Sleep apnoea in the asymptomatic elderly: a real issue for the brain?

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In the asymptomatic elderly, sleep apnoea does not seem to be associated with a change in local brain volume http://ow.ly/bKQs30jFNeX

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ABSTRACT The link between sleep apnoea and brain structure is unclear; although dysfunction of the hippocampus, middle temporal gyrus and brainstem/cerebellum have been observed previously. However, this link has been little explored in elderly subjects. The aim of this study was to explore the link between sleep apnoea and the brain in an elderly population.

226 asymptomatic elderly subjects (age mean±SD 75.3±0.9 years, range 72.3–77.8 years) from the PROOF (Evaluation of Ageing, Autonomic Nervous System Activity and Cardiovascular Events) cohort study were explored using linear voxel-based or cortical thickness with apnoea/hypopnoea index (AHI; mean±SD 15.9±11.5 events·h^{-1}, range 6–63.6 events·h^{-1}) as a covariate of main interest. The brain volumes of 20 control subjects, 18 apnoeic (AHI >29 events·h^{-1}) treated patients and 20 apnoeic untreated patients from this population were compared using voxel-based morphometry, cortical thickness or surface-based analyses.

AHI was not associated with any change in local brain volume, cortical thickness or cortex surface. Control subjects, apnoeic treated and untreated patients were not different in terms of local brain volume, cortical thickness or surface.

In a specific population of asymptomatic elderly healthy subjects, sleep apnoea does not seem to be associated with a change in local brain volume or in cortical thickness.

This study is registered at ClinicalTrials.gov as NCT00759304.

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Introduction

Obstructive sleep apnoea (OSA) is a prevalent disease characterised by repeated episodes of respiratory airway flow cessation that is complete (apnoea) or not (hypopnoea) during sleep, followed by sudden openings of the upper airway. Chronic intermittent hypoxia and sleep fragmentation are the two main consequences of OSA. In 2001, an experiment showed an increase in apoptosis in the hippocampus in a model of intermittent hypoxia exposure in mice [1]. This publication opened the way for research into brain defects in humans suffering from OSA. After 15 years of research, no clear conclusion could be drawn from the OSA/brain literature, even if two meta-analyses pointed to the hippocampus or the temporal areas as the main structures affected in OSA [2, 3], *i.e.* the brain structure mostly affected during Alzheimer's disease [4]. However, while focusing on the 12 studies using voxel-based morphometry (VBM) [5], a classical method for exploring the anatomical brain, it was noticeable that only three results were reliable, and these showed inconsistent results: the first reporting no change in brain anatomy according to OSA [6]; the second reporting a decrease in cerebellum and middle temporal gyrus subvolumes [7]; and the third reporting a decrease in the hippocampal subvolume among OSA subjects [8]. Additionally, inconsistent results were encountered in studies using cortical thickness: Yun *et al.* [9] and Dalmases *et al.* [10] did not observe any difference between OSA subjects and healthy controls, whereas Joo *et al.* [11] noticed a lower cortical thickness in various brain areas in OSA patients and Baril *et al.* [12] showed a higher cortical thickness linked to hypoxaemic load, respiratory disturbance index or sleep fragmentation. This suggests that previous methodological choices, including the selection criteria for recruitment of participants, might have affected the interpretation of results.

Among the multiple variables and conditions influencing OSA in adults, the advance in age is certainly one of the most potent. Sleep apnoea prevalence increases with age, but reaches a plateau after 60 years [13]. Additionally, cognitive or cerebrovascular consequences of OSA in older adults remain a matter of much debate. Consequently, it has been proposed to dissociate sleep apnoea, and its brain consequences in adults from sleep apnoea in older subjects [14]. In this sense, we were able to report an implication of brainstem and cerebellum in sleep apnoea among adults aged 65 years [15]. However, more importantly, unpublished re-analyses with newer versions of the VBM software failed to confirm this finding, which suggests methodological issues [5]. We had the opportunity to propose an update of our findings in the same PROOF cohort, now aged 75 years, with the most recent and performant algorithms of VBM measurements. Based on published literature, we hypothesised that 1) some OSA-related brain changes among older adults would be retrieved; and 2) the following brain areas would present a lower grey matter volume: hippocampus, middle temporal gyrus and cerebellum (and brainstem). Our first objective was to determine the link between OSA and local brain volume change. Our second objective was to explore the relationship between cortical thickness and sleep apnoea in elderly subjects.

