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A combined neuropsychological and brain imaging study of obstructive sleep apnea

Running head: Cognitive and brain imaging study of OSA patients

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### **Disclosure statement**

This was not an industry-supported study. Dr Yaouhi, Dr Bertran, Dr Clochon, Miss Mézenge, Dr Denise, Dr Foret, Dr Eustache and Dr Desgranges have indicated no financial conflicts of interest.

### **SUMMARY**

Patients with obstructive sleep apnea show neuropsychological impairments ranging from vigilance decrements, attentional lapses and memory gaps to decreased motor coordination, but their cognitive profile, and the origin of the impairments, remain unclear. We sought to establish the neuropsychological profile of 16 newly-diagnosed apneics and to highlight both their morphological and functional brain abnormalities. We used an extensive neuropsychological test battery to investigate attention and vigilance, executive functions, episodic memory and motor domains. For brain imaging, we used the optimized voxel-based morphometry procedure for the MRI data, resting-state <sup>18</sup>F-DG-PET with correction for partial volume effects and voxel-based analyses. In terms of neurobehavioral performance, our patients displayed objective daytime somnolence but little impairment in memory and motor domains. Cerebral data revealed gray matter loss in the frontal and temporo-parieto-occipital cortices, the thalamus, hippocampal region, some basal ganglia and cerebellar regions, mainly in the right hemisphere. The decrease in brain metabolism was also right-lateralized, but more restricted than the gray matter density changes, and involved the precuneus, the middle and posterior cingulate gyrus, and the parieto-occipital cortex, as well as the prefrontal cortex. To conclude, despite the presence of only minor memory and motor impairments, our patients displayed significant cerebral changes in terms of both gray matter density and metabolic levels, and may have benefited from cognitive reserve and compensatory mechanisms. Thus, cerebral changes in OSA patients may precede the onset of notable neuropsychological consequences.

**KEYWORDS:** MRI, PET, neuropsychology, resting state, cognitive reserve

## **INTRODUCTION**

Obstructive sleep apnea (OSA) is characterized by chronically repeated apneic and hypopneic events during sleep. It results in intermittent blood gas abnormalities, repetitive

arousals and the disruption of normal sleep architecture. Furthermore, the respiratory disturbances are associated with dramatic changes in cerebral blood flow amount and velocity (Gillin *et al.* 2002). OSA patients show neuropsychological impairments ranging from vigilance decrements, attentional lapses and memory gaps to decreases in motor coordination (Aloia *et al.* 2004; Beebe *et al.* 2003). However their cognitive profile remains difficult to grasp, given the use of a wide diversity of tests (Decary *et al.* 2000; Fulda and Schulz 2001) and the lack of a clear-cut characterization of disease severity, which is often based on the respiratory disturbance index (Redline *et al.* 2000; Sauter *et al.*, 2000; Veasey 2006).

The possibility of structural impairment of the prefrontal cortex has been raised, given persistent neuropsychological deficits in apneics after treatment, especially in working memory and executive functions (Ferini-Strambi *et al.* 2003; Naëgelé *et al.* 1998). The first etiological model of OSA suggested a dysexecutive profile in apneics resulting from prefrontal cortex vulnerability to sleep fragmentation and blood gas abnormalities (Beebe and Gozal 2002). Other authors, however, have assumed that apneics suffer instead from attentional problems due to lack of sleep, and that there is, therefore no need to hypothesize structural brain damage (Verstraeten and Cluydts 2004).

Apneics' brain morphology has been investigated using magnetic resonance imaging (MRI), and hippocampal (Gale and Hopkins 2004; Morrell *et al.* 2003) and parahippocampal atrophies (Morrell *et al.* 2004) have been observed. Using the voxel-based morphometry (VBM) procedure, which makes it possible to assess the whole brain, Macey and colleagues reported a significant reduction in gray matter density in scattered areas in moderate to severe apneics (Macey *et al.* 2002). Conversely, O'Donoghue and colleagues (O'Donoghue *et al.* 2005) initially failed to find any significant gray matter loss in severe apneics. However, when they adopted a more lenient statistical threshold, they observed gray matter density loss in the posterior and mesial temporal lobe bilaterally and in the left insular region.

Functional neuroimaging methods can reveal subtle neural dysfunction more effectively than morphological MRI, but few studies have used such techniques so far to study apneics. An FDG-PET study of five patients showed hypometabolism in the right amygdala, left hippocampus and left medial parietal cortex (Dani *et al.* 1996). Another study of eight patients by the same authors revealed hypometabolism in the anterior cingulate gyrus and the right premotor area (Pietrini *et al.* 1998). To our knowledge, no PET study has been carried out on OSA patients which performed an objective and comprehensive voxel-based analysis using SPM software.

In this study, we sought to describe the profile of cognitive impairment in a group of mild to severe apneics using a comprehensive neuropsychological test battery, and to assess abnormalities in both gray matter density and resting-state brain glucose utilization in the same group of patients throughout the entire brain.

