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Association of Sleep-Disordered Breathing and Medial Temporal Lobe Atrophy in
Cognitively Unimpaired Amyloid-Positive Older Adults

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Abstract

Background and objectives: Sleep-disordered breathing (SDB) has been related to amyloid deposition and increased dementia risk. However, how SDB relates to medial temporal lobe neurodegeneration and subsequent episodic memory impairment is unclear. Our objective was to investigate the impact of amyloid positivity on the associations between SDB severity, medial temporal lobe subregions and episodic memory performance in cognitively unimpaired older adults.

Methods: Data were acquired between 2016 and 2020 in the context of the Age-Well randomized controlled trial of the Medit-Ageing European project. Participants aged over 65 years old, free of neurological, psychiatric or chronic medical diseases were recruited from the community. They completed a neuropsychological evaluation, in-home polysomnography, a Florbetapir positron emission tomography and magnetic resonance imaging, including a specific high-resolution assessment of the medial temporal lobe and hippocampal subfields. Multiple linear regressions were conducted to test interactions between amyloid status and SDB severity on the volume of MTL subregions, controlling for age, sex, education and the ApoE4 status. Secondary analyses aimed at investigating the links between SDB, MTL subregional atrophy and episodic memory performance at baseline and at a mean follow up of 20.66 months in the whole cohort and in subgroups stratified according to amyloid status.

Results: We included 122 cognitively intact community-dwelling older adults (mean age \pm SD: 69.40 \pm 3.85 years, 77 women, 26 A β + individuals) in baseline analyses and 111 at follow-up. The apnea-hypopnea index interacted with entorhinal ($\beta=-0.81$, $p<0.001$, $p\eta^2=0.19$), whole hippocampal ($\beta=-0.61$, $p<0.001$, $p\eta^2=0.10$), subiculum ($\beta=-0.56$, $p=0.002$, $p\eta^2=0.08$), CA1 ($\beta=-0.55$, $p=0.002$, $p\eta^2=0.08$) and DG ($\beta=-0.53$, $p=0.003$, $p\eta^2=0.08$) volumes, such that higher sleep apnea severity was related to lower MTL subregions volumes in amyloid-positive individuals, but not those who were amyloid-negative. In the whole cohort, lower whole hippocampal ($r=0.27$, $p=0.005$) and CA1 ($r=0.28$, $p=0.003$) volumes at baseline were associated with worse episodic memory performance at follow-up.

Discussion: Overall, we showed that SDB was associated with MTL atrophy in cognitively asymptomatic older adults engaged in the Alzheimer's continuum, which may increase the risk of developing memory impairment over time.

Trial Registration Information: ClinicalTrials.gov Identifier: NCT02977819

Abbreviations

A β = beta-amyloid; AHI = apnea-hypopnea index; ApoE4 = Apolipoprotein E ϵ 4; BA = Brodmann area; CA = Cornu Ammonis; CPAP = continuous positive airway pressure; CVLT = California Verbal Learning Test; DG = dentate gyrus; ERC = entorhinal cortex; FEW = family-wise error; GM = gray matter; MTL = medial temporal lobe; ODI = oxygen desaturation index; PHC = parahippocampal cortex; PRC = perirhinal cortex; RMI = respiratory microarousals index; SDB = Sleep-disordered breathing; SUB = subiculum; SUVr = standard uptake value ratio; TIV = total intracranial volume.

Introduction

Sleep-disordered breathing (SDB), characterized by recurrent upper airway collapse during sleep, is largely prevalent and underdiagnosed in older adults^{1,2}. SDB-induced intermittent hypoxia and sleep fragmentation are thought to trigger neurodegeneration³ and increase the risk of cognitive decline and dementia⁴. Previous studies have demonstrated that older adults with SDB exhibit higher amyloid deposition notably in posterior cortical regions⁵⁻⁷. Importantly, SDB may exacerbate amyloid pathology over time and interact with AD pathology to precipitate cognitive decline⁷⁻⁹. We have previously shown that cognitively healthy older adults with moderate-to-severe SDB exhibit greater amyloid deposition, gray matter (GM) volume, perfusion and metabolism in the precuneus and posterior cingulate cortex⁶. Contrary to our expectations and to previous reports¹⁰⁻¹⁴, we did not observe GM loss in the medial temporal lobe (MTL), which is known to play a key role in episodic memory^{15,16}, and to be atrophied in Alzheimer's disease, mainly (but potentially not exclusively) as the result of tau pathology spreading¹⁷⁻¹⁹. However, the MTL is composed of

several subregions, namely the entorhinal, perirhinal and parahippocampal cortices, as well as the hippocampus, which can be itself divided into distinct subfields, including the subiculum (SUB), Cornu Ammonis (CA1 to 3), and dentate gyrus (DG). MTL subregions are not homogeneously affected by Alzheimer's disease pathology in predementia stages. Previous studies have reported an early involvement of perirhinal and entorhinal cortices, as well as an early vulnerability of the CA1 subfield²⁰⁻²². Interestingly, animal studies have revealed that some MTL structures are particularly vulnerable to hypoxia, such as the hippocampus and CA1 subfield²³⁻²⁵. Yet, the links between SDB and MTL volume integrity in older populations still needs to be clarified. If most studies have reported SDB-related decreases in GM volume in MTL regions including the hippocampus¹¹⁻¹³, others have rather showed increases in hippocampal volume^{26,27}, or no link with MTL atrophy^{6,28}. First, these discrepancies are likely partly due to methodological limitations, with voxel-wise volumetry being less suitable to reveal subregional and focal neurodegeneration in small brain regions. Thus, segmentations of MTL subregions on high resolution MRI sequences may be better suited to assess the earliest GM changes associated with SDB. Second, SDB consequences may differ depending on its severity or the presence of underlying pathology²⁹. In Alzheimer's disease, the development and spreading of amyloid pathology is known to precede by several years, and thought to promote, neurodegenerative processes and cognitive deficits³⁰⁻³². Therefore, SDB-related neurodegeneration may be only evident, or more strongly measurable, once amyloid deposition becomes significant. Meanwhile, SDB alone may not be enough to lead to significant atrophy in amyloid-negative individuals, or could be associated to increases in GM volume due to inflammatory processes or edema, as previously suggested^{33,34}. Further investigating whether and in which conditions SDB impacts MTL atrophy is crucial given the involvement of these structures in episodic memory processes

and cognitive deterioration, as SDB could represent a modifiable risk factor for cognitive decline. Moreover, treating SDB may have the potential improve cognition⁷.

Our primary objective was to investigate the associations between SDB severity and the volume of MTL substructures, including hippocampal subfields specifically segmented on a high-resolution T2-weighted MRI sequence of the MTL, according to amyloid status, in cognitively healthy community-dwelling older adults. Our secondary objective was to assess the links between SDB and MTL subregions volumes with episodic memory performance, both cross-sectionally and longitudinally. Sensitivity and specificity analyses notably aimed at (i) investigating whether disrupted sleep architecture (e.g., reduced deep sleep and greater light sleep) mediated the associations between sleep apnea severity and MTL integrity, and (ii) verifying whether our results were influenced by sex.

We hypothesized that SDB would be associated with GM atrophy in regions which are early affected by Alzheimer's disease pathology and/or particularly sensitive to hypoxia (i.e., perirhinal, entorhinal and CA1 regions), especially in amyloid-positive participants. Lastly, we expected MTL atrophy and/or SDB severity to be associated with worse episodic memory performance.

Methods

Study design

Participants included in the present study were enrolled in the Age-Well randomized controlled trial (RCT) of the Medit-Ageing European project³⁵, sponsored by the French National Institute of Health and Medical Research (INSERM). As previously described⁶, between 2016 and 2018 we recruited cognitively unimpaired older adults from the community aged over 65 years old with no evidence of major neurological and psychiatric

disorders, chronic diseases, or current medication interfering with cognition (**Figure 1** and **Table 1**). Participants treated for SDB at baseline were excluded from the analysis sample. Baseline examinations consisted in a detailed neuropsychological assessment, polysomnography recording, structural MRI, ¹⁸F-Florbetapir PET scan and Apolipoprotein E ε4 (ApoE4) genotyping, performed within a mean (SD) time interval of 32.24 (17.32) days. Participants were randomized after baseline in one of the three following groups: meditation-based intervention, foreign language training or passive control arm. Interventions lasted for 18 months. Then, they underwent the same neuropsychological assessment than at baseline, within a mean (SD) time interval of 20.66 (0.76) months between cognitive evaluations. As we did not aim at investigating the effect of interventions, longitudinal analyses were controlled for the intervention group. Moreover, participants who presented with an apnea-hypopnea index >15 and a respiratory arousal index >10 were referred to a sleep medicine specialist via their general practitioner. Participants who started continuous positive airway pressure (CPAP) treatment after baseline were excluded from analyses using follow-up data (**Figure 1**).

