Neural Alterations and Depressive Symptoms in Obstructive Sleep Apnea Patients

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Study Objectives: Depressive symptoms are common in obstructive sleep apnea (OSA) patients, and brain injury occurs with both OSA and depression independently. The objective was to determine whether brain alterations in OSA bear relationships to depressive symptoms.

Design: Cross-sectional study.

Setting: University-based medical center.

Participants: 40 treatment-naive OSA subjects and 61 control subjects without diagnosed psychopathology.

Interventions: None.

Measurements and Results: Whole-brain maps of T2 relaxation time, a measure sensitive to injury, were calculated from magnetic resonance images, transformed to common space, and smoothed. Control and OSA groups were classified by Beck Depression Inventory (BDI)-II scores (≥12 symptomatic, <10 asymptomatic for depressive symptoms). The OSA group separated into 13 symptomatic (mean ± SD: BDI-II 21 ± 8; age 47.6 ± 11; apnea hypopnea index [AHI] 28.3 ± 17), and 27 asymptomatic (4 ± 3; 47.5 ± 8; 31.5 ± 16) subjects. The control group included 56 asymptomatic (BDI-II 2.5 ± 2.6; age 47.3 ± 9) subjects. Asymptomatic OSA subjects exhibited higher AHI. T2 maps were compared between groups (ANCOVA), with age and gender as covariates. Injury appeared in symptomatic vs asymptomatic OSA subjects in the mid- and anterior cingulate, anterior insular, medial pre-frontal, parietal, and left ventrolateral temporal cortices, left caudate nucleus, and internal capsule. Relative to asymptomatic controls, symptomatic OSA patients showed damage in the bilateral hippocampus and caudate nuclei, anterior corpus callosum, right anterior thalamus, and medial pons.

Conclusions: Neural injury differed between OSA patients with and without depressive symptoms. Depressive symptoms may exacerbate injury accompanying OSA, or introduce additional damage in affective, cognitive, respiratory, and autonomic control regions.

Keywords: Magnetic resonance imaging, neural injury, T2 relaxometry

Citation: Cross RL; Kumar R; Macey PM; Doering LV; Alger JR; Yan-Go FL; Harper RM. Neural alterations and depressive symptoms in obstructive sleep apnea patients. *SLEEP* 2008;31(8):1103-1109.

OBSTRUCTIVE SLEEP APNEA (OSA) PATIENTS EXHIBIT A HIGH INCIDENCE OF DEPRESSION, WITH REPORTS SHOWING UP TO HALF EXPERIENCE ELEVATED depressive symptoms.[1,2] The presence of depressive symptoms among OSA patients is of concern due to its relationship to diminished quality of life, decreased continuous positive airway pressure (CPAP) compliance,[3] and association with the development and progression of cardiovascular disease.[4,5] Furthermore, brain injury and abnormal brain function in OSA occur in sites that are also affected in depression,[6-11] raising the possibility that depressive symptoms contribute to the brain alterations found in OSA patients, or that the neural pathology accompanying OSA fosters development of depressive symptoms.

Despite overlap in characteristics, depressive symptoms are, at least in part, independent of the sleep disorder. While some studies report a partial improvement in depressive symptoms following CPAP,[12] others report no significant amelioration of the affective attributes.[13] The lack of improvement in depressive symptoms occurs despite adequate CPAP compliance and improvements in daytime somnolence.[12,13]

Depression is accompanied by gray matter loss in regions associated with affect. Compared to healthy controls, those with major depressive disorder show structural and functional deficits in the hippocampus, anterior cingulate, amygdala, and frontal cortex.[6,7,11] Dysfunction of the anterior cingulate, amygdala, and frontal cortex may play a role in anhedonia,[14] a cardinal symptom of depression, while the considerable negative affect may derive at least in part from injury to the amygdala,[15] which plays a significant role in negative emotions. The presence of gray matter loss, as well as evidence of disrupted sleep patterning, temperature regulation, and circadian rhythms, suggests that at least some depressive symptoms result from alterations in neural processes that regulate mood and essential physiological functions. Electrical stimulation of the anterior cingulate, for example, improves symptoms of depression,[16] implying that interventions to modify neural regulatory systems can correct deficient neural processes.

