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BACKGROUND. Tight relationships between sleep quality, cognition and amyloid-beta (Aβ) accumulation, a hallmark of Alzheimer's disease (AD) neuropathology, emerge in the literature. Sleep arousals become more prevalent with ageing and are considered to reflect poorer sleep quality. Yet, heterogeneity in arousals has been suggested while their associations with Aβ and cognition are not established.

METHODS. We recorded undisturbed night-time sleep with EEG in 101 healthy individuals in late midlife (50-70y), devoid of cognitive and sleep disorders. We classified spontaneous arousals according to their association with muscular tone increase (M+/M-) and sleep stage transition (T+/T-). We assessed cortical Aβ burden over earliest affected regions via PET imaging, and cognition via extensive neuropsychological testing.

RESULTS. Arousal types differed in their oscillatory composition in theta and beta EEG bands. Furthermore, T+M- arousals, which interrupt sleep continuity, were positively linked to Aβ burden (p=.0053, R²β*=0.08). By contrast, more prevalent T-M+ arousals, upholding sleep continuity, were associated with lower Aβ burden (p=.0003, R²β*=0.13), and better cognition, particularly over the attentional domain (p<.05, R²β*≥0.04).

CONCLUSION. Contrasting with what is commonly accepted, we provide empirical evidence that arousals are diverse and differently associated with early AD-related neuropathology […]

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Research Article

Heterogeneity in the links between sleep arousals, amyloid-beta and cognition

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ABSTRACT

Background. Tight relationships between sleep quality, cognition and amyloid-beta (Aβ) accumulation, a hallmark of Alzheimer's disease (AD) neuropathology, emerge in the literature. Sleep arousals become more prevalent with ageing and are considered to reflect poorer sleep quality. Yet, heterogeneity in arousals has been suggested while their associations with Aβ and cognition are not established.

Methods. We recorded undisturbed night-time sleep with EEG in 101 healthy individuals in late midlife (50-70y), devoid of cognitive and sleep disorders. We classified spontaneous arousals according to their association with muscular tone increase (M+/M-) and sleep stage transition (T+/T-). We assessed cortical Aβ burden over earliest affected regions via PET imaging, and cognition via extensive neuropsychological testing.

Results. Arousal types differed in their oscillatory composition in theta and beta EEG bands. Furthermore, T+M- arousals, which interrupt sleep continuity, were positively linked to Aβ burden (p=.0053, $R^2\beta^*$=0.08). By contrast, more prevalent T-M+ arousals, upholding sleep continuity, were associated with lower Aβ burden (p=.0003, $R^2\beta^*$=0.13), and better cognition, particularly over the attentional domain (p<.05, $R^2\beta^*\geq$0.04).

Conclusion. Contrasting with what is commonly accepted, we provide empirical evidence that arousals are diverse and differently associated with early AD-related neuropathology and cognition. This suggests that sleep arousals, and their coalescence with other brain oscillations during sleep, may actively contribute to the beneficial functions of sleep. This warrants re-evaluation of age-related sleep changes and suggests that spontaneous arousals could constitute a marker of favourable brain and cognitive health trajectories.

INTRODUCTION

Sleep is central to health and cognition, and deteriorates with ageing (1). In addition, sleep disruption is associated with Alzheimer's disease (AD), as assessed by hyper-phosphorylated tau and amyloid-beta (Aβ) brain accumulation, most likely in a bidirectional manner (2, 3). Poorer sleep quality(4), daytime sleepiness (5), reduced slow-wave sleep (6, 7), and sleep deprivation (8, 9) have been linked to higher Aβ levels, but also to poorer cognitive performance (7, 10).

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 (11). Although key elements of sleep microstructure, they can also shape its macrostructure and lead to a shallower sleep stage (12). 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 (13, 14). 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 (15). By contrast, other investigations did not find such a relationship, and imputed alterations in cognition in SDB to brain hypoxia (see (15) for review). In individuals devoid of sleep pathologies, arousals evoked by auditory stimuli were reported to impact subsequent daytime alertness (16). In addition, sleep fragmentation induced by auditory stimulation is associated with higher Aβ cerebrospinal fluid (CSF) content the following day (6).

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 (11) with some authors suggest that there may be physiologic and pathologic arousals. Understanding their respective roles might shed light on the

4

85   adaptive properties of the sleeping brain and provide insight into pathological mechanisms associated with

86   sleep disturbances (11).

87   Here, we assessed whether different types of spontaneous arousals during sleep were differentially associated

88   with Aβ cortical deposition and cognitive performance in a cohort of healthy individuals in late midlife. We

89   were able to tease apart different types of arousals, based on their temporal relationships with increased

90   muscular tone and sleep stage transitions. In line with the hypothesis that arousals perturb sleep, we

91   anticipated that arousals fragmenting sleep structure would be associated with both worse cognitive

92   performance and Aβ deposition in brain areas that are first affected by this AD-related neuropathological

93   process.

94

RESULTS

96 *EEG oscillations differ across arousal types*

97 We recorded undisturbed sleep at habitual sleep times under electroencephalogram (EEG) in 101 healthy

98 individuals aged 50 to 70 y (59 ± 5y; 68 women), following one week of regular sleep-wake schedule (Figure

99 1). In order to evaluate the potential heterogeneity of arousals, we split them according to two criteria, which

100 we considered as relevant in research settings as well as clinical practice. We first chose to focus on whether

101 arousals did trigger a sleep stage transition (T+) (when they occurred within 15s of a stage change) or not (T),

102 as arousals may or may not lead to a lighter sleep stage (12) and they have already been investigated in that

103 regard (17). Secondly, we considered their salience, reflected by the concomitant increase in electromyogram

104 (EMG) tone (M+) or its absence (M-), as it is among the arousal scoring criteria (needed to score an arousal in

105 REM sleep).

106 In a first step, we assessed whether characterising sleep arousals by their association with sleep stage

107 transition (T+ or T-), and the co-occurrence of an EMG tone increase (M+) or not (M-) resulted in differences

108 in their oscillatory properties. We computed individual relative power in the different EEG frequency bands

109 defining an arousal (theta - 4.5-7.5Hz, alpha – 8.5-11.5Hz, and beta – 16.5-29.5Hz). A generalised linear

110 mixed model (GLMM) with relative power as dependent variable (and adjusted for data distribution), first

111 indicated that relative power changed across frequency bands ($F_{2,294.1}=403.84$, $p<0.0001$, $R^2_{\beta*}=0.73$). More

112 importantly, it yielded a triple interaction between transition, EMG status and frequency band ($F_{2,880}=3.39$,

113 $p=0.034$, $R^2_{\beta*}=0.008$) implying that arousals differ in their spectral composition based on the presence or

114 absence of EMG changes and sleep stage transition (Figure 2A). This was further reflected in main effects of

115 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

116 as in interactions between transition and frequency band ($F_{2,709.5}=34.62$, $p<0.0001$, $R^2_{\beta*}=0.09$), between EMG

117 status and frequency band ($F_{2,979,2}=187.39$, $p<0.0001$, $R^2_{\beta*}=0.28$), and between EMG status and transition

118 ($F_{1,879.3}=22.55$, $p<0.0001$, $R^2_{\beta*}=0.025$). Based on this first analysis, we therefore concluded that the factors of

119 arousal heterogeneity eloquently define 4 types of arousals (T+M+, T+M-, T-M+, T-M-). We finally note that

120   multiple post-hoc comparisons within each band yielded significant differences across arousal types over the

121   theta and beta bands (see Table 1).