Polysomnography recording

Polysomnography was performed in the home environment using a portable device (Siesta®, Compumedics, Australia), with 20 EEG electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, P3, P4, Pz, O1, O2, vertex ground, and a bi-mastoid reference), an electrooculogram, electrocardiogram, chin electromyogram, thoracic and abdominal belts, nasal and oral thermistors, and a finger pulse oximeter. The EEG processing and scoring protocols have been described elsewhere⁶. Recordings were scored following the American Academy of Sleep Medicine rules³⁶, and sleep apnea was defined by a ≥90% drop of nasal pressure for at least 10 seconds, whereas sleep hypopnea was characterized by a ≥30% drop of nasal pressure for

a minimum of 10 seconds, associated with an arousal or a $\geq 3\%$ oxygen desaturation³⁶. We extracted three standard variables reflecting sleep apnea severity: the apnea-hypopnea index (AHI; the sum of apneas and hypopneas per hour of sleep), the oxygen desaturation index (ODI; the number of oxygen desaturations superior to 3% per hour of sleep) and the respiratory microarousals index (RMI; the number of respiratory arousals per hour of sleep) (**Table 1**). In our cohort, 91 out of 122 participants had moderate-to-severe SDB (AHI ≥ 15 /h), but were poorly symptomatic, with only 11 out of 91 exhibiting excessive daytime sleepiness (Epworth Sleepiness Scale score ≥ 10).

Neuroimaging examinations

Participants underwent structural MRI and a dual-phase Florbetapir-PET scanning at the Cyceron Center (Caen, France), respectively on a Philips Achieva 3T scanner (Eindhoven, The Netherlands) and a Discovery RX VCT 64 PET-CT scanner (General Electric Healthcare, Milwaukee, Wis., USA). Acquisition details have been previously reported^{6,35} and are available in **eMethods in the Supplement**.

Structural MRI

T1-weighted images were segmented using FLAIR images, spatially normalized to the Montreal Neurological Institute (MNI) template, modulated using the SPM12 segmentation procedure (<http://www.fil.ion.ucl.ac.uk>) and smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian filter. Images were then masked to exclude non-GM voxels from the analyses.

In addition, two high-resolution T2-weighted structural images were acquired perpendicularly to the long axis of the hippocampus (TR = 5,310 ms; TE = 110 ms; flip angle = 90°; 23 slices; slice thickness = 2.5 mm; FOV = 140 x 111 mm²; matrix = 352 x 352; in-plane resolution = 0.398 x 0.398 mm², acquisition time = 3min43). The two high resolution T2-

weighted structural images of the MTL were coregistered and averaged using SPM12. Hippocampal subfields (CA1, CA2, CA3, dentate gyrus [DG], subiculum [SUB]) and extra-hippocampal regions (entorhinal cortex [ERC], Brodmann areas 35 and 36, and parahippocampal cortex [PHC]) volumes were estimated automatically on averaged high-resolution T2-weighted images using the Automated Segmentation for Hippocampal Subfields (ASHS) software together with a custom atlas³⁷. We used a custom atlas because recent observations based on *ex vivo* MRI and histology data showed that the dark band, a hypointense line appearing within the hippocampal GM on T2 images frequently used in segmentation protocols as the boundary between DG and SUB/CA, is composed of the stratum lacunosum moleculare³⁸. Thus, dark band voxels should be labeled as SUB/CA only, but were splitted between SUB/CA and DG in the original atlas provided with ASHS (ashs_atlas_upennpmc_20170810)³⁷. Therefore, we manually edited the segmentations from the original atlas (29 subjects ranging from normal cognition to Mild Cognitive Impairment) to label all dark band voxels as SUB/CA and generated a new atlas. Leave-one-out cross-validation analyses showed similar accuracy as compared to the original atlas (Dice coefficients: CA1=0.82, CA2=0.56, CA3=0.53, DG=0.80, SUB=0.76, ERC=0.79, BA35=0.72, BA36=0.78, PHC=0.78). For complementary analyses, the ERC, perirhinal cortex (PRC), PHC and whole hippocampus were also segmented on T1-weighted images using a specific atlas (ashsT1_atlas_upennpmc_07202018)²². All MRI images and segmentations were visually inspected, and failed segmentations were manually edited when feasible or discarded (see **eMethods in the Supplement** for additional details). For statistical analyses, left and right hemispheres were averaged for each subregion to limit the number of statistical tests. Moreover, CA2 and CA3 on one hand, and BA35 and BA36 on the other hand, were pooled together and respectively referred to as CA2-3 region and the perirhinal cortex (PRC) hereafter. Of note, we verified *a posteriori* whether BA35 and BA36 showed

different associations with SDB parameters, and as it was not the case, we only display the results with the whole PRC. Total hippocampal volume was obtained by summing CA1, CA2-3, DG, and SUB regions. Bilateral averaged volumes (mm^3) were normalized to the total intracranial volume (TIV; obtained from SPM12) to compensate for interindividual variability in head size, as follows: averaged bilateral volume/(TIV*1000).

Florbetapir-PET

PET images were coregistered on their corresponding anatomical MRI. Resulting images were then normalized to the MNI template using deformation parameters derived from the anatomical MRI, scaled using cerebellar gray matter as a reference, smoothed at 10mm and masked to exclude non-GM voxels. Individual neocortical amyloid standard uptake value ratio (SUVr) was extracted from normalized and scaled Florbetapir-PET images using a neocortical GM mask excluding the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala and basal nuclei⁶. The threshold for amyloid positivity was defined as >0.99 , and corresponded to the 99.9th percentile of the neocortical SUVr distribution among 45 healthy young individuals aged <40 years from the IMAP cohort⁶.

Neuropsychological assessment

Participants underwent a neuropsychological assessment of global cognitive functioning, processing speed, attention, working memory, executive functions and episodic memory, detailed elsewhere^{6,35}. Verbal episodic memory was assessed using the French version of the California Verbal Learning Test (CVLT)³⁹. Short and long-term free recall scores were used in analyses.

Statistical analyses

Prior to statistical analyses, the distribution of all variables was visually inspected and checked for normality using Shapiro-Wilk tests. All non-normal variables were log-transformed. We first assessed the associations between SDB parameters and MTL subregions according to amyloid status by performing multivariable linear regressions with the volume of each MTL subregion as dependent variables, and SDB parameters and amyloid status as independent variables, with age, sex, education and the ApoE4 status as covariates. Separate models were carried out for each MTL subregion and each SDB parameter, and an interaction term was added between SDB parameters and amyloid status. When the interaction was significant, *post-hoc* partial correlations were conducted separately in amyloid-positive and negative individuals. Adding the body mass index as a covariate in regression models did not change the results, so it was not included in the final model to avoid statistical overfitting.

Then, we investigated the links between SDB parameters and SDB-associated MTL regions, and episodic memory performance at baseline and follow-up. We thus performed partial correlations between SDB parameters and/or MTL subregions volumes, and both the log-transformed short- and long-term free recalls of the CVLT at the two time points, controlling for age, sex, education, ApoE4 status and the intervention group for longitudinal analyses. These analyses were performed in the whole cohort and in subgroups stratified by amyloid status. Of note, CVLT scores at follow-up (i.e., performed after the interventions), did not statistically differ between the passive control, English-learning and meditation groups (**eFigure 1 in the Supplement**).

Finally, we performed several sensitivity and specificity analyses to ensure the robustness of our results.

First, we replicated multiple regressions analyses between SDB parameters and MTL subregions volumes derived from T1-weighted images, rather than high-resolution MRI sequences. We also checked whether our results were impacted by laterality, by replicating partial correlations between SDB severity parameters and left and right MTL volumes separately, rather than bilateral volumes, in amyloid positive and negative participants, controlling for age, sex, education and ApoE4 status. Second, to evaluate the specificity of our main results (i.e., to verify whether the links between SDB and atrophy were restricted or not to MTL subregions), we performed voxel-wise multivariable regressions between SDB parameters and GM volume, controlling for the same covariates, using a $p < 0.005$ (uncorrected) threshold combined with $p < 0.05$ FWE cluster-level threshold.

Third, we investigated the influence of sex on our results, by conducting partial correlations between SDB parameters and MTL subregions volumes in sex-stratified subgroups (in the whole sample and subgroups separated according to amyloid status), controlling for age, education and the ApoE4 status.

Finally, to verify whether the associations between sleep apnea severity and MTL integrity were mediated by alterations in sleep architecture (e.g., reduced deep sleep and increased lighter sleep and nocturnal awakenings), we assessed the associations between sleep architecture variables and both (i) SDB parameters and (ii) MTL subregions volumes, controlling for age, sex, education and the ApoE4 status. In case of significant associations, mediation analyses were carried out in order to confirm the mediating role of sleep architecture.

