A Review of Neuroimaging in Obstructive Sleep Apnea

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Study Objectives: The authors reviewed neuroimaging studies of obstructive sleep apnea (OSA) to summarize findings, evaluate their contribution to a current understanding of the neurophysiology of the disorder, and propose directions for future research.

Method: Manuscripts were identified using the National Institutes of Health PubMed literature search system. Search terms included obstructive sleep apnea, sleep apnea, imaging, neuroimaging, magnetic resonance imaging, MRI, functional magnetic resonance imaging, fMRI, magnetic resonance spectroscopy, and MRS. Inclusion criteria required that research articles (1) were written in English, (2) examined an adult population, and (3) focused on imaging of the brain.

Results: Support for structural abnormalities is mixed, but converging evidence suggests the hippocampus may be atrophic in patients with OSA. Neurochemical evidence is supportive of white-matter impairment in OSA, particularly in the frontal lobes. Functional studies utilizing respiratory challenges report widespread neural differences in motor, sensory, and autonomic brain regions. Functional neuroimaging cognitive challenges have reported either a lack of brain activation in dorsolateral prefrontal cortex or increased neural response in frontal lobe, cingulate, thalamus, cerebellum, and juncture of parietal and temporal lobes, depending on the cognitive task employed.

Conclusions: The current literature examining neuroimaging-derived neural correlates in patients with OSA has made many important preliminary contributions. Future studies would be strengthened by consideration of potential moderating participant characteristics, such as sex, age, education, OSA severity, and comorbid conditions. Additional investigation employing neuroimaging techniques is needed to advance our understanding of the neurophysiology of OSA.

Keywords: Obstructive sleep apnea, sleep-disordered breathing, neuroimaging, magnetic resonance imaging, magnetic resonance spectroscopy, functional magnetic resonance imaging, MRI, MRS, fMRI

Citation: Zimmerman ME; Aloia MS. A Review of Neuroimaging in Obstructive Sleep Apnea. J Clin Sleep Med;2(4):461-471.
tional and correlative in nature, thereby prohibiting establishment of cause-and-effect relationships. Finally, the majority of modern neuroimaging techniques do not allow the continuous monitoring of brain function that would be ideal for an examination of sleep disorders. Despite these drawbacks, we believe that the application of neuroimaging techniques to the study of OSA represents an emerging field of inquiry that may help elucidate fundamental pathophysiologic mechanisms and clinical outcomes of the disorder. The goal of the current review is to summarize findings of existing structural, neurochemical, and functional neuroimaging studies in individuals with OSA and to evaluate their contribution to an improved understanding of the disorder. Limitations and considerations for future research are also discussed.

METHODS

Publications were identified using the National Institutes of Health National Library of Medicine PubMed literature search system. Additional references included within identified articles were also evaluated for inclusion in the review. Search terms included obstructive sleep apnea, sleep apnea, imaging, neuroimaging, magnetic resonance imaging, MRI, functional magnetic resonance imaging, fMRI, magnetic resonance spectroscopy, and MRS. Different permutations of these search terms yielded between 2 (obstructive sleep apnea and MRS) and 392 (sleep apnea and imaging) articles that were considered for review. Inclusion criteria required that original research articles (1) were written in English, (2) examined an adult population, and (3) focused on imaging of the brain. Articles were excluded if they focused on a population of interest other than OSA or sleep-disordered breathing; examined children, adolescents, or preclinical samples; performed neuroimaging of the upper airway; were primarily focused on physical abnormalities thought to cause OSA (e.g., craniofacial dysplasia, congenital choanal atresia); or specifically examined brain function following surgical treatment interventions (e.g., extended uvulopalatal flap surgery, mandibular advancement). Published abstracts from national and international meetings and review articles were also excluded. In total, 17 studies were included in the current review.

REVIEW OF FINDINGS

The Table provides sample characteristics, summary of findings, and brief comments on all reviewed OSA neuroimaging studies. A detailed discussion of major findings by neuroimaging modality is presented below.

Structural Neuroimaging

Structural MRI (sMRI) is an important tool that promotes the examination of neuroanatomic volumetric and morphometric abnormalities that may be involved in pathologic processes. sMRI also provides an important context in which to consider both neurochemical and neurofunctional findings. Many recent advances have been made in MRI image acquisition and postprocessing techniques that have contributed to improved sensitivity and specificity of sMRI findings. A major limitation of MRI, however, is that measurements are acquired from a static image that may not correlate well with functional abnormalities or clinical variables. Nonetheless, sMRI studies facilitate an enhanced understanding of neuroanatomic substrates that inform both the development of neuropathologic models and the interpretation of neurochemical and functional examinations of the brain.

Several investigators have sought to characterize the structural neuroanatomy of individuals with OSA using sMRI. An early study by Davies and colleagues qualitatively examined white matter hyperintensities in deep white matter and periventricular regions in 45 patients with moderate to severe OSA and 45 controls who were closely matched on sex, body mass index (BMI), alcohol and cigarette use, hypertension, and history of heart disease. Participants were also given ambulatory blood pressure monitors. Analyses revealed higher nighttime and daytime diastolic blood pressure and higher nighttime systolic blood pressure in patients with OSA, compared with controls. However, there were no group differences on any sMRI-derived qualitative indicator of subclinical cerebrovascular disease; indeed, both groups exhibited a high prevalence of deep white matter and periventricular hyperintensities. Given existing reports of associations among hypertension, stroke risk, and MRI abnormalities, the investigators suggested that their unexpected finding indicated that causes of elevated blood pressure in patients with OSA may be differentially related to vascular risk compared to causes of elevated blood pressure in healthy subjects.

