performed over whole-night recordings split into 1s epoch in two successive steps computed over the power in the broad-alpha (7-13Hz), beta (16-30Hz) and lower-theta (3-7Hz) frequency bands. A fixed threshold is first applied to detect abnormal EEG activity relatively to the whole-night recording: any 1s epoch with power in any of the three frequency bands higher than the whole-night median value in each frequency band is considered as a potential arousal. The second step adapts the threshold to account for the specific EEG background activity in a shorter time window. A specific threshold is computed for each 30s window: all 1s epochs without concomitant EMG tone increase are selected, as well as the first ten 1s epochs without EMG increase before and after the 30s window being evaluated; threshold of each frequency band consists in the median power over the selected 1s epochs. Events composed of at least 3 consecutive 1s epochs with changes in EEG frequencies higher than twice the local median and one median of the whole recording for that frequency band were considered as arousals. For detailed explanations on the method, see\(^3\).

**MRI data**

Quantitative multi-parametric MRI acquisition was performed on a 3-Tesla MR scanner (Siemens MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany). Quantitative maps were obtained by combining images using different parameters sensitive to distinct tissue properties. Multi-parameter mapping was based on multi-echo 3D fast low angle shot at 1 mm isotropic resolution\(^4\). This included three datasets with T1, proton density (PD), and magnetization transfer (MT)–weighted contrasts imposed by the choice of the flip angle (FA = 6° for PD & MT, 21° for T1) and the application of an additional off-resonance Gaussian-shaped RF pulse for the MT-weighted acquisition. MRI multi-parameter maps were processed with the hMRI toolbox\(^5\) (http://hmri.info) and SPM12 (Welcome Trust Centre for Neuroimaging, London, UK) to obtain notably a quantitative MT map as well as segmented images (grey matter, white matter, CSF), normalised to the standard MNI space using unified...
Flow-field deformation parameters obtained from DARTEL spatial normalisation of the MT maps were applied to averaged co-registered PET images. Volumes of interest were determined using the automated anatomical labelling (AAL) atlas.

**PET-scan**

Aβ PET imaging was performed using $[^{18}\text{F}]$Flutemetamol, except for 3 volunteers for which $[^{18}\text{F}]$Florbetapir was used. PET-scans were performed on an ECAT EXACT + HR scanner (Siemens, Erlangen, Germany). Participants received a single dose of the radioligand in the antecubital vein (target dose 185 MBq); images acquisition started 85min after the injection and consisted of 4 frames of 5 minutes, followed by a 10 minutes transmission scan using $^{68}\text{Ge}$ line sources. Images were reconstructed using filtered back-projection algorithm including corrections for measured attenuation, dead time, random events, and scatter using standard software (Siemens ECAT – HR + V7.1, Siemens/CTI Knoxville, TN, USA). Individual PET average images were produced using all frames and were then manually reoriented according to Magnetisation Transfer (MT)-weighted structural MRI volumes (for MRI acquisition and processing method, see supplementary data) and coregistered to the individual space structural MT map. Standardised uptake value ratio (SUVR) was computed using the whole cerebellum as reference region. As images were acquired using 2 different radioligands, their SUVR values were converted into Centiloid Units. Aβ burden was averaged over a composite mask covering the previously reported earliest aggregation sites for Aβ pathology, that is: frontal medial cortex and basal part of temporal lobe (fusiform & inferior temporal gyri).

**Cognitive assessment**

A cognitive battery of neuropsychological tasks was carried out in two sessions, while well-rested. A first session of ~1h was performed in the afternoon prior to the sleep assessment, approximately 7.5h before habitual bedtime, and a second session of ~1.5h was performed on another day (between 12 and 6h prior to habitual bedtime). From those two sessions, three domain-specific composites scores were computed for the memory, executive function, and attentional domains, and consisted of the standardised sum of the standardised domain-specific scores, where higher values indicate better performance. A fourth global cognitive score consisted of the standardised sum of the domain-specific composite scores. Procedures are as in.

