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Predicting brain age based on sleep EEG and DenseNet

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***Abstract*— We proposed a sleep EEG-based brain age prediction model which showed higher accuracy than previous models. Six-channel EEG data were acquired for 6 hours sleep. We then converted the EEG data into 2D scalograms, which were subsequently inputted to DenseNet used to predict brain age. We then evaluated the association between brain aging acceleration and sleep disorders such as insomnia and OSA.**

The correlation between chronological age and expected brain age through the proposed brain age prediction model was 80% and the mean absolute error was 5.4 years. The proposed model revealed brain age increases in relation to the severity of sleep disorders.

In this study, we demonstrate that the brain age estimated using the proposed model can be a biomarker that reflects changes in sleep and brain health due to various sleep disorders.

***Clinical Relevance*— Proposed brain age index can be a single index that reflects the association of various sleep disorders and serve as a tool to diagnose individuals with sleep disorders.**

I. Introduction

Brain electrophysiological activities vary temporally during sleep. Different oscillations (slow < 4Hz vs fast wave) of brain activities during sleep imply different sleep stages (1 to 4, shallow to deep sleep). Some characteristics seen on sleep electroencephalogram (EEG) may indicate alterations in normal sleep throughout various aging phases [1]. In healthy sleepers, known aging trends include a decrease in deep sleep, namely in stages 3-4 sleep, and increases in intermittent wakefulness and stage 1 sleep [2]. In addition to changes in the duration of each sleep stage, the pattern of oscillations representing different sleep stages also alters with age [3].

In terms of the pathophysiology, insomnia is characterized not only by slow wave deficiency, but also by hyperarousal of the central nervous system, affecting both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep [4]. On the other hand, obstructive sleep apnea (OSA) is characterized by recurrent hypoxic, hypercapnic, and transient elevated blood pressure episodes that may damage or alter neural structures.

Therefore, measurement of brain electrophysiological activities during sleep, such as EEG, can be used to predict the age of a given subject as well as pathological aging in relation to sleep disorders.

The predicted age based on machine learning of brain structural or functional measurement often describes brain age as differing from chronological age due to neurological disease-dependent alterations in biological or physiological brain integrity.

Most brain age prediction studies have been based on magnetic resonance imaging (MRI), which holds less relevant information for understanding brain aging in relation to brain activities during sleep, as opposed to sleep EEG. Sleep EEG, a part of the standard process of polysomnography, is largely available in sleep clinics and is a relatively inexpensive test compared to imaging techniques such as brain MRI. Thus, the sleep EEG is advantageous to machine learning and deep learning.

Sun et al. predicted brain age through 102 feature sets using 2,532 sleep EEG data, demonstrating a mean absolute error (MAE) of 7.6 years between brain age and chronological age [5]. Non-sleep resting-state EEG has also been used to predict brain age. A recent study based on machine learning techniques using a 468 EEG data set, which revealed a MAE of 6.87 weeks [6]. However, limitations in reducing the MAE of conventional models exist due to its use of a hand craft feature-based machine learning technique.

Since different oscillations in time (slow vs fast wave) and magnitude (small vs large wave) can be characterized using the 2D scalogram, we converted sleep EEG data into the scalogram to explore its ability of predicting brain age.

Finally, using the convolutional neural network (CNN) based 3D DenseNet [7], we proposed a brain age prediction model to improve the accuracy of the existing EEG based models, and investigated the association between brain aging acceleration and sleep disorders such as insomnia and OSA. We also analyzed which polysomnography (PSG) parameters that quantified various aspects of sleep were explained by alterations in sleep EEG-based brain age.

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II. METHODS

A. Dataset

The cross-sectional dataset analyzed in this study comprised of 4,215 polysomnograms from Samsung Medical Center. The current deep learning-based brain age prediction (BAP) model was improved by optimizing the parameters based on the 1186 healthy sleeper group EEG data.

Each EEG data consisted of 6 channels (F3, F4, C3, C4, O3, O4). healthy, OSA, insomnia, and co-morbid insomnia and sleep apnea (COMISA) groups were defined by insomnia index (ISI) and apnea-hypopnea index (AHI) (Table 1). Also, for all groups, the age was limited from 20 to 70 years old. The median ages ± standard deviation (std) of healthy, OSA, insomnia, and COMISA groups were 42±14, 54±11, 52±14, and 56±11 years old, respectively.

