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Mapping Gray Matter Reductions in Obstructive Sleep Apnea: An Activation Likelihood Estimation Meta-Analysis

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Study Objectives: The authors reviewed the literature on the use of voxel-based morphometry (VBM) in obstructive sleep apnea (OSA) magnetic resonance imaging (MRI) studies via the use of a meta-analysis of neuroimaging to identify consistent and specific structural deficits in patients with sleep apnea compared with healthy subjects.

Design: Neuroimaging meta-analysis.

Data Sources: We used PubMed to retrieve articles published between January 2000 and February 2012.

Study Selection: The authors included all VBM research on patients with OSA and healthy controls. They compared the findings of the studies by using gray matter volume (GMV) or gray matter concentration (GMC) to index differences in gray matter.

Data Extraction: Stereotactic data were extracted from eight VBM studies of 213 patients with OSA and 195 control subjects.

Results: Regional gray matter reduction in the bilateral parahippocampus and less-convincing right superior frontal and left middle temporal gyri was demonstrated in patients with sleep apnea using an activation likelihood estimation (ALE) procedure to analyze significant differences.

Conclusions: Significant reductions in gray matter in patients with sleep apnea occurred in the bilateral parahippocampus and less-convincing frontotemporal regions, which may be related to the neurocognitive processing abnormalities that are common among populations of patients with sleep apnea.

Keywords: Meta-analysis, obstructive sleep apnea, voxel-based morphometry

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INTRODUCTION

Sleep apnea (SA) is characterized by repetitive episodes of apnea or hypopnea during sleep that lead to sleep fragmentation and are usually associated with intermittent hypoxia. Obstructive sleep apnea (OSA), the most common type of SA, affects approximately 2-4% of middle-aged adults;[1,2] however, its prevalence in elderly populations is 24-30%.[3,4] OSA has been shown to increase the risk of hypertension,[5] cardiovascular disease,[6] all-cause mortality,[7] diabetes,[8] stroke,[9] and death.[10,11]

The common symptoms of OSA include excessive daytime sleepiness and cognitive deficits, such as impaired memory, learning, and attention, because of both sleep disturbances and hypoxemia. In addition, the presence of impairments in vigilance, executive functioning, and motor coordination have been reported, whereas the presence of altered global intellectual dysfunction, verbal functioning, and visual perception remains controversial.[12,13] Both intermittent hypoxia and sleep fragmentation independently can lead to neuronal deficits in the hippocampus and prefrontal cortex (PFC), areas that are closely related to the neural processing of memory, learning, attention, and executive function.[14,15] The hippocampus region is closely associated with the neural processing of memory.[16,17] In addition to evidence gleaned from animal studies, recent neuroimaging studies have shown that OSA is associated with changes in brain morphology,[14,18-23] particularly the focal diminution of gray matter (GM) within the hippocampus and other cortical areas, such as the frontotemporal lobes, which are linked to neurocognitive function.

During the past 2 decades, functional and structural neuroimaging techniques have evolved and have been used to increase our understanding of neurocognitive processes and structural brain differences. Structural imaging methods, such as voxel-based morphometry (VBM) using Statistical Parametric Mapping (SPM; Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/), which is an automatic and quantitative method for detecting group differences in gray matter concentration (GMC) or volume (GMV), have been used.[24,25] "Optimized VBM" was a recursive procedure to provide a solution for improving the spatial normalization in SPM99 and SPM2 compared to a "standard VBM". It helps improve the spatial normalization, and also give better intersubject registration and have the effect of reducing the misinterpretation of significant differences relative to "standard VBM."[25,26] Diffusion tensor imaging (DTI)[27] is an extension of diffusion-weighted imaging (DWI) that can

