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RESEARCH ARTICLE

# Obstructive sleep apnea and cortical thickness in females and males

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## Abstract

### Introduction

Obstructive sleep apnea (OSA) affects approximately 10% of adults, and alters brain gray and white matter. Psychological and physiological symptoms of the disorder are sex-specific, perhaps related to greater injury occurs in female than male patients in white matter. Our objective was to identify influences of OSA separated by sex on cortical gray matter.

### Methods

We assessed cortical thickness in 48 mild-severe OSA patients (mean age±std[range] = 46.5±9.0[30.8–62.7] years; apnea-hypopnea index = 32.6±21.1[6–102] events/hour; 12 female, 36 male; OSA severity: 5 mild, 18 moderate, 25 severe) and 62 controls (mean age = 47.7±8.9[30.9–65.8] years; 22 female, 40 male). All OSA patients were recently-diagnosed via polysomnography, and control subjects screened and a subset assessed with sleep studies. We used high-resolution magnetic resonance imaging to identify OSA-related cortical thinning, based on a model with condition and sex as independent variables. OSA and OSA-by-sex interaction effects were assessed ( $P < 0.05$ , corrected for multiple comparisons).

### Results

Multiple regions of reduced cortical thickness appeared bilaterally in the superior frontal lobe in female OSA vs. all other groups. Significant thinning within the pre- and post-central gyri and the superior temporal gyrus, extending into the insula, appeared between the general OSA populations vs. control subjects. No areas showed increased thickness in OSA vs. controls or positive female OSA interaction effects.

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusions

Reduced cortical thickness likely represents tissue atrophy from long term injury, including death of neurons and supporting glia from repeated intermittent hypoxic exposure in OSA, although disease comorbidities may also contribute to thinning. Lack of polysomnography in all control subjects means results may be confounded by undiagnosed OSA. The greater cortical injury in cognitive areas of female OSA patients may underlie enhanced symptoms in that group. The thinning associated with OSA in male and females OSA patients may contribute to autonomic dysregulation and impaired upper airway sensori-motor function.

## Introduction

The repeated collapse of the upper airway in Obstructive Sleep Apnea (OSA) leads to neural changes from the resulting intermittent hypoxia and cardiovascular sequelae, which then result in psychological and physiological deficits, including increased sympathetic tone [1–3]. Symptoms and brain changes in OSA show sex differences, with female OSA patients exhibiting greater white matter injury than males, and more severe impairments in some neurological functions [4, 5]. Whether cortical gray matter is compromised similarly to white matter is unknown. The OSA-related injury in white matter will affect communication between cortical and subcortical structures, and almost certainly affect the cortical neurons from which those axons emerge.

Males have a two-fold higher incidence of OSA than females [6]. However, OSA characteristics differ between males and females. Prior studies suggest possible gender differences: Females with the disorder have a reported higher prevalence of chronic pulmonary disease, heart failure, tissue fluid retention, and hypothyroidism, while male OSA patients showed higher levels of cardiovascular disease and arrhythmia than females [7]. Additionally, females with OSA have a higher probability of experiencing neuropsychological disorders than males, including depression, insomnia and anxiety [8, 9]. Women with OSA, on average, have lower severity [10], but display more marked symptoms for equivalent condition severity (as measured by the apnea/hypopnea index, or AHI) [5, 10]. Since many OSA symptoms derive from central nervous system alterations, disparities in the expression of such symptoms may develop from sex differences in brain function and injury. The specific enhancement of axonal injury in OSA females appears in structures that serve a range of emotional, breathing and sleep integrity-mediating structures [4]. Since axonal injury is usually accompanied by damage to its cell body [11], such female-specific injury likely extends into cortical regions.

Injury specific to the cortex can be assessed by evaluating cortical thickness calculated from high resolution anatomical brain magnetic resonance imaging (MRI) scans; a set of software tools, FreeSurfer, has been developed to evaluate such brain structural properties [12]. The suite allows calculation and statistical analysis of group variations in cortical thickness at different locations. Reductions in cortical thickness reflect atrophy [13], which in OSA could arise from accelerated degeneration, including loss of neurons and glia [14].

The objective was to assess cortical thickness in separately female and male OSA and control subjects, based on high resolution MRI scans processed with FreeSurfer. We hypothesized that females with OSA would have decreased thicknesses in cortical areas, relative to male OSA and control participants, especially those areas associated with depression and anxiety, symptoms preferentially more common in females with OSA [8, 9]. Since OSA is accompanied by a range of behavioral and physiological deficits, as well as structural brain changes in mixed

patient populations, differences in cortical thickness between OSA and control subjects were also expected.

