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Original Article

Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis

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ABSTRACT

Objectives: Obstructive sleep apnea (OSA) is a disease with high prevalence, which reportedly influences our eyes, brain, cardiovascular system and endocrine metabolism system. Much of these symptoms are thought to be associated with damage to the brain. However, the basic neural pathophysiologic mechanism underlying these deficits is unclear. In this study, we investigate the specific and common neurostructural/functional abnormalities in OSA patients comparing with healthy people by conducting separate and multimodal meta-analysis of structural and functional magnetic resonance imaging studies.
Method: We search data from the original studies, extract height, coordinates of the peaks of the reported volumetric abnormalities, and recreate a map of the effect sizes of the differences between patients and controls. We use the anisotropic effect-size version of Signed Differential Mapping (AES-SDM) to clarify the robust regions in our brain when suffering from OSA.
Result: We find shared changes in the orbital frontal cortex (OFC), which showed both decreased gray matter volume (GMV) and functional response in OSA patients; as well as GMV of the bilateral anterior cingulate/paracingulate gyri (ACC/ApCC) and hippocampus/parahippocompalgyrus (Hippo/PHG), the orbital frontal cortex (OFC) and Left cerebellum VI decrease. The dorsolateral prefrontal cortex (DLPFC) exhibited hypoactivation relative to controls, whereas the insula showed hyperactivation.
Conclusion: We demonstrated the significant alterations of brain structural and functional response in OSA patients. These changes give us a description about underlying neural alterations in OSA patients and may explain the psychic disorders, memory deficits, cardiovascular abnormalities and endocrine metabolism system problems, suggesting the early diagnose and treatment.

1. Introduction

Obstructive sleep apnea (OSA) is a disease characterized by upper airway narrowing during sleep causing airflow reduction either partially or completely [1,2]. OSA is becoming increasingly common throughout the world due to the rising prevalence of obesity [1,2]. Epidemiological data suggest that the prevalence of OSA in the United States (USA) has increased by 14–55% since the early 1990s. Similar prevalence has been noted in other countries and specific ethnic groups globally, with a clear overall male preponderance until menopause age in women [3–9]. There are numerous consequences resulting from airflow reduction during sleep, such as daytime sleepiness occurred, impairing quality of life, causing traffic accidents, organ damage and economic burden. OSA is reported to have influences on many parts of the body (eg, eyes [1], brain, cardiovascular system [10–12], endocrine metabolism system [13,14] etc.). Currently, disruption of sleep physiology by OSA is an underappreciated factor, which, together with hypoxemia and other already recognized factors, might further aggravate age-related memory deficits [1,3]. Clinically, this dynamic interplay also underscores many subjective and objective cognitive as well as emotional complaints in some patients [3,15–17]. Persistent deficits, even after multi-level surgical or continuous positive airway pressure (CPAP) treatment in some patients, highlight early detection of the central nerve system (CNS) sequelae in OSA, which is essential for appropriate treatment given before irreversible brain atrophic and metabolic changes [18,19]. However, the basic neural pathophysiologic mechanism underlying these deficits is unclear.

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Over the past three decades, many studies have been conducted to detect neuro-structural/functional alterations underlying above-mentioned clinical manifestations through magnetic resonance imaging (MRI). For example, the voxel-based morphometry (VBM) was used measuring structural changes of brain, while task functional MRI (fMRI) and resting-state fMRI (rs-fMRI) has been used to evaluate the functional changes. Using VBM, which conducted the measurement of brain tissues (mostly gray matter), diverse regions of which gray matter volume differ from healthy people have been reported. Some studies indicated gray matter loss in the bilateral prefrontal cortex, bilateral inferior parietal gyrus and right temporal cortex [20]. While another reported gray matter volume decreasing in left hippocampus (entorhinal cortex) [21]. Alternately, there are some studies which showed no difference between OSA patients and controls [22,23]. In regards to fMRI, several studies indicate brain tissues signal intensities increasing in the left inferior parietal lobe, left precentral gyrus, bilateral anterior superior temporal gyrus, left frontal cortex, etc. [24]. Yet, others showed brain activation decrease in cingulate, frontal and parietal regions [25]. Thus, these findings bear inconsistencies.

The reason for this inconsistency might be associated with following factors. First, structural and functional measurements may lead to different outcomes. Second, even though the same modal, heterogeneities exist in several key aspects that differed in between-study patient groups such as sample size, mean age, body mass index (BMI), gender ratio, etc. To work out these problems and figure out significant difference between OSA patients and healthy people, an effective method is urgently needed. Coordinate based meta-analytic method has been proposed as a powerful methodology to obtain a general view of distributed findings in neuroimaging studies [26]. It also has additional strength that is using multimodal examination to detect potential convergence between structural and functional brain abnormalities [27].

Our aim is to address the brain changes in OSA patients; therefore, we will (1) conduct meta-analysis in structural and functional studies separately, and (2) undertake multimodal meta-analysis of structural and functional studies to detect converging findings that may be indicated as important brain nodes via different neuroimaging modalities. In addition, to evaluate whether there are some clinical characteristics that contribute to OSA, we will conduct meta-regression analyses. We expect to find brain alterations through these works, which may give us the answer of pathophysiologic changes underlying some clinical manifestations.

2. Method

2.1. Search strategies and inclusion criteria

A search for literature was performed on the PubMed, Science Direct, Medline, Embase and Web of Science databases from January 2000 to March 2018. The following key words were used: “obstructive sleep apnea”, “OSA”, “voxel-based morphometry”, “VBM”, “functional magnetic resonance imaging” and“fMRI”. We checked the reference lists of every study in order to find potential studies that had not been identified from internet searching. To qualify for the inclusion, the following criteria were used to extract studies: (1) only peer-reviewed cross-sectional studies were included; (2) the OSA patients included in these researches should be identified through apnea hypopnea index (AHI) and should not have another type of sleep disorder; (3) the studies should perform either fMRI or VBM imaging; (4) OSA patients should be compared with healthy controls; and (5) articles should report whole-brain gray matter alterations or functional changes in Montreal Neurological Institute (MNI) or Talairach stereotactic space coordinates (x, y, z). If the studies did not give the results or the coordinates, we contacted the authors to request the necessary information.

