International Journal of Innovative
Computing, Information and Control
Volume **10**, Number **6**, December **2014**

ICIC International ©2014 ISSN 1349-4198
pp. 2087–2095

QUANTITATIVE EVALUATION OF EEG AND EPILEPSY DISEASE DETECTION ON HYPERVENTILATION TEST

Tadanori Fukami[1], Hiromu Iyoda[1], Takamasa Shimada[2] and Fumito Ishikawa[3]

[1]Department of Informatics
Yamagata University
4-3-16 Jonan, Yonezawa, Yamagata 992-8510, Japan
fukami@yz.yamagata-u.ac.jp

[2]Department of Information Environment Integration and Design
Tokyo Denki University
2-1200 Muzai-Gakuendai, Inzai, Chiba 270-1355, Japan
tshimada@mail.dendai.ac.jp

[3]Hotokukai Utsunomiya Hospital
4-6-34 Yonan, Utsunomiya, Tochigi 320-8521, Japan

Received January 2014; revised May 2014

Abstract. *In this study, we propose an analysis method for electroencephalography (EEG) during hyperventilation (HV) test, a routine EEG examination. The HV test was performed for 4 min during HV and 4 min at rest after HV (POST HV). Our analysis method introduced an index (Z-score) to evaluate enhancement/suppression at a specific frequency during HV or POST HV compared with the reference EEG obtained 30 s before the HV test. We investigated the optimal frequency band, electrode, and period in the HV test for discriminating epilepsy patients from healthy subjects. The best EEG was theta wave measured at C_z in the period 1 min from HV start to 1.5 min after HV. In 44 healthy subjects and 23 epilepsy patients, using a support vector machine and evaluation of the performance by the leave-one-out cross-variation method, we obtained a 71.7% accuracy.*

Keywords: Hyperventilation, Epilepsy, Enhancement and suppression on frequency component, Z-score

1. **Introduction.** Electroencephalography (EEG) routine examinations are basic tests conducted at the hospital to detect diseases of brain function such as epilepsy. Examples of representative EEG examinations include EEG at awake rest, during photic stimulus (PS), at eye opening and closure, and during hyperventilation (HV). These latter three examinations are types of activated EEGs, whereby subjects are given a sensory stimulus or asked to overbreathe to enter a different state than the natural state at awakeness.

We previously proposed a new method for evaluating enhancement and suppression of EEG at a specific frequency by Z-score, which was obtained by comparing EEGs at two conditions [1]. We have also applied this method to PS response [1] and to eye opening and closure EEGs [2], and showed its effectiveness for disease detection. Compared with simpler indices, such as the ratio of averaged amplitude at rest and during PS in the PS test, we showed that our method can provide a stable assessment of enhancement and suppression of the EEG frequency component.

In this study, we applied our method to hyperventilation EEG and examined applicability to disease detection. The hyperventilation test is widely used to enhance preexisting

abnormalities and induce findings in an otherwise normal EEG. The test consists of deep and regular respirations at a rate of approximately 20/min for a period of 2-4 min [3].

The goal of this present study was to construct an integrated system covering all types of routine EEG examinations based on the use of a single index (the Z-score) in clinical diagnosis. If this system can be used successfully in the hyperventilation test, it will cover all activated EEGs measured. This method will allow diagnostic information on neurological disease without requirements for additional EEG examinations beyond those used routinely. Moreover, using an unified index for all types of examinations will simplify interpretation of EEG analysis.

HV has significant effect on background rhythm in EEG [4] and is considered as an effective procedure for provoking epileptic potentials and clinical seizures. Although many clinical studies have reported EEGs and clinical seizures provoked by the HV testing in large numbers of patients [5-7], there are few EEG signal processing method studies even in the engineering field, and they are prominently in children [8] rather than adults. Konishi previously reported a quantitative analysis of EEG during HV activation, where Fast Fourier Transform analysis (a popular signal processing tool) was used to investigate power for EEG frequency components such as delta, theta and alpha waves [9]. Further, Petersen et al. reported that the most dramatic EEG responses to HV usually occur between the ages of 8 and 12 years [10]. There are numerous analysis methods previously reported for detecting spikes due to epileptic seizures. Oweis and Abdulhay classified normal and ictal activities using a feature relied on Hilbert-Huang Transform [11]. Pachori used empirical mode decomposition and Fourier-Bessel expansion for the classification [12]. However, the main aim of our study is not to detect EEG during seizure, but rather finding the possibility of epilepsy at the stage of EEG examination. If we can evaluate the potential for epilepsy quantitatively by a defined index, it will be a useful tool in medical diagnosis.

