Brain Morphology Associated with Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is characterized by repeated occurrences of hypoxic, hypercapnic, and transient blood pressure elevation episodes that may damage or alter neural structures. Underdeveloped structures or pre-existing damage in brain areas may also contribute to the genesis of the syndrome. Brain morphology in 21 patients with OSA and in 21 control subjects was assessed using high-resolution T1-weighted magnetic resonance imaging. Three-dimensional brain images were obtained with voxels of approximately 1 mm^3. Images were spatially normalized and segmented into gray matter, white matter, and cerebrospinal fluid. For each segment, regional volumetric differences were determined relative to age, handedness, and group (patients with OSA versus control subjects), using voxel-based morphometry, with OSA effects weighted by disease severity. A significant age effect on total gray matter was found in control subjects but not in patients with OSA. Diminished regional and often unilateral gray matter loss was apparent in multiple sites of the brain in patients with OSA, including the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum. Unilateral loss in well-perfused structures suggests onset of neural deficits early in the OSA syndrome. The gray matter loss occurs within sites involved in motor regulation of the upper airway as well as in areas contributing to cognitive function.

Keywords: neuroanatomy; magnetic resonance imaging; hypoxia; ischemia

Obstructive sleep apnea (OSA) is a disorder characterized by atonia of the upper airway during sleep, with a concomitant loss of airflow in the presence of continued diaphragmatic efforts. The syndrome is frequently, but not exclusively, associated with gross anatomic features, including obesity, hypertrophied tongue or tonsillar structures, or other upper airway characteristics that contribute to increased airflow resistance. The accompanying acceleration of airflow with a narrowed air passage results in airway collapse from negative intrathoracic pressure (1). However, several characteristics of OSA suggest central neural participation in the genesis or maintenance of the syndrome that acts in concert with peripheral anatomic features. Obstructed breaths in OSA are frequently preceded by short breathing pauses, apparently of a central origin (2). In normal subjects, recovery from an obstruction occurs quickly by increased activation of airway muscles to restore tone (3, 4); however, in patients with OSA, restoration of airway muscle tone is delayed until arousal (5), implying dysfunction of normal control systems or afferent systems that respond to airway closure. In addition, the upper airway musculature remains atonic during apnea; diaphragmatic and thoracic muscle functions continue to be largely intact. The specificity of the musculature affected in the syndrome suggests regional deficiencies in brain areas mediating breathing during sleep. Moreover, the typical morphology of patients presenting with sleep apnea (e.g., obesity, short and large neck, small airway) is suggestive of altered central neuroendocrine or metabolic regulatory mechanisms (6); these deficiencies may manifest as brain structural differences. Finally, patients with OSA often exhibit a range of cognitive or language comprehension deficits, indicative of potential damage or dysfunction of neural structures separate from respiratory control sites (7).

The objective of this study was to examine brain morphology in patients with OSA to determine whether the anatomic features of their brain tissue differed from those of control subjects. The procedures used to examine this issue were validated by first examining age-related characteristics of brain structure; the effects of aging on neural structures are well described (8–10). Brain morphology in patients with OSA was then compared with that of control subjects.

METHODS

Subjects

Twenty-one male patients with a confirmed sleep laboratory diagnosis of OSA (mean age ± standard deviation [range]: 49 ± 11 years [28–7], mean body mass index 30 ± 4 [24–38]) and 21 healthy control male subjects (47 ± 11 years [29–65], body mass index 27 ± 4 [20–36]) participated. More patients with OSA were recruited, including females, but they could not participate due to scanner size limitations or claustrophobia. The time between OSA diagnosis and the study ranged from 0 to 6 years (mean 8 ± 14 months). OSA severity was diagnosed, according to standard practices (11), as mild (n = 1), mild-moderate (n = 2), moderate (n = 9), moderate-severe (n = 2), or severe (n = 7). Mean apnea/hypopnea index was 34 ± 20 [8–95], and mean respiratory disturbance index was 38 ± 24 [8–97]. Four control subjects and two subjects with OSA were left-handed. All subjects gave written informed consent before the commencement of the study. The research protocol was approved by the Institutional Review Board.

Data Collection

Anatomic T1-weighted image volumes were collected on a General Electric (GE Medical Systems, Waukesha, WI) 1.5 Tesla Signa magnetic resonance imaging (MRI) scanner, each consisting of 124 sagittal slices of 256 by 256 pixels. The field of view was 30 × 30 cm, slice thickness was 1.2 to 1.4 mm, with no interslice gap. The spoiled gradient recalled acquisition in the steady state sequence was used (repetition time = 24 ms, echo time = 9 ms, flip angle = 22°). All subjects were required to sleep in the scanner after data collection. Physiologic recording during the sleep period verified the absence of disturbed breathing in the control group.

