Published in final edited form as:

Depress Anxiety. 2009 ; 26(5): 480–491. doi:10.1002/da.20531.

Neural Alterations Associated with Anxiety Symptoms in >Obstructive Sleep Apnea Syndrome

Rajesh Kumar¹, Paul M. Macey^{2,4}, Rebecca L. Cross², Mary A. Woo², Frisca L. Yan-Go³,
and Ronald M. Harper^{1,4,*}

¹Department of Neurobiology, David Geffen School of Medicine at UCLA

²School of Nursing, University of California at Los Angeles, Los Angeles, CA 90095, USA

³Department of Neurology, David Geffen School of Medicine at UCLA

⁴Brain Research Institute, University of California at Los Angeles, Los Angeles, CA 90095, USA

Abstract

Background—Neuropsychological comorbidities, including anxiety symptoms, accompany obstructive sleep apnea (OSA); structural and functional brain alterations also occur in the syndrome. The objective was to determine if OSA patients expressing anxiety symptoms show injury in specific brain sites.

Methods—Magnetic resonance T2-relaxometry was performed in 46 OSA and 66 control subjects. Anxiety symptoms were evaluated using the Beck Anxiety Inventory (BAI); subjects with BAI scores > 9 were classified anxious. Whole-brain T2-relaxation maps were compared between anxious and non-anxious groups using analysis of covariance (covariates; age and gender).

Results—Sixteen OSA and seven control subjects showed anxiety symptoms, and 30 OSA and 59 controls were non-anxious. Significantly higher T2-relaxation values, indicating tissue injury, appeared in anxious OSA vs non-anxious OSA subjects in subgenu, anterior, and mid-cingulate, ventral medial prefrontal and bilateral insular cortices, hippocampus extending to amygdala, and temporal, and bilateral parietal cortices. Brain injury emerged in anxious OSA vs non-anxious controls in bilateral insular cortices, caudate nuclei, anterior fornix, anterior thalamus, internal capsule, mid-hippocampus, dorso-temporal, dorso-frontal, ventral medial prefrontal and parietal cortices.

Conclusions—Anxious OSA subjects showed injury in brain areas regulating emotion, with several regions lying outside structures affected by OSA alone, suggesting additional injurious processes in anxious OSA subjects.

Keywords

Sleep-disordered breathing; Intermittent hypoxia; Hippocampus; Amygdala; Fornix; Magnetic resonance imaging

*Correspondence to: Department of Neurobiology David Geffen School of Medicine at UCLA University of California at Los Angeles Los Angeles, CA 90095-1763, USA rharper@ucla.edu Tel: 310-825-5303 Fax: 310-825-2224 .

INTRODUCTION

Obstructive sleep apnea (OSA) patients show multiple physiological deficits and several neuropsychological comorbidities, including cognitive deficits and anxiety symptoms [1-3], the latter affecting 12-17% of adult OSA patients [4, 5]. The psychological symptoms may partially stem from daytime sleepiness or sleep deprivation accompanying the syndrome [6], but many deficits remain after apnea and arousal resolution [7, 8]. Since emotional deficits remain, sleep deprivation or repeated arousals are unlikely solely responsible for the psychological issues.

Routine magnetic resonance imaging (MRI) shows no obvious brain pathology in OSA subjects, except for white matter infarcts [9] or cerebellar injury [10]. Despite the absence of major gray matter injury, volumetric assessments show tissue loss in autonomic, motor, emotional, and cognitive areas [11, 12]. Gray matter volume loss differs between studies [11, 13], with outcomes likely dependent on patient selection criteria, statistical processing, syndrome intervention, and duration-of-condition issues [14]. Reduced brain metabolites, including N-acetylaspartate and choline appear in multiple regions in adult OSA [15, 16], and in the hippocampus and frontal cortex of pediatric OSA patients [17, 18]. Functional MRI deficits also emerge to autonomic and ventilatory challenges in regions of structural injury [19-22], indicating that the damage can alter neural processing within affected structures.

Brain structural injury, functional, and metabolic deficits in OSA occur in limbic regions classically associated with negative emotions, such as the amygdala, hippocampus, insular, and cingulate cortices [23, 24]. These sites help mediate emotional behaviors such as fear (amygdala, hippocampus) [24, 25] and dyspnea (insula, cingulate cortex) [26, 27]. However, the processes underlying the injury are unclear.

Magnetic resonance T2-relaxometry can evaluate white and gray matter injury, and assess free water content in tissue [28], a measure that increases with tissue injury, such as damage to myelin, axons, cell bodies, and membranes. Increased T2-relaxation values can result from sub-acute processes, such as vasogenic edema after hypoxia-ischemia [29], as well as chronic pathologic conditions, including long-lasting ischemia [30], gliosis [31], and demyelination [32]. T2-relaxometry has identified tissue changes, not visible on routine MRI, in several brain conditions [33-35], and may be useful to evaluate the nature and extent of structural injury associated with anxiety in OSA subjects.

The aim was to determine whether brain regions showing structural deficits in OSA patients with anxiety symptoms differ from those without such symptoms.

MATERIALS AND METHODS

Subjects

Forty-six OSA (mean age $\pm$ SD: 46.8 ± 9.3 years; male: 36) and 66 control subjects (47.1 ± 8.9 years; male: 43) participated. OSA subjects were recruited from the University of California at Los Angeles (UCLA) accredited sleep laboratory. OSA subjects were newly-

diagnosed via overnight polysomnography (apnea-hypopnea-index > 5), and were untreated. None had histories of psychiatric disorders, and were not evaluated with DSM-IV criteria during this study. Exclusion criteria included use of cardiovascular-altering medications (β -blockers, α -agonists, angiotension-converting enzyme inhibitors, vasodilators), mood altering drugs, e.g., serotonin reuptake inhibitors, or history of stroke, heart failure, diagnosed brain disorders, metallic implants, or body-weight > 125 kg (scanner limitation). Control subjects were interviewed, with their co-sleeper when possible, to screen for undiagnosed OSA, and referred for polysomnography if OSA was suspected. Control subjects were compatible with the MRI scanner environment, without medications that alter neural functioning, and recruited through the UCLA campus.

The study protocol was approved by the Institutional Review Board at UCLA, and all subjects gave written consent prior to the study.

Anxiety symptoms

The Beck Anxiety Inventory (BAI) was administered to all subjects; BAI scores of 0-9 are considered “normal,” 10-18, “mild-to-moderately anxious,” 19-29, “moderate-to-severe,” and > 30, “severely” anxious [36]. OSA and control subjects with BAI > 9 were categorized “anxious,” and < 10 were classified as “non-anxious.” Anxious OSA subjects were further categorized as mild-to-moderate (BAI < 19) and moderate-to-severe anxious (BAI > 18).

