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SCIENTIFIC INVESTIGATIONS

White matter alteration and autonomic impairment in obstructive sleep apnea

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Study Objectives: Autonomic impairment and white matter (WM) alterations have been noted as effects of obstructive sleep apnea (OSA). This study sought to evaluate the change of WM integrity in patients with OSA using diffusion tensor imaging (DTI) and to determine its relationship with autonomic impairment.

Methods: A total of 30 patients with moderate and severe OSA and 19 healthy volunteers were recruited. A cardiovascular autonomic survey was performed and the baroreflex sensitivity (BRS) for each participant was derived from changes in heart rate and blood pressure during the early part of phase II of the Valsalva maneuver. DTI-related indices were derived from DTI. The fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps were compared using voxel-based statistics to determine differences between the patients with OSA and the healthy controls. The correlations among DTI indices, clinical severity, and autonomic parameters were investigated.

Results: The BRS values were significantly worse in the OSA group than in the control patients. An exploratory group-wise comparison between the two groups revealed that the patients with OSA exhibited low FA, increased MD, AD, and RD in several brain locations. The declined DTI indices in autonomic-related areas were significantly correlated with increased clinical disease severity and baroreflex impairment.

Conclusions: OSA alters WM integrity in the cingulum and temporal lobe, and this impairment might play some role in autonomic dysfunction. The possible interaction between autonomic dysfunction and central nervous system microstructural alterations may represent variant hypoxic patterns, sympathetic activation, and their consequent processes in OSA.

Keywords: autonomous function, baroreflex, diffusion tensor imaging, magnetic resonance imaging, obstructive sleep apnea, white matter

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Autonomic impairment and white matter (WM) alterations have been noted as effects of obstructive sleep apnea (OSA). This study evaluates the change of WM integrity in patients with OSA using diffusion tensor imaging and to determine its relationship with autonomic impairment.

Study Impact: Obstructive sleep apnea alters WM integrity in the cingulum and temporal lobe, and this impairment might play some role in autonomic dysfunction. The possible interaction between autonomic dysfunction and central nervous system microstructural alterations may represent variant hypoxic patterns, sympathetic activation, and their consequent processes in OSA.

INTRODUCTION

Autonomic impairment[1] and white matter (WM) alterations[2] have been noted as effects of obstructive sleep apnea (OSA). An impairment of the arterial baroreflex control of circulation may be involved in the genesis of the sympathetic activation typical of OSA, and such dysfunction may contribute to the higher rate of cardiovascular and cerebrovascular morbidity and mortality reported in OSA.[3,4] In addition, the WM injuries in patients with OSA have been related to different cognitive function impairments, such as impairments of attention, executive functions, and memory.[2] However, the relationship between autonomic dysfunction and WM microstructural changes related to OSA has not been systematically investigated.

It is believed that the WM microstructure damage might result from repetitive apneic events during sleep, with consequent hypoxia and hypercapnia, in OSA. Hypoxia and hypercapnia, which result from respiratory obstructions and activate chemoreflexes, elicit increases in sympathetic nerve activity and blood pressure. Increased sympathetic drive during wakefulness and repetitive surges in blood pressure during sleep may decrease baroreflex sensitivity and/or reset the baroreflex function curve to higher levels of pressure.[5] Therefore, it is likely that the enhanced sympathetic to parasympathetic balance, along with the reduction of the baroreflex, could contribute to the impairment of heart rate variability

(HRV) and the impaired regulation of vasomotor tone in the blood vessels, finally eliciting systemic hypertension.[6] Epidemiological evidence implicates OSA as one of the modifiable and highly prevalent factors in the development of hypertension.[7]

Autonomic dysfunction is thought to be a common complication of ischemic stroke and has been associated with worse functional outcomes and increased mortality. In OSA, the effect of hypoxia on the central nervous system, especially the brainstem, has previously been demonstrated to affect autonomic and behavioral responses.[1] The nucleus tractus solitarius in the medulla constitutes an important cord region and, together with the caudal ventrolateral medulla, rostral ventrolateral medulla, and nucleus ambiguous, is thought to constitute the central autonomic network.[8] A recent study, in fact, has argued that changes to WM might constitute the main pathological process in OSA and that such changes may be associated with the disease severity and with consequent neuropsychiatric disorders.[9] It is possible that accumulated WM microstructural damage leads to the disruption of neural activity, including the impairment of the central autonomic function network.

Diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI) method, is potentially more sensitive than conventional MRI for the purposes of detecting WM microstructural changes. Previous studies have made use of DTI in reporting microstructural changes in WM fibers in OSA, including a global brain decrease in mean diffusivity (MD) values and the fact that certain regional sites are especially affected by decreased fractional anisotropy (FA) values.[10] However, the correlation, if any, between particular WM alterations and autonomic dysfunction in OSA has still not been well evaluated.

This study used DTI to evaluate WM integrity in patients with OSA and sought to explore its relationship with autonomic impairment. First, the differences in autonomic functioning and WM integrity between patients with OSA and healthy control patients were investigated. Second, any associations between the disease severity levels in the patients with OSA and the effects of sleep apnea on autonomic functioning and WM integrity were calculated. Third, the relationships between WM alterations and autonomic impairment were also evaluated. It is hypothesized that the increased sympathetic activity in patients with OSA correlates with the WM change.

METHODS

Patients

This prospective study targeted patients with moderate and severe OSA (apnea-hypopnea index [AHI] ≥ 15 events/h). Thirty patients with moderate or severe OSA (27 men and 3 women; mean age, 39.43 ± 10.31 years; AHI, 44.23 ± 21.64 events/h) and 19 healthy volunteers (13 men and 6 women; mean age, 39.37 ± 9.40 years; AHI, 2.21 ± 1.59 events/h) were recruited.

