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Frontal brain lobe impairment in obstructive sleep apnoea: a proton MR spectroscopy study

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ABSTRACT: Patients with obstructive sleep apnoea syndrome frequently have cognitive deficits, especially related to executive functions, which cannot be fully explained by daytime sleepiness and are partial irreversible after nasal continuous positive airway pressure treatment. The causal mechanism of these cognitive deficits is not yet known, but it has been proposed that they are associated with chemical and structural brain cell injury. The aim of this study was to investigate brain metabolism in patients with sleep apnoea syndrome.

Twenty-two patients with severe sleep apnoea and 10 healthy volunteers of comparable age were studied using single voxel proton magnetic resonance spectroscopy. Magnetic resonance spectra were obtained from prefrontal cortex, parieto-occipital and frontal periventricular white matter.

***N*-acetylaspartate-to-creatine and choline-to-creatine ratios were significantly lower in the frontal white matter of obstructive sleep apnoea patients when compared to controls. Absolute concentrations of *N*-acetylaspartate and choline were also significantly reduced in the frontal white matter of patients with sleep apnoea.**

Frontal lobe white matter lesions are known to be associated with cognitive executive dysfunction. The findings of this study may offer an explanation for the sometimes irreversible cognitive deficits associated with sleep apnoea.

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Obstructive sleep apnoea (OSA) syndrome (OSAS) is a common disorder occurring in up to 4% of the general adult population [1]. Cognitive impairment has been repeatedly reported in OSA patients. The areas most frequently affected are general intellectual functioning, attention, memory and, in particular, executive functions, such as problem solving, planning of goal-oriented behaviour and mental flexibility [1, 2]. To date, the pathophysiology of the cognitive deficits reported in OSA patients has not been determined. Some researchers argue that excessive daytime somnolence is the leading cause of the cognitive deficits, while others propose that nocturnal hypoxaemia is the main contributing factor [1, 2]. Moreover, several studies have shown that executive dysfunction in OSA patients may persist even after nasal continuous positive airway pressure (nCPAP) treatment [2–4]. Cognitive executive functions are associated with specific prefrontal-subcortical brain circuits [5], thus it has been proposed that OSAS may promote irreversible anoxic brain damage affecting the prefrontal cortex [4, 6].

Proton magnetic resonance spectroscopy (^{1}H MRS) provides a noninvasive *in vivo* assessment of brain metabolism. ^{1}H MRS has been applied to the study of many brain disorders, including Alzheimer's disease, brain tumours, epilepsy, multiple sclerosis, leukodystrophies and mitochondrial disorders [7, 8].

The aim of this study was to detect possible metabolic abnormalities in the brain of patients with severe OSAS using single voxel ^{1}H MRS. Both the prefrontal cortex and the frontal periventricular white matter were examined, as these regions are associated with executive cognitive dysfunction [5], which is frequently reported in OSA patients. The parieto-occipital periventricular white matter was also examined, as spectroscopic abnormalities have been previously reported in OSA patients [9, 10].

Materials and methods

Study subjects

Twenty-two consecutive patients with severe OSAS who fulfilled the following inclusion criteria were enrolled in this study: apnoea/hypopnoea index (AHI) >30, age <65 yrs, no history of stroke, and absence of neurological disease or history of head injury. Patients with claustrophobia or metallic implants were excluded. All patients were diagnosed in the Sleep Laboratory of the Pulmonary Dept of the Medical School (Athens University), in "Sotiria" Hospital for Chest Diseases, or in the Sleep Laboratory of "Sismanoglio" Hospital (both Athens, Greece), between June and December 2002. Ten healthy male volunteers of comparable age were used as the control group. The Ethics Committees of both hospitals approved the study, and all patients and control subjects gave written informed consent.

Study design

All subjects underwent a full-night polysomnography (Embla, Flaga ht; Medical Devices, Reykjavik, Iceland), with recordings of the following: electroencephalogram; electrooculogram; chin electromyogram; electrocardiogram; oral and nasal flow; abdominal and thoracic movements; oxyhaemoglobin saturation; and snoring [11]. Excessive daytime sleepiness was assessed by using the Epworth Sleepiness Scale (ESS). Within 2 weeks of polysomnography and before the initiation of nCPAP treatment, all eligible patients, as well as control subjects, underwent single voxel brain ^{1}H-MRS.