## Methods

### Patients

We studied a total of 110 subjects, which included 12 female (mean age $\pm$ SEM [range] = 51.3 $\pm$ 2.3 [37.0–62.2] years; mean apnea-hypopnea index [AHI]  $\pm$ std = 26.7 $\pm$ 7.2 [5–89.3] events/hour) and 36 male (mean age = 45.0 $\pm$ 1.5 [30.8–62.7] years; mean AHI = 34.6 $\pm$ 3.3 [10–100.7] events/hour) recently-diagnosed OSA patients (AHI  $\geq$  5), and 22 female (mean age = 50.7 $\pm$ 1.7 [40.2–65.8] years) and 40 male (mean age = 46.0 $\pm$ 1.4 [30.9–64.5] years) control subjects. OSA patients underwent a standard overnight in-lab polysomnographic study within three months of enrollment. The scoring was based on 1999 American Academy of Sleep Medicine criteria, including a definition of apnea/hypopnea of lasting 10 seconds or longer, and involving a desaturation of  $>3\%$  SaO<sub>2</sub> in the case of a hypopnea, although most apneas also show desaturations [15]. OSA subjects were not being treated for their condition, nor were they taking any cardiovascular or psychotropic medications. Control subjects were recruited from the neighborhood of UCLA via fliers, and were in good health with no reported sleep problems. All control participants were screened for indications of OSA by questionnaires and interviews, and based answers to those questions (high sleepiness, snoring), six were further assessed with an overnight polysomnographic study. Two of those were confirmed as having normal sleep, two as having OSA, and two as having mild sleep-disordered breathing not meeting criteria for OSA. All participants were free of metallic implants, and exclusion criteria included history of mental illness, history of tobacco use, other major disease (cancer, major cardiovascular events, stroke, neurological disorders, chronic obstructive pulmonary disease), or head injury. No participants were diagnosed with hypertension, although the condition was likely present in at least some OSA patients. At the time of recruitment, no participants were known to have diabetes, but subsequently four OSA patients were found to have Type II diabetes. The study was approved by the UCLA Institutional Review Board, and participants provided written informed consent.

### Sleepiness and neuropsychological questionnaires

We administered the Epworth Sleepiness Scale (ESS) questionnaire to assess daytime sleepiness [16]. This test is scored between 0 and 24, with any score greater than or equal to 10 classified as outside the range of normal. We used the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire that assessed self-reported sleep quality and sleep times, with a score greater than or equal to 5 signifying clinically relevant disturbed sleep. The Beck Depression Inventory (BDI), a 21-item questionnaire, assessed depressive symptoms with scores greater than or equal to 10 indicating greater levels of depressive symptoms [17]. Lastly, the Beck Anxiety Index (BAI), a 21-item questionnaire, assessed levels of anxiety with scores greater than or equal to 8 indicating enhanced anxiety levels [18].

### MRI scanning

Brain scans were collected using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany) with a receive-only 8-channel phased-array head-coil and a whole-body transmitter coil. Foam pads were placed on either side of the head to reduce head motion related artifacts, and subjects lay supine during data collection. We collected two high-resolution T1-weighted image scans using a magnetization prepared rapid acquisition gradient-echo

(MPRAGE) pulse sequence [repetition time (TR) = 2200 ms; echo time (TE) = 2.2 ms; inversion time = 900 ms; flip angle (FA) = 9°; matrix size = 256 × 256; field of view (FOV) = 230 × 230 mm; slice thickness = 1.0 mm; slices = 176].

### Cortical thickness processing

Data were preprocessed using SPM8. The two T1-weighted images were realigned and averaged, and rigid-body shifted into the common space.

We used FreeSurfer version 5.3.0 to process the averaged scans from each subject [19]. The initial skull stripping and boundary identification were performed, and skull strips of all subjects were manually assessed to ensure no brain areas were excluded or incorrectly included. Similarly, the pial and gray-white matter boundaries were visually assessed, and, if needed, edited to correct misidentified regions. To minimize bias, researchers not involved in the study performed the editing. Minor edits were required to adjust the automatically detected pial boundaries in most subjects, but the skull strip and white matter boundaries did not require adjustment.

### Statistical modeling

The FreeSurfer processing stream was followed to determine cortical thickness across the brain, excluding cerebellar areas, using a general linear model with condition (OSA/control) and sex as classification variables (10 mm smoothing). The linear model was implemented at each surface point. The model assessed cortical thinning as a function of condition, sex and their interaction, and was then interrogated to test specific hypotheses across the cortical surface. We corrected for multiple comparisons with Monte Carlo simulation with a threshold of  $P = 0.05$ . Results were displayed as colored “clusters,” that is, regions of adjoining surface points showing statistically significant differences, with color indicating statistical significance. We overlaid the areas of significant differences onto the pial cortical surface, and lateral views of the “inflated” surface (sulcal and gyral areas displayed as smooth adjacent regions without depth).

The FreeSurfer annotations were provided in table descriptions for consistency with the Desikan atlas provided in that software [20], although the terms do not always follow conventional anatomical labeling conventions. Hence, Brodmann areas (BAs) were also denoted.

