Chapter 8

NEURAL CONSEQUENCES OF SLEEP DISORDERED BREATHING: THE ROLE OF INTERMITTENT HYPOXIA

Mary J. Morrell and Gillian Twigg
Clinical and Academic Unit of Sleep and Breathing, National Heart and Lung Institute, Imperial College, Royal Brompton Campus, London, UK.

Abstract: Sleep disordered breathing is characterised by periodic breathing, episodes of hypoxia and repeated arousals from sleep; symptoms include excessive daytime sleepiness, impairment of memory, learning and attention. Recent evidence from animal studies suggests that both intermittent hypoxia and sleep fragmentation can independently lead to neuronal defects in the hippocampus and pre frontal cortex; areas known to be closely associated with neural processing of memory and executive function. We have previously shown that sleep disordered breathing is associated with loss of gray matter concentration within the left hippocampus (47). We have now confirmed and extended this finding in 22 right handed, newly diagnosed male patients (mean (sd): age 51.8 (15.4) yrs, apnea / hypopnea index 53.1 (14.0) events/hr, minimum nocturnal oxygen saturation 75 (8.4) %) and 17 controls matched for age and handedness. Voxel-based morphometry, an automated unbiased technique, was used to characterise changes in gray matter concentration. The magnetic resonance images were segmented and grey matter concentration determined voxel by voxel. Analysis of variance was then preformed, adjusted for overall image intensity, with age as a covariant. Additional to the deficit in the left hippocampus, we found more extensive loss of gray matter bilaterally in the parahippocampus. No additional focal lesions were seen in other brain regions. Based on our findings and data from other human and animal studies, we speculate that in patients with sleep disordered breathing intermittent hypoxia is associated with neural deficit, and further that such lesions may lead to cognitive dysfunction.

Key Words: sleep apnea, periodic breathing, cognitive, memory

Hypoxia and Exercise, edited by R.C. Roach *et al.*
Springer, New York, 2006.

INTRODUCTION

Sleep disordered breathing may present in several forms (I) obstructive sleep apnea / hypopnea, resulting from occlusion or partial closure of the pharyngeal airway (II) central sleep apnea, resulting from reduced efferent output to the respiratory pump muscles (III) mixed apnea, a combination of both obstructive and central events (IV) Cheyne-Stokes respiration: a periodic breathing pattern that is characterised by a crescendo-decrescendo fluctuation in tidal volume and may contain a central apnea or hypopnea. Obstructive sleep apnea / hypopnea is the most common form of sleep disordered breathing occurring in 1-4% of the middle-aged western male population (61, 67), increasing up to 24-30% in elderly males (37). Central sleep apnea and Cheyne-Stokes respiration are more often seen in patients with heart failure, or during conditions of chronic hypoxia as occurs at altitude. All forms of apnea and hypopnea produce intermittent hypoxia, to a greater or lesser extent (Figure 1).

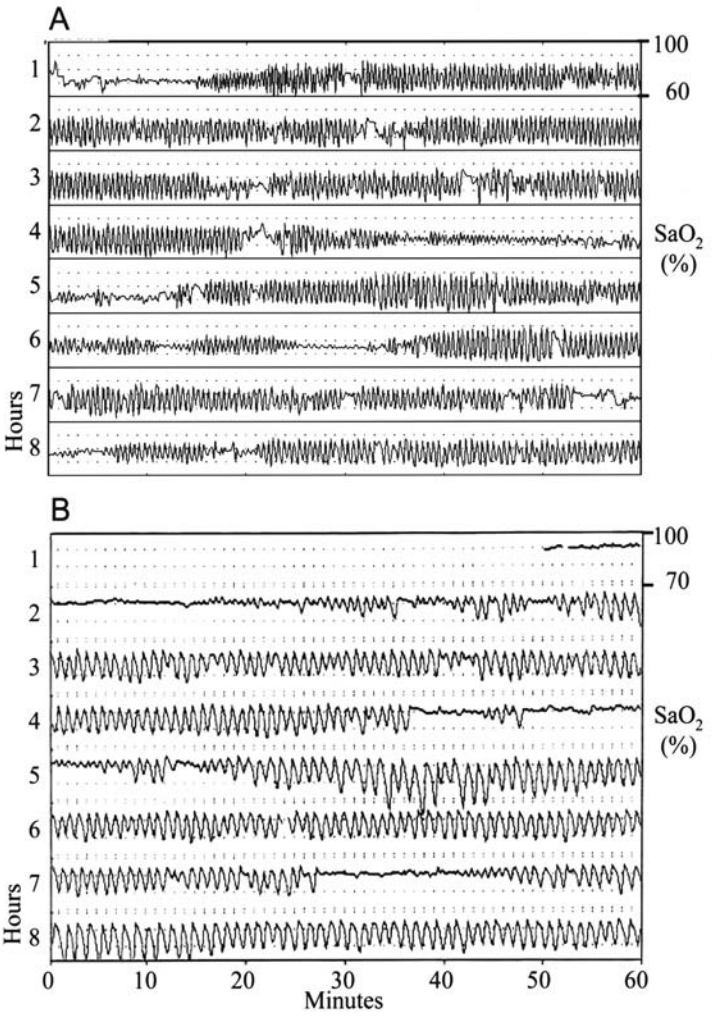

Figure 1. Intermittent hypoxia associated with obstructive sleep apnoea (Bottom Trace) and chronic hypoxia of altitude (Top Trace).