Brain tissue injury and a loss of gray matter, do not differ between OSA and control subjects on visual examination,[20] appear in both pediatric and adult OSA patients, as indicated by volumetric and spectroscopic measures,[9,10,17-19] although the reported extent of injury varies.[9,21] The structural deficits appear in multiple areas, and the damage apparently interferes with function, since the anatomic sites overlap areas that show altered functional magnetic resonance imaging (fMRI) signal

Disclosure Statement

This was not an industry supported study. Dr. Harper is on the advisory board of BAM Corporation. The other authors have indicated no financial conflicts of interest.

Submitted for publication October, 2007
Accepted for publication April, 2008

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responses to ventilatory and blood pressure challenges.[8,22-24] Structural and functional deficits in OSA appear in the anterior cingulate, frontal cortex, hippocampus, insular cortex, cerebellum, and amygdala[8-10]; these sites are also affected in depression.[6,7,11] The high incidence of depressive symptoms in patients with OSA, and the presence of sites showing injury in OSA and depression independently, suggest that a portion of the damage found in OSA may be related to injuries associated with depressive symptoms. The objective of this study was to determine whether brain alterations in OSA bear relationships to depressive symptoms.

METHODS

Design

This study used a comparative cross-sectional design to investigate OSA and control subgroups with and without depressive symptoms.

Subjects

Obstructive sleep apnea patients were recruited from the University of California at Los Angeles Sleep Disorders Laboratory. The OSA subjects underwent overnight polysomnography and were untreated with CPAP or other intervention at the time of enrollment. Control subjects were recruited from the greater Los Angeles area. All subjects were between 30 and 65 years of age, free from a known history of cerebrovascular accident, heart failure, myocardial infarction, neurological disorders, or psychopathology, and none were taking cardiovascular or psychotropic medications. No subjects weighed more then 125 kg or had metallic implants (scanner weight and safety limitations).

All subjects gave written informed consent prior to study entry. The research protocol was approved by the Institutional Review Board of the University of California at Los Angeles.

Depressive Symptom Severity

Severity of depressive symptoms was measured using the Beck Depression Inventory (BDI)-II, a commonly used tool to assess the level of depressive symptoms in psychiatric, healthy, and medical populations.[25] The BDI-II is a self-report questionnaire containing 21 items, each of which is scored 0-3, with higher scores denoting a greater severity of depressive symptoms. While scores ≥10 have traditionally been considered abnormal in healthy populations, scores ≥12 provide improved sensitivity and specificity for medical conditions in which fatigue may be present.[26,27] Thus, as a conservative approach, OSA and control subjects were classified as symptomatic with BDI-II ≥12, and asymptomatic with BDI-II <10. Individuals scoring between these two values were excluded from the analysis.

Magnetic Resonance Imaging

We used magnetic resonance T2 relaxometry to assess brain tissue injury, which differs from conventional T2-weighted imaging. T2 relaxation values increase with free water content, providing an index of tissue damage. The quantitative T2 relaxometry technique allows for a more sensitive determination of tissue injury than conventional visual assessment of T2-weighted scans.

Whole brain images were collected from all subjects with a 3.0 Tesla magnetic resonance imaging (MRI) scanner from all subjects (Magnetom Tim-Trio, Siemens, Erlangen, Germany). Subjects were positioned in the supine position with foam pads on either side of the head to minimize movement during scanning. Proton density (PD) and T2-weighted images [repetition time (TR) = 10,000 ms; echo-time (TE1, TE2) = 17, 134 ms; flip angle (FA) = 130°; scan time = 5:02 min] were collected simultaneously using a dual-echo turbo spin-echo pulse sequence in the axial plane, with a 256 × 256 matrix size, 230 × 230 mm field of view (FOV), 4.0 mm slice thickness, and no interslice gap. High-resolution T1-weighted images were also collected using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence (TR = 2200 ms; TE = 2.2 ms; inversion time = 900 ms; FA = 9°; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 1.0 mm; number of slices = 176; scan time = 5:25 min) to aid in anatomical identification and evaluation for structural defects.

Data Evaluation and Processing

The statistical parametric mapping package SPM5 (Wellcome Department of Cognitive Neurology, UK; www.fil.ion.ucl.ac.uk/spm/), and Matlab-based (MathWorks Inc, Natick, MA) custom software were used to process the images. All brain images, including T1-, PD-, and T2-weighted scans, were visually evaluated for major anatomical defects, including cystic lesions, infarcts, and other types of brain lesions. The images were also examined to verify the absence of motion artifacts.

