Title
Aberrant Insular Functional Network Integrity in Patients with Obstructive Sleep Apnea.

Journal
Sleep, 39(5)

ISSN
0161-8105

Authors
Park, Bumhee
Palomares, Jose A
Woo, Mary A
et al.

Publication Date
2016-05-01

DOI
10.5665/sleep.5738

Peer reviewed

pii: sp-00518-15 http://dx.doi.org/10.5665/sleep.5738

SLEEP DISORDERED BREATHING

Aberrant Insular Functional Network Integrity in Patients with Obstructive Sleep Apnea

Bumhee Park, PhD[1]; Jose A. Palomares, BS[1]; Mary A. Woo, RN, PhD[2]; Daniel W. Kang, MD[3]; Paul M. Macey, PhD[2,4]; Frisca L. Yan-Go, MD[5]; Ronald M. Harper, PhD[4,6]; Rajesh Kumar, PhD[1,4,7,8]

[1]Department of Anesthesiology, University of California at Los Angeles, Los Angeles, CA; [2]UCLA School of Nursing, University of California at Los Angeles, Los Angeles, CA; [3]Department of Medicine, University of California at Los Angeles, Los Angeles, CA; [4]The Brain Research Institute, University of California at Los Angeles, Los Angeles, CA; [5]Department of Neurology, University of California at Los Angeles; [6]Department of Neurobiology; University of California at Los Angeles, Los Angeles, CA; [7]Department of Radiological Sciences, University of California at Los Angeles, Los Angeles, CA; [8]Department of Bioengineering, University of California at Los Angeles, Los Angeles, CA

Study Objectives: Obstructive sleep apnea (OSA) is accompanied by tissue injury to the insular cortices, areas that regulate autonomic pain, dyspnea, and mood, all of which are affected in the syndrome. Presumably, the dysregulation of insular-related functions are mediated by aberrant functional connections with other brain regions; however, the integrity of the functional connectivity (FC) to other sites is undescribed. Our aim was to examine resting-state FC of the insular cortices to other brain areas in OSA, relative to control subjects.

Methods: We collected resting-state functional magnetic resonance imaging (MRI) data from 67 newly diagnosed, treatment-naïve OSA and 75 control subjects using a 3.0-Tesla MRI scanner. After standard processing, data were analyzed for the left and right insular FC.

Results: OSA subjects showed complex aberrant insular FC to several brain regions, including frontal, parietal, cingulate, temporal, limbic, basal ganglia, thalamus, occipital, cerebellar, and brainstem regions. Areas of altered FC in OSA showed linear relationships with magnitudes of sleep related and neuropsychologic-related variables, whereas control subjects showed no such relationships with those measures.

Conclusions: Brain functional connections from insular sites to other brain regions in OSA subjects represent abnormal autonomic, affective, sensorimotor, and cognitive control networks that may affect both impaired parasympathetic and sympathetic interactions, as well as abnormal sensorimotor integration, affected in the condition. The functional changes likely result from the previously reported structural changes in OSA subjects, as demonstrated by diverse neuroimaging studies.

Keywords: autonomic regulation, functional magnetic resonance imaging, resting-state functional connectivity, sleep disordered breathing

Citation: Park B, Palomares JA, Woo MA, Kang DW, Macey PM, Yan-Go FL, Harper RM, Kumar R. Aberrant insular functional network integrity in patients with obstructive sleep apnea. *SLEEP* 2016;39(5):989–1000.

Significance

Insula-related functional dysregulation can be mediated by aberrant functional connections with other brain regions that control autonomic, affective, sensorimotor, and cognitive functions, along with insular injury, as reported earlier in obstructive sleep apnea (OSA). Resting-state functional magnetic resonance imaging procedures, which have been applied in functional brain connectivity studies in diverse disease conditions, are useful in assessing such insular functional connectivity deficits in OSA subjects. The procedures can further help to understand how such abnormal functional connections show relationships with sleep- and neuropsychologic variables.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by frequent events of partial or complete obstruction of the upper airway, with continued diaphragmatic efforts to breathe during sleep.[1] The condition is associated with brain tissue injury in multiple regions, and especially the insular cortices, as altered free water content within tissue, brain metabolites, and regional gray matter volume. These tissue changes may contribute to the distorted autonomic, cognitive, affective, and sensorimotor functions found in the condition.[2–7]

Insular cortices play a significant role in regulating and/or integrating autonomic, cognitive, affective, and sensorimotor functions,[8–10] are involved in attention modulation,[8,10] and in integration of somatosensory input with interoceptive autonomic action,[9,11–14] all of which are important characteristics in OSA. Thus, insular changes may lead to the observed impaired regional functional magnetic resonance imaging (fMRI) responses to evoked autonomic, sensorimotor, and ventilatory challenges,[15–17] as well as altered insular resting state functional connectivity (FC) to other brain sites in OSA subjects.[18–20] However, insular FC to other brain regions and their characteristics in OSA remains unclear.

Resting-state functional magnetic resonance imaging (rs-fMRI) procedures have been widely used to assess FC, a term that denotes a statistical dependency between the time series of anatomically distinct brain sites.[21] Resting-state FC is measured as synchronized, spontaneous low-frequency (< 0.1 Hz) fluctuations of blood-oxygen-level-dependent (BOLD) signals across the resting brain,[22] and the phenomenon exhibits consistent patterns across healthy subjects.[23–26] The procedures have been applied in various functional brain network studies, ranging from psychiatric disorders to neurological conditions,[27] as well as in studies exploring human brain functions,[28–30] and thus, may be useful in assessing insular FC integrity in OSA subjects.

Our aim was to investigate how the insular cortices interact with other brain regions in newly diagnosed, treatment-naïve OSA patients, relative to age- and sex-comparable control subjects using resting-state FC procedures. We hypothesized that insular FC integrity to several other brain sites that regulate autonomic, affective, sensorimotor, and cognitive functions will be compromised in OSA subjects, and these altered functional connections will show relationships with sleep related and neuropsychologic-related variables in the condition.

Table 1—Demographic, neuropsychologic, cognitive, and sleep variables of obstructive sleep apnea and control subjects.

Variables	OSA (n = 67)	Controls (n = 75)	P
Age range, y	31–70	29–65	–
Age, y	48.0 ± 9.2	47.1 ± 9.3	0.6
Sex, male:female	51:16	56:19	0.8
BMI, kg/m^2	30.7 ± 6.0	25.1 ± 3.4	< 0.001
Handedness	9 Left; 52 Right; 6 Ambidextrous	12 Left; 58 Right; 5 Ambidextrous	–
Ethnicity	21 Asian; 38 White; 8 Hispanic; 4 African-American; 1 White-Asian; 1 Hispanic-White; 2 Iranian-White	11 Asian; 34 White; 11 Hispanic; 9 African-American; 1 Asian-White; 1 Iranian-White	–
AHI, events/h	35.6 ± 23.5	–	–
ESS	10.0 ± 4.9	5.2 ± 3.6	< 0.001
PSQI	8.9 ± 4.1	3.7 ± 2.5	< 0.001
BDI	8.6 ± 8.1	3.9 ± 5.0	< 0.001
BAI	9.6 ± 11.1	3.5 ± 4.7	< 0.001
Heart rate	79.6 ± 12.1 (n = 20)	3.9 ± 5.0 (n = 18)	0.338
Systolic BP	128.7 ± 15.0 (n = 20)	122.8 ± 13.5 (n = 18)	0.216
Diastolic BP	80.7 ± 9.5 (n = 20)	76.3 ± 12.0 (n = 18)	0.219
Global MoCA scores	25.4 ± 4.4 (n = 20)	26.7 ± 2.8 (n = 18)	0.306
MoCA: Visuospatial	3.8 ± 1.3 (n = 20)	4.5 ± 0.7 (n = 16)	0.041
MoCA: Naming	2.9 ± 0.3 (n = 20)	2.8 ± 0.5 (n = 16)	0.547
MoCA: Attention	5.2 ± 1.4 (n = 20)	5.4 ± 1.0 (n = 16)	0.585
MoCA: Language	2.5 ± 0.8 (n = 20)	2.4 ± 0.9 (n = 16)	0.966
MoCA: Abstraction	1.9 ± 0.4 (n = 20)	2 ± 0 (n = 16)	0.112
MoCA: Delayed recall	3.4 ± 1.7 (n = 20)	3.9 ± 1.2 (n = 16)	0.291
MoCA: Orientation	5.9 ± 0.3 (n = 20)	6 ± 0 (n = 16)	0.204

Values presented as mean ± standard deviation unless otherwise indicated. AHI, apnea-hypopnea index; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; BMI, body mass index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; BP, blood pressure; MoCA, Montreal Cognitive Assessment.