## Results

### Demographics

Demographic data are listed in Table 1. Body mass indices were significantly higher in OSA females and OSA males, compared to their respective controls. There were no significant differences between the control and OSA groups, separated by sex, in age or years of education (age,  $P = 0.5$ ; education,  $P = 0.2$ ).

### Cortical thinning: Effect of OSA independent of sex

Whole-brain group comparisons revealed cortical thinning associated with OSA accounting for sex as a covariate, compared to the control group in three defined clusters, after the Monte Carlo cluster correction was performed ( $P < 0.05$ ). Affected areas included the left precentral gyrus (Talairach peak: -35.0, -12.0, 40.3), the left superior temporal gyrus and insular cortex (Talairach peak: -35.5, -12.8, 0.4), and the right postcentral gyrus (Talairach peak x, y, z mm: -56.3, -8.3, 11.2; Table 2 & Fig 1). Representations of areas of cortical thickness differences between control and OSA groups in the left and right hemispheres are shown in Fig 1 from

**Table 1. Characteristics of OSA and control subjects, separate by sex, with group averages and standard deviations.** Significance levels for ANOVA tests are shown.

Variable Type	Variables	Female		OSA vs Control	Male		OSA vs. Control
		Control (Mean ± SEM)	OSA (Mean ± SEM)	P (F-test or Chi square)	Control (Mean ± SEM)	OSA (Mean ± SEM)	P (F-test or Chi square)
Demographic	N	22	12	-	40	36	-
	Age (years)	50.7±1.7	51.3±2.3	0.84	46.0±1.4	45.0±1.5	0.62
	Education (years)	16.6±1.4	16.0±0.0	0.89	18.5±1.4	19.7±0.9	0.47
Biophysical	BMI (m <sup>2</sup> /kg)	23.9±1.1	32.9±1.7	<0.001	25.4±0.4	29.6±0.8	<0.001
	Handedness	16 right, 6 left	10 right, 2 left	0.49	35 right, 5 left	32 right, 4 left	0.85
Neuropsychological	BDIcog	1.95±0.5	7.00±2.2	0.0049	2.45±0.7	3.97±0.7	0.13
	BDIsom	2.41±0.7	6.00±1.6	0.020	1.78±0.3	4.64±0.6	<0.001
	BDI (Depression)	4.45±1.0	13.83±3.4	0.0025	4.20±0.9	8.61±1.2	0.004
	Beck Anxiety	4.5±1.2	19.8±4.4	0.0002	3.65±0.7	8.58±1.6	0.005
Sleep	Epworth SS	6.59±0.7	12.5±1.5	0.0002	5.08±0.6	9.89±0.8	<0.001
	PSQI	3.91±0.6	10.17±1.2	<0.001	3.80±0.4	9.31±0.7	<0.001
Polysomnography	AHI (events/hour)	-	26.7±7.2	-	-	34.6±3.3	-
			Range: 6–89			Range: 12–102	
	OSA severity distribution	-	4 mild, 3 moderate, 5 severe	-	-	1 mild, 15 moderate, 20 severe	-
	O <sub>2</sub> saturation nadir (%)	-	86.3±1.8	-	-	78.2±1.6	-
	O <sub>2</sub> saturation baseline (%)	-	94.7±0.5	-	-	94.9±0.3	-

<https://doi.org/10.1371/journal.pone.0193854.t001>

multiple views overlaid onto the FreeSurfer template pial surface, and a lateral, inflated view. No regions showed increased cortical thickness in OSA patients.

### Cortical thinning: Sex and OSA interaction

Significant cortical thinning appeared in the female OSA group compared to all other groups in two focal brain regions after the Monte Carlo cluster correction ( $P < 0.05$ ). Thinning clusters were located bilaterally in the superior frontal lobe, in the left (Talairach peak: -8.5, 31.1, 28.3) and right hemisphere (Talairach peak: 6.6, 4.7, 57.3) (Table 3). Brain maps of the interaction effects between group and sex in mean thickness are shown for the left and right hemispheres (Fig 2). Quantitative data from each of these clusters are displayed in Table 3. No other interaction effects were present; that is, no areas showed male-specific cortical thinning in OSA (or lower thickness in control female or male groups).

## Discussion

### Overview

Patients with OSA show cortical thinning in three regions, each covering multiple structures, with additional bilateral areas showing sex-specific effects in females. We found left hemisphere cortical thinning associated with OSA independent of sex in the precentral motor gyrus, the postcentral sensory gyrus, and temporal and insular cortices. Thinning in cortical regions in OSA differed by sex, with bilateral thinning appearing specifically in female OSA subjects in the left superior medial frontal region, extending into the rostral mid-frontal lobe, and in a similar area on the right superior frontal cortex, extending into both the rostral mid-frontal lobes and the anterior paracentral/precentral lobule. These differences from males may

**Table 2. Areas of cortical thickness differences between OSA and control groups, as illustrated in Fig 1.** Areas are labelled according to the Desikan [20] and Brodmann [70] atlases.