122   ***Arousals heterogeneity reflects different associations with Aβ burden***

123   In line with our goal to consider very early AD-related neuropathological process, Aβ burden was quantified

124   over the regions previously reported as the earliest cortical aggregation sites[18], that is the frontal medial

125   cortex and basal part of temporal lobe (fusiform & inferior temporal gyri) in all but one participant. We tested

126   in a GLMM whether associations between arousal density varied with transition (T+, T-) and EMG (M+, M-)

127   statuses and were associated with Aβ burden, while regressing out age and sex effects. We first observed a

128   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,

129     $R^2_{β*}$=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),

130   indicating that density of arousal types significantly varied. Interestingly, we did not find any significant main

131   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).

132   Critically, the GLMM yielded a significant triple interaction between early cortical Aβ burden, EMG status

133   and transition ($F_{1,196}$=7.16, p=0.008, $R^2_{β*}$=0.035) implying that the association between arousals and early

134   cortical Aβ burden depends on the concomitant change in muscular tone and sleep stage transition. The

135   heterogeneity in spontaneous arousals was further reflected by the significant interactions between early

136   cortical Aβ burden and EMG status ($F_{1,98}$=8.64, p=0.004, $R^2_{β*}$=0.08). Figure 3 decomposes the associations

137   between each of the four types of arousals and early cortical Aβ burden.

138   We further computed a GLMM with early cortical Aβ burden as dependent variable to explore whether its

139   association with T-M+ and T+M- arousal truly differed in the part of Aβ burden variance they explained in a

140   more complex model, regressing out age and sex. Both associations were significant with a negative link

141   between Aβ and T-M+ arousals ($F_{1,95}$=14.15, p=0.0003, $R^2_{β*}$=0.13) and a positive association between Aβ and

142   T+M- arousals ($F_{1,95}$=8.16, p=0.0053, $R^2_{β*}$=0.08) – together with an expected main effect of age ($F_{1,95}$=13.02,

143   p=0.0005, $R^2_{β*}$=0.12) [19], and no main effect of sex ($F_{1,95}$=2.54, p=0.11). Critically, a post-hoc contrast

144 showed that the links between the two types of arousals and early cortical Aβ burden were significantly

145 different (t_{93}=3.73, p=0.0003). In addition, T-M+ and T+M- arousals were not correlated (Figure 2B).

146 Supplementary analysis showed the same statistical picture in a GLMM including all four arousal types

147 together, with a significant post-hoc contrast when considering T-M+ and T+M- arousals vs. early cortical Aβ

148 burden (Table 2). Results were not driven by arousals occurring in non-Rapid Eye Movement (NREM) or

149 REM sleep as statistical outputs were the same if we considered the four types of arousals in NREM/REM

150 separately (M+ only in REM as arousal definition is REM requires change in muscle tone) (Table 2).

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

152 We then tested whether cognition, as assessed in a global index through an extensive neuropsychological test

153 battery, was differentially associated with the two arousal types showing opposite association with early

154 cortical Aβ burden. In a GLMM, the association between global cognition and T-M+ arousal index was found

155 to be significant (p=0.048, $R^2_{β*}$=0.04), on top of the education effect, but no relation with T+M- arousal index

156 (p=0.25), age, or sex (Table 3; Figure 4) was found. Additional exploratory GLMMs with each specific

157 cognitive domain in turn showed this association was driven by the attentional domain (p=0.032, $R^2_{β*}$=0.047),

158 and was not significant for the executive (p=0.09) or memory domains (p=0.91).

159 We assessed the specificity of the findings for T-M+ arousals and considered the potential link between

160 number of full awakenings during sleep and wake after sleep onset (WASO) and the different cognitive

161 measures in separate exploratory GLMMs. We found no link between cognition and number of awakenings

162 (Figure 5, A-D), while a significant negative association was detected between WASO and global cognition

163 ($F_{(1,95)}$=4.66, p=0.03) which was driven by the executive domain ($F_{(1,95)}$=7.58, p=.007) (Figure 5, E-H).

164 Furthermore, neither WASO nor number of awakening were associated with early cortical Aβ burden (Figure

165 5, I and J**)**.

166

167

DISCUSSION

Brain dynamics which buttress cerebral functions entail stationary and non-stationary interactions between neuronal populations (20). 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 (21, 22). 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, i.e. not elicited by identifiable event, might also carry positive effects on brain functions. We quantified the prevalence of spontaneous arousals during undisturbed sleep in healthy individuals in late midlife, and assessed whether it was associated with early cortical Aβ deposition and cognitive performance. Based on the theoretical concept that sleep arousals are diverse (11), we classified them according to their temporal association with a change in muscular tone and a sleep stage transition. These criteria were deemed clinically relevant as arousals may or may not affect sleep macrostructure while muscular tone constitutes an arousal marker in REM. 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+M-) 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, the more prevalent T-M+ 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. Although sizes of the effects we detected remain modest, enduring small phenomenon can shape lifelong trajectories. The present findings may therefore be 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 (2).

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

9

193   tone. Aside from their different links with Aβ burden and cognition, T+M- and T-M+ arousals are not

194   correlated with each other and differ in their spectral composition: T+M- bear a larger proportion of theta

195   power while T-M+ arousal are composed of a higher proportion of beta power. The reason why T-M- and

196   T+M+ arousals are not significantly associated with Aβ and cognition is unclear and might reside in different

197   prevalence or in diverging effects of sleep transitions and EMG bursts, which would hinder the relationship.

198   Future studies are warranted to further investigate this issue.

199   Two hypotheses can be put forward to explain the heterogeneity in arousals. On the one hand, all arousals,

200   triggered by a common set of brain areas, might be part of a continuum in which each arousal is characterised

201   by the intensity in its driving neural activity, its spectral composition, its associated muscular tone and its

202   probability of sleep stage transition. Alternatively, the two arousal types are distinct physiological events

203   prompted by different triggering brain structures and propagation cerebral networks. Oddly enough, the origin

204   of spontaneous arousals remains elusive. Recent fMRI data showed that subcortical regions (including the

205   thalamus, midbrain, basal ganglia and cerebellum) were activated during non-REM arousals while cortical

206   regions were deactivated (23). A recent yet-to-be-reviewed study in rodents provides evidence that arousals

207   leading to sleep state transition are, at least partly driven by the locus coeruleus (LC), brainstem source of

208   norepinephrine with strong and ubiquitous influence on distant cortical brain regions, including during sleep

209   (24). In addition, optogenetic stimulation of the LC causes immediate sleep-to-wake transitions, from both

210   NREM and REM sleep and results in high-frequency EEG activity (25). Hence, subcortical activity, for

211   instance in the LC, could underlie transition-arousals while no-transition arousals could also merely be the

212   reflection of cortico-cortical or thalamo-cortical interplay (11). Identifying the brain sources of the two types

213   of arousals would require invasive animal testing, coupling EEG to fMRI recordings in humans, or source

214   reconstruction of high density EEG signals (22).

215   The cellular and molecular underpinnings of the distinct relationship between the two types of arousals, Aβ

216   burden, and cognition are currently unknown. We can reasonably speculate that T+M- arousals have 2

217   potentially deleterious impacts. Firstly, they interrupt a sleep stage and consequently all its associated cellular

218   phenomena, like plasticity (21). Secondly, it seems possible that they considerably increase cellular activity in

219   diffused cerebral regions, a condition conducive to increase Aβ release. By contrast, one could tentatively

220   speculate that T-M+ arousals promote Aβ clearance, hypothetically by increasing the pulsatility of cortical

221   penetrating arteries (26). Additionally, T-M+ arousals might offer recurring opportunities to transiently

222   synchronise distant brain areas, in frequency bands otherwise related to cognition during wakefulness (e.g.

