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A Novel EEG Index for Evaluating the Sleep Quality in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome

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Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a highly prevalent sleep disorder characterized by recurrent episodes of oxygen desaturation during sleep, decreased sleep quality, and excessive daytime sleepiness. A basic method of evaluating sleep quality is polysomnography (PSG) where sleep stages are identified from the electroencephalogram (EEG), electrooculogram and chin electromyogram. The implementation of PSG is limited to sleep laboratories because this test is rather complicated to perform and quite time-consuming to analysis, requiring skilled technicians. Development of simple alternative methods to PSG could enable sleep tests to be performed at home. Our study aimed to identify simple measures for evaluating the sleep quality. We focused on a simple index, entropy, which is derived from power spectrum of EEG signals throughout the night, and reflects the dynamics of EEG signals, and examined whether the entropy of EEG reflects the sleep quality of OSAHS. The EEG signals for the analysis of EEG entropy were recorded from the temple area. The EEG entropy was compared with the sleep quality by traditional approaches of EEG from PSG in 58 OSAHS patients and 8 healthy volunteers. The EEG entropy in each subject showed the negative values and fluctuated during sleep. There was a significant correlation between the EEG entropy and the sleep quality (r = 0.626, p < 0.001); namely, the amplitude of the fluctuation was increased with the increase in the sleep quality. We therefore propose that the EEG entropy could be useful for evaluating the sleep quality of OSAHS.

Keywords: sleep apnea; EEG entropy; biomarker; sleep architecture; polysomnography
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Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a highly prevalent sleep disorder characterized by recurrent upper airway obstruction during sleep leading to hypoxemia and sleep fragmentation. This disease has many potential consequences including excessive daytime sleepiness, neurocognitive deterioration, endocrinologic and metabolic effects, and decreased sleep quality (Guilleminault et al. 1976). Moreover, OSAHS patients are at increased risk for vascular events, which represent the greatest morbidity and mortality of all associated complications (Jennum and Riha 2009).

The sleep quality has been evaluated as the sleep efficiency [slow wave sleep (SWS)/total sleep time (TST)] by the manual scoring approaches of PSG as the gold standard for the diagnosis of OSAHS (Rechtschaffen and Kales 1968). Generally, normal persons and mild OSAHS patients show five stages of sleep [rapid eye movement (REM), stages 1 and 2, stages 3 and 4 (SWS)], and severe OSAHS patients show little SWS. Therefore, in severe OSAHS patients, sleep efficiency (SWS/TST) could be decreased (Landolt et al. 1996; Valladares et al. 2008).

The conventional PSG scoring is complicated and cannot be done in real time. Particularly, at least eight electrodes in addition to those for electrooculogram (EOG) and chin electromyogram (chin EMG) are needed on the scalp for sampling EEG signals to assess the sleep stage. Moreover, the visual scoring of the EEG is time-consuming and subjective. It takes approximately four hours to evaluate the sleep quality of one person. Therefore, there is considerable interest in the development of simple techniques for evaluating the sleep quality.

Recently, a novel method of analyzing the power spectrum of EEG has been reported (Pardey et al. 1996; Bein 2006; Ohisa et al. 2008; Sabeti et al. 2009). In this method, only two EEG electrodes are required, which can be placed on the skin of the head outside the hairline. Moreover, the analysis of EEG can be done on-line and the data are obtained in real-time. Therefore, if the EEG entropy could serve as a biomarker for the sleep dynamics and can discriminate regular dynamics from irregular dynamics

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(Jamasebi et al. 2008), it may be possible to use it as a measure of sleep quality.

In the present study, to determine whether the EEG entropy, which is derived from the power spectrum of EEG signals, can be used to evaluate the sleep quality of OSAHS, we compared the EEG entropy with the sleep efficiency by manual evaluation of EEG from PSG in 58 OSAHS patients and 8 healthy volunteers. We found significant correlation between the EEG entropy and the sleep efficiency obtained by EEG scoring.

Methods

Subjects

We recruited 61 clinically suspected OSAHS patients who had a history of habitual, intermittent snoring and excessive daytime sleepiness, and 8 control subjects who were free from snoring and daytime sleepiness.