We followed the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) guidelines [28] and the study selection procedures are summarized in Fig. 1. Two authors conducted the above-mentioned processes independently.

2.2. Standard meta-analyses of structural and functional abnormalities

First, separate voxel-based meta-analyses of regional GMV and functional brain abnormalities were conducted with the anisotropic effect-size version of signed differential mapping (ES-SDM) (http://www.sdmproject.com). ES-SDM is a statistical technique for meta-analyzing studies on differences in brain activity or structure which used neuroimaging techniques such as fMRI and VBM, which assigns effect size (standardized mean for one-sample designs or standardized mean difference for two-sample designs) to each voxel, referred to as Hedge's d (or g) at the sample level [26,29,30]. For each study, we extracted the height, coordinate of the peaks of the reported volumetric abnormalities, and recreated a map of the effect sizes of the differences between patients and controls. After, we conducted standard random-effects that were variance-weighted. We used the default ES-SDM kernel size and thresholds (FWHM = 20 mm, voxel P = 0.005), and cluster size > 100 [26].

Two authors separately extracted the data that needed to conduct the meta-analysis.

2.3. Multimodal analysis

Our intent was to try to summarize structural and functional findings in several brain regions then combine both the structural changes and functional alterations in a single map. We should note that it could be the case when a structural damage in a given cortical region produces a functional alteration in another brain region. The aim of this study was to localize those brain regions that display both structural and functional abnormalities in OSA. It could be, for example, that some patients present structural but not functional impairments, while other patients show functional but not structural impairments. In that case, the meta-analysis should detect both structural and functional impairments, and thus signal the region as multi-modally-affected. This approach is thoroughly described in Radua et al., [27] which has been fully validated in several studies and has been already used to meta-analyze studies on several neuropsychiatric disorders [31–33].

2.4. Meta-regression analysis

Several demographic and clinical factors including mean age, BMI, AHI, and Epworth Sleepiness Scale (ESS) were used as regressors in the meta-regression to explore whether they are associated with brain alterations in OSA patients [29].

2.5. Sensitivity meta-analysis

Whole-brain jack-knife sensitivity analysis was conducted to test the replicability of the results, which repeated the main analysis n times (n = the number of total datasets) and discarded a study each time, to determine whether the results remained significant.

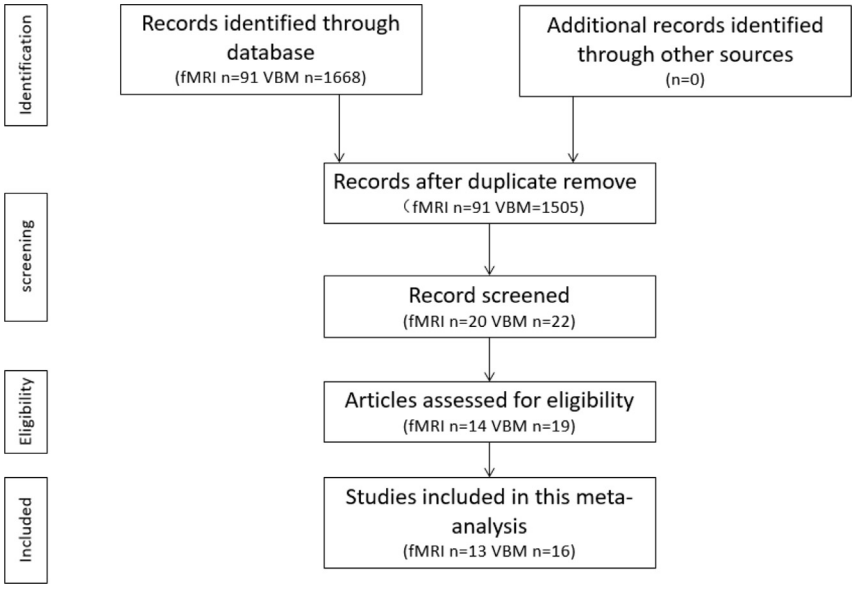


Fig. 1. Flowchart of the identification of the literature. Abbreviations: VBM = voxel-based morphometry; fMRI = magnetic resonance imaging.

3. Results

3.1. Included studies and sample characteristics

The records initially identified through database were 1759(fMRI, $n = 91$; VBM, $n = 1668$). After duplicate removing and full article assessment, 24 researches (fMRI, $n = 13$; VBM, $n = 16$) met our criteria. These studies contained 678 patients with OSA (567 males and 111 females) and 633 healthy controls (558 males and 75 females) (Tables 1 and 2). And the clinical characteristics (age, BMI) of these studies showed no differences (Fig. 4).

3.2. Meta-analysis

3.2.1. Changes in regional gray matter volume

Patients with OSA showed large and robust decreases of GMV that included the bilateral anterior cingulate/paracingulate gyri (ACC/ApCC) and hippocampus/parahippocompalgyrus (Hippo/PHG), the orbital frontal cortex (OFC) and Left cerebellum VI (Fig. 2A, Table 3).

3.2.2. Changes in regional brain response

Patients with OSA showed functional abnormalities in several regions. In the dorsolateral prefrontal cortex (DLPFC) there was hypoactivation relative to controls, whereas in the insula showing hyperactivation (Fig. 2B, Table 3).