For all analyses, we only report results which remained significant after correcting for multiple comparisons ($p = 0.05/\text{number of comparisons}$, see tables legends for details).

Standard Protocol Approvals, Registrations, and Patient Consents

All participants included in the Age-Well RCT of the Medit-Ageing European project gave their written informed consent prior to the examinations. The Age-Well RCT was approved by the ethics committee (CPP Nord-Ouest III, Caen; trial registration number: EudraCT: 2016- 002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819)³⁵.

Data availability

Data are made available on request following a formal data sharing agreement and approval by the consortium and executive committee (<https://silversantestudy.eu/2020/09/25/data-sharing>). The Material can be mobilized, under the conditions and modalities defined in the Medit-Ageing Charter, by any research team belonging to an Academic for carrying out a scientific research project relating to the scientific theme of mental health and well-being in older people. The Material may also be mobilized by non-academic third parties, under conditions, in particular financial, which will be established by separate agreement between Inserm and by the said third party. Data sharing policies described in the Medit-Ageing Charter are in compliance with our ethics approval and guidelines from our funding body.

Results

Participants' characteristics

Of the 136 participants included in the Age-Well RCT at baseline, 122 were included in the analysis sample (**Figure 1**). Their demographical and clinical characteristics are detailed in

Table 1. The mean age of the sample was 69.40 ± 3.85 years, with 77 (63.12%) women and 33 (27.05) ApoE4 carriers. Twenty-six (21.31%) participants were amyloid-positive and 96 were amyloid-negative. Amyloid-positive participants were significantly older and more susceptible to be ApoE4 carriers, but did not differ from amyloid-negative individuals in terms of sex ratio, education level, memory performance, MTL subregions volumes and sleep data (**Table 1**).

Associations between MTL subregional volumes and SDB according to amyloid status

The AHI and amyloid status significantly interacted on the volumes of the ERC ($\beta=-0.81$ [95% CI: -1.12 – -0.50]; $P<0.001$; $p\eta^2=0.19$), whole hippocampus ($\beta=-0.61$ [95% CI: -0.94 – -0.28]; $P<0.001$; $p\eta^2=0.10$), SUB ($\beta=-0.56$ [95% CI: -0.90 – -0.22]; $P=0.002$; $p\eta^2=0.08$), CA1 ($\beta=-0.55$ [95% CI: -0.89 – -0.22]; $P=0.002$; $p\eta^2=0.08$) and DG ($\beta=-0.53$ [95% CI: -0.88 – -0.19]; $P=0.003$; $p\eta^2=0.08$) extracted from high-resolution T2-weighted MTL images (**Table 2**). Post-hoc analyses showed that higher AHI was significantly associated with lower GM volume in the ERC ($r=-0.79$, $P<0.001$), whole hippocampus ($r=-0.72$, $P<0.001$), SUB ($r=-0.61$, $P=0.001$), CA1 ($r=-0.65$, $P=0.001$) and DG ($r=-0.70$, $P<0.001$), only in amyloid-positive participants (**Figure 2** and **Table 3**). Similarly, greater ODI, was associated with lower ERC, whole hippocampus, SUB and CA1 volumes only in amyloid-positive participants (**eTable 1 in the Supplement and Table 3**). The associations with the RMI were restricted to ERC and whole hippocampus (**eTable 2**).

Replication analyses performed using hippocampal, ERC, PRC and PHC volumes measured on T1-weighted images confirmed that greater AHI, ODI and RMI were associated with lower volumes of the ERC and hippocampus only in amyloid-positive participants (**eTable 3 in the Supplement and Table 3**). Moreover, the associations between SDB severity and

WH, ERC, SUB, CA1 and DG were all bilateral, as both left and right hemisphere volumes were significantly associated with SDB severity, while the links with PHC were only significant in the right hemisphere (**eTable 4**).

Associations between SDB and whole-brain GM volume in amyloid positive participants

To test whether the negative associations between SDB parameters and MTL subregions atrophy in amyloid-positive participants were restricted to the MTL or part of a larger pattern of neurodegeneration, we performed voxel-wise multiple regressions between SDB parameters and GM volume (**eFigure 2** and **eTable 5 in the Supplement**). The AHI was negatively associated with GM volume in the left superior temporal pole, hippocampus, PHC and amygdala ($P < 0.005$ unc., $k = 613$, $T = 3.85$), and right superior temporal pole, amygdala and PHC ($P < 0.005$ unc., $k = 191$, $T = 3.59$). Greater ODI was associated with lower volume in the right superior temporal pole, amygdala and PHC ($P < 0.005$ unc., $k = 181$, $T = 4.00$). The RMI was not significantly associated with GM volume.

Links with episodic memory at baseline and follow-up

In the whole cohort at baseline, CVLT scores were neither associated with SDB parameters, nor with the volume of SDB-associated MTL subregions (**eTable 6 in the Supplement**). However, baseline whole hippocampal ($r = 0.27$, $P = 0.005$) and CA1 volumes ($r = 0.28$, $P = 0.003$) were positively associated with long-term free recall scores at follow-up, such that lower MTL subregional volumes at baseline were associated with poorer episodic memory performance at follow-up (**Table 4**). No significant associations were observed between SDB parameters at baseline and memory scores at follow-up. Moreover, no significant associations were observed in subgroups stratified by amyloid status.

Sex-stratified analyses

Differences in demographical, sleep and MTL data between men and women are displayed in **eTable 7 in the Supplement**. Male participants exhibited greater AHI scores, and lower whole hippocampal, ERC, PHC, subiculum, CA1 and DG volumes. Female participants had greater memory scores at all time points, despite overall lower education level. Sex-stratified analyses revealed that the AHI was negatively associated with GM volume in the whole hippocampus ($r=-0.30$, $P=0.01$), ERC ($r=-0.50$, $P<0.001$), PHC ($r=-0.34$, $P=0.003$), CA1 ($r=-0.26$, $P=0.02$) and DG ($r=-0.30$, $P=0.01$), only in women (**Table 5**). Similar associations were obtained with the ODI and RMI. When stratifying female participants according to amyloid status, these associations were only significant in amyloid-positive women (**Table 5**). Marginal associations were observed in male participants (**Table 5**).

Associations with sleep architecture

The AHI was positively associated with N1 percentage ($r=0.41$, $P<0.001$) and the number of nocturnal awakenings per hour of sleep ($r=0.25$, $P=0.007$), and negatively associated with both N3 ($r=-0.26$, $P=0.005$) and REM sleep ($r=-0.30$, $P=0.001$) percentage (**eTable 8 in the Supplement**). Similar associations were obtained with the ODI and RMI, although more marginally for the ODI as it was only related to N1 and REM sleep percentage (**eTable 8**). However, no significant associations were obtained between MTL subregions volume and sleep architecture (**eTable 8**).

Discussion

This study shows that greater SDB severity, mainly reflected by higher AHI and ODI, was associated with reduced GM volume in the entorhinal cortex and hippocampus in amyloid-positive individuals only. Specifically, hippocampal subfields involved in these associations

included the subiculum, CA1 and DG subfields. Moreover, lower hippocampal and CA1 volumes at baseline were associated with poorer episodic memory performance at follow-up. Complementary analyses show that the links between SDB and GM atrophy were largely bilateral, restricted to temporal cortical areas, not due to changes in sleep architecture, and that women may be particularly vulnerable to the adverse effects of sleep apnea on the MTL. As SDB has been associated with a greater risk of cognitive decline⁴, a number of studies investigated SDB-related brain alterations. Some studies have previously demonstrated that SDB is associated with hippocampal damage^{11–14,40}. Our results demonstrate that MTL subregions particularly vulnerable to SDB, including the ERC and within the hippocampus, the subiculum, CA1 and DG subfields. Alzheimer's disease is known to affect the ERC before CA1 and subiculum subfields, due to the spreading of tau pathology in early stages of the disease^{17–19}. Interestingly, MTL subregions are also known to be sensitive to hypoxia, a major consequence of SDB. Animal studies indicate that CA1 may be the most vulnerable region to hypoxia within the MTL^{23–25,41}, while other subfields like CA3 are spared. Compared to those located in CA3, CA1 pyramidal neurons appear to be selectively vulnerable to oxidative stress, because of cellular and molecular specificities such as (i) a pre-existing pattern of high basal expression of genes associated to metabolic stress, (ii) high intrinsic levels of oxidative stress and reactive oxygen and nitrogen species, (iii) high concentration of glutamatergic receptors, which may be overstimulated in case of excessive glutamate release, (iv) lower ATP and energy reserves, etc^{24,42}. Other potential mechanisms for this selective vulnerability are more structural, including larger neuron size and potentially lower levels of vascularization in CA1 and lower angiogenesis-related genes expression^{24,42}. In humans, a recent post-mortem study has shown that greater SDB severity was related to cortical thinning in the dentate gyrus, CA1 and ERC¹⁰. In addition, in children with SDB, lower mean diffusivity in the DG has been associated with a higher AHI as well as

lower verbal learning and memory scores⁴³. It has been shown that hypoxia affects multiple stages of adult neurogenesis in the DG, leading to a reduction of newly generated adult-born neurons⁴⁴. If adult neurogenesis is known to decline with aging and to be largely reduced in Alzheimer's disease⁴⁵, it is still possible that hypoxia may affect DG neurogenesis in our sample, explaining its vulnerability to SDB, although this mechanism may be relatively marginal.