Methods

Subjects

The PROOF (Evaluation of Ageing, Autonomic Nervous System Activity and Cardiovascular Events) cohort study was designed in the early 2000s to evaluate the role of the autonomic nervous system in cardiovascular and cerebrovascular events and death (NCT identifier: NCT00759304) [16]. 111 subjects from Saint-Étienne, France were included in this study at the age of 65 years. All subjects signed an informed consent form and the study protocol was approved by the local ethics committee of Saint-Etienne, France.

Repeated examinations (noted as E1, E2, E3 and E4) consisted of clinical check-up, ambulatory blood pressure monitoring, biological measurements, ECG and polygraphic recordings and/or magnetic resonance imaging (MRI) acquisition. At each time point, results were sent to family practitioners.

In 2010, all volunteers were invited for a new sequence of examinations, with the fourth one (E4) comprising MRI acquisition and polygraphic recording: 226 subjects had valid ambulatory polygraphic and MRI recordings (duration between polygraphic recording and MRI mean±SD 10.5±73.6 days, range (−166–369) days). Subjects with treated sleep apnoea did not have a control polygraphic recording, but they provided daily use of their continuous positive airway pressure (CPAP) device (mean night duration of the treatment, % of night of use during the last year). We defined three groups: 1) patients who were chronically treated for sleep apnoea using CPAP; 2) patients with a pathological apnoea/hypopnoea index (AHI), but no treatment of their sleep related breathing disorder; and 3) healthy controls. Healthy controls and untreated patients were paired with treated patients according to sex, body mass index (BMI) and the presence (or absence) of an antihypertensive treatment. If numerical data were missing at the fourth time point, data from the previous time point were used.

Polygraphic recording

At baseline, all subjects underwent a full-night ambulatory recording using a polygraphic system (HypnoPTT; Tyco Healthcare, Puritan Bennett, Boulder, CO, USA). The following parameters were included: sound measurement, ECG, pulse transit time, nasal pressure, respiratory effort and body position. Arterial oxygen saturation was measured by pulse oximetry (S_{pO_2}). To minimise potential overestimation of sleep duration, subjects completed the St Mary's Hospital questionnaire, while wakefulness before lights-off was excluded from the analysis. All examinations were visually validated and manually scored for respiratory events and nocturnal S_{pO_2} according to the Chicago criteria [17] by a single scorer (FR), with intrascorer reliability for each evaluation being 87%. Hypopnoea was defined as a ⩾50% reduction in airflow from the baseline value lasting ⩾10 s and associated with ⩾3% oxygen desaturation. Apnoea was defined as the absence of airflow on the nasal cannula lasting for ⩾10 s. The absence of rib cage movements associated with apnoea defined the event as central, while a progressive increase in pulse transit time and respiratory efforts allowed definition of the episode as obstructive. AHI is defined as the ratio of the number of obstructive apnoeas and hypopnoeas per hour of reported sleeping time. The indices of nocturnal hypoxaemia were as follows: mean oxygen saturation (S_{pO_2}); percentage of recording time with a S_{pO_2} ⩽90%; minimum S_{pO_2} value recorded during sleep (minimum S_{pO_2}); and oxygen desaturation index (ODI), *i.e.* the number of episodes of oxyhaemoglobin desaturation per hour of reported sleep time during which the blood oxygen level fell by ⩾3%. Pulse transit time was continuously monitored, and autonomic respiratory-related and total autonomic arousal indices were calculated after visual correction.

Epworth sleepiness scale

Excessive daytime sleepiness was estimated using the Epworth sleepiness scale [18] (ESS) on each of the four examinations of the study.