223   beta oscillations (27)) without enduringly disrupting the underlying brain oscillations (i.e. sleep state),

224   similarly to what sleep spindles allow over sigma band (12-16Hz) oscillations (28). In complex dynamics

225   wordings, T-M+ arousals can be seen as distinct dynamics generated when the oscillatory trajectory is trapped

226   in a local submanifold of an attractor (29), meaning the arousal would represent only a temporary breakout

227   from the global oscillatory regime. These transient oscillations give rise to dynamic instability despite the fact

228   that the global manifold does not change. Dynamic instability is a form of complexity in neuronal systems,

229   which is critical for adaptive brain functions such as selection in self-organising systems, learning or memory

230   (20). On the other hand, T+M- arousals would represent a distinct type of complexity, where the involvement

231   of the brainstem would lead to a change in oscillatory regime through a change in the attractor manifold.

232   Similar transient oscillations have been previously reported during wakefulness and related to cognition(20).

233   Further studies are needed to unravel whether higher T+M-/lower T-M+ arousal indexes are facilitating Aβ

234   aggregation or if, conversely, accumulating Aβ burden is disrupting sleep processes (2). Data in young

235   individuals, in which current Aβ detection is typically negative (18), as well as longitudinal studies are needed

236   to address this issue.

237   We emphasise that (1) our cohort only comprised healthy individuals, devoid of SDB, and (2) we focused on

238   spontaneous arousals, which are not generated in response to detectable endogenous or exogenous

239   perturbation (e.g. apnoea or noise). Therefore, our findings probably do not apply to potentially more

240   prevalent perturbation-induced arousals and their negative behavioural (15, 16) and neurodegenerative

241   aftermaths (6). We also underline that we aimed to investigate links between sleep and Aβ burden early on in

242   this neuropathological process, therefore our volunteers did not show large Aβ deposition (only 5 could be

243   considered as Aβ positive). Although Aβ is a hallmark of AD neuropathology, we do not know which

244   volunteer will develop AD and therefore which one can be considered to undergo a true AD process or an

245   AD-like or AD-related process. As for any Aβ signal, its predictive value remains debated. It is tantalising to

246   suggest, and empirically testable, that arousals found in SDB mostly consist in transition-arousals which

247   would contribute in part to the higher risk for AD reported in SDB (30). We further found no significant link

248   between early Aβ burden and the number of full night-time awakenings during sleep or with time spent awake

249   after sleep onset, two markers related to the fragmentation of sleep macrostructure defining in part sleep

250   quality. The associations we find with Aβ burden in healthy late midlife appear therefore to be stronger with,

251   if not specific to, sleep arousals, as compared to other indices of wakefulness during sleep or fragmentation of

252   sleep. This contrast with a previous actigraphy study that reported correlations between WASO and Aβ

253   burden in participants older than those included here (mean: $76.7\pm3.5y$) (31). Our findings may therefore

254   suggest that, at a younger age (~59y), the detrimental association between sleep quality and AD

255   neuropathology initially concerns transition-arousals leading to sleep macrostructure fragmentation, before

256   being subsequently detected over other markers of sleep fragmentation.

257   Sleep arousals may connect the sleeper's brain with the surrounding endogenous and exogenous relevant

258   incoming information and contribute to elements of cortico-cortical information processing (11, 29) as done

259   through sleep spindles, another fundamental feature of sleep microstructure (28). In other words, our findings

260   suggest that sleep arousals, and their coalescence with other brain oscillations during sleep, may actively

261   contribute to the beneficial functions of sleep. Arousals may interact with spindles and slow waves, however,

262   so that we cannot rule out a contribution of these events to the effects we report. Future research should assess

263   whether arousals are predictors of Aβ burden independent of other known neurophysiological

264   elements/oscillations of sleep linked to cognition and brain health. Visual inspection of the data indicates that

265   despite occasional co-occurrence, slow wave are not strongly nor systematically associated with any type of

266   arousals. Our findings constitute the first empirical evidence of the conceptual existence of different arousal

267   types differently associated to important parameters of cognitive and brain health (11). Sleep micro-

268   fragmentation, as easily indexed by automatic detection of spontaneous arousals, could therefore potentially

269   constitute a marker of favourable brain and cognitive trajectory in clinical practice, at least in late midlife

270   adults and/or in individuals with still early AD-related neuropathology.

271

SUBJECTS/MATERIALS AND METHODS

Study design and participants

In order to target early Aβ brain deposit (18), we recruited healthy older individuals aged 50-70y. 208 volunteers were recruited, of which 101 participated in the actual study (Table 4), 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; documented/diagnosed sleep pathologies such as insomnia and REM behaviour disorder; 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 (PSG) preceding the one that was analysed in the results section of this paper. This PSG included EEG (Fz, Cz, C3, PZ, Oz), 2 bipolar electrooculogram (EOGs), and 2 bipolar submental EMG electrodes, 2 bipolar electrocardiogram (ECGs), 2 sets of bipolar leg electrodes, thorax and abdominal belts, an oximeter, a nasal canula as well as a snoring sensor. As is typically done in similar sleep studies (7, 32), volunteers with an apnoea/hypopnea index ≥ 15/h were excluded (79 subjects had an AHI ≥0 and <5; 19 subjects had an AHI ≥5 and <10; 3 subjects had an AHI ≥10 and <15). Given the low arousal index of our volunteers and the low rate of PLMS in our sample (9 subjects had a PLM index ≥15), and given that controlling for those two covariates did not change the statistically significant associations we found in the reported models, we did not include them in the statistical analyses reported below. 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 4.

Sleep assessment

295   Participants came to the lab for an adaptation night under polysomnography after which those with sleep an

296   apnoea/hypopnoea index ≥15/h were excluded from further participation. Volunteers were required to follow

297   a regular sleep-wake schedule (±30 min) for 1 week based on their preferred bed and wake-up times before

298   sleep EEG recording, in order to record their sleep in settings as close as possible to habitual conditions.

299   Compliance was verified using sleep diaries and wrist actigraphy (Actiwatch©, Cambridge Neurotechnology,

300   UK). Participants then joined the laboratory ~6.5h prior to habitual sleep time and were maintained in dim-

301   light thereafter. Undisturbed habitual sleep was recorded with N7000 amplifiers (EMBLA, Natus, Planegg,

302   Germany) using 11 EEG derivations placed according to the 10-20 system (F3, Fz, F4; C3, Cz, C4; P3, Pz,

303   P4; O1, O2), 2 bipolar electrooculogram (EOGs), and 2 bipolar submental electromyogram (EMG) electrodes.

304   Recordings were sampled at 200 Hz, and re-referenced to the mean of the two mastoids.

305   *Arousal detection*

306   Sleep stage scoring and arousal detection were carried out in separate steps by two independent algorithms.

307   Sleep stage scoring was performed in 30s windows using a validated algorithm (ASEEGA, Physip, Paris,

308   France) (33, 34). Automatic arousal detection was then computed as it is objective, reproducible and time-

309   saving (35). We used an individually tailored validated algorithm based on the American Academy of Sleep

310   Medicine (AASM) definition (12) of arousal but without using sleep stage information. Automatic scorings

311   were visually inspected following computation.