## **METHODS**

### **Subjects** (see Table 1)

Sixteen newly-diagnosed patients (15 men and 1 woman; mean age = 54.75, S.D. = 5.71) with OSA were recruited. The inclusion criteria were a clinical profile and subjective complaints of OSA, in accordance with the International Classification of Sleep Disorders (1997) and an apnea-hypopnea index (AHI) of  $\geq 10/h$ . All patients were right-handed, had a mean AHI of 38.31 (S.D. = 14.33), at least seven years of schooling, and a normal score on the Mini Mental State Examination (MMSE). Given the lack of information about the interval between the disease's onset and its diagnosis, we asked our patients to estimate the date at which a significant decline had occurred in their quality of life and also when they experienced OSA symptoms for the first time. They estimated that the interval did not exceed a couple of years.

Fourteen healthy control subjects (13 men and 1 woman; mean age = 52.71, S.D. = 7.01) matched with the OSA group for age, education and handedness underwent polysomnographic recordings (PSG) and a neuropsychological assessment. Each subject was submitted to full overnight polysomnographic screening (mean AHI = 5.71, S.D. = 3.27). In addition to the exclusion criteria described above, no control had any history of snoring or sleep complaints, and none showed objective daytime somnolence. Brain imaging data were compared with those of another group of 19 strictly-selected, healthy age-matched controls (mean age = 55.26, S.D. = 6.67) from a brain database at the Cyceron Neuroimaging Center in Caen, France. This set of controls had been screened for cerebrovascular risk factors, mental disorder, substance abuse, head trauma, significant MRI or biological abnormality, and incipient dementia using a memory test battery (Baron *et al.* 2001). The study was approved by the Research and Ethics Committee. All participants gave informed written consent.

### **Protocol description**

Participants underwent two full-night polysomnographic recordings (PSG), the first one for familiarization. After the second night, a neuropsychological examination and a maintenance of wakefulness test (MWT) were carried out. Within a few days' interval at most, each patient also underwent an MRI scan and a PET-FDG study. Before undergoing brain imaging scans, we excluded any volunteers experiencing claustrophobia or anxiety in a confined environment. During data acquisition, they were reassured, knowing that they could remain in contact with us throughout the process. Finally, as stated on the consent form they signed, they knew that they could interrupt the experiment at any time. During the PET data acquisition, the wakefulness of our patients was monitored with a portable EEG device.

### **Sleep analysis**

We conducted a standard polysomnography (data acquisition system: CID-102; Cidelec, Angers, France) including an electroencephalogram (EEG), left and right electrooculogram (EOG), chin electromyogram (EMG) and electrocardiogram (ECG). EEG leads were used as follows: Fp1 and Fp2 (frontal), C3 and C4 (central), T3 and T4 (temporal), and O1 and O2 (occipital) according to the 10-20 International System, with ear reference. The sampling frequency was 64 Hz. Thoracoabdominal respiratory movements were recorded by strain gauges, nasal airflow by nasal cannula, snoring by tracheal microphone and oxygen saturation by finger pulse oximeter. The occurrence of respiratory efforts was validated by means of a suprasternal pressure transducer (Meslier *et al.* 2002). In addition, electromyographic recordings were made of the tibialis anterior muscles to detect periodic leg movements. Episodes of apnea were defined as complete cessations of airflow for 10 seconds or more, and episodes of hypopnea as decreases in nasal airflow of more than 50%, and lasting for at least 10 seconds, accompanied by desaturation  $\geq 3\%$  or microarousals. The mean AHI during total sleep time was used as a respiratory disturbance index. A decrease in oxygen saturation of 3% or more from the baseline level was regarded as clinically significant. A desaturation index (DI) during total sleep time was calculated. We also took into account the percentage of sleep time spent in desaturation  $\leq 90\%$  (TSD). Recordings were scored off-line by an experienced neurologist according to Rechtschaffen and Kales' criteria (Rechtschaffen and Kales 1968), with 30-second epochs. Microarousals were scored according to the criteria of the American Sleep Disorders Association (1992). Respiratory events and periodic leg movements were automatically detected and visually corrected when necessary. The microarousal index (MI) during total sleep time was used as a sleep fragmentation index. The following variables were determined: sleep-onset latency (SL), sleep efficiency (SE), total sleep time (TST) and the percentage of time spent in sleep stages (1+2) and (3+4), and rapid eye movement sleep (REM).

## **Neuropsychological examination**

Our patients underwent an extensive battery of neuropsychological tests. Attention and vigilance were assessed by means of four subtasks taken from the test battery for attentional performance (TAP; Zimmermann and Fimm 1993), namely 'bimodal vigilance', 'alertness', 'go/no-go' and 'visual scanning', and two subtasks of the Wechsler memory scale (WMS3; Wechsler, 2001), namely forward digit and spatial spans. Working memory was assessed by means of the 'working memory' subtask (TAP) and three subtasks of the WMS3, namely backward digit, spatial spans and 'letter-number sequencing'. Executive functions were measured with a verbal fluency test (Cardebat *et al.* 1990) and two TAP subtasks: 'divided attention' and 'flexibility'. Episodic memory was gauged using four WMS3 subtasks: two verbal ones, namely 'logical memory' and 'verbal paired associates', and two visual ones, namely 'faces' and 'family pictures', while the Purdue pegboard test was used to test motor coordination in 11 patients.