Daytime sleepiness and sleep quality

All subjects were evaluated for daytime sleepiness with the Epworth Sleepiness Scale (ESS), and sleep quality with the Pittsburg Sleep Quality Index (PSQI). Both measures are self-administered questionnaires and are commonly-used indices of daytime sleepiness and sleep quality [37].

Depressive symptoms

Depressive symptoms were measured in both groups using the Beck Depression Inventory (BDI)-II [38]. The BDI-II is a self-administered questionnaire, with scores ranging from 0-63, based on depressive symptom severity.

Magnetic resonance imaging

Brain images were collected using a 3.0 Tesla MRI unit (Siemens, Erlangen, Germany). Proton-density (PD) and T2-weighted images [repetition-time (TR) = 10,000 ms; echo-time (TE1, TE2) = 17, 134 ms; flip-angle (FA) = 130°; matrix-size = 256 × 256; field-of-view = 230 × 230 mm; slice-thickness = 4.0 mm] were collected, covering the entire brain, using a dual-echo turbo-spin-echo pulse sequence in the axial plane. High-resolution T1-weighted images were collected using a magnetization-prepared-rapid-acquisition-gradient-echo sequence (TR = 2200 ms; TE = 2.2 ms; inversion-time = 900 ms; FA = 9°; matrix-size = 256 × 256; field-of-view = 230 × 230 mm; slice-thickness = 1.0 mm) for background images and evaluation of anatomical defects.

Data evaluation and processing

Individual brain images were visually assessed for brain pathology, e.g., cystic or other lesions before data processing. Proton-density and T2-weighted images were also examined for motion artifacts.

Data were processed using the statistical parametric mapping package SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>), and Matlab-based (The MathWorks Inc, Natick, MA) custom software. Using PD- and T2-weighted images, voxel-by-voxel T2-relaxation time values were calculated [33], and whole brain T2 “maps” were constructed, consisting of T2-relaxation values at each voxel. These T2 maps were normalized to Montreal Neurological Institute (MNI) space, based on T2-weighted images of each subject, using *a priori*-defined distributions of tissue types, and smoothed (Gaussian filter, full-width-at-half-maximum = 10 mm).

High-resolution T1-weighted images of all subjects were normalized to the MNI template, and averaged to create a mean anatomical image for structural identification.

Data analysis

Subject characteristics—Demographic data and characteristics were analyzed with the Statistical Package for the Social Sciences (SPSS, V 15.0, Chicago, IL). Numerical data were compared using independent-samples t-tests, categorical measures with the Chi-square test, and correlation analyses were performed using Pearson’s correlation.

Voxel-based-relaxometry—We used voxel-based-relaxometry (VBR) procedures, which enable comparisons of T2-relaxation values voxel-by-voxel across the entire brain for identification of structural differences [39]. The normalized and smoothed T2-relaxation maps were compared between anxious vs non-anxious OSA, anxious OSA vs non-anxious controls, and anxious vs non-anxious controls at each voxel, using analysis-of-covariance (covariates; age and gender). Statistical parametric maps showing regions of significant T2-relaxation value differences between anxious vs non-anxious OSA were displayed ($p < 0.003$, uncorrected). The uncorrected threshold determines a t-value statistical threshold; the statistical threshold derived from anxious vs non-anxious OSA was applied to other group comparisons. The regions of significant T2-relaxation value differences were superimposed onto the background image for anatomical identification.

Region-of-interest and linear regression analyses—Region-of-interest (ROI) analyses were performed to determine the magnitude of T2-relaxation values for distinct brain locations identified as abnormal from the VBR procedures. Regions-of-interest masks were created for all distinct brain locations using clusters identified by the VBR procedures, and used to derive T2-relaxation values from each individual’s normalized and smoothed T2-relaxation maps. Group differences for different areas were evaluated using multivariate analysis-of-covariance (covariates; age and gender).

T2-relaxation values for different brain sites, derived from ROI analysis, were also compared between mild-to-moderate anxious vs non-anxious OSA, and moderate-to-severe

anxious vs non-anxious OSA groups using multivariate analysis-of-covariance, with age and gender included as covariates.

Linear regression analysis determined effects of clinical and demographic variables on injury using T2-relaxation values derived from ROI measures with anxious and non-anxious OSA subjects. The dependent variable was the T2-relaxation value for the specific brain ROI, and independent variables were those clinical (including sleep parameters) or demographic variables which were statistically significant on the bivariate analyses.

RESULTS

Subject characteristics

Demographic, polysomnographic, sleep, and psychological variables for all anxious and non-anxious subjects are summarized in Table 1; additional comorbidities and other variables of OSA subjects which may contribute to brain injury are summarized in Table 2. No significant correlations emerged between BAI and AHI in anxious and non-anxious OSA subjects ($r = -0.13$, $p = 0.39$).

Voxel-based-relaxometry

Several brain areas in anxious OSA subjects showed higher T2-relaxation values compared to non-anxious OSA subjects. However, no sites showed higher T2 values in non-anxious vs anxious OSA subjects. Regions with prolonged T2-relaxation values in anxious OSA subjects emerged in the anterior (Fig. 1A, E, M, K), mid (Fig. 1D), and subgenu (Fig. 1C) cingulate cortices, extending to ventral medial prefrontal cortex (Fig. 1B, F, G, H), bilateral insular cortices (Fig. 1I, J, L; Fig. 2A, C, D, F), uncus of the left hippocampus, extending to the amygdala (Fig. 2H, I), and bilateral deep parietal cortices and nearby white matter (Fig. 2E, G, J, K). Abnormal brain sites also appeared in the ventral temporal lobe surface (Fig. 2B).

Anxious OSA vs non-anxious control subjects showed higher T2-relaxation values in the bilateral insular cortices (Fig. 3A, B, F, I), caudate nuclei (Fig. 3G, K, N), anterior fornix (Fig. 3C, H), left anterior thalamus (Fig. 3D, L), ventral medial prefrontal cortex (Fig. 3M), right anterior limb of internal capsule (Fig. 4A), left mid hippocampus and nearby white matter (Fig. 4D), bilateral dorsal temporal cortex and surrounding white matter (Fig. 3E; Fig. 4C, E, I), bilateral parietal cortices (Fig. 3J; Fig. 4B, F, G, J), and right dorsal frontal (Fig. 4H) cortex. Non-anxious controls showed no brain sites with higher T2-relaxation values than anxious OSA subjects.

Compared to non-anxious controls, increased T2-relaxation values in anxious controls appeared in the ventrolateral temporal cortex (Fig. 5A, B), and dorsal frontal cortex (Fig. 5C, D). No brain regions emerged with higher T2-relaxation values in non-anxious vs anxious control subjects.