METHODS

Subjects

Sixty-seven newly diagnosed, treatment-naïve OSA and 75 age- and sex-comparable healthy controls were studied. A subset of both OSA and control subjects included here were common in recently-published manuscripts related to other issues in OSA.[31–33] Demographic, biophysical, sleep, and neuropsychologic data of OSA and control subjects are tabulated in Table 1. We recruited OSA subjects from the Sleep Disorders Laboratory at the University of California at Los Angeles (UCLA) Medical Center, and all OSA subjects had a moderate-to-severe diagnosis [apnea-hypopnea index (AHI) ≥ 15 events/h]. All OSA subjects were medication free, without any cardiovascular-altering medications (e.g., β-blockers, α-agonists, angiotensin-converting enzyme inhibitors, or vasodilators) or any mood-changing drugs (e.g., selective serotonin reuptake inhibitors, hemodynamic-altering, or metabolic-altering drugs). OSA and control subjects had no history of neurological illness or psychiatric disorders. All subjects were recruited from the UCLA campus and West Los Angeles area. We determined the potential for sleep disordered breathing in controls by interviewing control subjects, and subjects suspected of showing such disturbed patterns underwent an overnight sleep. OSA and control subjects were without any metallic implants, and without any conditions contraindicated for an MRI scanner environment. Before MRI scanning and other data collection, all participants gave written informed consent, and the study protocol was approved by the Institutional Review Board at the UCLA.

Assessment of Sleep, Mood, and Anxiety Symptoms

We evaluated sleep quality and daytime sleepiness in OSA and control subjects using the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) questionnaires, respectively. Depressive symptoms were assessed by the Beck Depression Inventory II (BDI-II), and anxiety symptoms by the Beck Anxiety Inventory (BAI) in OSA and control subjects. BDI-II and BAI include self-administered questionnaires (21 questions; each score ranges from 0 to 3), with total scores ranging from 0–63, based on mood or anxiety symptom severity.

Cognition Assessment

We used the Montreal Cognitive Assessment (MoCA) test for cognitive assessment. Various cognitive domains, including attention, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation, can be examined using the MoCA test.[34]

Magnetic Resonance Imaging

All participants underwent functional and structural MRI studies in a 3.0-Tesla scanner (Siemens, Magnetom Tim-Trio, Erlangen, Germany). Head motion-related artifacts during scanning were minimized by using foam pads. Rs-fMRI data were obtained with an echo planar imaging (EPI)-based BOLD sequence in the axial plane [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field-of-view (FOV) = 230 × 230 mm^2; matrix size = 64 × 64; voxel size = 3.59 × 3.59 × 4.5 mm^3; volumes = 59]. During the rs-fMRI scanning, all participants were instructed to rest with eyes open, without focusing on specific thoughts for about 2 min. We also acquired high-resolution T1-weighted images from each subject using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence (TR = 2200 ms; TE = 2.2, 2.34 ms; FA = 9°; FOV = 230 × 230 mm^2; matrix size = 256 × 256, 320 × 320; voxel size = 0.72 × 0.72 × 0.9 mm^3, 0.72 × 0.72 × 0.9 mm^3). To examine for any potential gross brain changes in each participant, proton density (PD) and T2-weighted images were also obtained in the axial plane, using a dual-echo turbo spin-echo pulse sequence (TR = 10,000 msec; TE1, 2 = 17, 134 msec; FA = 130°; matrix size = 256 × 256; FOV = 230 × 230 mm^2; voxel size = 0.9 × 0.9 × 4.0 mm^3). All brain imaging data were obtained between 08:00 to 16:00.

Data Preprocessing

We first examined anatomical scans for any serious brain pathology, such as tumors, cysts, or major infarcts using high-resolution T1-weighted, PD-, and T2-weighted images in all subjects. Rs-fMRI data were also examined for imaging or head motion-related artifacts before data preprocessing. No subject revealed any visible brain pathology, head motion-related, or other imaging artifacts.

Prior to FC analysis, rs-fMRI data were spatially preprocessed, including realignment of all EPI brain volumes for eliminating potential head motion, co-registration to T1-weighted images, spatial normalization to a canonical space template using nonlinear transformation procedures, and spatial smoothing of all normalized images with a 6 mm full-width half-maximum (FWHM) Gaussian kernel. Before rs-fMRI data processing, we discarded the initial three brain volumes to avoid signal saturation issues, and used the remaining 56 EPI scans for analysis. Averaged cortical maps, derived from T1-weighted images of individuals, and averaged whole-brain T1-weighted images, calculated from normalized T1-weighted images of all OSA and controls, were used as background images/maps for anatomical references. The evaluation of images and for preprocessing of rs-fMRI data were performed by We used the statistical parametric mapping package (SPM8, Wellcome Department of Cognitive Neurology, London, UK)[21] and MRIcroN software (http://www.mccauslandcenter.sc.edu/mricro/mricron/) for data processing and examination of images.

Resting-State FC Analysis

We applied canonical signal processing procedures to calculate the resting-state FC for each rs-fMRI data.[35] Each time series was band-pass filtered (0.009–0.08 Hz) and effects of six rigid-body motion parameters, their first derivatives, and global white matter, cerebrospinal fluid, and whole-brain signal changes were removed by regression. Head motion-related effects are a common issue in resting-state FC studies,[36–38] and the first derivatives of the motion parameters were added in the statistical model to minimize motion-related signal fluctuations.[38] Using MRIcroN software, the left and right insular seed regions were drawn directly on the population anatomical landmarks (i.e., background images derived from individual T1-weighted images of all OSA and control subjects) by a PhD-level researcher experienced with human brain anatomy. FC maps, between regional mean time series for left and right insular seed regions and whole-brain voxels, were calculated with a correlation approach. Individual correlation maps were converted into z-scored maps with Fisher r-to-z transformation to improve normality.

Statistical Analyses

We used the IBM Statistical Package for the Social Sciences (IBM SPSS, version 22, Armonk, NY) software to examine demographic, biophysical, sleep, and neuropsychologic scores. Demographic, biophysical, sleep, and neuropsychologic variables were examined by chi-square and independent samples *t*-tests.