All the patients with OSA and the healthy control patients were enrolled through the Sleep Center at Chang Gung Memorial Hospital in Kaohsiung with a chief complaint of snoring. The severity of sleep-disordered breathing was classified according to the number of apneas and hypopneas during sleep, which was reported as the AHI. All participants underwent overnight polysomnography (PSG) at Kaohsiung Chang Gung Memorial Hospital, and were scored and classified into patient and control groups according to standard diagnostic criteria. All those in the patient group had recently received a diagnosis and had not yet been treated for OSA. Patients with a diagnosis of central sleep apnea, which might lead to autonomic dysfunction, were excluded from the study. In central sleep apnea, the PSG results will show five or more central apneas and/or central hypopneas per hour of sleep, representing at least 50% of total respiratory events in the AHI, and reveal a correlation with the absence of attempts to breathe. Furthermore, none of the included participants had a history of major mental disorder, brain injury or illness, diabetes mellitus, cerebrovascular disease, major cardiovascular disorder, hypertension, or any central/peripheral disorders known to affect the autonomic nervous system. An experienced neuroradiologist blinded to each participant's status visually checked all of the MRI studies to ensure that the participants were free from significant brain injury. None of the participants in the study were excluded.

The Chang Gung Memorial Hospital Ethics Committee approved the study and all of the participants provided written informed consent.

Assessment of obstructive sleep apnea/hypopnea by PSG

The overnight PSG data were assessed according to the methods detailed in a previous report.[11] All-night comprehensive diagnostic sleep studies were performed at the hospital's sleep center in a temperature-controlled and sound-attenuated room. Electroencephalography, submental electromyography, and electro-oculography data were recorded with surface electrodes using standard techniques. Nasal and oral airflows were recorded by thermistors, while oxygen saturation was measured by pulse oximetry. Obstructive apnea was defined as a cessation of airflow for at least 10 seconds with effort to breathe during the cessation. Obstructive hypopnea was defined as an abnormal respiratory event with at least a 30% reduction in thoracoabdominal movement or airflow when compared to baseline, lasting at least 10 seconds, with < 4% oxygen desaturation.[12] The AHI was calculated per hour of electroencephalography sleep. Central respiratory events were excluded from severity classification.

The OSA severity was classified as normal for AHI between 0–5, mild for an AHI of 5–15, moderate for an AHI > 15 and < 30, and severe for AHI > 30 events/h. For comparison, participants categorized in the control group all had an AHI < 5 events/h. The oxygen desaturation index was defined as a drop of 3% oxygen saturation from baseline associated with a respiratory event, or a drop of oxygen saturation greater or equal to 4% from baseline.[13] Snoring episodes were detected via a Piezo crystal snore sensor (SleepSense, Scientific Laboratory Products, Elgin, Illinois, United States), and they were interpreted using the snoring index, which represents the frequency of snoring episodes.[14,15] All PSG tests were scored and read by a board-certified physician blinded to the study.

Assessment of cardiovascular autonomic function

All of the patients underwent the cardiovascular autonomic and MRI studies on the same day within 2 weeks of the PSG examination. The cardiovascular autonomic survey included

deep breathing and Valsalva maneuver tests.[16] Examinations were performed in a quiet room in the morning before noon to exclude any possible influence of circadian variations. Patients were asked to relax, breath regularly, and move as little as possible. A 5-minute resting recording of electrocardiography was conducted to perform a spectral analysis of HRV.

The following parameters were obtained through tests computed by Testworks (WR Medical Electronics Company, Stillwater, Minnesota, United States): heart rate response to deep breathing (HR_DB), valsalva ratio (VR), and baroreflex sensitivity (BRS). The determination of HR_DB and VR was performed as previously described by Low.[17] For HR_DB, the procedure required the patient to breathe maximally at a rate of six breaths per minute. The patient was instructed to follow an oscillating bar with a period of 10 seconds. The 5 largest consecutive responses were then read from the computer using a cursor and averaged, and the heart rate range (maximum − minimum) was derived. For VR, the patient was asked to maintain a column of mercury at 40 mm Hg (not exceeding 50 mm) for 15 seconds via a bugle with an air leak (to ensure an open glottis). The VR was then derived from the maximum heart rate generated by the Valsalva maneuver divided by the lowest heart rate occurring within 30 seconds of the peak heart rate. To quantify BRS, a linear regression analysis was performed between the systolic blood pressure (BP) and RR interval (RRI) changes during the early phase II of Valsalva maneuver. In this phase, there was a progressive decrease in systolic BP due to reduced preload (venous return) and stroke volume, with associated tachycardia (gradual shortening of RRI).[18]

Variations in the instantaneous heart rate, as determined via time series analysis of the normal-to-normal interbeat intervals or the RR intervals (RRIs) of the heart, are known as HRV. The signals were then transformed to the frequency domain with fast Fourier transform by using 512 samples. Spectral powers were divided into two frequency domains, namely, high frequency (HF, 0.15–0.4 Hz), and low frequency (LF, 0.04–0.15 Hz). The quotient of LF and HF components (LF/HF) was calculated as a measure of sympathovagal balance.

MRI data acquisition and preprocessing

The procedural details are summarized in the supplementary material. For each patient, an MRI study was performed using a 3.0 Tesla whole-body GE Signa MRI system (General Electric Healthcare, Milwaukee, Wisconsin, United States) equipped with an eight-channel head coil. The diffusion images gradient encoding schemes included 13 noncollinear directions with a b-value of 1000 s/mm^2 and a nondiffusion weighted image volume b-value of 0 s/mm^2.