Our results suggest that some individuals may be more vulnerable to the adverse effects of sleep apnea. Indeed, we demonstrate that participants who are engaged in the Alzheimer's pathological continuum (i.e., amyloid-positive) exhibit a specific vulnerability to SDB, which amyloid-negative participants did not show. The fact that no association between SDB and MTL integrity was found in amyloid-negative participants contrasts with some previous reports showing SDB-related hippocampal changes in younger populations who are unlikely to exhibit significant Alzheimer's disease pathology (i.e., young middle-aged individuals and children with obstructive sleep apnea)^{43,46,47}. We can speculate that SDB may exacerbate Alzheimer's disease pathology in all participants, but amyloid-negative individuals (i) may not suffer from SDB since enough time to exhibit neurodegeneration yet, or (ii) may be more resilient to the adverse effects of SDB than amyloid-positive individuals. Importantly, in our cohort, only a small proportion of participants with moderate-to-severe SDB exhibited symptoms of excessive daytime sleepiness (11 out of 91 participants). In addition, they were overall highly educated, had no cognitive deficits and may therefore present with a high cognitive reserve.. However, amyloid-negative participants may still be at risk of neurodegeneration over the long-term. Moreover, additional analyses showed that women (notably those with significant levels of amyloid pathology) seemed particularly vulnerable to the adverse effects of SDB, while greater SDB severity was not significantly associated with MTL volume changes in men. If these results are preliminary and pending replication in larger

samples, they are in line with recent reports showing that the links between SDB and cognitive decline may be stronger in women⁴⁸.

Finally, we found that lower baseline CA1 and whole hippocampus volumes were associated with poorer episodic memory performance measured approximately 21 months later in the whole cohort. This result provides preliminary evidence that, although neither SDB nor MTL structure are significantly associated with cognition cross-sectionally, the adverse effects of SDB on the MTL in amyloid-positive individuals could ultimately result in lower episodic memory performance later. It is not surprising to observe associations between hippocampal atrophy and poorer episodic memory, as we show that SDB affected regions of the MTL that are crucial for episodic memory formation and sleep-dependent consolidation^{15,16}. Furthermore, the neurodegeneration of MTL regions due to tau pathology is known to start early in the course of Alzheimer's disease, and to underlie memory deficits. In particular, CA1 atrophy has been associated with memory deficits in patients with Mild Cognitive Impairment and Alzheimer's disease^{49,50}. Given that our population was composed of cognitively healthy older participants, we surmise that longitudinal designs may be more powerful to detect subtle cognitive changes compared to cross-sectional analyses.

The strengths of our study include the combination of polysomnography, a high-resolution imaging and careful segmentation of MTL subregions and longitudinal cognitive assessment. However, our study is not without limitations. First, the same CVLT version was used at baseline and follow-up. If the time interval was long between these two time points (i.e., 20.66 ± 0.76 months), suggesting a rather modest test/re-test effect, we cannot exclude that this may have minimized memory decline measurements at follow-up. Second, the results of sex-stratified analyses should be replicated in larger samples, as our sample size was limited, especially when separating the groups according to amyloid status. Third, the polysomnography set-up did not include leg electrodes, preventing us from evaluating and

controlling for periodic limb movements. Overall, this study shows that SDB in cognitively unimpaired amyloid-positive individuals may exacerbate neurodegeneration in MTL subregions, which may in turn foster memory decline. Further studies should evaluate the impact of tau pathology, and assess the potentially beneficial effects of SDB treatment.

WNL-2023-000259_coinvestigator_appendix ---<http://links.lww.com/WNL/C820>
WNL-2023-000259_sup --- <http://links.lww.com/WNL/C821>

References

1. Senaratna C, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev.* 2017;34:70–81.
2. Morrell MJ, Finn L, McMillan A, Peppard PE. The impact of ageing and sex on the association between sleepiness and sleep disordered breathing. *European Respiratory Journal.* 2012;40:386–393.
3. Daulatzai MA. Evidence of neurodegeneration in obstructive sleep apnea: Relationship between obstructive sleep apnea and cognitive dysfunction in the elderly. *J Neurosci Res.* 2015;93:1778–1794.
4. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA Neurol.* 2017;74:1237–1245.
5. Yun C-H, Lee H-Y, Lee SK, et al. Amyloid Burden in Obstructive Sleep Apnea. *Journal of Alzheimer's Disease.* 2017;59:21–29.
6. André C, Rehel S, Kuhn E, et al. Association of Sleep-Disordered Breathing With Alzheimer Disease Biomarkers in Community-Dwelling Older Adults. *JAMA Neurol.* 2020;77:716–724.
7. Mullins AE, Kam K, Parekh A, Bubu OM, Osorio RS, Varga AW. Obstructive Sleep Apnea and Its Treatment in Aging: Effects on Alzheimer's disease Biomarkers, Cognition, Brain Structure and Neurophysiology. *Neurobiol Dis.* 2020;145.
8. Bubu OM, Umasabor-Bubu OQ, Turner AD, et al. Self-reported obstructive sleep apnea, amyloid and tau burden, and Alzheimer's disease time-dependent progression. *Alzheimer's & Dementia.* 2021;17:226–245.

9. Sharma RA, Varga AW, Bubu OM, et al. Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly. A Longitudinal Study. *Am J Respir Crit Care Med.* 2018;197:933–943.
10. Owen JE, Benediktsdóttir B, Gislason T, Robinson SR. Neuropathological investigation of cell layer thickness and myelination in the hippocampus of people with obstructive sleep apnea. *Sleep.* 2019;42.
11. Weng H-H, Tsai Y-H, Chen C-F, et al. Mapping Gray Matter Reductions in Obstructive Sleep Apnea: An Activation Likelihood Estimation Meta-Analysis. *Sleep.* 2014;37:167–175.
12. Tahmasian M, Rosenzweig I, Eickhoff SB, et al. Structural and functional neural adaptations in obstructive sleep apnea: An activation likelihood estimation meta-analysis. *Neurosci Biobehav Rev.* 2016;65:142–156.
13. Huang X, Tang S, Lyu X, Yang C, Chen X. Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis. *Sleep Med.* 2019;54:195–204.
14. Macey PM, Prasad JP, Ogren JA, et al. Sex-specific hippocampus volume changes in obstructive sleep apnea. *Neuroimage Clin.* 2018;20:305–317.
15. Spaniol J, Davidson PSR, Kim ASN, Han H, Moscovitch M, Grady CL. Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. *Neuropsychologia.* 2009;47:1765–1779.
16. Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nat Rev Neurosci.* 2011;12:585–601.

17. Jack CR, Dickson DW, Parisi JE, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology*. 2002;58:750–757.
18. de Souza LC, Chupin M, Lamari F, et al. CSF tau markers are correlated with hippocampal volume in Alzheimer’s disease. *Neurobiol Aging*. 2012;33:1253–1257.
19. Das SR, Xie L, Wisse LEM, et al. Longitudinal and cross-sectional structural magnetic resonance imaging correlates of AV-1451 uptake. *Neurobiol Aging*. 2018;66:49–58.
20. Pini L, Pievani M, Bocchetta M, et al. Brain atrophy in Alzheimer’s Disease and aging. *Ageing Res Rev*. 2016;30:25–48.
21. de Flores R, la Joie R, Chételat G. Structural imaging of hippocampal subfields in healthy aging and Alzheimer’s disease. *Neuroscience*. 2015;309:29–50.
22. Xie L, Wisse LEM, Pluta J, et al. Automated segmentation of medial temporal lobe subregions on in vivo T1-weighted MRI in early stages of Alzheimer’s disease. *Hum Brain Mapp*. 2019;40:3431–3451.
23. Bartsch T, Döhring J, Reuter S, et al. Selective neuronal vulnerability of human hippocampal CA1 neurons: Lesion evolution, temporal course, and pattern of hippocampal damage in diffusion-weighted MR imaging. *Journal of Cerebral Blood Flow and Metabolism*. 2015;35:1836–1845.
24. Schmidt-Kastner R. Genomic approach to selective vulnerability of the hippocampus in brain ischemia-hypoxia. *Neuroscience*. 2015;309:259–279.
25. Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. *Neuroscience*. 1991;40:599–636.

