Brief communication

Changes in brain morphology associated with obstructive sleep apnea

Mary J. Morrell*, Donald W. McRobbie, Rebecca A. Quest, Andrew R.C. Cummin, Ramesh Ghiassi, Douglas R. Corfield

*National Heart and Lung Institute, Charing Cross Campus, Faculty of Medicine, Imperial College of Science Technology and Medicine, London, UK
Radiological Sciences Unit, Charing Cross Hospital, London, UK
Department of Respiratory Medicine, Charing Cross Hospital, London, UK
School of Life Sciences, Keele University, Staffordshire ST5 5BN, UK

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Abstract

Objective: Obstructive sleep apnea (OSA) causes hypoxemia and fragmented sleep, which lead to neurocognitive deficits. We hypothesised that focal loss of cortical gray matter generally within areas associated with memory processing and learning and specifically within the hippocampus would occur in OSA.

Methods: Voxel-based morphometry, an automated processing technique for magnetic resonance images, was used to characterise structural changes in gray matter in seven right handed, male patients with newly diagnosed OSA and seven non-apneic, male controls matched for handedness and age.

Results: The analysis revealed a significantly lower gray matter concentration within the left hippocampus (p = 0.004) in the apneic patients. No further significant focal gray matter differences were seen in the right hippocampus and in other brain regions. There was no difference in total gray matter volume between apneics and controls.

Conclusion: This preliminary report indicates changes in brain morphology in OSA, in the hippocampus, a key area for cognitive processing.

Keywords: Obstructive sleep apnea; Brain morphology; Hypoxia

1. Introduction

Obstructive sleep apnea (OSA) is characterised by periodic breathing, episodic hypoxemia and repeated arousals from sleep. It affects 1–4% of middle-aged adults [1], rising to 24–30% in the elderly [2]. Symptoms include significant excessive daytime sleepiness and cognitive deficits. When untreated, it is associated with an increased likelihood of hypertension, cardiovascular diseases, and road traffic crashes [3,4].

Both hypoxia and sleep fragmentation independently result in cognitive deficits. It has recently been shown in rats, that chronic exposure to intermittent hypoxia during sleep results in cellular damage within the CA1 region of the hippocampus [5]. Clinical observations also indicate that the hippocampal cortex is particularly sensitive to hypoxic damage. The hippocampus is a region known to be closely associated with the neural processing of memory [6]. Since OSA patients have repetitive nocturnal dips in oxygen saturation and impairment of memory, learning and attention, we investigated the hypothesis that OSA is associated with changes in brain morphology; in particular, a focal loss of gray matter within the hippocampus and other cortical areas linked with cognitive function.

2. Methods

This was a non-invasive, controlled, cross-sectional study, performed with local ethical approval. Voxel-based morphometry (VBM), an automated and unbiased technique, was used to characterise structural changes in cortical gray matter [7,8]. We studied seven right handed, male patients with newly diagnosed OSA (median, range: age
50, 28–65) and seven healthy, non-apneic male controls matched for handedness and age.

Patients were recruited from our sleep clinic following an overnight home study during which breathing (oro-nasal thermistor and snoring), O₂ saturation, heart rate and body position were monitored (Synogram, Synectic Medical). An apnea was defined as a greater than 50% reduction in airflow for more than 10 s, and hypopnea as a less than 75% but greater than 50% reduction in airflow for more than 10 s. For the group, pre-treatment, the median apnea–hypopnea index (AHI) = 28 (25–40) events/h; baseline nocturnal O₂ saturation = 94% (97–92%); mean nocturnal O₂ desaturation = 9% (7–11%); nadir of nocturnal O₂ saturation = 71% (61–79%); Epworth sleepiness score = 14 (4–17). All patients and controls had normal lung function. No patients had started continuous positive airway pressure treatment prior to the MRI study. Patients with a body weight in excess of 130 kg or a girth measurement greater than 152 cm were excluded from the study because we were unable to scan them due the technical weight and size limit of the magnetic resonance (MR) scanner.

T1-weighted, magnetic resonance brain scans (Siemens 1.5T Vision, 3D MP-RAGE, TI = 300 ms, TE = 4 ms, TD = 300 ms, 1 mm × 1 mm × 2 mm) were performed between 14:00 and 17:00 h. VBM was performed using the optimised protocol of Good et al. [7]. In essence, the process involves three procedures. Normalisation: To account for normal differences in brain size and shape and in the positions of the gyri, each brain image is resized and reshaped to fit a standardised brain template (standard stereotaxic space: Montreal Neurological Institute, MNI), using both linear and non-linear transformations. Segmentation: Each brain image is segmented into three compartments (cerebrospinal fluid, gray and white matter), based on the signal intensity of the MR image and on a priori knowledge of brain structure obtained from the standardised MNI brain template. Smoothing: To account for small scale differences in brain morphology that will remain after normalisation, the gray matter images are spatially smoothed (12 mm full width half maximum). The signal intensity at each voxel of this image is then taken to represent gray matter concentration.