We compared the z-scored maps voxel-by-voxel between OSA and control subjects using analysis of covariance (ANCOVA; covariates, age and sex). We performed 5,000 Monte Carlo simulations using the AlphaSim program, implemented in the REST toolbox (http://restfmri.net/) to control for multiple comparison issues. The simulations were examined with the following parameters: individual voxel level threshold, $P < 0.005$; cluster connection radius, 3.4 mm (edge connected); FWHM, 6 mm; individual voxel resolution, 2 × 2 × 2 mm^3, whole-brain gray matter mask. Based on these simulations, we obtained a corrected significance level of $P < 0.05$, with an extent threshold of 70 contiguous voxels (i.e., $P < 0.05$, cluster corrected). In addition, we also examined correlations between regionally averaged FC values, sites showing abnormal FC with the insular cortices in OSA, and sleep, AHI, and neuropsychologic variables. For correlation analyses, we performed partial correlation procedures (covariates; age, sex), and applied threshold levels of false discovery rate (FDR) < 0.05, FDR < 0.1, and FDR < 0.15 for multiple comparison correction with the number of regions. Although a conservative level, FDR < 0.05, is usually used in brain imaging study, dealing with large number of dependent variables, FDR control levels in the range 0.1~0.2 are originally known to be acceptable for multiple comparison correction.[39] All resting-state FC analyses were performed using MATLAB-based custom software.

RESULTS

Demographic, Sleep, Cognitive, and Neuropsychologic Values

We found no significant differences in age ($P = 0.6$), sex ($P = 0.8$), heart rate ($P = 0.338$), and systolic ($P = 0.216$) or diastolic blood pressure ($P = 0.219$) between OSA and control subjects (Table 1). However, sleep variables, including the PSQI and ESS scores, and neuropsychologic values, including the BDI-II

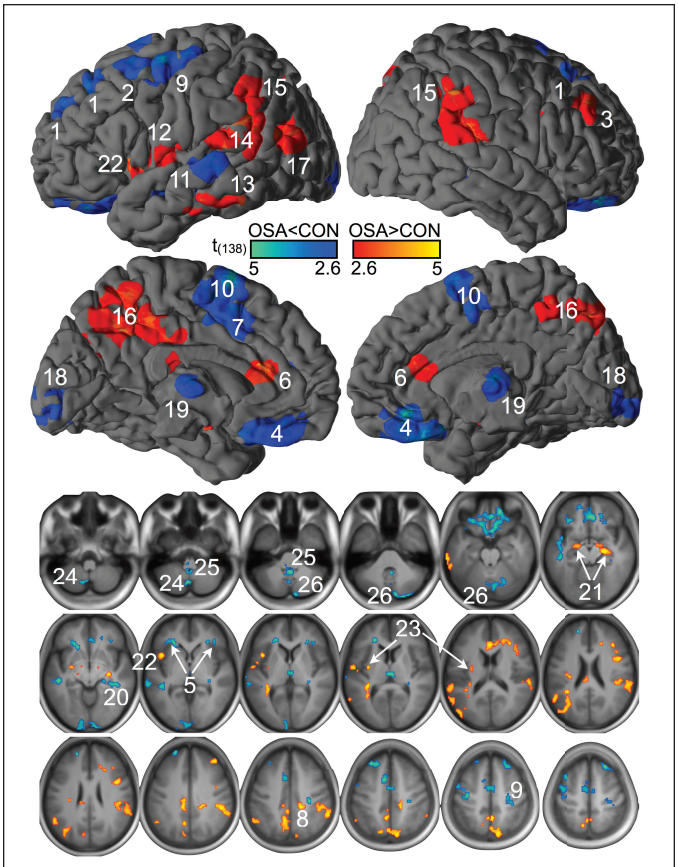

Figure 1—Altered left insular resting-state functional capacity (FC) to various brain areas in OSA subjects. Significantly compromised FC emerged from the left insula to (1) the superior frontal gyrus, (2–3) middle frontal gyrus, (4) ventral medial prefrontal gyrus/orbital frontal gyrus, (5) inferior frontal gyrus, (6) anterior cingulate cortex, (7–8) mid cingulate cortex, (9) precentral gyrus, (10) somatosensory motor area, (11) middle temporal gyrus, (12) rolandic operculum, (13) inferior temporal gyrus, (14) superior temporal gyrus, (15) inferior parietal lobe, (16) precuneus, (17) mid orbital gyrus, (18) calcarine, (19) thalamus, (20–21) hippocampus, (22–23) insula, (24) vermis, (25) cerebellar tonsil, and (26) cerebellar crus II. CON, control.

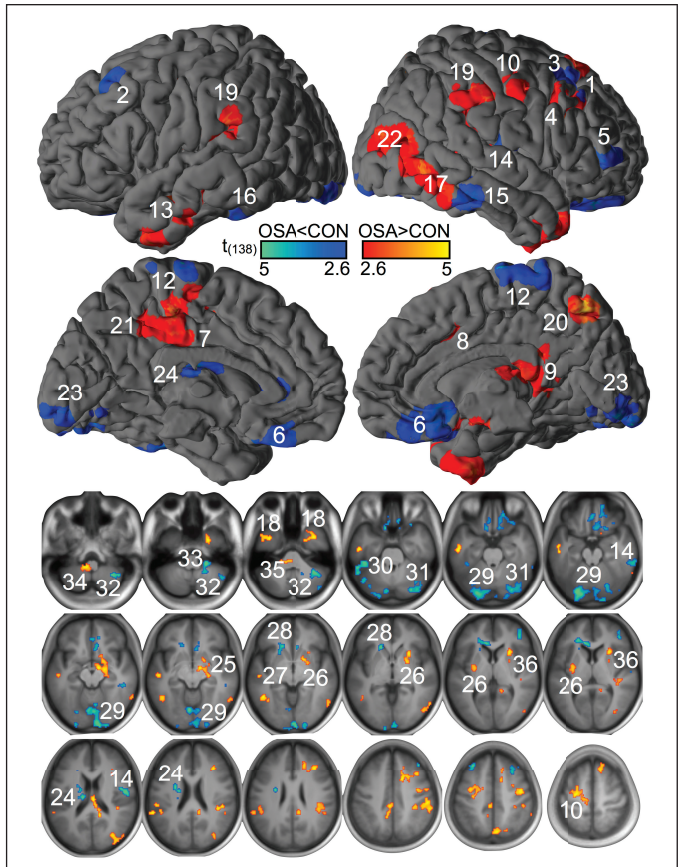

Figure 2—Altered right insular resting-state FC to other brain regions in obstructive sleep apnea (OSA) subjects. Significantly different FC appeared from the right insula to (1) the superior frontal gyrus, (2–5) middle frontal gyrus, (6) ventral medial prefrontal gyrus/orbital frontal gyrus, (7–8) mid cingulate cortex, (9) posterior cingulate cortex, (10–11) precentral gyrus, (12) paracentral lobule, (13) mid temporal gyrus, (14) rolandic operculum, (15–17) inferior temporal gyrus, (18) temporal pole, (19) inferior parietal lobe, (20–21) precuneus, (22) mid orbital gyrus, (23) calcarine, (24) thalamus, (25) hippocampus, (26–27) putamen, (27–28) caudate, (29) cerebellar crus I and lingual gyrus, (30–31) cerebellar crus I, (32) cerebellar crus I and II, (33) cerebellar crus II, (34) medulla, and (35) pons. CON, control.

and BAI scores, showed significant differences between OSA and control subjects (PSQI, $P < 0.001$; ESS, $P < 0.001$; BDI-II, $P < 0.001$; BAI, $P < 0.001$). BMI values were significantly larger in OSA over control subjects ($P < 0.001$). Although limited number of OSA and control subjects, global MoCA scores did not differ significantly between groups ($P = 0.306$), but significant difference emerged in the visuospatial domain between groups ($P = 0.041$).