MRI acquisition

MRIs were acquired on a whole-body 1.5 T scanner (Magnetom Avento; Siemens Healthcare, Erlangen, Germany). The acquisition protocol included a three-dimensional T1-weighted magnetisation prepared rapid gradient echo acquisition (echo time (TE) 3.23 ms, repetition time (TR) 2060 ms, inversion time (TI) 1100 ms, field of view 250×250, image matrix 241×256, voxels size: 1×1×1 mm^3); a T2-weighted two-dimensional turbo spin echo axial acquisition (TE 109 ms, TR 6270 ms), and a fluid-attenuated inversion recovery two-dimensional axial acquisition (TE 350 ms, TR 5000 ms, TI 1800 ms) covering the whole brain.

Visual analysis was performed by an experienced radiologist (CB) to exclude main morphological issues.

VBM

VBM has been described elsewhere [19]. Briefly, it is a technique to investigate brain differences in local grey matter or white matter. Unlike classical volumetry, which is interested in structure volumes, the object of analysis of VBM is voxels, *i.e.* three-dimensional pixels, in which a statistical test is performed on each voxel of the three-dimensional MRI. To permit a comparison at such a small scale, MRI images are first segmented into grey matter and white matter to give a grey matter/white matter probability for each voxel. They are then registered to a common reference, most often the Montreal Neurological Institute (MNI) space for a better comparison between studies. Finally, a spatial smoothing is applied within the conditions of the general linear model used in the statistics. We performed an additional optional step called modulation to preserve local volumes (see [5] for our recommendation on the use of modulation). Deformations that appear during the registration step change local volumes and a correction is thus needed.

In this study, we used SPM12, which includes the latest segmentation (unified segmentation [20]) and registration (DARTEL [21]) algorithms. Unified segmentation is an important improvement of segmentation, as it models six head components (fat signal and signals from large veins) instead of three. DARTEL, which includes a fluid deformation with a high number of degrees of freedom, is also an important improvement of registration. In the DARTEL algorithm, a study-specific template is created, which is further registered to the common MNI template.

Default parameters were all used throughout and the final smoothing kernel was set at 8×8×8 mm^3.

Volumes of potential discovered clusters were extracted for further analyses.

Cortical thickness analysis

Cortical thickness analysis was performed using the Freesurfer image analysis suite version 5.3 (http://surfer.nmr.mgh.harvard.edu/), which is documented and freely available for download online [22].

Freesurfer provides a full processing stream for structural MRI data, including reconstruction of cortical surface models, nonlinear registration of the cortical surface with a stereotaxic atlas and labelling of regions on the cortical surface. Briefly, Freesurfer used the MRI signal to determine the grey matter, white matter and cerebrospinal fluid boundaries. Cortical thickness was calculated as the shortest distance between the pial surface and grey matter/white matter boundary at each vertex of the entire cortical mantle of each hemisphere. Moreover, Freesurfer offers the possibility to perform a volume-based approach. In this study, we used both approaches.

Statistical analyses

Classical analyses for demographic variables were performed using Stata 11.0 for Unix (StataCorp, College Station, TX, USA) (tables 1 and 2). Data from the first (E1), second (E2) and fourth (E4) time points were used (table 2).

VBM analyses were performed with SPM12 on data from E4. Firstly, grey matter differences between the three groups were studied using ANOVA. Secondly, we investigated grey matter differences associated to AHI with a linear regression analysis in the whole set of 226 subjects. In these two studies, sex and total intracranial volume, obtained by summing the volumes of grey matter, white matter and cerebrospinal fluid components calculated after segmentation were introduced as covariates. Pre-processings in these two studies were independent. To limit false positives, an absolute masking threshold of 0.2, a value commonly used in the literature (for instance, see [23]), was added to the model. As previously stated [5], the use of a correction for multiple comparison is necessary. Thus, statistical significance was defined as a family-wise error (FWE) p-value of 0.05 on a voxel level or an uncorrected p-value of 0.001 associated with a FWE cluster p-value of 0.05, a cluster being a set of voxels.