A diffusion tensor model was fitted in each voxel for the calculation of FA values; axial diffusivity (AD) values, λ1; radial diffusivity (RD) values, (λ2 + λ3) / 2; and mean diffusivity (MD) values, (λ1 + λ2 + λ3) / 3.

Statistical analysis

Analysis of demographic data differences between groups

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software package (version 17, SPSS Inc. Chicago, Illinois, United States). Age and sex data for the study groups were compared using the independent *t* test and Pearson chi-square test, whereas an analysis of covariance (ANCOVA) model with age and sex as covariates was used to determine differences in the body mass index (BMI) scores between the groups. ANCOVA with age, sex, and BMI as potential confounding variables was used to compare the groups in terms of AHI score, desaturation index, snoring index, average oxygen saturation, percentage of time with oxygen saturation less than 90% (mO_2 < 90%), blood sugar, HbA1c, BP, and autonomic parameters. Statistical significance was set at $P < .05$.

Analysis of group comparison of DTI indices

Statistical analyses were conducted using the SPM8 (Statistical Parametric Mapping; University College London, London, United Kingdom) software package, which itself used Matlab R2010a (Mathworks, Natick, Massachusetts, United States) for voxel-wise group comparisons. Smoothed, normalized FA images were analyzed using SPM8 within the framework of a General Linear Model, whereas ANCOVA was performed with age and sex as covariates to investigate the FA, MD, AD, and RD differences between the OSA and control groups. The FA threshold of the mean WM was set at 0.2 to successfully exclude voxels, which consisted of gray matter or cerebrospinal fluid in most patients. The statistical threshold was set at an uncorrected $P < .005$ and $P < .001$, respectively, with a cluster of > 200 contiguous voxels. The extended cluster size was arbitrary and was used to putatively detect significant differences between groups with a cluster size < 200 voxels, which might not represent reliable findings.[19] The most probable fiber tracts and anatomic location of each significant cluster were determined using the FSL atlas tool (https://www.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

Analysis of region of interest

Region of interest (ROI) analyses were conducted to determine the individual mean FA, MD, AD, and RD values of each significantly different area between the two groups based on whole-brain voxel-wise comparisons. The Marsbar toolbox (http://marsbar.sourceforge.net/download.html) was used to extract the ROI masks. The mean DTI-related indices (including FA, AD, RD, and MD) of these areas were compared between groups by multivariate analysis of covariance, with age, sex, and BMI as covariates. Significance was set at a Bonferroni corrected $P < .05$, accounting for multiple ROI comparisons.

Correlations among regional DTI-related indices, clinical severity indicators, and cardiovascular autonomic parameters

After checking the data normality and removing the outliers, the correlations were performed using Spearman correlation method to evaluate the relationships among the regional DTI-related indices and both the clinical severity indicators and the cardiovascular autonomic parameters. The threshold for statistical significance was set at $P < .05$, with Bonferroni correction for multiple comparisons.

Table 1—Demographic characteristics of patients with moderate/severe obstructive sleep apnea and control patients.

	OSA (n = 30)	Control (n = 19)	*P*
Age (years)	39.43 ± 10.31	39.37 ± 9.40	.982
Sex (M:F)	27:3	13:6	.720
BMI (kg/m^2)	26.40 ± 3.68	24.65 ± 2.36	.107
AHI (events/h)	44.23 ± 21.64	2.21 ± 1.59	**< .001**
Desaturation index (events/h)	34.27 ± 23.99	0.54 ± 0.70	**< .001**
mO_2 < 90% (%)	12.68 ± 19.01	0.41 ± 1.11	.053
Average O_2 saturation (%)	94.32 ± 3.97	96.79 ± 0.76	.072
Snoring index (events/h)	436.82 ± 215.27	176.44 ± 168.82	**< .001**
Blood sugar (mg/dL)	92.17 ± 10.51	93.17 ± 7.41	.839
HbA1c (%)	5.69 ± 0.38	5.55 ± 0.27	.150
Systolic BP (mmHg)	137.12 ± 14.29	128.18 ± 12.56	.256
Diastolic BP (mmHg)	83.60 ± 10.61	76.47 ± 8.64	.074
Autonomic parameters			
HR_DB (beats/min)	15.44 ± 6.80	15.59 ± 5.65	.855
Valsalva ratio	1.63 ± 0.19	1.65 ± 0.27	.618
BRS (ms/mmHg)	2.28 ± 1.07	3.18 ± 1.32	**.029**
LF/HF ratio	3.11 ± 2.90	1.85 ± 1.52	.093
LF (normalized unit)	67.11 ± 15.19	55.83 ± 21.05	.067
HF (normalized unit)	32.79 ± 15.14	44.08 ± 21.00	.067

Data presented as mean ± standard deviation. Age data compared by independent *t* test. Sex data compared by Pearson chi-square test. BMI data compared by analysis of covariance (ANCOVA) after controlling for age and sex. AHI score, desaturation index, average O_2 saturation, snoring index, sugar, HbA1c, BP data, and autonomic parameters compared by ANCOVA after controlling for age, sex, and BMI. *P* values < .05 considered statistically significant, in bold. AHI = apnea-hypopnea index, BMI = body mass index, BP = blood pressure, BRS = baroreflex sensitivity, HF = high frequency, HR_DB = heart rate response to deep breathing, LF = low frequency, OSA = obstructive sleep apnea, mO_2 < 90% = percentage of time with oxygen saturation less than 90%.

RESULTS

Demographic characteristics of the participants

The demographic characteristics of the 30 patients with moderate and severe OSA and the 19 control patients are listed in Table 1. There were no significant differences in age, sex, and BMI between the two groups. The OSA group had significantly increased desaturation index ($P < .001$) and increased snoring index ($P < .001$) results compared to the control group.