Macey and colleagues performed a quantitative sMRI analysis of gray and white matter in patients with OSA. They employed a voxel-based morphometric analytic technique in 21 men with OSA and 21 controls. Voxel-based analyses differ from manual volumetric methods in that they involve an automated comparison of gray matter concentrations between 2 groups of interest on a voxel-by-voxel basis using MRI images that have been spatially normalized into stereotactic space. Although this technique allows the investigator to rapidly acquire a large amount of data across the entire brain, image-normalization processes may distort smaller regions of interest. The large number of resulting statistical comparisons should also be controlled in data analyses. Using these techniques, the investigators reported regional gray matter loss in the frontal cortex, parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum of patients with OSA. The extent of volumetric decline was found to be related to the severity of OSA, with patients with more severe OSA demonstrating the greatest amounts of gray matter volume loss. Total gray matter volume decreased with age in controls but not in patients with OSA. This study was the first comprehensive, quantitative examination of MRI-derived neuromorphometry in OSA. These findings served to stimulate future neuromorphometric investigations of OSA and provided an important initial framework for hypothesis generation. General interpretation of the results was limited, however, by the inclusion of patients with OSA with a wide range of comorbid conditions (e.g., medical and psychiatric disorders), as well as analyses of data that were uncorrected for multiple comparisons.

A second comprehensive morphometric analysis of brain structures in OSA was conducted by O’Donoghue and colleagues. This study examined 27 patients with untreated severe OSA and 24 age-matched controls using voxel-based morphometry and manual tracing of hippocampus, temporal lobe, and whole brain. Twenty-three patients with OSA were rescanned following 6 months of positive airway pressure (PAP) treatment, with average adherence of 5.8 hours of use per night. Participants were excluded who had a history of cerebrovascular disease, diabetes, central nervous system disorder, alcohol or illicit drug use, or cur-
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<td>Davies, 2001</td>
<td>sMRI</td>
<td>45 No 52(10) Age, y &gt; 10 episodes of &gt; 4% fall in SaO_2/night</td>
<td>45 No 52(10) Age, y</td>
<td>No group differences in deep white matter or periventricular hyperintensities</td>
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<td>Macey, 2002</td>
<td>sMRI</td>
<td>21 No 49(11) AHI: 34(20)</td>
<td>21 No 47(11) Age, y</td>
<td>OSA: ↓ gray matter in anterior cingulate, hippocampus, cerebellum, and frontal, parietal, and temporal lobes</td>
<td>Men only, included patients with comorbid conditions bid</td>
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<td>O’Donoghue, 2005</td>
<td>sMRI</td>
<td>27 No 46(10) AHI: 72(17)</td>
<td>24 No 43(9) Age, y</td>
<td>No group differences in gray matter in any regions of interest; slight decrease in whole brain volume in patients with OSA after 6 months of PAP treatment</td>
<td>23 patients re-examined after 6 months PAP treatment</td>
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<td>Morrell, 2003</td>
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<td>7 No 50 (28-65) AHI: 28 (25-40)</td>
<td>7 No 50 (28-65) Age, y</td>
<td>OSA: ↓ gray matter in left hippocampus</td>
<td>Men only</td>
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<td>Gale, 2004</td>
<td>sMRI</td>
<td>14 No 52(11) RDI: 84(18)</td>
<td>36% OSA group: ↓ hippocampus</td>
<td>36% OSA group: ↓ hippocampus</td>
<td>Comparison group: patients with CO poisoning SHHS</td>
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<td>Ding, 2004</td>
<td>sMRI</td>
<td>No WMD: 78(4); WMD: 79(5)</td>
<td>No WMD: AHI:10 (12); WMD: AHI: 9 (12)</td>
<td>No differences in participants with and without brainstem white matter disease in AHI, central or obstructive sleep apnea index, or % sleep time &lt; 90% oxygen saturation; inverse relationship between frequency of arousals and white matter disease</td>
<td>SHHS, longitudinal data</td>
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<td>Robbins, 2005</td>
<td>sMRI</td>
<td>77(4) AHI: 11</td>
<td>843</td>
<td>Participants with brainstem white matter disease progression more likely to exhibit increase in central apace Moderate to severe OSA: ↓ NAA/Cho ratio in white matter compared to mild OSA patients and controls</td>
<td>Did not control for comorbid disorders No control group</td>
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<td>Kamba, 1997</td>
<td>MRS</td>
<td>23 No 49(13) AI: &lt; 20 (mild), 15 &gt; 20 (mod)</td>
<td>46(18)</td>
<td>Significant negative relationship between OSA severity and NAA/Cho ratio in white matter</td>
<td>Men only, cognitive assessment</td>
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<td>Kamba, 2001</td>
<td>MRS</td>
<td>55 No 47(13) AHI: 44(30)</td>
<td>5 No 52(16) Age, y</td>
<td>OSA: ↑ NAA/Cre, ↓ Cre in left hippocampus, associated with ↓ cognitive performance and OSA severity</td>
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<td>Bartlett, 2004</td>
<td>MRS</td>
<td>8 No 47(16) RDI: 45 (43)</td>
<td>15 No 45(3) Age, y</td>
<td>Group signal differences in cerebellum, insular cortex, hippocampus, cingulate, precentral gyrus, and frontal, temporal, and parietal cortices</td>
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<td>Alchanatis, 2004</td>
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<td>OSA: ↓ NAA/Cre and Cho/Cr ratios, NAA, and Cho in frontal white matter</td>
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<td>Henderson, 2002</td>
<td>fMRI</td>
<td>8 No 44(4) RDI: 42</td>
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<td>Group signal differences in cerebellum, insular cortex, hippocampus, cingulate, frontal cortex, thalamus, and medulla/ midbrain</td>
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<td>Harper, 2003</td>
<td>fMRI</td>
<td>10 No 46(12) AHI: 38(27)</td>
<td>16 No 47(10) Age, y</td>
<td>Cold pressor challenge, men only</td>
<td>Men only</td>
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<td>Macey, 2003</td>
<td>fMRI</td>
<td>9 No 45(12) AHI: 40(28)</td>
<td>16 No 4(11) Age, y</td>
<td>Group signal differences in cerebellum, insular cortex, hippocampus, limbic regions, frontal cortex, thalamus, and midbrain/pons</td>
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<td>Macey, 2006</td>
<td>fMRI</td>
<td>7 No 46 (5) AHI: 42(11)</td>
<td>11 No 47(3) Age, y</td>
<td>Timing delay in basal ganglia in patients with OSA; group differences in cerebellum, insular cortex, hippocampus, limbic regions, supplementary motor areas, temporal cortex, thalamus, and basal ganglia</td>
<td>Inspiratory loading challenge, men only</td>
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<td>Thomas, 2005</td>
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<td>Age, y</td>
<td>40(7)</td>
<td>OSA: absence of activity in dorsolateral prefrontal cortex both before and after treatment; patients with OSA performed more poorly on cognitive task, compared with controls</td>
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<td>Ayalon, in press</td>
<td>fMRI</td>
<td>12</td>
<td>44(12)</td>
<td>AHI: 35(21)</td>
<td>Intact verbal learning performance in patients with OSA associated with increased brain activity in right inferior frontal gyrus, middle frontal gyrus, cingulate gyrus, junction of the inferior parietal and superior temporal lobes, thalamus, and cerebellum</td>
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Age is presented as the mean (SD) for all studies, with the exception of Morrell et al, which is presented as the mean (range), and Bartlett et al, which is presented as the median (interquartile range).