Apneic and hypopneic events are usually terminated by an arousal from sleep. As a result, sleep disordered breathing is typically associated with poor nocturnal sleep quality and excessive daytime sleepiness. The term obstructive sleep apnea / hypopnea syndrome (OSAHS) is usually taken to mean patients presenting with an apnea / hypopnea index (AHI) > 5 events / hour together with excessive daytime somnolence, not explained by other factors, or any two of the following factors: choking or gasping during sleep, recurrent awakenings during sleep, unrefreshing sleep, daytime fatigue, impaired concentration.

COGNITIVE FUNCTION AND SLEEP DISORDERED BREATHING

Cognitive dysfunction includes the impaired ability to problem solve, manipulate information, plan, inhibit responses and maintain attention (14, 15). It is a frequently reported problem in patients with sleep disordered breathing, with over 50% having some form of memory impairment (34). The mechanisms leading to the cognitive and memory deficits are unclear. Excessive daytime somnolence may result in an inability to focus and sustain attention (44), put simply patients fall asleep during boring repetitive tasks. Alternatively, sleep deprivation may lead to impaired memory by altering neural function (31). Cognitive dysfunction may be a consequence of hypoxia related neuronal deficits, in particular intermittent hypoxia (56). These mechanisms will be addressed fully in the latter sections of this paper. In the remainder of this section we will review in more detail the relationship between sleep disordered breathing and aspects of cognitive function.

Previous research has examined many aspects of cognitive functioning in patients with sleep disordered breathing, including facets of memory, attention, vigilance and executive functions. In patients with mild sleep disordered breathing (AHI 10-30 events/hour) some, but not all aspects of working memory (e.g. the ability to hold information long enough to make use of it, such as a phone number) are deficient compared to healthy controls (AHI < 5 events / hour) (54). In patients with more severe OSAHS, the recall of word lists is reduced and these patients make less efficient use of semantic cues to assist their memory. However, recognition memory and retention of previously learned information are not significantly affected (58). Taken together, these data suggest that not all aspects of memory are equally affected by sleep disordered breathing, and that the severity of the disease may influence the extent of the dysfunction.

In an important study into the effects of OSAHS on pre frontal lobe-related executive functions, Feuerstein et al found that patients were significantly impaired on a number of functions; in particular, deficits where found in tests of planning and flexibility, plus tests requiring inhibition of a learned response (21). In addition, phonemic fluency, another frontal lobe task, is impaired in OSAHS patients, compared to controls matched for age and educational status (58).

If sleep disordered breathing is associated with impairment of cognitive tasks involving the pre frontal cortex, it is reasonable to question: *to what extent treatment reverses the cognitive dysfunction?* The treatment of choice for OSAHS is continuous positive airway pressure (CPAP). This treatment has been successfully used to reduce the number of apneas / hypopneas, and the number of respiratory-related arousals, which in turn improves the quality of sleep. Patients who use CPAP frequently report a reduction in daytime som-

nolence, which is confirmed objectively with an increase in sleep latency (59). However, a summary review of the effectiveness of CPAP in improving cognitive function is confounded by the fact that different researchers have used different cognitive test batteries, and CPAP treatment for varying periods of time; additionally, compliance is frequently poor or not reported. Nevertheless, OSAHS patients using CPAP treatment have shown an improvement in some aspects of cognitive function. In particular, mental flexibility, such as trail making B (17, 18), psychomotor vigilance (17, 35) and measures of attention (20, 21) all improve following CPAP treatment.

The duration of CPAP treatment required to reverse cognitive dysfunction varies. Significant improvements in tests of sustained attention, spatial memory, motor agility and dexterity have been shown after fifteen days of CPAP treatment (20). When examined again at four months, these improvements had been maintained but no further significant improvements had been made. Some cognitive deficits noted prior to CPAP were not reversed by treatment; these included tests of executive function. These data are in accordance with other studies which have reported significant improvements in tests of vigilance after one night of CPAP treatment, with further significant improvements after fourteen nights (36) and six months of treatment (5); the latter study having no interim analysis at fourteen / fifteen nights.