Cardiovascular autonomic parameters of the two groups

The cardiovascular autonomic results of the two groups are also listed in Table 1. The BRS values were significantly lower in the OSA group than in the control group ($P = .029$).

Regional WM integrity aberrances of the two groups

The location and extent of regions with significant differences in the FA map between the OSA and control groups are presented in Table 2. Patients with moderate and severe OSA had lower FA values in the right frontal WM (BA6), right superior longitudinal fasciculus (BA31, BA9, BA3), and left superior longitudinal fasciculus (BA40); higher MD and AD values in the right cortical spinal tract (pons); and higher RD values in the right cortical spinal tract (pons) and right superior longitudinal fasciculus (BA3) (Figure 1). The major results of the group differences in the regional DTI indices were similar between $P < .001$ and $P < .005$.

In the FA map, we found that these lower FA values in OSA were also associated with changes in other diffusivity indices, including the following: (1) increased RD values in the right superior longitudinal fasciculus (BA31, BA3), and (2) increased MD values and decreased AD values in the right superior longitudinal fasciculus (BA9). In the RD map, the higher RD values in the right superior longitudinal fasciculus (BA3) in OSA were also consistently associated with decreased FA and increased MD values.

Relationship between DTI indices and clinical severity

Correlation analyses were conducted to evaluate the relationships between the DTI indices and clinical severity indicators, including AHI, desaturation index, and snoring index ($P < .05$ for multiple comparisons, indicated by a dagger in Table 3).

FA values and clinical severity

The AHI scores were negatively correlated with FA values in the right frontal WM (BA6), right superior longitudinal fasciculus (BA31, BA9, BA3), and left superior longitudinal fasciculus (BA40). Likewise, the desaturation index was negatively correlated with FA values in the right frontal WM (BA6), right superior longitudinal fasciculus (BA31, BA9, BA3), and left superior

Table 2—Regions showing diffusion tensor imaging index differences between patients with moderate/severe obstructive sleep apnea and control patients.

WM Tract	MNI Atlas Coordinates			Voxel Size	BA	Near Cortical Area	FA Mean (SD)		t_{max}	Diffusivity Values (OSA-NC)		
	X	Y	Z				Controls	OSA		MD (×10⁻⁶)	AD (×10⁻⁶)	RD (×10⁻⁶)
***P* < .001, cluster > 200**												
Decreased FA												
R frontal WM	10	-22	57	359	6	R precentral gyrus	0.331 (0.038)	0.287 (0.045)	5.58	51	20	67
R superior longitudinal fasciculus	15	-40	43	599	31	R cingulate gyrus	0.437 (0.029)	0.382 (0.034)	4.72	-3	-34	57*
R superior longitudinal fasciculus	51	5	20	228	9	R inferior frontal gyrus	0.388 (0.050)	0.330 (0.046)	4.22	27*	-79*	34
R superior longitudinal fasciculus	31	-27	32	1243	3	R postcentral gyrus	0.431 (0.037)	0.389 (0.026)	4.12	11	-25	29*
L superior longitudinal fasciculus	-32	-30	36	408	40	L postcentral gyrus	0.394 (0.038)	0.344 (0.042)	3.84	15	-29	37*
Increased FA												
None												
Decreased MD												
None												
Increased MD							MD mean (SD) (×10⁻⁶)			FA	AD (×10⁻⁶)	RD (×10⁻⁶)
R corticospinal tract	9	-30	-44	570		R pons	1121 (112)	1144 (162)	4.14	0.015	48	11
Decreased AD												
None												
Increased AD							AD mean (SD) (×10⁻⁶)			FA	MD (×10⁻⁶)	RD (×10⁻⁶)
R Corticospinal tract	9	-30	-44	576		R pons	1619 (133)	1679 (172)	4.22	0.014	32	18
Decreased RD												
None												
Increased RD							RD mean (SD) (×10⁻⁶)			FA	MD (×10⁻⁶)	AD (×10⁻⁶)
R corticospinal tract	9	-30	-44	503		R pons	938 (121)	949 (177)	4.11	0.014	21	44
R superior longitudinal fasciculus	28	-35	33	442	3	R postcentral gyrus	575 (39)	617 (27)	3.76	-0.051*	19*	-28
***P* < .005, cluster > 200**												
Decreased FA							FA mean (SD) (×10⁻⁶)			MD (×10⁻⁶)	AD (×10⁻⁶)	RD (×10⁻⁶)
R frontal WM	10	-22	57	635	6	R precentral gyrus	0.338 (0.027)	0.299 (0.033)	5.58	47	18	62*
R superior longitudinal fasciculus	15	-40	43	5434	31	R postcentral gyrus	0.444 (0.024)	0.408 (0.02)	4.72	15	-20	32*
R superior longitudinal fasciculus	51	5	20	540	9	R inferior frontal gyrus	0.377 (0.037)	0.327 (0.033)	4.22	7.6	-54*	39*
L frontal WM	-28	22	-16	452	47	L frontal orbital cortex	0.353 (0.041)	0.316 (0.037)	3.91	24	-9.1	41*
L superior longitudinal fasciculus	-32	-30	36	2032	40	L postcentral gyrus	0.405 (0.029)	0.367 (0.032)	3.84	14	-22	32*
R hippocampus	19	-31	-8	495	35	R parahippocampal gyrus	0.351 (0.028)	0.317 (0.03)	3.73	55	27	69*
R inferior fronto-occipital fasciculus	34	30	-1	270	47	R inferior frontal gyrus	0.329 (0.05)	0.285 (0.05)	3.72	36	-6.9	58*
L frontal WM	-20	4	49	463	6	L superior frontal gyrus	0.515 (0.044)	0.477 (0.049)	3.49	19	-20	39*
R corticospinal tract	9	-15	-26	332	-	R pons	0.559 (0.028)	0.532 (0.031)	3.49	-8.4	-55	15
R cerebellar WM	12	-54	-21	338	-	R cerebellum (fastigial nucleus)	0.302 (0.018)	0.287 (0.033)	3.43	-13	-33*	-2.5
R temporal WM	45	-39	11	243	41	R superior temporal gyrus	0.41 (0.043)	0.372 (0.033)	3.34	9.8	-29*	29*
L thalamus	-16	-15	15	374	-	L thalamus	0.337 (0.015)	0.322 (0.033)	3.29	12	6.2	15*
R inferior fronto-occipital fasciculus	23	22	-6	206	-	R putamen	0.408 (0.028)	0.386 (0.033)	3.29	12	-11	24*
Increased FA												
None												
Decreased MD												
None												
Increased MD							MD mean (SD) (×10⁻⁶)			FA	AD (×10⁻⁶)	RD (×10⁻⁶)
R corticospinal tract	9	-30	-44	1344		R pons	1017 (66)	1038 (90)	4.14	0.014	41	11
L corticospinal tract	-16	-28	-26	253		L pons	1210 (162)	1276 (164)	3.43	0.004	85	56
L inferior frontal-occipital fasciculus	-37	-9	-11	663	21	L temporal gyrus	819 (21)	836 (36)	3.38	-0.013	3	24
R frontal WM	23	-11	49	451	6	R medial frontal gyrus	695 (33)	721 (33)	3.34	-0.007	38*	20
L corticospinal tract	-13	-30	-39	316		L pons	1135 (185)	1210 (211)	3.31	-0.005	81	71
R superior longitudinal fasciculus	32	-38	30	415		R supramarginal gyrus	746 (30)	778 (27)	3.05	-0.019	27	34*
Decreased AD												
None												
Increased AD							AD mean (SD) (×10⁻⁶)			FA	MD (×10⁻⁶)	RD (×10⁻⁶)
R corticospinal tract	9	-30	-44	1261		R pons	1477 (87)	1528 (108)	4.22	0.014	28	16
L corticospinal tract	-16	-28	-26	215		L pons	1826 (230)	1924 (229)	3.48	0.002	79	69
R frontal WM	22	-10	50	578	6	R medial frontal gyrus	1193 (61)	1243 (57)	3.37	0.005	24	10
L corticospinal tract	-12	-29	-41	250		L pons	1709 (255)	1802 (293)	3.25	-0.010	89	87
L anterior corona radiata	-19	18	29	270	32	L cingulate gyrus	1145 (47)	1187 (43)	3.14	0.011	16	3
Decreased RD												
None												