Obstructive sleep apnea (OSA) severity measures are presented as the mean (SD) for all studies, with the exception of Bartlett, which is presented as the median (interquartile range).

sMRI refers to structural magnetic resonance imaging; MRS, magnetic resonance spectroscopy; fMRI, functional magnetic resonance imaging; PAP, positive airway pressure; AHI, apnea hypopnea index; RDI, respiratory disturbance index; AI, apnea index; NAA, N-acetylaspartate; Cho, choline; Cre, creatine; CO, carbon monoxide; SHHS, the Sleep Heart Health Study, an epidemiologic population-based sample of older adults > age 68 years.

rent use of psychoactive medications. Using an optimized post data-processing approach with adjustments for multiple comparisons, the investigators found no evidence of gray matter change in any regions of interest in patients with OSA. Manual tracings were employed to reduce sources of error associated with automated post data-processing techniques, such as masked effects due to normalization of brain tissue. Application of this technique similarly failed to reveal any structural differences between participants with OSA and controls. A slight decrease in whole brain volume, however, was observed in patients with OSA following 6 months of PAP treatment. In an additional attempt to replicate the earlier findings of Macey and colleagues, a posthoc analysis was conducted in which the data were reanalyzed using the same version of a postprocessing program employed by Macey et al, with consistent negative results. The authors suggested that the findings of Macey and colleagues may have resulted, in part, from inclusion of patients with comorbid medical and psychiatric conditions, analyses of data using a lenient threshold of signal detection, and failure to correct for multiple comparisons. Additional published comments from both groups provide a provocative discussion of methodologic and statistical differences in neuroimaging study design and data analysis. Macey and colleagues argue that their positive findings reflect the utilization of a statistical threshold that allowed detection of known age-related effects on the brain, whereas O’Donoghue and colleagues state that their negative findings result from the utilization of an MRI scanner with a stronger field strength, a homogeneous sample, and statistical correction for both multiple comparisons and age. Both groups appear to agree that the effects of OSA on brain structure are relatively small and may not be evident when highly stringent and conservative statistical methods are applied. These compelling studies and their respective follow-up arguments serve to highlight the variability that may exist in study cohorts and post-processing techniques. Further, they illustrate an urgent need for additional well-controlled morphometric studies of patients with a wide range of OSA severity to replicate findings and further investigate volumetry associated with OSA.

Two additional studies have also examined structural brain integrity in OSA. Morrell and colleagues conducted a cross-sectional voxel-based morphometric study on 7 patients with newly diagnosed moderate OSA and 7 controls matched for handedness and age. Results indicated that patients with OSA had significantly smaller left gray matter hippocampal volumes, as compared with controls. There was no difference between the groups in any other gray matter brain region or in total gray matter volume. Cognitive correlates of hippocampal volume were examined in a study by Gale and Hopkins. To examine the effects of hypoxemia on the brain, MRI and comprehensive neuropsychological assessment were performed on patients with severe OSA and patients with carbon monoxide poisoning. Time between carbon monoxide exposure and MRI scan or neuropsychological testing was 22.4 + 13.8 months for the patients with carbon monoxide poisoning, whereas the patients with OSA underwent testing within several days of diagnosis and before treatment with PAP. There were no racial or ethnic differences between the 2 patient groups. Results revealed that 36% of patients with OSA exhibited hippocampal atrophy in the context of normal ventricle-to-brain ratios. Brain atrophy was identified through comparisons with a previously established normative sample of quantitative brain volumes. The presence of hippocampal atrophy in the OSA group was significantly associated with cognitive measures of nonverbal memory and information processing. There was also a statistically significant relationship between baseline oxygen saturation and hippocampal volume in patients with OSA. Interestingly, the OSA group generally performed relatively better than the carbon monoxide poisoning group across different neuropsychological tests, although they did exhibit impairments on selective tests, particularly executive function, when their performance was compared with that of a normative sample.