Insular Resting-State FC

The insular resting-state FC differences between OSA and control groups are displayed in Figures 1 and 2 and summarized in Tables 2 and 3. We found significantly altered functional connections from insular areas to other whole-brain regions ($P < 0.05$, cluster-corrected). Decreased resting-state FC in OSA emerged from the left insula to the bilateral ventral medial prefrontal cortex (MPFC) and orbitofrontal gyrus (OFG), bilateral superior frontal gyrus (SFG), bilateral midfrontal gyrus (MFG), right inferior frontal gyrus (IFG), bilateral somatosensory motor area (SMA), bilateral precentral gyri, left mid cingulate cortex (MCC), left mid-temporal gyrus (MTG), bilateral thalamus, right posterior hippocampus, bilateral calcarine, and bilateral tonsil, right crus II, and left vermis of the cerebellum (Figure 1). However, increased FC in OSA appeared between the left insula and the right IFG, right MFG, bilateral anterior cingulate cortex (ACC), right MCC, bilateral anterior hippocampus, left insula, left mid orbital gyrus (MOG), bilateral inferior parietal lobe (IPL), bilateral precuneus, left superior temporal gyrus (STG) and inferior temporal gyrus (ITG), and left rolandic operculum (Figure 1). Decreased right insular FC in OSA appeared to the bilateral ventral MPFC and OFG, bilateral MFG, bilateral paracentral lobule, right ITG, right rolandic operculum, bilateral crus I, right crus II, bilateral calcarine, left caudate, left anterior putamen, and left thalamus (Figure 2). However, increased right insular FC in OSA emerged to the right SFG, right MFG, right anterior and left posterior cingulate cortex (PCC), right hippocampus, right

Table 2—Significantly decreased insular functional connectivity in obstructive sleep apnea subjects.

Category	Location	Regions	Hemisphere	Cluster size	Peak z-value	MNI coordinates
Left	Frontal lobe	Ventral MPFC, OFG	L and R	1661	5.12	14 44 −20
		SFG	R	87	4.86	26 30 56
		MFG	L	94	4.12	−22 52 34
		SFG	L	91	3.98	−30 36 48
		IFG	L and R	72	3.95	28 32 0
		SMA	L and R	532	4.49	0 6 72
	Parietal lobe	Precentral gyrus, MFG	L	277	4.4	−38 12 60
		Precentral gyrus	R	130	4.02	30 −26 42
	Temporal lobe	MTG	L	386	4.2	−46 −28 −12
	Thalamus/basal ganglia	Thalamus	L and R	84	3.95	4 −18 8
	Limbic lobe/insula	Posterior hippocampus	R	155	3.85	38 −34 −6
		MCC	L	123	4.1	−8 8 48
	Occipital lobe	Calcarine	L and R	282	3.83	10 −102 −8
	Cerebellum	Cerebellar tonsil	L and R	154	4.64	−2 −50 −44
		Cerebellar crus II	R	304	4.25	10 −86 −40
		Vermis	L	77	4.21	−4 −66 −50
Right	Frontal lobe	MFG	R	176	4.66	32 30 54
		Ventral MPFC, OFG	L and R	526	4.23	−10 18 −26
		MFG	L	71	4.13	−30 32 48
		MFG	R	84	3.71	42 40 4
	Parietal lobe	Paracentral lobule	L and R	216	4.91	0 −26 78
	Temporal lobe	ITG	R	119	4.03	62 −36 −20
		Rolandic operculum	R	113	3.84	56 −14 16
	Thalamus/basal ganglia	Caudate, putamen	L	223	4.17	−10 30 4
		Thalamus	L	151	4.16	−14 −20 16
	Cerebellum	Cerebellar crus I, lingual gyrus	L and R	1197	5.64	−22 −84 −22
		Cerebellar crus I	L	269	4.73	−52 −50 −30
		Cerebellar crus I	R	336	4.67	30 −78 −26
		Cerebellar crus I and II	R	295	4.53	36 −52 −38
		Cerebellar crus II	R	113	4.45	22 −38 −48

IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; MCC, middle cingulate cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MPFC, middle prefrontal cortex; MTG, middle temporal gyrus; OFG, orbital frontal gyrus; R, right; SFG, superior frontal gyrus; SMA, somatosensory motor area.

PCC, bilateral ITG, left MTG, bilateral temporal pole, bilateral IPL, bilateral precuneus, bilateral precentral gyri, right MOG, right anterior and left posterior putamen, left ventrolateral medulla, and left pons.

Correlations between the Insular FC and Clinical Variables

AHI values showed positive correlations with regionally averaged increased left insular FC, and negative correlations with decreased FC in OSA subjects (FDR < 0.15; Figure 3). PSQI, BDI-II, and BAI showed positive correlations with regionally averaged left insular FC values for areas showing significantly decreased connectivity in OSA, and manifested negative correlations with those values for regions significantly increased FC in OSA (FDR < 0.15; Figure 4). ESS values did not show any significant relationship with either increased or decreased FC values in OSA subjects. Also, the right insular FC did not show any significant correlation with those clinical variables in OSA subjects. However, FC values of control subjects showed no correlations with PSQI, ESS, BDI-II, and BAI measures.

AHI values were positively correlated with connection weights at the precuneus, IPL, Rolandic operculum, ITG, and