Using PD and T2-weighted images, voxel-by-voxel T2 relaxation values were calculated[28] and whole-brain maps of T2 relaxation times were constructed. Each subject's map was normalized to the standard Montreal Neurological Institute (MNI) space template based on warping the T2-weighted image to the MNI template, and applying the resulting warping parameters to the T2 map. The normalized T2 maps were smoothed using a Gaussian filter (full-width-at-half-maximum = 10 mm). High-resolution T1-weighted images were also normalized to the MNI template, and averaged across all subjects to create a mean background image for structural identification.

Statistical Analysis

All non-MRI data were evaluated using the Statistical Package for the Social Sciences (SPSS for Windows, Version 15, Chicago, IL). Measures of central tendency and dispersion were utilized to describe the sample. The Chi-square test was used to examine group differences among the categorical variables, while we employed multivariate analysis of variance to compare group means for the remainder of the non-MRI data. The Bonferroni post hoc test was implemented, where appropriate, to determine specific group differences.

We used voxel-based relaxometry to identify brain regions with significant T2 value differences.[28] The procedure is a multisubject whole-brain comparison of regional T2 values between

groups. The normalized and smoothed T2 maps were compared between symptomatic and asymptomatic OSA subjects and between symptomatic OSA subjects and asymptomatic controls at each voxel using analysis of covariance, with age and gender as covariates. Regions of significant T2 value differences between symptomatic and asymptomatic OSA subjects were displayed ($P < 0.05$, false discovery rate correction for multiple comparisons). The correction for multiple comparisons establishes a *t*-value statistical threshold; the threshold derived from symptomatic vs asymptomatic OSA was applied to the additional group comparison. Brain regions of T2 value differences were superimposed onto the subjects' mean anatomical images for structural identification.

RESULTS

Forty-six OSA subjects and 67 controls were enrolled in the study. Of those, 40 OSA and 61 controls were included in the analysis based on their BDI-II scores. Table 1 shows subject characteristics separated by OSA vs controls, and subgroups with and without depressive symptoms. The groups did not significantly differ in age or gender. The OSA subgroups had higher body mass index (BMI) scores than asymptomatic controls ($P < 0.001$). The apnea-hypopnea index (AHI) was higher among asymptomatic OSA (mean ± SD; 31.5 ± 16) as compared to the symptomatic OSA (28.3 ± 17) subgroup ($P = 0.04$).

Depressive Symptoms

Thirteen (33%) of the OSA subjects were classified as having elevated depressive symptoms with BDI-II scores ≥ 12, as were five (8%) of the controls. No significant differences in BDI-II scores appeared between the two symptomatic groups (OSA 21 ± 8; control 16.4 ± 7; $P = 0.18$) or the two asymptomatic groups (OSA 4.2 ± 3; control 2.5 ± 2.6; $P = 0.56$).

Brain Structure

Higher T2 values, indicating neural injury, emerged in symptomatic OSA compared to asymptomatic OSA patients in several brain areas. The symptomatic OSA subgroup showed more extensive damage than the asymptomatic OSA subgroup in the mid-cingulate, extending to anterior cingulate and medial pre-frontal cortex on the left side, and from the anterior cingulate to subgenu regions and medial pre-frontal cortex on the right side (Figure 1G, H, I). The posterior insular cortex bilaterally (Figure 1C, D), extending to nearby parietal and posterior superior temporal cortices (Figure 1J, K, L) , and the bilateral anterior insular cortices showed injury. The left caudate nucleus and left internal capsule were also affected (Figure 1F). The cin-

