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ORIGINAL RESEARCH

Deep Learning–Based Assessment of Brain Connectivity Related to Obstructive Sleep Apnea and Daytime Sleepiness

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Purpose: Obstructive sleep apnea (OSA) is associated with altered pairwise connections between brain regions, which might explain cognitive impairment and daytime sleepiness. By adopting a deep learning method, we investigated brain connectivity related to the severity of OSA and daytime sleepiness.

Patients and Methods: A cross-sectional design applied a deep learning model on structural brain networks obtained from 553 subjects (age, 59.2 ± 7.4 years; men, 35.6%). The model performance was evaluated with the Pearson's correlation coefficient (R) and probability of absolute error less than standard deviation ($P_{AE<SD}$) between the estimated and the actual scores. In addition, we investigated sex effects on deep learning outputs for OSA and daytime sleepiness and examined the differences in brain connectivity related to daytime sleepiness between OSA and non-OSA groups.

Results: We achieved a meaningful R (up to 0.74) and $P_{AE<SD}$ (up to 0.92) in a test dataset of whole group and subgroups. Motor, frontal and limbic areas, and default mode network were the prominent hubs of important connectivity to predict OSA severity and daytime sleepiness. Sex affected brain connectivity relevant to OSA severity as well as daytime sleepiness. Brain connectivity associated with daytime sleepiness also differed by the presence vs absence of OSA.

Conclusion: A deep learning method can assess the association of brain network characteristics with OSA severity and daytime sleepiness and specify the relevant brain connectivity.

Keywords: convolutional neural network, obstructive sleep apnea, daytime sleepiness, diffusion tensor imaging, structural brain network

Introduction

Sufficient sleep of good quality is essential for optimal brain health. Nevertheless, sleep problems such as insufficient sleep, insomnia, and obstructive sleep apnea (OSA) are common.[1,2] OSA is characterized by repetitive cessations or reductions in airflow due to upper airway collapse during sleep, resulting in intermittent hypoxia and sleep fragmentation.[1] OSA not only causes harmful systemic responses including oxidative stress, inflammation, hypertension, and insulin resistance, but also leads to functional impairment and structural alteration of brain.[3] OSA is related to diminished excessive daytime sleepiness by several mechanisms, including blood–brain barrier dysfunction,[4] brain edema,[5] amyloid deposition,[6] cerebral structure changes,[7] and altered anatomical brain connections.[8,9]

Discrete brain areas communicate with each other for diverse functions through anatomical connections to generate and integrate information from multiple

1561

sources.[10] Structural network properties depend on the integrity of brain structure and connections as well as the efficiency of functional segregation and integration. Altered network properties and their topography can explain neurocognitive defects and symptom diversity in OSA.[8,9] A good example of phenotypic diversity is excessive daytime sleepiness that does not only impair daytime function and quality of life but also determines cardiometabolic outcomes and therapeutic responses.[11,12] For the same degree of OSA, the level of daytime sleepiness varies substantially. Its mechanisms are still elusive.

Previous neuroimaging studies highlight the need to address OSA and daytime sleepiness as a network disorder underpinned by brain structure or activity that connects heterogeneous regional function. One study analyzed structural brain networks constructed from diffusion tensor imaging (DTI) and found altered anatomical connections driven by white matter injury in OSA.[8] Another study demonstrated that OSA led to alterations of global topological characteristics in the brain network constructed by statistical associations of cortical volumes.[9] Functional MRI studies also report that OSA severity is associated with abnormal functional connectivity as well as cognitive dysfunction.[13–16] Although very few studies have examined the relationship between daytime sleepiness and brain connectivity, one study reported that daytime sleepiness is associated with functional connectivity in the default mode network (DMN), which has a crucial role in cognition.[17] An increased rate of β-amyloid accumulation particularly in the DMN areas is associated with sleepiness.[18] Residual sleepiness in treated OSA patients may be partially explained by white matter abnormality on DTI.[19,20] However, it is still unclear which clusters of brain connectivity (ie, pairwise connections between brain regions) specifically correlate with the degree of OSA and daytime sleepiness.

Prior methods for network analysis have limitations in specifying brain connectivity related to OSA severity and daytime sleepiness since it is a complicated task to solve the relationship between a nonlinear complex system (ie, brain network) and continuous measures (ie, degree of OSA severity and daytime sleepiness scale). Thus, it is necessary to develop novel approaches to estimate linear properties from a nonlinear complex system and to understand which brain connections are linearly associated with OSA severity and daytime sleepiness. The deep learning algorithm is a computational technique to assess complex relationships between input features and target variables.[21]

The purpose of this algorithm is to learn a mapping function from input features to targets, achieved by adjusting the weights of the neural network in response to the errors between predicted and actual outputs the model makes on the training dataset. The adjusting processes are intended to continually reduce errors until a good enough model is found.[21] Contributions of individual input features to performance of decision-making by a trained model can be calculated by gradient information associated with the change in weights in relation to the change in errors (eg, input features with a larger gradient can have a greater effect on the predicted output).[22] Therefore, deep learning can determine brain connections that are the most susceptible to OSA severity or sleepiness, by maximizing the relationship between predicted and actual scores based on structural network organization while minimizing the errors between the two scores.

The purpose of this study was to investigate anatomical brain connectivity related to OSA severity and daytime sleepiness in a representative sample from a general population in middle-to-late adulthood by using structural network analysis implemented with a deep learning model referred to as BrainNetCNN, which has been recently described as a powerful prediction model for structural brain networks.[23] We also investigated differences in deep learning outputs according to sex and presence of OSA. Our specific hypothesis was that a deep learning analysis can be predictive of OSA severity and daytime sleepiness. Such an analysis could be an effective tool to improve our understanding of the neuroanatomical substrates for OSA and daytime sleepiness in adult populations.

Methods
Study Subjects

Study procedures were approved by the Institutional Review Board of Korea University Ansan Hospital (approval no. 2006AS0045), which is a sub-study of the Korean Genome and Epidemiology Study (KoGES), an ongoing prospective community-based cohort study. In 2001–2002, the original cohort was established in Ansan, South Korea, and consisted of 5012 adults aged 40–69 years. Furthermore, it was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent from all study participants was obtained. Participants in KoGES have been biennially evaluated for demographic characteristics, medical history, health status,

and sleep-related factors. As sleep and cognitive aging were adopted as an adjunct research agenda, polysomnography (PSG) and structural MRI were introduced in 2011. In contrast to the core KoGES evaluations performed every 2 years, MRI and PSG was aimed to cover all participants in a 4-year cycle.