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quantify white matter (WM) architecture *in vivo*. DTI may detect white matter axonal changes in various white matter structures in patients with OSA.[28] Functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI), are sensitive to the changes in the oxidative state of hemoglobin, which reflect oxygen extraction and, hence, regional brain activation.[29] Task-based fMRI[30] demonstrated a reduction in the activation of the prefrontal cortex in a working memory task, and an increase in the activation of the bilateral inferior and middle frontal gyri, cingulate gyrus, superior and parietal lobules, bilateral parietotemporal junction, and thalamus in a verbal learning task in patients with OSA. In addition, two-back working memory task fMRI[31] revealed a deactivation of the default network in the posterior cingulate and right postcentral gyrus during continuous positive airway pressure (CPAP) withdrawal. Brain proton magnetic resonance spectroscopy (MRS) can be performed using protons to report changes in either the concentration or distribution of chemical substances. The three major compounds acquired in proton MRS are *N*-acetyl aspartate (NAA), creatine (Cr), and choline (Cho). The ratio of NAA/Cho serves as an indicator of cerebral metabolic impairment, including neuronal loss, axonal injury, and gliosis. Proton MRS can show an elevated ratio of NAA/Cr and lowered Cr levels in the left hippocampal area, which is associated with neurocognitive performance and OSA severity.[32] Patients with OSA exhibited decreased parietal-occipital NAA levels[33] and a decreased frontal NAA/Cho ratio and hippocampal Cho/Cr ratio[34] compared with control subjects, which persisted after CPAP treatment.

Desseilles et al. summarized the altered regional brain morphology associated with GM reduction in OSA subjects, as assessed using VBM, as occurring in the following structures: (1) left anterior cingulate cortex, (2) posterior lateral parietal cortex, (3) inferior temporal gyrus, (4) parahippocampal gyrus, (5) right quadrangular lobule, and (6) left hippocampus.[35] However, VBM studies have found variable and conflicting results; for example, one study failed to identify any regions of GM reduction,[36] whereas another study found significantly lower GMC, but only within the left hippocampus.[37] Moreover, another study showed widespread loss of more than 20 foci of GMC.[19] The conclusions drawn by the authors of these separate neuroimaging studies are limited by the small size of the samples used, especially in defined clinical populations. The controlled experimental conditions and clinical features varied substantially between studies.

Recently, quantitative methods for neuroimaging meta-analysis have emerged and become available. The method used most commonly, activation likelihood estimation (ALE), is an objective technique for performing coordinate-based meta-analyses (CBMA) of neuroimaging studies. The CBMA approach uses the reported activation peaks in standardized spaces, rather than raw images, as the input.[38-42] These meta-analytical methods have been applied successfully to the identification of the most consistent structural brain changes in psychiatric disorders, such as schizophrenia and bipolar disorder,[43] and neurological disorders, such as Parkinson disease[44] and epilepsy.[45]

To date, no meta-analysis of VBM studies of OSA has been reported. In this study, we aimed to perform a quantitative meta-analysis using the ALE approach to assess the concordance of neural correlates across multiple VBM studies of OSA involving adult participants.

MATERIALS AND METHODS

Search Strategies and Selection Criteria

This meta-analysis was performed according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) criteria.[46] We searched the PubMed database (beginning in the year 2000 to February 2012) using the terms "sleep apnea," "sleep disordered breathing," "sleep disordered breathing," "sleep related breathing disorders," "sleep related breathing disorders," "voxel," "morphometry," "voxel-based morphometry," and "VBM." No language restrictions were applied. We restricted our search to humans. In addition, we reviewed manually the references cited in articles that were retrieved. The processes of selecting eligible studies (listed in Table 1) were performed according to the Quality of Reporting of Meta-Analyses (QUOROM) statement.[47] We did our best to perform this meta-analysis following the rules of QUOROM. QUOROM initially proposed to improve the quality of reporting of meta-analysis of clinical randomized controlled trials (RCTs). We adhere our report to the checklist items as closely as possible. The flow chart of the study selection process is illustrated in Figure 1. All data were recorded in standardized form by two investigators (WHH and TYH). We extracted demographic data from each article, including the first author's name, year of publication, journal title, patient mean age and range, total patient number, sex distribution, the method of matching, and SPM methods and thresholds.

Study Selection

We selected studies according to the following inclusion criteria: (1) published as an article (and not a letter or an abstract); (2) compared groups of adult OSA subjects with healthy control groups; (3) used the VBM procedure for magnetic resonance anatomical analysis to investigate alterations in whole-brain structure caused by either GMV or GMC; and (4) reported peak activation coordinates of brain changes in Talairach and Tournoux[48] or Montreal Neurological Institute (MNI)[49] stereotactic space.