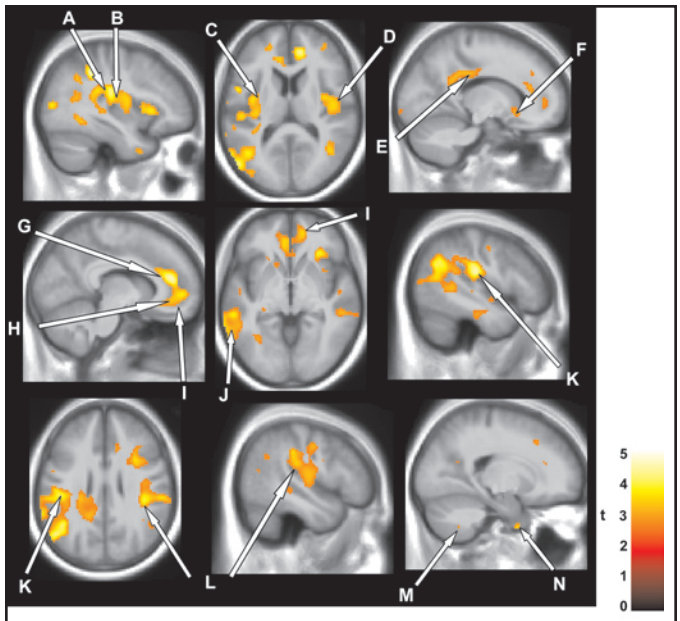

Figure 1—OSA with depressive symptoms vs OSA without depressive symptoms. Regions of significant increase in T2 relaxometry values are shown for 13 obstructive sleep apnea (OSA) subjects with depressive symptoms vs 27 OSA subjects without elevated depressive symptoms and are overlaid on an averaged anatomic image of all subjects. The color scale represents *t*-statistic values, with all highlighted regions exceeding the significance threshold of $P < 0.05$. The affected regions included: A, parietal and dorsal surface of the temporal cortex near the cingulum bundle; B, C, D, posterior insula; E, posterior corpus callosum; F, caudate bordering internal capsule; G, H, anterior cingulate extending to sub-genu cingulate and to I; medial pre-frontal cortex; J, temporal cortex; K, left parietal cortex; L, right parietal cortex; M, cerebellar cortex; N, temporal cortex near right amygdala. Figures are in neurological convention, i.e., left side of image represents left side of brain.

Table 1—Demographic and Clinical Characteristics for OSA and Control Subjects

	Control		OSA		p			
	A Symptomatic (n = 5)	B Asymptomatic (n = 56)	C Symptomatic (n = 13)	D Asymptomatic (n = 27)	A vs B	C vs D	A vs C	B vs D
Female: Male	3:2	20:36	5:8	4:23	0.28	0.09	0.41	0.07
	M (± SD)	M (± SD)	M (± SD)	M (± SD)				
Age *years*	48 (5)	47 (9)	48 (11)	48 (8)	0.99	0.99	0.99	0.99
BMI *kg/m²*	27 (6)	25 (4)	30 (4)	29 (4)	0.99	0.99	0.422	<0.001
AHI *events/hour*	n/a	n/a	28 (17)	32 (16)	n/a	0.04	n/a	n/a
BDI-II	16 (7)	3 (3)	21 (8)	4 (3)	<0.001	<0.001	0.18	0.56

Abbreviations = BMI: body mass index; AHI: apnea hypopnea index; BDI-II: Beck Depression Inventory-II; M: mean; n/a: not applicable; SD: standard deviation

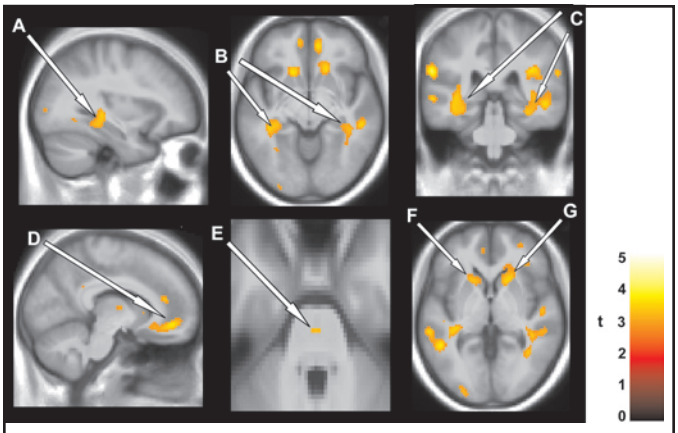

Figure 2—OSA with depressive symptoms vs controls without depressive symptoms. Highlighted areas represent regions where OSA with elevated depressive symptoms expressed higher T2 values compared to controls without elevated depressive symptoms: A, left hippocampus; B, C, left and right hippocampus; D, medial pre-frontal cortex; E, midline pons (enlarged to enhance visibility of the region of interest); F, G, left and right caudate. Color-coding and laterality attributes are as in Fig. 1.

gulum bundle within the posterior temporal lobe (Figure 1A), left ventral lateral temporal cortex, bilateral cortex surrounding the amygdala (Figure 1N), and isolated clusters of the ventral lateral cerebellar cortex also showed higher T2 values (Figure 1M). The asymptomatic OSA subgroup demonstrated no areas of higher T2 values relative to their symptomatic counterparts.

The symptomatic OSA group also expressed higher T2 values in a number of areas compared to the asymptomatic control group. These areas included bilateral damage to the hippocampus and caudate nuclei (Figure 2A-C, F, G) and unilateral damage to the right anterior thalamus and right internal capsule. Greater T2 values also appeared in the anterior corpus callosum bordering onto the anterior cingulate, bilateral medial prefrontal cortex (Figure 2D), bilateral superior temporal cortices, bilateral parietal cortices, extending deep medially, and medial pons (Figure 2E).