Overnight sleep study

An overnight sleep study was carried out in a darkened, quiet room using standard PSG (Rechtschaffen and Kales 1968). The recording of PSG was performed from 20:00 at night until 6:00 in the morning using an Alice III (Chest Co. Ltd., Tokyo, Japan) as the conventional PSG test. Briefly, four EEG channels (C3-A2, C4-A1, O1-A2, O2-A1), two electrooculogram channels, two electromyograms (chin and leg), 5 respiration channels (nasal pressure flow, thermister flow, snoring by microphone, respiratory movements of the rib cage and abdomen with inductive plethysmography), percutaneous arterial oxygen saturation with a finger pulse oximeter (SpO2) and an electrocardiogram channel (II lead) were simultaneously recorded.

The EEG entropy was obtained by analyzing the power spectrum of EEG (MemCalc/Makin2, GMS Co. Ltd., Tokyo, Japan). The EEG for analyzing the EEG entropy was recorded by the monopolar lead from the fronto-polar zone (front of head) according to the international 10/20 system, using an Ag/AgCl electrode referenced to the left earlobe.

Visual scoring of sleep respiratory parameters using PSG

The EEG in PSG recording was analyzed by visual scoring. Visual sleep-stage scoring was performed using the standard procedure defined by Rechtschaffen and Kales (1968) and the criteria for EEG arousals defined by the American Sleep Disorders Association (Bonnet et al. 1992) on 30 second epochs. TST, SWS/TST and REM/TST were obtained.

Apnea was defined as a cessation of airflow lasting 10 seconds or more, while hypopnea was defined as a more than a 50% decrease in the thoraco-abdominal amplitude associated with a decline in SpO2 of more than 3% from the preceding value (Gould et al. 1988).

The apnea-hypopnea index (AHI), the arousal index and oxygen desaturation index (ODI) were defined as the average number of apneas and hypopneas per hour of sleep, the average number of EEG arousals per hour of sleep, and the average number of oxygen desaturations that were 3% or more below the baseline level per hour, respectively.

Calculating entropy using the maximum entropy method

The meaning of entropy was adapted from the information theory of Shannon as a measure of information comprised in a given amount of signals (Shannon 1948). As used in information theory and signal analysis, entropy is concerned with the irregularity, complexity or unpredictability characteristics of a signal. In past decades, different types of entropy analysis have been applied to study EEG signals (Ignaccolo et al. 2010). The entropy is generally provided by the power spectral density (PSD). In the present study, we analyzed the PSD of the EEG (Terachi and Tanaka 2001). The EEG power spectrum has exponential characteristics, which means that the overall trend of the spectrum indicates exponential decay up to 30Hz (Terachi and Tanaka 2001). By this method, the EEG entropy was obtained on-line and in real-time. Recently, it was reported that the EEG entropy could discriminate the regular dynamics of sleep from the irregular dynamics of sleep (Jamasebi et al. 2008).

In this study, the EEG entropy was calculated using the MemCalc method and analyzed in real time every 2 seconds (Terachi and Tanaka 2001). A graphical display of the EEG entropy as mean values was made every 30 seconds. The EEG entropy in each subject was estimated as the average EEG entropy during sleep. Next, we determined the optimum cut-off point of the EEG entropy for predicting the sleep quality by logistic regression and receiver operating characteristic (ROC) analysis.

Ethical issues

All experimental procedures and risks were explained prior to recording, and written informed consent was obtained from each patient and subject. This study was approved by the ethics committee on clinical investigations of Tohoku University School of Medicine.

Statistical analysis

Data of PSG were expressed as means ± S.D. PSG variables in OSAHS patients were analyzed by one way analysis variance (ANOVA). If significance was identified by ANOVA, a comparison of variables among the subgroups of OSAHS was made using unpaired *t* test. Comparisons between the OSAHS subgroup and the control group were also made using unpaired *t* test. Pearson correlation analysis was used to assess correlations between the EEG entropy and sleep respiratory disturbance index. The significance level was set at $p < 0.05$.