A first session of approximately one hour was performed in the afternoon prior to the sleep assessment, approximately 7.5h before habitual bedtime, and comprised: (1) Mnemonic Similarity Task (MST); (2) Category Verbal Fluency (letter and animals); (3) Digit Symbol Substitution Task (DSST); (4) Visual N-back Task (1, 2 and 3-back variants); and (5) Choice Reaction Time (CRT). A second session of ~1.5h was performed on another day (between 12 and 6h prior to habitual bedtime) and comprised: (1) Direct and Inverse Digit Span Task; (2) Free and Cued Selective Reminding Test (FCSRT); (3) a computerised version of the Stroop Test; (4) Trail Making Test (TMT) and (5) D2 Attention Test.
Composite scores were computed for the memory, executive function, and attentional domains, and consisted of the standardised sum of the standardised, domain-specific scores, where higher scores indicate better performances. The memory score consisted of the FCSRT (sum of all 4 free recalls) and the recognition memory score from the MST. The executive function score included Verbal Fluency tests (letter and animals score for 2min), inverse order digit span, TMT (part B), N-back (3-back variant) and Stroop Test (interfering items errors). The attentional score comprised the DSST, TMT (part A), N-back (1-back variant), D2 (Gz-F) and CRT (reaction time to dissimilar items).

Statistical analyses

Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) using Generalised Linear Mixed Models (GLMMs). The distribution of dependent variables was determined by fitting all parametric probability distributions to data, using the “allfitdist” function in Matlab (http://amir.eng.uci.edu/MvCAT.php) and GLMMs were adapted accordingly. Subject was treated as a random factor (intercept): each model included sex and age as covariates, as well as education where relevant. Statistical significance threshold was set at $p < 0.05$. Kenward-Roger’s correction was used to determine degrees of freedom. Semi-partial $R^2 (R^2_{\beta*})$ values were computed to estimate the effect sizes of significant fixed effects and statistical trends in all GLMMs.

Declarations

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Competing interests:

The authors declare no conflict of interest.

Author contributions:
Study concept and design: E.S., P.M., C.P., C.B., F.C. and G.V. Data acquisition, analysis and interpretation: all authors. D.C. and G.V. drafted the first version of the manuscript. All authors revised the manuscript, and had final responsibility for the decision to submit for publication.

**Data availability**

The dataset, including deidentified participant data, can be made available upon request after approval of a proposal with a signed data access agreement. In order to access the data, the requestor may contact the corresponding author.

**References**

1. Luyster, F. S., Strollo, P. J., Zee, P. C. & Walsh, J. K. Sleep: A health imperative. *Sleep* **35**, 727–734 (2012).
2. Landolt, H. P., Dijk, D. J., Achermann, P. & Borbély, A. A. Effect of age on the sleep EEG: Slow-wave activity and spindle frequency activity in young and middle-aged men. *Brain Res.* **738**, 205–212 (1996).
3. Redline, S. et al. The Effects of Age, Sex, Ethnicity, and Sleep-Disordered Breathing on Sleep Architecture. *Arch. Intern. Med.* **164**, 406–418 (2004).
4. Van Egroo, M. et al. Sleep-wake regulation and the hallmarks of the pathogenesis of Alzheimer’s disease. *Sleep* **42**, 1–13 (2019).
5. Ju, Y. E. S., Lucey, B. P. & Holtzman, D. M. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat. Rev. Neurol.* **10**, 115–119 (2014).
6. Spira, A. P. et al. Self-reported sleep and β-amyloid deposition in community-dwelling older adults. *JAMA Neurol.* **70**, 1537–1543 (2013).
7. Branger, P. et al. Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. *Neurobiol. Aging* **41**, 107–114 (2016).
8. Sprecher, K. E. et al. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology* **89**, 445–453 (2017).
9. Carvalho, D. Z. et al. Association of excessive daytime sleepiness with longitudinal β-Amyloid accumulation in elderly persons without dementia. *JAMA Neurol.* **75**, 672–680 (2018).
10. Ju, Y. S. et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-b levels. *Brain* **140**, 2104–2111 (2017).
11. Mander, B. A. et al. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat. Neurosci.* **18**, 1051–1057 (2015).
12. Ju, Y. S. et al. Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. **80**, 154–159 (2016).
13. Varga, A. W. et al. Reduced Slow-Wave Sleep Is Associated with High Cerebrospinal Fluid Aβ42 Levels in Cognitively Normal Elderly. *Sleep* **39**, 2041–2048 (2016).
14. Ooms, S. *et al.* Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men a randomized clinical trial. *JAMA Neurol.* **71**, 971–977 (2014).