Anatomical Location of Cluster	Functional structures in cluster	Previous OSA/control findings overlapping this cluster	Figure	Cluster size (mm <sup>2</sup> )	Peak (Talairach coordinates in mm)			
					X	Y	Z	P*
<ul style="list-style-type: none"> <li>L. precentral gyrus<sup>a</sup> (BA 4)</li> <li>L. postcentral gyrus (BA 1, 2, 3)</li> <li>L. superior temporal gyrus (BA 41, 42)</li> <li>L. superior parietal lobe (BA 5, 7)</li> <li>L. supramarginal gyrus (BA 40)</li> <li>L. inferior parietal lobe (BA 39)</li> </ul>	<ul style="list-style-type: none"> <li>L. partial coverage of mid sensory gyrus (lips, face, hand)</li> <li>L. mid motor gyrus (neck to wrist)</li> <li>L. superior temporal gyrus: Wernicke’s area, speech perception/upper airway</li> <li>L. supramarginal gyrus: language perception and processing</li> <li>L. inferior parietal lobe: integration of visual and somatosensory information, maintaining attention [71], interpretation of emotions [72]</li> </ul>	[46], [45], [43]	Fig 1i	3685	-35.0	-12.0	40.3	0.00010
<ul style="list-style-type: none"> <li>L. insula (BA 13, 14, 15, 16)</li> <li>L. temporal pole (BA 38)</li> </ul>	<ul style="list-style-type: none"> <li>L. insula posterior short gyrus/long gyrus (autonomic regulation, interoception &amp; emotion)</li> <li>L. temporal pole: semantic memory [73]</li> </ul>	[73]	Fig 1ii	1485	-35.5	-12.8	0.4	0.00700
<ul style="list-style-type: none"> <li>R. postcentral gyrus<sup>a</sup> (BA 1, 2, 3)*</li> <li>R. precentral gyrus (BA 4)</li> </ul>	<ul style="list-style-type: none"> <li>R. sensory gyrus in head/airway region (neck to tongue / swallowing)</li> <li>R. inferior motor gyrus (tongue/upper airway)</li> </ul>	[44]	Fig 1iii	1822	56.3	-8.3	11.2	0.00190

Abbreviations: L, left; R, right

a, FreeSurfer principal anatomical location of the peak (label of region most representative of area)

BA: Brodmann’s area

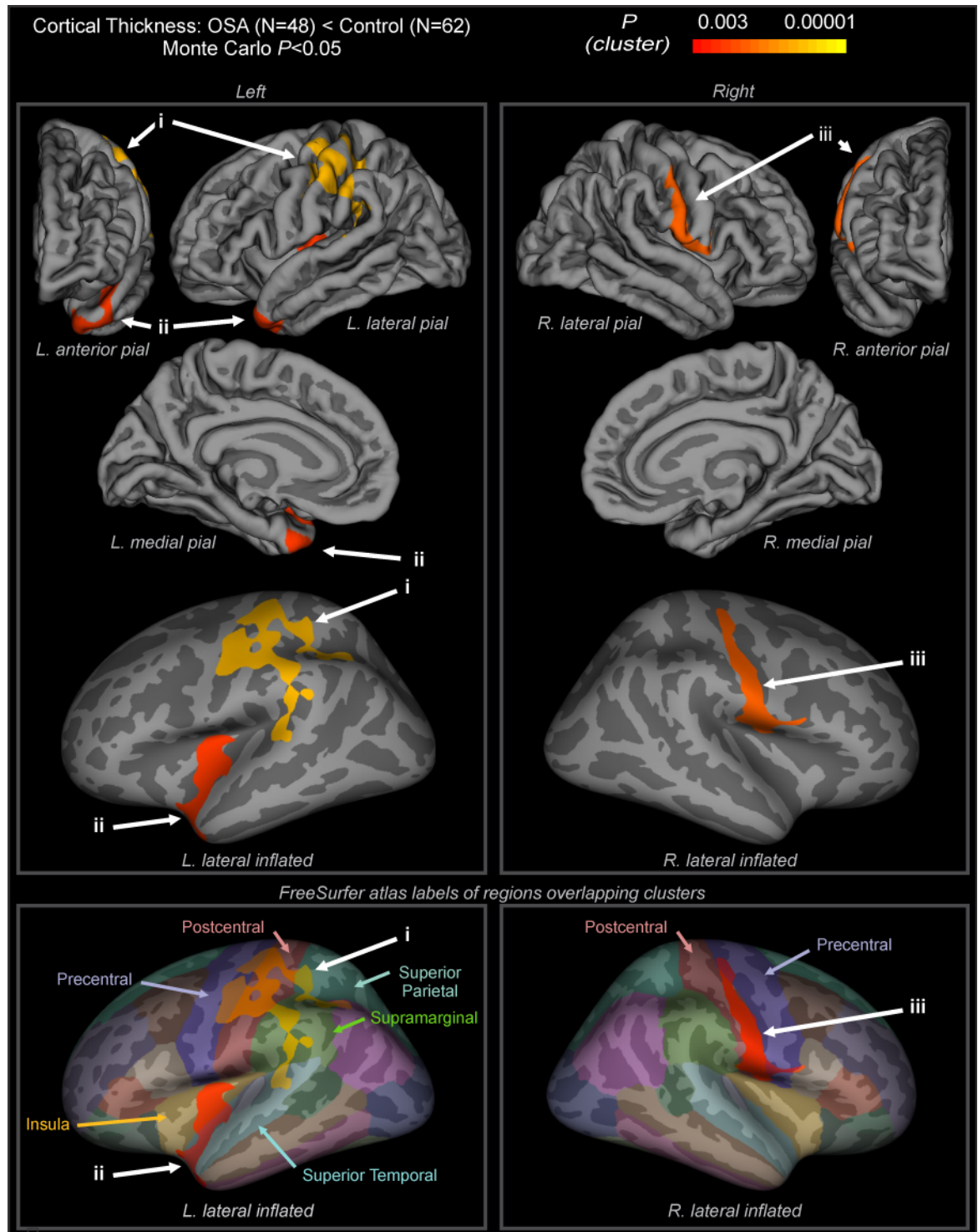
\* cluster-wise P-value.