3.3. Multimodal analysis of gray matter volume and brain response

Regions of OFC exhibited hypoactivation and reduced GMV. However, the Cerebellum VI, ACC/ApCC and amygdala/hippo showed hyperactivation with GMV reduction (Fig. 2C, Table 3).

3.4. Meta-regression analysis

The GMV changes in the bilateral ACC/ApCC was positively associated with BMI among patients with OSA ($r = 0.75$, permutation-derived $p < 0.0001$), and the rest factors such as AHI, ODI, and ESS were found no relationship with brain structural alterations (Fig. 3).

3.5. Sensitivity analysis

The whole-brain jack-knife sensitivity analysis was conducted and showed GMV reductions in the bilateral ACC/ApCC and OFC were highly reliable and preserved throughout all 16 dataset combinations. The GMV changes in the Hippo/PHG and Left cerebellum VI were preserved in 15 dataset. The brain functional response in the insula was preserved in all 13 dataset whilst the results in the DLPFC were repeated throughout 12 dataset. Meanwhile, other clusters were not repeated in several combinations.

4. Discussion

To our knowledge, this is the first multimodal neuroimaging meta-analytic study that detects shared and contrasting GMV and functional brain alterations; investigating more consistent regional abnormalities that may underlie neural mechanism of OSA. Shared changes were found in the OFC which showed both decreased GMV and functional response. Contrasting abnormalities were also demonstrated, however, in the cerebellum VI, ACC/ApCC, and the amygdala/hippo, with GM atrophy but hyperactivation.

The most robust decreases in GMV and brain functional response were demonstrated in the OFC. OFC is a crucial structure in the brain function that facilitates cognitive functions and the integration of cognitive and emotional processes and guide the decision-making [34]. Previously, it was reported that the GM atrophy of the OFC may result from low sleep quality and hypoxia during sleep, leading to the cognitive deficits and emotional problems in patients with OSA [35]. In this study, we found in the OFC there were both GMV atrophy and hypoactivation. This may indicate that OFC is a vulnerable and sensitive region in the brain. In one of our included studies, brain structure of OSA patients was measured before and after CPAP treatment. As a result, the structural brain abnormalities were found changeable with treatment, suggesting that even the negative neurologic effects of hypoxemia may be reversed with consistent and thorough treatment [21]. Since we found the OFC has both structural and functional damages, it is noteworthy to suggest early treatment with CPAP to avoid further damage of OFC.

In addition, we found regions in the ACC/ApCC, and Cerebellum VI, amygdala have the gray matter atrophy but hyper-activation.

Table 1
Demographic and clinical characteristics in studies that measure the structural changes.

	Study	OSA											HC					Main findings
		N	Age (years)		Male		BMI		ESS		AHI		*N*	Age (years)		Male		
			Mean	SD	*N*	%	Mean	SD	Mean	SD	Mean	SD		Mean	SD	*N*	%	
1	Baril et al., 2017 [67]	59	65.8	5.9	14	0.24	26.50	3.10	7.20	4.80	9.20	2.50	12	62.30	4.70	2	0.17	No significant differences
2	Fatouleh et al., 2014 [61]	17	55	12.4	15	0.88	31.00	2.00	9.00	1.00	36.00	4.00	15	53.00	11.60	12	0.80	GMV ↑ in the medulla/pons and cerebellum, bilateral insula, primary motor cortex, left hippocampus, left premotor cortex
3	Canessa et al., 2011 [21]	17	44	7.63	17	1.00	31.24	4.35	11.94	5.47	55.83	19.08	15	42.15	6.64	15	1.00	GMV ↓ in left hippocampus, left posterior parietal cortex and right superior frontal gyrus
4	Joo et al., 2010 [22]	36	44.7	6.7	26	0.72	26.00	2.70	10.40	3.70	52.50	21.70	31	44.80	5.40	31	1.00	GMV ↓ in left gyrus rectus, bilateral SFG, left precentral gyrus, bilateral frontomarginal gyri, bilateral ACC, right insular gyrus, bilateral caudate nuclei, bilateral thalami, bilateral amygdalo-hippocampi, bilateral ITG, and bilateral quadrangular and biventer lobules in the cerebellum
5	Kim et al., 2016 [44]	21	49.8	7.7	21	1.00	27.40	3.80	13.90	4.80	60.40	23.50	59	44.3	10.1	59	1.00	GMV ↓ in bilateral lateral prefrontal, central, and ACC/ApCC; left medial prefrontal, right orbitofrontal, left superior temporal, right middle/inferior temporal, right insular, left hippocampal, right parahippocampal, and right lateral occipital cortices, and the left cuneus; thalamus, cerebellum
6	Lin et al., 2016 [18]	21	40.14	10.8	18	0.86	26.24	3.40	NA	NA	38.77	19.91	15	39.8	9.53	11	0.73	GMV ↑ in right insular; GMV ↓ in left anterior cingulate gyrus
7	Morrell et al., 2003 [23]	7	NA	NA	7	1.00	NA	NA	14.00	NA	28.00	NA	7	NA	NA	7	1.00	No significant differences
8	Morrell et al., 2006 [68]	22	51.8	15.4	22	1.00	32.40	5.60	13.30	4.20	53.10	14.00	17	53.1	14	17	1.00	GMV ↓ in left hippocampus, bilateral parahippocampus
9	Morrell et al., 2010 [45]	60	47.3	NA	57	0.95	32.00	NA	13.20	NA	55.00	NA	60	46.1	NA	55	0.92	GMV ↓ in right middle temporal gyrus and left cerebellum
10	Philby et al., 2017 [69]	16	6.9	2.8	9	0.56	30.00	NA	NA	NA	NA	NA	9	6.8	2.2	5	0.56	GMV ↓ in frontal and prefrontal cortices, parietal cortices, temporal lobe, and brainstem
11	Taylor et al., 2017 [70]	22	59	2	17	0.77	31.00	1.00	7.00	1.00	31.00	4.00	19	59	2	13	0.68	GMV ↑ in bilateral thalamic regions
12	Torelli et al., 2011 [71]	16	55.8	6.7	13	0.81	31.70	4.40	8.50	4.50	52.50	26.00	14	57.6	5.2	9	0.64	GMV ↓ in right hippocampus
13	Yaouhi et al., 2009 [20]	16	54.75	5.71	15	0.94	NA	NA	12.50	4.50	38.31	14.33	14	52.71	7	13	0.93	GMV ↓ in bilateral prefrontal cortex, bilateral IPG, right temporal cortex, occipital cortex right thalamus, some of the basal ganglia, right hippocampus and parahippocampal gyrus and cerebellum
14	Yılmaz et al., 2016 [72]	28	NA	NA	19	0.68	32.50	NA	11.50	NA	30.80	NA	15	NA	NA	7	0.47	No significant differences
15	Zhang et al., 2013 [73]	24	44.6	7.4	24	1.00	29.80	4.40	15.20	7.30	54.70	19.90	21	40.6	11.4	21	1.00	GMV ↓ in left medial prefrontal cortex and left posterior inferior frontal gyrus
16	O'Donoghue et al., 2005 [74]	27	45.7	10.1	27	1.00	33.20	4.70	13.10	3.90	71.70	17.00	24	43.3	9.4	24	1.00	No significant differences