Finally, it is important to note that not all studies of CPAP treatment have shown improvements in cognitive function. A placebo controlled study, examining the effects of CPAP on cognitive functioning after one week found no improvements in any neuropsychological tests used (2). The authors suggest that this may be due to the short duration of treatment use prior to evaluation, or poor compliance. However, this is unlikely since an earlier placebo controlled study of CPAP in OSAHS patients found that four weeks of treatment significantly improved objective and subjective measures of sleepiness, but failed to detect any improvement on the neuropsychological function (19). Similarly, sleepiness and cognitive function were compared in patients who did, and did not comply well with CPAP; in those who were compliant there was a significant improvement in sleepiness but not cognitive function (16). The results of these studies, compared to those mentioned earlier may be explained in part by the differences in cognitive test batteries. Nevertheless, the latter studies are placebo controlled and as such must be taken into account.

From this review of the literature we conclude that the use of CPAP in OSAHS leads to reversal of day time somnolence and vigilance; improvements in some, but not all aspects of cognitive dysfunction are seen in the majority of studies. We speculate that treatment of sleep disordered breathing may improve vigilance and aspects of memory by reversing daytime somnolence; whereas it has a reduced and inconsistent effect on the cognitive dysfunction, because cognitive function results from neurodegeneration associated with chronic intermittent hypoxia. This suggestion is supported by correlation studies which have shown that tests of executive functions and visuo-constructional ability correlate strongly with measures of nocturnal hypoxemia (6, 46). However, deficits in memory and attention correlated more strongly with measures of daytime somnolence (46).

STRUCTURAL CHANGES IN BRAIN MORPHOLOGY ASSOCIATED WITH SLEEP DISORDERED BREATHING

It is widely accepted that episodes of anoxia and / or hypoxia in humans can result in defuse neurodegeneration (33) and in selected cases, bilateral focal lesions of the hippocampus can occur (22). Conversely the effects of chronic intermittent hypoxia are less clear. In rats, exposure to intermittent hypoxia during sleep results in cellular damage within the CA1 region of the hippocampus and adjacent cortex (27, 55).

In humans several recent studies have investigated the suggestion that the intermittent hypoxia associated with OSAHS leads to changes in brain morphology (22, 39, 47, 48). In the first of these studies, Macey et al (39) reported widespread changes in gray matter concentration across the brain in twenty one patients with OSAHS compared to twenty one age matched controls; including the frontal and parietal cortex, the temporal lobe, anterior cingulate, hippocampus and cerebellum (Figure 2, top panel). In these patients, the decrease in gray matter concentration was related to the severity of the OSAHS disease. For each group the magnetic resonance images were analysed using voxel-based morphometry (VBM; Figure 2, top panel: A). This is an automated and unbiased technique that can be used to characterise changes in grey matter concentrations between groups (23, 26, 43, 65). It has the potential advantage of being able to detect subtle changes in relatively small structures such as the hippocampus (40). However, interpretation of the data obtained using this technique may be confounded by the statistical analysis. Macey et al (39) used a relatively low level of significance to report their findings; $p<0.001$, uncorrected for multiple comparisons, which may explain the wide spread gray matter loss in their study.

In the recent study of O'Donoghue et al (48) changes in brain morphology were examined in twenty five patients with severe OSAHS compared to twenty three healthy controls. Using VBM these authors found some reduction in gray matter concentration when the data were reported at $p<0.001$, uncorrected for multiple comparisons (Figure 2, bottom panel). However, when the data were analysed at $p<0.05$, corrected for multiple comparisons no significant reductions in gray matter in were seen. The authors corroborated their findings using a second method of MRI analysis; region of interest analysis (Figure 2, bottom panel: B)

The differences between the studies of Macey et al (39) and O'Donoghue et al (48) may in part be explained by differences in patient selection. The patients studied by O'Donoghue et al (48) had more severe OSA compared to those of Macey et al (39). However, this would have maximised the chances of O'Donoghue et al (48) finding changes in gray matter concentration. On the other hand, the study by Macey et al (39) included some patients known to have neurological and cardiovascular co-morbidity, most commonly hypertension; this could have had an independent effect on brain morphology and resulted in a reduction in gray matter concentration.