Region-of-interest and linear regression analyses

T2-relaxation values extracted from distinct brain locations from anxious and non-anxious groups are summarized in Table 3. Significantly higher T2-relaxation values appeared in

multiple brain regions of anxious groups, and areas showing differences are consistent with the VBR findings.

Mean T2-relaxation values for mild-to-moderate and moderate-to-severe anxious OSA subjects are summarized in Table 4. Moderate-to-severe anxious OSA subjects showed more structural deficits and more severe injury than the mild-to-moderate anxious OSA subjects.

Using age, PSQI, AHI, oxygen desaturation, BAI, and BDI-II scores as covariates, linear regression analyses in anxious and non-anxious OSA subjects showed that BAI and age are independent predictors of brain injury, with increased T2-relaxation values in the left anterior and mid-cingulate, bilateral insular cortices, and bilateral parietal cortices and nearby white matter. BDI-II and age were independent predictors of brain damage in the right anterior and mid-cingulate cortex, the subgenu of the cingulate cortex extending to the ventral medial prefrontal cortex, and left hippocampus extending to amygdala. BAI alone was an independent predictor for right ventral temporal lobe injury (Table 5).

DISCUSSION

Overview

Anxious OSA subjects showed damage in multiple brain sites compared to non-anxious OSA subjects, as indicated by prolonged T2-relaxation values. Most of these sites serve roles in processing emotion, including anxiety, or physiology, e.g., blood pressure changes accompanying emotion. The affected brain regions included the ventral medial prefrontal, cingulate, parietal and insular cortices, and the uncus of the hippocampal formation, extending to the amygdala; many of these sites also show functional deficits to autonomic and respiratory challenges in OSA subjects [19-22], and overlapped areas of gray matter loss [11]. Injured brain regions also appeared when anxious OSA were compared with non-anxious controls; these regions included the caudate nuclei, insular cortices, anterior fornix, anterior thalamus, internal capsule, mid hippocampus, ventral medial prefrontal, dorsal frontal, temporal, and parietal cortices. Brain areas, such as the caudate nuclei and anterior fornix principally show functional deficits rather than structural injury in OSA reports, but had been noted as structurally affected in adult [40] and hypoxic-ischemic neonatal mouse models of OSA [41].

Anxiety-related injury and breathing

Anxious OSA subjects showed neural injury in areas that regulate fear emotion, cognition, sensory and motor action; some structures also assist autonomic and somatic motor systems, including breathing control [42-45]. Anxious vs non-anxious OSA group comparisons allowed evaluation of anxiety effects over injury from OSA alone. The regions impacted by anxiety included the insular, cingulate, parietal and prefrontal cortices, and hippocampus and amygdala. However, additional brain regions appeared when comparing anxious OSA vs non-anxious controls, and revealed sites primarily affected by OSA, and included the caudate nuclei, anterior fornix, thalamus, mid hippocampus, internal capsule, and areas within the temporal and frontal cortices. Damage to the caudate nuclei, septum, and basal forebrain, and cell loss from dose-dependent hypoxia in the hippocampus occurs in

intermittent hypoxic models [40, 46]. Basal ganglia structures are especially susceptible to other hypoxic damage, such as carbon monoxide poisoning [47]; intermittent hypoxia accompanying OSA may contribute to the basal ganglia and septal injury. The septum contributes to both negative and pleasurable emotional behavior, with rage accompanying septal damage in rodents [48], and stimulation related to reward [49]. Roles for the fornix fibers in emotion, some projecting to the septum [50], are unclear, but may assist inhibition of negative emotions from the hippocampus.

Common injured sites appeared in anxious vs non-anxious OSA, and anxious OSA vs non-anxious controls, including the bilateral insular cortices, ventral medial prefrontal cortex, and deep parietal cortices, but injury appears more extensive in the anxious vs non-anxious OSA group, suggesting a more severe impact from anxiety in those sites than the OSA condition alone.

Many sites affected in anxious OSA also serve respiratory control roles, especially breathing responses to emotion. The cingulate and insular cortices react to challenges inducing dyspnea [26, 27], and activate to respiratory and blood pressure manipulations [19-22]. Amygdala stimulation elicits negative emotions, including anxiety [23], while single-pulse stimulation can pace breathing [51]. The hippocampus, anterior cingulate, and cerebellum respond to inspiratory onset after apneic pauses in central apnea [52]. The insula, cingulate, hippocampus, and cerebellar deep nuclei functionally respond to hypercapnia, suggesting modulation of chemoreception [53, 54], and hippocampal single neurons discharge to breathing in humans [55]. The evidence suggests that structural deficits found in anxious OSA subjects involve brain areas that modify both emotion and breathing, and especially may be involved in the drive to breathe from perception of smothering, i.e., low oxygen or high CO₂, inspiratory efforts with startle, or enhanced thoracic pressure in response to fear in preparation for escape. Because low O₂ or high CO₂ conditions accompany apnea, we speculate that ventilatory restoration after obstruction may be compromised with impaired, although perhaps unconscious, emotional contributions from low oxygen and hypercapnia caused by these damaged sites.

Pathological processes

Although mechanisms underlying tissue injury are unclear in anxious OSA subjects, two possibilities emerge. Some damage may emerge from stress-related hormones, while intermittent hypoxia or ischemia may also contribute. Increased cortisol results from stress induced by multiple means, including immobilization [56], anxiety-like behavior [57], and pain [58]; levels are increased in elderly anxious populations [59] and young adolescents with persistent anxiety [60]. Cortisol acts on glucocorticoid (GC) receptors, and GC-induced neurotoxicity accompanying repeated episodes of apnea and anxiety can damage the hippocampus [61], amygdala, and prefrontal cortex, all regions with high concentrations of GC receptors [62]. Hippocampal dendrites show reversible damage after a single GC exposure [63], and repeated exposure may elicit injury.

The intermittent hypoxia accompanying OSA can affect neuronal cells, axons, and glia directly. In addition, hypoxia triggers endothelial cell dysfunction that may promote tissue injury in chronic stages.

Anxiety and depression

Depression is common in anxious subjects, and the two conditions share several symptoms, including disturbances in sleep, fatigue, and difficulty in concentration. The commonality of characteristics suggests sharing of neural anatomical deficits. Both anxious and depressive symptoms are frequently encountered in OSA subjects [3, 5]. Hypothalamic-pituitary-adrenal axis dysregulation may occur in both anxiety and depression, leading to brain injury through increased cortisol levels. Subjects with major depressive symptoms show structural and functional deficits in anterior cingulate, hippocampus, amygdala, and prefrontal cortex [64-67]; all these regions showed injury in anxious OSA subjects, and many appeared with depressive symptoms; pontine injury, expected in anxiety from earlier studies [68], showed injury in depression [69]. However, brain areas, such as cerebellar structures typically affected in depression [70], showed no structural injury in anxious OSA subjects.