26. Rosenzweig I, Kempton MJ, Crum WR, et al. Hippocampal Hypertrophy and Sleep Apnea: A Role for the Ischemic Preconditioning? *PLoS One*. 2013;8:e83173.
27. Cross NE, Memarian N, Duffy SL, et al. Structural brain correlates of obstructive sleep apnoea in older adults at risk for dementia. *European Respiratory Journal*. 2018;52:1800740.
28. Baril A-A, Gagnon K, Brayet P, et al. Gray Matter Hypertrophy and Thickening with Obstructive Sleep Apnea in Middle-aged and Older Adults. *Am J Respir Crit Care Med*. 2017;195:1509–1518.
29. Legault J, Thompson C, Martineau-Dussault MÈ, et al. Obstructive sleep apnea and cognitive decline: A review of potential vulnerability and protective factors. *Brain Sci*. MDPI AG; 2021;11.
30. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol*. 2013;12:357–367.
31. Villemagne VL, Pike KE, Chételat G, et al. Longitudinal assessment of A β and cognition in aging and Alzheimer disease. *Ann Neurol*. 2011;69:181–192.
32. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14:535–562.
33. Martineau-Dussault M-È, André C, Daneault V, et al. Medial temporal lobe and obstructive sleep apnea: Effect of sex, age, cognitive status and free-water. *Neuroimage Clin*. 2022;36:103235.

34. Baril AA, Martineau-Dussault MÈ, Sanchez E, et al. Obstructive Sleep Apnea and the Brain: a Focus on Gray and White Matter Structure. *Curr Neurol Neurosci Rep.* 2021;21:11.
35. Poisnel G, Arenaza-Urquijo E, Collette F, et al. The Age-Well randomized controlled trial of the Medit-Ageing European project: Effect of meditation or foreign language training on brain and mental health in older adults. *Alzheimer's & Dementia: Translational Research & Clinical Interventions.* 2018;4:714–723.
36. Berry RB, Brooks R, Gamaldo C, et al. AASM Scoring Manual Updates for 2017 (Version 2.4). *Journal of Clinical Sleep Medicine.* 2017;13:665–666.
37. Yushkevich PA, Pluta JB, Wang H, et al. Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. *Hum Brain Mapp.* 2015;36:258–287.
38. de Flores R, Berron D, Ding SL, et al. Characterization of hippocampal subfields using ex vivo MRI and histology data: Lessons for in vivo segmentation. *Hippocampus.* 2020;30:545–564.
39. Poitrenaud J, Deweer B, Kalafat M, van der Linden M. *Adaptation en langue française du California Verbal Learning Test.* Paris: Les Éditions du Centre de psychologie appliquée.; 2007.
40. Marchi NA, Ramponi C, Hirotsu C, et al. Mean Oxygen Saturation during Sleep Is Related to Specific Brain Atrophy Pattern. *Ann Neurol.* 2020;87:921–930.
41. Wilde GJC, Pringle AK, Wright P, Iannotti F. Differential vulnerability of the CA1 and CA3 subfields of the hippocampus to superoxide and hydroxyl radicals in vitro. *J Neurochem.* 1997;69:883–886.

42. Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. *Front Aging Neurosci.* 2010;2:12.
43. Cha J, Zea-Hernandez JA, Sin S, et al. The effects of obstructive sleep apnea syndrome on the dentate gyrus and learning and memory in children. *Journal of Neuroscience.* 2017;37:4280–4288.
44. Khuu MA, Pagan CM, Nallamotheu T, et al. Intermittent hypoxia disrupts adult neurogenesis and synaptic plasticity in the dentate gyrus. *Journal of Neuroscience.* 2019;39:1320–1331.
45. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat Med.* 2019;25:554–560.
46. Kheirandish-Gozal L, Sahib AK, Macey PM, Philby MF, Gozal D, Kumar R. Regional brain tissue integrity in pediatric obstructive sleep apnea. *Neurosci Lett.* 2018;682:118–123.
47. Canessa N, Castronovo V, Cappa SF, et al. Obstructive sleep apnea: Brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med.* 2011;183:1419–1426.
48. Thompson C, Legault J, Moullec G, et al. Association between risk of obstructive sleep apnea, inflammation and cognition after 45 years old in the Canadian Longitudinal Study on Aging. *Sleep Med.* 2022;91:21–30.
49. Apostolova LG, Morra JH, Green AE, et al. Automated 3D mapping of baseline and 12-month associations between three verbal memory measures and hippocampal atrophy in 490 ADNI subjects. *Neuroimage.* 2010;51:488–499.

50. Fouquet M, Desgranges B, la Joie R, et al. Role of hippocampal CA1 atrophy in memory encoding deficits in amnesic Mild Cognitive Impairment. *Neuroimage*. 2012;59:3309–3315.

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Figure 1: Flowchart of the study.

Abbreviations: CPAP, continuous positive airway pressure; MRI, magnetic resonance imaging.

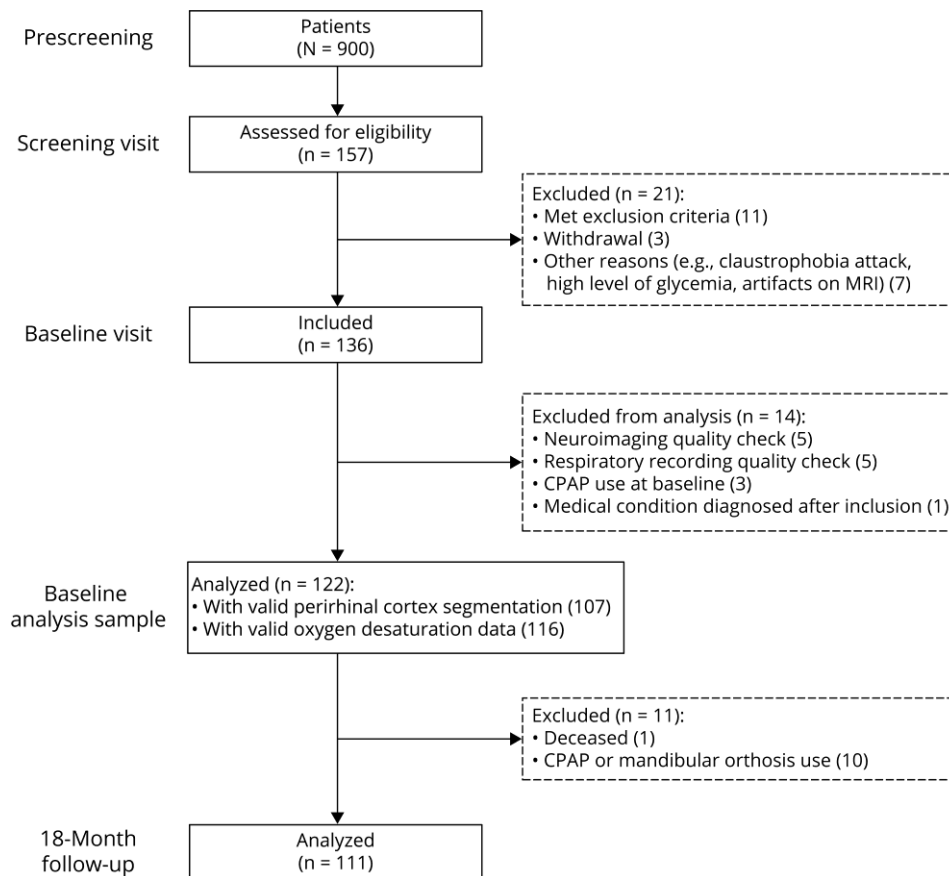


Figure 2: Significant associations between the apnea-hypopnea index and medial temporal subregions volumes according to amyloid status.

Scatterplots of partial correlations between the AHI and medial temporal subregional volumes, according to amyloid status. Detailed statistics are provided in Table 3.

Abbreviations: A β , beta-amyloid; BA, Brodmann area; CA, Cornu Ammonis; DG, dentate gyrus; ERC, entorhinal cortex; HPC, hippocampus; PHC, parahippocampal gyrus; PRC, perirhinal cortex.