For this cross-sectional analysis, we included 625 participants (age, 59.5 ± 7.6 years; men, 34.7%) who completed both MRI and PSG evaluations in 2011. We excluded subjects with 1) major neurological disorders (stroke, n = 16; major head trauma, n = 4; dementia, n = 1; hydrocephalus, n = 4), 2) incomplete Epworth Sleepiness Scale (ESS) assessment (n = 7), and 3) loss of MR image slices through the manual review of MRI image quality (n = 40). Finally, 553 participants (age 59.2 ± 7.4 years, men 35.6%) were included in the present study.

To perform an analysis of brain connectivity related to apnea–hypopnea index (AHI), oxygen desaturation index (ODI), the minimum oxygen saturation ($_{min}SpO_2$) and ESS scores, all subjects were randomly assigned into one of three data-sets: a training set (n = 398) to perform deep learning of a connectivity matrix, a validation set (n = 100) to confirm convergence of the deep learning model established in the training set, and a test set (n = 55) to evaluate the reliability of the deep learning model. In addition, a sex effect on the relationship of brain connectivity with OSA severity and ESS was examined in the subgroup analysis of men (n = 142/35/20 for training/validation/ testing sets) and women (n = 256/64/36). The ESS-associated connectivity was compared between non-OSA (n = 222/55/31 for training/validation/testing sets) and OSA (n = 176/44/25) groups.

All participants underwent overnight PSG. Apneas and hypopneas were defined according to standard methods.[24] The AHI was calculated by averaging the total number of obstructive apneas and hypopneas occurring per hour of sleep. OSA was defined as an AHI ≥ 5/hour of sleep and the non-OSA group had an AHI < 5/hour. Daytime sleepiness was assessed using the ESS.[25] The time interval between overnight PSG and brain MRI was within 2 weeks. The characteristics and sleep variables were presented in Tables 1 and 2. Before the analysis, we investigated the relationship between AHI and ESS to determine whether ESS should be regarded as an independent variable and found no significant correlation ($R = -0.1$, $P = 0.12$); therefore, ESS was considered as an independent variable.

Data Acquisition and Processing

DTI data was acquired using a 1.5-Tesla MRI scanner (General Electric, Milwaukee, WI) at TR = 15,000 ms, TE = 93.8 ms, 15 isotropic gradient directions with b = 1000 s/mm^2, and single b = 0 image acquisition. T1-weighted images were also obtained with the following parameters: TR = 7.7 ms, TE = 3.4 ms, flip angle = 12$^°$, slice thickness = 1.6 mm. Artifacts including head motion, noise, physiological artifacts, susceptibility-induced distortion, B1 field inhomogeneity, and eddy current-induced

Table 1 Demographic Data from All Participants

	Whole (n=553)	Men (n=197)	Women (n=356)	P	Non-OSA (n=308)	OSA (n=245)	P
Age (years)	59.2 ± 7.4	60.0 ± 7.3	58.7 ± 7.5	0.06	57.0 ± 6.4	61.9 ± 7.7	<0.01
Men	197 (35.6)				90 (29.2)	107 (43.7)	<0.01
BMI (kg/m^2)	24.7 ± 3.0	24.7 ± 2.9	24.7 ± 3.1	0.94	23.9 ± 2.6	25.6 ± 3.2	<0.01
Education							
<6 years	101 (18.3)	18 (9.1)	83 (23.3)	<0.01	43 (14.0)	58 (23.7)	<0.01
7–9 years	113 (20.4)	32 (16.2)	81 (22.8)	0.07	69 (22.4)	44 (18.0)	0.20
10–12 years	240 (43.4)	87 (44.2)	153 (43.0)	0.79	139 (45.1)	101 (41.2)	0.36
13–16 years	90 (16.3)	53 (26.9)	37 (10.4)	<0.01	53 (17.2)	37 (15.1)	0.51
> 16 years	9 (1.6)	7 (3.6)	2 (0.5)	<0.01	4 (1.3)	5 (2.0)	0.49
Current smokers	47 (8.5)	41 (20.8)	6 (1.7)	<0.01	24 (7.8)	23 (9.4)	0.50
Current drinkers	215 (38.9)	122 (61.9)	93 (26.1)	<0.01	114 (37.0)	101 (41.2)	0.31
Hypertension	202 (36.5)	83 (42.1)	119 (33.4)	0.04	83 (26.9)	119 (48.6)	<0.01
Diabetes mellitus	132 (23.9)	52 (26.4)	80 (22.5)	0.30	46 (14.9)	86 (35.1)	<0.01
BDI	8.8 ± 7.4	6.8 ± 6.7	10.0 ± 7.5	<0.01	8.8 ± 6.7	8.9 ± 8.2	0.88

Notes: Data are presented as n (%) or mean ± SD, unless otherwise stated.
Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index; BDI, Beck Depression Inventory.