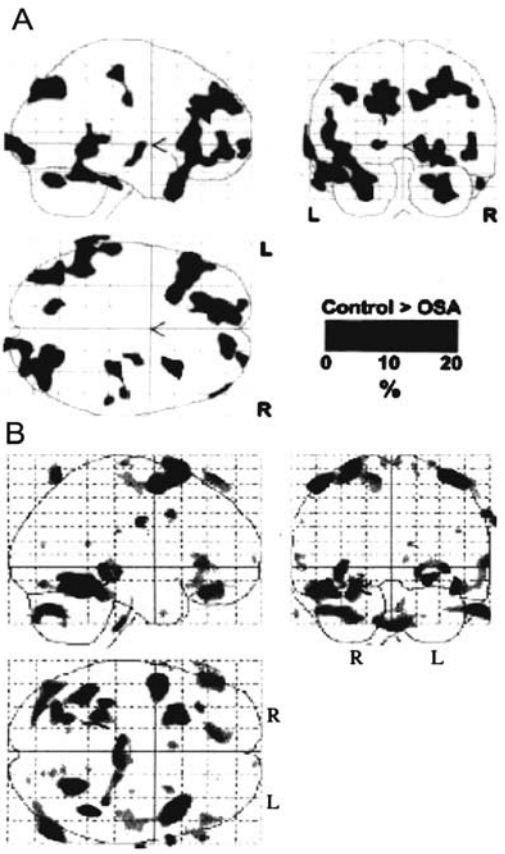

Figure 2. Glass brain display of regions of significantly reduced gray matter ($p<0.001$, uncorrected for multiple comparisons) in 21 subjects with OSAHS, weighted by disease severity and 21 healthy controls, matched for handedness and age (Macey et al (39) Top Panel and O'Donoghue et al (48).

Our group have also carried out a study to investigate the hypothesis that OSAHS is associated with changes in brain morphology, particularly a focal loss of grey matter within the hippocampus. Seven male right-handed, newly-diagnosed OSAHS patients were investigated using VBM. Compared to controls our study revealed a loss of grey matter concentration within the left hippocampus in patients with OSAHS (47). The level of significance used was $p=0.01$, corrected for multiple comparisons based on a hippocampal region of interest; this was selected on the basis of an *a priori* hypothesis of hippocampal gray matter loss in the OSA patients. We have now confirmed and extended this finding in twenty-two OSAHS patients compared to seventeen controls. See Table 1 for subject details. Additional to the deficit in the left hippocampus, this larger group of patients had more extensive loss of grey matter bilaterally in the para-hippocampus ($p<0.001$, a priori region of interest, uncorrected for multiple comparisons, with age as a covariant); no additional focal grey matter reductions were seen in other brain regions ($p>0.05$, corrected for multiple comparisons) (Figure 3). Five of our OSAHS patients and one of the control subject had a clinically diagnosed hypertension or were on antihypertensive medications. Therefore we carried out a second analysis removing these subjects. The focal lesions in the hippocampus and para hippocampus remained present on re-analysis.

Table 1. Subject characteristics.

	OSA patients (n=22)	Controls (n=17)
Age (years)	51.8 (15.4)	53.1 (14.0)
BMI (Kg/m^2)	32.4 (5.6)	24.8 (4.3)
Epworth Sleepiness Score	13.3 (4.2)	3.4 (1.2)
AHI (events/hour)	53.1 (14.0)	< 10
Minimum nocturnal oxygen saturation (%)	75 (8.4)	n/a

As we have alluded to above, sensitivity of VBM has been questioned by some. Therefore it is of significant interest that a fourth study has been published in which neuronal deficit in the hippocampus has been examined using another method of MRI analysis. In this study Gale and Hopkins (22) found bilateral hippocampal volumetric loss in 36% of the severe OSAHS patients they studied (n=14; respiratory disturbance index 84 (18) events / hour; mean percentage sleep time < 90% saturation 65 (34)%). The MRI scans were analysed using an alternative quantitative (volumetric) method (7).

So far we have discussed the impact of sleep disordered breathing on changes in gray matter concentration in humans. We conclude that some, but not all available data, supports the concept that OSAHS is associated with reduced gray matter in the hippocampus. However, before concluding this section we must mention that the relationship between OSAHS and with white matter disease has also been investigated (11, 13, 63). These studies have found no relationship between OSAHS and sub-clinical white matter disease (11, 63) or AHI and brainstem white matter disease (13).