Methods

Spectroscopy was performed at 1.5 Tesla using PROBE (Signa Hispeed; General Electric, Milwaukee, WI, USA). Prior to ^{1}H MRS, axial T1-weighted and FLAIR (fluid-attenuated inversion recovery) images were obtained, in order to exclude neurological disease and to localise the voxels. Two OSA patients had punctuated white matter hyperintensities. Voxels were carefully placed outside these lesions, in normal-appearing brain tissue. No magnetic resonance imaging abnormalities were found in the control group. Proton spectra were obtained from: 1) right parieto-occipital white matter, next to the occipital horn of the lateral ventricle; 2) left frontal white matter, next to the frontal horn of the lateral ventricle; and c) left prefrontal cortex (figs 1a, 2a and 3a).

A single voxel spin-echo PRESS (point-resolved spectroscopy) sequence was used with echo time (tE) 35 ms, repetition time (tR) 1,500 ms and 96 signal acquisitions, resulting in an acquisition time of 3 min per pixel. The choice of single-voxel MRS instead of chemical-shift imaging (CSI) was made for two reasons: first, in order to assure accurate placement of the volume of interest and to avoid signal contamination with unwanted tissue; and, secondly, in order to assure higher accuracy in quantitation, knowing that significant quantitation differences exist across all voxels of a CSI slab. The choice of tR/tE was made basically for signal-to-noise ratio optimisation for the given spectral acquisition time. Voxel volumes were 6.7 ± 1.8 cm^3 (mean±SD) for the frontal white matter, 8.2 ± 2.4 cm^3 for the posterior white matter and 5 ± 0.8 cm^3 for the frontal grey matter. This variability in volumes was necessary in order to ensure that, in spite of individual anatomical differences, only white or only gray matter were included in each voxel. Voxels were placed in the same regions for all subjects, by the same experienced investigator (E. Gotsis), to decrease intra-subject variation. Peaks corresponding to *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho) and myo-inositol (mI) were measured, and the NAA/Cho, NAA/Cr, Cho/Cr and mI/Cr ratios were calculated [12]. The absolute concentrations of NAA, Cho, Cr and mI were also calculated, with direct comparison of patient spectra to the spectrum of an external phantom of known metabolite concentrations (GE phantom of known concentrations), correcting for filling factor differences of the coil for each patient, as well as for the phantom (actually using the head coil transmitter gain in each case). Concentrations were calculated in mmol per kg wet tissue. The use of metabolite ratios in MRS studies reduces systematic errors, because they would affect all metabolites for a particular voxel in the same proportion. However, this method cannot distinguish between numerator and denominator changes. Conversely, the calculation of absolute metabolite concentrations, although sensitive to technical errors, can be very helpful for the interpretation of ratio changes.

Analysis

All values are expressed as mean±SD. The Mann-Whitney U-test was used to compare age, metabolite ratios and concentrations between the two groups. This nonparametric test was chosen because of the small sample size and the lack of previous data showing a normal distribution for the examined ratios and concentrations in OSA patients. Correlations between metabolite ratios, metabolite concentrations and specific respiratory parameters, ESS and age, were determined using Spearman′s correlation. A p-value <0.05 was considered statistically significant. A general linear model test (multivariate ANOVA) was used in order to examine the effect of interactions of age, ESS, AHI, minimal nocturnal oxyhaemoglobin saturation (Sa,O$_2$,min), mean nocturnal oxyhaemoglobin saturation (Sa,O$_2$,mean) and absolute time of oxyhaemoglobin saturation <90% during sleep (t<90%) on metabolite ratios and concentrations.

Results

The clinical characteristics of OSA patients and control subjects, as well as statistical comparisons between them, are presented in table 1. Fourteen out of the 22 patients did not have cardiac disease or cardiovascular risk factors, including hypertension, hyperlipidaemia and diabetes mellitus, according to their medical history. Out of the eight remaining patients, one had ischaemic heart disease, one had atrial fibrillation, six had hypertension, two had hyperlipidaemia and two had diabetes mellitus, all under medical treatment.

