# BRAIN STRUCTURAL CHANGES UNDERLYING COGNITIVE DISABILITIES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS): A VBM STUDY

**G. Giulietti[1,2], F. Torelli[1,3], M. Bozzali[1], G. Garreffa[1,2], N. Moscufo[3], S. Zannino[1,4], L. Serra[1], F. Placidi[4], F. Fasano[1], G. Hagberg[1], B. Maraviglia[1,2], I. Djonlagic[5], J. Saboisky[5], A. Malhotra[5], M. Marciani[1,4], and C. Guttmann[3]**

[1]IRCCS "Santa Lucia Foundation", Rome, Italy, [2]"Enrico Fermi" Center, Rome, Italy, [3]Center for Neurological Imaging, Brigham and Women's Hospital, Harvard Medical School, Boston, United States, [4]Department of Neuroscience, University "Tor Vergata", Rome, Italy, [5]Division of Sleep Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, United States

## INTRODUCTION

Previous MRI studies have reported inconsistent findings on the association between the presence and severity of obstructive sleep apnea syndrome (OSAS) and brain tissue abnormalities [1]. So far, it still remains a matter of debate whether patients with OSAS present with an increased risk for developing a neurological impairment. The principal aim of this study was to assess, using voxel based morphometry (VBM) [2], the presence and extension of both gray (GM) and white matter (WM) changes in patients with OSAS at different clinical stages. The secondary aim was to ascertain the relationship between these changes and specific cognitive profiles.

## METHODS

We recruited 16 patients (F/M=3/13; mean [SD] age=55.8 [6.7] years) suffering from OSAS as assessed by their Apnea/Hypopnea Index (AHI) (mean [SD] AHI=53 [26] $h^{-1}$). Twelve of them were characterized by a severe form of OSAS (AHI>30 $h^{-1}$), while the remaining 4 were at a moderate clinical stage (15≤AHI≤30 $h^{-1}$) [3]. Fourteen age-matched healthy volunteers (F/M=5/9; mean [SD] age=57.4 [5.3] years) were also recruited as controls. All subjects underwent an extensive neuropsychological battery exploring the principal cognitive domains, including memory, attention, language, reasoning, executive functions and visuospatial abilities [4-9]. Then, each subject underwent MRI scanning at 3 T, including the following acquisitions: axial 3D MPRAGE T1(FOV 20.8x25.6 $cm^2$, matrix 208x256, in plane resolution 1x1 $mm^2$, 176 slices, 1 mm thickness); sagittal 3D TSE T2 (FOV 22.0x25.6 $cm^2$, matrix 220x256, in plane resolution=1x1 $mm^2$, 176 slices, 1 mm thickness) and sagittal 3D TSE T2 FLAIR (FOV 20.8x25.6 $cm^2$, matrix 208x256, in plane resolution=1x1 $mm^2$, 144 slices, 1.3 mm thickness). T2 and FLAIR scans were used to assess the presence of macroscopic WM lesions.

All T1 images were segmented and normalized into GM, WM, and cerebrospinal fluid, using respectively NewSegment and Dartel modules included in SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Two ANOVA models, including respectively GM and WM modulated and smoothed (10 mm FWHM kernel) maps were employed for VBM analysis and group comparisons with healthy controls, patients with moderate and patients with severe OSAS as independent groups.

Age, sex and intra-cranial volume (ICV) were included as covariates of no interest. Additional multiple regression analyses, including GM maps from all subjects, were performed to investigate correlations between scores obtained at individual neuropsychological tests and regional GM volumes, by selecting only those tests where patients reported significantly different scores than controls (see below). As in cross-sectional group analyses, age, sex, and ICV were entered as nuisance variable together with education level.