312   In brief, arousal detection is performed over all electrodes on whole-night recordings split into 1s epoch in

313   two successive steps computed over the power in the broad-alpha (7-13Hz), beta (16-30Hz) and lower-theta

314   (3-7Hz) frequency bands, excluding the sigma band (11-16Hz), i.e. corresponding to frequency of sleep

315   spindles, which cannot be considered as arousals. A fixed threshold is first applied to detect abnormal EEG

316   activity relatively to the whole-night recording: any 1s epoch with power in any of the three frequency bands

317   higher than the whole-night median value in each frequency band is considered as a potential arousal. The

318   second step adapts the threshold to account for the specific EEG background activity in a shorter time

15

319 window. A specific threshold is computed for each 30s window: all 1s epochs without concomitant EMG tone

320 increase are selected, as well as the first ten 1s epochs without EMG increase before and after the 30s window

321 being evaluated; threshold of each frequency band consists in the median power over the selected 1s epochs.

322 Events composed of at least 3 consecutive 1s epochs with changes in EEG frequencies higher than twice the

323 local median and one median of the whole recording for that frequency band were considered as arousals. For

324 detailed explanations on the method, see (35).

325 In order to evaluate the potential heterogeneity of arousals, we split them according to two criteria, which we

326 considered as relevant in research settings as well as clinical practice. Firstly, whether arousals did trigger a

327 sleep stage transition (T+) (when they occurred within 15s of a stage change – in the second half of an epoch

328 preceding a stage change or in the first half of an epoch assigned a different stage than the previous epoch) or

329 not (T-); and secondly, their salience, reflected by the concomitant increase in EMG tone (M+) or its absence

330 (M-).

331 Spectral analysis of arousals' power was carried out through a time-frequency analysis on the first 3 seconds

332 of arousals using Morlet's wavelet transform in SPM12

333 (https://github.com/spm/spm12/blob/master/spm_eeg_specest_morlet.m) on Fz electrode. Detrending was

334 done over the 500ms prior to arousal event. Data was then averaged per arousal type prior to summing in the

335 typical EEG bands that may compose an arousal (theta - 4.5-7.5Hz, alpha – 8.5-11.5Hz, and beta – 16.5-

336 29.5Hz). Given the variety of factors that impact total power (e.g. conductivity of the involved tissues, i.e.

337 scalp, skull, CSF etc) (36) and thus renders it complex to compare across subjects, relative power of each

338 band was computed through a normalisation relative to 0.5-to-30Hz total power.

339 *MRI data*

340 MRI data was used in order to determine the region of interest used for extraction of Aβ burden value based

341 on PET images. Quantitative multi-parametric MRI acquisition was performed on a 3-Tesla MR scanner

342 (Siemens MAGNETOM Prisma, Siemens Healthineers, Germany) to get a magnetization transfer (MT)-

343 weighted contrast, based on multi-echo 3D fast low angle shot at 1 mm isotropic resolution (37) (with flip

344 angle = 6° and application of additional off-resonance Gaussian-shaped RF pulse). MRI multi-parameter

345 maps were processed with the hMRI toolbox (38) (http://hmri.info) and SPM12 (Welcome Trust Centre for

346 Neuroimaging, London, UK) to obtain a quantitative MT map and segmented images (grey matter, white

347 matter, CSF), normalised to the standard MNI space using unified segmentation (39).

348 *PET-scan*

349 Aβ PET imaging was performed using [^{18}F]Flutemetamol, except for 3 volunteers for which [^{18}F]Florbetapir

350 was used. PET-scans were performed on an ECAT EXACT+ HR scanner (Siemens, Erlangen, Germany).

351 Participants received a single dose of the radioligand in the antecubital vein (target dose 185 MBq); images

352 acquisition started 85min after the injection and consisted of 4 frames of 5 minutes, followed by a 10 minutes

353 transmission scan using ^{68}Ge line sources. Images were reconstructed using filtered back-projection algorithm

354 including corrections for measured attenuation, dead time, random events, and scatter using standard software

355 (Siemens ECAT – HR + V7.1, Siemens/CTI Knoxville, TN, USA). Individual PET average images were

356 produced using all frames and were then manually reoriented according to Magnetisation Transfer (MT)-

357 weighted structural MRI volumes and coregistered to the individual space structural MT map. Flow-field

358 deformation parameters obtained from DARTEL spatial normalisation of the MT maps were applied to

359 averaged co-registered PET images (40). We did not provide correction for partial volume effect, as this type

360 of PET processing was not included in Centiloid scaling pipeline (41). Volumes of interest were determined

361 using the automated anatomical labelling (AAL) atlas (42). Standardised uptake value ratio (SUVR) was

362 computed using the whole cerebellum as reference region (41). As images were acquired using 2 different

363 radioligands, their SUVR values were converted into Centiloid Units (41). Aβ burden was averaged over a

364 composite mask covering the previously reported earliest aggregation sites for Aβ pathology (18), that is:

365 frontal medial cortex and basal part of temporal lobe (fusiform & inferior temporal gyri).

366 *Cognitive assessment*

17

367 A cognitive battery of neuropsychological tasks was carried out in two sessions, while well-rested. A first

368 session of ~1h was performed in the afternoon prior to the sleep assessment, approximately 7.5h before

369 habitual bedtime, and a second session of ~1.5h was performed on another day (between 12 and 6h prior to

370 habitual bedtime). From those two sessions, three domain-specific composites scores were computed for the

371 memory, executive function, and attentional domains, and consisted of the standardised sum of the

372 standardised domain-specific scores, where higher values indicate better performance. A fourth global

373 cognitive score consisted of the standardised sum of the domain-specific composite scores.

374 The first session and comprised: (1) Mnemonic Similarity Task (MST)(43); (2) Category Verbal Fluency

375 (letter and animals) (44); (3) Digit Symbol Substitution Task (DSST) (45); (4) Visual N-back Task (1, 2 and

376 3-back variants) (46); and (5) Choice Reaction Time (CRT) (47). The second session of ~1·5h was performed

377 on another day (between 12 and 6h prior to habitual bedtime) and comprised: (1) Direct and Inverse Digit

378 Span Task (45); (2) Free and Cued Selective Reminding Test (FCSRT) (48); (3) a computerised version of the

379 Stroop Test (49); (4) Trail Making Test (TMT) (50) and (5) D2 Attention Test (51).The memory score

380 consisted of the FCSRT (sum of all 4 free recalls) and the recognition memory score from the MST. The

381 executive function score included Verbal Fluency tests (letter and animals score for 2min), inverse order digit

382 span, TMT (part B), N-back (3-back variant) and Stroop Test (interfering items errors). The attentional score

383 comprised the DSST, TMT (part A), N-back (1-back variant), D2 (Gz-F) and CRT (reaction time to dissimilar

384 items).

385

386 ***Statistics***

387 Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) using Generalised Linear Mixed

388 Models (GLMMs). The distribution of dependent variables was determined by fitting all parametric

389 probability distributions to data, using the "allfitdist" function in Matlab 2015

390 (http://amir.eng.uci.edu/MvCAT.php) and GLMMs were adapted accordingly as preconised by SAS

391 statisticians. Subject was treated as a random factor (intercept): each model included sex and age as

392 covariates, as well as education for models with cognitive score as dependent variables. Statistical

393 significance threshold was set at $p < 0.05$ as no correction for multiple comparisons were required. The

394 association between arousals and Aβ was tested in a single model including arousal density as dependent

395 variable together with transition (T+, T-) and EMG (M+, M-) arousal statuses and early Aβ burden as

396 regressors (as well as sex and age). The association between arousal and cognition Aβ was tested in a single

397 model including global cognition score as dependent variable together T+M- and T-M+ arousal density as

398 regressors (as well as sex and age). Kenward-Roger's correction was used to determine degrees of freedom.