In comparison to the control group, OSA patients showed a significant reduction in the NAA/Cr and Cho/Cr ratios in frontal white matter (p=0.012 and p=0.008, respectively). Table 2 summarises the results of the comparison of the metabolite ratios between OSA patients and controls in the three examined areas. Figures 1b, 2b, 3b and 1c, 2c, 3c display representative spectra of one OSA patient and one control subject, respectively. In figure 4, scatter plot diagrams of NAA/Cr and Cho/Cr ratios in frontal white matter are shown. OSA patients had significantly decreased NAA and Cho absolute concentrations in frontal white matter compared to controls (p=0.04 and p=0.017, respectively), as demonstrated in table 3. No statistically significant differences were found between patients and controls in the parieto-occipital white matter and in the prefrontal cortex, regarding either metabolite ratios or absolute concentrations.

In table 4, metabolite ratios of a subgroup (OSA subgroup) of the 22 OSA patients, consisting of those without a history of cardiac disease or cardiovascular risk factors (hypertension, hyperlipidaemia and diabetes mellitus) are compared to controls. This subgroup of 14 OSA patients, without having significant age difference from controls, had statistically significant decreases in NAA/Cr and Cho/Cr ratios in frontal white matter when compared to the control group (p=0.03 and 0.01, respectively). As demonstrated in table 5, Cho concentration was significantly decreased in frontal white matter of the OSA subgroup as compared to controls (p=0.03), whereas NAA showed only a trend to decrement (p=0.09). Correlations between metabolite ratios in all three examined areas, and AHI, Sa,O$_2$,min, Sa,O$_2$,mean and t<90% were not significant.

In the control group, age showed an inverse correlation only with anterior white matter NAA level (r=-0.648, p=0.043). In the same area, the mI/Cr ratio of the control group was correlated with age (r=0.732, p=0.016). Metabolite concentration, as well as metabolite ratios, of the patient group did not correlate with age. The effect of interactions of age, ESS, AHI, Sa,O$_2$,min, Sa,O$_2$,mean and t<90% on

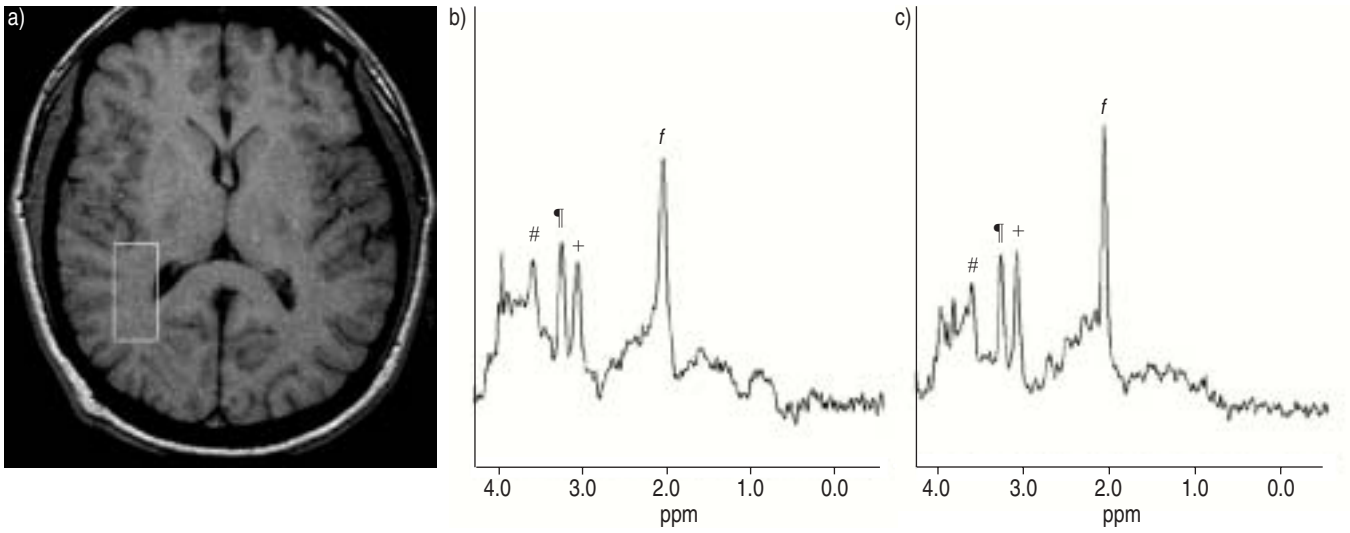

Fig. 1. – a) Location of the examined voxel in the right parieto-occipital white matter (PWM), next to the occipital horn of the lateral ventricle (see box). b) A representative spectra of an obstructive sleep apnoea patient from PWM. c) A representative spectra of a control subject from PWM. #: myo-inositol; ¶: choline; +: creatine; f: *N*-acetylaspartate.