TABLE 1. DEFINITION OF HEALTHY, OSA, INSOMNIA AND COMISA GROUPS

Group	criteria	No. patients
Healthy	20<age<70 ISI ≤ 14 AHI ≤ 15	1186 (male: 751)
OSA	20<age<70 AHI > 15	1715 (male: 1482)
Insomnia	20<age<70 ISI > 14	649 (male: 280)
COMISA	20<age<70 AHI > 15 ISI > 14	672 (male: 518)

B. Brain age prediction model

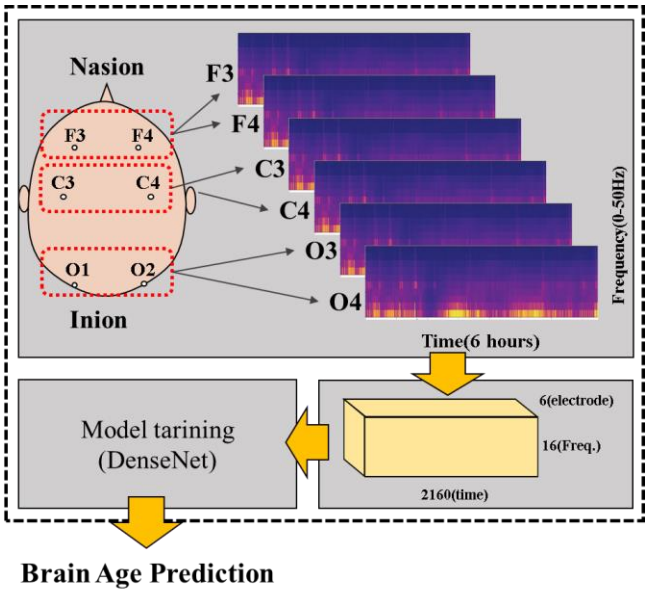

Figure 1. Overall scheme of brain age prediction model

50 Hz low pass filtering was performed on all EEG data used for model training, with length fixed to 6 hours. The data was then converted into scalograms based on continuous Morlet wavelet transform as shown in Eq. (1) [8] and trained to simultaneously reflect the temporal and frequency characteristics of sleep EEG data (Fig 1).

$$WT_{u,a} = [s, \varphi_{u,a}] = \int_{-\infty}^{\infty} s(t)\varphi_{u,a}^{*}(t)dt \quad (1)$$

where

$$\varphi_{u,a} = \frac{1}{\sqrt{a}}\varphi\left(\frac{t-u}{a}\right) \quad (2)$$

$WT_{u,a}$ represent the wavelet coefficients. $\varphi_{u,a}$ represents a continuous wavelet, in which u is the shift factor and a is the scale factor of the wavelet. $\varphi_{u,a}^{*}$ represents the complex conjugate of $\varphi_{u,a}$.

We used DenseNet [7] to train the BAP model. The network used a previously established and well-tested three dimensional (2,160 time epochs x 16 frequency bands x 6 EEG channels) C-P-T-D4-T-D4-T-D-P-FC architecture with 121 layers, in which C is a convolution layer, P is a pooling layer, T is a transition layer, D is a dense block and FC is a fully-connected layer. Each layer is followed by ReLU non-linearity. Mean squared error (MSE) was used as the loss function with an Adam optimizer, a learning rate of 0.001 and a batch size of 2. 10-fold cross validation was used to validate the BAP model.

Brain age index(BAI), which reflects a subject's relative brain health status, is measured by subtracting chronological age from predicted brain age [9]. Due to regression dilution [10, 11], however, it is also possible that regression models bias the predicted brain age toward the mean, underestimating the age of older subjects and overestimating the age of younger subjects [12]. When deriving the BAI, this bias thus needs to be corrected using a strategy that was introduced in [10].

III. RESULTS

After a 10-fold cross validation for the healthy sleeper group data, the correlation between chronological age and expected brain age through the proposed brain age prediction model was 80% and the MAE (std) was 5.4 (7.3) years. BAI of the sleep disorder groups increased as the corresponding chronological age increased. The difference between the BAI of the healthy sleeper group and sleep disorder groups increased as the corresponding chronological increased (Fig 2).

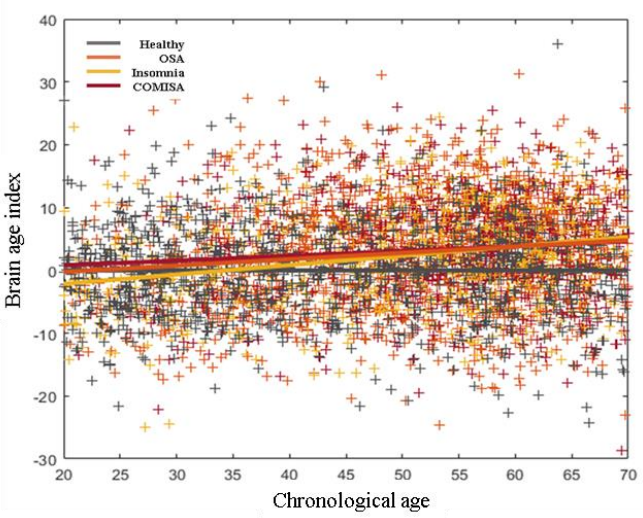

Figure 2. Linear regression models fitted into healthy sleeper (grey), OSA (red), insomnia (yellow), and COMISA (green) subjects

The average BAI of the OSA group was 2.9, insomnia 2.1, and COMISA 3.3 years (i.e., their brains 2.1-3.3 years older than healthy sleepers). As expected, the BAI of COMISA was the highest, followed by OSA and insomnia. In addition, sleep disorder groups were significantly different from the healthy sleeper group. Between sleep disorder groups, significant differences in BAI were found except for between OSA and COMISA (Table 2).