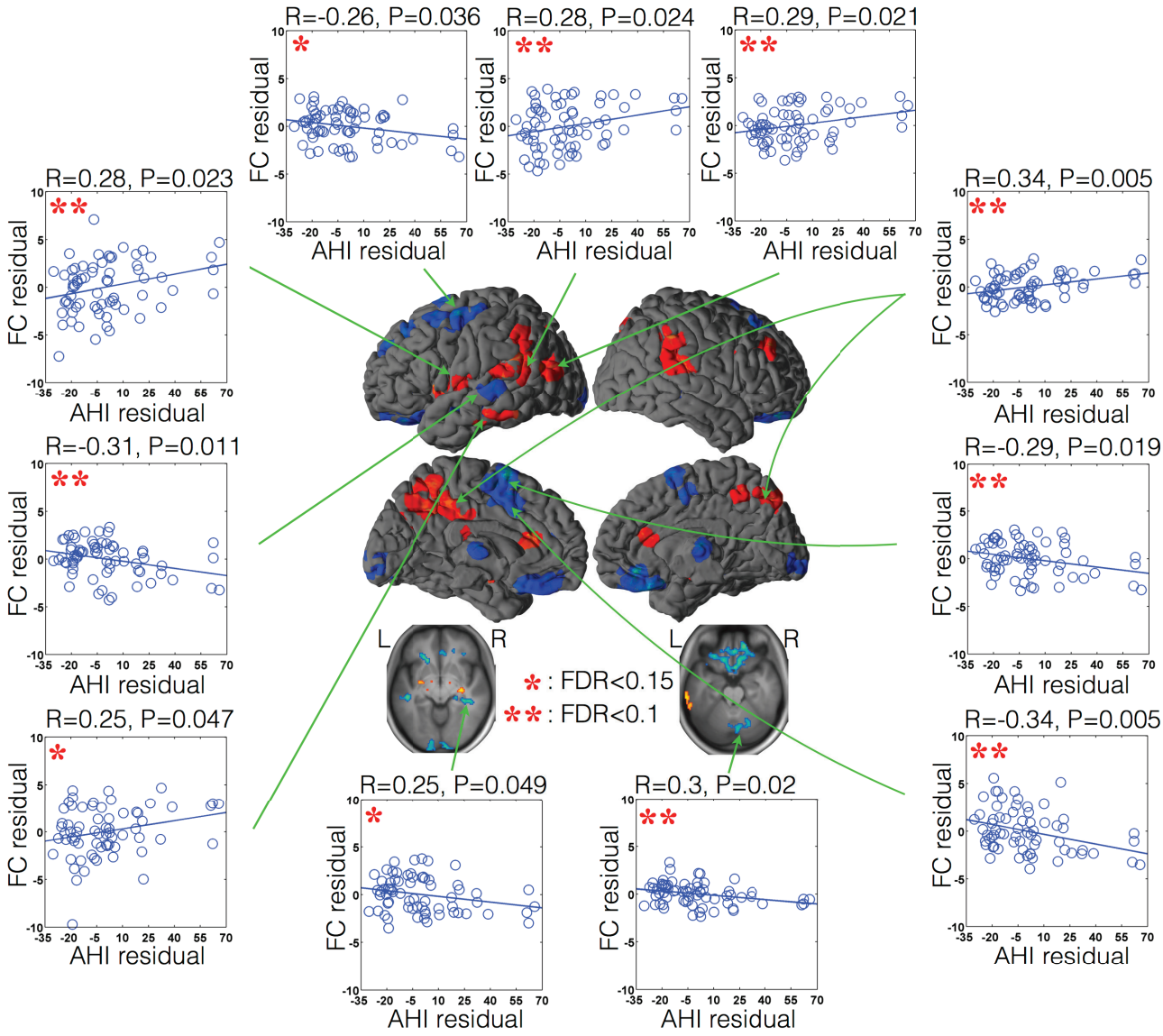

Figure 3—Significant partial correlations between the left insular z-scored functional capacity (FC) and apnea-hypopnea index (AHI) values in obstructive sleep apnea (OSA) subjects (covariates: age, sex). Blue dot and line represent each estimated residual value pair after controlling age and sex and the corresponding regression line for OSA subjects. Symbols, * and **, indicate a threshold of false discovery rate (FDR) < 0.15 and FDR < 0.1, respectively.

MOG from the left insular resting-state FC, and were negatively correlated with connection weights at the bilateral SMA, left MCC, left MTG, left precentral gyrus, right posterior hippocampus, and right cerebellar crus II from the left insular resting-state FC in OSA subjects.

PSQI values of OSA subjects showed negative correlation with connection weights at the left STG from the left insular resting-state FC. BDI-II values showed positive correlations with connection weights at the vermis from the left insular resting-state FC. We found that BAI values are positively correlated with connection weights at the left SFG, bilateral ventral MPFC and OFG, the vermis, and the tonsil from the left insular resting-state FC. The connection weights at the bilateral anterior hippocampus and precuneus from the left insular resting-state FC showed negative correlations with BAI values.

DISCUSSION

Previous OSA studies, using exploratory rs-fMRI procedures, have discovered decreased local FC in frontal, temporal, and parietal regions, and increased regional FC in the sensorimotor, thalamic, and cerebellar areas.[18–20] However, each previous study was limited by exclusion of the cerebellum or only by applying seven functionally defined subnetworks, without specific hypotheses. In the current study, we examined the insular resting-state FC in OSA with the hypotheses that autonomic and affective connections of whole-brain regions would be compromised. A core question was how the insular cortices abnormally interplay with other brain sites in OSA, and how such abnormal connections will show relationships with sleep and neuropsychologic variables. We observed considerably aberrant FC patterns using both seed regions of left and right insular cortices. The abnormal functional connections were

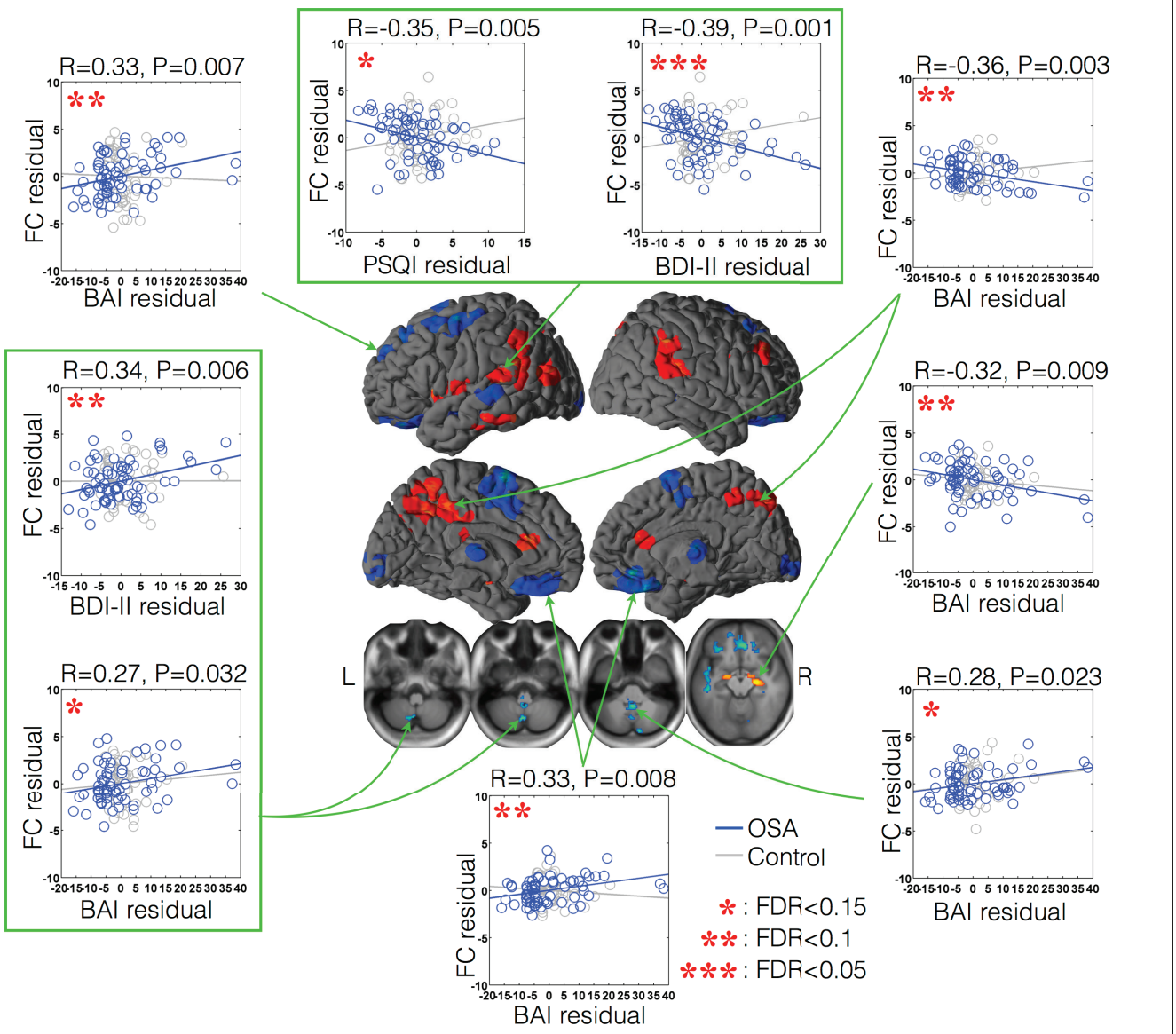

Figure 4—Significant partial correlations between the left insular z-scored functional capacity (FC) and Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI)-II, and Beck Anxiety Inventory (BAI) values in obstructive sleep apnea (OSA) subjects. Blue dot and line represent each estimated residual value pair after controlling the effects of age and sex and the corresponding regression line for OSA subjects. Light gray dot and line represent estimated residual value and corresponding regression line for control subjects. Correlation coefficients, R, and P values, P, are for OSA data; control subjects' data did not show any significant correlations. Symbols *, **, and *** indicate a threshold of false discovery rate (FDR) < 0.15, FDR < 0.1, and FDR < 0.05, respectively.

broadly distributed in various brain regions that control autonomic, affective, cognitive (executive, attention, and memory function), and sensorimotor functions, sites that appeared either structurally or functionally impaired in previous OSA studies.[2,4,7,15,18–20,40,41] Moreover, the connection weights to these regions showed significant correlations with sleep and neuropsychologic values.