Regression analyses indicated that injury relationships to depressive signs or anxiety scores depended on laterality for cingulate structures, with depressive signs, together with age, related to right-sided and subgenual cingulate cortex, and the left hippocampus and amygdala, while anxiety scores, together with age, related to left cingulate, bilateral insular, and parietal cortices and nearby white matter. The overlap of structural deficits in depression and anxiety disorder suggests similar mechanisms operating to induce the injury.

High T2-relaxation values and tissue injury

T2-relaxation values increase with increased free water content in tissue [28], in the absence of diamagnetic and paramagnetic substances. OSA subjects experience intermittent hypoxia from repetitive airflow cessation, and free water content may increase from sub-acute and chronic processes after intermittent hypoxia [29, 30]. Cerebral vasogenic edema results in increased free water content in extracellular space after intermittent hypoxia in sub-acute stages [71]. However, chronic stages of hypoxia, as well as hormonal contributions can lead to axonal injury, cell loss, demyelination, and gliosis, which reduce macromolecules and increases free water content in tissue, and thus, increased T2-relaxation values. T2-relaxation value differences between groups were close to, or greater than 10 ms. T2-relaxometry procedures are widely used to study pathological conditions, especially temporal lobe epilepsy, where 10 ms differences between control and affected sites showed pathologic evidence of hippocampal sclerosis [72]. The pathologic conditions here may include mild vasogenic edema, axonal loss, demyelination, and gliosis; the latter three pathologies may be more prominent than mild edema in chronic OSA patients with anxiety.

Clinical significance

The data suggest that processes involved in inducing anxiety symptoms are additive to brain injury associated with OSA. However, OSA may induce injury in areas that mediate the emotional characteristics, although precise mechanisms underlying the interaction of OSA and anxiety characteristics are unclear. Treatment for anxiety symptoms may alleviate the characteristics of both conditions. Certainly, evaluation of anxiety symptoms would be valuable in OSA assessment.

Limitations

We did not select for anxious patients for either the OSA or control groups. Thus, the numbers with anxious symptoms are small for both groups, and limits inferences, especially for anxious vs non-anxious controls. Despite the significant differences between groups, findings need to be replicated with larger samples. The necessity of evaluating the entire brain limited resolution of images, and hindered thorough brainstem evaluation. We normalized each subject's brain T2-relaxation maps into a common space for voxel-based T2-relaxometry procedures, a relatively inexact process between subjects, limiting precision to a few millimeters, with outcomes that vary, depending on brain area and degree of smoothing.

Conclusions

Anxious OSA subjects showed neural alterations in sites with roles in negative emotion, and have respiratory and autonomic regulatory functions. These structures include the amygdala, hippocampus, and cingulate, insular, and prefrontal cortices. Some sites lie outside structures typically affected by intermittent hypoxic or other injury accompanying OSA, suggesting that other injurious processes also operate in anxious OSA subjects. Additional brain-injured regions also appeared in anxious OSA vs non-anxious controls, including the caudate nuclei, anterior fornix, thalamus, internal capsule, frontal, and temporal cortices, suggesting these regions are primarily affected by the breathing condition. Evaluation of OSA patients for anxiety symptoms, and treatment of these symptoms together with the sleep-disordered breathing, may improve outcomes in OSA.

Acknowledgments

The authors thank Ms. Rebecca Harper, Dr. Stacy L. Serber, and Mr. Edwin M. Valladares for assistance. This research was supported by HL-60296.

REFERENCES

1. Bedard MA, Montplaisir J, Richer F, et al. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. *J Clin Exp Neuropsychol.* 1991; 13(6):950–964. [PubMed: 1779033]
2. Berry DT, Webb WB, Block AJ, et al. Nocturnal hypoxia and neuropsychological variables. *J Clin Exp Neuropsychol.* 1986; 8(3):229–238. [PubMed: 3722349]
3. Sforza E, de Saint Hilaire Z, Pelissolo A, et al. Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. *Sleep Med.* 2002; 3(2):139–145. [PubMed: 14592233]
4. DeZee KJ, Hatzigeorgiou C, Kristo D, Jackson JL. Prevalence of and screening for mental disorders in a sleep clinic. *J Clin Sleep Med.* 2005; 1(2):136–142. [PubMed: 17561627]
5. Sharafkhaneh A, Giray N, Richardson P, et al. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep.* 2005; 28(11):1405–1411. [PubMed: 16335330]
6. Kahn-Greene ET, Killgore DB, Kamimori GH, et al. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med.* 2007; 8(3):215–221. [PubMed: 17368979]
7. Borak J, Cieslicki JK, Koziej M, et al. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. *J Sleep Res.* 1996; 5(2):123–127. [PubMed: 8795813]
8. Marshall NS, Neill AM, Campbell AJ, Sheppard DS. Randomised controlled crossover trial of humidified continuous positive airway pressure in mild obstructive sleep apnoea. *Thorax.* 2005; 60(5):427–432. [PubMed: 15860720]