Studies were excluded if the data reported were insufficient to enable the extraction of the number of subjects in each group, sample sizes were too small (fewer than seven subjects) in either the OSA group or the comparison group,[37] or the data were included in another study, in which case the study with the largest group size was selected.

Quality Assessment

Two independent reviewers (WHH and TYH) evaluated the methodology and the risk of bias of the eligible studies. The reviewers analyzed all articles in terms of patient selection and their comparable controls, blinding, diagnostic criteria, and regression methods.

Data Extraction

The x, y, and z peak activation MNI coordinates of all eligible contrasts constituted the meta-analysis input. The data from MNI coordinates[50,51] were input in a text file and implemented

Table 1—Overview of the eight obstructive sleep apnea voxel-based morphometry studies included in this meta-analysis

Name	Year	Journal	Sample/Male		Mean age ± SD		Matched control	Foci No.	Scanner	SPM	Pre-processing protocol	Smoothing kernel (mm)	Statistical threshold	GMV or GMC	Tal or MNI
			Case	Control	Case	Control									
Macey[20]	2002	Am J Respir Crit Care Med	21/21	21/21	49 ± 11	47 ± 11	Age, sex	12	GE 1.5 T	99	optimized	12	P < 0.001, uncorrected, cluster > 350 voxels	GMV	MNI
O'Donoghue[36]	2005	Am J Respir Crit Care Med	25/25	23/23	45.7 ± 10.1	43.3 ± 9.4	Age, sex	0	GE 3 T	2	optimized	NA	P < 0.05, corrected	GMC	MNI
Morrell[14]	2006	Adv Exp Med Biol	22/22	17/17	51.8 ± 15.4	53.1 ± 14.0	Age, sex, handedness	2	Siemens 1.5 T	99	optimized	12	P < 0.001, uncorrected	GMC	MNI
Yaouhi[23]	2009	J Sleep Res	16/15	14/13	45.8 ± 7.1	52.7 ± 7.0	Age, education	7	GE 1.5 T	2	optimized	12	P < 0.005, uncorrected, cluster > 50 voxels	GMV	MNI
Joo[19]	2010	Sleep	36/36	31/31	44.7 ± 6.7	44.8 ± 5.4	Age, sex	27	GE 1.5 T	2	optimized	12	P < 0.05, corrected, FDR, cluster > 200 voxels	GMC	MNI
Morrell[21]	2010	Thorax	60/NA	60/NA	47.3	46.1	NA	4	GE 3 T & Siemens 1.5T	8		8 or 12	P < 0.05, corrected, FDR	GMV	MNI
Canessa[18]	2011	Am J Respir Crit Care Med	17/17	15/15	44 ± 7.6	42.2 ± 6.6	Age, sex, education	6	Philips 3 T	5		NA	P < 0.05, FWE corrected	GMV	MNI
Torelli[22]	2011	Neuroimage	16/13	14/9	55.8 ± 6.7	57.6 ± 5.2	Age, handedness	1	Siemens 3 T	8		10	P < 0.05	GMV	MNI
Total			213	195				59							

FDR, false discovery rate; FWE, family-wise error; GMC, gray matter concentration; GMV, gray matter volume; MNI, Montreal Neurological Institute; NA, not available; OSA, obstructive sleep apnea; SD, standard deviation; Tal, Talairach and Tournoux space; VBM, voxel-based morphometry; SPM, Statistical Parametric Mapping.