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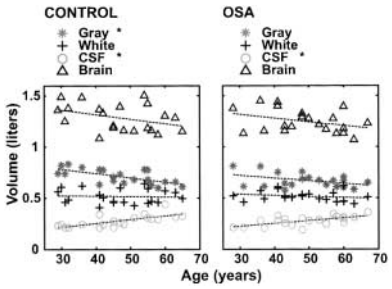

Figure 1. Scatter plots of volume versus age for 21 subjects with OSA and 21 control subjects for gray matter, white matter, whole brain, and CSF. Linear regression estimates are shown as *dashed lines*, and segmented volumes that change significantly with age ($p < 0.05$, linear regression) are marked with *asterisks*.

Analysis: Voxel-based Morphometry

Data were analyzed using SPM99 (12) and Matlab 6.1 (Mathworks Inc., Natick, MA). Voxel-based morphometry, a method optimized to detect regional gray matter volume changes in MR images (13–15), provides for whole-brain analysis of large samples, as opposed to manual definition of regions on a subject-by-subject basis. The method consists of a series of analysis steps; whole-brain volumes were spatially registered to a template derived from 152 normal subjects (16). Registered volumes were segmented into gray and white matter, cerebrospinal fluid (CSF), and brain (white + gray matter). Regions outside the brain were removed, and the total volume was calculated for each segment. For regional comparisons, segmented images were smoothed using a 12-mm Gaussian filter and compared using standard MRI analyses, resulting in statistical maps of structural differences with group, age, or other variables. For group effects, significant voxels were color-coded as the percentage difference between groups.

Statistics: Age, Handedness, and OSA Severity

Structural changes with age were examined as a validation of the methodology, because its effects are known (10), with handedness and OSA severity (control = 0, mild = 1, moderate = 2, severe = 4) included as covariates. Linear regression was used to estimate the relationship between total volumes and age, and analysis of variance was used to evaluate group effects. Age and handedness were subsequently included as covariates to study OSA and control regional volumetric differences. Voxel-based morphometry was used to model the effects of all three variables, presenting results above a significance threshold of $p < 0.001$ and minimum cluster size of 350 voxels, values consistent with previous studies (17–19).

Additional subject- and voxel-based morphometry details are provided in the online data supplement.

RESULTS

Total Volumes of Gray Matter, White Matter, and CSF

Four volume measurements were calculated for each subject: gray matter, white matter, brain (the combination of gray and white matter), and CSF. These volumes are plotted by age for each group in Figure 1. In control subjects, gray matter decreased with age. Volumes of white matter and brain did not change significantly, whereas CSF volumes increased with age in both groups. The ratio of total gray-to-white matter volumes was calculated for both groups and was significantly ($p < 0.05$, analysis of variance) greater in control subjects compared with subjects with OSA. In addition, the ratio of total gray-to-white matter decreased significantly ($p < 0.05$, linear regression) with age in control subjects but not in subjects with OSA. Handedness, hypertension, and tobacco use had no significant effect on the global volume of gray matter, white matter, or CSF.

Regional Effect of Age

The effects of age on morphology were calculated while partitioning contributions from group and handedness. The effects of aging on specific regions of the brain are shown in Figure 2 using a transparent "glass brain" display. This analysis controlled for handedness and OSA severity. Areas of significantly ($p < 0.001$, minimum cluster size = 350 voxels) decreased volume with age were shaded according to their t value and collapsed across the entire brain volume into two-dimensional images. The glass brain display allows for visualization of overall extent and location of areas of significant change using only three images (12). Gray matter decreased across much of the brain, especially in the frontal and parietal cortex. White matter showed little regional change with age, and CSF increased in regions surrounding the frontal and parietal cortex and cerebellum.