White matter integrity has also been a focus of sMRI popula-
tion-based studies. The relationship between white matter disease and sleep-disordered breathing was examined in an epidemiologic dataset comprised of 789 older community-dwelling adults over the age of 68 years from the Sleep Heart Health Study. Because spectral imaging was active PAP treatment, have a tracheotomy, or be on cur for the Sleep Heart Health Study were that participants could not use MRI to examine the relationship between cardiovascular disease and sleep-disordered breathing. Evaluation of white matter disease was conducted in the midbrain, pons, and medulla. Sleep-disordered breathing was defined using an apnea-hypopnea index, arousal index, and both obstructive and central apnea indexes. Polysomnography was obtained from 1995 to 1998, and MRI was obtained from 1997 to 1998. Blood pressure, weight, BMI, smoking history, age, alcohol use, history of coronary heart disease, and diabetes history were examined as possible covariates. The results indicated that approximately 27% of participants in the sample exhibited evidence of white matter disease in the brainstem, predominantly in the pons. There were no differences between participants with and without white matter disease in apnea-hypopnea index, central or obstructive sleep apnea indexes, or percentage of sleep time with an oxygen saturation less than 90%. However, individuals with white matter disease did exhibit fewer arousals per hour of sleep; these variables maintained a significant association even after adjusting for age, sex, race, BMI, and blood pressure. The authors concluded that their negative findings may be related to the relatively mild severity of sleep-disordered breathing in their population-based sample, survival biases, or the high comorbidity of other vascular risk factors that may be present in a sample of older adults. Regarding the unexpected inverse relationship observed between frequency of arousals and prevalence of white matter disease, the authors speculated that the arousal response may be protective against white matter disease in the brainstem. However, they also cautioned that the clinical significance of this association should be more fully investigated.

Longitudinal data from the Sleep Heart Health Study were utilized to examine temporal relationships between sleep-disordered breathing and MRI-derived indexes of white matter infarcts in the brain. The sample was comprised of 843 individuals with a mean age of 77 years who received MRI scans in 1992 to 1993 and 1998 to 1999 and polysomnography in 1995 to 1997. Exclusion criteria for the Sleep Heart Health Study were that participants could not be in active PAP treatment, have a tracheotomy, or be on current home oxygen therapy. Characterization of sleep-disordered breathing included consideration of both central and obstructive apneas. The results indicated that participants who displayed progression in white matter disease on MRI were significantly more likely to have an increase of central, but not obstructive, apneas compared with individuals without evidence of progression of white matter infarcts. The authors concluded that this relationship suggests that central sleep apnea either contributes to the progression of white matter disease or may be a marker of subclinical cerebrovascular disease.

**Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy (MRS) is an imaging technique that permits investigation of neuronal cellular chemical activity through examination of neurotransmitters and amino acids. In existing MRS studies of populations with OSA, spectral resolutions of N-acetylaspartate (NAA), choline (Cho), creatine (Cre), and myo-inositol (mI) metabolites have been examined. NAA, an amino-acid derivative, is primarily located in neurons and is thought to be a marker of neuronal viability. Reductions of NAA may reflect neurodegeneration. Abnormal levels of Cho suggest inflammation, cellularity, and membrane degradation associated with demyelination. A decrease in the ratio of NAA to Cho has been utilized as an indicator of cerebral metabolic injury, such as gliosis and impairment of neuronal and axonal function. Creatine reflects biochemical energy reserves of glia and neurons and is presumed to be stable in the context of pathologic processes. As a result of its relative stability, creatine is frequently utilized as a control in metabolic ratio values (e.g., Cho/Cre). Finally, an increase in mI metabolites may be an indicator of glial-cell proliferation or gliosis. Because spectral data from MRS studies are acquired from relatively small levels of neural metabolites, regions of interest are often limited in size. Nonetheless, MRS is a useful neuroimaging tool for the study of OSA because it provides a measure of cerebral metabolic change that may reflect pathologic insults to brain integrity.

Kamba and colleagues conducted 2 MRS studies in patients with OSA. A 1997 brief report applied MRS in patients with mild OSA, moderate to severe OSA, and controls to obtain NAA/Cho, NAA/Creatine, and Cho/Creatine ratios in both cerebral cortex and white matter. Many patients with OSA had comorbid medical conditions, including hypertension, cardiac hypertrophy, bronchial asthma, nasal allergy, tonsillectomy, cervical spondylosis, and diabetes mellitus. The findings revealed a significant group difference in the NAA/Cho ratio for cerebral white matter, with a significantly lower ratio in the patients with moderate to severe OSA, compared with those with mild OSA and controls. The authors concluded that metabolic changes occur in normal-looking white matter of patients with moderate to severe OSA. These results represent an important early contribution to the study of OSA using neuroimaging techniques that provide support for possible cerebral damage associated with the disorder. However, the findings are limited in their specificity because the authors did not control for common comorbid medical conditions in OSA that may be independently related to cerebral ischemia and metabolic impairment.

A follow-up MRS study was implemented to address the effects of potentially confounding comorbid conditions on the examination of cerebral metabolic activity in OSA. Fifty-five patients with severe OSA underwent MRS to acquire NAA/Cho ratios for cerebral cortex and periventricular white matter. Patients were evaluated for the presence of hypertension, cardiac disease, diabetes mellitus, and hyperlipidemia. Patients with evidence of brain infarction, hemorrhage, or white-matter hyperintensity lesions on MRI were excluded from analyses. Results indicated that the NAA/Cho ratio for cerebral cortex decreased with age. Although no significant relationship was found between severity of OSA and the NAA/Cho ratio for gray matter of the cerebral cortex, severity of OSA was found to have a significant negative association with NAA/Cho ratio for normal-appearing white matter that was independent of age and the presence of cardiac disease. The investigators reported that severity of OSA may be associated with the degree of white-matter metabolic impairment and that this impairment may be related, in part, to comorbid cerebrovascular risk factors. Although this investigation did not include a healthy control comparison group, the findings are generally supportive of those previously obtained by the authors. Furthermore, they extend those findings by emphasizing the importance
of consideration of comorbid medical conditions that may also have an effect on metabolic findings as measured by MRS.