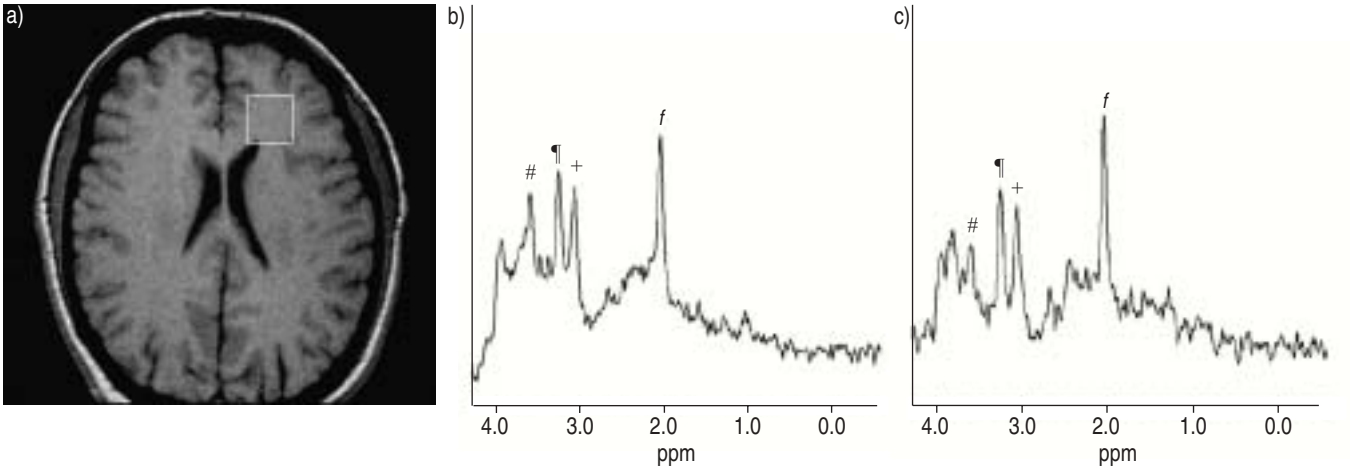

Fig. 2. – a) Location of the examined voxel in the left frontal white matter (FWM), next to the frontal horn of the lateral ventricle (see box). b) A representative spectra of an obstructive sleep apnoea patient from FWM. c) A representative spectra of a control subject from FWM. #: myo-inositol; ¶: choline; +: creatine; f: *N*-acetylaspartate.