Abbreviations: OSA = obstructive sleep apnea, *N* = number, BMI = body mass index, ESS = Epworth sleepiness scale, AHI = apnea-hypopnea index, HC = healthy control, GMV = gray matter volume, MFG = middle frontal gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, IPG = inferior parietal gyrus, SFG = superior frontal gyri, ACC = anterior cingulate/paracingulate gyri.

Table 2
Demographic and clinical characteristics in studies that measure the functional changes.

	Study	OSA											HC					Main findings
		N	Age (years)		Male		BMI		ESS		AHI		*N*	Age (years)		Male		
			Mean	SD	*N*	%	Mean	SD	Mean	SD	Mean	SD		Mean	SD	*N*	%	
1	Ayalon et al., 2006 [46]	12	44.2	11.9	11	0.92	31.30	5.90	NA	NA	NA	NA	12	43	9.1	11	0.92	Activation ↑ in right IFG, bilateral MFG, bilateral cingulate gyrus, and bilateral junction of the inferior parietal and superior temporal lobes; BOLD response ↑ in bilateral thalamic nuclei and bilateral cerebellar regions
2	Ayalon et al., 2009 [25]	14	45.6	11.7	13	0.93	30.60	5.70	NA	NA	NA	NA	14	43.6	8.6	13	0.93	Activation ↓ in cingulate, frontal, and parietal regions
3	Fatouleh et al., 2014 [61]	17	55	12.4	15	0.88	31.00	2.00	9.00	1.00	36.00	4.00	15	53.00	11.60	12	0.80	Activation ↑ in left and right dlPFC, medial PFC (mPFC), dorsal precuneus, anterior cingulate cortex (ACC), retrosplenial cortex and caudate nucleus
4	Harper et al., 2003 [56]	10	46	12	10	1.00	31.00	6.00	NA	NA	38.00	27.00	16	47	10	16	1.00	Activation ↑ in quadrangular lobe of the cerebellar cortex, anterior insula and medial frontal cortex, and anterior and posterior cingulate gyri; Activation ↓ in ventral thalamus, ventral anterior insula, and regions within the hippocampus
5	Henderson et al., 2003 [24]	8	44	11.3	8	1.00	31.00	2.00	NA	NA	NA	NA	15	45	11.6	15	1.00	Activation ↑ in left inferior parietal lobe, left precentral gyrus, bilateral anterior STG, left frontal cortex, confined to the superior frontal gyrus
6	Macey et al., 2003 [75]	9	45	12	9	1.00	31.00	6.00	NA	NA	40.00	28.00	16	47	10	16	1.00	Activation ↓ in the right insula, the MFG; Activation ↑ in right hippocampus, ventral midbrain
7	Macey et al., 2006 [76]	7	46	13.2	7	1.00	29.10	2.40	NA	NA	42.00	11.00	11	47	9.9	11	1.00	Activation ↓ in the caudate, putamen and globus pallidus, nucleus accumbens bilaterally, the claustrum and left insula; signal deficits in anterior cerebellar cortex and deep nuclei, including the fastigial nuclei
8	Prilipko et al., 2011 [77]	17	43.2	8.4	17	1.00	27.80	4.00	NA	NA	39.70	22.80	7	43.2	8.4	7	1.00	Activation ↑ left temporo-occipital area; Activation ↓ in bilateral parahippocampal regions, right insula, bilateral claustrum, left precentral gyrus, and right precuneus
9	Li et al., 2015 [78]	25	39.4	1.7	25	1.00	27.80	3.40	15.20	7.30	60.00	18.60	25	39.5	1.6	25	1.00	lower-ALFF in the cluster of the right precuneus and bilateral posterior cingulate gyrus; higher-ALFF area in the left inferior frontal gyrus
10	Li et al., 2016 [18]	40	39	8.1	40	1.00	27.80	3.50	12.00	4.00	56.50	19.00	40	38.8	11.2	40	1.00	Regional DC ↓ in left middle occipital gyrus, posterior cingulate cortex, left superior frontal gyrus, and bilateral inferior parietal lobule; DC ↑ in the right orbital frontal cortex, bilateral cerebellum posterior lobes, and the putamen, the hippocampus, and the inferior temporal gyrus
11	Zhang et al., 2013 [73]	24	44.6	7.4	24	1.00	29.80	4.40	15.20	7.30	54.70	19.90	21	40.6	11.4	21	1.00	RsFC ↓ in medial prefrontal cortex and left dorsolateral prefrontal cortex; rsFC ↑ in right posterior cingulate cortex
12	Park.B et al., 2016 [79]	67	48	9.2	51	0.76	30.70	6.00	10.00	4.90	35.60	23.50	75	47.1	9.3	56	0.75	FC ↓ in the left insula to the bilateral MPFC and OFG, bilateral SFG, bilateral MFG, right IFG, bilateral SMA, left MCC, left MTG, bilateral thalamus, right posterior hippocampus, bilateral calcarine, and bilateral tonsil, right crus II, and left vermis of the cerebellum
13	Santarnecchi et al., 2013 [80]	19	43.2	8	16	0.84	30.3	2	14.4	3	36.3	13	19	41	6	14	0.74	Regional homogeneity ↓ in the Right superior parietal lobule, precuneus, inferior parietal lobule, middle occipital gyrus; Left superior parietal lobule, precuneus, IFG,MFG, parahippocampal gyrus; regional homogeneity ↑ Right MCC, PCC, Left ACC, thalamus, STG, MTG