9. Davies CW, Crosby JH, Mullins RL, et al. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep*. 2001; 24(6):715–720. [PubMed: 11560186]
10. Chokroverty S, Sachdeo R, Masdeu J. Autonomic dysfunction and sleep apnea in olivopontocerebellar degeneration. *Arch Neurol*. 1984; 41(9):926–931. [PubMed: 6383299]
11. Macey PM, Henderson LA, Macey KE, et al. Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002; 166(10):1382–1387. [PubMed: 12421746]
12. Morrell MJ, McRobbie DW, Quest RA, et al. Changes in brain morphology associated with obstructive sleep apnea. *Sleep Med*. 2003; 4(5):451–454. [PubMed: 14592287]
13. O'Donoghue FJ, Briellmann RS, Rochford PD, et al. Cerebral structural changes in severe obstructive sleep apnea. *Am J Respir Crit Care Med*. 2005; 171(10):1185–1190. [PubMed: 15699018]
14. Macey PM, Harper RM. OSA brain morphology differences: magnitude of loss approximates age-related effects. *Am J Respir Crit Care Med*. 2005; 172(8):1056–1057. [PubMed: 16216840]
15. Kamba M, Inoue Y, Higami S, et al. Cerebral metabolic impairment in patients with obstructive sleep apnoea: an independent association of obstructive sleep apnoea with white matter change. *J Neurol Neurosurg Psychiatry*. 2001; 71(3):334–339. [PubMed: 11511706]
16. Tonon C, Vetrugno R, Lodi R, et al. Proton magnetic resonance spectroscopy study of brain metabolism in obstructive sleep apnoea syndrome before and after continuous positive airway pressure treatment. *Sleep*. 2007; 30(3):305–311. [PubMed: 17425226]
17. Bartlett DJ, Rae C, Thompson CH, et al. Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. *Sleep Med*. 2004; 5(6):593–596. [PubMed: 15511707]
18. Halbower AC, Degaonkar M, Barker PB, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. *PLoS Med*. 2006; 3(8):e301. [PubMed: 16933960]
19. Henderson LA, Woo MA, Macey PM, et al. Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. *J Appl Physiol*. 2003; 94(3):1063–1074. [PubMed: 12433858]
20. Macey PM, Macey KE, Henderson LA, et al. Functional magnetic resonance imaging responses to expiratory loading in obstructive sleep apnea. *Respir Physiol Neurobiol*. 2003; 138(2-3):275–290. [PubMed: 14609516]
21. Harper RM, Macey PM, Henderson LA, et al. fMRI responses to cold pressor challenges in control and obstructive sleep apnea subjects. *J Appl Physiol*. 2003; 94(4):1583–1595. [PubMed: 12514164]
22. Macey KE, Macey PM, Woo MA, et al. Inspiratory loading elicits aberrant fMRI signal changes in obstructive sleep apnea. *Respir Physiol Neurobiol*. 2006; 151(1):44–60. [PubMed: 15993658]
23. Antoniadis EA, McDonald RJ. Amygdala, hippocampus and discriminative fear conditioning to context. *Behav Brain Res*. 2000; 108(1):1–19. [PubMed: 10680753]
24. Hasler G, Fromm S, Alvarez RP, et al. Cerebral blood flow in immediate and sustained anxiety. *J Neurosci*. 2007; 27(23):6313–6319. [PubMed: 17554005]
25. Williams LM, Phillips ML, Brammer MJ, et al. Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *Neuroimage*. 2001; 14(5):1070–1079. [PubMed: 11697938]
26. Evans KC, Banzett RB, Adams L, et al. BOLD fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. *J Neurophysiol*. 2002; 88(3):1500–1511. [PubMed: 12205170]
27. Peiffer C, Poline JB, Thivard L, et al. Neural substrates for the perception of acutely induced dyspnea. *Am J Respir Crit Care Med*. 2001; 163(4):951–957. [PubMed: 11282772]
28. Barnes D, du Boulay EG, McDonald WI, et al. The NMR signal decay characteristics of cerebral oedema. *Acta Radiol Suppl*. 1986; 369:503–506. [PubMed: 2980541]
29. Loubinoux I, Volk A, Borredon J, et al. Spreading of vasogenic edema and cytotoxic edema assessed by quantitative diffusion and T2 magnetic resonance imaging. *Stroke*. 1997; 28(2):419–426. [PubMed: 9040700]

30. Kato H, Kogure K, Ohtomo H, et al. Characterization of experimental ischemic brain edema utilizing proton nuclear magnetic resonance imaging. *J Cereb Blood Flow Metab.* 1986; 6(2):212–221. [PubMed: 3958065]
31. Kumar R, Gupta RK, Rathore RK, et al. Multiparametric quantitation of the perilesional region in patients with healed or healing solitary cysticercus granuloma. *Neuroimage.* 2002; 15(4):1015–1020. [PubMed: 11906241]
32. Karlik SJ, Strejan G, Gilbert JJ, Noseworthy JH. NMR studies in experimental allergic encephalomyelitis (EAE): normalization of T1 and T2 with parenchymal cellular infiltration. *Neurology.* 1986; 36(8):1112–1114. [PubMed: 3736878]
33. Kumar R, Gupta RK, Rao SB, et al. Magnetization transfer and T2 quantitation in normal appearing cortical gray matter and white matter adjacent to focal abnormality in patients with traumatic brain injury. *Magn Reson Imaging.* 2003; 21(8):893–899. [PubMed: 14599540]
34. Papanikolaou N, Papadaki E, Karampekios S, et al. T2 relaxation time analysis in patients with multiple sclerosis: correlation with magnetization transfer ratio. *Eur Radiol.* 2004; 14(1):115–122. [PubMed: 14600774]
35. Townsend TN, Bernasconi N, Pike GB, Bernasconi A. Quantitative analysis of temporal lobe white matter T2 relaxation time in temporal lobe epilepsy. *Neuroimage.* 2004; 23(1):318–324. [PubMed: 15325379]
36. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol.* 1988; 56(6):893–897. [PubMed: 3204199]
37. Knutson KL, Rathouz PJ, Yan LL, et al. Stability of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Questionnaires over 1 year in early middle-aged adults: the CARDIA study. *Sleep.* 2006; 29(11):1503–1506. [PubMed: 17162998]
38. Beck, AT.; Steer, RA.; Brown, GK. Manual for the Beck Depression Inventory-II. The Psychological Corporation; San Antonio, Texas: 1996.
39. Pell GS, Briellmann RS, Waites AB, et al. Voxel-based relaxometry: a new approach for analysis of T2 relaxometry changes in epilepsy. *Neuroimage.* 2004; 21(2):707–713. [PubMed: 14980573]
40. Veasey SC, Davis CW, Fenik P, et al. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep.* 2004; 27(2):194–201. [PubMed: 15124711]
41. Skoff RP, Bessert DA, Barks JD, et al. Hypoxic-ischemic injury results in acute disruption of myelin gene expression and death of oligodendroglial precursors in neonatal mice. *Int J Dev Neurosci.* 2001; 19(2):197–208. [PubMed: 11255033]
42. Cechetto DF, Chen SJ. Subcortical sites mediating sympathetic responses from insular cortex in rats. *Am J Physiol.* 1990; 258(1 Pt 2):R245–R255. [PubMed: 2301638]
43. Frysinger RC, Harper RM. Cardiac and respiratory relationships with neural discharge in the anterior cingulate cortex during sleep-walking states. *Exp Neurol.* 1986; 94(2):247–263. [PubMed: 3770117]
44. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology.* 1992; 42(9):1727–1732. [PubMed: 1513461]
45. Holstege G. The emotional motor system. *Eur J Morphol.* 1992; 30(1):67–79. [PubMed: 1642954]
46. Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J Neurosci.* 2001; 21(7):2442–2450. [PubMed: 11264318]
47. O'Donnell P, Buxton PJ, Pitkin A, Jarvis LJ. The magnetic resonance imaging appearances of the brain in acute carbon monoxide poisoning. *Clin Radiol.* 2000; 55(4):273–280. [PubMed: 10767186]
48. Goodlett CR, Engellenner WJ, Burrig RG, Donovan PJ. Influence of environmental rearing history and postsurgical environmental change on the septal rage syndrome in mice. *Physiol Behav.* 1982; 28(6):1077–1081. [PubMed: 7111451]
49. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol.* 1954; 47(6):419–427. [PubMed: 13233369]
50. Raisman G. The connexions of the septum. *Brain.* 1966; 89(2):317–348. [PubMed: 5939044]