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be related to sex-specific symptom patterns, especially cognitive symptoms that are more prominent in female OSA patients. The results add localized cortical atrophy to the brain characteristics that differ between males and females with OSA. Furthermore, an unanticipated finding was OSA thinning in regions associated with upper airway sensory and motor control. The thinning was especially noticeable in sensory and motor cortex, including upper airway, thoracic, abdominal and diaphragmatic regions.

### OSA effects: Relationships between affected areas and symptoms

A principal finding in OSA, independent of sex, was the cortical thinning in the motor and sensory areas of the upper airway musculature. Based on the motor homunculus, the damage within the left pre-central cortex in the OSA group represents regions that innervate the neck, face, lips, tongue, jaw muscles, as well as hands and arms [21]. Bilateral cortical damage was present within the somatosensory cortex in areas that innervate the face, upper and lower lip, tongue, pharynx, and nasal sensory areas [22]. In the left hemisphere, the region of damage extended into the superior parietal lobe, the supramarginal gyrus, the superior temporal gyrus, and the inferior parietal lobe. Progressive hypercapnia, hypoxia, and negative airway pressure enhance drive to upper airway dilator muscles [23–25]. Different muscle groups maintain upper airway patency, including muscles that control the tongue, palate, and hyoid [26]. The cortical thinning apparent in the sensory and motor integrative regions likely contributes to the atonia of genioglossal and upper airway pharyngeal dilator muscles in the presence of active diaphragmatic movements [26]. Being a cross-sectional study, we cannot distinguish whether the findings present cause or effect, and the cortical alterations may have preceded the



**Fig 1. Cortical thinning in OSA.** Regions showing cortical thinning in OSA compared to controls, accounting for sex ( $p < 0.05$ , Monte Carlo correction for multiple comparisons). Color scale shows the cluster-level  $p$  value. Hemisphere views include lateral, medial, frontal, and posterior. Pial and inflated views depicted, with light gray indicating gyri and dark gray sulci. (i) left hemisphere cluster extending into postcentral gyrus from lips and face to fingers sensory areas, precentral gyrus from neck to hand motor areas, supramarginal gyrus, Wernicke's area, and superior temporal lobe; (ii) left hemisphere cluster extending into mid and posterior insula, temporal pole; (iii) right hemisphere cluster extending along the postcentral gyrus from upper airway to hand sensory areas, precentral gyrus in pharynx/tongue to lip motor areas. See [Table 2](#).

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**Table 3. Interaction effect between condition and sex in mean thickness, as illustrated in Fig 2.** Areas are labelled according to the Desikan[20] and Brodmann[70] atlases.