(continued on following page)

Table 2—Regions showing diffusion tensor imaging index differences between patients with moderate/severe obstructive sleep apnea and control patients. (continued)

WM Tract	MNI Atlas Coordinates			Voxel Size	BA	Near Cortical Area	FA Mean (SD)		t_{max}	Diffusivity Values (OSA-NC)		
	X	Y	Z				Controls	OSA		MD (×10⁻⁶)	AD (×10⁻⁶)	RD (×10⁻⁶)
Increased RD							RD mean (SD) (×10⁻⁶)			FA	MD (×10⁻⁶)	AD (×10⁻⁶)
R corticospinal tract	9	-30	-44	1320		R pons	803 (64)	813 (87)	4.11	0.012	19	36
R superior longitudinal fasciculus	28	-35	33	2195	31	R postcentral gyrus	557 (29)	591 (26)	3.76	-0.039*	18*	-15
L inferior frontal-occipital fasciculus	-37	-8	-11	693	21	L temporal gyrus	612 (23)	635 (36)	3.54	-0.015*	16	<-1
R frontal WM	12	-21	56	258	6	R precentral gyrus	548 (32)	567 (37)	3.50	-0.024	5	-21
L superior longitudinal fasciculus	-31	-29	36	1812	40	L postcentral gyrus	582 (28)	616 (33)	3.44	-0.037*	18*	-16
L corticospinal tract	-16	-28	-26	228		L pons	982 (157)	1041 (157)	3.35	0.005	70	90
L corticospinal tract	-13	-30	-39	371		L pons	847 (153)	912 (173)	3.33	-0.003	69	76

Location of maximum effect was shown in the MNI space. Group FA, MD, AD, and RD mean values in each cluster are presented as mean (standard deviation). The FA, MD, AD, and RD values in the regions of interest were further compared between two groups by analysis of covariance after controlling for age, sex, and body mass index. *P < .05 with a Bonferroni corrected, accounting for multiple region of interest comparisons. AD = axial diffusivity, BA = Brodmann area, FA = fractional anisotropy, L = left, MD = mean diffusivity, MNI = Montreal Neurological Institute, NC = controls, OSA = obstructive sleep apnea, R = right, RD = radial diffusivity, ROI = region of interest, SD = standard deviation, WM = white matter.

longitudinal fasciculus (BA40). The snoring index, however, revealed no statistically significant correlation with the FA values.

MD values and clinical severity

The MD values in the right cortical spinal tract (pons) revealed no statistically significant correlations with the AHI scores, desaturation index, or snoring index.

AD values and clinical severity

The AD values in the right cortical spinal tract (pons) revealed no statistically significant correlations with the AHI scores, desaturation index, or snoring index.

RD values and clinical severity

The RD values in the right superior longitudinal fasciculus (BA3) were positively correlated with the AHI scores, desaturation index, and snoring index.