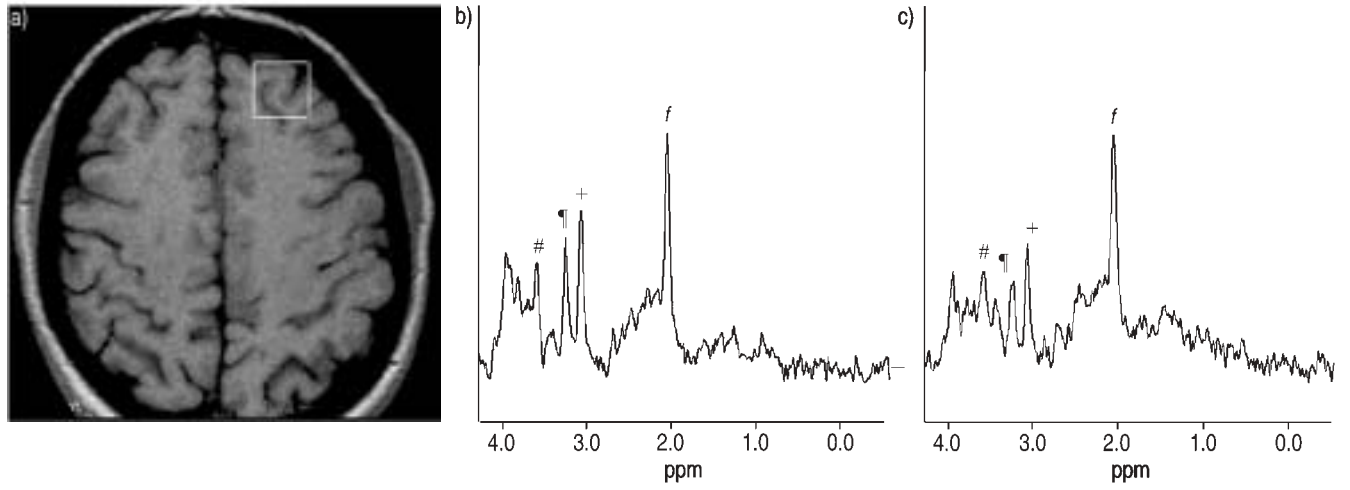

Fig. 3. – a) Location of the examined voxel in the left prefrontal cortex (PFC) (see box). b) A representative spectra of an obstructive sleep apnoea patient from PFC. c) A representative spectra of a control subject from PFC. #: myo-inositol; ¶: choline; +: creatine; f: *N*-acetylaspartate.

Table 1. – Clinical characteristics of obstructive sleep apnoea (OSA) patients and controls

	OSA patients	OSA subgroup#	Controls	p-value	
				OSA to control	Subgroup to controls
Subjects n	22	14	10		
Sex	All male	All male	All male		
Age yrs	49±9.7	48±10.1	42.9±10.5	0.12	0.2
AHI events·h^{-1}	70.6±19.4	70.1±19.8	3.4±1.5	<0.0001	<0.0001
Sa,O_2,min %	66.7±12	65.5±13.6	94.3±1.3	<0.0001	<0.0001
Sa,O_2,mean %	87.7±5.6	88.1±6.4	95.7±0.7	<0.0001	<0.0001
t<90% min	122±84	133.1±99.5	0	<0.0001	<0.0001
ESS score	8.2±3.3	8.4±2.5			

Data are presented as mean±SD. AHI: apnoea hypopnoea index; Sa,O_2,min: minimal nocturnal oxyhaemoglobin saturation; Sa,O_2,mean: mean nocturnal oxyhaemoglobin saturation; t<90%: absolute time of oxyhaemoglobin saturation <90% during sleep; ESS: Epworth Sleepiness Scale. #: OSA patients without history of cardiac disease or cardiovascular risk factors (hypertension, hyperlipidaemia and diabetes mellitus).

Table 2. – Comparison of metabolite ratios between obstructive sleep apnoea (OSA) patients and controls

	OSA patients	Controls	p-value
Subjects n	22	10	
PWM			
mI/Cr	0.68±0.09	0.69±0.05	0.92
NAA/Cho	1.75±0.32	1.62±0.28	0.29
NAA/Cr	1.81±0.18	1.74±0.16	0.34
Cho/Cr	1.07±0.19	1.09±0.12	0.44
FWM			
mI/Cr	0.66±0.10	0.73±0.15	0.14
NAA/Cho	1.60±0.29	1.49±0.25	0.35
NAA/Cr	1.59±0.16	1.74±0.15	0.012
Cho/Cr	1.01±0.15	1.19±0.17	0.008
PFC			
mI/Cr	0.64±0.08	0.62±0.09	0.49
NAA/Cho	2.18±0.35	2.07±0.36	0.36
NAA/Cr	1.56±0.12	1.58±0.15	0.54
Cho/Cr	0.74±0.13	0.78±0.13	0.45

Data are presented as mean±SD. PWM: parieto-occipital white matter; FWM: frontal white matter; PFC: prefrontal cortex; mI: myo-inositol; NAA: *N*-acetylaspartate; Cr: creatine; Cho: choline.

Table 3. – Comparison of absolute metabolite concentrations between obstructive sleep apnoea (OSA) patients and controls

	OSA patients	Controls	p-value
Subjects n	22	10	
PWM			
Cho	1.80±0.35	1.98±0.43	0.26
Cr	4.91±0.64	5.14±0.84	0.45
NAA	7.52±1.01	7.56±1.06	0.97
mI	5.48±0.74	5.8±0.93	0.26
FWM			
Cho	1.75±0.33	2.18±0.44	0.017
Cr	5.03±0.69	5.18±0.64	0.6
NAA	6.76±1.06	7.68±1.06	0.04
mI	5.53±1.38	6.16±1.17	0.18
PFC			
Cho	1.41±0.26	1.57±0.35	0.25
Cr	5.55±0.56	5.66±0.72	0.57
NAA	7.32±0.81	7.6±0.75	0.36
mI	5.86±0.99	5.6±0.97	0.34

Data are expressed in mmol per kg and presented as mean±SD. PWM: parieto-occipital white matter; FWM: frontal white matter; PFC: prefrontal cortex; Cho: choline; Cr: creatine; NAA: *N*-acetylaspartate; mI: myo-inositol.