## **Brain imaging**

### Data acquisition

A high-resolution T1-weighted volume MRI scan was conducted for each patient. This consisted of a set of 128 adjacent axial slices parallel to the anterior-posterior commissure (AC-PC line), with a slice thickness of 1.5 mm and a pixel size of 0.94 x 0.94 mm, using the spoiled gradient echo sequence (SPGR) (time repetition (TR) =10.3 ms; echo time (TE) =2.1 ms; field of view (FOV) =24\*18; matrix=256\*192). All the MRI data sets were acquired on the same scanner (1.5 T Signa Advantage EchoSpeed; General Electric) using the same parameters. Standard correction for field inhomogeneities was applied during acquisition.

Each subject also underwent a PET-FDG study. Data were collected using the high-resolution PET-FDG ECAT Exact HR+ device with an isotropic resolution of  $4.6 \times 4.2 \times 4.2$  mm (FOV = 158 mm). The patients were fasted for at least 4 hours prior to scanning. To minimize anxiety, the PET-FDG procedure was explained in detail beforehand. The head was positioned on a headrest according to the canthomeatal line and gently restrained with straps.  $^{18}\text{F}$ FDG uptake was measured in the resting condition, with eyes closed, in a dark, quiet environment. A catheter was introduced into a vein in the arm to inject the radiotracer. Following Ga transmission scans, three to five mCi of  $^{18}\text{F}$ FDG were injected as a bolus at time 0 and a 10-minute PET-FDG data acquisition period started at 50 minutes post-injection. Sixty-three planes were acquired with septa out (volume acquisition), using a voxel size of  $2.2 \times 2.2 \times 2.43$  mm (x y z). During the PET-FDG data acquisition, head motion was continuously monitored with laser beams projected onto ink marks drawn on the forehead and corrected whenever necessary.

#### Image processing and conversion

MRI data were analyzed using SPM2 and the optimized VBM protocol, described in detail elsewhere (Ashburner and Friston 2001; Good *et al.* 2001), and already in use in our laboratory (Chételat *et al.* 2003; Chételat *et al.* 2005; Desgranges *et al.* 2007). Briefly, the procedure included customized template creation (of the whole brain and of the gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) data sets) based on the MRI data of all the patients and controls ( $n = 35$ ), segmentation and normalization of the original (i.e. in native space) scans using these customized priors to determine optimum normalization parameters, application of these optimum parameters to the original scans, segmentation of the normalized data and smoothing of the resulting GM partitions, using a 12-mm Gaussian filter.

Glucose metabolic values measured using PET may sometimes be biased, due to partial volume effects (PVE), i.e. radiotracer concentration in small structures being influenced by surrounding structures. For this reason, the PET-FDG data were first corrected for PVE due to both CSF and WM, using the optimum voxel-by-voxel method described in detail by Quarantelli and colleagues (Quarantelli *et al.* 2004) and already in use in our laboratory (Chételat *et al.* 2003; Desgranges *et al.* 2007). All image processing steps were carried out using ‘PVE-lab’ software. Using SPM2, corrected PET-FDG data were then subjected to coregistration onto their respective MRIs and normalized to the same customized template as that used for the normalization of MRI data, reapplying the optimum normalization parameters estimated by means of the VBM protocol. The corrected and spatially normalized PET-FDG sets were then smoothed using a classic Gaussian kernel of 14 mm.

### Statistical analysis

Mean differences in PSG and neuropsychological variables between patients and controls were calculated by means of the one-tailed Mann-Whitney U test. Spearman’s rank correlation coefficients were then calculated in the patient group between the PSG variables: apnea/hypopnea index (AHI), microarousal index (MI), desaturation index (DI), percentage of sleep time spent in desaturation <90% (TSD), mean score on the maintenance of wakefulness test (MWT) and the deficient neuropsychological scores. We used a statistical significance threshold of  $p < 0.05$ , uncorrected for multiple comparisons.

Regarding the MRI and PET data, we assessed group differences to obtain maps of significant gray matter density decrease and significant hypometabolism in patients with OSA compared with controls. Two independent analyses were performed on the MRI and PET data, both using the “compare-populations: 1 scan/subject” (two sample t-test)” SPM2

routine. To minimize “edge effects”, only those voxels with values above 60% of the mean for the whole brain were selected for statistical analysis. We used the “proportional scaling” routine to control for individual variations in PET data. For these analyses, we used a statistical significance threshold of  $p < 0.005$  (uncorrected for multiple comparisons) for the voxels and  $p$  corrected  $< 0.05$  for the clusters.

Lastly, using the “single-subject: covariates only” SPM2 routine, with PSG variables (see above) and the MWT and deficient neuropsychological scores as covariates, correlations were computed across the 16 OSA patients with PET data. For each correlation, the influence of age was controlled by setting age as a confounding variable. For these correlative analyses, we used a threshold of  $p < 0.005$  uncorrected, with a minimum cluster size of 50 voxels, to limit the risk of false positives. A more liberal threshold in correlative analyses may not fully protect against results due to chance, but has previously been used with the same approach not only by our group (Chételat *et al.* 2003; Desgranges *et al.* 1998) but also by others (Teipel *et al.* 2006; Zahn *et al.* 2006).