In the present study, we analyzed a large number of healthy subjects and epilepsy patients over 20 years of age, and then classified them.

2. **Methods.** Multichannel EEG was recorded using a Nihon Koden polygraph (EEG-1100) with a 0.3 s time constant, a 60 Hz high cut filter, and a 97.5 nV quantization level. EEG signals digitized at a sampling frequency of 200 Hz were recorded from 19 electrodes placed according to the international 10/20 system with monopolar derivation from bilateral reference electrodes attached to the corresponding earlobes.

The HV test consists of the 4 min period during HV and the 4 min period after HV (POST HV), as shown in Figure 1. All data reported in this study were recorded from participants at Utsunomiya Hospital after obtaining informed consent and ethics committee approval of the hospital. Technicians ensured that the subject executed the HV correctly.

We introduced the Z-score, which we used as an indicator for measuring the distance between two amplitude distributions obtained from EEGs at 30 s before HV start (PRE HV) and during HV or POST HV. The analysis method was previously described in detail [1]. A brief explanation of our processing and additional parameter settings are described below.

As shown in Figure 1, the periods of PRE HV, during HV, and POST HV are first segmented into small 30 s sections to investigate temporal changes. One section is divided into the shortest block of data for analysis, referred to hereafter as the analysis window. Here, we set the window size to 200 points in 1 s, providing a frequency resolution of 1 Hz when analyzing the data by discrete Fourier transform (DFT). We divided the EEG waveform into a large number of short analysis windows because the EEG amplitude of all frequency components varies within a short time. Using this window without overlap, one

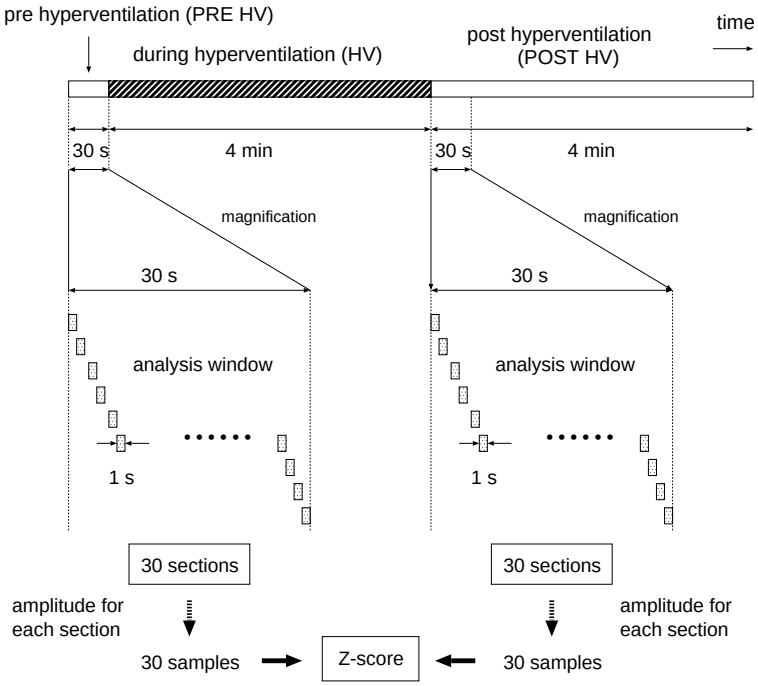


FIGURE 1. Calculation of Z-score in HV test. (Example for evaluation of EEG in the section including the first 30 s in POST HV by comparing to the standard EEG in PRE HV.)

section then consists of 30 analysis windows. One sample amplitude value was calculated from each analysis window. Thus, we obtained 30 samples from 30 analysis windows to construct a distribution of Z-scores for each analysis frequency. By comparing two distributions obtained from EEGs in two different sections, Z-scores can be obtained as an indicator, as described below.