Anatomical Location of Cluster	Functional structures in cluster	Figure	Cluster size (mm <sup>2</sup> )	Peak (Talairach coordinates in mm)			
				X	Y	Z	P*
<ul style="list-style-type: none"> <li>• L. superior frontal<sup>a</sup> (BA 9, 10)</li> <li>• L. Rostral middle frontal (BA 10)</li> </ul>	<ul style="list-style-type: none"> <li>• L. Superior frontal partial coverage executive decision making</li> <li>• L. Rostral middle frontal: apex of executive system underlying decision-making [74]</li> <li>• L. Cingulate (partial mid/partial anterior) adjacent (autonomic blood pressure regulation, cognitive decision-making/emotion)</li> </ul>	Fig 2iv	1125	-8.5	31.1	28.3	0.04170
<ul style="list-style-type: none"> <li>• R. Superior frontal<sup>a</sup> (BA 8, 9, 10)</li> <li>• R. rostral middle frontal (BA 10)</li> <li>• R. paracentral lobe (BA 6)</li> </ul>	<ul style="list-style-type: none"> <li>• R. Superior frontal-prefrontal cortex: extensive coverage of executive decision making area</li> <li>• R. Rostral middle frontal: prospective memory [75]</li> <li>• R. Cingulate (superior mid/partial anterior) adjacent (autonomic blood pressure regulation, cognitive decision-making)</li> <li>• R. Paracentral/precentral: supplementary motor area</li> </ul>	Fig 2v	3088	6.6	4.7	57.3	0.00010

Abbreviations: L, left; R, right

a, FreeSurfer principal anatomical location of the peak (label of region most representative of area)

BA: Brodmann's area

\* cluster-wise P-value.

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development of OSA [27]. As mentioned above, one region showing indications of thinning regulates upper airway musculature, so if injury lead to atonia, the patterns seen her could contribute to the onset of the sleep disorder.

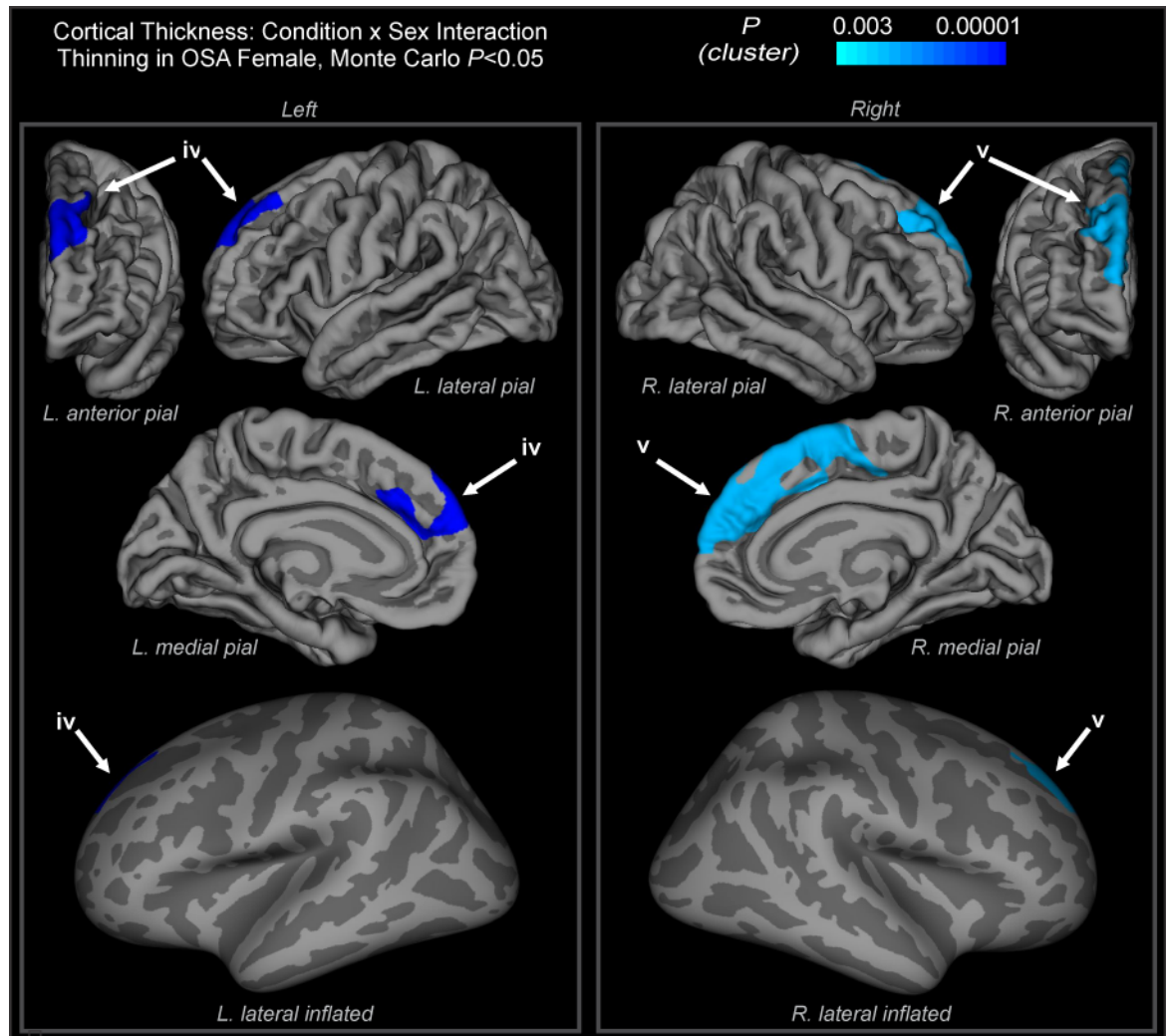
The cortical thinning of the insula may contribute to the sympathetic dysregulation in OSA. The insula helps to mediate sympathetic and parasympathetic outflow, and receives nociceptive and visceral sensory input to help integrate that outflow [28, 29]. The role of the insula in response to autonomic challenges has been described elsewhere in OSA and control populations [30–33]. The cortical thinning within the left insular cortex may contribute to the elevated sympathetic activity in OSA through reduction in inhibition of normal insular influences on the hypothalamus [34, 35].