51. Harper RM, Frysinger RC, Trelease RB, Marks JD. State-dependent alteration of respiratory cycle timing by stimulation of the central nucleus of the amygdala. *Brain Res.* 1984; 306(1-2):1–8. [PubMed: 6466967]
52. Henderson LA, Macey KE, Macey PM, et al. Regional brain response patterns to Cheyne-Stokes breathing. *Respir Physiol Neurobiol.* 2006; 150(1):87–93. [PubMed: 16337439]
53. Corfield DR, Fink GR, Ramsay SC, et al. Activation of limbic structures during CO₂-stimulated breathing in awake man. *Adv Exp Med Biol.* 1995; 393:331–334. [PubMed: 8629509]
54. Harper RM, Macey PM, Woo MA, et al. Hypercapnic exposure in congenital central hypoventilation syndrome reveals CNS respiratory control mechanisms. *J Neurophysiol.* 2005; 93(3):1647–1658. [PubMed: 15525806]
55. Frysinger RC, Harper RM. Cardiac and respiratory correlations with unit discharge in human amygdala and hippocampus. *Electroencephalogr Clin Neurophysiol.* 1989; 72(6):463–470. [PubMed: 2471614]
56. Domanski E, Przekop F, Wolinska-Witort E, et al. Differential behavioural and hormonal responses to two different stressors (footshocking and immobilization) in sheep. *Exp Clin Endocrinol.* 1986; 88(2):165–172. [PubMed: 3556404]
57. Bristow DJ, Holmes DS. Cortisol levels and anxiety-related behaviors in cattle. *Physiol Behav.* 2007; 90(4):626–628. [PubMed: 17196624]
58. Hashem AA, Claffey NM, O'Connell B. Pain and anxiety following the placement of dental implants. *Int J Oral Maxillofac Implants.* 2006; 21(6):943–950. [PubMed: 17190305]
59. Chaudieu I, Beluche I, Norton J, et al. Abnormal reactions to environmental stress in elderly persons with anxiety disorders: evidence from a population study of diurnal cortisol changes. *J Affect Disord.* 2008; 106(3):307–313. [PubMed: 17727959]
60. Greaves-Lord K, Ferdinand RF, Oldehinkel AJ, et al. Higher cortisol awakening response in young adolescents with persistent anxiety problems. *Acta Psychiatr Scand.* 2007; 116(2):137–144. [PubMed: 17650276]
61. Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci.* 1990; 10(9):2897–2902. [PubMed: 2398367]
62. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry.* 2003; 54(3):338–352. [PubMed: 12893109]
63. Watanabe Y, Gould E, Cameron HA, et al. Phenytoin prevents stress- and corticosterone-induced atrophy of CA3 pyramidal neurons. *Hippocampus.* 1992; 2(4):431–435. [PubMed: 1308199]
64. Wang L, LaBar KS, McCarthy G. Mood alters amygdala activation to sad distractors during an attentional task. *Biol Psychiatry.* 2006; 60(10):1139–1146. [PubMed: 16713587]
65. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry.* 2004; 161(4):598–607. [PubMed: 15056502]
66. Coryell W, Nopoulos P, Drevets W, et al. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *Am J Psychiatry.* 2005; 162(9):1706–1712. [PubMed: 16135631]
67. Tang Y, Wang F, Xie G, et al. Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. *Psychiatry Res.* 2007; 156(1):83–86. [PubMed: 17825533]
68. Bracha HS, Garcia-Rill E, Mrak RE, Skinner R. Postmortem locus coeruleus neuron count in three American veterans with probable or possible war-related PTSD. *J Neuropsychiatry Clin Neurosci.* 2005; 17(4):503–509. [PubMed: 16387990]
69. Cross RL, Kumar R, Macey PM, et al. Neural alterations and depressive symptoms in obstructive sleep apnea patients. *Sleep.* (in press).
70. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum -insights from the clinic. *Cerebellum.* 2007; 6(3):254–267. [PubMed: 17786822]
71. Ten VS, Pinsky DJ. Endothelial response to hypoxia: physiologic adaptation and pathologic dysfunction. *Curr Opin Crit Care.* 2002; 8(3):242–250. [PubMed: 12386504]

72. Jackson GD, Connelly A, Duncan JS, et al. Detection of hippocampal pathology in intractable partial epilepsy: increased sensitivity with quantitative magnetic resonance T2 relaxometry. *Neurology*. 1993; 43(9):1793–1799. [PubMed: 8414034]

Fig. 1.

Overlays of abnormal brain areas in cingulate, frontal, and insular cortices in OSA subjects with anxious symptoms vs non-anxious OSA subjects. Brain areas showing higher T2-relaxation values appeared in anterior (A, E, M, K), mid (D), and subgenual (C) cingulate cortices, extending to ventral medial prefrontal cortex (B, F, G, H), and bilateral insular cortices (I, J, L). All brain images are in neurological convention (L = Left, M = Midline, R = Right), and the color scale represents t-statistic values ($p < 0.003$, uncorrected, absolute threshold = 2.89).

Fig. 2.

Injury in hippocampus, amygdala, temporal and parietal cortices in anxious OSA, compared to non-anxious OSA subjects. Abnormal regions included the left hippocampus extending to amygdala (H, I), bilateral deep parietal cortices (E, G, J, K), and ventral temporal cortex (B). Figure conventions are as in Fig. 1.

Fig. 3. Limbic sites with structural injury in anxious OSA compared to non-anxious controls. Deficits appeared in bilateral insular cortices (A, B, F, I), caudate nuclei (G, K, N), anterior fornix (C, H), anterior thalamus (D, L), and ventral medial prefrontal cortex (M). Figure conventions are as in Fig. 1.

Fig. 4.

Overlays of abnormal regions in anxious OSA subjects in hippocampus, temporal and parietal cortices, compared to non-anxious controls. Regions with increased T2-relaxation values emerged in the anterior limb of internal capsule (A), mid hippocampus and nearby white matter (D), dorsal temporal cortex and surrounding white matter (C, E, I), bilateral deep parietal cortices (B, F, G, J), and right dorsal frontal cortex (H). Figure conventions are as in Fig. 1.

Fig. 5. Abnormal brain sites in a small sample of anxious vs non-anxious controls. Abnormal sites emerged in ventral temporal (A, B) cortex, and dorsal frontal cortex (C, D). Figure conventions are as in Fig. 1.

Table 1

Demographic data and characteristics of anxious and non-anxious OSA and control subjects.