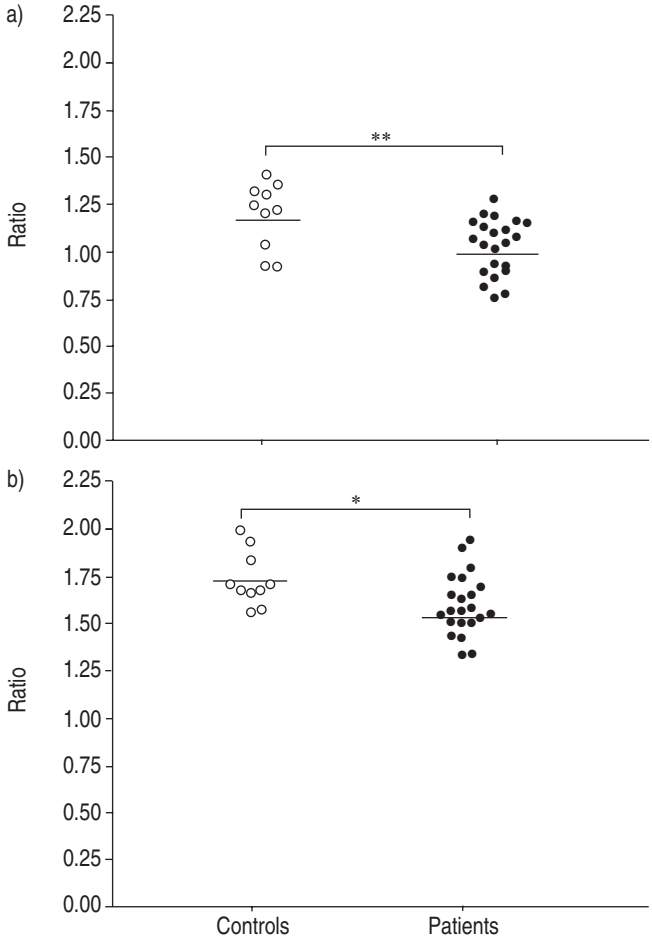

Fig. 4. – Scatterplots of a) choline (Cho)/creatine (Cr) and b) *N*-acetylaspartate (NAA)/Cr ratios of controls (○) and obstructive sleep apnoea (●) patients in frontal white matter. —: mean values. *: p<0.05; **: p<0.01.

metabolic ratios and concentrations was not statistically significant for the control nor for the patient group. ESS was correlated significantly only with NAA/Cho ratio in the posterior white matter (r=-0.476, p=0.025).

Discussion

In the present study, brain metabolism was investigated in patients with severe OSAS. The results demonstrate a

Table 4. – Comparison of metabolite ratios between obstructive sleep apnoea (OSA) subgroup (patients without cardiac disease or cardiovascular risk factors) and controls

	OSA subgroup	Controls	p-value
Subjects n	14	10	
PWM			
mI/Cr	0.7±0.08	0.69±0.05	0.56
NAA/Cho	1.75±0.30	1.62±0.28	0.36
NAA/Cr	1.84±0.19	1.74±0.16	0.27
Cho/Cr	1.07±0.2	1.09±0.12	0.77
FWM			
mI/Cr	0.65±0.1	0.73±0.15	0.15
NAA/Cho	1.66±0.31	1.49±0.25	0.22
NAA/Cr	1.61±0.13	1.74±0.15	0.03
Cho/Cr	1.0±0.17	1.19±0.17	0.01
PFC			
mI/Cr	0.63±0.08	0.62±0.09	0.49
NAA/Cho	2.19±0.40	2.07±0.36	0.44
NAA/Cr	1.56±0.11	1.58±0.15	0.64
Cho/Cr	0.74±0.13	0.78±0.13	0.5

Data are presented as mean±SD. PWM: parieto-occipital white matter; FWM: frontal white matter; PFC: prefrontal cortex; mI: myo-inositol; NAA: *N*-acetylaspartate; Cr: creatine; Cho: choline.