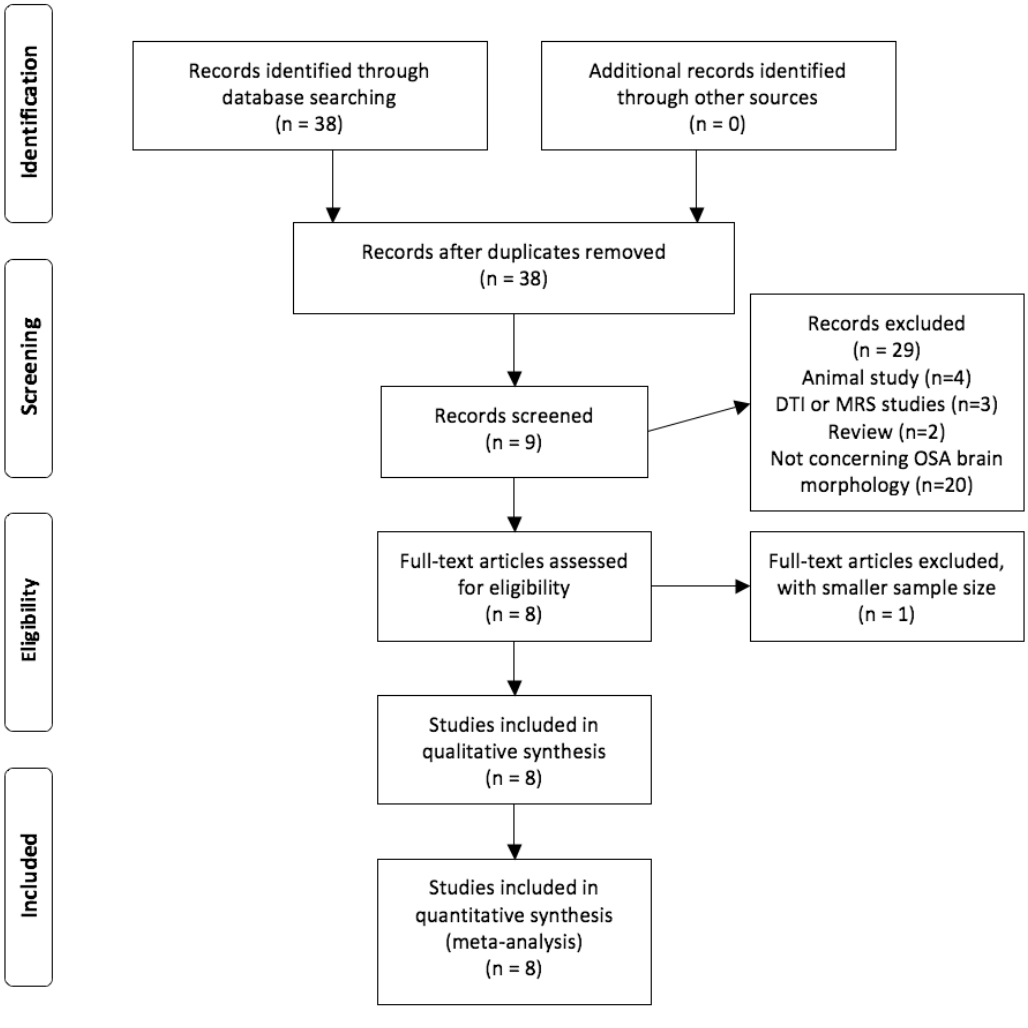

Figure 1—Flow chart of the study selection process used to determine the studies to be included in the meta-analysis. DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy; OSA, obstructive sleep apnea.