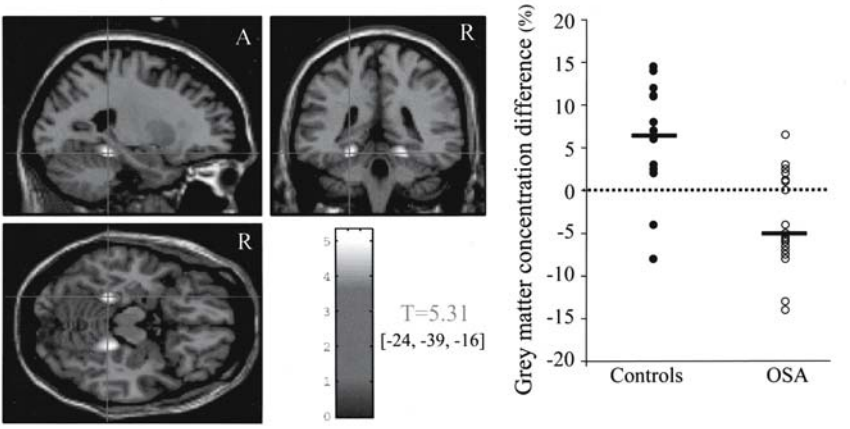

Figure 3. Shading indicates a statistically significant bilateral reduction in grey matter concentration within the para-hippocampus for the group of 22 OSAHS patients minus the 17 controls, overlaid on a standard brain template. Cross hairs indicate voxel of maximum significance ($p < 0.001$, *a priori* region of interest, uncorrected for multiple comparisons) at –24 (left), -16 (posterior), -34 (superior) mm, relative to the midline of the anterior commissure; no reductions were seen in other brain regions ($p>0.05$, corrected for multiple comparisons). Images oriented to a horizontal plane through the anterior and posterior commissures.

FUNCTIONAL IMPLICATIONS OF NEURONAL DEGENERATION IN THE HIPPOCAMPUS AND FONTAL CORTEX

To examine the functional implications of neuronal deficit in the hippocampus, studies have been carried out in patients with bilateral hippocampal degeneration, resulting from diseases other than sleep disordered breathing. In these patients aspects of memory are impaired. In one study, there was a reduction in recall of factual knowledge for several years prior to the onset of memory loss, although factual information acquired from greater than eleven years prior to onset of memory impairment remained intact (41). However, patients with bilateral hippocampal lesions do not always have complete loss of memory recall, suggesting either that other brain regions are recruited in the absence of hippocampal function, or that some cells in the hippocampus are spared (42).

Patients with damage limited to the hippocampus appear to show a reduction in source memory (41); the recognition of something as familiar and knowing the context in which it was first encountered (60). However, it must be noted that source memory is supported by other areas of the brain. Indeed studies have shown deficits in this function in patients with damage to the left prefrontal cortex, implicating this area as a vital component in the capacity for memory for source (24, 60).

Interestingly, the hippocampus has not been specifically implicated in working memory (10), whereas it does appear to be involved in spatial memory, particularly for navigation (40, 49). Bilateral dorsal hippocampal lesions have resulted in impaired spatial memory in rats, even when the lesion size encompassed as little as 30% of the total hippocampal volume (8). In addition, the medial prefrontal cortex has also been implicated in spatial memory, with lesions to either the hippocampus or the medial prefrontal cortex resulting in disruption of spatial memory capacity (62).

MECHANISMS OF NEURONAL DEGENERATION IN SLEEP DISORDERED BREATHING: THE ROLE OF INTERMITTENT HYPOXIA

As mentioned earlier at least two studies (6, 46), have examined the correlation between respiratory measures of disease severity, and performance on particular tests of cognitive function in order to address the question: *to what extent are cognitive deficits seen in patients with sleep disordered breathing attributable to hypoxemia, versus daytime somnolence?* In a large population based study, Adams et al (2001) have used factor analysis to show that respiratory disturbance index and nocturnal hypoxemia are significant predictors of declarative memory and signal discrimination (1). Furthermore, performances on tests which tap working memory, such as reverse digit span, were found to be predicted by the respiratory disturbance index (1). Performance on tasks involving attention, were significantly predicted by sleepiness (1). These data indicate that hypoxemia contributes to cognitive dysfunction in OSAHS. Consistent with this suggestion correlations between AHI and measures of visuo-spatial organisation (9, 29), visuo-motor coordination (9), reaction time (9), motor speed (29) and distractibility (9) have been shown.

From our study (47), we speculate that the changes in brain morphology which occur in patients with OSAHS resulted from the intermittent hypoxic insult. The mechanisms contributing to the hypoxic-induced hippocampal neurodegeneration are likely to have included several processes, with much of the recent research focused on the role of oxidative stress (3, 52, 53).

Brain function is critically dependent on oxygen supply. During any hypoxic insult, protection of the brain is dependent on a rapid cerebral vascular response otherwise cerebral ischemia with neuronal deficit will ensue. Recent research in healthy humans suggests that the cerebral vascular responses to both hypoxia and hypercapnia are significantly altered during stable non rapid eye movement sleep compared to wakefulness *(for a full review - see Corfield and Meadows Chapter 7 in this volume).*

Cellular responses to hypoxia include changes in the mediation ions channels, release of vasoactive substances from the endothelium and neighbouring tissues, regulation of gene expression and tissue remodelling (38). Hypoxia causes modulation of ion channels and in the hippocampal neurones immediate hyperpolerisation occurs via activation of the K_{ca} channels (32). Exposure to intermittent hypoxia during sleep results in cellular damage within the cerebella cortex (50), wake-promoting regions of the brainstem and basal forebrain (64), and CA1 region of the hippocampus and adjacent cortex (27, 30, 55). In the animals with hippocampal damage evidence of increased membrane lipid peroxidation and oxidative stress occurs, which is attenuated with administration of antioxidants (56). The susceptibility of the hippocampal neurones to neural dysfunction may be age dependent, with very young and elderly animals being more vulnerable (12, 28). The importance of this finding is that the prevalence of sleep disordered breathing increases with age (37) and in the young, sleep disordered breathing has been linked with attention deficit / hyperactivity disorder (4).