Bartlett and colleagues34 conducted a preliminary spectroscopy study of 8 men with severe OSA and 5 age-matched controls. Data were obtained for NAA and Cre compounds in the left hippocampus. Participants also underwent cognitive assessment of both vigilance and processing speed prior to and following the spectroscopy scan. The findings revealed a significant increase in NAA/Cre ratio in the left hippocampus of patients with OSA that the authors reported was likely the result of an observed decrease in the Cre metabolite. In the OSA group, NAA/Cre was significantly correlated with arousal index but not with total respiratory disturbance index or average oxygen desaturation. Creatine was significantly associated with increased vigilance performance prior to and following the MRS scan, whereas NAA was associated with vigilance performance only prior to the scan. The authors did not specifically examine differences in cognitive performance between the patient and control groups. They concluded from their findings that decreased Cre levels in the hippocampus of patients with OSA may be related to intermittent hypoxemia associated with the disorder because creatine is involved in energy homeostasis and has been shown to improve performance on cognitive tests.35 Although obtained from a small sample size, these results offer additional evidence of both metabolic abnormalities in OSA and hippocampal dysfunction. A novel contribution of this study includes identification of a significant association of metabolic levels and cognitive test performance, supporting the continued investigation of these relationships in patients with OSA.

A recent MRS study36 examined brain metabolism in the prefrontal cortex, parieto-occipital, and frontal periventricular white matter of patients with untreated severe OSA and age- and sex-matched healthy controls. MRS was utilized to obtain spectral data for NAA/Cho, NAA/Cre, Cho/Cre, ml/Cre ratios, and absolute concentrations of NAA, Cho, Cre, and ml metabolites. The results revealed a decrease in NAA/Cre and Cho/Cre ratios and absolute concentrations of NAA and Cho in the prefrontal white matter of patients with OSA, compared with controls. Although 8 of the 22 patients reported a history of cerebrovascular risk factors, analyses of a subgroup of patients without comorbid medical conditions revealed that the findings were essentially unchanged. Taken together, these MRS-derived findings provide important additional support for the presence of neurochemical abnormalities thought to reflect white matter impairment in individuals with moderate to severe OSA.

Functional Neuroimaging

Although there are several different functional neuroimaging approaches, to our knowledge, existing functional neuroimaging studies of OSA have utilized only functional MRI (fMRI). fMRI allows the researcher to examine cerebral activation in response to an external probe. fMRI images are generally acquired using the blood-oxygen level-dependent (BOLD) technique. This non-invasive, high spatial and temporal resolution technique enables acquisition of images that are dependent on the sensitivity of the MR signal to excesses of cerebral blood flow associated with an increase of synaptic activity in the brain. Functional neuroimaging techniques are ideal for investigations of acute changes in the brain associated with performance of various challenges. Coupled with this, however, is the limitation that fMRI data can only reflect relative changes in neural activity that are specifically associated with those challenges.37 Furthermore, fMRI is an indirect measure of vascular function that may be compromised in individuals with vascular pathology. These are crucial considerations when interpreting fMRI findings in both healthy and clinical populations. Current fMRI studies of OSA employ either respiratory or cognitive challenges, described in greater detail below, designed to activate specific brain regions during image acquisition. In brief, respiratory challenges employ forced alterations of breathing effort to evoke changes in the autonomic nervous system similar to those experienced by individuals with breathing disorders, whereas cognitive challenges elucidate neural mechanisms associated with performance on complex mental tasks.

Respiratory Challenges

A complementary series of 4 fMRI studies investigated neural function associated with respiratory challenge in patients with OSA. The first of these38 utilized the Valsalva maneuver, an expiratory challenge in which participants are instructed to exhale vigorously against a resistant force that causes a closed glottis. Clinically, the Valsalva maneuver has been used to assess autonomic nervous system function and treat cardiovascular disorders, such as angina pectoris and paroxysmal tachycardia.39 Prolonged expiratory effort results in increased upper airway pressure and an initial increase in blood pressure associated with expiratory strain. The maintenance of this strain results in a rapid decline in blood pressure, followed by an eventual drastic overcompensation.40 Changes in cerebral hemodynamics associated with the challenge include altered flow velocity in the middle cerebral artery.41 Henderson and colleagues42 performed a series of 3 repeated 18-second Valsalva maneuvers at a load pressure of 30 mm Hg during fMRI in patients with OSA and in controls. None of the patients with OSA was taking medications, and both patients and controls had similar BMIs. Absence of sleep-disordered breathing was verified in healthy controls through respiratory monitoring and electroencephalography conducted during sleep in the MR scanner. Analyses indicated that the Valsalva maneuver was associated with group differences in regional neural signal intensity in the left inferior parietal lobe, left precentral gyrus, anterior superior temporal gyrus, superior frontal gyrus, posterior insular gyrus, cerebellum, anterior cingulate, and hippocampus. Group differences in neural response-time patterns were also noted in the cerebellum, posterior insula, anterior cingulate, and precentral gyrus. The authors concluded that the OSA-related regional specificity of these results supported those of previously reported17 areas of gray matter volume loss. They also stated that these findings suggested the presence of neural functional reorganization that may mediate cardiovascular and respiratory mechanisms in patients with OSA performing the Valsalva maneuver.