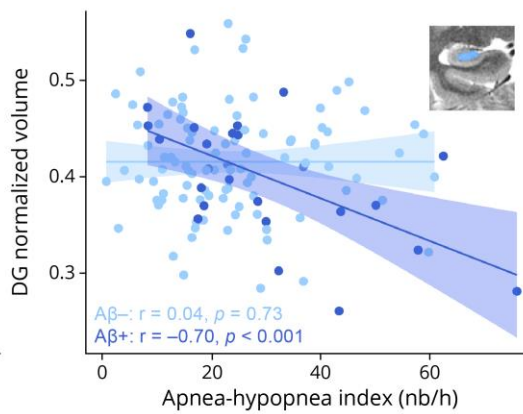
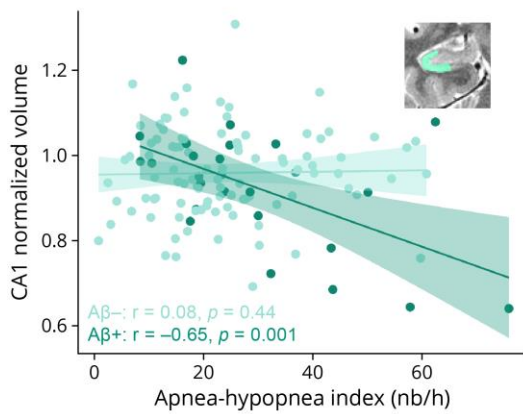
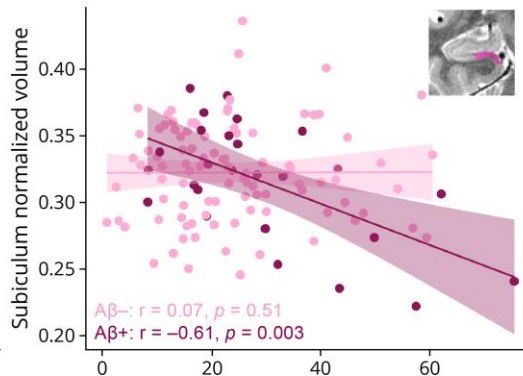
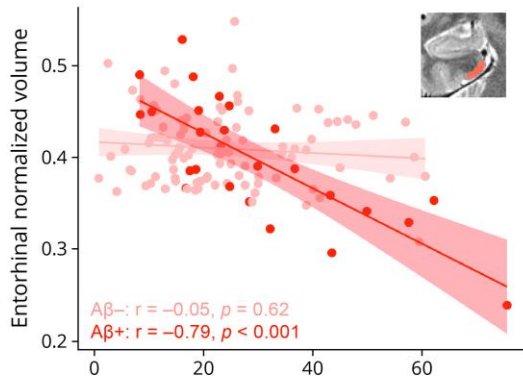
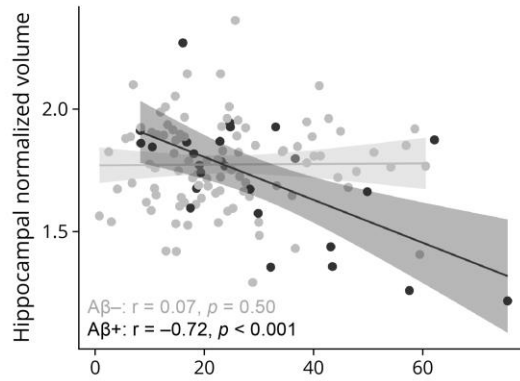
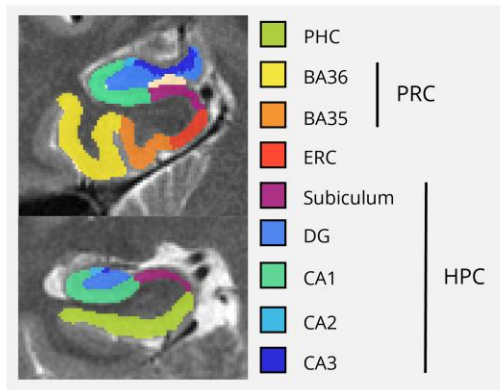


Table 1: Participants' characteristics.

	Whole sample (n=122)	A β -participants (n=96)	A β + participants (n=26)	Between- group differences
Demographics				
Age: years	69.40 \pm 3.85	69.04 \pm 3.53	70.76 \pm 4.72	p=0.04
Sex: number (%) of women	77 (63.12)	61 (63.54)	16 (61.54)	p=0.85
Education: years	13.07 \pm 3.04	13.17 \pm 2.95	12.69 \pm 3.41	p=0.48
Body mass index: kg/m ²	26.02 \pm 4.27	26.19 \pm 4.43	25.39 \pm 3.60	p=0.40
ApoE4 carriers: number (%)	33 (27.05)	20 (20.83)	13 (50)	p=0.003
Cognition				
MMSE: total score	29.04 \pm 1.04	29.14 \pm 1.00	28.69 \pm 1.12	p=0.05
MDRS: total score	141.01 \pm 2.71	141.03 \pm 2.73	140.92 \pm 2.67	p=0.86
CVLT: short-term free recall score				
Baseline	11.99 \pm 2.77	12.13 \pm 2.68	11.50 \pm 3.10	p=0.31
Follow-up ^a	12.05 \pm 2.75	12.26 \pm 2.54	11.29 \pm 3.34	p=0.13
CVLT: long-term free recall score				
Baseline	12.51 \pm 2.80	12.64 \pm 2.77	12.04 \pm 2.92	p=0.34
Follow-up ^a	12.38 \pm 2.56	12.61 \pm 2.38	11.54 \pm 3.02	p=0.07
Sleep				
Pittsburgh Sleep Quality Index: total score	5.03 \pm 3.07	5.06 \pm 3.17	4.92 \pm 2.70	p=0.84
Epworth Sleepiness Scale: total score	5.25 \pm 3.45	5.04 \pm 3.26	6.00 \pm 4.03	p=0.21
Insomnia Severity Index: total score	6.46 \pm 4.91	6.27 \pm 4.66	7.15 \pm 5.81	p=0.13
Total sleep time: min	359.46 \pm 64.30	361.59 \pm 64.13	351.60 \pm 65.56	p=0.48
Sleep latency: min	21.09 \pm 13.96	20.88 \pm 13.76	21.88 \pm 14.93	p=0.75
Sleep efficiency: %	76.77 \pm 10.01	77.00 \pm 9.75	75.93 \pm 11.08	p=0.63
NREM-1 sleep: % of TST	13.52 \pm 7.30	13.68 \pm 7.62	12.91 \pm 6.09	p=0.63
NREM-2 sleep: % of TST	48.40 \pm 8.68	48.89 \pm 8.83	46.59 \pm 7.98	p=0.23
NREM-3 sleep: % of TST	19.83 \pm 9.76	19.00 \pm 9.27	22.91 \pm 11.05	p=0.07
REM sleep: % of TST	18.25 \pm 5.59	18.43 \pm 5.55	17.59 \pm 5.79	p=0.50
Apnea-hypopnea index: number/h	25.02 \pm 14.64	23.86 \pm 13.81	29.30 \pm 16.99	p=0.09
\geq 3% oxygen desaturation index: number/h ^b	13.53 \pm 10.94	12.44 \pm 9.59	17.50 \pm 14.42	p=0.04
Respiratory microarousal index: number/h	20.47 \pm 12.53	19.72 \pm 12.15	23.25 \pm 13.73	p=0.20
Neuroimaging				
Florbetapir neocortical SUVR	1.25 \pm 0.16	1.18 \pm 0.07	1.48 \pm 0.18	p<0.001
Amyloid positive participants: number (%)	26 (21.31)	0 (0)	26 (100)	-
Hippocampal bilateral normalized volume	1.76 \pm 0.20	1.77 \pm 0.18	1.72 \pm 0.24	p=0.24
CA1 bilateral normalized volume	0.95 \pm 0.11	0.96 \pm 0.11	0.93 \pm 0.14	p=0.18
CA2-3 bilateral normalized volume	0.07 \pm 0.01	0.07 \pm 0.01	0.08 \pm 0.01	p=0.12
DG bilateral normalized volume	0.41 \pm 0.06	0.42 \pm 0.05	0.40 \pm 0.07	p=0.25
SUB bilateral normalized volume	0.32 \pm 0.04	0.32 \pm 0.04	0.32 \pm 0.04	p=0.42
ERC bilateral normalized volume	0.41 \pm 0.05	0.41 \pm 0.04	0.40 \pm 0.07	p=0.27
PHC bilateral normalized volume	0.67 \pm 0.09	0.67 \pm 0.09	0.66 \pm 0.09	p=0.53
PRC bilateral normalized volume ^c	1.61 \pm 0.21	1.60 \pm 0.21	1.61 \pm 0.22	p=0.91

Data are indicated as mean \pm standard deviation, unless otherwise specified. Group differences were computed between A β - and A β + participants using Student T-tests for continuous variables and Chi-squared tests for categorical variables.