Abbreviations: OSA = obstructive sleep apnea, *N* = number, BMI = body mass index, ESS = Epworth sleepiness scale, AHI = apnea-hypopnea index, HC = healthy control, GMV = gray matter volume, MFG = middle frontal gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, IPG = inferior parietal gyrus, SFG = superior frontal gyri, PFC = dorsolateral prefrontal cortex, MCC = mid-cingulate cortex, MTG = middle temporal gyrus, DC = degree centrality, OFG = orbital frontal gyrus, FC = functional connectivity, SFG = superior frontal gyrus.

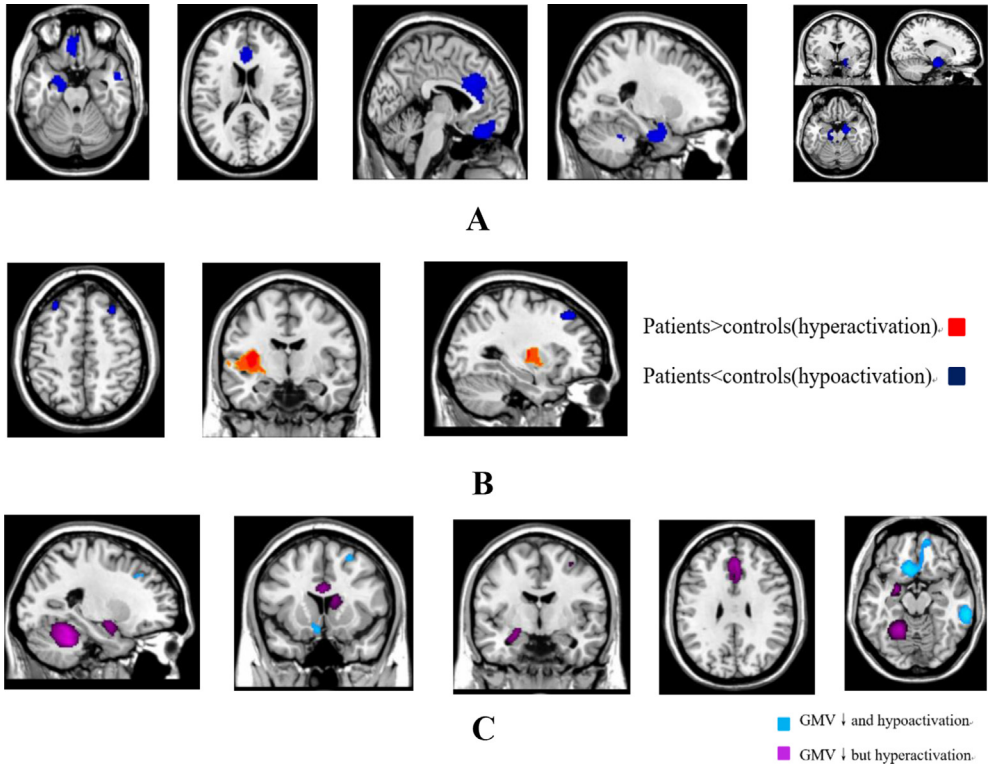


Fig. 2. The brain regions showing difference in patients with OSA compared with that in healthy controls: (A) the reduced gray matter in patients with OSA; (B) the regions with functional alteration in OSA; (C) results of multimodal analysis.

The ACC is crucial for integrating cognitive and emotional processes in support of goal-directed behavior. The previous studies indicated that alterations in ACC are related to psychotic disorders [36] and through examining the connectivity of ACC with amygdala again pointing to a role of these alterations in emotional regulation [37]. In addition, research clearly establishes that the ACC is involved in central cardiovascular and respiratory control [38,39]. A recent AES-SDM meta-analysis confirmed ACC GMV reductions in subjects presenting OSA, suggesting that the general salience and emotional regulation network is abnormal in OSA [35]. In our meta-analysis, we detected not only gray matter volume but also brain functional response of ACC, only to find they were not concordant. OSA patients have the ACC volume reduction compared with controls but they exhibited hyper-activation while the healthy controls are normal. To interpret the mechanistic of our findings, we speculate there are several conditions. First, damage of ACC volume appeared before functional alteration accompanied by a compensatory hyper-functionality of the remaining gray matter. Because of these hyper-activation compensatory subregions, the whole ACC seems have a high brain functional response. Second, hypoxemia, low brain blood flow, or other factors which are characterized in OSA lead to a hyper-activation in ACC due to some sort of mechanism. The increased activation required more blood and oxygen, result in relative ischemia and hypoxia. Whatever hypothesis it is, numerous studies revealed the correlation between ACC alteration and OSA. Moreover, our study provided a new perspective to detect the relationship among ACC structure, function, and OSA manifestations.