### OSA by sex interactions: Relationships between affected areas and symptoms

The cortical damage in female OSA patients was localized bilaterally in the superior frontal regions, which have functions related to some sex-specific symptoms. Volume reductions in these areas could contribute to mood disturbances, such as depression [36]. Additionally, damage here may provide neuroanatomical substrates underlying disturbed executive function [37] and working memory [38]. The cortical thinning within the superior frontal regions extended into regions adjacent, or slightly overlapping the superior frontal gyrus, including the anterior cingulate cortex (ACC), which plays significant roles in executive processes of both cognition [39] and mood regulation [40], and projects to other limbic and prefrontal cortex sites [41]. However, depression-related areas are principally associated with the sub-genu of the ACC [42], while cortical thinning appeared only in the posterior aspect of the dorsal ACC; thus, the relationship of the enhanced depression signs in females to the thinning is not clear cut.

### OSA effects: Relationships with previous studies

The findings extend the existing body of OSA knowledge by demonstrating left motor and bilateral sensory strip cortical thinning in upper airway regions. The areas of cortical thinning



**Fig 2. Sex-specific cortical thinning in OSA.** Regions showing an interaction of condition and sex, with blue areas showing cortical thinning in OSA females ( $p < 0.05$ , Monte Carlo correction for multiple comparisons). Color scale shows the cluster-level  $p$  value. Pial and inflated views depicted, with light gray indicating gyri and dark gray sulci. (iv) left hemisphere cluster extending into superior medial frontal cortex, superior aspect of mid-to-anterior cingulate; (v) right hemisphere cluster extending into superior medial frontal cortex, prefrontal cortex, superior aspect of mid-to-anterior cingulate, supplementary motor cortex. See [Table 3](#).

<https://doi.org/10.1371/journal.pone.0193854.g002>

also overlap with data from earlier studies showing gray matter impairments in OSA. Reduced regional gray matter volume occurs in the right post-central gyrus, a site involved in sensory regulation of the upper airway, and in the temporal lobe [43, 44]. Severe apneic patients have been previously shown to have showed localized cortical thinning in regions overlapping, or adjacent to the current findings in the insular cortex and inferior parietal lobe [45]. Reduced gray matter integrity also appears in the pre-central gyrus in severe OSA patients [46]. The variation between studies likely relates to several factors, including variation between samples in terms of OSA severity, co-morbidities, and sex distributions, as well as inherent heterogeneity of the condition of OSA.

OSA is associated with specific reductions in gray matter in some structures, while white matter exhibits less volume reduction or potentially volume increases. In addition to the present and earlier findings of specific thinning in the cortex, additional studies, restricted to

individual gray matter structures, showed volume reductions, including the mammillary bodies [47], sub-regions of the putamen [48], and the hippocampus in a small sample [49]. White matter volume has not been specifically assessed, but changes could arise from astrocyte activation to hypoxia and increased water content [50]. For brain imaging studies, such processes would confound the standard voxel-based morphometry (VBM) analyses of regional gray matter volume, because VBM calculations are performed on a whole-brain scan, and influences of white matter structure will be present in determination of gray matter volume of the analyzed image. This confound could underlie the weaker findings of the VBM studies in the literature.

Sex is a factor that influences findings of OSA-related brain changes. Our group's work suggests OSA has a greater impact in females [4], so it is possible male-only samples would have a lower magnitude of structural change. Indeed, a recent study of 27 male-only patients showed no OSA effects on regional gray matter volume differences, although that same study did demonstrate hypoxia-related volume reductions in temporal bilateral temporal regions [51]. An earlier study of 27 OSA males also showed no large effect of OSA on gray matter volume [52], although when combined with a larger sample, volume reductions were apparent [43].

### OSA by sex interactions: Relationship with previous studies

The majority of studies of brain structure in OSA to date have either been only in males [44–46, 51, 52], or have included sex as a nuisance variable, but did not evaluate findings in males and females separately [47, 53]. Our earlier study of white matter integrity did show sex-specific differences [4], with greater reduction in axonal integrity in female OSA than male OSA patients. Using a diffusion tensor imaging (DTI)-derived measure to assess axonal structural integrity, namely fractional anisotropy (FA), OSA patients show extensive structural white matter changes. Affected axonal bundles include interconnecting fibers to limbic structures, such as the bilateral cingulum and right stria terminalis, and axons to bilateral frontal and parietal cortices and the left superior cerebellar peduncle [54]. The cortical damage associated with OSA to the left superior parietal cortex, the left inferior parietal cortex, and the bilateral pre- and post-central gyri may either be a cause of, or induced by, this white matter damage. However, only the superior frontal cortex showed sex-specific thinning associated with female OSA.