DISCUSSION

Obstructive sleep apnea patients symptomatic for depressive characteristics showed significant areas of neural injury compared to OSA patients without such affective signs. The damage emerged principally in cingulate, insular, and frontal cortices, and temporal cortex areas near the amygdala and hippocampus. A majority of these areas show volume loss or injury in depressed patients who were not reported to have OSA, but may not have been evaluated for a breathing disorder. Relative to asymptomatic control subjects, symptomatic OSA patients showed markedly greater injury. The OSA patients symptomatic for depressive characteristics showed damage in the bilateral hippocampus and caudate nuclei, right anterior thalamus, and right internal capsule, as well as the bilateral parietal, temporal, and frontal cortices, corpus callosum, and medial pons. Several of these white matter regions (corpus callosum, internal capsule) may reflect injury accompanying the intermittent hypoxic aspects of OSA. A number of the affected structures are associated with regulation of mood, cognitive decision making, and motoric control, and many also participate in various aspects of breathing or cardiovascular action.[29-31]

The findings highlight potential detrimental interactions of depressive symptoms and OSA. Bilateral hippocampal damage, which emerged when comparing symptomatic OSA subjects to asymptomatic controls (but not in symptomatic OSA vs asymptomatic OSA subjects), suggests that OSA may contribute to the hippocampal injury. Similarly, bilateral caudate nuclei damage appeared in the symptomatic OSA group vs the asymptomatic control group, whereas only left caudate damage emerged when compared to OSA subjects asymptomatic for depressive characteristics. Thus, OSA may play a role in the caudate damage—a finding that was not surprising, given the susceptibility of the basal ganglia to forms of hypoxic damage other than intermittent hypoxia, such as carbon monoxide poisoning.[32] Injury to the anterior insulae and anterior cingulate emerged in both OSA groups, but injury was greater (i.e., larger number of significant voxels appeared) with depressive symptoms. Such a finding suggests that aspects of depression, rather than OSA alone, may account for much of the injury occurring in these regions.

Several processes, we speculate, may contribute to the neural alterations demonstrated in the symptomatic OSA group, including mechanisms suggested to be also operating in depression without OSA. Injury from inflammatory action[33] and hypothalamic-pituitary-adrenal axis dysfunction[34] may damage areas that play roles in autonomic regulation and breathing control, essential elements in processes underlying apnea. Sites of neural alterations and potential mechanisms underlying the damage have been described in major depressive disorders.[6,7,11,35] However, it is unclear whether these findings extend to patients with elevated depressive symptoms but no diagnosed psychopathology. Despite the uncertainty of low-level depression characteristics on brain alterations, an apparent dose-response relationship exists, in which those with multiple episodes, higher depressive symptoms, and untreated depression experience more neural alterations than depressed individuals with one episode and fewer symptoms.[11]

The brain sites affected in major depression include the anterior cingulate, hippocampus, and cerebellum—all structures which are not traditionally associated with breathing control, but which play roles in ventilation other than contributing to oscillatory breathing drive. Timing of upper airway muscles with diaphragmatic action is coordinated by cerebellar structures, central chemoreception is mediated at several levels of the neuraxis, ranging from the cerebellum through the ventral medulla,[36-38] and more rostral limbic and cortical structures can exert arousal and pacing influences on respiration.[39,40] Input from these structures, if the areas are damaged, can play significant roles in recovery from apnea or exacerbating sleep disordered breathing.[41,42] Several of the affected limbic structures share negative-affect regulation properties which may mediate emotions associated with depression, and are recruited in respiratory control behaviors accompanying extreme negative feelings. The cingulate and insular cortices, for example, are activated by challenges which evoke dyspnea.[39,43] In addition, the structures respond to a number of respiratory and blood pressure challenges (e.g., cold pressor, Valsalva maneu-

ver, and tidal volume manipulation).[30,39] Amygdala stimulation, in addition to evoking negative emotions,[44] also can pace breathing,[40] presumably by excitatory influences on parabrachial pontine areas, and the hippocampus, anterior cingulate, and cerebellum are recruited at inspiratory onset after apneic pauses in central apnea.[42] The insula, cingulate, hippocampus, and cerebellar deep nuclei respond to hypercapnia in humans, suggesting chemoreceptive modulatory functions.[37] A respiratory role for the hippocampus in breathing is indicated also by respiratory-dependent discharge of single neurons,[45] and fMRI responses to the Valsalva maneuver.[30] The cerebellum has more overt relationships to OSA, including an increased incidence of OSA with olivopontocerebellar degeneration[41] and aberrant fMRI signals in response to multiple respiratory challenges.[43] Thus, we speculate that structural brain abnormalities found in depression may contribute to both affective characteristics and impaired breathing in OSA.