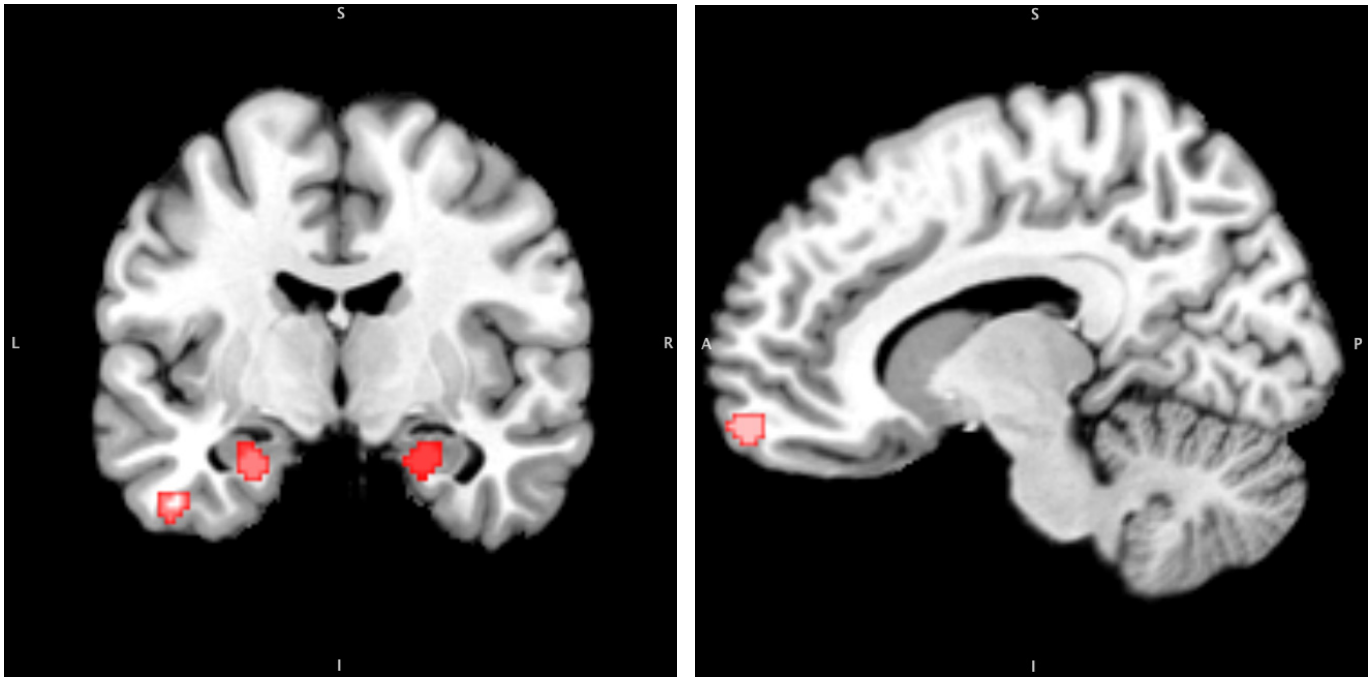

Figure 2—Coronal and sagittal sections of regions of gray matter reduction in obstructive sleep apnea compared with normal controls. Results are from the Activation Likelihood Estimation for sleep apnea meta-analyses. All activations are significant at P < 0.05 corrected for multiple comparisons using the false discovery rate. The left side of the image represents the left side of the brain.

in GingerALE 2.1 (http://brainmap.org/ale/, Research Imaging Institute of the University of Texas Health Science Center, San Antonio, Texas). We used the reported foci as raw data. All stereotactic spaces are available for analysis. We did not contact any authors.

ALE Meta-Analysis

The current version of the ALE approach[52-54] is used in the CBMA of neuroimaging results.[40,55] Briefly, all reported stereotactic coordinates were modeled as center peaks of a three-dimensional (3D) gaussian probability distribution. A modeled activation (MA) map was computed and served to summarize the results of study-specific localization probabilities. The spatial uncertainty associated with the activation foci was estimated with respect to the sample size from each study.[56] We calculated the overlap of these distributions across different experiments. ALE values were calculated on a voxel-by-voxel basis by measuring the union MA maps modeled mentioned previously. This revised analysis tested for convergence by studies (random effects) instead of foci (fixed effects).

A P threshold corrected for multiple comparisons using the false-discovery rate (FDR; q) to correct for multiple comparisons was set at a significance threshold of 0.05.[57,58] The volume of the minimum cluster threshold was set at 200 mm^3. Each ALE map was overlaid onto an anatomical template generated by spatial normalization of the International Consortium for Brain Mapping (ICBM) template to the Talairach space.[59] The image output files were created using the NIfTI (.nii) format. Results were visualized with Mango (multi-image analysis graphical user interface [GUI]), using the Colin brain template in the MNI space.[60] Anatomical labels of final cluster locations were provided by the Talairach Daemon (http://www.talairach.org/).[61,62] We also performed a contrast study to compare two different sets of foci and examined the statistically significant differences of covariates, such as 1.5 T versus 3 T scanners. We applied 10,000 permutations, a relaxed P threshold uncorrected P value of 0.01, and a minimum cluster volume threshold of 200 mm^3 to achieve the results. Although the explanation of the results depends on the size of meta-analysis and there are no community-accepted criteria for the results, generally speaking for a study of this size, if six or more foci contribute to a cluster, it is considered very robust, and if three to five foci contribute to a cluster, it is acceptable. It is not convincing if only one or two foci contribute to a cluster.[63]

RESULTS

We selected eight English studies from our search for use in our analysis (Table 1), and no foreign language literature was identified (however, it should be noted that only seven of these studies contributed to the ALE analysis because one study did not find any significant group differences). These studies comprised 213 patients with OSA and 195 healthy controls. The subjects of cases and controls from each study are generally comparable by age, sex, education, and handedness.