Connection Changes in Autonomic Neural Circuits

OSA subjects show impaired autonomic regulation, such as distorted timing to autonomic challenges (e.g., delayed onset of heart rate changes)[42] and excessive sympathetic tone.[17,43,44] In this study, we showed significantly altered resting-state FC in OSA subjects from insular to cingulate cortices, ventral MPFC and OFG, and putamen, sites that are involved in autonomic and motor neural circuitry. The insular cortices are known as significant brain regions for autonomic regulation, and influence both sympathetic and parasympathetic activity.[44,45] Previous structural MRI studies showed gray matter tissue loss[3,46,47] and altered mean diffusivity[2] in multiple sites, including the insular cortices, in OSA subjects. Functional MRI studies in OSA also showed disturbed insular signals cold pressor[17] and Valsalva maneuver challenges,[16] and compromised brain insular metabolites.[40,48–50] The cingulate cortex is another significant brain region for autonomic and respiratory control,[51] and also showed gray matter tissue

Table 3—Significantly increased insular functional connectivity in obstructive sleep apnea subjects.

Category	Location	Regions	Hemisphere	Cluster size (number of voxels)	Peak z-value	MNI coordinates
Left	Frontal lobe	IFG, MFG	R	438	4.53	42 4 26
	Limbic lobe/insula	ACC	L and R	139	4.69	0 28 16
		MCC	R	145	4.26	18 −34 42
		Anterior hippocampus	R	153	5.75	24 −18 −12
		Insula	L	75	4.63	−44 10 2
		Insula	L	90	3.87	−34 −8 8
		Anterior hippocampus	L	84	3.6	−30 −8 −10
	Occipital lobe	MOG	L	495	4.43	−34 −46 20
	Parietal lobe	IPL	R	676	4.24	50 −36 38
		Precuneus	L and R	760	4.19	−8 −58 40
		IPL	L	95	3.4	−58 −56 40
	Temporal lobe	ITG	L	94	4.48	−66 −22 −28
		STG	L	160	4.19	−54 −54 24
		STG	L	76	4.1	−62 −42 18
		Rolandic operculum	L	71	3.64	−58 −8 8
Right	Limbic lobe	PCC	R	202	4.14	10 −42 26
	Multiple regions	Putamen, hippocampus, SFG/MFG, MCC	R	1079	4.85	26 16 2
		MCC, precuneus, precentral gyrus	L	602	4.1	−8 −26 34
	Occipital lobe	MOG	R	209	3.88	52 −76 14
	Parietal lobe	Precuneus	R	162	4.44	6 −72 50
		Precentral gyrus	R	195	4.29	44 −8 46
		IPL	R	642	4.21	40 −28 32
		IPL	L	121	3.71	−60 −42 22
	Temporal lobe	MTG	L	136	4.03	−52 −20 −10
		ITG	L	81	3.88	−46 −54 −8
		ITG	R	128	3.77	60 −64 −4
		Temporal pole	L	114	3.66	−48 6 −38
		Temporal pole	R	183	3.65	36 4 −40
	Thalamus/basal ganglia	Putamen	L	81	3.95	−30 −6 6
	Brainstem	Medulla	L	90	4.97	−8 −42 −54
		Pons	L	91	4.13	−14 −34 −36

ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; L, left; MCC, mid cingulate cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MOG, mid orbital gyrus; MTG, mid temporal gyrus; PCC, posterior cingulate cortex; R, right; SFG, superior frontal gyrus; STG, superior temporal gyrus.

loss and thinning [4,46,52] and reduced mean diffusivity in OSA subjects.[2] The putamen, which serves autonomic and motor regulation roles, and receives projections from the insular cortices,[53] is also structurally injured and shows functional deficits during autonomic and respiratory challenges in OSA subjects.[2,41,54,55] Moreover, injury in the ventral MPFC in OSA subjects, a cortical region involved in autonomic control, was also reported.[4]

In this study, we found exaggerated connection weights from the insular cortices to ACC, MCC, PCC, and putamen, and decreased connection weights in the bilateral ventral MPFC and OFG, a part of the putamen, and MCC. Moreover, it is also evident that the connection weights of the MCC in OSA subjects were correlated with AHI scores, although the control group did not show such relationships. Thus, it is possible that diverse abnormal characteristics in each region, as

previously reported in several studies, affect functional integration among regions in autonomic neural circuit.

Connection Changes in Affective Circuits

OSA subjects often reveal enhanced depressive symptoms and high levels of anxiety,[56] and such OSA subjects also show exaggerated brain injury in particular brain areas over OSA subjects without these symptoms.[47,57] As previously reported,[47,57] damage in the insular and cingulate cortices, frontal regions, hippocampus, and amygdala are involved in affective disorders, such as depression and anxiety symptoms in OSA subjects.[2,4,47,57,58] Notably, the ACC showed significantly more injury in OSA patients with high depressive symptoms over those without such signs,[47,57] and stimulating the ACC greatly improves depressive signs.[58] The hippocampus is structurally impaired in adults with OSA[2,3,6] and in children with OSA,[59] and functionally impaired in OSA subjects, and is involved in cognition, especially short-term memory.[60]

Similarly, we found aberrant, but largely increased, functional connection weights and significant correlations with BAI values. Increased connections included those between the left insula and bilateral dorsal ACC and bilateral anterior hippocampus, and between the right insula and right hippocampus. However, decreased FC emerged between the left insula and the right posterior hippocampus. The connections between the bilateral anterior hippocampus and the left insular cortices were negatively correlated with BAI. Also, BAI values showed positive correlations with connection weights to the left SFG in the left insula resting-state FC. Thus, these compromised connections from insular to other affective regulatory brain areas may contribute to affective deficits in the condition.

Connection Change in Attention, Sensorimotor, and Executive Circuit

Sleep disturbances in OSA subjects can lead to dysfunction in the attention domain. Previous studies have shown that reduced gray matter volume[61] and cortical thickness[46] occur in the SFG and posterior parietal cortex in OSA, which may influence attention processing.[62,63] We also found abnormal functional connections between insular cortices and these sites, including the SFG, IPL, and precuneus regions, and deficient attention in OSA may originate from abnormal integration of these functional connections. Also, the connection weights from the left insular areas to the left IPL and bilateral precuneus show significant correlations with AHI scores, indicating an influence from disturbed breathing to structures regulating attention.

In OSA subjects, damage resulting from mechanical vibration or trauma and/or hypoxemia associated with repetitive upper airway collapse may further impair sensorimotor function.[64] OSA subjects show cortical thinning in bilateral precentral and postcentral gyrus,[46] and the ventrolateral thalamus, as primary projection areas, can also be affected as demonstrated.[2–4] As reported earlier, the connection weight from the left insular areas to the left precentral gyrus shows significant correlations with AHI scores.

In this study, we discovered evidence of functional deficits consisting of decreased insular connections to sensorimotor regions, such as bilateral precentral gyrus, bilateral paracentral lobule, and bilateral thalamus, which is consistent with a recent report that also showed decreased sensorimotor FC in OSA using resting-state FC procedures.[20] Meanwhile, increased connections between the right PCC and right insular cortices might also reflect diverse functional compensation, including sensorimotor function, as reported recently in a resting-state FC study.[20]

Deficient executive functions are other characteristics of OSA subjects.[65,66] Executive function deficits in OSA may originate from neuronal damage in regions among the prefrontal cortex, caudate nuclei, SMA, ACC, and insular cortices,[2,4,52,54] projections that are well known intrinsic executive networks, discovered by resting-state FC.[67] Consistently, our study showed decreased insular functional connections to the bilateral SFG, MFG, ACC, and ventral MPFC and OFG, left caudate nuclei, and SMA that may contribute to deficient executive functions in the condition.