^a n=111 participants due to one death between baseline and follow-up (87 A β -, 24 A β +).

^b n=116 due to missing data on the finger pulse oximeter (91 A β -, 25 A β +).

^c n= 107 due to missing data after segmentation quality check (83 A β -, 24 A β +).

Abbreviations: A β , beta-amyloid; ApoE4, Apolipoprotein E allele ϵ 4; CA, Cornu Ammonis; CVLT, California Verbal Learning Test; DG, dentate gyrus; ERC, entorhinal cortex; MDRS, Mattis Dementia Rating Scale; min, minutes; MMSE, Mini Mental State Examination; NREM, non-rapid eye movement sleep; PHC, parahippocampal cortex; PRC, perirhinal cortex; REM, rapid eye movement sleep; SUB, subiculum; SUV_r, standard uptake value ratio; TST, total sleep time.

Table 2: Multiple regressions analyses between the apnea-hypopnea index and medial temporal subregions volumes.

Dependent variables	Independent variables	Adjusted R2	β	Confidence interval		p	$p\eta^2$
				-95%	95%		
Whole hippocampus	<i>Whole model</i>	<i>0.17</i>				<i><0.001</i>	
	Sex		0.25	0.08	0.43	0.004	0.069
	ApoE		0.08	-0.1	0.25	0.385	0.007
	A β status		0.49	0.16	0.83	0.005	0.068
	Age		-0.15	-0.32	0.02	0.093	0.025
	Education		0	-0.17	0.17	0.987	<0.001
	AHI		-0.26	-0.45	-0.07	0.007	0.063
	Aβ status*AHI		-0.61	-0.94	-0.28	<0.001	0.103
Entorhinal cortex	<i>Whole model</i>	<i>0.29</i>				<i><0.001</i>	
	Sex		0.22	0.06	0.38	0.007	0.061
	ApoE		0.02	-0.15	0.18	0.845	<0.001
	A β status		0.66	0.34	0.97	<0.001	0.132
	Age		-0.04	-0.2	0.12	0.621	0.002
	Education		-0.08	-0.24	0.08	0.318	0.009
	AHI		-0.49	-0.67	-0.32	<0.001	0.217
	Aβ status*AHI		-0.81	-1.12	-0.5	<0.001	0.191
Perirhinal cortex	<i>Whole model</i>	<i>0.003</i>				<i>0.408</i>	
	Sex		0.01	-0.19	0.21	0.925	<0.001
	ApoE		0.01	-0.19	0.22	0.915	<0.001
	A β status		0.13	-0.27	0.53	0.513	0.004
	Age		-0.25	-0.45	-0.05	0.016	0.057
	Education		-0.06	-0.26	0.15	0.585	0.003
	AHI		-0.09	-0.3	0.12	0.394	0.007
	Aβ status*AHI		-0.05	-0.44	0.33	0.785	0.001
Parahippocampal cortex	<i>Whole model</i>	<i>0.13</i>				<i>0.002</i>	
	Sex		0.26	0.09	0.44	0.004	0.071
	ApoE		0.03	-0.15	0.2	0.778	0.001
	A β status		0.22	-0.13	0.56	0.219	0.013
	Age		-0.08	-0.26	0.09	0.356	0.007
	Education		-0.13	-0.3	0.05	0.153	0.018
	AHI		-0.27	-0.47	-0.08	0.006	0.065
	Aβ status*AHI		-0.26	-0.6	0.09	0.141	0.019
Subiculum	<i>Whole model</i>	<i>0.12</i>				<i>0.003</i>	
	Sex		0.25	0.07	0.42	0.008	0.061
	ApoE		0.04	-0.14	0.22	0.686	0.001
	A β status		0.46	0.11	0.8	0.011	0.056
	Age		-0.08	-0.25	0.1	0.397	0.006
	Education		-0.01	-0.19	0.16	0.882	<0.001
	AHI		-0.25	-0.44	-0.05	0.013	0.053
	Aβ status*AHI		-0.56	-0.9	-0.21	0.002	0.083
CA1	<i>Whole model</i>	<i>0.15</i>				<i>0.001</i>	
	Sex		0.23	0.06	0.41	0.01	0.057
	ApoE		0.09	-0.09	0.26	0.336	0.008
	A β status		0.43	0.09	0.77	0.014	0.051
	Age		-0.16	-0.33	0.01	0.07	0.029
	Education		0.03	-0.14	0.21	0.697	0.001
	AHI		-0.22	-0.41	-0.03	0.023	0.044
	Aβ status*AHI		-0.55	-0.89	-0.21	0.002	0.084
CA2-3	<i>Whole model</i>	<i>0.07</i>				<i>0.035</i>	
	Sex		0.02	-0.16	0.21	0.791	0.001
	ApoE		0.15	-0.04	0.33	0.124	0.021
	A β status		0.53	0.17	0.89	0.004	0.069

	Age		-0.15	-0.33	0.04	0.113	0.022
	Education		-0.12	-0.3	0.06	0.202	0.014
	AHI		-0.23	-0.43	-0.03	0.024	0.044
	A β status*AHI		-0.35	-0.7	0.01	0.054	0.032
Dentate gyrus	<i>Whole model</i>	<i>0.12</i>				<i>0.003</i>	
	Sex		0.23	0.05	0.41	0.012	0.054
	ApoE		0.03	-0.15	0.21	0.712	0.001
	A β status		0.4	0.06	0.75	0.024	0.044
	Age		-0.1	-0.27	0.08	0.278	0.01
	Education		-0.03	-0.2	0.15	0.749	0.001
	AHI		-0.24	-0.43	-0.05	0.016	0.05
	Aβ status*AHI		-0.53	-0.88	-0.19	0.003	0.076

Separate multiple linear regressions models including the volume of each MTL subregion as dependent variables, the AHI and amyloid status as independent variables, controlling for age, sex, education and the ApoE4 status. An interaction term was added between the AHI and amyloid status, and interactions indicated in bold are still significant after correction for multiple comparison ($p=0.05/\text{number of comparisons}=0.05/8=0.006$).

Abbreviations: A β , beta-amyloid; AHI, apnea-hypopnea index; ApoE4, Apolipoprotein E allele ϵ 4; β , standardized regression coefficient; CA, Cornu Ammonis.

Table 3: Post-hoc partial correlations between SDB severity parameters and medial temporal subregional volumes according to amyloid status.

Variable	AHI		Log(ODI)		RMI	
	A β + individuals (n=26)	A β - individuals (n=96)	A β + individuals (n=25)	A β - individuals (n=91)	A β + individuals (n=26)	A β - individuals (n=96)
High-resolution T2 images						
Entorhinal cortex	r=-0.79 p<0.001	r=-0.05 p=0.62	r=-0.75 p<0.001	r=0.01 p=0.95	r=-0.71 p<0.001	r=-0.06 p=0.56
Whole hippocampus	r=-0.72 p<0.001	r=0.07 p=0.50	r=-0.68 p=0.001	r=0.08 p=0.48	r=-0.64 p=0.001	r=0.06 p=0.56
Subiculum	r=-0.61 p=0.003	r=0.07 p=0.51	r=-0.63 p=0.002	r=0.12 p=0.26	r=-0.51 p=0.02	r=0.07 p=0.52
CA1	r=-0.65 p=0.001	r=0.08 p=0.44	r=-0.63 p=0.002	r=0.10 p=0.34	r=-0.57 p=0.006	r=0.07 p=0.54
DG	r=-0.70 p<0.001	r=0.04 p=0.73	r=-0.63 p=0.002	r=0.03 p=0.81	r=-0.63 p=0.002	r=0.04 p=0.71
T1-weighted images						
Entorhinal cortex	r=-0.64 p=0.001	r=0.05 p=0.61	r=-0.64 p=0.002	r=0.01 p=0.93	r=-0.58 p=0.005	r=0.06 p=0.60
Whole hippocampus	r=-0.68 p<0.001	r=0.07 p=0.50	r=-0.62 p=0.003	r=0.06 p=0.57	r=-0.61 p=0.003	r=0.07 p=0.55

Partial correlations between SDB severity parameters and medial temporal subregional volumes were performed separately in amyloid positive (A β +) and amyloid negative (A β -) participants, controlling age, sex, education and the ApoE4 status.

Abbreviations: A β , beta-amyloid; AHI, apnea-hypopnea index; CA, Cornu Ammonis; DG, dentate gyrus; ODI, $\geq 3\%$ oxygen desaturation index; RMI, respiratory microarousals index; SDB, sleep-disordered breathing.

Table 4: Partial correlations between medial temporal subregional volumes and episodic memory at follow-up, in the whole cohort and in subgroups stratified by amyloid status.