TABLE 2. BAI OF OSA, INSOMNIA AND COMISA

	BAI (std)	***P*-value**			
		Healthy	*OSA*	*Insomnia*	*COMISA*
OSA	2.9 (8.4)	****	-	***	-
Insomnia	2.1 (7.9)	****	***	-	***
COMISA	3.3 (8.5)	****	-	***	-

* - Not significant, **** $p < 0.0001$, *** $p < 0.005$

TABLE 3. UNIVARIATE REGRESSION ANALYSIS OF BAI COVARIATES

Covariate	**Whole data**	
	RC(SE)	*P-value*
OSA	2.262 (0.25)	<0.001
Insomnia	1.064 (0.27)	<0.001
Sleep stage 1	0.100 (0.01)	<0.001
Pittsburgh sleep quality index	0.100(0.03)	0.002
Age	0.092 (0.01)	<0.001
Insomnia index	0.065 (0.02)	<0.001
Arousal index	0.060 (0.01)	<0.001
Body mass index	0.027 (0.03)	0.371
Apnea hypopnea index	0.026 (0.01)	<0.001
Oxygen desaturation index	0.015 (0.01)	0.011
Non-REM	0.009 (0.01)	0.261
Beck depression inventory	-0.003 (0.01)	0.828
REM	-0.044 (0.02)	0.014
Sleep stage 2	-0.061 (0.01)	<0.001
Sleep stage 3	-0.126 (0.02)	<0.001

* Abbreviations: RC=regression coefficient, SE=standard error

Coefficients of covariates in a linear regression model that estimated BAI are shown in Table 3. OSA had the highest positive regression coefficient with BAI (regression coefficient ± standard error: 2.262 ± 0.25; $P < .001$), followed by insomnia (1.064 ± 0.27; $P < .001$). Age (0.092 ± 0.01; $P < .001$), percentage of the length of sleep stage 1 (0.100 ± 0.01; $P < .001$), insomnia index (ISI) (0.065 ± 0.02; $P < .001$) [13], arousal index (0.060 ± 0.01; $P < .001$), apnea-hypopnea index (0.026 ± 0.01; $P < .001$), oxygen desaturation index (0.015 ± 0.01; $P < .001$), and Pittsburgh Sleep Quality Index (0.100 ± 0.03; $P = .002$) [14] were associated with accelerated brain aging. The percentages of the lengths of REM sleep (-0.044 ± 0.02; $P = .014$), stage 2 (-0.061 ± 0.01; $P < .001$), and stage 3 (-0.126 ± 0.02; $P < .001$) were negatively correlated with BAI.

IV. Discussion

The BAI of each sleep disorder group was significantly different when compared to the healthy sleeper group. Furthermore, BAI was significantly different between the disease groups except between OSA and COMISA groups. In particular, significant differences were shown between the OSA and insomnia groups, suggesting that the proposed brain age prediction model can reveal differences in pathological brain aging between sleep disorder groups. In addition, the BAI of COMISA, which includes both OSA and insomnia diseases, was 1.2 and 0.4 higher than insomnia and OSA groups, respectively, which suggests that a co-morbid effect may contribute to increasing BAI.

Univariate analysis of covariates demonstrated that, as expected, the presence of OSA and insomnia was strongly associated with an increase in BAI. Moreover, BAI increased as the insomnia index and apnea hypopnea index scores increased, indicating that the severity of insomnia and OSA is the main driving force of accelerated brain aging. In addition, oxygen desaturation index as the measurement related to the repetitive hypoxic events in OSA, may also lead to faster brain aging. These results demonstrate that the change in BAI estimated using the proposed BAP model is sensitive to the severity of sleep disorders. Chronological age in sleep disorder groups significantly correlated with faster brain aging; because it is assumed that the higher the age is, the longer is the period of exposure to the disease, it may be

harmful to brain health when sleep disorders are untreated for a long time. In terms of the percentage of sleep stage duration, it was revealed that the higher the BAI, the longer the shallow sleep and the shorter the deep sleep. Thus, the proposed BAI model reflected the sleep pattern-dependent aging shown in a prior study [15].

Although the proposed EEG-based brain age prediction model showed lower accuracy in healthy sleepers compared to image-based models (MAE: 5 vs 3 years), it nonetheless showed the highest performance among the existing EEG-based brain age prediction models. Furthermore, our model showed sufficient sensitivity to the pathological aging difference between the OSA and the insomnia groups. In addition, sleep EEG has an advantage in brain aging study due to its greater accessibility in PSG and sleep clinics compared to that of imaging (e.g., costly installation and maintenance of MRI scanner).

In conclusion, the BAI estimated using the proposed brain age prediction model can serve as a biomarker that reflects changes in sleep quality and brain health due to various sleep disorders and their severity and progression.

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