Results

Among the 61 OSAHS-suspected patients, 58 subjects were diagnosed as OSAHS by PSG. The severity of the OSAHS patients was categorized according to the level of AHI as follows: Mild, $5 \leq \text{AHI} < 15$; Moderate, $15 \leq \text{AHI} < 30$; Severe, $30 \leq \text{AHI}$ (Iber et al. 2002). In Table 1, the physical characteristics and polysomonographic variables in the three subgroups of 58 OSAHS patients and 8 healthy volunteers are shown. In the severe group, the ODI and arousal index were significantly increased, and SWS/TST was significantly decreased in comparison with the mild and control groups. In the moderate group, the ODI and arousal index were significantly increased compared to the mild group, and SWS/TST was significantly decreased compared to the control group. BMI and REM/TST were not significantly different among the subgroups of OSAHS, nor between the subgroups and control group. Furthermore, there was no difference between the mild group and the

Table 1. Various Polysomnographic indices in Patients and Control.

	OSAHS			Control
	Mild	Moderate	Severe	
AHI (%)	5 ≤ AHI < 15	15 ≤ AHI < 30	30 ≤ AHI	1.8 ± 2.0
No. of Subject	6	9	43	8
Age	38.2 ± 22.1	54.6 ± 15.0	58.6 ± 14.4†	26.8 ± 10.5
BM I (Kg/m^2)	25.4 ± 5.8	26.7 ± 3.8	28.4 ± 6.4	23.3 ± 3.9
ODI (%)	5.3 ± 3.0	14.1 ± 7.6*	44.2 ± 18.6*†	2.8 ± 0.8
Arousal Index (/h)	30.2 ± 18.9	34.6 ± 13.8*	54.2 ± 15.3*†	22.8 ± 5.9
SWS/TST (%)	16.0 ± 7.1	11.3 ± 7.5†	7.5 ± 5.3*†	23.3 ± 7.0
REM /TST (%)	13.7 ± 3.7	13.3 ± 6.9	12.5 ± 6.7	18.6 ± 8.1

Values are mean ± S.D., *$P < 0.05$ vs. Mild OSAHS, † $P < 0.05$ vs. Control

OSAHS, obstructive sleep apnea hypopnea syndrome; AHI, apnea / hypopnea index; BMI, body mass index; ODI, oxygen desaturation index; SWS / TST, slow wave sleep / total sleep time; REM / TST, rapid eye movement / total sleep time.