A second fMRI autonomic respiratory challenge61 was conducted in participants with OSA and controls using a cold pressor technique. This assessment of the integrity of the autonomic nervous system involves the application of a cold stimulus to a participant’s forehead to elicit an involuntary autonomic reflex that physiologically results in decreased breathing and heart rate and increased blood pressure. In the current study, the cold stimulus consisted of a 4°C bag of deuterium oxide. Participants in this sample overlapped with those of the previously described Henderson et al study.38 Several patients with OSA were unable
to participate in the study due to scanner weight limitations or claustrophobia. Cluster analyses indicated that patients with OSA exhibited decreased neural responses relative to controls in the ventral thalamus, ventral anterior insula, and hippocampus. Relative signal increases in patients with OSA were observed in cerebellum, anterior insula, medial frontal cortex, and cingulate gyrus. It was concluded that the cold pressor challenge produces OSA-related neural differences in multiple brain regions, particularly cerebellum and limbic areas.

Macey and colleagues conducted an expiratory-loading breathing challenge to examine associated neural response in OSA. Expiratory-loading challenges require a sustained breathing effort that produces low positive airway pressure with few exaggerated muscle exertions. In this study, the 90-second period of sustained expiratory-loading airflow differed from the repetitive, short, breathe-pause efforts associated with the Valsalva maneuver. Participants were instructed to sustain expiratory effort at a pressure of 10 mm Hg or greater, and all participants practiced the exhalation at least 20 minutes prior to initiation of the challenge. The participant sample overlapped with that of the 2 previously described studies. In the current sample, 3 patients with OSA were prescribed PAP treatment but did not use it the night before the scan. Analyses revealed group differences in neural signal intensity in several cortical and subcortical regions. A relative signal decrease was observed in the subjects with OSA in the right insula, left anterior cingulate, and middle frontal gyrus, whereas a relative signal increase was observed in the right hippocampus, ventral midbrain, left dorsal midbrain, and right ventral pons. Variability in neural response in the patients with OSA was noted in the amygdala, cerebellum, and posterior insula. The authors suggested that these brain regions may mediate neural response to resistive breathing challenges and may play a role in the abnormal physiologic mechanisms associated with OSA.

The most recent study in this series of fMRI respiratory challenges examined inspiratory loading in 7 patients with OSA and 11 controls. Inspiratory challenges involve increased negative pressure on the upper airway resulting from prolonged periods of inspiration followed by brief expiration. This produces autonomic changes to blood pressure associated with alterations of breathing effort similar to those observed in individuals with OSA. In the current study, each inspiratory challenge consisted of 60 seconds of unrestricted breathing and 90 seconds of inspiratory loading at a pressure ranging between 6 and 15 mm Hg. The authors hypothesized that inspiratory loading would elicit different neural responses in patients with OSA and controls in motor regions and sensory areas that mediate autonomic stimulation. Similar to the results from the 3 other studies in this series, altered neural signal intensities in response to inspiratory loading were observed in patients with OSA in multiple brain regions. The largest clusters of group differences were found in the basal ganglia and left insula. Signal differences were also observed in the medial cingulate cortex, right ventral posterior thalamus, anterior thalamus, right hippocampus, left medial temporal cortex, medial midbrain, and cerebellum. Response-timing alterations were exhibited in the basal ganglia. The authors concluded that timing and signal-intensity differences in these motor, sensory, and autonomic integration regions of the brain may underlie nocturnal pathologic breathing abnormalities in patients with OSA. It was also noted that many of the functional abnormalities observed in these studies were in brain regions that were shown previously to have volumetric gray matter abnormalities.

Considered in concert, the results from this series of respiratory-challenge studies illustrate the importance of examination of neural activity in response to various breathing paradigms in patients with OSA. Whether the observed brain abnormalities are a cause or effect of disordered breathing patterns, however, remains an issue for further study. Furthermore, the effect of treatment on neural function of the patient with OSA in response to a respiratory challenge also requires additional clarification. Although no patient with OSA used PAP the night before MR scanning, some patients were prescribed PAP treatment prior to enrollment in the study. Overall, the findings from these studies provide a vital contribution to an improved understanding of the effects of disordered breathing on brain function in the patient with OSA.

**Cogntive Challenges**

Thomas and colleagues utilized a cognitive activation paradigm to examine brain activity in 16 patients with untreated OSA and 16 controls. Six patients with OSA were also resampled following a minimum of 8 weeks of compliant use of PAP treatment (> 7 hours/night or 100% of total sleep time). Patients reported excessive daytime sleepiness and a duration of OSA symptoms of at least 5 years. All participants were reported to be medically and psychiatrically healthy. The cognitive challenge utilized in this study was the 2-back verbal working memory task, which requires mental comparison of rapidly presented verbal stimuli to stimuli presented in 2 previous trials. Cognitive comparisons require the participant to maintain a dynamic mental representation of previously presented stimuli in short-term working memory. Using a blocked data-acquisition design, the investigators reported an absence of dorsolateral prefrontal activation and decreased working-memory speed in patients with OSA, as compared with controls. An fMRI blocked design involves repeated exposure to 1 condition (A) alternating with repeated exposure to a second condition (B), resulting in an “AB block” design that can be presented sequentially during scan acquisition. Hypoxemia did not contribute to the finding in the patient group. Following PAP treatment, patients demonstrated an improvement in subjective sleepiness and partial recovery of posterior parietal activation. However, they also continued to exhibit an absence of dorsolateral prefrontal activation. The authors concluded that their data supported a functional anatomic model of excessive sleepiness; that is, altered functional neurocircuity was demonstrated in the dorsolateral prefrontal cortex in patients with OSA, similar to neural activation patterns observed under conditions of sleep deprivation.