Variable	Whole cohort (n=111)		A β + individuals (n=24)		A β - individuals (n=87)	
	Log(CVLT STFR)	Log(CVLT LTFR)	Log(CVLT STFR)	Log(CVLT LTFR)	Log(CVLT STFR)	Log(CVLT LTFR)
AHI: nb/h	r=-0.05 p=0.62	r=-0.07 p=0.48	r=-0.08 p=0.76	r=-0.17 p=0.50	r=-0.04 p=0.75	r=-0.01 p=0.95
RMI: nb/h	r=-0.07 p=0.47	r=-0.11 p=0.27	r=-0.18 p=0.46	r=-0.29 p=0.23	r=-0.05 p=0.64	r=-0.04 p=0.69
log(ODI): nb/h ^a	r=-0.06 p=0.59	r=-0.05 p=0.62	r=-0.04 p=0.86	r=-0.11 p=0.66	r=0.03 p=0.77	r=0.07 p=0.57
Whole hippocampus	r=0.20 p=0.04	r=0.27 p=0.005	r=0.20 p=0.41	r=0.31 p=0.20	r=0.13 p=0.26	r=0.18 p=0.12
Entorhinal cortex	r=0.05 p=0.64	r=0.08 p=0.39	r=-0.08 p=0.76	r=-0.01 p=0.98	r=0.08 p=0.49	r=0.07 p=0.55
Subiculum	r=0.16 p=0.10	<i>r=0.17</i> <i>p=0.07</i>	r=0.27 p=0.27	r=0.32 p=0.18	r=0.10 p=0.35	r=0.09 p=0.44
CA1 subfield	<i>r=0.25</i> <i>p=0.01</i>	r=0.28 p=0.003	r=0.31 p=0.19	r=0.40 p=0.09	r=0.14 p=0.20	r=0.15 p=0.17
Dentate gyrus	r=0.08 p=0.39	<i>r=0.21</i> <i>p=0.03</i>	r=-0.07 p=0.79	r=0.05 p=0.83	r=0.05 p=0.66	r=0.19 p=0.08

Result of the associations between medial temporal subregional volumes and episodic memory at follow-up, controlling for age, sex, education, the ApoE4 status and the intervention group. Results indicated in italics are significant at the $p < 0.05$ uncorrected level, and results indicated in bold are still significant after correction for multiple comparisons ($p = 0.05/8 = 0.006$).

^a whole cohort: n=106, A β + individuals: n=23, A β - individuals: n=83.

Abbreviations: A β , beta-amyloid; AHI, apnea-hypopnea index; CA, Cornu Ammonis; CVLT, California Verbal Learning Test; LTFR, long-term free recall; nb, number; ODI, $\geq 3\%$ oxygen desaturation index; RMI, respiratory microarousals index; STFR, short-term free recall.

Table 5: Sex-stratified partial correlations between SDB severity parameters and medial temporal subregional volumes according to amyloid status.

Variables	Whole sample			A β - individuals			A β + individuals		
	AHI	log(ODI)	RMI	AHI	log(ODI)	RMI	AHI	log(ODI)	RMI
Women									
WH	r=-0.30 p=0.01	r=-0.29 p=0.01	r=-0.23 p=0.05	r=-0.14 p=0.29	r=-0.10 p=0.45	r=-0.13 p=0.34	r=-0.75 p=0.003	r=-0.67 p=0.012	r=-0.69 p=0.009
ERC	r=-0.50 p<0.001	r=-0.36 p=0.002	r=-0.43 p<0.001	r=-0.23 p=0.08	r=-0.10 p=0.47	r=-0.21 p=0.12	r=-0.87 p<0.001	r=-0.72 p=0.006	r=-0.83 p<0.001
PHC	r=-0.34 p=0.003	r=-0.22 p=0.07	r=-0.28 p=0.01	r=-0.23 p=0.09	r=-0.13 p=0.35	r=-0.19 p=0.16	r=-0.71 p=0.007	r=-0.41 p=0.17	r=-0.72 p=0.006
PRC	r=-0.06 p=0.62	r=-0.14 p=0.28	r=-0.04 p=0.77	r=-0.09 p=0.53	r=-0.04 p=0.81	r=-0.07 p=0.61	r=-0.14 p=0.68	r=-0.46 p=0.16	r=-0.24 p=0.49
SUB	r=-0.22 p=0.06	r=-0.21 p=0.08	r=-0.16 p=0.17	r=-0.05 p=0.70	r=-0.03 p=0.84	r=-0.04 p=0.75	r=-0.67 p=0.01	r=-0.53 p=0.07	r=-0.63 p=0.02
CA1	r=-0.26 p=0.02	r=-0.30 p=0.01	r=-0.20 p=0.09	r=-0.13 p=0.33	r=-0.11 p=0.40	r=-0.12 p=0.36	r=-0.63 p=0.02	r=-0.62 p=0.02	r=-0.58 p=0.04
CA2-3	r=-0.20 p=0.08	r=-0.09 p=0.45	r=-0.16 p=0.17	r=-0.04 p=0.77	r=0.08 p=0.58	r=-0.02 p=0.88	r=-0.76 p=0.003	r=-0.51 p=0.08	r=-0.76 p=0.002
DG	r=-0.30 p=0.01	r=-0.26 p=0.03	r=-0.24 p=0.04	r=-0.17 p=0.19	r=-0.12 p=0.37	r=-0.15 p=0.25	r=-0.80 p=0.001	r=-0.69 p=0.009	r=-0.74 p=0.004
Men									
WH	r=0.19 p=0.22	r=0.17 p=0.31	r=0.20 p=0.22	r=0.38 p=0.03	r=0.35 p=0.07	r=0.37 p=0.04	r=-0.76 p=0.046	r=-0.48 p=0.34	r=-0.62 p=0.14
ERC	r=0.08 p=0.63	r=-0.04 p=0.81	r=0.06 p=0.69	r=0.31 p=0.09	r=0.21 p=0.30	r=0.28 p=0.12	r=-0.41 p=0.36	r=-0.62 p=0.19	r=-0.33 p=0.47
PHC	r=-0.03 p=0.86	r=-0.08 p=0.63	r=0.003 p=0.99	r=-0.02 p=0.93	r=-0.05 p=0.81	r=0.01 p=0.96	r=-0.23 p=0.62	r=-0.46 p=0.36	r=-0.20 p=0.67
PRC	r=-0.06 p=0.71	r=-0.06 p=0.74	r=-0.03 p=0.88	r=-0.08 p=0.71	r=-0.08 p=0.71	r=-0.05 p=0.80	r=-0.40 p=0.38	r=-0.56 p=0.25	r=-0.36 p=0.43
SUB	r=0.06 p=0.70	r=0.12 p=0.47	r=0.08 p=0.61	r=0.24 p=0.18	r=0.33 p=0.08	r=0.25 p=0.18	r=-0.79 p=0.035	r=-0.93 p=0.008	r=-0.59 p=0.16
CA1	r=0.21 p=0.18	r=0.23 p=0.18	r=0.20 p=0.20	r=0.39 p=0.03	r=0.41 p=0.03	r=0.37 p=0.04	r=-0.76 p=0.046	r=-0.44 p=0.39	r=-0.64 p=0.12
CA2-3	r=0.03 p=0.86	r=-0.12 p=0.49	r=0.02 p=0.89	r=-0.07 p=0.70	r=-0.18 p=0.36	r=-0.08 p=0.67	r=0.80 p=0.03	r=0.54 p=0.27	r=0.76 p=0.049
DG	r=0.17 p=0.28	r=0.06 p=0.74	r=0.19 p=0.24	r=0.33 p=0.06	r=0.15 p=0.45	r=0.35 p=0.048	r=-0.33 p=0.47	r=-0.03 p=0.96	r=-0.31 p=0.51

Partial correlations between SDB parameters and MTL subregional volumes performed separately in women (n=77, 61 A β - and 16 A β +) and men (n=45, 35 A β - and 10 A β +), controlling for age, education and the ApoE4 status. Of note, only 76 women had valid ODI data (69 A β - and 16 A β +), and 68 women had valid PRC data (54 A β - and 14 A β +). Similarly, only 40 men had valid ODI data (31 A β - and 9 A β +), and 39 men had valid PRC

data (29 A β - and 10 A β +). Results in bold are significant after correction for multiple comparisons ($p=0.05/8=0.006$).

Abbreviations: A β , beta-amyloid; AHI, apnea-hypopnea index; CA, Cornu Ammonis; DG, dentate gyrus; ERC, entorhinal cortex; ODI, $\geq 3\%$ oxygen desaturation index; PHC, parahippocampal cortex; PRC, perirhinal cortex; RMI, respiratory microarousals index; SDB, sleep-disordered breathing; SUB, subiculum.

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