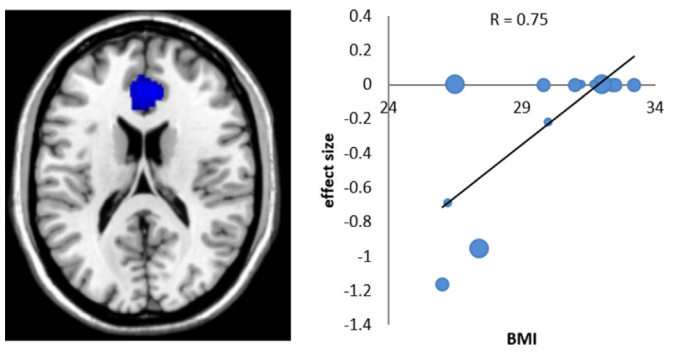
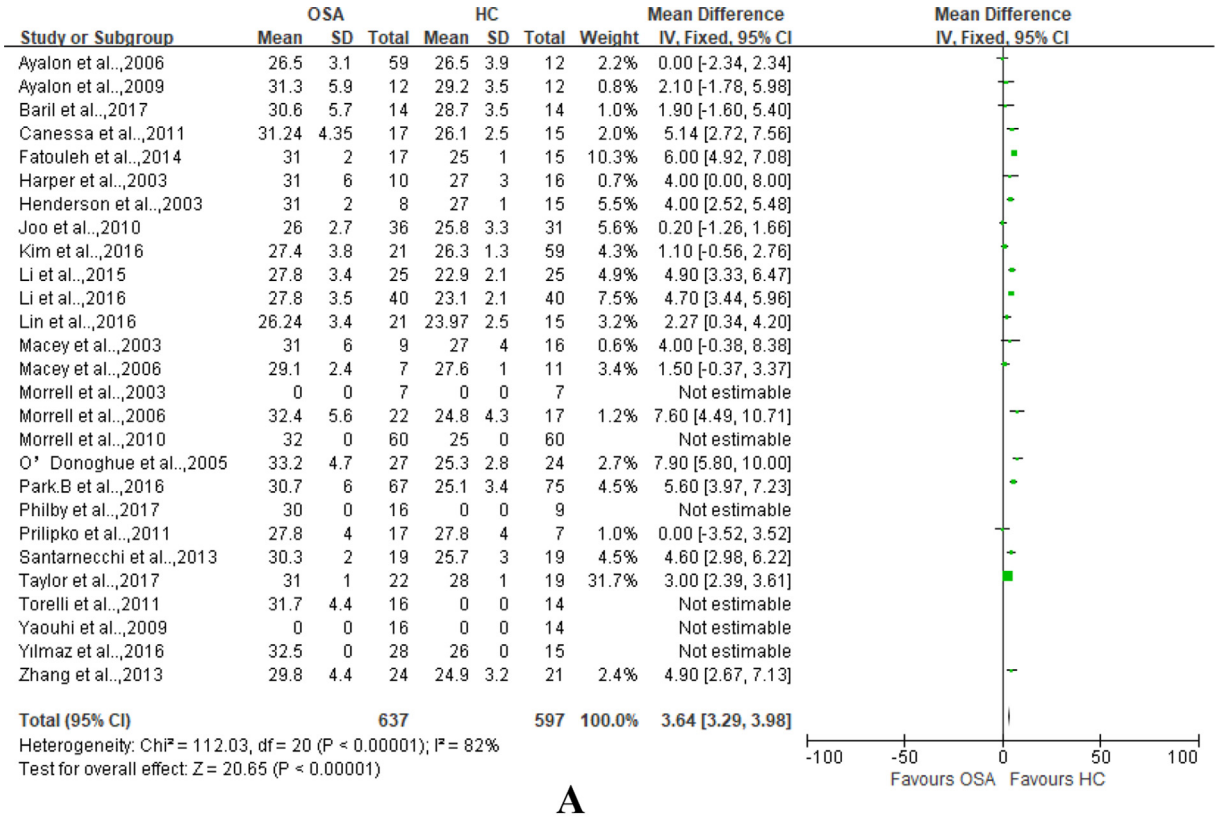


Fig. 3. Meta-regression result.

Our meta-regression found the GMV changes in the bilateral ACC/ApCC was positively associated with BMI among patients with OSA. In the previous study, obese (BMI > 30) subjects exhibited GM atrophy in the ACG and OFC compared with normal-BMI subjects [40]. In our study, however, with the increasing of BMI, ACC atrophy become less remarkable. This seems paradoxical because OSA is very relevant to obesity. Theoretically, patients with higher BMI might present severe GMV atrophy [1]. However, this is to an extent sensible since studies included in our meta-analysis contain patients with a high BMI (ranging from 26.5 to 33.2) but lacking of normal BMI patients. Thus, it needs to expand sample size bringing into lower BMI patients to minimize the statistic bias.

We also found Cerebellum VI and amygdala have the gray matter atrophy but hyper-activation. Cerebellum is traditionally believed as a module in motor control systems. It also connected to numerous brain regions, including cortical association areas and limbic system. Studies proved that cerebellum is involved in respiratory modulation [41], sensorimotor activities, motor learning, emotional functions [42], and even social functions [43]. Many studies have reported decreased GMV and increased brain functional response of the cerebellum in patients with OSA compared with those in healthy controls [20,22,44–47]. Reduction in