Relationship between DTI indices and cardiovascular autonomic parameters

Results of the analysis regarding differences in the BRS values and DTI indices are listed in **Table 3** and **Figure 2**. Because of the relatively small sample size of our study, and in order to increase the sensitivity of the correlation analysis, the lower threshold of $P < .05$ under uncorrected statistics was applied here (indicated by an asterisk in **Table 3**).

FA values and BRS values

The BRS values were positively correlated with the FA values in the right superior longitudinal fasciculus (BA31) and right temporal WM (BA41).

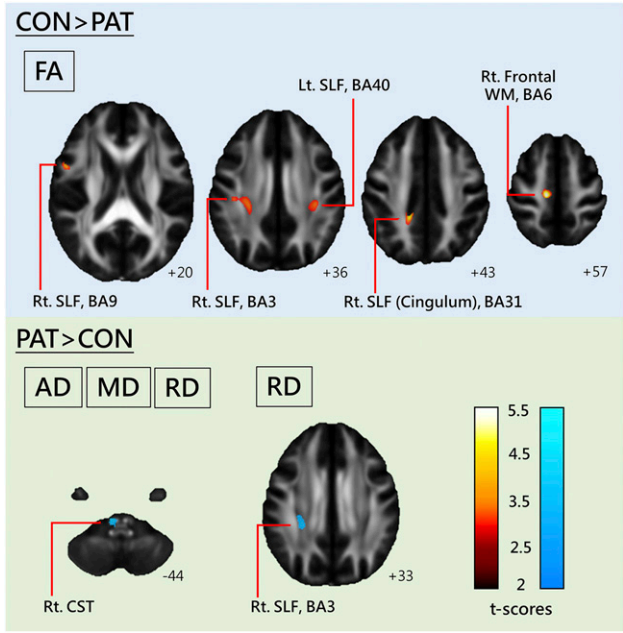
MD values and BRS values

The BRS values were negatively correlated with the MD values in the left inferior frontal-occipital fasciculus (BA21).

RD values and BRS values

The BRS values were negatively correlated with the RD values in the left inferior frontal-occipital fasciculus (BA21).

Figure 1—Regions with different diffusion tensor imaging index values in patients with OSA.



Lower FA values were found in patients with OSA (n = 30) versus control patients (n = 19) in the right frontal WM (BA6), right SLF (BA31, BA9, BA3), and left SLF (BA40). Higher MD, AD, and RD values were found in patients with OSA versus control patients in the right CST (pons), and higher RD values were found in the right SLF (BA3). AD = axial diffusivity, BA = Brodmann area, BRS = baroreflex sensitivity, CST = cortical spinal tract, FA = fractional anisotropy, MD = mean diffusivity, OSA = obstructive sleep apnea, RD = radial diffusivity, SLF = superior longitudinal fasciculus, WM = white matter.

DISCUSSION

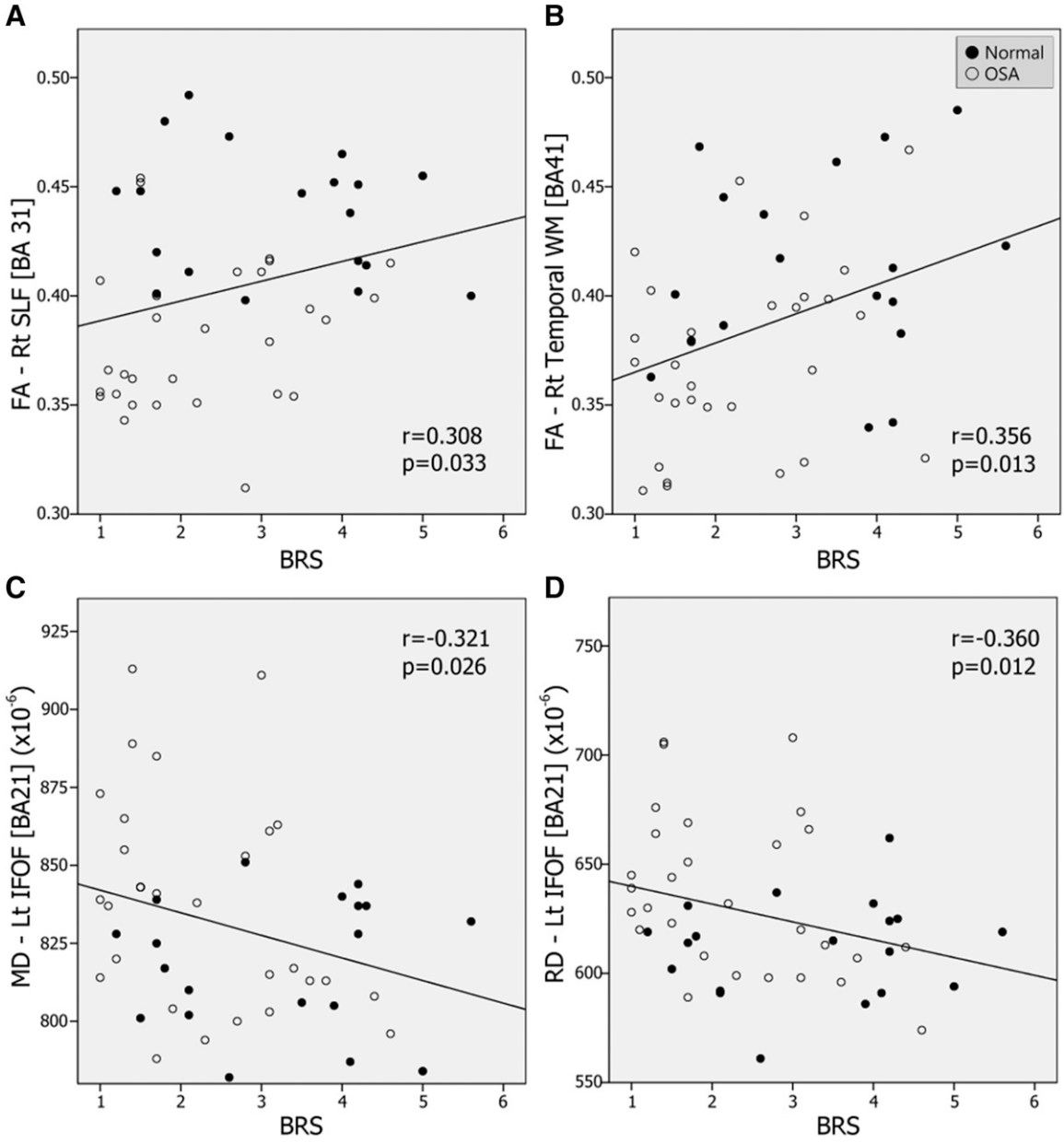
In the evaluation of cardiovascular autonomic functioning, the patients with OSA also showed significantly decreased BRS values, suggesting impaired autonomic functioning. Diffusion imaging revealed alterations of fiber integrity in the patients