In animal experiments mentioned above the onset of intermittent hypoxia is abrupt, this is not the case in humans where the development of sleep disordered breathing is insidious. This is of interest since the neural degeneration in these experiments may be time-course dependent. In one study the neuronal deficit peaked at 3 days, returning to normoxic levels within 14 days in animals exposed to intermittent hypoxia (25). These findings lead to the suggestion that long-term potentiation, may play an important role in the impact of intermittent hypoxia on neural function (51).

MECHANISMS OF NEURONAL DEGENERATION IN SLEEP DISORDERED BREATHING: THE ROLE OF SLEEP DEPRIVATION

Although the focus of this paper is the role of intermittent hypoxia on the neural degeneration associated with sleep disordered breathing any review of sleep disordered breathing would be incomplete without considering the role of sleep *per se*.

Recent research has demonstrated the vulnerability of the hippocampus to damage in sleep deprivation (57). Selective REM sleep deprivation can also lead to a reduction in neuronal excitability in the CA1 pyramidal neurones, but not the dentate gyrus granule cells of the hippocampus (45). Sleep deprivation using a treadmill paradigm has also shown a

reduction in the proliferation of cells in the dentate gyrus (31). If sleep deprivation in and of itself can result in neuronal deficits it is interesting to speculate on the combined effects of sleep deprivation and intermittent hypoxia on neuronal plasticity in humans, an area which thus far has not been investigated.

CLINICAL IMPLICATIONS OF CHANGES IN MORPHOLOGY ASSOCIATED WITH OSAHS

As outlined earlier treatment of OSAHS using CPAP produces a considerable improvement in daytime somnolence (19). However, despite the obvious benefits of CPAP treatment in patients with severe OSAHS, there remains considerable debate as to the clinical and economic benefits of treating the large number of patients with relatively-mild disease (66). In concluding this paper we suggest that if sleep disordered breathing is associated with focal changes in brain morphology, it is possible that early treatment of the disease with CPAP may prevent structural changes and subsequent cognitive dysfunction in some patients.

ACKNOWLEDGMENTS

Research supported by the Wellcome Trust and The Hammersmith Hospitals Research Council. GT was supported by an NHLI foundation studentship. The authors thank Dr DR Corfield for his partnership in all aspects of this project, including carrying out the VBM analysis.

REFERENCES

1. Adams N, Strauss M, Schluchter M, and Redline S. Relation of measures of sleep-disordered breathing to neuropsychological functioning. *Am J Respir Crit Care Med* 163: 1626-1631, 2001.
2. Bardwell WA, Ancoli-Israel S, Berry CC, and Dimsdale JE. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: a placebo-controlled study. *Psychosom Med* 63: 579-584, 2001.
3. Barnham KJ, Masters CL, and Bush AI. Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov* 3: 205-214, 2004.
4. Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, Schonwald A, Wilker RE, Stehle S, and Kinane TB. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics* 114: 805-816, 2004.
5. Bedard MA, Montplaisir J, Malo J, Richer F, and Rouleau I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). *J Clin Exp Neuropsychol* 15: 330-341, 1993.
6. Bedard MA, Montplaisir J, Richer F, Rouleau I, and Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. *J Clin Exp Neuropsychol* 13: 950-964, 1991.