## **RESULTS**

Patients differed significantly from controls in terms of PSG variables, sleep architecture, daytime sleepiness and quality of life (Table 1), as well as several neuropsychological (episodic memory and motor domains) and cerebral findings (Tables 2 and 3)

Insert Table 1

### **Neuropsychological outcomes**

Apneics performed more poorly than controls on two of the WMS3 episodic memory subtests (‘verbal paired associates’ learning curve, percentage of retained items in ‘family pictures’) and on both components of the Purdue pegboard test (‘dominant hand’ and

'assembly task') (Table 2). The remaining neuropsychological test scores were within the normal range.

Insert Table 2

There were no significant correlations between these deficient neuropsychological scores, the PSG variables or the MWT score.

### **Gray matter density changes**

Significant gray matter loss (Fig. 1 and Table 3) was found in the bilateral prefrontal cortex (inferior, middle and superior gyri), bilateral inferior parietal gyrus, right temporal cortex (inferior, middle and superior temporal gyri), occipital cortex (left middle occipital gyrus, right fusiform and lingual gyri), right thalamus, some of the basal ganglia (left putamen, caudate nucleus and pallidum), right hippocampus and parahippocampal gyrus and cerebellum (right cerebellar hemisphere and vermis). Most of these abnormalities were right-lateralized.

Insert Table 3 and Figure 1

### **Cerebral metabolic changes**

Apneics only showed significant hypometabolism in the right hemisphere (Fig. 2 and Table 4), in the precuneus, middle and posterior cingulate gyrus, parietal cortex (supramarginal gyrus, inferior parietal gyrus, angular gyrus), occipital cortex (cuneus and superior occipital gyrus) and superior temporal gyrus. There was also a trend ( $p$  corrected < 0.08 for the clusters) towards hypometabolism in the prefrontal cortex (inferior and middle frontal gyri). Note that the peak located in this region was most significant at the voxel level (see Table 4).

Insert Table 4 and Figure 2

## **Links between PSG/neuropsychological and brain metabolism**

All the significant correlations went in the expected direction. Regarding PSG data, we found only a negative correlation between MI and the metabolism of the bilateral superior motor area and the left superior parietal cortex (Fig. 3 and Table 5).

Objective daytime sleepiness, i.e. the MWT score, correlated positively with cerebellar metabolism, bilaterally (Fig. 3 and Table 5). The paired associates and Purdue pegboard (both measures) scores were also positively correlated with this region (Fig. 3 and Table 5).

## **DISCUSSION**

We studied a group of patients suffering from mild to severe OSA, using a comprehensive neuropsychological test battery and, for the first time, both gray matter density and resting-state brain glucose utilization examinations in the same group of patients, including 1) an optimized VBM procedure using a customized template from both patients and controls, 2) the correction of PET data for PVE and 3) the same threshold for assessing both atrophy and hypometabolism statistics.

### **Neuropsychological performances**

Compared with controls, our patients showed relatively preserved attentional performance. We did not find any group effect in our patients, although some displayed scattered attentional impairments (reaction time and/or errors). Mazza and colleagues (Mazza *et al.* 2005) reported vigilance and/or attentional impairment in the majority of their patients. These authors used an attentional test battery comprising three long-lasting tasks: 1) Oxford sleep resistance (OSleR), which is an objective daytime somnolence test resembling the MWT condition, 2) a driving simulator task and 3) the continuous performance test (CPT). Our longest attention test was ‘bimodal vigilance’, which lasted 15 minutes, whereas all the

attentional tasks in the study conducted by Mazza and colleagues (Mazza *et al.* 2005) lasted more than 20 minutes. In addition, our patient group fell asleep within approximately 20 minutes on average (MWT score), suggesting that potential attentional impairments might have been revealed by long-lasting tasks (Decary *et al.* 2000).

Alchanatis and colleagues (Alchanatis *et al.* 2005) showed that high-intelligence patients had the same attention/alertness performances as high-intelligence controls, and assumed that high intelligence offers some protection against OSA-related cognitive decline, possibly in the form of increased cognitive reserve. In our study, most of the patients were highly educated (graduate and postgraduate levels) and had professions involving permanent intellectual and/or attentional constraints (e.g. entrepreneurs, directors, a corporate lawyer, two medical professionals and three subjects occupying a position of responsibility). There is reason to believe that their professional experience may have allowed them to cope somewhat better with routine attentional requirements. However, they did acknowledge having to struggle to maintain their attention in monotonous and long-lasting situations.

In the executive function assessment, our patients performed similarly to controls, in agreement with some authors (Redline *et al.* 1997; Verstraeten *et al.* 2004) but in contrast to others (Bedard *et al.* 1991; Montplaisir *et al.* 1992). A critical review (Verstraeten and Cluydts, 2004) regarding the executive control of attention in apneics suggested that several findings in the literature, interpreted as evidence of dysexecutive performance, should be viewed with caution, given the lack of careful methodology (e.g. basic attentional performances were only infrequently monitored in executive tasks). Our findings i.e., only vigilance decrements, as evidenced by MWT scores, suggest a probable decrease in the basic tonic attention level in apneics (Lis *et al.* 2008; Verstraeten and Cluydts 2004).