Variables	Anxious OSA (n = 16) [A]	Non-anxious OSA (n = 30) [B]	Anxious controls (n = 7) [C]	Non-anxious controls (n = 59) [D]	<i>p</i> values			
					[A] vs [B]	[A] vs [D]	[C] vs [D]	[A] vs [C]
Mean age $\pm$ SD (years)	48.9 $\pm$ 10.8	45.7 $\pm$ 8.3	48.3 $\pm$ 8.6	47.0 $\pm$ 9.0	0.258	0.464	0.721	0.888
Male : Female	9:7	27:3	4:3	39:20	-	-	-	-
Mean BMI $\pm$ SD (kg/m ²)	32.0 $\pm$ 5.8	29.0 $\pm$ 4.3	25.4 $\pm$ 3.8	25.3 $\pm$ 4.6	0.052	< 0.001	0.977	0.005a
Mean AHI $\pm$ SD (events/ hour)	29.2 $\pm$ 16.9	30.7 $\pm$ 16.6	NA	NA	0.764			
*Mean AI $\pm$ SD (events/ hour)	24.3 $\pm$ 20.1	30.0 $\pm$ 21.5	NA	NA	0.412			
**Mean SpO ₂ $\pm$ SD (%)	13.1 $\pm$ 4.8	20.1 $\pm$ 11.3	NA	NA	0.009a			
Mean BAI $\pm$ SD	24.2 $\pm$ 11.9	3.7 $\pm$ 2.8	15.9 $\pm$ 5.2	2.7 $\pm$ 2.7	< 0.001 ^a	< 0.001 ^a	< 0.001 ^a	0.029a
Mean ESS $\pm$ SD	11.1 $\pm$ 4.1	9.6 $\pm$ 4.8	8.3 $\pm$ 5.4	5.2 $\pm$ 3.2	0.296	< 0.001	0.186 ^a	0.190
Mean PSQI $\pm$ SD	11.6 $\pm$ 3.0	8.3 $\pm$ 4.4	5.7 $\pm$ 2.7	3.8 $\pm$ 2.5	0.012	< 0.001	0.060	< 0.001
Mean BDI-II $\pm$ SD	18.1 $\pm$ 9.1	5.3 $\pm$ 4.0	11.1 $\pm$ 8.2	3.5 $\pm$ 4.0	< 0.001 ^a	< 0.001 ^a	0.050 ^a	0.097

SD = Standard deviation; BMI = Body mass index; AHI = Apnea hypopnea index; NA = Not applicable; AI = Arousal index; SpO₂ = Oxygen desaturation; BAI = Beck Anxiety Inventory; ESS = Epworth sleepiness scale; PSQI = Pittsburg Sleep Quality Index; BDI-II = Beck Depression Inventory-II;

* = 14 anxious OSA vs 28 non-anxious OSA;

** = 13 anxious OSA vs 27 non-anxious OSA;

^a = Equal variances not assumed.

Table 2

Comorbidities and other conditions in anxious and non-anxious OSA subjects.

Comorbidities/ Conditions	Anxious OSA (n = 16) [A]	Non-anxious OSA (n = 30) [B]	<i>p</i> values [A] vs [B]
Hypertension	8	7	0.066
Diabetes	3	0	0.014
Gout	1	1	0.644
Smoking	2	4	0.936
Cardiovascular disease	0	0	-
Migraine	0	0	-

Table 3

Mean T2-relaxation ROI values derived from distinct brain locations from anxious and non-anxious OSA and control subjects.

Groups	Brain regions	Subjects		Voxels (8 mm ³)	p values	Figures
		Anxious OSA (Mean $\pm$ SD) (in ms)	Non-anxious OSA (Mean $\pm$ SD) (in ms)			
Anxious OSA vs Non-anxious OSA	Left anterior cingulate extending to mid cingulate	136.6 $\pm$ 18.0	124.4 $\pm$ 7.9	256	< 0.001	Fig. 1A, M
	Right anterior cingulate extending to mid cingulate	118.4 $\pm$ 12.6	110.2 $\pm$ 4.9	391	< 0.002	Fig. 1E, D, K
	Subgenu of cingulate extending to ventral medial prefrontal cortex	135.0 $\pm$ 17.7	124.2 $\pm$ 7.0	329	< 0.001	Fig. 1C, B, F, G, H
	Left insular cortex	137.8 $\pm$ 18.3	123.9 $\pm$ 8.0	565	< 0.001	Fig. 1J, L; Fig. 2C, F
	Right insular cortex	133.8 $\pm$ 14.9	121.7 $\pm$ 8.9	317	< 0.001	Fig. 1I; Fig. 2A, D
	Hippocampus extending to amygdala	120.0 $\pm$ 9.6	111.2 $\pm$ 6.0	58	< 0.001	Fig. 2H, I
	Left parietal cortex and bordering white matter	124.2 $\pm$ 17.7	110.8 $\pm$ 6.2	664	< 0.001	Fig. 2G, K
	Right parietal cortex and bordering white matter	107.5 $\pm$ 8.9	100.0 $\pm$ 4.2	199	< 0.002	Fig. 2E, J
	Right ventral surface of the temporal lobe	120.7 $\pm$ 14.3	111.7 $\pm$ 4.9	54	< 0.002	Fig. 2B
Anxious OSA vs Non-anxious controls		Anxious OSA	Non-anxious controls			
	Left insular cortex	126.7 $\pm$ 15.5	116.0 $\pm$ 8.8	45	< 0.001	Fig. 3A, F, I
	Right insular cortex	106.6 $\pm$ 8.0	100.6 $\pm$ 5.7	15	< 0.001	Fig. 3B
	Left caudate nucleus	178.1 $\pm$ 32.8	158.0 $\pm$ 15.8	27	< 0.001	Fig. 3G, K, N
	Anterior fornix	241.3 $\pm$ 40.3	215.4 $\pm$ 22.7	7	< 0.001	Fig. 3C, H
	Left anterior thalamus	97.8 $\pm$ 8.8	92.8 $\pm$ 4.7	4	< 0.001	Fig. 3D, L
	Left ventral medial prefrontal cortex	136.9 $\pm$ 20.2	126.1 $\pm$ 9.0	7	< 0.001	Fig. 3M
	Right internal capsule	94.6 $\pm$ 7.5	89.7 $\pm$ 4.5	8	< 0.001	Fig. 4A
	Left mid hippocampus extending to white matter	114.4 $\pm$ 16.4	105.2 $\pm$ 6.9	137	< 0.001	Fig. 4D
	Left dorsal temporal cortex and surrounding white matter	103.7 $\pm$ 8.8	98.3 $\pm$ 4.3	31	< 0.001	Fig. 3E
	Right dorsal temporal cortex and surrounding white matter	104.6 $\pm$ 9.8	98.6 $\pm$ 4.4	187	< 0.001	Fig. 4C, E, I
	Left parietal cortex and bordering white matter	153.0 $\pm$ 24.3	134.3 $\pm$ 11.9	347	< 0.001	Fig. 3J; Fig. 4F, J
	Right parietal cortex and bordering white matter	143.5 $\pm$ 30.6	125.8 $\pm$ 12.8	94	< 0.001	Fig. 4B, G
	Right dorsal frontal cortex	152.3 $\pm$ 22.7	136.9 $\pm$ 13.2	19	< 0.001	Fig. 4H
Anxious controls vs Non-anxious controls		Anxious controls	Non-anxious controls			