Connection Change in Cerebellar, Brainstem, Temporal, and Occipital Regions

The cerebellum contains areas important for blood pressure and respiratory muscle coordination, and is a region most affected in OSA subjects, which is evident from several MRI-based neuroimaging studies.[2–4] Such impairment in the cerebellum may also contribute to autonomic deficit in OSA and be observed as altered functional connections with multiple brain sites, including the insula. OSA patients show diminished gray matter volume in cerebellar cortices and deep nuclei.[3] Multiple cerebellar sites, including the left cerebellar uvula, bilateral cerebellar crus I, and right cerebellar crus II, extending to the middle cerebellar peduncle, right medial/inferior cerebellar peduncle in OSA subjects showed altered tissue integrity, based on mean diffusivity procedures.[2] Also, OSA patients reveal broadly distributed alteration of white matter integrity in projections between the cerebellum and cerebral major structures.[4]

Similarly, our study showed decreased insular FC with several cerebellar regions. The left insula showed diminished FC with the bilateral tonsil, right cerebellar crus II, and left vermis, and the right insula with the bilateral cerebellar crus I (some regions were contiguous to the lingual gyrus), and right cerebellar crus II. Also, a significant relationship appeared between AHI and connection weights in the bilateral cerebellar crus II from the left insular cortices. Meanwhile, the cerebellar damage in OSA subjects may exert influences on disruption of higher order cognitive processes, as well as loss of coordination of upper airway muscle activity and failure to dampen both parasympathetic and sympathetic tone. As one piece of evidence, we show that the connection weights to the vermis and tonsil from the left insular cortices are positively correlated with neuropsychological variables, including BDI-II and BAI scores.

Our current study also found abnormal FC in OSA subjects from the insula to the bilateral temporal regions, occipital regions, ventrolateral medulla, and mid to lateral caudal pons. The findings are consistent with previous studies which show affected structures in OSA subjects.[2–4,20,49,68] Medullary injury appeared in a recent diffusion tensor imaging (DTI) study, in

which damage was located in dorsal, ventral, and ventrolateral medulla sites in OSA subjects.[2] The medullary and pons are involved in breathing regulation, and also influence sympathetic tone. The current study also showed positive correlations with AHI and connection weights to the left pons.

Limitations

The current study used a temporal scale of 120 sec, which is relatively short, and a modest duration for a time series. However, recent FC studies have addressed importantly temporal dynamics of brain network within a session, e.g., studies with temporal scale less than 60 sec.[69–71] We believe that our findings are acceptable and supplemented with a large number of subjects, even if we used relatively short length of time series. Also, we acquired rs-fMRI data after high-resolution T1-weighted, T2- and proton density-weighted, and DTI, because this resting-state examination was a part of a large study, we assume that subjects have sufficient time to come down to their resting state. Global signal regression applied in our study still remains a controversial issue, because the procedure can translate FC density to negative ranges.[72,73] However, we decided to use the procedure as a necessary noise reduction step, because global signal accounts for spatially shared variance and its primary fraction may be related to residual effects of head-motion or respiration.[38,74,75] Global signal regression procedure could also effectively minimize nonneural noise[76] or improve the FC specificity.[30,77] We did not include BMI values as a covariate in our ANCOVA model, because increased BMI is one of the main characteristics of OSA, and difference between two groups is natural. Also, we did not record metabolic data from OSA and control subjects, which may contribute to neural changes, and further investigation is required to assess any contribution from metabolic syndrome in OSA subjects.

CONCLUSIONS

Recently diagnosed treatment-naïve OSA subjects show complex aberrant FC between the insular cortices and several other brain regions regulating autonomic, affective, sensorimotor, and cognitive functions. The aberrant FC values were correlated to several sleep related and neuropsychologic variables. The altered FC may affect both parasympathetic and sympathetic interactions, as well as sensorimotor integration, all of which are affected in OSA. The functional changes likely result from the prominent structural changes with the condition in these regions.

ABBREVIATIONS

ACC, anterior cingulate cortex
DTI, diffusion tensor imaging.
IFG, inferior frontal gyrus
ITG, inferior temporal gyrus
IPL, inferior parietal lobule
MCC, middle cingulate cortex
MFG, middle frontal gyrus
MOG, middle occipital gyrus
MPFC, medial prefrontal cortex
MRI, magnetic resonance imaging
MTG, middle temporal gyrus
OFG, orbitofrontal gyrus
SFG, superior frontal gyrus
PCC, posterior cingulate cortex
SMA, supplementary motor area
STG, superior temporal gyrus

REFERENCES

1. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Annu Rev Med 1976;27:465–84.
2. Kumar R, Chavez AS, Macey PM, Woo MA, Yan-Go FL, Harper RM. Altered global and regional brain mean diffusivity in patients with obstructive sleep apnea. J Neurosci Res 2012;90:2043–52.
3. Macey PM, Henderson LA, Macey KE, et al. Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 2002;166:1382–7.
4. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM. Brain structural changes in obstructive sleep apnea. Sleep 2008;31:967–77.
5. Torelli F, Moscufo N, Garreffa G, et al. Cognitive profile and brain morphological changes in obstructive sleep apnea. NeuroImage 2011;54:787–93.
6. Morrell MJ, McRobbie DW, Quest RA, Cummin AR, Ghiassi R, Corfield DR. Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 2003;4:451–4.
7. Kumar R, Pham TT, Macey PM, Woo MA, Yan-Go FL, Harper RM. Abnormal myelin and axonal integrity in recently diagnosed patients with obstructive sleep apnea. Sleep 2014;37:723–32.
8. Hatton SN, Lagopoulos J, Hermens DF, Naismith SL, Bennett MR, Hickie IB. Correlating anterior insula gray matter volume changes in young people with clinical and neurocognitive outcomes: an MRI study. BMC Psychiatry 2012;12:45.
9. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans. Clin Auton Res 1996;6:131–40.
10. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42:1727–32.
11. Craig AD. Emotional moments across time: a possible neural basis for time perception in the anterior insula. Philos Trans R Soc Lond B Biol Sci 2009;364:1933–42.
12. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nat Neurosci 2000;3:184–90.
13. Zhang ZH, Dougherty PM, Oppenheimer SM. Monkey insular cortex neurons respond to baroreceptive and somatosensory convergent inputs. Neuroscience 1999;94:351–60.
14. Yasui Y, Breder CD, Saper CB, Cechetto DF. Autonomic responses and efferent pathways from the insular cortex in the rat. J Comp Neurol 1991;303:355–74.
15. Macey PM, Kumar R, Ogren JA, Woo MA, Harper RM. Global brain blood-oxygen level responses to autonomic challenges in obstructive sleep apnea. PLoS One 2014;9:e105261.
16. Henderson LA, Woo MA, Macey PM, et al. Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. J Appl Physiol 2003;94:1063–74.
17. 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;94:1583–95.
18. Peng DC, Dai XJ, Gong HH, Li HJ, Nie X, Zhang W. Altered intrinsic regional brain activity in male patients with severe obstructive sleep apnea: a resting-state functional magnetic resonance imaging study. Neuropsychiatr Dis Treat 2014;10:1819–26.
19. Santarnecchi E, Sicilia I, Richiardi J, et al. Altered cortical and subcortical local coherence in obstructive sleep apnea: a functional magnetic resonance imaging study. J Sleep Res 2013;22:337–47.
20. Zhang Q, Wang D, Qin W, et al. Altered resting-state brain activity in obstructive sleep apnea. Sleep 2013;36:651–9B.

21. Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994;2:56–78.
22. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Res Med 1995;34:537–41.
23. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700–11.
24. De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM. FMRI resting state networks define distinct modes of long-distance interactions in the human brain. NeuroImage 2006;29:1359–67.
25. Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 2006;103:13848–53.
26. Beckmann CF, Smith SM. Tensorial extensions of independent component analysis for multisubject fMRI analysis. NeuroImage 2005;25:294–311.
27. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Front Syst Neurosci 2010;4:19.
28. Sadaghiani S, Kleinschmidt A. Functional interactions between intrinsic brain activity and behavior. NeuroImage 2013;80:379–86.
29. Laird AR, Eickhoff SB, Rottschy C, Bzdok D, Ray KL, Fox PT. Networks of task co-activations. NeuroImage 2013;80:505–14.
30. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009;106:13040–5.
31. Tummala S, Palomares J, Kang DW, et al. Global and regional brain non-Gaussian diffusion changes in newly diagnosed patients with obstructive sleep apnea. Sleep 2016;39:51–7.
32. Palomares JA, Tummala S, Wang DJ, et al. Water exchange across the blood-brain barrier in obstructive sleep apnea: an MRI diffusion-weighted pseudo-continuous arterial spin labeling study. J Neuroimaging 2015;25:900–5.
33. Park B, Palomares JA, Woo MA, et al. Disrupted functional brain network organization in patients with obstructive sleep apnea. Brain Behav 2016 Feb 1. [Epub ahead of print].
34. Nasreddine ZS, Phillips NA, Bedirian V, et al. The montreal cognitive assessment, MOCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.
35. Weissenbacher A, Kasess C, Gerstl F, Lanzenberger R, Moser E, Windischberger C. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. NeuroImage 2009;47:1408–16.
36. Yan CG, Cheung B, Kelly C, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. NeuroImage 2013;76:183–201.
37. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. NeuroImage 2012;59:431–8.
38. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity mri networks arise from subject motion. NeuroImage 2012;59:2142–54.
39. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 2002;15:870–8.
40. Yadav SK, Kumar R, Macey PM, Woo MA, Yan-Go FL, Harper RM. Insular cortex metabolite changes in obstructive sleep apnea. Sleep 2014;37:951–8.
41. Kumar R, Farahvar S, Ogren JA, et al. Brain putamen volume changes in newly-diagnosed patients with obstructive sleep apnea. NeuroImage Clin 2014;4:383–91.
42. Macey PM, Kumar R, Woo MA, Yan-Go FL, Harper RM. Heart rate responses to autonomic challenges in obstructive sleep apnea. PLoS One 2013;8:e76631.
43. Henderson LA, Macey PM, Macey KE, et al. Brain responses associated with the valsalva maneuver revealed by functional magnetic resonance imaging. J Neurophysiol 2002;88:3477–86.
44. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897–904.
45. Cechetto DF, Chen SJ. Subcortical sites mediating sympathetic responses from insular cortex in rats. Am J Physiol 1990;258:R245–55.
46. Joo EY, Jeon S, Kim ST, Lee JM, Hong SB. Localized cortical thinning in patients with obstructive sleep apnea syndrome. Sleep 2013;36:1153–62.
47. Kumar R, Macey PM, Cross RL, Woo MA, Yan-Go FL, Harper RM. Neural alterations associated with anxiety symptoms in obstructive sleep apnea syndrome. Depress Anxiety 2009;26:480–91.
48. Algin O, Gokalp G, Ocakoglu G, Ursavas A, Taskapilioglu O, Hakyemez B. Neurochemical-structural changes evaluation of brain in patients with obstructive sleep apnea syndrome. Eur J Radiol 2012;81:491–5.
49. Yaouhi K, Bertran F, Clochon P, et al. A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 2009;18:36–48.
50. Sarchielli P, Presciutti O, Alberti A, et al. A 1h magnetic resonance spectroscopy study in patients with obstructive sleep apnea. Eur J Neurol 2008;15:1058–64.
51. Critchley HD, Mathias CJ, Josephs O, et al. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 2003;126:2139–52.
52. Joo EY, Tae WS, Lee MJ, et al. Reduced brain gray matter concentration in patients with obstructive sleep apnea syndrome. Sleep 2010;33:235–41.
53. Saper CB. Convergence of autonomic and limbic connections in the insular cortex of the rat. J Comp Neurol 1982;210:163–73.
54. Macey KE, Macey PM, Woo MA, et al. Inspiratory loading elicits aberrant fmri signal changes in obstructive sleep apnea. Respir Physiol Neurobiol 2006;151:44–60.
55. Henderson LA, Richard CA, Macey PM, et al. Functional magnetic resonance signal changes in neural structures to baroreceptor reflex activation. J Appl Physiol 2004;96:693–703.
56. Douglas N, Young A, Roebuck T, et al. Prevalence of depression in patients referred with snoring and obstructive sleep apnoea. Intern Med J 2013;43:630–4.
57. Cross RL, Kumar R, Macey PM, et al. Neural alterations and depressive symptoms in obstructive sleep apnea patients. Sleep 2008;31:1103–9.
58. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45:651–60.
59. Halbower AC, Degaonkar M, Barker PB, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med 2006;3:e301.
60. Ferini-Strambi L, Baietto C, Di Gioia MR, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 2003;61:87–92.
61. Canessa N, Castronovo V, Cappa SF, et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med 2011;183:1419–26.
62. Chan RC, Shum D, Toulopoulou T, Chen EY. Assessment of executive functions: review of instruments and identification of critical issues. Arch Clin Neuropsychol 2008;23:201–16.
63. Cohen R, Salloway S, Sweet L. Neuropsychiatric aspects of disorders of attention. In: Yudofsky SC, Hales RE, eds. Textbook of neuropsychiatry. Washington, DC: American Psychiatric Press, 2008:405–44.
64. Mayer P, Dematteis M, Pepin JL, et al. Peripheral neuropathy in sleep apnea. A tissue marker of the severity of nocturnal desaturation. Am J Respir Crit Care Med 1999;159:213–9.
65. Naegele B, Thouvard V, Pepin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;18:43–52.

66. Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol 1991;13:950–64.
67. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349–56.
68. Joo EY, Tae WS, Han SJ, Cho JW, Hong SB. Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. Sleep 2007;30:1515–20.
69. Hutchison RM, Womelsdorf T, Allen EA, et al. Dynamic functional connectivity: promise, issues, and interpretations. NeuroImage 2013;80:360–78.
70. Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M. Time-resolved resting-state brain networks. Proc Natl Acad Sci U S A 2014;111:10341–6.
71. Kucyi A, Salomons TV, Davis KD. Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. Proc Natl Acad Sci U S A 2013;110:18692–7.
72. Chai XJ, Castanon AN, Ongur D, Whitfield-Gabrieli S. Anticorrelations in resting state networks without global signal regression. NeuroImage 2012;59:1420–8.
73. Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? NeuroImage 2009;44:893–905.
74. Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. NeuroImage 2006;31:1536–48.
75. Thomas JB, Brier MR, Bateman RJ, et al. Functional connectivity in autosomal dominant and late-onset alzheimer disease. JAMA Neurol 2014;71:1111–22.
76. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 2014;84:320–41.
77. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005;102:9673–8.

ACKNOWLEDGMENTS

The authors thank Mrs. Rebecca K. Harper and Mrs. Karen Harada for assistance with data collection.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2015
Submitted in final revised form December, 2015
Accepted for publication December, 2015
Address correspondence to: Rajesh Kumar, PhD, Department of Anesthesiology, 56-141 CHS, 10833 Le Conte Avenue, David Geffen School of Medicine at UCLA, University of California at Los Angeles, Los Angeles, CA 90095-1763; Tel: (310) 206-1679; (310) 206-6133; Fax: (310) 825-2236; Email: rkumar@mednet.ucla.edu

DISCLOSURE STATEMENT

This was not an industry supported study. This work was supported by National Institutes of Health R01 HL-113251 and R01 NR-015038. The authors have indicated no financial conflicts of interest. Study site: University of California at Los Angeles, Los Angeles, CA.