Table 2 Sleep Variables of All Participants

	Whole (n=553)	Men (n=197)	Women (n=356)	P	Non-OSA (n=308)	OSA (n=245)	P
AHI (events/hour)	6.9 ± 8.5	8.5 ± 10.0	6.0 ± 7.4	<0.01	1.8 ± 1.4	13.2 ± 9.5	<0.01
Mild (5–14)	175 (31.6)	73 (37.1)	102 (28.7)	0.04		175 (71.4)	
Moderate (15–29)	56 (10.1)	26(13.2)	30 (8.4)	0.07		56 (22.9)	
Severe (≥30)	14 (2.5)	8 (4.1)	6 (1.7)	0.09		14 (5.7)	
$_{min}SpO_2$ (%)	87.8 ± 4.9	86.8 ± 5.1	88.4 ± 4.7	<0.01	90.4 ± 3.1	84.6 ± 4.8	<0.01
$_{mean}SpO_2$ (%)	95.7 ± 1.3	95.5 ± 1.1	95.9 ± 1.4	<0.01	96.2 ± 1.2	95.1 ± 1.2	<0.01
TS90 (min)	4.7 ± 13.3	2.5 ± 5.5	2.5 ± 11.8	0.99	0.7 ± 9.5	4.7 ± 10.2	<0.01
PTS90 (%)	1.5 ± 3.9	0.7 ± 1.5	0.7 ± 3.2	0.99	0.2 ± 2.5	1.3 ± 2.8	<0.01
ODI (events/hour)	6.2 ± 8.0	7.6 ± 9.3	5.5 ± 7.1	<0.01	1.6 ± 1.4	12.0 ± 9.0	<0.01
ESS	5.0 ± 3.2	4.6 ± 2.8	5.3 ± 3.4	0.01	5.2 ± 3.4	4.9 ± 3.0	0.03
TST (min)	391.4 ± 74.2	384.8 ± 74.3	395.0 ± 74.0	0.12	395.1 ± 73.7	386.7 ± 74.8	0.19
Stage N1 (%)	6.1 ± 4.9	6.7 ± 5.8	5.5 ± 4.2	0.01	5.2 ± 3.8	6.9 ± 6.0	<0.01
Stage N2 (%)	56.9 ± 11.0	56.3 ± 12.3	57.4 ± 10.0	0.26	57.1 ± 10.7	56.7 ± 11.3	0.71
Stage N3 (%)	3.2 ± 4.1	2.4 ± 4.1	2.6 ± 3.7	0.51	2.7 ± 3.9	2.3 ± 3.8	0.23
Stage R (%)	20.8 ± 6.7	20.1 ± 6.9	21.2 ± 6.7	0.08	21.3 ± 7.0	20.0 ± 6.5	0.04

Notes: Data are presented as n (%) or mean ± SD, unless otherwise stated.
Abbreviations: AHI, apnea–hypopnea index; $_{min}SpO_2$, minimum oxygen saturation; $_{mean}SpO_2$, mean oxygen saturation; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale; TST, total sleep time; TS90, time spent with oxygen saturation below 90%; PTS90, percentage of time spent with oxygen saturation below 90%.

distortion in DTI data were corrected by using the FSL eddy tool.[26] Whole brain streamlines were then reconstructed using second-order integration over fiber orientation distributions[27] incorporating anatomically constrained tractography[28] with 1000 dynamically randomized seeding points on the gray-matter/white-matter interface.

A parcellation scheme was applied to whole brain streamlines using an automated anatomical labeling (AAL) atlas,[29] segmented into 90 cerebral areas in order to construct a structural brain network. Each AAL region represented a node in the brain network, and an edge in the brain network was defined as the number of white-matter streamlines connecting the nodes normalized by volume of the nodes to stabilize inter-subject variability. Before training by using deep learning model, the strength of brain connections was adjusted for age, sex, education, drink, smoke, hypertension, and diabetes mellitus using a multiple linear regression model. For the subgroup analysis by sex, sex was not included in the model. To reduce the effect of inter-subject variability on the training process, the resulting residuals were used to substitute for the raw connection strength.

Conventional DTI Metrics

To investigate the correlation of conventional DTI metrics including diffusivity and network properties with OSA severity and daytime sleepiness, we employed fractional anisotropy

(FA) and three network parameters including node strength, nodal efficiency, and node betweenness centrality. FA measures the microstructural integrity of white matter.[5,8] Node strength is the sum of connection weights connecting neighbor nodes, assessing the ability of information interactions with these nodes.[30] Nodal efficiency reflects the importance of the node for reciprocal communication within the brain network, estimated by the average path length between any node and other nodes.[31] Node betweenness centrality is defined as the fraction of shortest paths between any two nodes that pass through a given node, and indicates the relative importance of a node on information flow in a complex network.[32]

Convolutional Neural Network Architecture

Before applying the deep learning algorithm to connectivity matrices, as overfitting which corresponds exactly or closely to target variables in the analysis model was expected due to the relatively small size of the training dataset (n = 398/142/256/222/176 for whole/men/women/non-OSA/OSA group), we employed the synthetic minority over-sampling technique[33] based on a randomly interpolated resampling procedure across the nearest neighbors, which enlarges the training dataset by triple augmentations for each subject.

Prior neural network techniques have a limitation when applied to brain network data to determine the relationship between anatomical brain connectivity related to OSA severity and daytime sleepiness. Fully connected neural networks may ignore the topological relationships between edges or nodes by treating the input connection weights as a vector of features.[23] Conventional convolutional neural networks (CNNs) use traditional convolutional filters (ie, square filters) designed to capture the spatial 2D grid locality of images, which treat connectivity matrix as an image.[23] It also cannot capture topological relationships in the brain network. Therefore, in the present study, we applied the BrainNetCNN,[23] which is a novel type of CNN optimized for the connectivity matrix. It consists of three types of layers (Figure 1): an Edge-to-Node (E2N) layer, which works by assigning weights to the edges of the network, a node-to-graph (N2G) layer, which reduces the dimensionality of the input by taking a weighted combination of nodes to output a single response and a final fully connected (FC)