15. Lucey, B. P.* et al.* Effect of sleep on overnight cerebrospinal fluid amyloid β kinetics. *Ann. Neurol.* **83**, 197–204 (2018).

16. Scullin, M. K. & Bliwise, D. L. Sleep, Cognition, and Normal Aging: Integrating a Half Century of Multidisciplinary Research. *Perspect. Psychol. Sci.* **10**, 97–137 (2015).

17. Halasz, P., Terzano, M., Parrino, L. & Bodizs, R. The nature of arousal in sleep. 1–23 (2004).

18. Iber, C., Ancoli-Israel, S., Chesson, A. & Quan, S. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. **3**, 752 (2007).

19. Philip, P., Strohs, R. & Guilleminault, C. Sleep Fragmentation in Normals: A Model for Sleepiness Associated With Upper Airway Resistance Syndrome. **17**, 242–247 (1994).

20. Roehrs, T., Merlotti, L., Petrucelli, N., Stepanski, E. & Roth, T. Experimental sleep fragmentation. *Sleep* **17**, 438–443 (1994).

21. Martin, S., Engleman, H., Deary, I. & Douglas, N. The effect of sleep fragmentation on daytime function. *Am. J. Respir. Crit. Care Med.* **153**, 1328–1332 (1996).

22. Rudzik, F. *et al.* Sleep spindle characteristics and arousability from nighttime transportation noise exposure in healthy young and older individuals. *Sleep* **41**, 1–14 (2018).

23. Aloia, M. S., Arnedt, J. T., Davis, J. D., Riggs, R. L. & Byrd, D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: A critical review. *J. Int. Neuropsychol. Soc.* **10**, 772–785 (2004).

24. Grothe, M. J.* et al.* In vivo staging of regional amyloid deposition. *Neurology* **89**, 2031–2038 (2017).

25. Friston, K. J. The labile brain. I. Neuronal transients and nonlinear coupling. *Philos. Trans. R. Soc. B Biol. Sci.* **355**, 215–236 (2000).

26. Tononi, G. & Cirelli, C. Sleep and the Price of Plasticity: From Synaptic to cellular Homeostasis to Memory Consolidation and Integration. **49**, 1841–1850 (2014).

27. Dang-Vu, T. T. *et al.* Spontaneous neural activity during human slow wave sleep. *Proc. Natl. Acad. Sci. U. S. A.* **105**, 15160–15165 (2008).

28. Zou, G.* et al.* Functional MRI of arousals in nonrapid eye movement sleep. *Sleep* **43**, 1–19 (2019).

29. Kjaerby, C. *et al.* Dynamic fluctuations of the locus coeruleus-norepinephrine system underlie sleep state transitions. *BioRxiv* (2020).

30. Carter, M.* et al.* Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat. Neurosci.* **13**, 1526–1533 (2010).

31. Hayat, H.* et al.* Locus coeruleus norepinephrine activity mediates sensory-evoked awakenings from sleep. *Sci. Adv.* **6**, 1–14 (2020).

32. Plog, B. A. & Nedergaard, M. The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future. *Annu. Rev. Pathol. Mech. Dis.* **13**, 379–394 (2018).

33. Steriade, M. The corticothalamic system in sleep. *Front. Biosci. a J. virtual Libr.* **8**, d878-899 (2003).
34. Friston, K. J. The labile brain. II. Transients, complexity and selection. *Philos. Trans. R. Soc. B Biol. Sci.* **355**, 237–252 (2000).

35. Bubu, O. M. *et al.* Sleep, Cognitive impairment, and Alzheimer’s disease: A Systematic Review and Meta-Analysis. (2018).