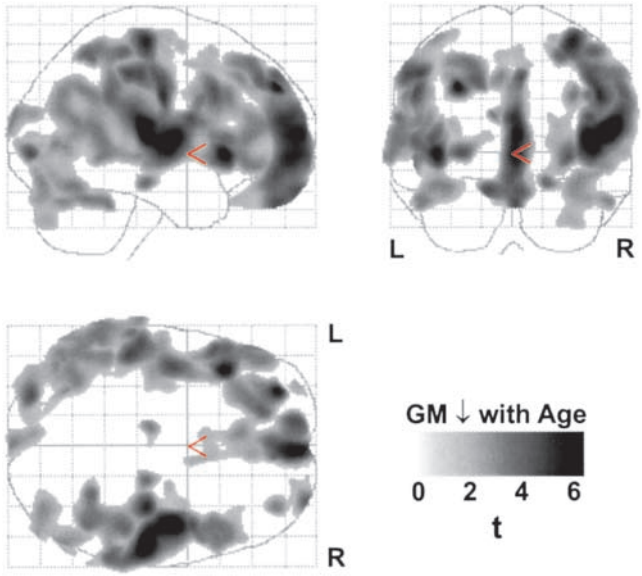

Figure 2. Glass brain display of age-related regions of significant ($p < 0.001$, cluster > 350 voxels) gray matter volume reduction, derived from 21 subjects with OSA and 21 control subjects, and controlling for OSA severity and handedness. The glass brain displays all regions of statistically significant volume difference, with *darker shading* indicating increased significance (t statistic). Images are displayed in neurologic convention, i.e., right side of the brain on the right side of the image (R = right, L = left).

Control and OSA Group Regional Differences

Significant regional differences emerged, consisting of multiple areas of decreased gray matter in subjects with OSA (Figure 3). Weighting by OSA severity resulted in a greater number of statistically significant regions, indicating that the extent of decreased gray matter increased with severity. Overall, the group effects were smaller than the age effects. Significant regional differences in gray matter between groups ranged from approximately 2 to 18%, as shown in Figure 3.

Regions showing significantly less gray matter volume in subjects with OSA are depicted in Figure 4 on the mean of the 42 registered brain images displayed on the brain surface. Areas of gray matter loss included a portion of the right postcentral gyrus, and the posterior lateral parietal cortex bilaterally, encompassing Brodmann's area 7. Within the frontal lobes, three regions showed decreased gray matter volume: the anterior superior frontal gyrus in both hemispheres, encompassing Brodmann's area 9 and extending medially on the left side to the anterior cingulate gyrus; the left ventral lateral frontal cortex, encompassing Brodmann's areas 45 and 47 (including Broca's area); and multiple sites within the lateral prefrontal cortex. In

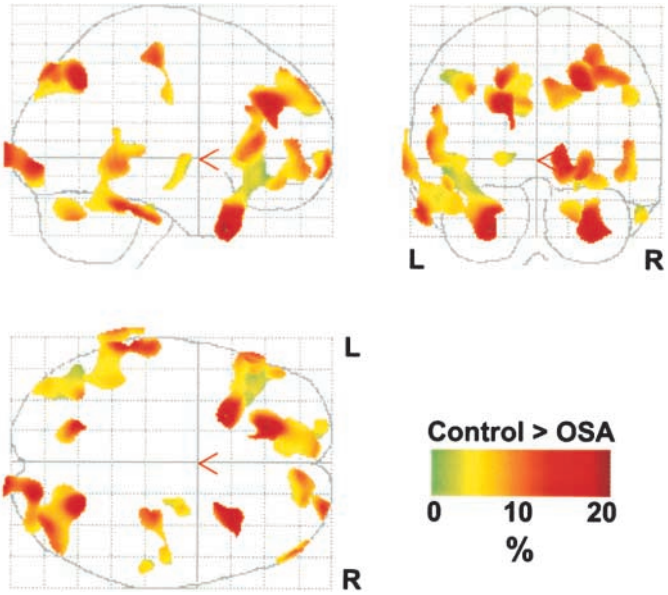

Figure 3. Glass brain display of regions of significantly ($p < 0.001$, cluster > 350 voxels) reduced gray matter in 21 subjects with OSA, weighted by disease severity, relative to 21 control subjects, controlling for age and handedness. The glass brain displays all regions of statistically significant volume difference, color-coded according to the percent difference between groups (scale at bottom; *R* = right, *L* = left).