layer. The E2N layer takes a 90×90 connectivity matrix derived from DTI and uses a 256×1 × 90 filter, which allows to extract topological features in the brain network. It gives a unique output value for each node i as it takes the average of weights of each edge connected to node i. The outputs of the E2N layer, 1×90 × 256 feature maps, are the inputs to N2G layer which acts as a 1D convolution to compress the node information. Finally, the number of features is reduced to the number of target variables through an FC layer with 1×1 × 64 feature maps. To avoid overfitting on the training set, we engaged an additional measure, adopting a dropout layer of 0.5 before the FC layer and to prevent vanishing gradient a leaky rectified linear unit with a negative slope of 0.2 was employed. Furthermore, we empirically set the number of training iterations as 30,000 for the whole group and 20,000 for other groups. To minimize the Euclidean distance loss with a weighted L2 regularization term between the predicted and actual scores on the training set, BrainNetCNN was trained using a stochastic gradient
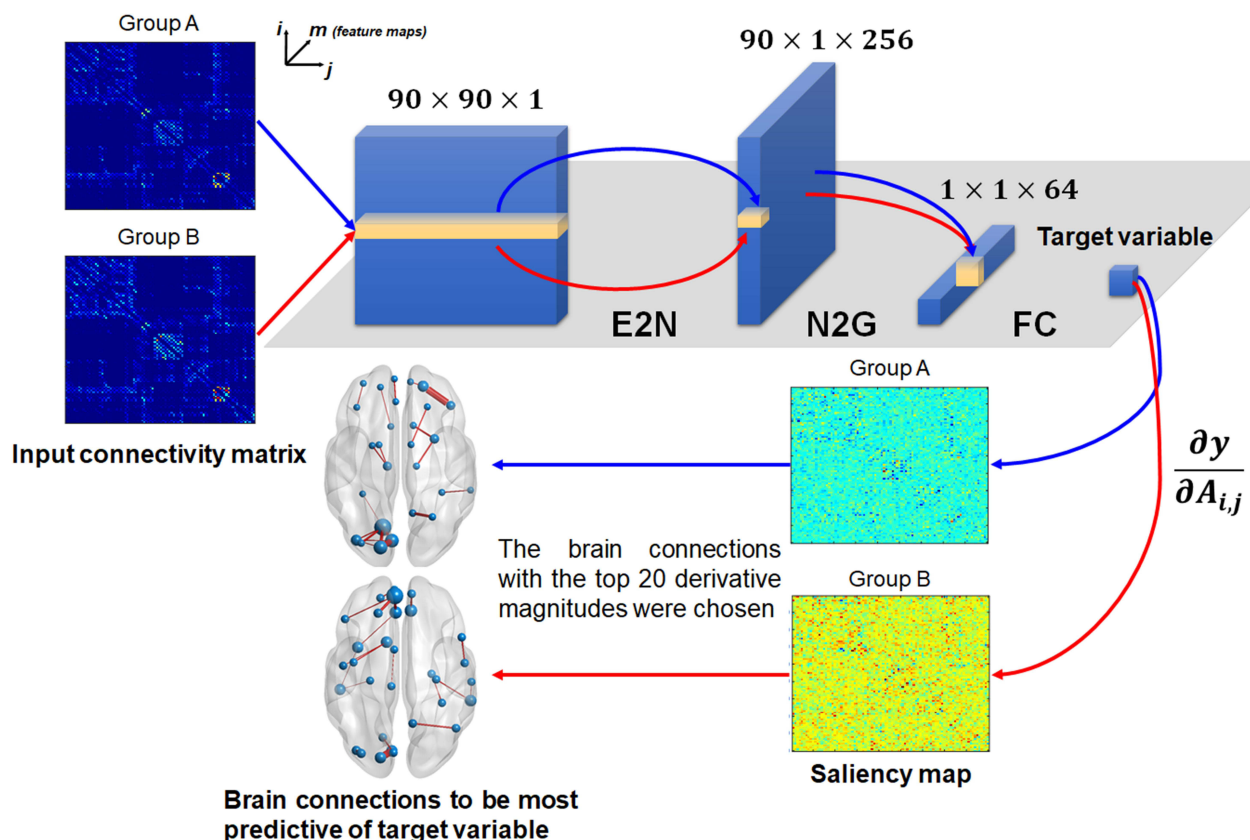
Figure 1 Schematic overview of the convolutional neural network architecture used to estimate the sleep variables. The convolutional neural network consists of an Edge-to-Node (E2N) layer, a node-to-graph (N2G) layer and fully connected (FC) layer. The E2N layer takes a 90×90 connectivity matrix and works by assigning weights to the edges of the network, a node-to-graph (N2G) layer reduces the dimensionality of the input by taking a weighted combination of nodes to output a single response and a final fully connected (FC) layer reduces the number of features for estimating a target variable. The saliency map is obtained by computing the partial derivatives of the output with respect to the input connectivity matrix for every input edge. Edges with a larger partial derivative were determined to be more predictive of the target variable.

descent algorithm, which updates the weights by a linear combination of the negative gradient and the previous weight update at the learning rate of 0.01.

Statistical Analysis

The general characteristics are reported as means and standard deviations and proportions with group comparisons using *t*-tests and standard chi-squared test for continuous and categorical variables, respectively. The statistical significance was set at p<0.05. For the conventional DTI metrics analyses, statistical significance was set at p<0.05, after false discovery rate controlled for multiple comparisons.

To evaluate consistency and performance of the BrainNetCNN model, we performed Three-fold Cross-Validation on the training and validation sets, and calculated the mean absolute error (MAE), the Pearson's correlation coefficient (*R*) and the probability of absolute error less than standard deviation ($P_{AE<SD}$) between the predicted and the actual scores. In the present study, we report average and standard deviation of MAE, *R* and $P_{AE<SD}$ over cross-validation folds. The statistical significance for *R* was set at p<0.05 in all cross-validations. When the *R* between the predicted and actual scores met the statistical significance (p<0.05) in all cross-validations, the deep learning model was accepted as a meaningful prediction model. To determine which pairwise connections were learned by BrainNetCNN to be predictive of AHI, ODI, $_{min}SpO_2$ and ESS, we used the method of saliency visualization[22] that computes the partial derivatives of the output (ie, predicted score) with respect to the input connectivity matrix for

every input edge.[23] Edges with a larger partial derivative were determined to be more predictive of the actual score, which have higher pairwise connections contributing to better prediction (Figure 1). The BrainNetCNN was implemented with deep a learning framework (Caffe, https://caffe.berkeleyvision.org/).

Results
Conventional DTI Metrics

There were no meaningful correlations ($R < 0.3$ and $P > 0.05$) between any conventional DTI metrics including FA, node strength, regional efficiency, and node betweenness centrality and OSA severity and daytime sleepiness in the whole dataset, and in all the subgroups. This suggests that conventional DTI metrics may not be a proper predictor of OSA severity and daytime sleepiness although they were different by group comparisons between non-OSA and OSA groups as reported in previous studies including our own, based on the same population.[8,9]

Prediction of OSA Severity

The results of using the BrainNetCNN model to predict AHI, ODI and $_{min}SpO_2$ scores are summarized in Table 3. We achieved meaningful Pearson's correlation coefficients and $P_{AE<SD}$ for AHI, ODI and $_{min}SpO_2$ in the test dataset of whole group and the subgroups, suggesting that the deep learning method is better than conventional DTI at predicting the degree of OSA severity indicated by AHI, ODI, and $_{min}SpO_2$.