Cortical thickness analysis was performed with the linear analysis script of Freesurfer 5.3 and was performed with a 10 mm full width at half-maximum smoothing with precomputed Z Monte Carlo simulation with a vertex-wise/cluster-forming threshold of $p<0.0001$ and cluster-wise $p<0.05$. Only sex was introduced as a covariate.

Moreover, Freesurfer provides the mean thickness of automatically selected parcellation of cortical thickness. These data were exported into Stata 11.0 for Unix. Firstly, differences of thickness of each anatomical region defined by Freesurfer between the three groups were studied using ANOVA. Secondly, linear regressions were used to explore the association between AHI and the thickness of each anatomical region in the whole set of 226 subjects. In those two studies, sex was introduced as a covariate.

Effect size

To facilitate the interpretation of our findings, we performed a sensitivity power analysis for the VBM analysis. As VBM deals with thousands of measures, we chose to focus only on the left hippocampus which has been hypothesised as the main region of decrease. We extracted the left hippocampus volumes

TABLE 1 Population characteristics according to apnoea/hypopnoea index (AHI) status

	AHI <15 events·h^{-1}	AHI ⩾15 and ⩽30 events·h^{-1}	AHI >30 events·h^{-1}	p-value
Subjects n	127	69	30	
Age years	75.2±0.9 (72.2–77.8)	75.3±0.9 (72.5–77.7)	75.4±0.7 (73.8–77.8)	0.438
Male/female n	42/85	34/35	19/11	0.003
BMI# kg·m^{-2}	24.4±4.3 (17.9–33.3)	25.4±3.5 (17.8–35.6)	26.0±2.9 (19.2–30.9)	0.03
ESS#	5.4±3.3 (0–20)	5.5±4.2 (0–20)	6.6±3.5 (1–15)	0.257
AHI events·h^{-1}	7.8±3.6	21.0±4.1	38.3±7.8	<0.001
ODI# events·h^{-1}	4.5±3.0 (0–16.7)	12.3±5.0 (2.4–25.1)	25.4±9.4 (9.9±44.5)	<0.001
S_{pO_2} <90%# %	1.4±5.9 (0–50.0)	3.4±7.7 (0–40.2)	6.7±9.7 (0–41)	<0.001
24-h SBP# mmHg	114.9±13.1 (81–159)	117.0±14.4 (79–157)	120.8±10.8 (101–143)	0.100
24-h DBP# mmHg	71.1±7.9 (51–94)	71.2±8.4 (55–98)	73.7±6.5 (57–84)	0.301
MMS	28.3±1.8 (20–30)	28.4±1.32 (24–30)	28.4±2.1 (22–30)	0.981
TIV L	1.40±0.13 (1.13–1.82)	1.42±0.14 (1.04–1.81)	1.42±0.12 (1.13–1.66)	0.553
HT# yes/no n	59/38	38/18	14/12	0.452

Data are presented as mean±SD (range), unless otherwise stated. BMI: body mass index; ESS: Epworth sleepiness scale; ODI: oxyhaemoglobin desaturation index; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; SBP : systolic blood pressure; DBP: diastolic blood pressure; MMS: mini-mental score; TIV: total intracranial volume; HT: hypertension treatment. #: some data were missing, thus for BMI n=225, ESS n=206, ODI n=224, S_{pO_2} n=224, ambulatory 24-h blood pressure n=213, and HT status n=179.