399 Semi-partial R² ($R^2_{\beta*}$) values were computed to estimate the effect sizes of significant fixed effects and

400 statistical trends in all GLMMs(52). P values in post-hoc contrasts (difference of least square means) were

401 adjusted for multiple testing using Tukey's procedure. Cook's distance was used to assess the potential

402 presence of outliers driving the associations, and as values ranged below 0.4 no datapoint was excluded from

403 the analyses (a Cooks distant > 1 is typically considered to reflect outlier value).

404 ***Study approval***

405 The study was registered with EudraCT 2016-001436-35. All procedures were approved by the Hospital-

406 Faculty Ethic Committee of ULiège. All participants signed an informed consent prior to participating in the

407 study.

408

409 **Author contributions:** Study concept and design: E.S., P.M., C.P., C.B., F.C. and G.V. Data acquisition,

410 analysis and interpretation: all authors. D.C. and G.V. drafted the first version of the manuscript. All authors

411 revised the manuscript, and had final responsibility for the decision to submit for publication. While all co-

412 first authors tightly collaborated to acquire and analyse the data for an equivalent time and workload, each of

413 the co-first authors had his own aspect of the data to deal with in priority. The order reflects these priorities.

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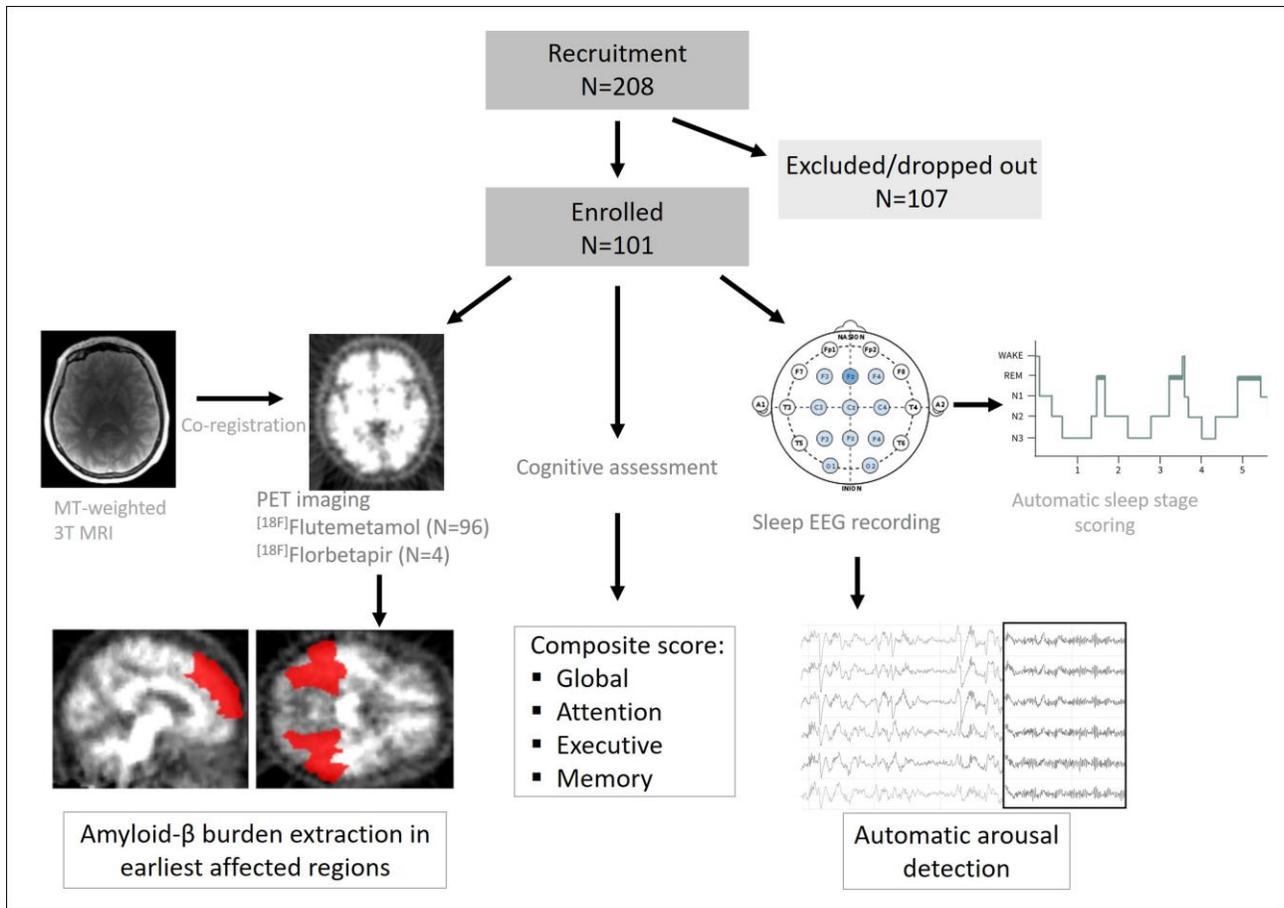
531

Figure 1. Overview of the study. 208 participants were recruited, of which 107 did not participate in the study, as they were excluded based on inclusion criteria (see methods section), if sleep apnoea were detected (>15/h) or decided to withdraw. Participants underwent [18F]Flutemetamol (N=96) / [18F]Florbetapir (N=4) PET scan to assess Aβ burden, which we extracted over the earliest affected regions; they were also tested via an extensive battery of neuropsychological tasks from which we extracted global score, as well as performance over 3 main cognitive domains (attention, executive and memory); and habitual sleep was recorded via EEG from which arousals were automatically detected.

A **B**
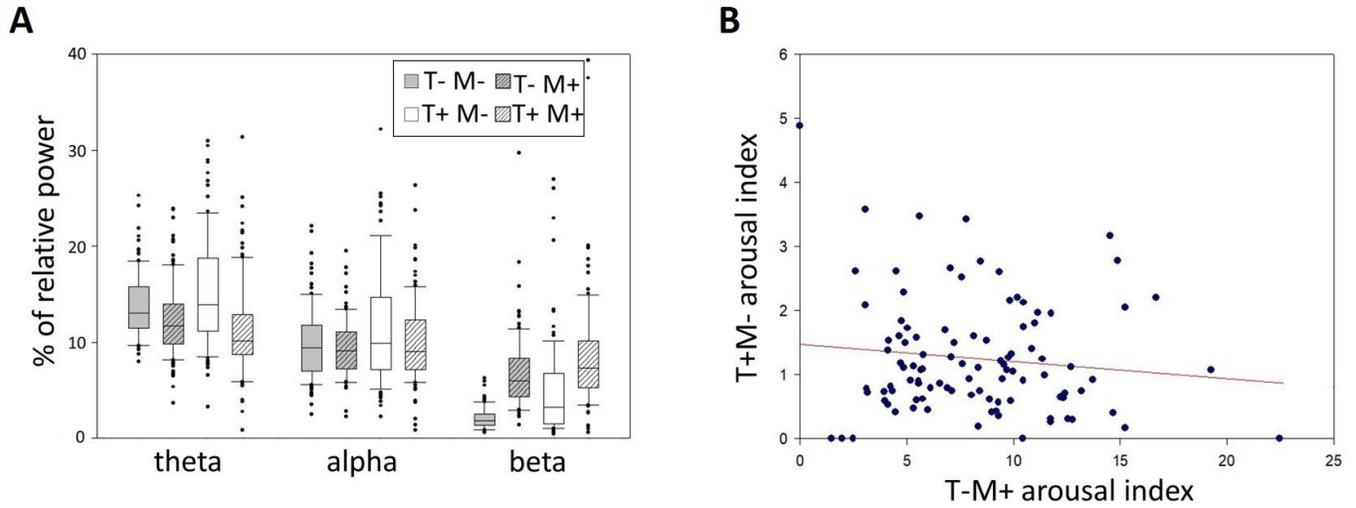
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580 **Figure 2. (A) Spectral composition of arousal types.** Box plot of relative power in the theta (4.5-7.5Hz),

581 alpha (8.5-11.5Hz) and beta (16.5-29.5Hz) band for T-M-, T-M+, T+M- and T+M+ arousals with error bars.