In terms of memory, our patients displayed minor impairment in word list learning, confirming the findings of Salorio and colleagues (Salorio *et al.* 2002). They also displayed

slightly decreased recall in a visual episodic memory task. In their group of patients, Naëgelé and colleagues (Naëgelé *et al.* 2006) observed a free recall deficit in episodic memory but normal maintenance, recognition and forgetfulness, suggesting that memory impairment in OSA is mild (Fulda and Schulz 2001) and does not affect all memory processes (Naëgelé *et al.* 1995; Naëgelé *et al.* 2006; Salorio *et al.* 2002). Thus, in our study, a memory task, namely 'Paired associates', evidenced some learning difficulties and, another one, namely 'Family pictures', showed a mild free recall impairment, in accordance with the literature, these two tasks being usually used to assess the same cognitive function, i.e. episodic memory.

Lastly, in the motor domain, the Purdue pegboard test evidenced both simple motor speed and fine coordination deficits, in accordance with several previous studies (Bedard *et al.* 1991; Beebe *et al.* 2003; Greenberg *et al.* 1987).

In sum, our apneic sample displayed only minor impairment when they underwent a comprehensive neuropsychological test battery, in agreement with other studies (Kim *et al.* 1997; Redline *et al.* 1997). Our findings do not corroborate the presumed dysexecutive profile (Beebe and Gozal 2002).

It should be pointed out that OSA without notable cognitive impairments has been fortuitously discovered in about half a non-clinical population (Quan *et al.* 2006). The daytime neurobehavioral manifestations of OSA may simply be an epiphenomenon of respiratory disturbances during sleep and many resilience factors may temporarily prevent apneics from sustaining substantial neurobehavioral deficits (Beebe 2005). These factors include sleep deprivation tolerance (Mu *et al.* 2005) and cognitive reserve that allows patients to cope relatively well with daytime challenges (Stern 2002).

The relationship between neuropsychological deficits and OSA features is rarely strong and consistent (Adams *et al.* 2001; Kingshott *et al.* 1998; Sauter *et al.*, 2000), and there were no significant correlations in our sample between the deficient neuropsychological

scores, the PSG and the MWT variables. Such links would, however, appear to exist in more severely affected patients, as suggested by a number of studies highlighting the impact of nocturnal hypoxemia on vigilance, executive and psychomotor tasks and the impact of vigilance impairment on attention and memory functions (Bedard *et al.* 1991; Montplaisir *et al.* 1992). Unlike the aforementioned studies which comprised patients with profound hypoxemia, our sample did not seem to be severely hypoxemic (very few patients were under 80% in terms of the percentage of time spent under this degree of desaturation). Furthermore, our patients were mostly in their mid-fifties, and possibly at disease onset. In most cases, they estimated that changes in their quality of life had occurred within the last couple of years. Hence, untreated OSA is likely to have a more substantial effect on cognitive functioning with advancing years. In fact, a recent study showed that aging apneics demonstrate cognitive decline, while younger patients with the same disease severity are somehow able to compensate for this effect (Alchanatis *et al.* 2008). Moreover, elderly patients may have a risk of dementia comorbidity (Bliwise 2002; O'Hara *et al.* 2005).

### **Cerebral changes**

Taken together, our findings revealed cerebral changes (mainly right-lateralized) regarding both gray matter density and metabolism. PET measurements of resting-state brain glucose utilization reflect local baseline integrated synaptic activity and therefore both neuronal lesions and synaptic dysfunction, whereas VBM only assesses gray matter loss. The latter was located in scattered sites, i.e. the frontal and temporo-parieto-occipital cortices, the thalamus, some of the basal ganglia and the cerebellar regions, whereas the decrease in brain metabolism was more localized than gray matter density changes, restricted to the cuneus and precuneus, temporo-parieto-occipital cortices and middle and posterior cingulate area, as well as the prefrontal cortex (as a statistical trend).

Our patients showed significant gray matter loss in several brain areas previously identified by Macey and colleagues (Macey *et al.* 2002). Interestingly, some of the affected brain areas happen to be particularly vulnerable to anoxia, such as the basal ganglia, the cerebellum and the hippocampal region (Gozal *et al.* 2001; Konaka *et al.* 2007). Hypoxemia may cause brain structural changes, as shown in animal models (Gozal *et al.* 2001). That said, our patients did not seem to be severely hypoxemic and the controlled hypoxia of rodent models in a laboratory setting (e.g. Gozal and coworkers) cannot be likened to our patients' condition, in terms of exposure to hypoxia. Thus, the decrease in gray matter density may also be induced by factors other than apneic events, i.e. brain lesions that are congenital in nature, acquired (Macey *et al.* 2002) or subsequent to cardiovascular comorbidities (Macey and Harper 2005; O'Donoghue *et al.* 2005). As in the study conducted by Macey and colleagues, it is noteworthy that our sample encompassed patients with cardiovascular comorbidities (controlled hypertension, dyslipidemia and prior but no recent history of myocardial infarction).