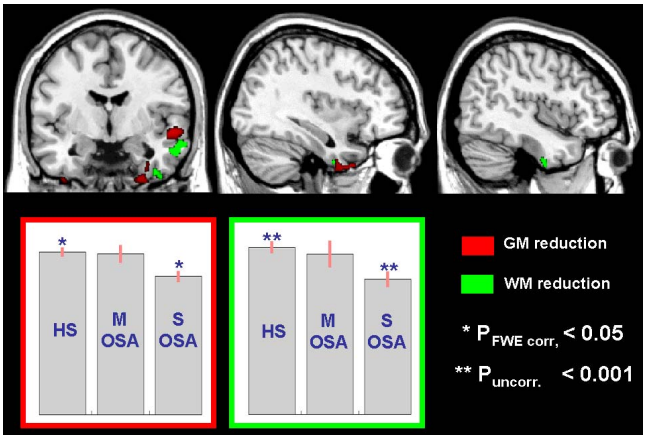


**Figure 1.** Regions of GM and WM atrophy in patients with severe OSAS compared to healthy controls. Plots show changes of GM volume in the right hippocampus (MNI: 30; -5; -48) and changes of WM volume in an anatomically contiguous region, across groups (**HS**: healthy subjects, **M**: moderate, **S**: severe).

## RESULTS

Neuropsychological data analysis revealed that patients with OSAS had significantly lower scores than healthy controls on Rey's 15 word list test (immediate recall) [6] which explores verbal memory. Patients with OSAS at a moderate stage did not reveal any significant difference in GM or WM volumes when compared either with healthy controls or patients with OSAS at a severe stage. Conversely, patients with OSAS at a severe stage compared to healthy controls showed a region of decreased GM volume in the right hippocampus ($P_{FWE}$ cluster level corr. <0.05; MNI Coordinates [x,y,z] = 30; -5; -48). The same contrast revealed also a symmetric region of GM loss in the left hippocampus, together with additional localisations within more lateral temporal areas, although none of these results survived after FWE correction (puncorr.<0.001). Moreover, patients with severe OSAS compared to healthy controls showed two regions of reduced WM volume within the right temporal lobe (p uncorr.<0.001). Interestingly, one of them was localized nearby the hippocampal region also showing GM atrophy. Multiple regression analysis revealed a direct association between scores obtained on Rey's 15 word list and GM volume in the left orbitofrontal cortex (OFC) (MNI Coordinates [x,y,z] = -6; 41; -24; p uncorr.<0.001).

## DISCUSSION

The results of this study indicate that the brain tissue of patients with OSAS is vulnerable to reccurrent episodes of apnea, with detectable abnormalities in the hippocampal regions of patients with a severe clinical form (AHI>30 $h^{-1}$). This finding is consistent with previous reports indicating the hippocampus as a brain structure particularly sensitive to hipoxia [10-12]. Additionally, the hippocampus is directly implicated in memory functions, which was found to be impaired in our cohort of patients.

WM atrophy was also present in a region nearby the right hippocampus of patients with severe OSAS. This suggests that not only regional GM atrophy, but also brain disconnection may contribute to cognitive deficits in patients with OSAS. Finally, a direct association was found between scores obtained on Rey's 15 word list test and GM volumes in the OFC, a region known to take part in memory processing [13, 14]. Thus, it seems plausible that, in addition to the hippocampal involvement, the memory deficits observed in our patients might be linked also to changes in other regions.

**References** **[1]** Zimmerman ME et al, Journal of Clinical Sleep Medicine, vol.2, No.4, 2006 **[2]** Good CD et al. NeuroImage 14, 21–36, 2001 **[3]** American Academy of Sleep Medicine. International Classification of Sleep Disorders. Diagnostic and coding manual, 2nd edn, Vol. III. Westchester: AASM; 2005 **[4]** Folstein MF et al, J Psychiatr Res, 12:189-198, 1975 **[5]** Magni E et al, Eur J Neurol, 3:198-202, 1996 **[6]** Carlesimo GA et al, Eur Neurol, 36 (6):378-384, 1996 **[7]** Orsini A et al, Ital J Neurol Sci 8, 539-548, 1987 **[8]** Golden CJ. Stroop colour and word test. Chicago, IL: Stoeting, 1978 **[9]** Carlesimo GA, et al, Nuova Rivista di Neurologia, 12, 1-13, 2002 **[10]** Di Paola M et al Hippocampus. 18(7):719-28, 2008 **[11]** Allen JS et al, J Clin Exp Neuropsychol. 28(4):457-76, 2006 **[12]** Morrell MJ et al, Sleep Med. 4(5):451-4, 2003 **[13]** Duarte A et al, J Cogn Neurosci. 2009 (Epub ahead of print) **[14]** Bonilha L et al, Hum Brain Mapp. 28(12):1376-90, 2007.