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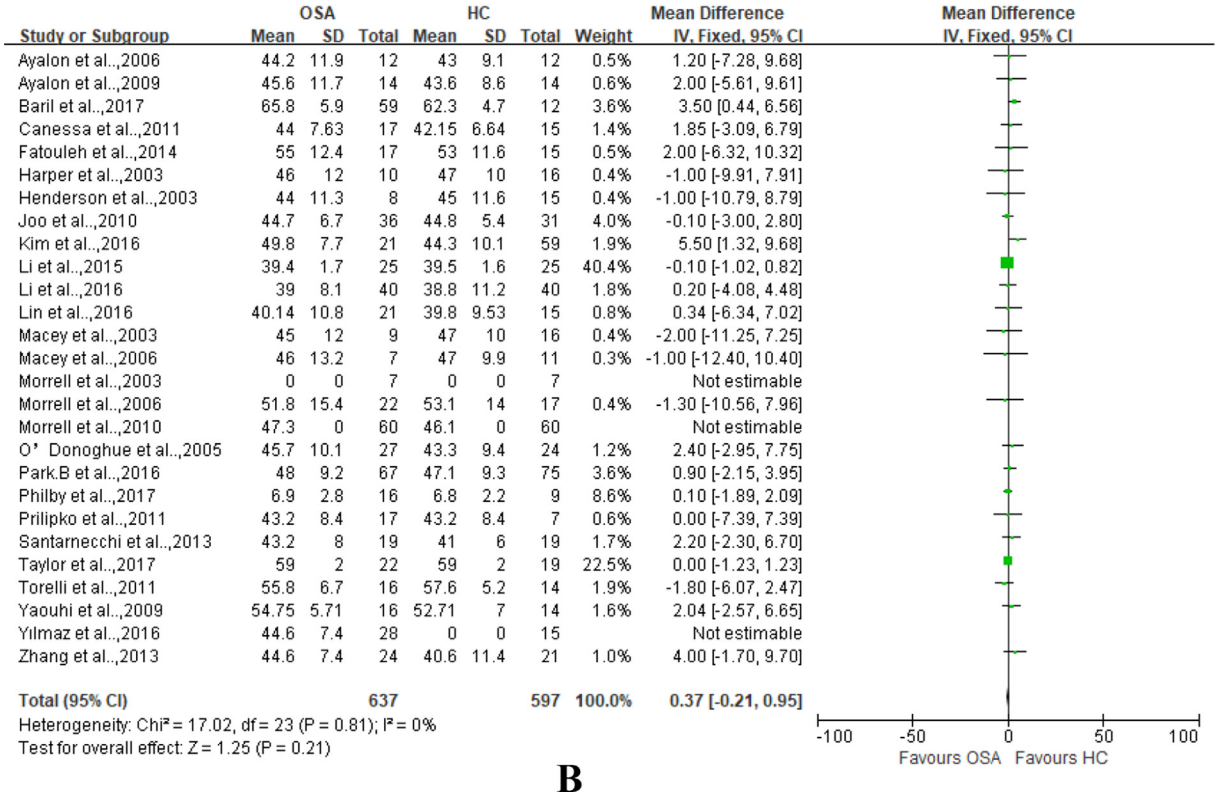

B

Fig. 4. Comparison of the age and BMI in studies included in this meta-analysis: (A) BMI, (B) age.

Table 3
Meta-analysis results of regional difference in GMV and functional activation.

Region	Local maximum			Cluster		Jackknife sensitivity analysis
	MNI coordinates	SDM-Z	Uncorrected *P*	No. of voxels	Breakdown (No. of voxels)	
Sample from VBM						
OSA < HC						
ACC	−2,42,12	−2.506	0.000202835	1071	L-ACC (487) R-ACC (277) L-SFG (145)	16/16
OFC	−2,34,−24	−2.54	0.000169814	1014	Left gyrus rectus (377) Corpus callosum (164) Right gyrus rectus (124) L-SFG (163) R-SFG (196)	16/16
Hippo/PHG	−22,−12,−22	−2.211	0.001076043	162	L-PG (59) Left hippocampus (23)	15/16
Left cerebellum VI	−24,−46,−30	−2.019	0.002697527	48	Middle cerebellar peduncles (22) Left cerebellum, hemispheric lobule VIt (18)	15/16
Sample from fMRI						
OSA > HC						
Insula	−34,−16,10	3.079	~0	1445	Left insula (404) Left superior temporal gyrus (302) Left rolandic operculum (138) Left heschl gyrus (127)	12/13
OSA < HC						
R-SFG	30,26,52	−2.126	0.000696719	102	Right superior frontal gyrus (74) Right middle frontal gyrus (23)	10/13
L-MFG	−28,30,46	−2.132	0.000665724	108	Left middle frontal gyrus (86)	10/13

Abbreviations: OSA = obstructive sleep apnea, MNI = Montreal Neurological Institute, HC = healthy control, OFC = orbital frontal cortex, ACC = anterior cingulate cortex, Hippo/PHG = hippocampus/parahippocompalgyrus, MFG = middle frontal gyrus, SFG = superior temporal gyrus, L = left, R = right.

hippocampal volume has been observed in sleep disorders in association with impairments in memory disturbances [48]. Hippocampus, as part of the limbic system, plays a critical role in binding item and contextual information together and processing the relationships between individual items [49]. Patients with damage limited to the hippocampus appear to show a reduction in source memory and spatial memory, particularly for navigation [50–52]. It has been reported that bilateral dorsal hippocampal injury could break the spatial memory in rats even though the lesion size is as little as 30% of the total hippocampal volume [53]. In addition, the hippocampus contains neurons which control the respiratory and cardiac cycles, and electrical stimulation within the hippocampus evokes dramatic changes in blood pressure [54]. In addition, direct stimulation of the hippocampus has been reported evoking marked decreases in blood pressure and heart rate [55]. In one previous study, subjects were explored to cold pressor, during this test OSA and control subjects showed significant differences in heart rate and respiratory responses [56]. The mechanistic interpretation of our findings is highly speculative. We believe that functional alteration in hippocampus may be the key reason of memory deficits or cardiovascular/respiratory disease and structural changes could just be a result or inducement in OSA patients. If the

Table 4
Meta-analysis results of regional difference in multimodal analysis.