7. Blatter DD, Bigler ED, Gale SD, Johnson SC, Anderson CV, Burnett BM, Ryser D, Macnamara SE, and Bailey BJ. MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: correlation with neuropsychological outcome. *AJNR Am J Neuroradiol* 18: 1-10, 1997.
8. Broadbent NJ, Squire LR, and Clark RE. Spatial memory, recognition memory, and the hippocampus. *Proc Natl Acad Sci U S A* 101: 14515-14520, 2004.
9. Cheshire K, Engleman H, Deary I, Shapiro C, and Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. *Arch Intern Med* 152: 538-541, 1992.
10. Cowey CM and Green S. The hippocampus: a "working memory" structure? The effect of hippocampal sclerosis on working memory. *Memory* 4: 19-30, 1996.
11. Davies CW, Crosby JH, Mullins RL, Traill ZC, Anslow P, Davies RJ, and Stradling JR. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep* 24: 715-720, 2001.
12. Decker MJ, Hue GE, Caudle WM, Miller GW, Keating GL, and Rye DB. Episodic neonatal hypoxia evokes executive dysfunction and regionally specific alterations in markers of dopamine signaling. *Neuroscience* 117: 417-425, 2003.
13. Ding J, Nieto FJ, Beauchamp NJ, Jr., Harris TB, Robbins JA, Hetmanski JB, Fried LP, and Redline S. Sleep-disordered breathing and white matter disease in the brainstem in older adults. *Sleep* 27: 474-479, 2004.
14. Duncan J and Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 23: 475-483, 2000.
15. Elliott R. Executive functions and their disorders. *Br Med Bull* 65: 49-59, 2003.
16. Engleman HM, Cheshire KE, Deary IJ, and Douglas NJ. Daytime sleepiness, cognitive performance and mood after continuous positive airway pressure for the sleep apnoea/hypopnoea syndrome. *Thorax* 48: 911-914, 1993.
17. Engleman HM, Martin SE, Deary IJ, and Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 343: 572-575, 1994.
18. Engleman HM, Martin SE, Deary IJ, and Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. *Thorax* 52: 114-119, 1997.
19. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, and Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 53: 341-345, 1998.
20. Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, and Cappa SF. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). *Brain Res Bull* 61: 87-92, 2003.
21. Feuerstein C, Naegele B, Pepin JL, and Levy P. Frontal lobe-related cognitive functions in patients with sleep apnea syndrome before and after treatment. *Acta Neurol Belg* 97: 96-107, 1997.
22. Gale SD and Hopkins RO. Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. *J Int Neuropsychol Soc* 10: 60-71, 2004.
23. Gitelman DR, Ashburner J, Friston KJ, Tyler LK, and Price CJ. Voxel-based morphometry of herpes simplex encephalitis. *Neuroimage* 13: 623-631, 2001.
24. Glisky EL, Rubin SR, and Davidson PS. Source memory in older adults: an encoding or retrieval problem? *J Exp Psychol Learn Mem Cogn* 27: 1131-1146, 2001.
25. Goldbart A, Row BW, Kheirandish L, Schurr A, Gozal E, Guo SZ, Payne RS, Cheng Z,

Brittian KR, and Gozal D. Intermittent hypoxic exposure during light phase induces changes in cAMP response element binding protein activity in the rat CA1 hippocampal region: water maze performance correlates. *Neuroscience* 122: 585-590, 2003.
26. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, and Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14: 21-36, 2001.
27. Gozal D, Daniel JM, and Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J Neurosci* 21: 2442-2450, 2001.
28. Gozal D, Row BW, Kheirandish L, Liu R, Guo SZ, Qiang F, and Brittian KR. Increased susceptibility to intermittent hypoxia in aging rats: changes in proteasomal activity, neuronal apoptosis and spatial function. *J Neurochem* 86: 1545-1552, 2003.
29. Greenberg GD, Watson RK, and Deptula D. Neuropsychological dysfunction in sleep apnea. *Sleep* 10: 254-262, 1987.
30. Gu XQ and Haddad GG. Decreased neuronal excitability in hippocampal neurons of mice exposed to cyclic hypoxia. *J Appl Physiol* 91: 1245-1250, 2001.
31. Guzman-Marin R, Suntsova N, Stewart DR, Gong H, Szymusiak R, and McGinty D. Sleep deprivation reduces proliferation of cells in the dentate gyrus of the hippocampus in rats. *J Physiol* 549: 563-571, 2003.
32. Haddad GG and Jiang C. Mechanisms of anoxia-induced depolarization in brainstem neurons: in vitro current and voltage clamp studies in the adult rat. *Brain Res* 625: 261-268, 1993.
33. Hopkins RO, Gale SD, Johnson SC, Anderson CV, Bigler ED, Blatter DD, and Weaver LK. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. *J Int Neuropsychol Soc* 1: 501-509, 1995.
34. Kales A, Caldwell AB, Cadieux RJ, Vela-Bueno A, Ruch LG, and Mayes SD. Severe obstructive sleep apnea--II: Associated psychopathology and psychosocial consequences. *J Chronic Dis* 38: 427-434, 1985.
35. Kribbs NB, Pack AI, Kline LR, Getsy JE, Schuett JS, Henry JN, Maislin G, and Dinges DF. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *Am Rev Respir Dis* 147: 1162-1168, 1993.
36. Lamphere J, Roehrs T, Wittig R, Zorick F, Conway WA, and Roth T. Recovery of alertness after CPAP in apnea. *Chest* 96: 1364-1367, 1989.
37. Levy P, Pepin JL, Malauzat D, Emeriau JP, and Leger JM. Is sleep apnea syndrome in the elderly a specific entity? *Sleep* 19: S29-38, 1996.
38. Lopez-Barneo J, Pardal R, and Ortega-Saenz P. Cellular mechanism of oxygen sensing. *Annu Rev Physiol* 63: 259-287, 2001.
39. Macey PM, Henderson LA, Macey KE, Alger JR, Frysinger RC, Woo MA, Harper RK, Yan-Go FL, and Harper RM. Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med* 166: 1382-1387, 2002.
40. Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, and Frith CD. Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci U S A* 97: 4398-4403, 2000.
41. Manns JR, Hopkins RO, Reed JM, Kitchener EG, and Squire LR. Recognition memory and the human hippocampus. *Neuron* 37: 171-180, 2003.
42. Manns JR, Hopkins RO, and Squire LR. Semantic memory and the human hippocampus. *Neuron* 38: 127-133, 2003.
43. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, and Goadsby PJ. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med* 5: 836-838, 1999.
44. Mazza S, Pepin JL, Naegele B, Plante J, Deschaux C, and Levy P. Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests.