582 The boxes' central line indicates the median of power values, with the bottom and upper edges showing the

583 25th and 75th percentiles, respectively. T: arousal associated (T+) or not (T-) with sleep stage transition; M:

584 arousal associated (M+) or not (M-) with an increase in EMG tone. Indexes correspond to hourly prevalence.

585 **(B) Absence of significant correlation between T-M+ arousals and T+M- arousals** (Spearman r=-.0.05

586 p=.60)**.**

587

A — **B** — **C** — **D**

588
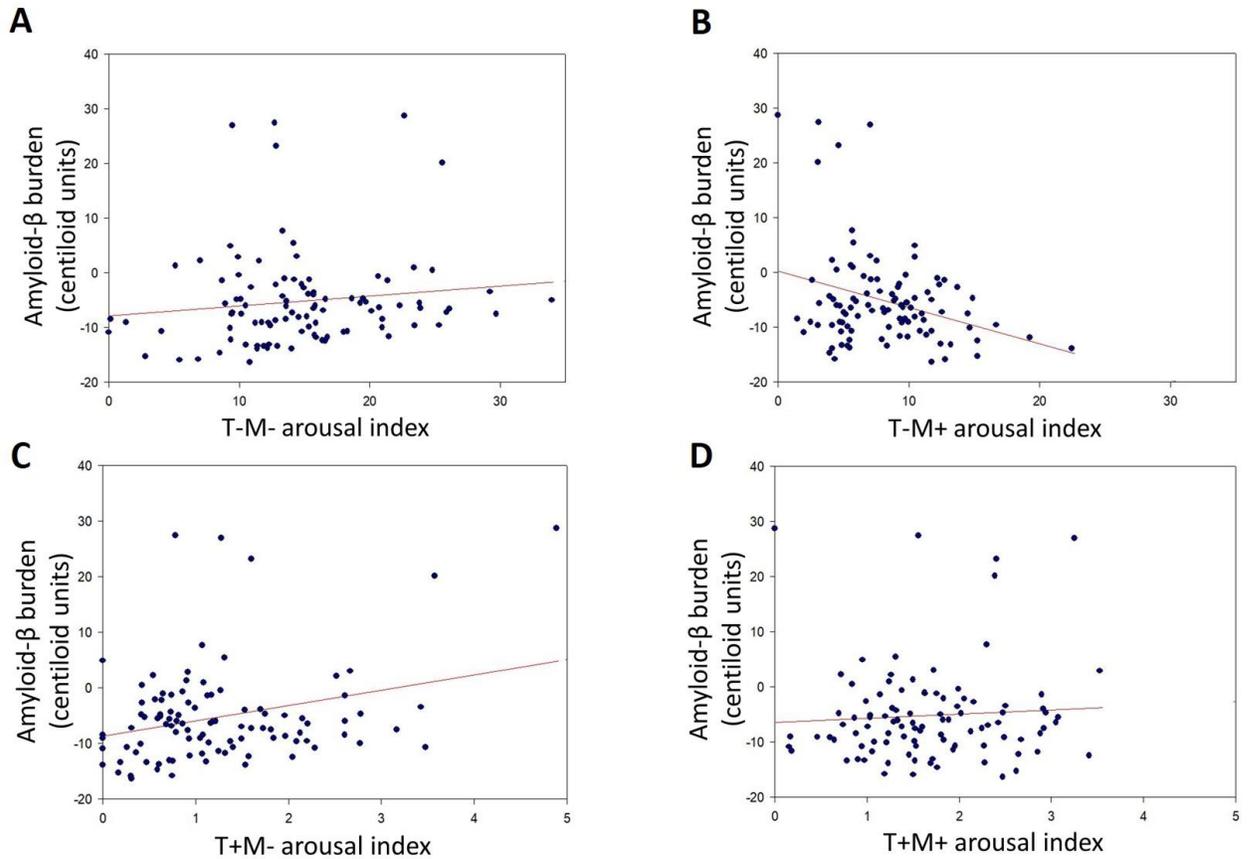
Figure 3. Associations between prevalence of different types of arousals and early cortical Aβ burden.
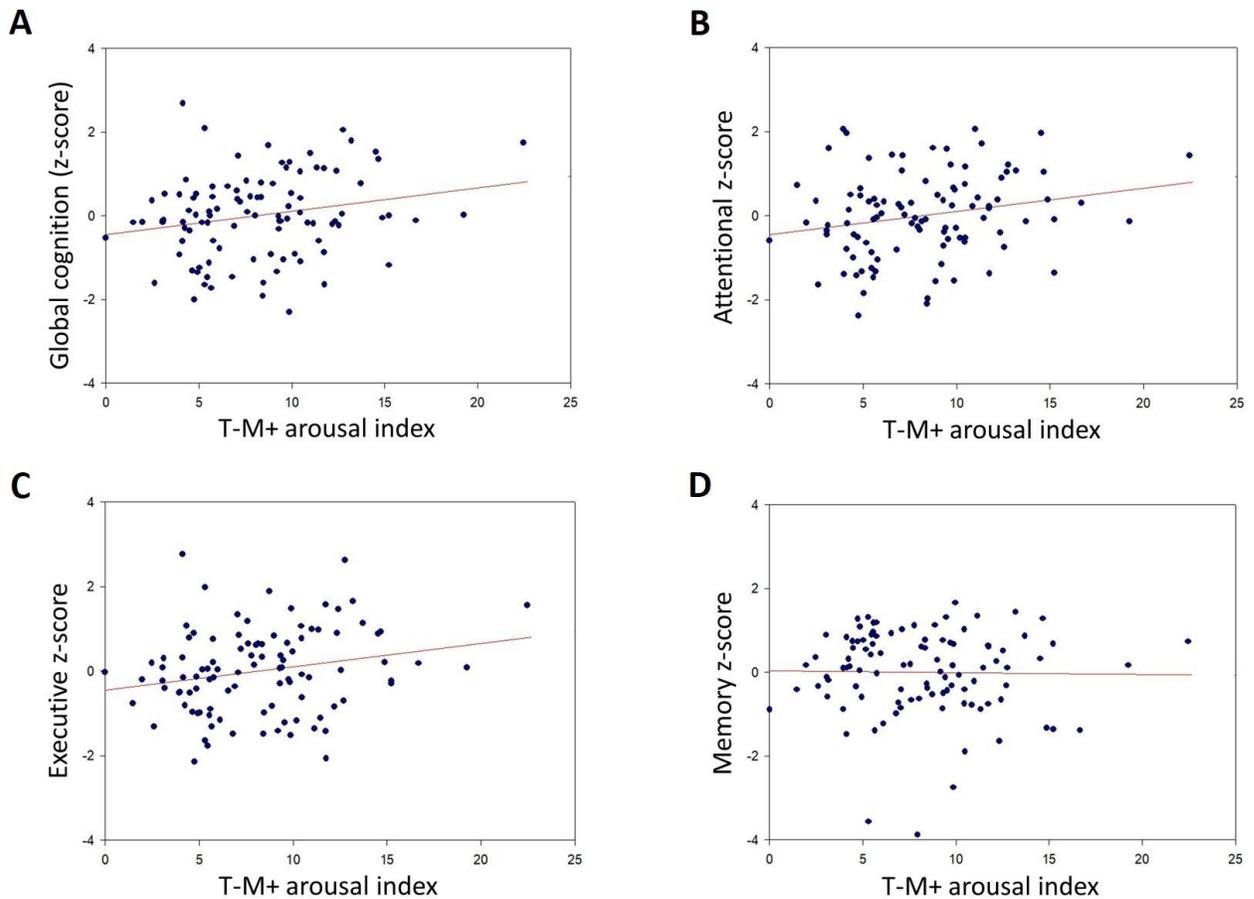**(A)** no correlation between T-M- arousals and Aβ burden (Spearman r=.16, p=.11); **(B)** significant negative correlation between T-M+ arousals and Aβ burden (Spearman r=-.16, p = .11); **(C)** significant positive correlation between T+M- arousals and Aβ burden (Spearman r=.17, p=.08); **(D)** no correlation between T+M+ arousals (Spearman r=.07, p=.46). See main text for full GLMM output controlling for several covariates. T: arousal associated (T+) or not (T-) with sleep stage transition; M: arousal associated (M+) or not (M-) with an increase in EMG tone. Indexes correspond to hourly prevalence.