TABLE 2 Clinical characteristics based on the three groups

	Healthy controls	Subjects	Treated patients	Subjects	Untreated patients	Subjects	p-value
Age years	75.55±0.65	20	75.12±1.11	18	75.40±1.12	20	0.33
Female/male	15/5	20	14/4	18	15/5	20	0.976
BMI E4 kg·m^{-2}	27.38±2.82	20	27.77±3.50	17	26.33±2.82	20	0.325
AHI E4 events·h^{-1}	7.85±3.50	20	33.15±7.99	2	39.95±8.86	20	<0.001
ESS E4	6±3.54	18	6.93±3.36	14	7.42±3.66	19	0.473
AHI E2 events·h^{-1}	13.15±7.38	20	44.80±16.37	18	34.61±14.62	19	<0.001
ESS E2	5.63±2.71	19	8.17±3.68	18	8.11±2.94	19	0.024
ESS E1	6.10±3.02	20	8.11±4.73	18	6.95±3.68	20	0.280
HT E4 yes/no	15/5	20	11/5	16	12/8	20	0.609

Data are presented as mean±SD or n, unless otherwise stated. BMI: body mass index; E1, E2, E4: time points of the study; AHI: apnoea/hypopnoea index; ESS: Epworth sleepiness scale; HT: hypertension treatment.

with the help of an anatomy toolbox [24]. For ANOVA, we used the partial η^2 squared approach calculated as the effect sum of squares divided by the total sum of squares. For linear regression, R^2 was used as a metric of effect size. To be more accurate and according to Selya *et al.* [25], the variation of Cohen's f^2 may be more relevant to the importance of AHI in the hippocampus.

Results

The whole population had a mean AHI of 15.9±0.8 events·h^{-1}, a mean ODI of 9.7±0.6 events·h^{-1} and a mean ESS of 5.6±0.3, with 17 subjects out of 206 (20 missing) being strictly above the threshold of 10. Clinical characteristics according to AHI status are given in table 1. OSA treated patients had a mean CPAP treatment duration of 32.2±6.2 months. Moreover, patients used their CPAP for 6.3±0.2 h·night $^{-1}$, 6.9±0.7 nights·week^{-1}.

VBM analysis on 226 subjects did not show any linear relationship between AHI and local grey matter volume. We did not find any significant linear relationship between AHI and cortical thickness in each of the studied brain regions.

Healthy controls, treated patient and untreated patient groups comprised 20, 18 and 20 subjects, respectively. Clinical characteristics are presented in table 2 for three examinations: E1 in 2001, E2 in 2003 and E4 in 2010. Briefly, the three groups did not differ in terms of BMI, sex or treatment for hypertension on the fourth examination. At E1, the three groups differed in AHI, with the treated patient group having a higher AHI than the untreated patient group, and the untreated patient group having a higher AHI than the healthy control group. The treated patient group had a higher ESS than either the untreated patients or healthy controls.

At the chosen VBM threshold, in we did not notice any grey matter difference between the healthy controls, untreated patient and treated patient groups. In addition, ANOVA did not show any cortical thickness difference between the healthy controls, untreated patients and treated patients. Finally, volume-based analysis did not show any difference.

Effect size

The partial η^2 of three-way ANOVA analysis was 0.029. For linear regression, the size of effect was equal to 0.38, but this is mainly due to the link between hippocampus volume and total intracranial volume. The calculated effect size only due to AHI was f^2=0.004.

Discussion

Unlike our hypothesis, we found neither any grey matter difference between OSA patients under CPAP treatment and untreated apnoeic subjects, nor between treated or untreated apnoeic patients and healthy controls. In addition, linear analysis did not show any grey matter modification associated with a change of AHI. ANOVA, as well as linear analysis of cortical thickness did not show any cortical thickness changes associated with the groups we defined or with a change in AHI.

Four main explanations may be proposed for our results. Firstly, it is possible that OSA is not associated with grey matter changes. This assumption would be in agreement with Joo *et al.* [6] who did not observe any grey matter difference using modulated data (a better understanding on VBM methodology is presented in [5]) or with the multiple studies in which results disappeared with an adequate threshold [15, 26, 27].

Interestingly, in 2017, Baril *et al.* [12] did not find any grey matter defects using VBM either, but noted some cortical thickness differences associated with hypoxaemia or respiratory disturbances. However, we did not notice such differences in our elderly population. This is in agreement with the study from Dalmases *et al.* [10], but not with Joo *et al.* [11], in which the population was younger.