Region	Local maximum			Cluster	
	MNI coordinates	SDM-Z	Uncorrected *P*	No. of voxels	Breakdown (No. of voxels)
Decreased both GM and brain activity					
Left gyrus rectus	−10,22,−22	2.672	~0	673	L-gyrus rectus (157) Corpus callosum (126) SFG (166) Striatum (71) Left olfactory cortex (47)
Right rolandic operculum	46,−14,18	1.886	~0	686	R-rolandic operculum (330) R-heschl gyrus (132) R-STG (115) R-insula (51)
Right cerebellum	20,−40,−48	2.188	~0	391	R-cerebellum (235)
R-ITG	64,−34,−18	2.195	~0	356	R-ITG (345)
Decreased GM but increased brain activity					
Middle cerebellar peduncles	−20,−48,−30	2.819	~0	1385	L-cerebellum, hemispheric lobule VI (814) Middle cerebellar peduncles (231) L-fusiform gyrus (191)
ACC	6,28,26	2.245	~0	519	R-anterior cingulate/paracingulate gyri (150) L-superior frontal gyrus (73) L-anterior cingulate/paracingulate gyri (124)
Left amygdala	−24,−4,−14	1.706	~0	165	Left amygdala (88)

Abbreviations: MNI = Montreal Neurological Institute, GM = gray matter, ACC = anterior cingulate cortex, Hippo/PHG = hippocampus/parahippocompalgyrus, MFG = middle frontal gyrus, ITG = inferior temporal gyrus, SFG = superior temporal gyrus, STG = superior temporal gyrus, L = left, R = right.

functional abnormalities happened before the gray matter atrophy, it is significant to suggest early treatment of OSA in case an irreversible brain atrophy appear as we mentioned before. Furthermore, we found the right amygdala with decreased GMV but increased functional response. It has been shown that basolateral nucleus of amygdala is involved in spatial and motor learning [57]. Furthermore, facial emotions processing, emotional blunting and even aberrant sexual behaviors, as well as dysfunctional memory and olfactory processing are all associated with damage to amygdala [57,58]. Conversely, one meta-analysis which reported amygdala with functional and structural alteration which did not give us the shared or contrary results. In some way, our study may extend their findings since we have done the multimodal analysis. Thus, our study can explain the aberrant facial cues processing previously noted in children and may interpret other emotional blunting or sexual behaviors.

The interpretation of our findings about cerebellum and amygdala/hippocampus alterations is similar to ACC. In OSA patients, intermittent hypoxemia, hypercapnia, sleep fragment, and other factors may lead to the cerebellum and amygdala/hippocampus damages. We can assume that structure atrophy is the first manifestation, and then the remaining subregions become compensatory hyper-activation as a result, the high functional state further damage the remaining part by exhaustion. Therefore, our findings that structural and functional impairments in hippocampus extend previous reports of cerebellum alterations, pointing out damage in these regions may both contribute to recognition problems.

In this meta-analysis, we find the insula has a hyper-activation but no structural damages. The insula is a cortical structure connected with many areas of the cortex and limbic system, specifically the amygdala. It also integrates external sensory input with the limbic system and is integral to the awareness of the body's state [59]. Whilst the insula is reported plays a crucial role in emotional processing and structural and functional alterations in these areas that have been consistently demonstrated in a range of anxiety disorders [60]. The insula has been reported to be abnormal in OSA, exhibiting both significant GM atrophy [22,60] and enlargement [61]. We found insula with a hyper-activation but no structural changes, which may indicate that due to some unknown mechanism the brain response of insula becomes significantly high. As previously mentioned, in OSA, patients have a low reaction to external environment and may stay in a vulnerable condition. To avoid injury, our body makes an adaptive alteration and has a hyper-activation in the insula. As to the gray matter volume, we speculate that it is not a specific measurement since different study has different findings of GMV. These findings need more research to be demonstrated. Conversely, the DLPFC found hypoactivation but no structural changes. Additionally, the DLPFC is reported to be involved in a bottom-up system, which responds to unexpected stimuli in an involuntary, stimulus-driven exogenous manner and this network of regions is sometimes referred to as the Ventral Attention Network (VAN). The right DLPFC is found to be active only when reorienting to unexpected stimuli [62–64] Damages of DLPFC are associated with attention to exogenous stimulus. Moreover, it is reported that OSA patients are 2–13 times more likely to experience a driving-related traffic accident [65,66], the reason of which may be the damage of VAN system. Finally, the decreased brain function of DLPFC may explain that.

4.1. Future directions

Through our study, we find some significant results but there are still several challenges that need to be noted in the future exploration. First, some prior studies only included male subjects, which might overlook the potential difference between males and females. Future preliminary studies that detect female patients or directly compare male patients with female patients are needed. Second, patients with OSA are likely to be accompanied with cardiovascular diseases, respiratory diseases, or metabolism diseases as we mentioned, so how these comorbidities influence brain abnormalities in OSA is worthy of exploration. Third, clinically, patients often seek medical which may influence the brain structure and function. However, these information are scarce in most of our included studies. Thus, studies such as cohort research before and after treatment would be helpful to clarify the treatment effects.

5. Conclusion

This multimodal meta-analysis demonstrated the significant alterations of brain structural and functional response in OSA patients. Patients with OSA showed both decreased GMV and functional response in the OFC compared with healthy controls. While in the cerebellum VI, ACC/ApCC, and the amygdala/hippocampus, OSA patients exhibited GM atrophy but increased activity relative to controls. These changes give us a description about underlying neural alterations in OSA patients and may explain the psychic disorders, memory deficits, cardiovascular abnormalities and endocrine metabolism system problems; suggesting that early diagnosis and treatment are crucial.

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Conflict of interest

The authors have declared that no conflict of interests exist.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.025.

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