A total of 59 peak foci were reported. We did not contact the authors and used the reported foci as raw data. Consistent gray matter reductions in patients with OSA relative to healthy control subjects were identified in the bilateral parahippocampus and right uncus (Brodmann area [BA] 28). Gray matter decreases were also detected in the right superior frontal gyrus (BA 10) and in the left middle temporal gyrus (BA 21) (Figure 2). However, because only two foci contributed to these latter two clusters (BAs 10 and 21), it may not be very reliable. Table 2 displays the coordinates of cluster maxima. There were

Table 2—Regions of gray matter reduction in obstructive sleep apnea relative to healthy controls

Region	BA	MNI coordinates			ALE extrema value	Cluster size (mm^3)	No. of contributed foci
		x	y	z			
R parahippocampal gyrus		22	-6	-24	0.0142	664	4
R uncus	28	22	2	-32	0.0092		
L parahippocampal gyrus		-26	-8	-24	0.0123	616	3
R superior frontal gyrus	10	10	64	-14	0.0139	344	2
L middle temporal gyrus	21	-48	-4	-36	0.0132	320	2

ALE, activation likelihood estimation; BA, Brodmann area; L, left; MNI, Montreal Neurological Institute; R, right.

no significant clusters between different scanners of magnetic strength in the contrast studies.

DISCUSSION

To our knowledge, this is the first neuroimaging meta-analysis to assess the brain structural differences between patients with OSA and healthy control subjects. We identified significant GM reductions in the bilateral parahippocampus, left temporal lobe (BA 21), and right frontal lobe (BA 10), which may be related to the neurocognitive processing abnormalities that are common in this patient population. The robust reductions in GM observed in subjects with OSA is consistent with findings from previous studies.[18-20,37] The hippocampus, uncus, and limbic system are specifically vulnerable in this disease. The correlations found between imaging alterations and neurocognitive deficits in these regions are not surprising because the parahippocampus plays a significant role in memory and learning[64] and the frontosubcortical systems are involved in attention and executive functions that involve the PFC.[65]

In the current study, GM was reduced on both sides of the parahippocampus, albeit to a greater extent on the right side. The parahippocampus is one of the most frequently reported areas exhibiting abnormalities in OSA. Cumulative OSA evidence implicates the parahippocampus in impaired cognitive processing and memory. Hippocampal atrophy has been reported in patients with OSA using the following approaches: animal modeling,[66] VBM,[14,18-23] volumetric MRI,[67] and MRS.[32] The spectrum of parahippocampal atrophy in OSA included VBM results in the range of absent,[21,23,36] unilateral,[18,37] or bilateral.[14,19,20,22] Parahippocampal atrophy was noted on both sides in most of the studies, including our meta-analysis. In the rat brain, the hippocampus is the region most strongly and readily affected by hypoxic and hypercapnic episodes, because of its sensitivity to hypoxia and innervation with small vessels.[68] The hippocampus is extremely sensitive to hypoxic damage, and chronic exposure to episodic hypoxia during sleep impairs spatial learning and is associated with increased programmed cell death (apoptosis) within the CA1 region in rats.[66] OSA and carbon monoxide poisoning cause hypoxic effects on the brain that are related to memory impairment.[67] Altered brain activation was detected in working memory tasks and decreased activation was reported in the prefrontal and hippocampal regions after CPAP treatment.[69,70] In addition to the hippocampus, the medial PFC appears to be involved in spatial memory and navigation.[17,71] In their review, Burgess et al. concluded that the human hippocampus is associated with spatial and episodic memory.[16] These findings suggest that the hippocampus plays an important role in the impairment of memory and spatial learning associated with OSA. Future studies are required to evaluate the relationship between the volumetric and functional abnormalities of the parahippocampus observed in OSA.