Table 3 Pearson's Correlation Coefficient (*R*), Mean Absolute Error (MAE), and Probability of Absolute Error Less Than Standard Deviation ($P_{AE<SD}$) Between Measured and Predicted Apnea–Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), and Minimum Oxygen Saturation ($_{min}SpO_2$) Scores with Three-fold Cross-Validation

		AHI			ODI			$_{min}SpO_2$		
		*R**	MAE	$P_{AE<SD}$	*R**	MAE	$P_{AE<SD}$	*R**	MAE	$P_{AE<SD}$
Whole group	Train	0.74 ± 0.0	4.37 ± 0.3	0.89 ± 0.0	0.74 ± 0.0	4.09 ± 0.3	0.89 ± 0.0	0.73 ± 0.0	2.95 ± 0.3	0.83 ± 0.0
	Valid	0.60 ± 0.1	5.01 ± 0.7	0.86 ± 0.0	0.61 ± 0.1	4.66 ± 0.6	0.86 ± 0.0	0.56 ± 0.0	3.42 ± 0.3	0.78 ± 0.1
	Test	0.65 ± 0.0	6.10 ± 0.1	0.81 ± 0.0	0.67 ± 0.0	5.59 ± 0.3	0.84 ± 0.0	0.60 ± 0.0	3.61 ± 0.2	0.74 ± 0.0
Men group	Train	0.95 ± 0.0	3.60 ± 0.3	0.95 ± 0.0	0.95 ± 0.0	3.13 ± 0.2	0.94 ± 0.0	0.92 ± 0.0	3.10 ± 0.5	0.83 ± 0.1
	Valid	0.77 ± 0.1	5.05 ± 1.2	0.90 ± 0.1	0.76 ± 0.1	4.52 ± 1.1	0.90 ± 0.1	0.73 ± 0.1	3.85 ± 0.1	0.72 ± 0.0
	Test	0.71 ± 0.0	5.01 ± 0.3	0.90 ± 0.1	0.69 ± 0.0	4.59 ± 0.2	0.92 ± 0.0	0.72 ± 0.0	3.60 ± 0.5	0.73 ± 0.0
Women group	Train	0.86 ± 0.0	3.93 ± 1.4	0.87 ± 0.1	0.85 ± 0.0	3.87 ± 0.6	0.83 ± 0.1	0.84 ± 0.0	2.32 ± 0.1	0.89 ± 0.0
	Valid	0.77 ± 0.0	4.47 ± 0.6	0.84 ± 0.0	0.75 ± 0.0	4.32 ± 0.5	0.82 ± 0.0	0.60 ± 0.1	2.86 ± 0.4	0.86 ± 0.1
	Test	0.73 ± 0.1	4.22 ± 1.2	0.85 ± 0.1	0.74 ± 0.1	4.21 ± 0.5	0.82 ± 0.1	0.55 ± 0.0	3.04 ± 0.3	0.78 ± 0.0

Notes: *All Pearson's correlation coefficients (*R*) were statistically significant at *P* < 0.01. Values are Listed for Three Different Groups/Subgroups: Whole Dataset (n = 553), Men Group (n = 197) and Women Group (n = 356).

Anatomical Brain Connectivity Related to OSA Severity

The partial derivatives predictive of AHI, ODI and $_{min}$SpO$_2$ scores are plotted with edges connecting nodes of AAL atlas regions (see Figures 2 and 3). In the whole group, we could delineate the prominent hubs of important connections such as the left motor area, left fusiform gyrus, and the limbic system, for predicting OSA severity (Figure 2). In the subgroup analysis, anatomical connections related to OSA severity differed by sex (Figure 3). AHI and ODI were predicted by the connections of hubs located in left occipital and right prefrontal areas for men, and in left occipital,

prefrontal areas and the limbic system for women. The lowest value of oxygen saturation, $_{min}$SpO$_2$, was closely related to left occipital areas and the limbic system in men, and to left occipital, temporal areas and limbic system in women.