596

Figure 4. Association between T-M+ arousals prevalence and cognitive performance. (A) T-M+ arousals and global cognition (Spearman r=.21, p=.04); **(B)** T-M+ arousals and attention (Spearman r=.22, p=.03); **(C)** T-M+ arousals and executive functioning (Spearman r=.21, p=.03); **(D)** T-M+ arousals and memory (Spearman r=-.03, p=.71). See Table 3 for full GLMM outputs. T: arousal associated (T+) or not 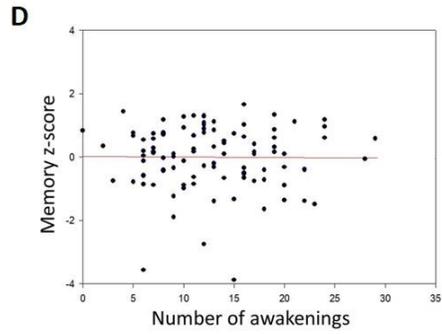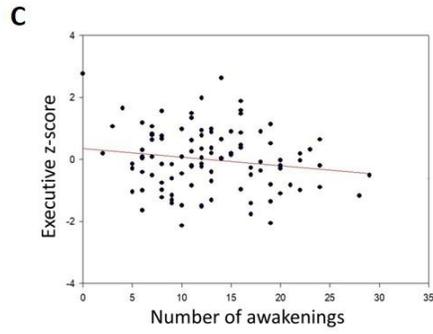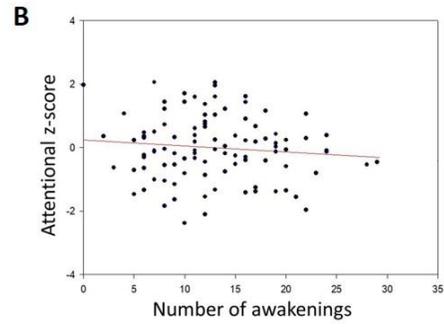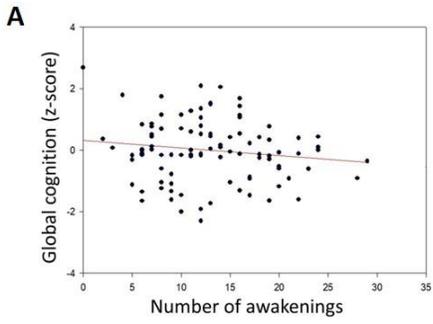(T-) with sleep stage transition; M: arousal associated (M+) or not (M-) with an increase in EMG tone. Indexes correspond to hourly prevalence.

603
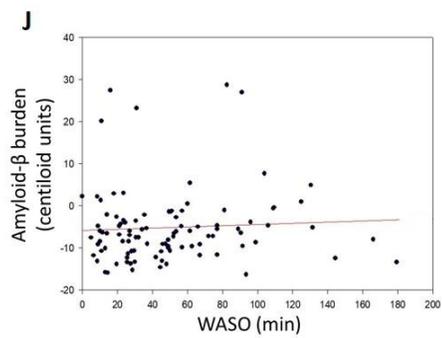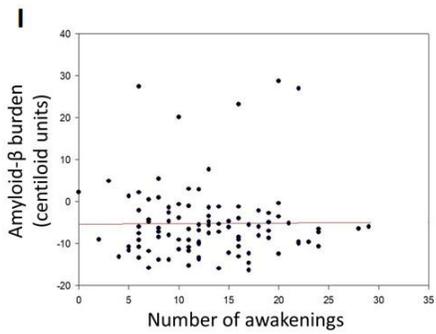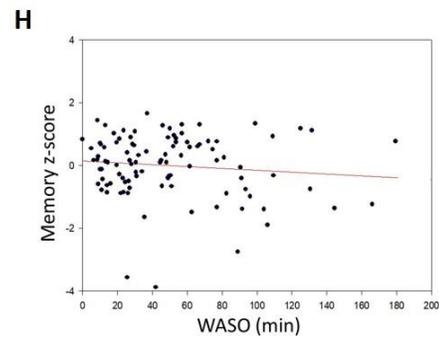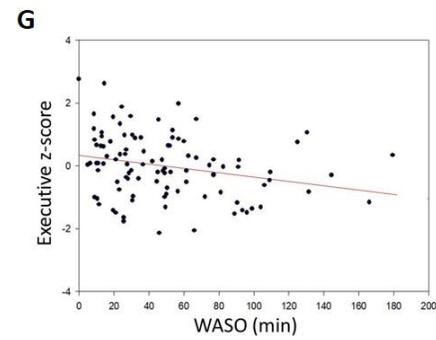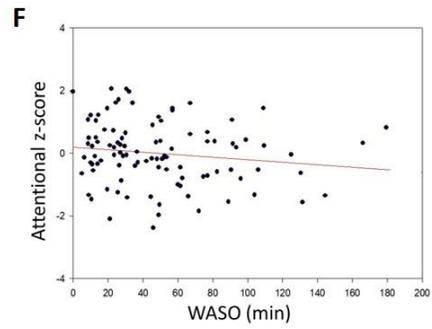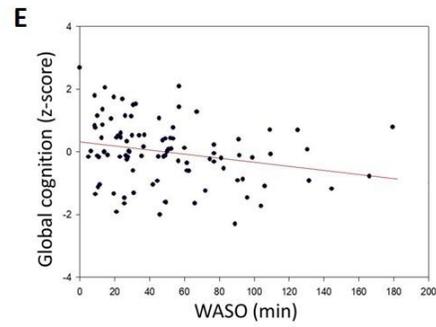
605 **Figure 5. Association between number of awakenings and cognition** **(A)** Global cognitive performance