One of the key findings of the current study was the GM reduction in the right superior frontal gyrus (BA 10), located within the rostral PFC, which is the largest and most anterior region of the human PFC.[72-74] Attentional and executive functional deficits are associated with GMV reduction in the superior parietal and frontal regions associated with attention[75] and working memory (the short-term storage of ongoing events; memory for information just received and necessary for the "on-line" performance of a task).[76] The rostral PFC is often activated by prospective memory tasks,[72] and its functions are impaired in patients with rostral frontal lesions.[77] Gilbert et al.[73] reviewed fMRI studies systematically and reported the involvement of the medial rostral PFC in mentalizing (i.e., the ability to represent another person's psychological perspective) and multitasking.[78] This region is associated with cognitive processes specifically, and is involved in processing the motivational or emotional values of incoming information, such as taste, smell, and touch.[79] Sleep disturbances may also damage PFC function and result in impairment of various executive functions, such as behavioral inhibition, set shifting, and self-regulation of affect and arousal.[65] Hemisphere specialization is found in the PFC region. The left PFC (BA10) was associated preferentially with categorical visual spatial memory, whereas the right PFC (BA9/10) was associated preferentially with coordinate visual spatial memory.[80] MacLeod et al. reported that the right anterior PFC (BA10) is activated routinely by episodic-retrieval working memory tasks.[81] Although the hippocampus and the PFC process spatiotemporally discrete events while maintaining goal-directed working memory tasks, a study of the neural activities between the two regions in animals showed that coordination and interaction are needed for specific task completion.[82] Functional connectivity also was shown between the PFC and the hippocampus in humans during successful episodic encoding.[83]

The middle temporal gyrus (BA 21) has been associated with processes such as recognition of known faces and accessing word meaning during reading exercises. The inferior and medial temporal cortex contributions to visual working memory maintenance have been reported.[84] The hippocampus

and the inferior temporal cortex exhibit enhanced functional connectivity between these two areas during working memory maintenance.[85] The inferior and medial temporal cortices, hippocampus, and PFC are associated with the activation of visual memories.[86] The inferior temporal cortex, PFC, and hippocampus also contribute to visual working memory maintenance and associative memory retrieval (i.e., recalling a previously experienced item by thinking of something that is lined with it).[87] In our meta-analysis, the hippocampus, PFC, and inferior temporal cortex emerged as significant foci related to OSA, which suggests that these structures play a crucial role in the working memory impairment observed in OSA. Our findings regarding regional GM reduction in the inferior temporal regions are consistent with this view and support the OSA neuropsychological models.

The neuroimaging findings regarding GM reduction in OSA have varied. We reported the most concordant brain regional reduction, such as that found in the frontal and parietal cortices, the right hippocampus, and deep cerebellar nuclei, mentioned by Macey et al.[20] and Joo et al.[19] Morrell et al. found GM lesions in the temporal gyrus and cerebellum,[21] whereas Canessa et al. reported reduced GM volumes in the hippocampus and frontoparietal cortices.[18] On the contrary, O'Donoghue et al. described the absence of regional reductions in GM.[36] We also found insignificant atrophic GM areas in this meta-analysis. The areas included (1) the insula and cingulate gyri, which are involved in cardiovascular control; (2) the caudate nucleus, which is involved in the prefrontal circuit; and (3) the cerebellum, which plays roles in the regulation of autonomic and respiratory patterns.[19,22,23] The differences observed among studies may be explained in part by the differences in patient selection. Some of the subjects in the study by Macey et al. exhibited neurological and cardiovascular comorbidity, most commonly hypertension, which may have generated independent effects on brain morphology that resulted in reduced GM concentrations. In this study, covariates such as the magnetic strength of the scanner (1.5 T versus 3 T) did not yield any significant effects.

Structural neuroimaging changes associated with OSA have been confirmed recently using modern magnetic resonance techniques, such as VBM for GM or DTI for white matter, although conventional MRI, such as T2-weighted imaging, usually reveals no signs of abnormality. However, the region-of-interest (ROI) method can be applied to the detection of neuroanatomical differences via high-resolution T1-weighted MRI.[88] Nevertheless, the ROI method could be problematic because it is time consuming, labor dependent, and exhibits intrarater and interrater variability. Unlike the ROI method, VBM is an automatic and unbiased imaging analytic method for detecting whole-brain differences.[89] Although the studies evaluated here used the same VBM method, the detailed processes used were different (e.g., the SPM version, modulated or unmodulated, grand mean scaling, absolute or relative thresholding, and study subjects);[25] thus, the VBM results may be inconsistent. These inconsistencies may also be due to discrepancies in the data-analysis procedures used.[90] The unified segmentation technique was based on SPM5, instead of the optimized SPM2 method. Regarding statistical significance (P values), FDR, and family-wise error, these methods provide more stringent statistical thresholds compared with the uncorrected thresholds used commonly.[91] This explains why usually fewer GM foci were reported in the articles that used techniques via corrections for multiple comparisons, such as FDR.