The gray matter density changes seen in our patients do partially corroborate the prefrontal hypothesis, given the changes found not only in the PFC region but also in the basal ganglia and thalamus which are linked to this region (Alexander and Crutcher 1990; MacDonald *et al.* 2000).

These gray matter density changes may account for certain neurobehavioral impairments seen in our patients, as many of the atrophic sites (right frontoparietal circuit extending to basal ganglia) are involved in attentional abilities (Sturm *et al.* 1999; Sturm and Willmes 2001). The cerebral damage (especially the prefrontal and thalamic ones) may also account for our patients' sleepiness (Coull 1998; Portas *et al.* 1998) and for the residual somnolence reported in treatment studies (Marshall *et al.* 2006).

In addition, some brain areas in which gray matter is significantly decreased in our patients (hippocampus and thalamus which belong to the Papez circuit, as well as frontoparietal regions) play an important role in episodic memory (Eustache and Desgranges 2008), which is in agreement with the mild memory deficit seen in our patients. Lastly, the motor speed and fine motor coordination impairments displayed by our patients may be linked with cerebellar changes (Ramnani *et al.* 2001; Verleger *et al.* 1999).

Hypometabolism was more restricted than the gray matter density changes and was found in the precuneus, the parieto-occipital cortex and the cingulate gyrus (middle and posterior areas), as well as in the prefrontal cortex (as a statistical trend). Some of these structures were also atrophic, in particular the right inferior parietal cortex and prefrontal cortex, the latter finding reinforcing the frontal hypothesis. The functional impairment of the precuneus and cingulate gyrus, which were not atrophic, may have been caused partly by remote effects originating from morphologically-impaired areas with decreased connectivity (Chételat *et al.* 2003), although we cannot exclude the possibility that minor structural changes in these areas may also have been partly responsible for this hypometabolism (at a lenient threshold of  $p < 0.01$  uncorrected, GM loss was observed in these structures).

Some of the brain areas found to be hypometabolic in our sample (i.e. the precuneus, cingulate areas and inferior parietal cortex) belong to the ‘default mode’ circuit, a “novel and only recently appreciated brain system that participates in internal modes of cognition”, i.e. a neural circuit of ‘normal’ mental activity in the conscious resting state (Buckner *et al.* 2008; Cavanna and Trimble 2006; Raichle *et al.* 2001). Although the wakefulness of our patients was monitored during the PET data acquisition period using a portable EEG device, unlike healthy subjects, they probably had disturbed neural activity in brain regions that are usually active during the normal resting state. Similarly, using quantitative electroencephalographic

analysis (qEEG), Morisson and colleagues (Morisson *et al.* 1998) recorded an EEG slowing in awake apneics, in all the cortical regions they examined. This suggests that, during wakefulness, the apneics' functional neural abnormalities may disturb the mental activity needed in the resting condition.

All the significant correlations between the PET data and MWT scores and the deficient neuropsychological scores were found in cerebellar regions. Our findings not only underline the well-known links between motor function and cerebellum, but also point to the involvement of this region in cognitive functions, notably in episodic memory (Andreasen *et al.* 1999; Leiner *et al.* 1991; Schmahmann and Pandya 1997). In addition, we found significant correlations between the MI index and the metabolism of the bilateral superior motor area and the left superior parietal cortex, which may reflect a negative effect of sleep fragmentation, and could be linked to psychomotor vigilance decrements seen in healthy subjects after sleep deprivation (Drummond *et al.* 2005a).

### Limitations

One of the limitations of this study was the relatively small sample of patients, which prevented us from generalizing our findings to all apneics, notably the neuropsychological results. Given the small size of this group, we chose not to correct for multiple comparisons as far as the neuropsychological data were concerned, in order to highlight cognitive abnormalities, even mild ones, and clarify their links with the brain imaging results. Regarding the imaging analysis, the whole-brain VBM method has sometimes been criticized because of the normalization process (inducing some deformations) and has been regarded as less sensitive than the region-of-interest method when it comes to detecting abnormalities in small subcortical structures. However, the use of an optimized VBM technique, i.e. obtaining a customized template from both samples (patients and their controls), has proved to be

effective in studies of several pathologies (Chételat *et al.* 2003; Desgranges *et al.* 2007; Mevel *et al.* 2007 ; Salmon *et al.* 2008, for a review) as well as of healthy aging (Kalpouzos *et al.*, in press). Furthermore, this method presents notable advantages and only minor drawbacks. While the region-of-interest method leaves large brain areas unexplored and is very time-consuming and expertise-dependent, the automatic time-saving voxel-by-voxel method provides a prospective and fully comprehensive assessment of the brain, without bias. Regarding functional imaging, the use of a resting-state PET assessment allowed us to study the functional cerebral changes throughout the entire brain, while an activation study would have been informative in terms of the cerebral structures involved in a given neuropsychological function but would have been confined to that function.