Prediction of Degree of Daytime Sleepiness

The performance of the BrainNetCNN model to predict daytime sleepiness is summarized in Table 4. The deep learning method predicted ESS in the whole group analysis as well as in the subgroup analysis by sex and presence of OSA.
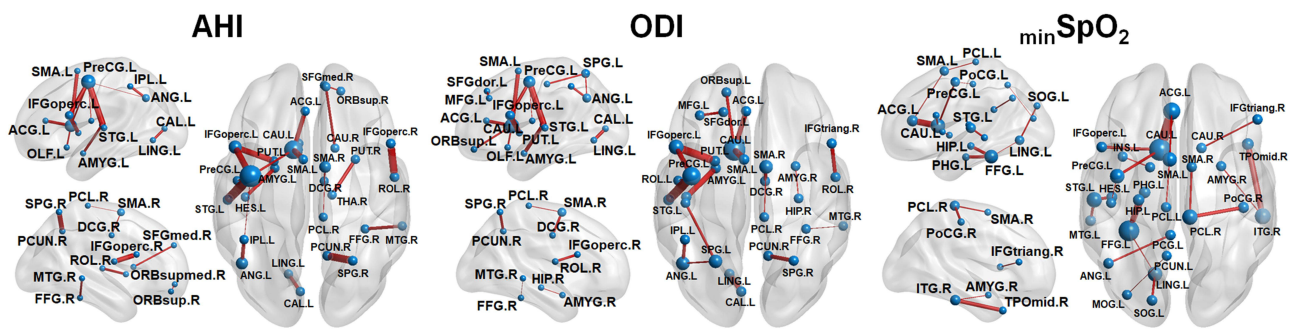
Figure 2 The brain connectivity most predictive of the apnea–hypopnea index (AHI), oxygen desaturation index (ODI), and minimum oxygen saturation ($_{min}$SpO$_2$) scores in the whole group. The brain connectivity with the top 20 derivative magnitudes were chosen for clarity. On the 3D surface images, the thickness of individual edge (red) indicates the partial derivative magnitude and the size of each sphere (blue) indicates the sum of the partial derivative magnitude, with respect to AHI, ODI, $_{min}$SpO$_2$ scores, respectively. A complete list of the region labels is available in Table S1.
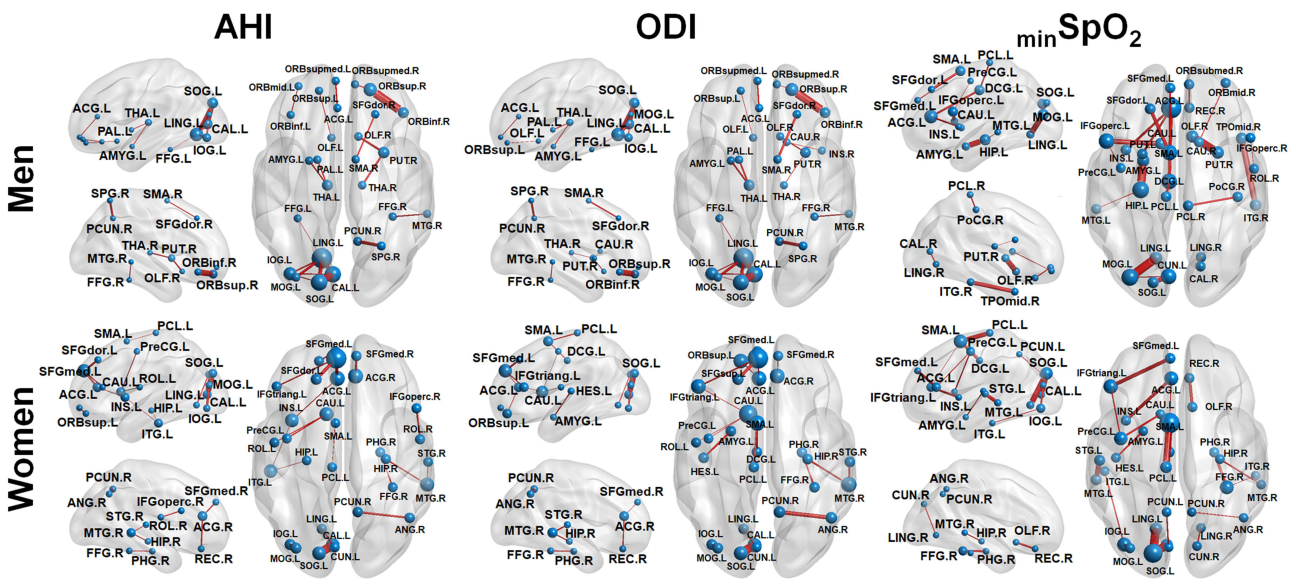
Figure 3 The brain connectivity to be most predictive of apnea–hypopnea index (AHI), oxygen desaturation index (ODI), and minimum oxygen saturation ($_{min}$SpO$_2$) score for two different subgroups: men and women. The brain connections with the top 20 derivative magnitudes were chosen for clarity. On the 3D surface images, the thickness of individual edge (red) indicates the partial derivative magnitude and the size of each sphere (blue) indicates the sum of the partial derivative magnitude, with respect to AHI, ODI, $_{min}$SpO$_2$ scores, respectively. A complete list of region names corresponding to the region labels is available in Table S1.

Table 4 Pearson's Correlation Coefficient (R), Mean Absolute Error (MAE), and Probability of Absolute Error Less Than Standard Deviation ($P_{AE<SD}$) Between Measured and Predicted Epworth Sleepiness Scale (ESS) Scores with Three-fold Cross-Validation

		Train Set	Valid Set	Test Set
Whole group	R*	0.75±0.0	0.60±0.1	0.54±0.0
	MAE	1.93±0.0	2.39±0.3	2.13±0.1
	$P_{AE<SD}$	0.82±0.0	0.72±0.1	0.76±0.0
Men group	R*	0.92±0.0	0.70±0.0	0.68±0.1
	MAE	1.73±0.3	1.94±0.4	2.39±0.6
	$P_{AE<SD}$	0.78±0.1	0.77±0.1	0.60±0.1
Women group	R*	0.85±0.0	0.67±0.1	0.60±0.0
	MAE	1.85±0.2	2.37±0.3	2.43±0.2
	$P_{AE<SD}$	0.85±0.0	0.77±0.1	0.74±0.0
Non-OSA group	R*	0.87±0.0	0.74±0.0	0.73±0.0
	MAE	1.55±0.1	2.03±0.2	2.70±0.1
	$P_{AE<SD}$	0.92±0.0	0.81±0.0	0.72±0.0
OSA group	R*	0.91±0.0	0.73±0.0	0.74±0.0
	MAE	1.25±0.1	1.91±0.1	2.35±0.1
	$P_{AE<SD}$	0.95±0.0	0.79±0.0	0.72±0.0

Notes: *All Pearson's correlation coefficients (R) were statistically significant at $P < 0.01$. Values are Listed for Five Different Groups/Subgroups: Whole Dataset (n = 553), Men Group (n = 197), Women Group (n = 356), Non-Obstructive Sleep Apnea (OSA) Group (n = 308) and OSA Group (n = 245).

Anatomical Brain Connectivity Related to Daytime Sleepiness

The partial derivatives to be predictive of ESS scores are plotted with edges connecting nodes of the AAL atlas regions (see Figure 4). In the whole group, prominent hubs were the left superior frontal areas, the cingulate, precuneus, angular, occipital temporal, prefrontal, hippocampal, and posterior inferior parietal areas known as components of the right DMN in a previous study.[34] In the subgroup analysis, sex differences were found in brain connectivity related to daytime sleepiness. The right DMN appeared to be a prominent hub of important connectivity in men. In contrast, the right prefrontal areas and the left DMN were important in women. The presence of OSA also influenced the characteristics of anatomical connections. Important connectivity related to sleepiness were in the right DMN and the left limbic system in the OSA group, but in bilateral prefrontal areas and the right limbic system in the non-OSA group.