Statistical comparisons of gray matter concentration were then performed using analysis of variance [9] (http://www.fil.ion.ucl.ac.uk/spm) to determine any difference between the two groups (control vs OSA). Due to our a priori hypothesis of hippocampal damage, the statistical threshold for a significant difference in gray matter concentration within this structure was set at \( p = 0.01 \), corrected for multiple comparisons within a small volume (two spheres, each of 15 mm radius centred at co-ordinates 31 (right), −17 (posterior), −18 (inferior) and −31 (left), −17 (posterior), −18 (inferior) mm in MNI space. See Fig. 1). As we had no strong hypotheses for changes within other specific foci, the statistical threshold for significance in other brain regions was set at \( p = 0.01 \), corrected for multiple comparisons across the whole brain.

### Fig. 1

(a) The shading indicates a region of statistically significant reduction in gray matter concentration within the left hippocampus for the group overlaid on a standard brain template. Cross hairs indicate voxel of maximum significance \( (p = 0.004, F(1,11) = 78 \) corrected for multiple comparisons based on a priori, bilateral, hippocampal region of interest) at −34 (left), −20 (posterior), −20 (superior) mm relative to the midline of the anterior commissure; the images are oriented to a horizontal plane through the anterior and posterior commissures (R, right; A, anterior). (b) Individual gray matter signal changes from the seven control and seven OSA patients in the left hippocampus (upper panel) at the voxel of maximum significance indicated in (a) and at the comparable voxel within the right hippocampus (lower panel; i.e. 34 (right), −20 (posterior), −20 (superior) mm); the change at this focus failed to reach significance, due to the increased variability of the data.
3. Results

The VBM revealed a significantly lower gray matter concentration in the OSA patients within the left hippocampus (Fig. 1a, statistical maximum: p = 0.004 corrected for multiple comparisons based on a priori, bilateral, hippocampal region of interest). The T1 signal of the gray matter segment (reflecting gray matter concentration) was, at its maximum, 6% less in OSA patients (mean ± SEM; 68.8 ± 0.4 vs 73.7 ± 0.3 arbitrary units, Fig. 1b). No further significant focal gray matter differences were seen in the right hippocampus (Fig. 1b) and in other brain regions (no a priori region of interest, p < 0.05 corrected for multiple comparisons for entire brain). There was no difference in total gray matter volume between apneics and controls (mean ± SEM; 0.914 ± 0.012 vs. 0.913 ± 0.013 l).

4. Discussion

Acute hypoxia produces both molecular and cellular neuronal damage. In particular, hippocampal neurones show increased sensitivity to low-O2 conditions and repetitive intermittent hypoxia reduces neuronal excitability in the CA1 region [5]. We speculate that the gray mater loss in our patients results from the hypoxic insult: The role of frequent arousals and the associated sleep fragmentation on any structural change is less clear. However, cortical excitability is reduced following sleep deprivation [10]. The combined effects of hypoxia and sleep fragmentation on neuronal plasticity are unknown.

VBM is one of a number of computer-assisted imaging approaches that have been developed to quantify changes in neuroanatomical structure; an overview of these approaches and their relative advantages has appeared recently [11]. To date, studies using VBM have reported changes in gray matter in ageing [7], schizophrenia [12] and Alzheimer’s disease [13,14]. Whilst there is generally good concordance between assessment of such differences using VBM and expert region of interest analysis performed manually [13], some differences do exist [14]. A number of studies have documented changes in the hippocampus using VBM [e.g. 6,13,15].

In the present study, the absence of gray matter concentration differences in the right hippocampus, or of differences elsewhere in the cortex, may reflect the relatively small study size and the relatively moderate AHI and hypoxaemia present in our patient group compared to that which can occur in the most severe form of the disease. Using VBM, Macey et al. [16] have recently reported morphological changes in OSA patients. Albeit at a relatively low level of statistical significance (p < 0.001 un-corrected for multiple comparisons), they reported gray matter loss in multiple sites of the brain including the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus and cerebellum; the degree of gray matter loss was related to the disease severity. The reasons for the more extensive findings of Macey et al. are not entirely clear. However, their patient group was larger (21 vs 7) and the severity of OSA in their patients was, overall, probably greater than those in the present study. Finally, it is noteworthy that a high proportion of Macey’s patients had additional, co-related morbidity. Our own findings emphasise that gray matter loss is associated with less severe disease but, due to our small study numbers, we were not able to relate the disease severity to the amount of gray matter loss. Neither study correlated gray matter loss with indices of cognitive function.

OSA can be treated with continuous positive airway pressure; however, there remains considerable debate as to the clinical and economic benefits of treating the large number of patients with relatively mild disease [17,18]. Our findings show that moderate OSA is associated with focal gray matter loss in areas required for cognitive function and raise the question as to whether treatment of the OSA could prevent the neuronal damage.

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References