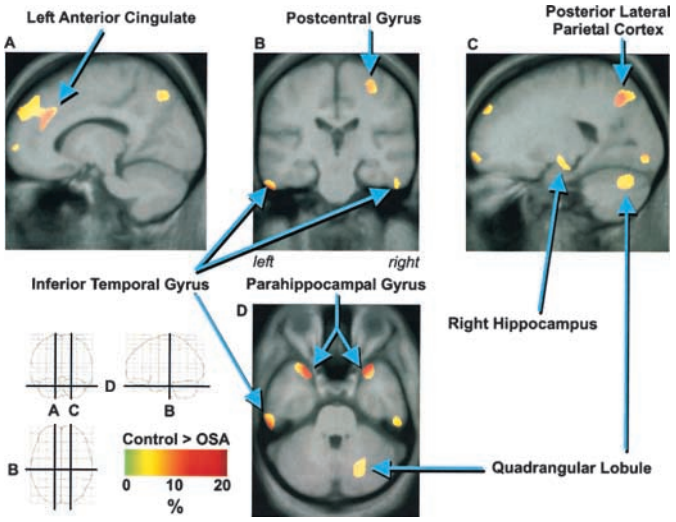

Figure 5. Regions of significant decrease in gray matter of subjects with OSA overlaid onto slices through the average of 42 registered brains. Voxels of significant ($p < 0.001$, cluster > 350 voxels) difference are color-coded in percent difference between the 21 subjects with OSA and 21 control subjects (scale at *lower-left*). Slice locations through axial, coronal, and sagittal views are indicated by the *diagrams* on the *lower-left*.

the temporal lobes, decreased gray matter volume occurred in the inferior temporal gyrus, corresponding to Brodmann's area 37, and bilaterally in the parahippocampal gyrus, extending toward the anterior temporal pole (Figures 4 and 5). On the left side, the volume decline extended dorsally to include the area immediately surrounding the caudal extent of the lateral sulcus. Gray matter loss occurred in the right hippocampus, and an area in the medial, deep cerebellar cortex (quadrangular lobule) also showed significantly less gray matter in subjects with OSA compared with control subjects.

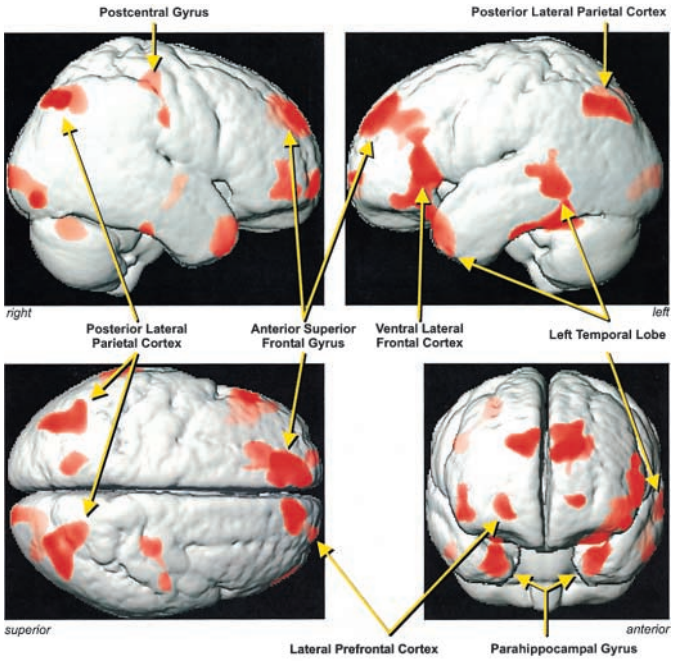

Figure 4. Significant ($p < 0.001$, cluster > 350 voxels) regional decreases in gray matter of subjects with OSA rendered onto the brain surface of the mean of the 42 registered brain images. *Red shading* indicates regions of significant difference, with red intensity decreasing as depth increases.

There were no regional differences between control subjects and subjects with OSA regarding white matter or CSF, and there were no regions where subjects with OSA had more gray matter than did control subjects.

Other Results

Handedness improved the significance of the model and therefore was included as a covariate in the regional analyses. There were no significant age-by-group interactions. Covariates that did not show significant effects included hypertension, all cardiovascular disorders, and tobacco use.

DISCUSSION

The morphology of brain areas in subjects with OSA and control subjects differs, with gray matter volume reductions up to 18% in some regions of the brain in patients with OSA; the extent of decline increased with the severity of the syndrome. Total gray matter volume decreased with age in control subjects but not in subjects with OSA, and the ratio of total gray-to-white matter was lower in subjects with OSA. Regionally, gray matter volume declines appeared bilaterally in portions of parietal, frontal, and temporal cortical sites in subjects with OSA. Unilateral reductions were found in other portions of the parietal, frontal, and temporal cortices, hippocampus, anterior cingulate gyrus, and superficial and deep cerebellar cortex. The morphologic differences suggest two possibilities: (*1*) gray matter loss may be a consequence of apnea, or (*2*) pre-existing abnormalities may contribute to the genesis or maintenance of the disorder. Damage to certain areas, e.g., frontal and temporal lobe regions, may contribute to cognitive deficits frequently accompanying OSA (7).