CBMA approaches use published activation peaks that have been reported in standardized coordinate spaces (i.e., activation foci), rather than raw images, as their input. The most commonly used CBMA, method, ALE, is used typically to identify concordance across functional imaging studies of a specific cognitive process, or to compare activity between processes or populations. In addition, it has been used to synthesize VBM results[92] or in functional connectivity analyses.[38] ALE uses gaussian probability density distributions to model the uncertainty of trying to localize activation foci. The voxelwise union of these distributions yields the ALE value, which is an estimate of the likelihood that at least one of the foci in a dataset is truly located at a given voxel. The latest version of the ALE software overcomes several drawbacks inherent to the original version, such as the need to set the full width at half maximum value manually and to use anatomical uninformed analysis space and its fixed-effects inference. Consequently, increased specificity of the results occurs without any loss in the sensitivity of the original approach.[53] Further, CBMA only uses reported peak activations; thus, a large amount of spatial information from the original statistical parametric images is discarded. An ALE meta-analysis is only designed to answer the question: "if there are significant response observed across studies, where do they converge in space?" Therefore, the analysis cannot account for papers reporting no significant responses. Others have proposed that image-based meta-analyses provide more information than do CBMA methods. However, a recent comparison of image- and coordinate-based meta-analyses revealed the presence of a good agreement between meta-analyses based on full statistical contrast images and reduced 3D coordinates. Given this evaluation and the difficulties associated with obtaining full image data from a sufficient amount of published experiments, a coordinate-based approach, such as ALE, appears to represent the most practical tool for conducting meta-analyses of neuroimaging data.[93]

Our ALE analysis of VBM study results confirmed that GM reductions in a network of frontal, temporal, limbic, and cerebellar regions are among the most frequently reported in patients with OSA, and that their precise nature (i.e., volume reduction) varies across brain regions, which is consistent with a heterogeneous pathological process. Further examination of how differences in brain morphology affect VBM results, and how these changes relate to underlying neuropathological changes, will be necessary. There is some evidence to suggest frontal/temporal gyrus involvement, but that it is not statistically significant and further research is necessary due to the limited number of foci for those two clusters.

Limitations

The meta-analysis described here had certain limitations. First, the application of formal meta-analytic methods to observational studies has been controversial because the bias inherent to the study design may distort the strength of associations within the data.[46] However, confounding is not likely after controlling the demographic characteristics of subjects. We believe that bias is unlikely because OSA was confirmed by

a diagnostic test with homogeneous criteria. That detection bias is also unlikely; because VBM is a wholly automated computer-calculating process, the reviewers would be blind in the process of calculation. In addition, the literature authors did not report any covariate regressors in the neuroimaging models. The latent effect on heterogeneity of OSA is mostly due to menopause, according to literature. The reported mean age of cases and controls of most included studies is below 51, latent effects are therefore unlikely. Second, the studies included in our meta-analysis varied regarding inclusion and exclusion criteria. The heterogeneity of the methodologies used in the VBM studies included, such as different preprocessing protocols (traditional or optimized), smoothing kernels, and statistical thresholding methods, may have yielded an inappropriate combination of results across studies. Third, a publication bias appears to exist regarding smaller gray literature findings or unpublished studies. However, we believe this did not happen in our case because MRI scans are rather expensive. The authors will make efforts to publish their results, even if negative, like those of O'Donoghue et al.[36]

CONCLUSION

Using the ALE method of meta-analysis and by performing whole-brain VBM studies, we identified consistent GM reductions in patients with OSA, specifically in the bilateral hippocampus and less-convincing right superior frontal and left middle temporal lobes. These changes may be related to the neurocognitive processing abnormalities that are common in populations of patients with OSA.

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DISCLOSURE STATEMENT

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