Groups	Brain regions	Subjects		Voxels (8 mm ³)	p values	Figures
		Anxious OSA (Mean $\pm$ SD) (in ms)	Non-anxious OSA (Mean $\pm$ SD) (in ms)			
	Right ventrolateral temporal cortex	152.3 $\pm$ 46.9	126.7 $\pm$ 14.2	13	< 0.012	Fig. 5A, B
	Right dorsal frontal cortex	206.8 $\pm$ 25.6	179.8 $\pm$ 21.3	9	< 0.001	Fig. 5C, D

Table 4

Mean T2-relaxation values of different brain sites for mild-to-moderate, moderate-to-severe anxious OSA, and non-anxious OSA subjects.

Brain regions	Anxious OSA		Non-anxious OSA	[A] vs [C]		[B] vs [C]	
	Mild-to-moderate (n = 6) (Mean $\pm$ SD, ms) [A]	Moderate-to-severe (n = 10) (Mean $\pm$ SD, ms) [B]	(n = 30) (Mean $\pm$ SD, ms) [C]	p values	Observed power	p values	Observed power
Left anterior cingulate extending to mid cingulate	125.7 $\pm$ 9.9	143.2 $\pm$ 18.9	124.4 $\pm$ 7.9	0.033		< 0.001	
Right anterior cingulate extending to mid cingulate	114.4 $\pm$ 11.0	120.9 $\pm$ 13.4	110.2 $\pm$ 4.9	0.248	0.345	< 0.001	
Subgenu of cingulate extending to ventral medial prefrontal cortex	126.3 $\pm$ 9.5	140.3 $\pm$ 19.8	124.2 $\pm$ 7.0	0.194	0.394	< 0.001	
Left insular cortex	127.2 $\pm$ 5.5	144.2 $\pm$ 20.5	123.9 $\pm$ 8.0	0.001	-	< 0.001	-
Right insular cortex	126.1 $\pm$ 4.9	138.4 $\pm$ 17.2	121.7 $\pm$ 8.9	0.001	-	< 0.001	-
Hippocampus extending to amygdala	117.2 $\pm$ 12.9	121.7 $\pm$ 7.4	111.2 $\pm$ 6.0	0.177	0.412	< 0.001	
Left parietal cortex and bordering white matter	115.7 $\pm$ 6.1	129.2 $\pm$ 20.7	110.8 $\pm$ 6.2	0.081	0.556	< 0.001	
Right parietal cortex and bordering white matter	103.7 $\pm$ 5.9	109.7 $\pm$ 9.8	100.0 $\pm$ 4.2	0.316	0.297	< 0.001	
Right ventral surface of the temporal lobe	118.4 $\pm$ 7.6	122.1 $\pm$ 17.4	111.7 $\pm$ 4.9	0.018		< 0.002	

SD = Standard deviation; ms = millisecond; - = Sufficient statistical power.

Table 5

Comparison of initial and multivariate p values and B values of demographic and clinical variables of the linear regression analyses in anxious and non-anxious OSA subjects.

Brain regions	Covariates	Initial p-values	Multivariate p-values	B
Left anterior cingulate extending to mid cingulate	Age	0.258	< 0.001	0.767
	PSQI	0.012	0.481	-
	AHI	0.764	0.814	-
	Oxygen desaturation	0.009	0.438	-
	BAI	< 0.001	0.007	0.407
	BDI-II	< 0.001	0.268	-
Right anterior cingulate extending to mid cingulate	Age	0.258	0.013	0.320
	PSQI	0.012	0.432	-
	AHI	0.764	0.803	-
	Oxygen desaturation	0.009	0.852	-
	BAI	< 0.001	0.648	-
	BDI-II	< 0.001	0.001	0.480
Subgenu of cingulate extending to ventral medial prefrontal cortex	Age	0.258	0.007	0.511
	PSQI	0.012	0.680	-
	AHI	0.764	0.689	-
	Oxygen desaturation	0.009	0.725	-
	BAI	< 0.001	0.420	-
	BDI-II	< 0.001	0.004	0.583
Left insular cortex	Age	0.258	< 0.001	0.787
	PSQI	0.012	0.225	-
	AHI	0.764	0.119	-
	Oxygen desaturation	0.009	0.322	-
	BAI	< 0.001	< 0.001	0.590
	BDI-II	< 0.001	0.510	-
Right insular cortex	Age	0.258	< 0.001	0.683
	PSQI	0.012	0.186	-
	AHI	0.764	0.092	-
	Oxygen desaturation	0.009	0.259	-
	BAI	< 0.001	0.001	0.475
	BDI-II	< 0.001	0.385	-
Hippocampus extending to amygdala	Age	0.258	0.006	0.365
	PSQI	0.012	0.438	-
	AHI	0.764	0.461	-
	Oxygen desaturation	0.009	0.638	-
	BAI	< 0.001	0.714	-
	BDI-II	< 0.001	0.002	0.439

Brain regions	Covariates	Initial p-values	Multivariate p-values	B
Left parietal cortex and bordering white matter	Age	0.258	0.006	0.535
	PSQI	0.012	0.174	-
	AHI	0.764	0.496	-
	Oxygen desaturation	0.009	0.701	-
	BAI	< 0.001	< 0.001	0.610
	BDI-II	< 0.001	0.291	-
Right parietal cortex and bordering white matter	Age	0.258	0.029	0.223
	PSQI	0.012	0.231	-
	AHI	0.764	0.941	-
	Oxygen desaturation	0.009	0.838	-
	BAI	< 0.001	0.002	0.284
	BDI-II	< 0.001	0.424	-
Right ventral surface of the temporal lobe	Age	0.258	0.055	-
	PSQI	0.012	0.171	-
	AHI	0.764	0.819	-
	Oxygen desaturation	0.009	0.483	-
	BAI	< 0.001	0.003	0.383
	BDI-II	< 0.001	0.949	-

AHI = Apnea hypopnea index; BAI = Beck Anxiety Inventory; PSQI = Pittsburgh Sleep Quality Index; BDI-II = Beck Depression Inventory-II.