Table 3—Correlations among the diffusion tensor abnormalities and both the clinical severity indicators and the cardiovascular autonomic parameters.

WM Tract	Correlation (*r*) of Clinical Variable			
	AHI	Desaturation Index	Snoring Index	BRS
***P* < .001, cluster > 200**				
FA map				
Right frontal WM	−.422†	−.407†	−.322*	.175
Right superior longitudinal fasciculus [BA31]	−.644†	−.625†	−.346*	.308*
Right superior longitudinal fasciculus [BA9]	−.577†	−.580†	−.302*	.113
Right superior longitudinal fasciculus [BA3]	−.446†	−.490†	−.303*	.193
Left superior longitudinal fasciculus [BA40]	−.396†	−.499†	−.337*	.215
MD map				
Right corticospinal tract	−.049	−.070	−.065	−.138
AD map				
Right corticospinal tract	.025	.004	.011	−.151
RD map				
Right corticospinal tract	−.055	−.071	−.086	−.143
Right superior longitudinal fasciculus [BA3]	.407†	.450†	.346†	−.272
***P* < .005, cluster > 200**				
FA map				
Right frontal WM [BA6]	−.441†	−.435†	−.266	.229
Right superior longitudinal fasciculus [BA31]	−.620†	−.623†	−.404*	.266
Right superior longitudinal fasciculus [BA9]	−.593†	−.592†	−.347*	.166
Left frontal WM [BA47]	−.413†	−.390*	−.346*	−.029
Left superior longitudinal fasciculus [BA40]	−.399*	−.479†	−.371*	.230
Right hippocampus [BA35]	−.476†	−.448†	−.338*	.250
Right inferior fronto-occipital fasciculus [BA47]	−.248	−.295*	−.330*	−.017
Left frontal WM [BA6]	−.381*	−.357*	−.318*	−.100
Right corticospinal tract [pons]	−.399*	−.352*	−.389*	.059
Right cerebellar WM	−.410†	−.367*	−.360*	.104
Right temporal WM [BA41]	−.342*	−.459†	−.094	.356*
Left thalamus	−.344*	−.355*	−.385*	.193
Right inferior fronto-occipital fasciculus [putamen]	−.285*	−.306*	−.078	.239
MD map				
Right corticospinal tract [pons]	.009	.008	.012	−.138
Left corticospinal tract [pons]	.291*	.251	.062	−.032
Left inferior frontal-occipital fasciculus [BA21]	.246	.205	.128	−.321*
Right frontal WM [BA6]	.250	.287	.197	−.131
Left corticospinal tract [pons]	.038	.122	.130	−.060
Right superior longitudinal fasciculus	.314*	.369*	.233	−.176
AD map				
Right corticospinal tract [pons]	.119	.095	.076	−.179
Left corticospinal tract [pons]	.272	.248	.090	−.008
Right frontal WM [BA6]	.183	.161	.136	−.114
Left corticospinal tract [pons]	.037	.139	.126	−.052
Left anterior corona radiata [BA32]	.309*	.343*	.090	−.189
RD map				
Right corticospinal tract [pons]	−.013	.008	.049	−.086
Right superior longitudinal fasciculus [BA31]	.416†	.488†	.374*	−.224
Left inferior frontal-occipital fasciculus [BA21]	.341*	.286	.174	−.360*
Right frontal WM [BA6]	.251	.298*	.087	−.144
Left superior longitudinal fasciculus [BA40]	.261	.338*	.246	−.246
Left corticospinal tract [pons]	.275	.217	.020	−.056
Left corticospinal tract [pons]	.049	.137	.130	−.071

Correlations among the diffusion tensor abnormalities and both the clinical severity indicators and the cardiovascular autonomic parameters were performed by Spearman correlation after removing the outliers. **P* < .05, uncorrected. †*P* < .05, Bonferroni corrected, accounting for multiple region of interest comparisons. AD = axial diffusivity, AHI= apnea-hypopnea index, BA = Brodmann area, BRS = baroreflex sensitivity, FA = fractional anisotropy, RD = radial diffusivity, WM = white matter.

Figure 2—Spearman correlations between baroreflex sensitivity and diffusion tensor imaging index indices.