Ayalon and colleagues recently conducted an fMRI study to examine brain activity associated with a cognitive challenge (verbal list learning) in patients with untreated OSA and controls. There were no differences between the patients and controls on BMI, blood pressure, age, education, or English fluency. The authors reported that the patients with OSA and controls performed similarly on the verbal list learning task across multiple indexes, including immediate and delayed recall and recognition memory. However, a significant task-associated increase in brain activation in the patients with OSA was observed in the right inferior frontal gyrus, middle frontal gyrus, cingulate gyrus, junction of the inferior parietal and superior temporal lobes, thalamus, and cerebellum. Better verbal learning performance in patients with...
OSA was associated with increased brain activation in the left inferior frontal gyrus and left supramarginal area, whereas poorer performance was associated with increased activation response in left inferior parietal lobe. The authors concluded that the unique pattern of cerebral activation in patients with OSA in the context of intact cognitive performance may reflect recruitment of additional neural resources consistent with an adaptive compensatory response, similar to that seen in healthy adults following total sleep deprivation and elderly adults. Inconsistencies between these findings and those of Thomas and colleagues are likely due to differences in the cognitive-challenge paradigm and severity of OSA. The Thomas study utilized a working-memory cognitive task, whereas Ayalon and colleagues employed a test of verbal learning. Given that these 2 tasks presumably involve different cognitive processes, it is not surprising that each is associated with varying patterns of neural signal abnormalities in the patient with OSA. Taken together, the findings from these functional neuroimaging cognitive-challenge studies provide an important framework for the development of additional studies that examine neural activity of patients with OSA.

CONCLUSIONS

Summary of Findings

The Table summarizes characteristics of the OSA sample and neuroimaging findings. Structural neuroimaging studies have provided inconsistent evidence for generalized changes in gray matter, which may be related to differences in individual study samples. More consistent findings, however, have been reported regarding decreased hippocampal volume. This abnormality has been hypothesized to be associated with the effects of chronic, intermittent, nocturnal hypoxemia, although this model has not been explicitly tested. Epidemiologic studies of structural white-matter integrity generally have not found evidence of abnormalities in community-dwelling older adults with undiagnosed breathing difficulties.

OSA-associated dysfunction of the hippocampus is also supported from the findings from at least one MRS study. Perhaps the most consistent finding of MRS studies, however, involves white-matter dysfunction, particularly in the frontal lobes. The lack of convergence between MRS and structural MRI white-matter findings should not be a primary concern, given variability in methodologic approaches and sample characteristics. Specifically, negative structural white-matter studies were often composed of older adults from the general population, whereas spectroscopy samples contained middle-aged adults with clinically diagnosed OSA. In general, these results suggest that white-matter abnormalities may be present in selected individuals who are at the greatest risk of developing vascular disease as a result of chronic apneic events. Existing models of central nervous system dysfunction have suggested that vascular compromise and endothelial dysfunction in OSA may preferentially damage small vessels in the brain, which could result in small-vessel, white-matter ischemia. Utilization of emerging MRI techniques that have been specifically developed to examine white-matter integrity in normal-appearing white matter, such as diffusion-weighted tensor imaging, may further advance our understanding of white-matter dysfunction in OSA.

Functional neuroimaging studies have also made vital contributions to the OSA literature. fMRI respiratory challenges provide support for OSA-related differences in neural function in multiple brain regions involved in respiratory and cardiovascular control, including regions in the motor, sensory, and autonomic integration brain areas. Although respiratory challenges conducted during wakefulness do not directly mimic the physiology of sleep-disordered breathing, these studies nonetheless provide important insights into the neural mechanisms that may underlie the etiology or be involved in the physiologic consequences associated with OSA. Results from the few fMRI studies utilizing cognitive probes in individuals with OSA are mixed. Task-related results dependent upon the activation paradigm were evident in all studies. Some findings were consistent with fMRI studies of sleep deprivation, demonstrating compensatory recruitment of brain regions in untreated individuals. Treatment-related findings require further replication, given that only 1 study to date has examined the effects of compliant PAP treatment in 6 individuals with OSA.

Considered together, these neuroimaging findings provide support for the presence of OSA-associated neurofunctional and white-matter impairments, particularly in the frontal lobes and hippocampus. Such impairment is consistent with proposed models of central nervous system and cognitive dysfunction in OSA implicating small vessel disease and prefrontal cortex. Given the relative paucity of experimental inquiry, however, additional studies are needed to more fully substantiate these models.

Limitations and Considerations

Several important limitations and considerations emerge from a review of the existing neuroimaging literature in OSA. Most notably, the vast majority of studies have included only male participants, thereby limiting generalizability of findings to men with OSA. Although the clinical presentation of OSA is more common in men than in women, the sex ratio of published studies does not generally reflect this prevalence. Consideration of the potential moderating effects of IQ and education is also important, particularly with respect to treatment-adherence studies and performance on cognitive challenges. Although prior studies have shown relationships between IQ and normal brain development and potentially protective effects of high IQ against OSA-associated cognitive decline, only 2 studies in the current review reported measures of intellectual or educational achievement. Age may also moderate the effect of OSA on brain structure and function. For instance, advanced age may mask the effects of OSA on cerebral integrity. Associations between sleep parameters and neuroimaging may be less robust among older adults, given the myriad of age-related comorbid factors that could affect this relationship. Likewise, length of illness is a potentially confounding variable that is difficult to assess in the patient with OSA and, therefore, is difficult to adequately investigate. Several investigators have specifically focused on treatment-naive patients in an attempt to address this issue (e.g., see references 19, 21, 36, and 45), but more-direct assessment methods (e.g., bed-partner questionnaire) may be necessary. Taken together, these considerations indicate that researchers should seek to adequately match OSA patients and healthy subjects on a wide range of demographic variables while considering individual differences in order to more clearly elucidate the pathophysiology of OSA.