In summary, our patients had significant metabolic and gray matter density changes, contrasting with minor neuropsychological deficits, suggesting that cognitive reserve may have averted a more significant impact of OSA. Some of these cerebral changes partially corroborate the prefrontal hypothesis. However, the neuropsychological assessment failed to reveal significant attentional or executive deficits. Nonetheless, physiological measurements (MWT latencies) did show decreased ability in our patients to resist sleepiness, evidencing to some extent a decline in vigilance. Thus, the relatively intact behavioral performances of our patients may have been due to compensatory mechanisms (Stern 2002). In line with this idea, an fMRI study found that, relative to controls, apneics demonstrated intact performances on a verbal learning task, but with greater brain activation (Ayalon *et al.* 2006). Likewise, after sleep deprivation, healthy subjects have been found to display additional brain activation during demanding cognitive tasks (Drummond *et al.* 2005b). In the resting-state condition, our patients showed a metabolic defect in the default-mode circuit. Further studies are needed to improve our understanding of the neurobehavioural sequelae of this functional impairment.

Our findings also highlight the contribution of cerebellar changes to impairments in the memory and motor domains.

To conclude, in apneics without notable cognitive impairments, cerebral imaging may be more sensitive when it comes to detecting the impact of silent OSA on brain morphology and function. The disease probably starts many years before it is clinically expressed, slowly becoming more severe and apparent in terms of significant neurobehavioral manifestations.

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**Table 1: OSA patient and control characteristics**

Characteristics	Patients (n=16)	Controls (n=14)	p value
Age	54.75 ± 5.71	52.71 ± 7.01	NS
Education (years)	13.38 ± 4.56	11.93 ± 3.50	NS
Mini mental state examination (MMSE)	28.88 ± 1.75	29.07 ± 0.73	NS
Apnea/apopnea index (AHI)	38.31 ± 14.33	5.71 ± 3.27	<0.001
Desaturation index (DI)	35.00 ± 13.53	5.29 ± 4.12	<0.001
% desaturation time < 90% (TSD)	12.63 ± 17.64	0.07 ± 0.27	<0.001
Microarousal index (MI)	29.69 ± 13.39	16.86 ± 9.57	0.005
Sleep latency (SL)	12.77 ± 9.31	17.47 ± 9.67	NS
Sleep efficiency (SE)	85.63 ± 7.27	81.14 ± 8.01	0.049
Total sleep time (TST)	407.31 ± 40.97	384.80 ± 54.00	NS
% stages 1+2 (sleep period time)	54.40 ± 8.91	45.09 ± 9.36	0.0034
% stages 3+4 (sleep period time)	19.49 ± 7.05	25.69 ± 6.72	0.005
% REM stage	14.52 ± 4.77	14.52 ± 3.06	NS
Epworth sleepiness scale (ESS)	12.50 ± 4.50	4.36 ± 3.61	<0.001
Maintenance of wakefulness test (MWT)	20.40 ± 13.98	37.00 ± 3.97	<0.001
Beck depression inventory (BDI)	2.81 ± 2.37	2.43 ± 2.38	NS
Calgary SAQLI, daily functioning	4.80 ± 1.21	6.36 ± 0.84	<0.001
Calgary SAQLI, social interactions	4.80 ± 0.94	6.36 ± 0.74	<0.001
Calgary SAQLI, emotional functioning	5.73 ± 0.80	6.29 ± 0.61	0.037
Calgary SAQLI, pre-treatment symptoms	10.60 ± 4.88	2.43 ± 2.56	<0.001

**Table 2: Cognitive performances in OSA patients and controls**

<b>Neuropsychological tasks*</b>	<b>Patients (n=16)</b>	<b>Controls (n=14)</b>	<b><i>p</i> value</b>
WMS3, paired associates, learning curve	4.25 ± 1.44	5.50 ± 1.16	0.01
WMS3, family pictures, % retained	94.56 ± 10.30	99.53 ± 3.22	0.03
<b>Neuropsychological tasks*</b>	<b>Patients (n=11)</b>	<b>Controls (n=14)</b>	<b><i>p</i> value</b>
Purdue pegboard, dominant hand	11.64 ± 2.11	14.29 ± 3.63	0.028
Purdue pegboard, assembly	29.82 ± 8.29	35.29 ± 5.43	0.025

**\*This table only features tests which revealed significant differences**

**Table 3: Significant gray matter loss in the apneic group compared with controls**

MNI coordinates			T value	k	P cluster-level	Label	% cluster
x	y	z					
12	66	-15	6.47	46814	.000	R. Sup. Temporal G	12.5
						R. SupraMarginal G	11.9
						R. Mid. Temporal G	8.5
						R. Sup Orbital Frontal G	5.5
						R. Inf. Frontal G	5.3
						R. Mid. Frontal G	5
						R. Inf. Orbital Frontal G	4.1
						R. Rectus G	3.9
						R. Inf. Parietal G	3.1
						R. Angular G	2.2
-35	-80	43	5.31	3435	0.01	L. Mid. Occipital G	52.6
						L. Inf. Parietal_G	11.8
						L. Angular G	2.8
24	-48	-47	4.96	6568	0.001	R. Cerebellum_9	37.5
						R. Cerebellum_8	34.3
						R. Cerebellum_10	2.5
						Vermis	16
-17	10	-3	4.60	5369	0.003	L. Putamen	34.3
						L. Pallidum	9.6
						L. Caudate nucleus	9.3
						L. Olfactory	7.6
39	-51	-15	4.47	6118	0.001	R. Fusiform G	50.4
						R. Lingual G	14.5
						R. Inf. Temporal G	8.2
						R Hippocampus	8.1