Eur Respir J 25: 75-80, 2005.
45. McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, and Magee JC. Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. *J Neurosci* 23: 9687-9695, 2003.
46. Montplaisir J, Bedard MA, Richer F, and Rouleau I. Neurobehavioral manifestations in obstructive sleep apnea syndrome before and after treatment with continuous positive airway pressure. *Sleep* 15: S17-19, 1992.
47. Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, and Corfield DR. Changes in brain morphology associated with obstructive sleep apnea. *Sleep Med* 4: 451-454, 2003.
48. O'Donoghue F J, Briellmann RS, Rochford PD, Abbott DF, Pell GS, Chan CH, Tarquinio N, Jackson GD, and Pierce RJ. Cerebral Structural Changes in Severe Obstructive Sleep Apnea. *Am J Respir Crit Care Med*, 2005.
49. O'Keefe J and Conway DH. Hippocampal place units in the freely moving rat: why they fire where they fire. *Exp Brain Res* 31: 573-590, 1978.
50. Pae EK, Chien P, and Harper RM. Intermittent hypoxia damages cerebellar cortex and deep nuclei. *Neurosci Lett* 375: 123-128, 2005.
51. Payne RS, Goldbart A, Gozal D, and Schurr A. Effect of intermittent hypoxia on long-term potentiation in rat hippocampal slices. *Brain Res* 1029: 195-199, 2004.
52. Prabhakar NR, and Kumar, GK. Oxidative stress in the systemic and cellular responses to intermittent hypoxia. *Biol Chem* 385: 217-221, 2004.
53. Nanduri R, and Prabhakar NR. Sleep Apneas . An Oxidative Stress? *Am J Respir Crit Care Med* 165: 859-860, 2002.
54. Redline S, Strauss ME, Adams N, Winters M, Roebuck T, Spry K, Rosenberg C, and Adams K. Neuropsychological function in mild sleep-disordered breathing. *Sleep* 20: 160-167, 1997.
55. Row BW, Kheirandish L, Neville JJ, and Gozal D. Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. *Pediatr Res* 52: 449-453, 2002.
56. Row BW, Liu R, Xu W, Kheirandish L, and Gozal D. Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. *Am J Respir Crit Care Med* 167: 1548-1553, 2003.
57. Ruskin DN, Liu C, Dunn KE, Bazan NG, and LaHoste GJ. Sleep deprivation impairs hippocampus-mediated contextual learning but not amygdala-mediated cued learning in rats. *Eur J Neurosci* 19: 3121-3124, 2004.
58. Salorio CF, White DA, Piccirillo J, Duntley SP, and Uhles ML. Learning, memory, and executive control in individuals with obstructive sleep apnea syndrome. *J Clin Exp Neuropsychol* 24: 93-100, 2002.
59. Sforza E and Krieger J. Daytime sleepiness after long-term continuous positive airway pressure (CPAP) treatment in obstructive sleep apnea syndrome. *J Neurol Sci* 110: 21-26, 1992.
60. Slotnick SD, Moo LR, Segal JB, and Hart J, Jr. Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. *Brain Res Cogn Brain Res* 17: 75-82, 2003.
61. Stradling JR and Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 46: 85-90, 1991.
62. Sutherland RJ, Kolb B, and Whishaw IQ. Spatial mapping: definitive disruption by hippocampal or medial frontal cortical damage in the rat. *Neurosci Lett* 31: 271-276, 1982.
63. Thomas RJ, Rosen BR, Stern CE, Weiss JW, and Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. *J Appl Physiol*, 98: 2226-

2234, 2005.
64. Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, and Gow A. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 27: 194-201, 2004.
65. Wright IC, McGuire PK, Poline JB, Travere JM, Murray RM, Frith CD, Frackowiak RS, and Friston KJ. A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *Neuroimage* 2: 244-252, 1995.
66. Wright J and Sheldon T. The efficacy of nasal continuous positive airway pressure in the treatment of obstructive sleep apnea syndrome is not proven. *Am J Respir Crit Care Med* 161: 1776-1778, 2000.
67. Young T, Palta M, Dempsey J, Skatrud J, Weber S, and Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 328: 1230-1235, 1993.