606 (Spearman r=-0.10, p=0.30; GLMM $F_{1,95}$=2.21, p=0.14); **(B)** attentional (Spearman r=-0.07, p=0.48; GLMM

607 $F_{1,95}$=0.89 p=0.35); **(C)** executive (Spearman r=-0.11, p=0.25; GLMM $F_{1,95}$=3.53, p=0.06); **(D)** memory

608 performances (Spearman r=-0.03, p=0.80; GLMM $F_{1,95}$=0.00, p=0.98); **between WASO and cognition (E)**

609 Global cognitive performance (Spearman: r=-0.24, p=0.01; GLMM $F_{1,95}$=4.66, p=0.03); **(F)** attentional

610 (Spearman: r=-0.17, p=0.11;GLMM: $F_{1,95}$=0.56, p=0.46); **(G)** executive (Spearman: r=-0.28,

611 p=0.005;GLMM: $F_{1,95}$=7.58, p=0.007); **(H)** memory performances (Spearman: r=-0.06, p=0.59; GLMM:

612 $F_{1,95}$=1.11 , p=0.30); **between early cortical Aβ burden and (I)** number of awakenings (Spearman: r=0.01,

613 p=0.90; GLMM $F_{1,95}$=0.22, p=0.64); **(J)** WASO (Spearman: r=0.11, p=0.28; GLMM $F_{1,95}$=0.05, p=0.83).

614

615 **Table 1. Post-hoc comparisons of the relative power for each arousal type within each frequency band.**

Arousal type		vs. arousal type		Frequency band relative power					
				Theta		Alpha		Beta	
M	T	M	T	t value	Adj p	t value	Adj p	t value	Adj p
-	-	-	+	-1.03	0.73	-2.02	0.18	**-10.26**	**<.0001**
-	-	+	-	1.99	0.19	0.01	1.00	**-18.92**	**<.0001**
-	-	+	+	**4.08**	**0.0003**	-0.35	0.99	**-20.91**	**<.0001**
-	+	+	-	**3.30**	**0.006**	2.02	0.18	**-11.41**	**<.0001**
-	+	+	+	**5.11**	**<.0001**	1.39	0.51	**-12.73**	**<.0001**
+	-	+	+	**2.61**	**0.005**	-0.43	0.97	**-3.29**	**0.006**

616 T: arousal associated (T+) or not (T-) with sleep stage transition; M: arousal associated (M+) or not (M-) with
617 an increase in EMG tone. Indexes correspond to hourly prevalence. Significant contrasts are in bold
618

Table 2. Output of the GLMM with Aβ burden as dependent variable, and arousal types.

When considering arousals in all sleep stages together

	Age	*Sex*	*T-M-*	*T-M+*	*T+M-*	*T+M+*
Aβ burden	**F = 11.98** **p = 0.0008** **$R^2_{\beta*}$=0.11**	F = 2.11 p = 0.15	F = 0.00 p = 0.99	**F = 15.22** **p = 0.0002** **$R^2_{\beta*}$=0.14**	F = 3.22 p = 0.076	F = 2.02 p = 0.16
	T-M+ T+M- contrast: t = -2.71, p = 0.008, adjusted = 0.048, estimate = -2.87					

When considering arousals in NREM/REM separately

	Age	*Sex*	*T-M- NREM*	*T-M+ NREM*	*T+M- NREM*	*T+M+ NREM*
Aβ burden	**F = 12.57** **p = 0.0006**	F = 2.59 p = 0.11	F = 0.13 p = 0.72	**F = 11.94** **p = 0.0008**	F = 3.54 p = 0.06	F = 1.05 p = 0.31

	Age	*Sex*		*T-M+ REM*		*T+M+ REM*
Aβ burden	**F = 8.55** **p = 0.0043**	F = 0.63 p = 0.43		**F = 5.95** **p = 0.017**		F = 0.14 p = 0.71

All F tests had 1 (main effect) and 93 (error) degrees of freedom; except for the models with arousals in NREM/REM, which had 1 (main effect) and 95 (error) degrees of freedom. Significant associations are in bold and are accompanied by their corresponding Semi-partial R^2 ($R^2\beta*$).

Table 3. Outputs of GLMMs assessing associations between cognitive performances (global and specific domains-dependent variables) and arousal types, while adjusting for age, sex and education (independent variables).

	T-M+ arousal index	*T+M- arousal index*	*Age*	*Sex*	*Education*
GLOBAL	**F = 4.01** **p = 0.048** **$R^2_{\beta*} = 0.04$**	F = 1.36 *p = 0.25*	F = 3.41 *p = 0.068*	F = 0.11 *p = 0.74*	**F = 10.92** **p = 0.0013** **$R^2_{\beta*} = 0.10$**
ATTENTION	**F = 4.74** **p = 0.032** **$R^2_{\beta*} = 0.047$**	F = 0.83 *p = 0.36*	**F = 6.08** **p = 0.015** **$R^2_{\beta*} = 0.06$**	F = 0.10 *p = 0.75*	**F = 4.48** **p = 0.037** **$R^2_{\beta*} = 0.045$**
EXECUTIVE	F = 2.92 p = 0.09	F = 0.99 *p = 0.32*	F = 0.92 *p = 0.34*	F = 0.34 *p = 0.56*	**F = 10.84** **p = 0.0014** **$R^2_{\beta*} = 0.10$**
MEMORY	F = 0.01 p = 0.91	F = 0.33 *p = 0.57*	F = 0.08 *p = 0.77*	F = 3.15 *p = 0.08*	F = 2.35 *p = 0.13*

All F tests had 1 (main effect) and 95 (error) degrees of freedom. Significant associations are in bold and are accompanied by their corresponding Semi-partial R^2 ($R^2\beta*$). *T: arousal associated (T+) or not (T-) with sleep stage transition; M: arousal associated (M+) or not (M-) with an increase in EMG tone.*

632 **Table 4. Sample characteristics of our dataset (mean ± SD) N=101.**

Sex	**68 ♀ / 33 ♂**
Age (y)	59.4 ± 5.3
Education (y)	15.2 ± 3
Race	White
Dementia rating scale (N=97)(53)	142.5 ± 1.9
BMI (kg/m^2)	24.6 ± 2.9
Apnoea/hypopnoea index (nb/hr)	3.1 ± 2.9
PLMs (nb/hr)	5.3 ± 15.4
TST (min)	393.2 ± 45.9
WASO (min)	49.3 ± 37.2
Awakenings index (nb/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 (nb/hr) ±SD [range]	27.6 ± 9
* T- arousal index (nb/hr) ±SD [range]	23±8 [2-46]
* T-M- index (nb/hr) ±SD [range]	15±6 [0-34]
* T-M+ index (nb/hr) ±SD [range]	8±4 [0-22]
* T+ arousal index (nb/hr) ±SD [range]	3±1 [0-6]
* T+M- index (nb/hr) ±SD [range]	1±1 [0-5]
* T+M+ index (nb/hr) ±SD [range]	2±1 [0-4]
* M- arousal index (nb/hr) ±SD [range]	16±7 [0-36]
* M+ arousal index (nb/hr) ±SD [range]	10±4 [0-24]

633 T: arousals associated (T+) or not (T-) with a sleep stage transition; M: arousals associated (M+) or not (M-)
634 with an increase in EMG signal.