Contradictory results among several of the reviewed studies may be partially due to a failure to adequately examine the ef-
fect of common comorbid medical conditions that may also be associated with alterations in brain structure and function. For instance, hypertension is commonly reported in patients with OSA and has known independent effects on brain structure and function.\textsuperscript{6} fMRI studies that seek to examine hypertension as a potential mediator of the relationship between OSA and brain dysfunction should also consider the effect of hypertension on the BOLD signal, given its reliance on blood flow.\textsuperscript{59,60} Similarly, OSA severity and its relationship with other clinical symptoms is an important factor to consider when designing neuroimaging studies. Several of the studies included in the current review included participants from the general population with subclinical symptoms of OSA,\textsuperscript{24,25} rather than clinically referred OSA patients with more severe symptomatology. Although examination of patients with a wide range of OSA severity is necessary to gain a thorough understanding of the clinical and physiologic characteristics of the disorder, caution should be taken when comparing and interpreting results across studies. There may be a critical threshold associated with the clinical expression of OSA-related pathologic insult to the brain. Similarly, patients with very severe OSA may be more likely to have comorbid illness that may independently compromise the brain. In a recent study of hypertension in the Wisconsin Sleep Cohort, investigators suggested that the relationship between OSA and hypertension varied across levels of OSA severity.\textsuperscript{61} Clearly, continued examination of the complex relationship between disease severity and comorbid medical conditions is critical.

Perhaps one of the most significant problems associated with neuroimaging in OSA involves the sampling bias that exists when conducting MRI scans on obese patients with OSA. Although BMI is often reported in the reviewed studies, the effect of BMI on observed findings is generally not explored or discussed. In a practical sense, many patients with OSA are unable to appropriately fit into the MRI scanner. It is therefore likely that OSA samples included in neuroimaging studies represent only a subgroup of patients with the disorder. This limits interpretation regarding the interaction of OSA and obesity and/or any pathophysiologic differences in OSA among obese and nonobese patients. There will likely be methods to remedy this problem as continued efforts increasingly focus on the utilization of neuroimaging techniques in obesity, but investigators should be aware of this sampling bias until these issues are resolved.

An additional limitation and consideration that emerges from a review of the OSA imaging studies is that, with the exception of Robbins et al’s study,\textsuperscript{25} all reviewed studies examined cross-sectional rather than longitudinal, data. Although cross-sectional studies provide valuable information for the investigation and characterization of a sample, longitudinal data may allow the researcher to more specifically examine the development of underlying neuropathologic processes associated with OSA. When designing a longitudinal study, the investigator may benefit from consideration of the feasibility of acquiring and comparing repeated scans over time in the same participant using the same MR scanner. The effects of treatment on the brain of the OSA patient are also only beginning to be understood. Two studies included in the current review\textsuperscript{19,44} that examined change associated with treatment provide an excellent model for the consideration of PAP-adherence data when interpreting treatment outcomes. However, these studies included participants with high levels of nightly PAP adherence. Given the difficulties that many patients experience maintaining recommended nightly PAP use,\textsuperscript{62-64} future neuroimaging studies investigating the effect of varying amounts of adherence on brain structure and function would be an important contribution to the OSA literature.

Future Research Directions

Although existing neuroimaging studies have made critical contributions to a scientific understanding of the underlying biologic mechanisms of OSA, several directions for future research emerge from a review of the literature:

1. Explore individual differences and potentially moderating effects of demographic variables on the neural structure and function of the patient with OSA, including sex, education, IQ, and BMI.
2. Describe the course of OSA and the effect of varying levels of treatment using both cross-sectional and longitudinal experimental neuroimaging designs.
3. Examine the relationship between neuroimaging findings and more comprehensive assessments of cognitive and behavioral outcomes in patients with OSA.
4. Expand the characterization of neurochemical abnormalities in the patient with OSA using MRS and examination of additional metabolites, such as glutamate.
5. Replicate fMRI studies using cognitive and respiratory challenges in patients with OSA.

In summary, neuroimaging studies have broad scientific appeal for the study of OSA. We believe that it is becoming increasingly important to apply neuroimaging techniques to neuropathologic models of OSA with a priori working hypotheses. In this way, neuroimaging studies of OSA may serve to help clarify underlying biologic mechanisms associated with the onset and maintenance of the disorder. They may also help characterize response to treatment, at both therapeutic and subtherapeutic levels. Objective findings from neuroimaging investigations may provide useful clinical motivators for patients with OSA struggling with treatment adherence. Whole-brain neuroimaging approaches represent a useful preliminary approach and should continue as attempts are undertaken to develop consensus on pathologic regions of interest in OSA. Theory- and model-based approaches, however, guide researchers toward rigorous scientific examination of specific questions and encourage modification of existing theoretic models of OSA. This will aid in the development of complementary research ideas that promote innovative translational research efforts. Convergence of multimodal neuroimaging efforts may also serve to inform theory development and refinement. Large-scale community studies may consider including sleep-related measures in their assessments to ensure that their participants exhibit normal sleep functions. Ongoing advances in imaging techniques will likely remedy some of the current limitations inherent in neuroimaging investigations of OSA. For example, magnetoencephalography, a noninvasive direct measure of magnetic fields generated by neural electrical activity, can more readily accommodate the obese patient. Similarly, optical imaging, although limited in spatial resolution, provides a mobile imaging technique that affords continuous imaging throughout sleep. Finally, consideration should be given to the development and continual review of standards for neuroimaging research in OSA. This will facilitate comparison of findings and help eliminate methodologic differences across studies.
ACKNOWLEDGEMENTS

The work presented in this paper was supported by NIH grant R01 HL 075366.

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