36. Ettore, E. *et al.* Relationships between objectives sleep parameters and brain amyloid load in subjects at risk to Alzheimer’s disease: the INSIGHT-preAD Study. *Sleep* **42**, 1–30 (2019).

37. Mattis, S. Mental status examination for organic mental syndrome in the elderly patients. in *Geriatric psychiatry: A handbook for psychiatrists and primary care physicians* (eds. Bellak, L. & Karasu, T.) 77–121 (1976).

38. Berthomier, C. *et al.* Automatic Analysis of Single-Channel Sleep EEG: Validation in Healthy Individuals. *Sleep* **30**, 1587–1595 (2007).

39. Chylinski, D. *et al.* Validation of an Automatic Arousal Detection Algorithm for Whole-Night Sleep EEG Recordings. *Clocks & Sleep* **2**, 258–272 (2020).

40. Weiskopf, N. & Helms, G. Multi-parameter mapping of the human brain at 1mm resolution in less than 20 minutes. *Proc. Int. Soc. Magn. Reson. Med.* **16**, 2241 (2008).

41. Tabelow, K. *et al.* hMRI – A toolbox for quantitative MRI in neuroscience and clinical research. *Neuroimage* **194**, 191–210 (2019).

42. Ashburner, J. & Friston, K. J. Unified segmentation. *Neuroimage* **26**, 839–851 (2005).

43. Ashburner, J. A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95–113 (2007).

44. Tzourio-Mazoyer, N. *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273–289 (2002).

45. Klunk, W. E. *et al.* The Centiloid project: Standardizing quantitative amyloid plaque estimation by PET. *Alzheimer’s Dement.* **11**, 1-15.e4 (2015).

46. Navitsky, M. *et al.* Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale. *Alzheimer’s Dement.* **14**, 1565–1571 (2018).

47. Battle, M. R. *et al.* Centiloid scaling for quantification of brain amyloid with [18 F]flutemetamol using multiple processing methods. *EJNMMI Res.* **8**, (2018).

48. Van Egroo, M. *et al.* Preserved wake-dependent cortical excitability dynamics predict cognitive fitness beyond age-related brain alterations. *Commun. Biol.* **2**, 1–10 (2019).

49. Stark, S. M., Yassa, M. A., Lacy, J. W. & Stark, C. E. L. A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia* **51**, 2442–2449 (2013).

50. Cardebat, D., Doyon, B., Puel, M., Goulet, P. & Joanette, Y. Évocation lexicale formelle et sémantique chez des sujets normaux: performances et dynamiques de production en fonction du sexe, de l’âge et du niveau d’étude. *Acta Neurol. Belg.* **90**, 207–217 (1990).

51. Wechsler, D. *The WAIS III – WMS III Technical Manual.* (Psychological Corporation, 1997).
52. Kirchner, W. K. Age differences in short-term retention of rapidly changing information. *J. Exp. Psychol.* **55**, 352–358 (1958).

53. Zimmermann, P. & Fimm, B. A test battery for attentional performance. in *Applied Neuropsychology of Attention: Theory, Diagnosis and Rehabilitation* (eds. Leclercq, P. & Zimmermann, P.) 110–151 (Psychology Press, 2002).

54. Grober, E., Buschke, H., Crystal, H., Bang, S. & Dresner, R. Screening for dementia by memory testing. *Neurology* **38**, 900–900 (1988).

55. Stroop, J. R. Studies of interference in serial verbal reactions. *J. Exp. Psychol.* **18**, 643–662 (1935).

56. Bowie, C. R. & Harvey, P. D. Administration and interpretation of the Trail Making Test. *Nat. Protoc.* **1**, 2277–2281 (2006).

57. Brickenkamp, R. *Test d2. Test d’attention concentrée*. (Editest, 1966).

58. Jaeger, B. C., Edwards, L. J., Das, K. & Sen, P. K. An R2statistic for fixed effects in the generalized linear mixed model. *J. Appl. Stat.* **44**, 1086–1105 (2017).