### Underlying pathophysiology of cortical thinning

Cortical thickness correlates with the number of neurons in a given region of the cortex, and reduced thickness suggests the presence of neuronal damage [55]. Reduced cortical thickness can represent neuronal degeneration as well as loss of supporting glia. Such damage could arise from several processes, including hypoxia, impaired perfusion, inflammation, or inadequate nutrient support, such as insufficient thiamine and magnesium, essential for glucose metabolism; this mechanism of injury is suspect in other regions [47]. Intermittent hypoxia produces both molecular and cellular neuronal damage, with sex-specific effects [56–58], and likely directly contributes to some of the injury identified here [59]. Impaired perfusion and hemodynamic changes presumably also contribute to the cortical structural deficits in OSA patients through ischemic processes. Regional cerebral blood flow in OSA is reduced in major sensory and motor fiber systems and motor regulatory sites [60], and may lead to the cortical damage observed in the pre- and post-central gyri. Intermittent hypoxia inflammation-induced microglia result in neuron apoptosis and CNS dysfunction [61], and presumably, cortical thinning would appear at the end of such processes (since the early stages of inflammation would be expected to be associated with volume increases rather than decreases). Pre-clinical stages of common co-morbidities of OSA such as type-2 diabetes and hypertension may

contribute to neural injury [52, 62], but whether such contributions to neural injury differ between sexes has not been examined.

## Limitations

A greater number of female OSA patients would have been preferable, but this was a secondary analysis as at the time of data collection sex-specific analyses were not planned. The OSA severity ranged from mild to very severe, with more mild patients in the female group, so the findings may have masked further sex differences, and variations with severity, especially given mild OSA (at least in males) may have limited clinical impact [63, 64]. While the cortical thickness-specific procedures are more sensitive to cortical changes than other techniques, the analysis is limited in spatial accuracy, as individual differences mean the necessary normalization (that is, matching individual brain scans to a reference template brain) will contain inaccuracies. A possible consequence of such limitations is that smaller regions impacted in OSA could have been missed. The possible inclusion of undiagnosed OSA in the control group may also have diluted the findings. The OSA subjects in the present study had, on average, fewer co-morbidities, lower medication usage, and lower BMI than the general OSA patient population, and therefore the findings may not generalize. The most likely difference in the general OSA population would be greater cortical thinning due to neurodegenerative consequences of comorbid conditions. Many symptoms with OSA and sex-specific associations such as age, BMI, and psychological symptoms are associated with changes to the brain [65–67], and a larger study could assess such effects in the OSA female and male populations; the group differences in these symptoms may have contributed to some of the effects seen. Handedness may have confounded the findings since both left and right-handed subjects were included. Since there were no differences in the proportions of right and left handed in OSA or control groups, the effect would likely be lower sensitivity to findings related to dominant handedness. The cerebellum was excluded from this analysis due to limitations of FreeSurfer software, but cerebellar cortex likely includes equivalent thinning given previous findings of reduced gray matter volume and axonal deficits in that region [43, 44, 46, 53, 68, 69]. With current sleep studies measures such as oxygen desaturation index we could assess the relationship between severity of intermittent hypoxia and cortical thinning; the AHI is known to be a poor indication of neurological symptoms [5].

## Conclusions

Newly-diagnosed OSA patients without major comorbidities showed cortical thinning in distinct regions of the cortex. One caveat is that polysomnography was not performed in all control subjects, so the results may be confounded by undiagnosed OSA in that group; such a confound would likely lead to higher false negatives. In particular, sensory and motor gyri in areas representing the upper airway and other respiratory control regions had thinner cortex in OSA relative to healthy control subjects. Distinct female and male patterns of OSA-related cortical thinning appeared, with thinning in female patients in the bilateral superior medial frontal and prefrontal cortices, which may underlie some of the sex differences in disease characteristics and comorbidities. In light of previously-shown gray and white matter changes in deeper brain structures of OSA patients, the CNS-related dysfunction in the condition likely arises from both poor axonal communication, due to the widespread white matter injury, and poor neural function, due to the localized gray matter injury. Damage to glia might also indirectly impair neural function. The alterations could arise from OSA directly, as well as from comorbidities and pathophysiology of the sleep disorder. These structural changes could include both long term neurodegeneration and short term processes, such as inflammation

and glial activation. The latter should be reversible with treatment, but the degree to which brain function deficits are reversible is unclear.

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