Significant Spearman correlations were plotted for the **(A)** right SLF (BA31) FA values, **(B)** right temporal WM (BA41) FA values, **(C)** right IFOF (BA21) MD values ($\times 10^{-6}$), and **(D)** right IFOF (BA21) RD values ($\times 10^{-6}$) in relation to the BRS values ($P < .05$ in Table 3 are shown here). BA = Brodmann area, BRS = baroreflex sensitivity, FA = fractional anisotropy, IFOF = inferior fronto-occipital fasciculus, MD = mean diffusivity, RD = radial diffusivity, SLF = superior longitudinal fasciculus, WM = white matter.

with OSA, indicating increased WM microstructural changes. These WM alterations were further associated with disease severity and higher autonomic dysfunction. This study is the first to report an association between intracranial WM integrity and impaired autonomic functioning in patients with OSA.

We explored widespread WM alterations adjacent to the brainstem, cortical regions, and subcortical regions in the patients with OSA. In previous studies, patients with OSA have been reported as displaying aberrant cardiovascular responses associated with altered activity in regions such as the hypothalamus, amygdala, hippocampus, and the insular, cingulate, and prefrontal cortices,[14,15] perhaps as a consequence of limbic, cerebellar, and motor area gray matter losses.[16] Regions of the brainstem, such as the nucleus tractus solitarius, caudal ventrolateral medulla, and rostral ventrolateral medulla, are important central structures in sympathetic activity and are highly connected, both functionally and structurally, to other subcortices and neocortices.[6] In addition, some cortical areas, such as the medial prefrontal cortex and the orbitofrontal cortex,[6] are involved in excessive arousal and functional autonomic consequences. White matter changes in those susceptible regions as a consequence of elevated hypoxia and

endothelial dysfunction may disrupt the modulation of functional networks in autonomic control. In this study, the altered fiber integrities in regions, such as the pons, basal ganglia, and thalamus, associated with autonomic functioning further support the fundamental theory that OSA damages regions involved in autonomic regulation. However, it is unclear why we failed to demonstrate interactions between the nucleus of the brainstem and baroreflex dysfunction in this DTI study. Initial pseudonormalization of the autonomic function might be a result of compensation in other cortical areas or the intrinsic autonomic networks, even if changes had occurred in the brainstem. The brain stem might be altered with a certain degree of severity to reveal the misregulation of autonomic function. Otherwise, the small sample size coupled with only moderate and severe OSA enrollment may have biased the correlation study or results from a ceiling effect in this study. Further research is obviously required, but this is an exciting first step.

In addition to being regulated by the brainstem, autonomic cardiovascular function could be regulated by various cortical areas.[20] Our patients with OSA displayed altered fiber integrity within the temporal WM (BA 41, BA21) that was correlated with impaired baroreflexes. The temporal insular cortex that folds into the inner temporal lobe is thought to be associated with blood pressure and heart rate regulation.[21] The temporal insular cortex is also part of the reward system[22] and the salience network,[23] contributing to control behavior by inducing bodily stimuli[24] (eg, thirst, heartbeat, visceral distension, temperature, pain) and various cognitive processes. Fatouleh et al have demonstrated that elevated muscular sympathetic nerve activity in OSA may result from functional changes within the hippocampus, changes that are known to be directly or indirectly involved in the modulation of sympathetic outflow via the brainstem.[25] It has been suggested that the hippocampus may play a modulatory role in autonomic functioning. The higher FA and lower MD and RD values in the temporal WM are highly pertinent to decreased BRS in the current study, which supports the reduced modulatory role of the temporal lobe and hippocampus in OSA.

Even though the current study offers some valuable insights, it is not without limitations. First, the study only assessed cases of moderate and severe OSA in a relatively small number of patients, and because it was a preliminary study, we used relatively loose statistical criteria to explore the global view of this issue. It is possible, then, that the results of the study will not be replicable in all disease spectrums of OSA. Second, the study results-related ratio of sex imbalance was not an intentional outcome of the study design; rather, this occurred simply because most of the patients who asked for treatment were men. However, there was no significant difference between groups by sex. Third, because of a need for smoothing in voxel-wise analyses using SPM, the use of SPM might have induced problems from partial volume effects and the cross-contamination of different tissues. However, the SPM method is more sensitive to pathological changes in gray matter than tract-based spatial statistics analysis, which achieves spatial comparability by projecting the data on a common skeleton. Fourth, although this study was similar to previous reports[26] in terms of finding worse HRV, the differences between the groups failed to achieve statistical significance. The discrepancy results between HRV and BRS suggests the complicated pathophysiology of autonomic dysfunction in OSA involving different target organs from central to peripheral. Finally, although we found correlations between anatomical integrity and autonomic function in OSA, there is still no conclusive proof regarding the possible mediators and pathophysiologic timeline of the disease. Further animal studies would be necessary to clarify the causal relationships among hypoxia, autonomic dysfunction, and white matter changes and to make any definite claims along these lines.

In conclusion, OSA alters WM integrity in the temporal lobe, hippocampus, and cerebellum, with subsequent alterations in autonomic functioning. This apparent pathophysiological link between autonomic dysfunction and central nervous system architectural alterations may represent variant hypoxic patterns, sympathetic activation, and their consequent processes in OSA.

ABBREVIATIONS

AD, axial diffusivity
ANCOVA, analysis of covariance
AHI, apnea-hypopnea index
BRS, baroreflex sensitivity
BMI, body mass index
BP, blood pressure
DTI, diffusion tensor imaging
FA, fractional anisotropy
HR_DB, heart rate response to deep breathing
HRV, heart rate variability
HF, high frequency
LF, low frequency
MRI, magnetic resonance imaging
MD, mean diffusivity
OSA, obstructive sleep apnea
PSG, polysomnography
ROI, region of interest
RRI, RR-intervals
SPSS, Statistical Package for Social Sciences
SPM, statistical parametric mapping
VR, Valsalva ratio
WM, white matter

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