Gray Matter Loss as a Consequence of the Syndrome

At least a portion of the anatomic differences is likely to result from hypoxic, hypercarbic, or reduced-perfusion consequences of repeated apnea. Systemic hypoxia and hypercapnia, as well as transient elevation of blood pressure, accompany obstructed breathing (20). These consequences modify perfusion (21, 22) and can injure or alter neural structures (23, 24). Peripheral tissue oxygen saturation during apneic episodes in severe OSA drops alarmingly, often to 70% or less (25). Although autoregulatory mechanisms may prevent severe oxygen deficits in the brain (26), the potential for damage to neural sites from intermittent hypoxia, hypercapnia, and cardiovascular changes is large. Repetitive, intermittent hypoxemic episodes result in gray matter damage, and subjects with OSA show reduced cerebral blood flow (27) and exhibit axonal damage that is related to the extent of desaturation episodes (28). The cerebral cortex is particularly susceptible to ischemia (24, 29, 30). The diffuse and bilateral nature of the majority of the parietal and frontal cortex changes, as well as the bilateral gray matter loss in the parahippocampal gyrus of the temporal lobe, suggest that at least a portion of the damage results from consequences of apnea.

The parietal lobe volume loss in subjects with OSA encompassed the posterior parietal association area bilaterally, a region of extensive polymodal convergence. Deficits in these regions impair the ability to consciously perceive sensory stimuli from the upper airway and also interfere with sensory–motor integration. Lesions in posterior parietal association cortex typically result in abnormalities of body image and perception of spatial relations, language, and motor disorders, including intention to move (31). Functional MRI in humans has revealed significant increases in activation in the posterior parietal cortex during transition from unconscious to conscious breathing (32), suggesting that damage to the parietal cortex may lead to deficits in the integration of sensory and motor function, particularly during arousal from OSA.

Gray Matter Loss Potentially Promoting the Genesis or Maintenance of the Syndrome

Certain components of the reduced regional gray matter volume may have preceded the onset of OSA and contributed to the genesis of the syndrome. Such gray matter reduction may have been congenital or acquired. Gray matter loss showed a decline with age in control subjects but not in patients with OSA, suggestive of circumstances in which damage occurs early in the afflicted group. The unilateral and specific nature of the gray matter deficiency in particular sites also argues against global effects of apnea as an exclusive factor in the volume losses. Furthermore, unilateral volume loss emerged in the left ventral lateral frontal cortex, an upper airway motor region, and in the anterior cingulate cortex, and the cerebellum. A greater proportion of regions showing unilateral gray matter loss is located in well-perfused areas and should be less susceptible to ischemic damage. The unilateral cerebellar sites are an exception to this generalization for hypoxic damage because the affected regions receive climbing fibers with particular sensitivity to ischemia (33); however, damage would be expected to be distributed bilaterally in this case.

Cerebellar structures, although not usually considered to be involved in breathing or blood pressure control, play an essential role in the onset of inspiration after apnea (34) and in the recovery from extremes of blood pressure change (35), and may participate in some components of carbon dioxide regulation (36). Imaging studies show significantly increased cerebellar activation in response to hypercapnia and during hunger for air (32, 37). Cerebellar damage results in a high incidence of disordered breathing during sleep, including OSA; in adults, this damage includes olivopontocerebellar atrophy (38) and in children, the Chairi Type-II malformation (herniation of the cerebellar vermis), Dandy-Walker malformations (absence or hypoplasia of the vermis) (39), and congenital apnea (hypoplasia of the inferior olive, a major source of afferent input to deep cerebellar nuclei) (40). Pathologies in victims of sudden infant death syndrome show delayed development of cerebellar cortex neurons (41), reduced serotonergic innervation to the inferior olive (42), and diminished neural density in this latter structure (43).