Table 5. – Comparison of metabolite concentrations between obstructive sleep apnoea (OSA) subgroup (patients without cardiac disease or cardiovascular risk factors) and controls

	OSA subgroup	Controls	p-value
Subjects n	14	10	
PWM			
Cho	1.80±0.37	1.97±0.42	0.27
Cr	4.89±0.65	5.13±0.84	0.36
NAA	7.50±0.79	7.56±1.05	0.97
mI	5.55±0.70	5.82±0.88	0.46
FWM			
Cho	1.74±0.36	2.17±0.44	0.03
Cr	5.11±0.77	5.18±0.63	0.97
NAA	6.90±1.13	7.67±1.06	0.09
mI	5.57±1.5	6.16±1.17	0.27
PFC			
Cho	1.39±0.18	1.56±0.35	0.18
Cr	5.49±0.6	5.65±0.71	0.50
NAA	7.19±0.64	7.60±0.75	0.20
mI	5.74±0.93	5.59±0.96	0.46

Data are expressed in mmol per kg and presented as mean±SD. PWM: parieto-occipital white matter; FWM: frontal white matter; PFC: prefrontal cortex; Cho: choline; Cr: creatine; NAA: *N*-acetylaspartate; mI: myo-inositol.

significant decrease in NAA/Cr and Cho/Cr ratios, as well as a reduction in absolute concentrations of NAA and Cho, in the FWM of OSA patients when compared to controls.

NAA is an intraneuronal molecule and, in the mature brain, it is found only in neurons and axons. NAA is reduced in many brain disorders, in the presence of neuronal and/or axonal loss or dysfunction, such as infarcts, dementia, brain tumours, hypoxic encephalopathy and multiple sclerosis [7, 8].

The Cr signal is generated by the sum of creatine and phosphocreatine, and reflects energy metabolites. Because this peak remains relatively stable, it is frequently used as a reference peak to normalise metabolite signal intensities.

mI originates almost exclusively from glial cells. Elevated mI represents both the accumulation of myelin breakdown products and astrocytosis [7, 8, 13].

The Cho peak measures total levels of mobile choline, which include free choline, glycerophosphocholine (a byproduct of phosphatidylcholine breakdown), phosphocholine (a phosphatidylcholine precursor) and minute amounts of acetylcholine. Elevated Cho represents increased membrane turnover or increased cellular density, and it has been reported in cases of active demyelination, brain tumours and glial proliferation [7, 8, 13].

Decreased NAA in the frontal white matter of OSA patients indicates axonal loss and/or dysfunction [7, 8]. The deep white matter, where metabolic impairment was found in the current study, seems to be selectively affected in OSAS. Previous studies applying MRS with chemical shift imaging have demonstrated a decrease in the NAA/Cho ratio in the posterior periventricular white matter [9, 10] and lactate production in the centrum semiovale of OSA patients during sleep, indicating that hypoxia is causing anaerobic glycolysis [14]. Absolute concentrations were not calculated in these studies, so it is not clear if the decreased ratio was due to a decrease in NAA and/or an elevation in Cho. A recent study, using computed tomography, demonstrated that white matter disease severity in patients with acute stroke and OSAS correlated independently with AHI [15]. One possible explanation is that the arterial supply of the deep white matter is not sufficient to compensate for the decreased and fluctuating cerebral perfusion and the impaired cerebral vascular autoregulation that have been reported in OSA patients [10, 16, 17]. In fact, the arterial networks of the deep white matter, the so-called internal border zone, are terminals without collaterals or anastomoses [18].

An interesting finding in this study is the decrement of Cho in the frontal white matter of OSA patients. Decreased Cho has been reported in mitochondrial, hypomyelinotic and metabolic diseases, hepatic encephalopathy [7, 8], Grave′s disease [19], Lewy body dementia [20], and chronic obstructive pulmonary disease [21]. It has been suggested that decreased *in vivo* Cho levels indicate loss of myelin lipids or phospholipid metabolism dysfunction [17, 18, 22]. These results are in agreement with the report of SHIM *et al.* [21]. These investigators found a reduction in NAA, Cr and Cho concentrations in the parietal white matter of COPD patients with resting normoxaemia and nocturnal desaturation, a respiratory profile similar to OSAS. A previous study has demonstrated a decrease in Cho metabolites as a consequence of brief ischaemic episodes in an experimental animal model [22]. Nevertheless, if chronic haemodynamic impairment were the sole pathogenic factor related to OSA, one would expect elevation of Cho and perhaps of mI due to gliosis and myelin breakdown [13, 18, 23]. It is suggested here that a possible interpretation for the Cho decrement is that OSA does not promote gliosis but induces brain metabolic impairment through a unique combination of fluctuating haemodynamic impairment, sleep fragmentation and intermittent hypoxia. Experimental intermittent hypoxia per se can induce neuronal apoptosis and biochemical changes in animals′ brains, perhaps in a different manner than chronic sustained hypoxia [24, 25]. In addition, recent studies have shown that the prefrontal areas are especially sensitive to sleep deprivation and recovery sleep, presumably because these regions have a unique requirement for sleep-related recovery [6, 26] and that sleep deprivation can alter Cho metabolism. DORSEY *et al.* [27] found an increase of glycerophosphocholine concentration in healthy volunteers after the recovery night, following a night of sleep deprivation [27]. In the current study, although the patients did not have severe sleepiness, ESS score is correlated with NAA/Cho ratio, but only in the posterior white matter.