Discussion

This study was motivated by a desire to overcome the limitations of conventional approaches to brain network analyses, which could not readily estimate a continuous property (ie, OSA severity and daytime sleepiness) in relation to a nonlinear complex system (ie, structural brain network). For this goal, we applied a novel deep learning algorithm that can effectively discriminate subtle differences in the strength of anatomical brain connections. Three major findings in the present study support our hypothesis. First, while conventional DTI metrics did not predict OSA severity and daytime sleepiness ($R < 0.3$ and $P > 0.05$), the deep learning technique accurately predicted AHI ($R = 0.69 \pm 0.1$, $P < 0.01$), ODI ($R = 0.66 \pm 0.1$, $P < 0.01$), $_{min}SpO_2$ ($R = 0.62 \pm 0.1$, $P < 0.01$), and ESS ($R = 0.70 \pm 0.0$, $P < 0.01$) for test datasets of all group/subgroup analyses. The high correlation as well as the high probability of absolute error within 1 standard deviation (up to 92%) indicate that the predicted OSA severity and daytime sleepiness is a close proxy of the actual OSA severity and daytime sleepiness. Second, the deep learning technique can determine anatomical brain connectivity associated with OSA and daytime sleepiness. Finally, our approach revealed the effects of sex and OSA on the relationship of anatomical brain connectivity with daytime sleepiness. Sex also influenced network connectivity related to OSA severity. Although previous studies showed group differences, OSA vs non-OSA, in white matter integrity and network properties,[5,8,9] we could not find any topographic features of FA values and network properties that explained incremental changes in OSA severity and daytime sleepiness with conventional network analysis in this study. The present findings suggest that deep learning techniques are promising tools to provide neuroimaging biomarkers of OSA severity and daytime sleepiness and to explain the phenotypic diversity in OSA.

OSA affects a wide range of brain areas related to medullary respiratory regulatory, cognitive and autonomic function.[35] In the present study, OSA severity was related to brain connectivity including the left motor system that consists of the precentral gyrus, the supplementary area, and its connections and the left limbic system that includes amygdala, caudate, cingulate, putamen and its neighboring connections. These brain systems are susceptible to OSA and related to breathing control, mood, cognition, and cardiovascular regulation.[35] These findings suggest that the neural substrates for common clinical manifestations of OSA such as cardiovascular dysregulation, cognitive dysfunction, and affective change can be better identified. Chronic exposure to repetitive hypoxia in OSA results in myelin and axonal damage as well as alterations in the
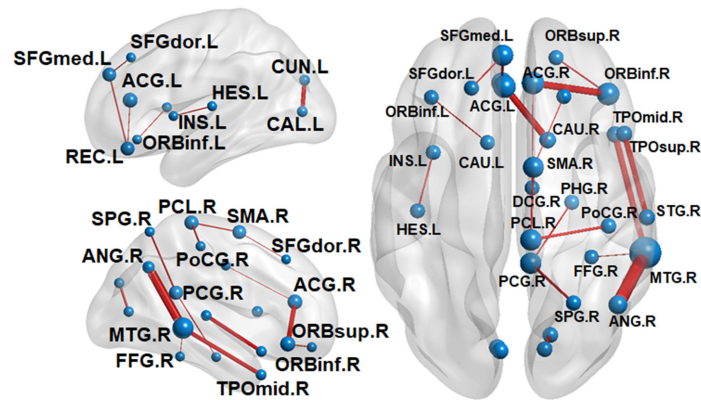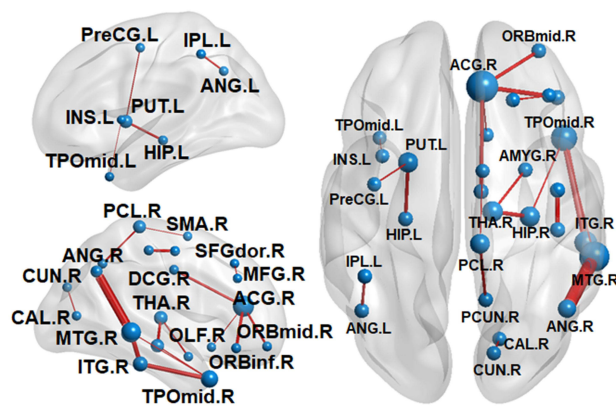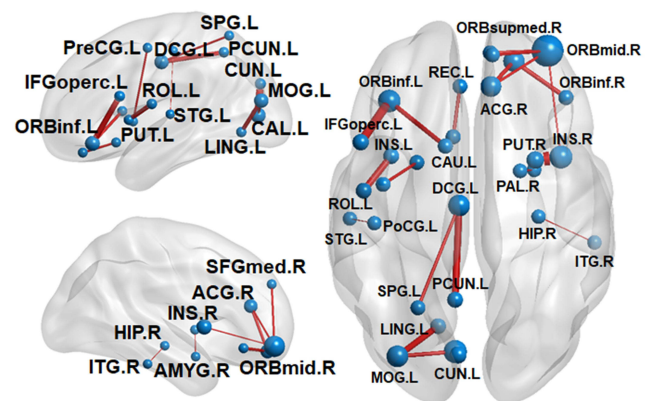
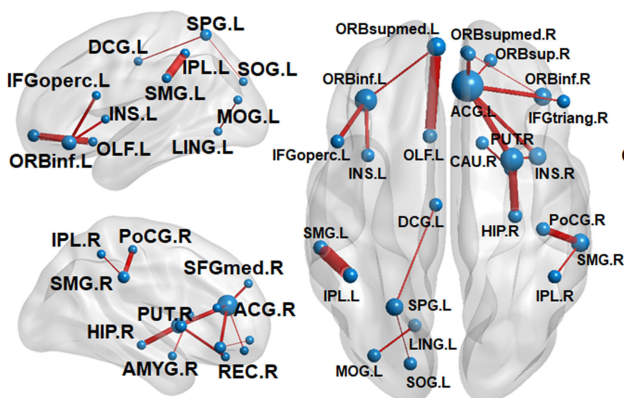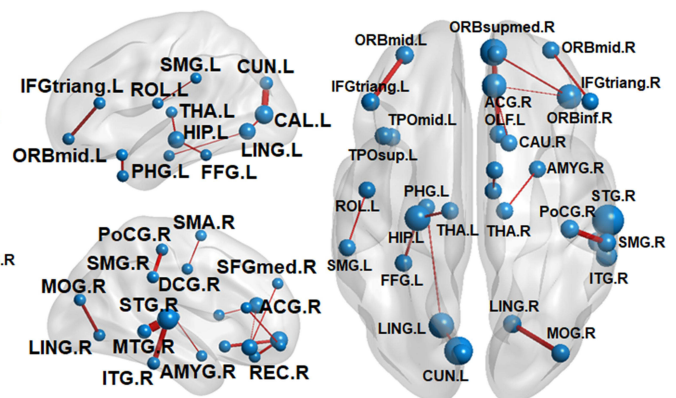**Figure 4** The brain connectivity maps to be most predictive of the Epworth Sleepiness Scale (ESS) scores for five different groups/subgroups: whole dataset, Men group, Women group, non-OSA group and obstructive sleep apnea (OSA) group. The brain connectivity with the top 20 derivative magnitudes were chosen for clarity. On the 3D surface images, the thickness of individual edges (red) indicates the partial magnitude and the size of each sphere (blue) indicates the sum of the partial derivative magnitude, with respect to ESS scores, respectively. A complete list of region names corresponding to the region labels is available in Table S1.