The sensitivity of inferior olive climbing fibers projecting to cerebellar Purkinje neurons to toxic damage or to ischemia (44, 45) may be playing a critical role in the gray matter loss found in the quadrangular lobule of the cerebellum. The potential for an early hypoxic event to affect the climbing fibers of the inferior olive represents a condition in which patterns for OSA could be established. Damage to the climbing fibers would effectively reduce afferent input to deep cerebellar structures, resulting in a potential for ineffective coordination of upper airway motor action by the cerebellum conducive to maintenance of conditions for OSA. Diminished gray matter volume of the cerebellar cortex was found in this study, but the resolution of the procedure was too gross to distinguish climbing fiber alterations. Together, these data suggest a significant role for the cerebellum in sleep-disordered breathing, a suggestion that was not unexpected, considering the well-recognized role for the cerebellum in motor "error correction." We speculate the inappropriate coordination of upper airway muscles from cerebellar dysfunction to be a principal mechanism underlying OSA. The initial trigger may be a severe hypoxic event or exposure to a toxic agent that results in climbing fiber damage.

The ventral lateral motor region in the frontal lobe contralateral to the principal cerebellar volume loss also showed significant gray matter loss. This area responds significantly to inspiration, as indicated by functional magnetic resonance and positron emission tomography evidence (46, 47). Because termination of obstructive apnea involves return of inspiratory effort to upper airway muscles, we speculate that this frontal area, if damaged, may contribute to failure to initiate breathing after apnea.

Unilateral gray matter loss in the anterior cingulate gyrus, a limbic structure classically associated with perception of pain and aspects of addictive behavior (48), would initially appear to be unrelated to disordered breathing. However, cingulate neurons discharge in a dependent relationship to the respiratory cycle (49). Dyspnea activates cingulate areas (37), and cingulate structures are activated by a variety of breathing and blood pressure challenges (50). Even if the neural damage resulted only from consequences of apnea, the specific sites of gray matter loss in hippocampal, anterior cingulate, and cortical sites associated with upper airway sensation and motor control have the potential to significantly worsen the syndrome. The unilateral gray matter loss is not suggestive of a generalized hypoxic outcome; however, the mechanisms by which the anterior cingulate could be damaged are unclear.

The hippocampus contained regions of unilateral gray matter loss in subjects with OSA, and the parahippocampal gyrus showed significant bilateral gray matter loss. As in the case of cingulate structures, the hippocampus is seldom considered a breathing control area. However, hippocampal structures have been implicated in inspiratory onset after apnea and appear to play an excitatory role in breathing (51). Optical imaging of the hippocampus shows substantially increased activity accompanying inspiratory onset after an apnea (52). Single neuron recordings in the human hippocampus demonstrate discharge at rates dependent on the respiratory cycle (53). Functional MRI studies show increased hippocampal signal changes during a

Valsalva maneuver (50). Collectively, these data suggest that hippocampal damage may impair resumption of breathing after an apnea. The bilateral damage to parahippocampal cortical regions surrounding the hippocampus could well derive from hypoxic damage; the means by which the unilateral gray matter loss developed at the head of the hippocampus remains unknown.

The structural deficits within the left ventral frontal cortex included an area generally recognized as mediating aspects of expressive components of speech, i.e., Broca's area. Although 8 of 21 subjects in the OSA group (versus 2 of 21 control subjects) reported a history of stuttering or other motor speech impediments, a rate higher than that in the general population (54), it is unclear whether upper airway muscle control associated with articulation is especially affected in this patient group. However, the area of gray matter loss includes ventral motor strip supplementary areas mediating muscle control of the head and neck region, including airway muscles. An examination of deficits in language expression in OSA may be fruitful in the elaboration of underlying neural dysfunction.

Limitations

Voxel-based morphology has limited spatial resolution. We were unable to differentiate a very fine structure of cerebellar gray and white matter features. Perfusion changes associated with OSA may well give rise to fiber damage that was irresolvable with procedures used in this study. White matter damage after OSA is well documented (55). However, these lesions are small, covering volumes in the order of only a few cubic millimeters, and would make little change to the overall white matter volume. The presence of these lesions is diverse and scattered and on averaging over many subjects, is obscured. Thus, the regional volumetric measures may be too gross to indicate the extent of white matter lesions in OSA.

Conclusions

Brain gray matter volume is reduced in subjects with OSA in a severity-dependent fashion. A portion of the reductions may result from ischemic or other physiologic changes accompanying obstruction, especially in bilateral areas of the parietal, frontal, and temporal lobes. However, a portion of the volume changes may have been present before the onset of OSA and may have contributed to the characteristics of the syndrome. These regions include the anterior cingulate gyrus, ventral lateral frontal cortex, hippocampus, and portions of the deep cerebellar cortex. The nature of the volume loss in this latter scenario is speculative, but may originate from an initial brain insult or ischemic event, which leads to a cascade of neural damage resulting in ineffective capabilities to respond to otherwise minor respiratory challenges within sleep.

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