						R. Parahippocampal G	4.7
-36	39	25	4.30	3359	0.01	L. Mid. Frontal G	66.6
						L. Inf. Frontal G	19.8
						L. Sup. Frontal G	13.5
11	-3	5	4.07	4094	0.007	R. Thalamus	66.2

Location and MNI coordinates of peaks of significant gray matter density loss ( $p < 0.005$  uncorrected for multiple comparisons for the voxels and  $p$  corrected  $< 0.05$  for the clusters) in apneic patients compared with controls. Cluster size is indicated by  $k$ = number of voxels in the particular cluster. Labels and percentages were obtained using the AAL toolbox (Tzourio-Mazoyer *et al.* 2002). Cerebral changes were considered to be significant when they represented at least 2% of the cluster. R = right; L = left; Sup = superior; Mid = middle; Inf = inferior; Results are listed in decreasing order of  $T$  score value.

**Table 4: Significant hypometabolism in the apneic group compared with controls**

MNI coordinates			T value	k	p cluster- level	Label	% cluster
x	y	z					
58	32	20	4.54	278	0.08	R. Inf. Frontal G	71.22
						R. Mid. Frontal G	19.78
12	-60	30	4.17	417	0.03	R. Precuneus	72.66
						R. Cuneus	10.55
						R. Sup. Occipital G	6.71
						R. Mid. Cingulum	4.08
						R. Posterior Cingulum	2.64
52	-62	44	3.68	753	0.008	R. Angular G	35.59
						R. Inf. Parietal G	22.58
						R. Supramarginal G	14.08
						R. Sup. Temporal G	4.78

Location and MNI coordinates of peaks of significant hypometabolism ( $p < 0.005$  uncorrected for multiple comparisons for voxels and  $p$  corrected  $< 0.05$  for clusters) in apneic patients compared with controls.

**Table 5: Significant correlations in the apneic group between brain metabolism and A) Microarousal index, B) maintenance of wakefulness test, C) Paired associates, D) Purdue pegboard test (dominant hand) and E) Purdue pegboard test (assembly task)**

MNI coordinates			T value	k	P voxel	r	Label	% cluster
x	y	z			level			
<b>A) Microarousal index</b>								
-4	-8	72	4.41	159	0.000	-0.77	L. sup motor area	56.6
							R. sup motor area	32.7
-34	-46	66	4.04	204	0.001	-0.74	L sup parietal	66.7
							L postcentral gyrus	17.6
<b>B) Maintenance of wakefulness test</b>								
32	-90	-38	5.10	63	0.000	0.68	R. Cerebellum crus 2	46
							R. Cerebellum crus 1	3
-14	-42	-24	4.02	64	0.001	0.61	L. Cerebellum 4-5	70.3
							L. Cerebellum 3	14
-10	-40	-2	3.86	55	0.001	0.60	L. lingual gyrus	60
							L. Cerebellum 4-5	10.9
<b>C) Paired associates</b>								
14	-84	-28	4.10	163	0.001	0.75	R. Cerebellum crus 1	83
							R. Cerebellum crus 2	17
<b>D) Purdue pegboard test (dominant hand)</b>								
-6	-88	-36	4.67	53	0.001	0.78	L. Cerebellum crus 2	43.4
<b>E) Purdue pegboard test (assembly task)</b>								
-6	-66	-12	6.72	131	0.000	0.89	vermis	28.24
							L. Cerebellum 4-5	26
							L. Cerebellum 6	21.4
							R. Cerebellum 4-5	21.4

Location and MNI coordinates of significant ( $p < 0.005$  uncorrected;  $k > 50$  voxels) correlation peaks (with the corresponding  $r$  values) in the patient group. See legend Fig. 1

**Figure 1:** Significant gray matter loss ( $p < 0.005$  uncorrected for multiple comparisons for voxels and  $p$  corrected  $< 0.05$  for clusters) in the apneic group compared with controls, as shown by superimposition onto axial slices of the customized template (right hemisphere corresponds to right side of figure)

**Figure 2:** Significant hypometabolism ( $p < 0.005$  uncorrected for multiple comparisons for voxels and  $p$  corrected  $< 0.05$  for clusters) in the apneic group compared with controls, as shown by superimposition onto axial slices of the customized template (right hemisphere corresponds to right side of figure)

**Figure 3:** Significant positive correlations ( $p < 0.005$  uncorrected;  $k > 50$  voxels) in the apneic group between brain metabolism and A) Microarousal index, B) maintenance of wakefulness test, C) Paired associates, D) Purdue pegboard test (dominant hand) E) Purdue pegboard test (assembly task), as shown by superimposition onto axial slices of the customized template (on the left) and by the “plots” of the correlations with the main peak (on the right).