OSA patients frequently have a combination of vascular risk factors, including hypertension, diabetes mellitus, hyperlipidaemia and central obesity [28]. All these factors are

associated with increased risk of stroke and could possibly promote brain metabolic impairment. Nevertheless, in the present study, the subgroup of OSA patients without a medical history of cardiac disease or cardiovascular risk factors also had significantly depressed NAA/Cr and Cho/Cr ratios, as well as a diminished Cho concentration in frontal white matter, when compared to controls. This finding suggests that OSAS may promote brain metabolic impairment even in the absence of cardiovascular co-morbidities.

Frontal periventricular white matter lesions, to the best of the current authors' knowledge, have not been reported previously in OSA patients without a history of stroke. Frontal white matter lesions could be associated with the neuropsychological deficits that complicate OSAS. Patients with OSAS frequently have mild impairment in attention-concentration, memory and, in particular, executive functions, such as problem solving, planning of goal-oriented behaviour and mental flexibility, which are sometimes irreversible, even after nCPAP treatment [1–4, 6]. Cognitive executive functions are associated with the prefrontal cortex and prefrontal-subcortical brain circuits [5], thus it has been proposed that OSAS induces chemical and structural cellular injury, affecting the prefrontal cortex [4, 6]. In the study presented here, no metabolic impairment was found in the examined prefrontal cortex, but it was demonstrated that patients with severe OSAS have metabolic impairment in the frontal white matter. It is, therefore, suggested that these findings may offer an explanation for the specific pattern of cognitive deficits frequently reported in OSA patients, as it is well known that anterior white matter lesions can induce executive dysfunction by interrupting prefrontal-subcortical circuits [5, 29, 30].

An important limitation to this study is the lack of neuropsychological measures in the examined patients, although is well documented that frontal lobe-mediated executive functions are usually impaired in patients with severe OSAS [1]. A second limitation is that, because only patients with severe OSA were included, there were not enough variances in the respiratory parameters that could predict the metabolic changes. KAMBA *et al.* [10], who studied OSA patients with wide range of severity (mean AHI 43.78±30), found a significant negative association between AHI and NAA/Cho ratio for the posterior cerebral white matter. A third consideration is about the effect of aging on brain metabolism. MRS studies on the effect of aging on brain metabolites are often discrepant. Results of quantitative MRS studies vary from increased Cr and Cho levels to unchanged or decreased NAA levels and lack of any significant change [22, 31, 32]. In the present study, anterior white matter NAA levels of the OSA patient group did not show a significant correlation with aging, but the anterior white matter NAA level of the control group was inversely correlated with aging. These data suggest that, although the age difference between the patient and the control group was not statistically significant, it could be responsible for some of the reported NAA decrement. Nevertheless, if the results were biased by some kind of age effect, one would expect, according to the literature, a decrement in NAA and an increment in Cho, or *vice versa*, and not a decrement in both metabolites.

In conclusion, the results of this study demonstrate that severe obstructive sleep apnoea syndrome can promote axonal loss or dysfunction, as well as myelin metabolism impairment in the frontal periventricullar white matter. These lesions are in the territory of crucial frontal-subcortical circuits and they could be associated with the, sometimes irreversible, cognitive executive deficits reported in obstructive sleep apnoea patients. Further studies are needed to confirm whether there is a direct correlation between frontal metabolic dysfunction and cognitive impairment in obstructive sleep apnoea patients, and to examine the reversibility of the spectroscopic abnormalities after nasal continuous positive airway pressure treatment.

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