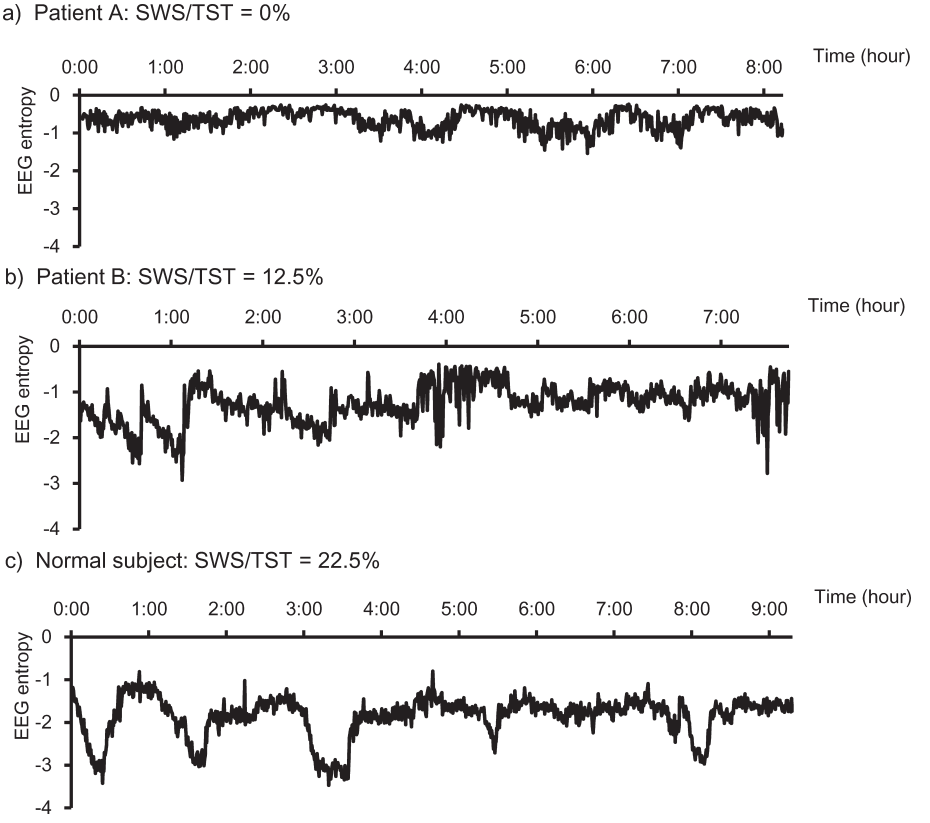

Fig.1. Representative traces of EEG entropy during sleep recording.
Time 0 indicates the onset of sleep. Patient A: OSAHS patient with SWS/TST 0% and average EEG entropy −0.640; patient B: OSAHS patient with SWS/TST 12.5% and average EEG entropy −1.249; Control subject: SWS/TST 22.5% and average EEG entropy −1.855. EEG entropy of control subject shows a more negative value than that of patient A.

control group.

Fig. 1 shows the representative traces of EEG entropy during sleep in one patient (patient A) of the severe group, one patient (patient B) of the mild group and one healthy subject. The EEG entropy in each subject showed the negative values and fluctuated during sleep. The amplitude of the fluctuation was increased with the increase in SWS/TST. The mean values of the EEG entropy during sleep (from the beginning of sleep to awakening in the morning) were −0.640, −1.249 and −1.855 in patients A, B and a normal subject, respectively.

Fig. 2 shows the relationship between EEG entropy and SWS/TST in OSAHS patients and healthy volunteers. We found a significant correlation between two parameters ($r = -0.626$, $p < 0.001$). Patients with more negative values of EEG entropy showed greater values of SWS/TST. This

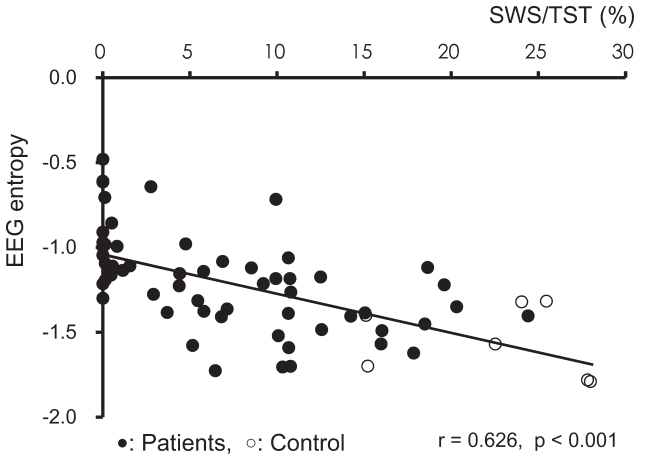

Fig.2. The relationship between SWS/TST and EEG entropy.
Shown is the relationship between SWS/TST and EEG entropy ($r = 0.626$, $p < 0.001$). OSAHS, ●; normal subjects, ○.