cellular space that lead to changes in structural network properties in these brain areas.[8] In addition, we found that excessive daytime sleepiness is associated with brain connectivity in the left superior frontal areas and right DMN

that consists of cingulate, prefrontal, angular, temporal, and parahippocampus areas. The DMN is closely tied to memory performance[36] and the prefrontal cortex subserves several cognitive domains.[37] DMN areas are

vulnerable to increased amyloid accumulation in older adults who experience daytime sleepiness.[18] These findings can be interpreted as one of the mechanisms for cognitive impairment in subjects with daytime sleepiness, especially in the elderly population.[17]

The men and women brains show anatomical, functional and biochemical differences across the whole life span.[38] In the present study, we investigated sex differences in brain connectivity related to OSA severity and daytime sleepiness. Men and women had different patterns of brain connectivity related to AHI, ODI, $_{min}SpO_2$ and ESS. AHI and ODI was associated with prefrontal area-related connectivity, left side in women but right side in men. The prefrontal area is involved in decision-making and associated with sex differences in its response to stress.[39] Prefrontal lesions impair decision-making by right-sided lesions in men but by left-sided lesion in women.[40] In the women, but not in men, AHI and ODI were related to left limbic system-related connectivity. Women have a larger deep limbic system, which has been proposed as one explanation for sex differences in the susceptibility to depression.[41] Our findings may help explain why depression is reported more frequently as a presenting symptom in women than men with OSA.[42]

The range of excessive daytime sleepiness across severities of sleep apnea or pathological sleep in general remains a mystery. In our analysis, daytime sleepiness was associated with right prefrontal areas and left DMN-related connectivity in women, but with right DMN-related connectivity in men. Daytime sleepiness contributes to memory and mood impairment in OSA.[43] Interestingly, left and right DMNs are associated with verbal and spatial memory performance, respectively.[44] In women, right prefrontal areas that play a key role in working memory and executive functioning were also associated with excessive daytime sleepiness, and might be related to the decline in OSA-related attention and executive function.[45] Sex effects need to be considered when interpreting neuroimaging studies in OSA.

In both groups, anterior cingulate-, parietal-, and orbitofrontal-related connections were common brain connections susceptible to daytime sleepiness. These areas are known to be vulnerable to daytime sleepiness and are associated with increasing amyloid accumulation.[18] Besides these areas, ESS was related to right limbic system and bilateral prefrontal areas-related connectivity in the non-OSA group, but to right DMN and left limbic system-related connectivity in the OSA group. Affected brain connections were more widely distributed in the

OSA group. In particular, the hippocampus-related connections were susceptible to daytime sleepiness in the OSA group. Hippocampus damage caused by OSA may lead to worsening daytime sleepiness as well as cognitive impairments.[46]

The present study has several limitations. The DTI data had a limited number of isotropic gradient directions (n = 15) and were measured at a relatively low diffusion weight (b = 1000 s/mm^2). Thus, the tractography analysis may not be fully resolved in voxels with crossing, kissing, fanning, and curving fiber configurations although we utilized state-of-the-art algorithms.[27,28] This may lead to incorrect and ambiguous estimates of fiber orientation.[47] The sample size (n = 553) in this retrospective and observational study is not large enough to determine the heterogeneity of high dimensional structural brain network data by using the present deep learning technique. To minimize this limitation, we applied data augmentation. Since this approach may also cause model overfitting for the training dataset, our approach needs to be tested and refined in a larger independent sample including other institutional data sets. It is likely that different severities and clinical vs population-based differences exist, which our results do not address, nor the dynamics of network connectivity over time. Racial differences in connectivity and OSA impact will need assessments in a diverse population. Our subjects were a non-clinical population, mostly diagnosed with milder OSA (71.4%). Although our trained model successfully predicted OSA severity and found OSA severity-related brain connections, the number of severe OSA was quite small during the training process. Therefore, since there might be the probability of large absolute error for severe OSA, additional validation is needed for severe OSA. In addition, only 6.2% of our subjects experienced excessive daytime sleepiness (ESS > 10), which may result from underestimation in ESS domains in older adults.[48] Therefore, although our trained model successfully predicted ESS, the number of severe ESS was relatively small during the training process; additional validation is needed for severe subjective sleepiness. Finally, in the present study, we did not compare cognitive performance between groups. Although most brain connections susceptible to OSA severity and daytime sleepiness determined by deep learning model are related to cognitive performance, decline associated with OSA and sleepiness could not be quantitatively explained. It remains an important line of inquiry for future research.

Conclusion

In summary, the present study provides a novel approach to determine the anatomical blueprint underlying OSA and daytime sleepiness-related brain connectivity in middle and late adulthood. This approach has clinical implications to delineate the mechanism of functional impairment and daytime sleepiness, and to predict the risk of subsequent cognitive impairment in OSA.

Acknowledgments

Disclosure

Dr R. J. Thomas reports personal consulting fees from GLG Councils, Guidepoint Global, and Jazz Pharmaceuticals, outside the submitted work. In addition, RJT has a patent ECG-spectrogram with royalties paid by MyCardio, LLC, a patent PAPGAM issued, and a patent Auto CPAP licensed to DeVilbiss-Drive. All other authors declare no potential conflict of interest.

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