Conversely, processes associated with OSA may contribute to the neural alterations associated with the high incidence of depression in this population; these processes include intermittent hypoxia and inflammatory processes, or alterations in perfusion accompanying the breathing condition. Recurrent, intermittent hypoxia, a principal feature of OSA, has been used in animal models to simulate characteristics of OSA, and results in dose-dependent cell loss in the hippocampus, deep cerebellar nuclei, and cortical regions in the rat,[46,47] and in the septum, basal forebrain, hypothalamus, and raphe nuclei of mice.[48] Further, injury to noradrenergic and dopaminergic systems appear to be a major concomitant of long-term exposure to intermittent hypoxia.[49] Such findings may provide an additional mechanism for depression in an OSA population, as both norepinephrine and dopamine regulation are altered in depressed individuals.

Inflammation is a potentially damaging process present in both OSA and depression. In OSA, inflammation may be a consequence of long-term hypoxia.[50] While equivocal evidence exists regarding C-reactive protein (CRP),[51] several studies report elevated circulating levels of interleukin-6 (IL-6), and tumor necrosis factor-α (TNF–α) in OSA patients over age- and BMI-matched controls.[52,53] Similar findings appear in patients with major depressive disorder. Inflammatory markers such as IL-6 and CRP are most commonly elevated in depressed patients,[33,54] but increased IL-1β and TNF-α also appear in depressed individuals as compared to healthy controls.[33,55] Although proinflammatory cytokines are a necessary component for healthy immune system functioning, prolonged elevation of these inflammatory components can exert numerous deleterious effects, including neurotoxicity. TNF-α causes cytotoxic damage to oligodendrocytes and dopaminergic neuronal death in vitro[56,57] and induces demyelination in vivo.[57] This study did not directly assess inflammation, though the neural injury seen in this population may be due in part to such inflammatory processes.

Clinical Implications

The finding of neural injury among OSA patients with elevated depressive symptoms reinforces the importance of screening OSA patients for depression, and treating the mood disorder if depressive symptoms are found, rather than solely managing the breathing disorder and expecting the depressive symptoms to resolve. In addition to quality-of-life improvement and the potential to decrease cardiovascular risk that such treatment would provide, successful management of depression in patients with OSA may elicit beneficial effects on sleep-disordered breathing, improve OSA treatment compliance, or slow the progression of depression-related neural injury.

Limitations

We were limited by the absence of psychiatric interview data, and hence lack of Diagnostic and Statistical Manual-IV diagnoses. However, the BDI-II allows quantification of depressive symptoms and is in reasonable agreement with psychiatric interviews.[58] We did not specifically recruit for depressed subjects in either the control or OSA group. As a result, we obtained few controls with depressive symptoms, and the limited numbers precluded a comparison between the control groups with and without depressive symptoms.

Fatigue, a symptom of both OSA and depression, is measured by the BDI-II; thus, elevated BDI-II scores may contribute to OSA symptoms. However, when both OSA and elevated depressive symptoms are present, depressive symptoms appear to account for more of the fatigue than does OSA.[59]

Sleep disturbances, such as insomnia, are commonly associated with major depressive disorders. Sleep deprivation accompanying insomnia associated with depressive symptoms may contribute to the neural alterations independent of mechanisms induced by OSA.[60]

Lastly, obesity is a risk factor for OSA; due to physical limitations of the MRI scanner, we could not include subjects weighing more than 125 kg. Thus, our OSA subjects did not represent the spectrum of the OSA population.

Conclusions

Obstructive sleep apnea patients with elevated depressive symptoms show significantly more extensive and different neural injury from OSA patients without such symptoms. The affected brain regions overlapped areas reported to be structurally and functionally affected in both previous studies of OSA and clinically depressed populations. Given the high incidence of depressive symptoms in the OSA population, the findings suggest that processes which contribute to brain injury may be additive in depression and OSA.

ACKNOWLEDGMENTS

The authors thank Edwin Valladares, BS, Rebecca Harper, MA, and Stacy Serber, PhD, for technical assistance.

Supported by NIH HL- 60296

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