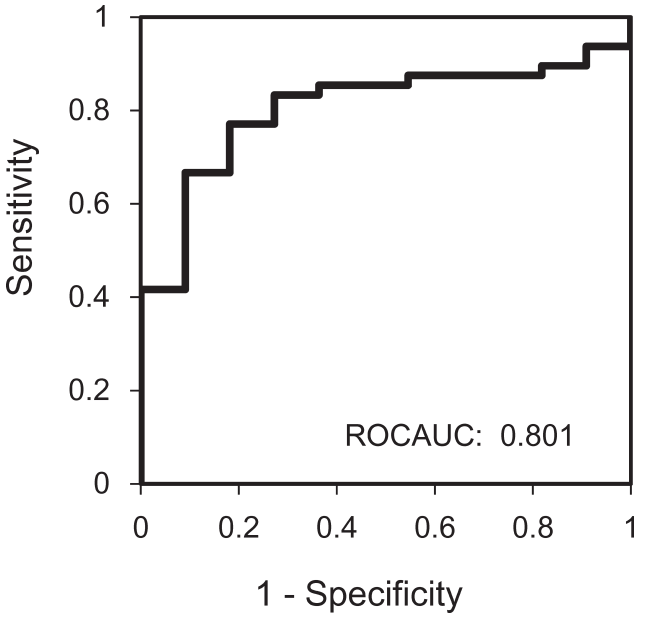

Fig. 3. ROC curve for EEG entropy.
Shown is the ROC curve for EEG entropy using SWS/TST < 15% as poor sleep quality. The EEG entropy cut-off value was −1.313, corresponding to the greatest sum of sensitivity (77.1%) and specificity (81.8%), and the area under the ROC curve was 80.1%.

result suggests that patients with less negative values of EEG entropy would have poorer sleep quality.

To determine the cut-off value of the EEG entropy as a sleep quality index, the ROC analysis was used. With SWS/TST < 15% for the detection of low sleep quality, the EEG entropy cut-off value was −1.313, corresponding to the greatest sum of sensitivity (77.1%) and specificity (81.8%), and the area under the ROC curve was 80.1% (Fig. 3).

Discussion

In this study, we examined whether the EEG entropy was related to SWS/TST obtained by PSG scoring and found that this biomarker could be helpful in predicting the sleep quality of OSAHS.

The estimation of the sleep state is generally performed through the classification of the sleep structure. The sleep structure consists of the five stages: stage 1, stage 2, stage 3, stage 4 and REM. Each stage is characterized by the presence of one or more indicators corresponding to elementary activities and several graphical elements in the recorded signals. The sleep stages are classified visually and manually by skilled technicians. The manual scoring of EEG signals is a time-consuming process and the EEG signals need to be recorded at several specific skull areas. These points are inconvenient for screening tests in terms of educating technicians, the inefficiency of testing including the analysis of the sleep stages, and the placement of the EEG electrodes on the specific skull areas. Therefore, there is considerable interest in the development of simple techniques for the evaluation of the sleep quality.

The present study showed the usefulness of the EEG entropy measures as an alternative index for conventional EEG staging. The EEG entropy is determined by analyzing the power spectrum of EEG on-line, the data are obtained in real-time, and only two electrodes are attached to the skin of the head outside the hairline. The fronto-polar zone is a site where we can attach the electrodes ourselves. Furthermore, we observed that the average value of the EEG entropy during sleep had a significant correlation with SWS/TST (Fig. 2). We believe it would be useful to apply the average entropy during sleep as a screening index for the sleep quality, for example for monitoring at the bedside or at home.

Because the entropy is calculated by the time-frequency analyzing method (Bein 2006; Sabeti et al. 2009), the accuracy depends on the analysis. In this study, the Maximum Entropy Method (MEM), one of the methods for frequency analysis, was used for calculation of the entropy. In the present study we used the MemCalc method, which is a combination of the MEM method and the non-linear squares method for fitting analysis (Sawada et al. 1997), and is a reliable time-series analysis method (Pardey et al. 1996; Terachi and Tanaka 2001; Ohisa et al. 2008).

To facilitate the use of the EEG entropy, the cut-off value was determined by ROC analysis. When it was presumed that low sleep quality was less than 15% SWS/TST, the cutoff value, the sensitivity and specificity in ROC curve were −1.313, 77.1% and 81.8%, respectively. That is, if the EEG entropy during sleep is less negative than the value of −1.313, the sleep quality might be considered to be poor.

In this study, the control subjects were relatively young compared to the OSAHS groups. Because the SWS/TST decreases with age (Ohayon et al. 2004), the EEG entropy

in the control group might be more negative by aging effects. However, as the mean values of ODI and the arousal index were lowest, and that of SWS/TST was largest among the four groups, the sleep quality seemed to be best, showing more negative values in the EEG entropy.

In conclusion, we found that the EEG entropy determined by analyzing the power spectrum of EEG would be useful as a biomarker for predicting the sleep quality of OSAHS. Further study will be needed to determine whether the evaluation of the EEG entropy would be applicable for home-based, unattended screening of sleep disordered breathing using portable devices.

Conflict of Interest

The authors declare that no potential conflict of interest exists with any companies/organizations whose products or services may be discussed in this manuscript.

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