From this perspective, the previously observed differences [7, 8] could be the result of comorbidities in OSA patients. Indeed, the PROOF cohort is a highly selected cohort, without any clinically recognised sleep apnoea syndrome at the beginning of the study, thus suggesting that comorbidities were well controlled over the three groups. Moreover, to our knowledge, the present analysis is the first one conducted in a general senior population, *i.e.* among subjects not recruited for sleep complaints. However, as a second hypothesis, even in our highly selected population, comorbidities such as hypertension are present and may influence brain changes as much as, or even more than sleep apnoea. OSA would then be only one among many potential causes that could alter brain volumes. However, testing the influence of OSA only in a 75-year-old population would be a hard task, if possible. A third possible explanation is that the deleterious impact of sleepiness associated to OSA may have been underevaluated. In 2015, Killgore *et al.* [28] explored the link between sleepiness and brain using a VBM approach: they observed a grey matter reduction in the hippocampus in excessive daytime sleepiness subjects, a result we could confirm in the PROOF cohort study using FreeSurfer [29]. In the three groups we designed, excessive daytime sleepiness was not significantly different. The lack of sleepiness (14–26% of this population defined as an ESS >10) may then explain the absence of grey matter changes. Such a deleterious impact of excessive daytime sleepiness in OSA has also been found by others according to hypertension [30]. Finally, a fourth reliable explanation is that sleep apnoea in older adults could not be considered as similar to that encountered in younger adults. As early as 1985, Littner and McGinty [31] questioned the recognition of asymptomatic sleep related breathing disorders as a disease in older adults. More than 30 years later, the debate is still open [32]. Asymptomatic sleep-related breathing disorder patients do not seem to have an impaired quality of life [33] and OSA seems to not have such a dramatic impact on cognition in the elderly as previously expected [34]. To our knowledge, the PROOF cohort is the only study to assess brain changes on apnoeic older adults. It is therefore difficult to compare our results to those published previously in the field of OSA.

In addition to using the most recent and efficient neuroimaging algorithms, the main strengths of this work are the inclusion of a population of both sexes, homogeneous in terms of age and comorbidities and recruited independently of any sleeping complaint, which revealed the lack of association between OSA and brain changes.

A number of limitations should be acknowledged. The main one was the restricted number of participants included in each group; a limitation directly related to its main questioning, *i.e.* sleep apnoea in asymptomatic elderly subjects. At inclusion in 2001, no subject had a diagnosed OSA, despite a proportion of 40% of participants exhibiting an AHI >15 events·h^{-1}. The PROOF study is an open study and all results were sent to the general practitioners (GPs) who chose to treat or not treat their patients. This explains why some participants with severe apnoea were treated with CPAP, while others were not. Our results show that, ultimately, the treatment option was rarely chosen, suggesting that GPs did not consider asymptomatic sleep apnoeas as a disease to be treated imperatively in a lack of symptoms. As a consequence, the present study had a limited number of participants in each group. The second limitation we faced was the impossibility of performing a longitudinal brain morphometry study, because the MRI equipment changed between our first study and this one. To our knowledge, longitudinal studies have only been performed before and after short-term CPAP treatment, and brain evolution of moderate apnoeic subjects has not yet been explored. The third limitation is the size of the effect, which is small according to Cohen's partial η^2=0.029 for ANOVA analysis and f^2=0.004 for AHI in linear regression.

Conclusion

In the highly selected nonhypersomnolent elderly PROOF population, OSA subjects did not present grey matter volume alterations compared to nonapnoeic controls. In the apnoeic patient group, grey matter volume did not differ between CPAP-treated patients and untreated patients. Moreover, there was no association between linear AHI, ESS and local grey matter changes. Further research is needed to confirm these results in the elderly population, since the PROOF cohort is very specific and may not reflect the elderly population *per se*. Moreover, studying longitudinal cohorts could bring important information about the evolution of AHI in the elderly population as well as its association with brain defects.

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