Applying the DFT in Equation (1) to EEG waveform in each analysis window, we obtained the amplitude distribution including the variation in a section.

$$X_N(f) = \Delta t \sum_{k=0}^{N-1} x(k\Delta t) e^{-j2\pi fk\Delta t} \tag{1}$$

where N is the number of sample points in the analysis window.

In this study, we performed the above calculation after elimination of bias (0 Hz) component by subtraction of the average in the analysis window. We then obtained the amplitude spectrum, $X_a(f)$, in the following equation.

$$X_a(f) = \frac{2|X_N(f)|}{\Delta t \cdot N} = 2|X_b(f)| = 2\sqrt{Re[X_b(f)]^2 + Im[X_b(f)]^2} \quad (f \neq 0) \tag{2}$$

Here, $X_b(f)$ is expressed by next equation.

$$X_b(f) = \frac{1}{N} \sum_{k=0}^{N-1} x(k\Delta t) e^{-j2\pi fk\Delta t} \tag{3}$$

We calculated the Z-scores in Mann-Whitney U-tests as an indicator for measuring the distance between two amplitude distributions at the section with PRE HV as a reference section and at the section in HV or POST HV. This test is based on the non-parametric Wilcoxon rank-sum test for assessing whether two sample sets of observations come from the same distribution. However, the Z-scores are not used for statistical testing, but rather

for measuring the distance between two distributions. This method has the advantage of suppressing the influence of outliers in a local window and providing more stable frequency characteristics in Z-scores as it uses the rank of the amplitude rather than an original amplitude. We defined the rank-sum of the two groups consisting of amplitudes at the reference section (PRE HV) and at the window in HV or POST HV as: R_1 and R_2 ($R_1 \geq R_2$) after arranging data in descending rank order for amplitude. We denoted the sample numbers as N_1 and N_2 and set them at 30. U-statistics for the above two distributions are expressed as:

$$U_1 = R_1 - \frac{N_1(N_1+1)}{2} \tag{4}$$

$$U_2 = R_2 - \frac{N_2(N_2+1)}{2} = N_1N_2 + \frac{N_1(N_1+1)}{2} - R_1 \tag{5}$$

The latter equation of Equation (5) is derived from the relation, $U_1 + U_2 = N_1N_2$. For large samples, the normal distribution approximation can be applied. Finally, the Z-score is calculated by the following equation.

$$Z = \frac{N_1 \cdot N_2/2 - U_2}{\sqrt{N_1 \cdot N_2(N_1+N_2+1)/12}} \tag{6}$$

Positive and negative values in the above Z-scores show that EEGs are increased and decreased compared to PRE HV, respectively.

3. **Results.** We analyzed EEGs in the range from 1 to 40 Hz per 1 Hz and evaluated the frequency characteristics using Z-scores. In the analysis, we examined the results of five frequency bands, delta (1 $\sim$ 3 Hz), theta (4 $\sim$ 7 Hz), alpha (8 $\sim$ 13 Hz), beta (14 $\sim$ 29 Hz), and gamma (30 $\sim$ 40 Hz), which are generally used. Among these frequency bands, the theta band showed the largest difference of Z-score between healthy subjects and epileptic patients, suggesting that the theta band is the most appropriate frequency band for distinguishing epilepsy patients from healthy subjects. As such, only theta band data are presented hereafter. In Figure 2, electrodes with significant difference ($p < 0.05$) by t-test between 44 healthy subjects (age: 37.3 $\pm$ 20.9 years old) and 23 epileptic patients (age: 37.0 $\pm$ 16.8 years old) in theta band are shown as the black filled circle. Bonferroni correction was not conducted here as this statistical test is solely used for determining the best electrode and period that distinguishes epilepsy patients from healthy subjects. As an example, 'HV 0:30' in the figure shows the result of comparing PRE HV and the period of 30 s from the start of HV. These results show multiple electrodes with significant differences in the time section from HV 1:30 to POST HV 1:30. Especially, C_z is marked with black at most time sections. The temporary changes for averages of Z-score at C_z in the group of healthy subjects and epilepsy patients are shown in Figure 3. Although the two groups show similar changes until 1.5 min from the HV start, thereafter the Z-score of epilepsy patients increased markedly. This temporal change can also be seen from Figure 4, which shows the temporal change of p-value obtained from t-test.

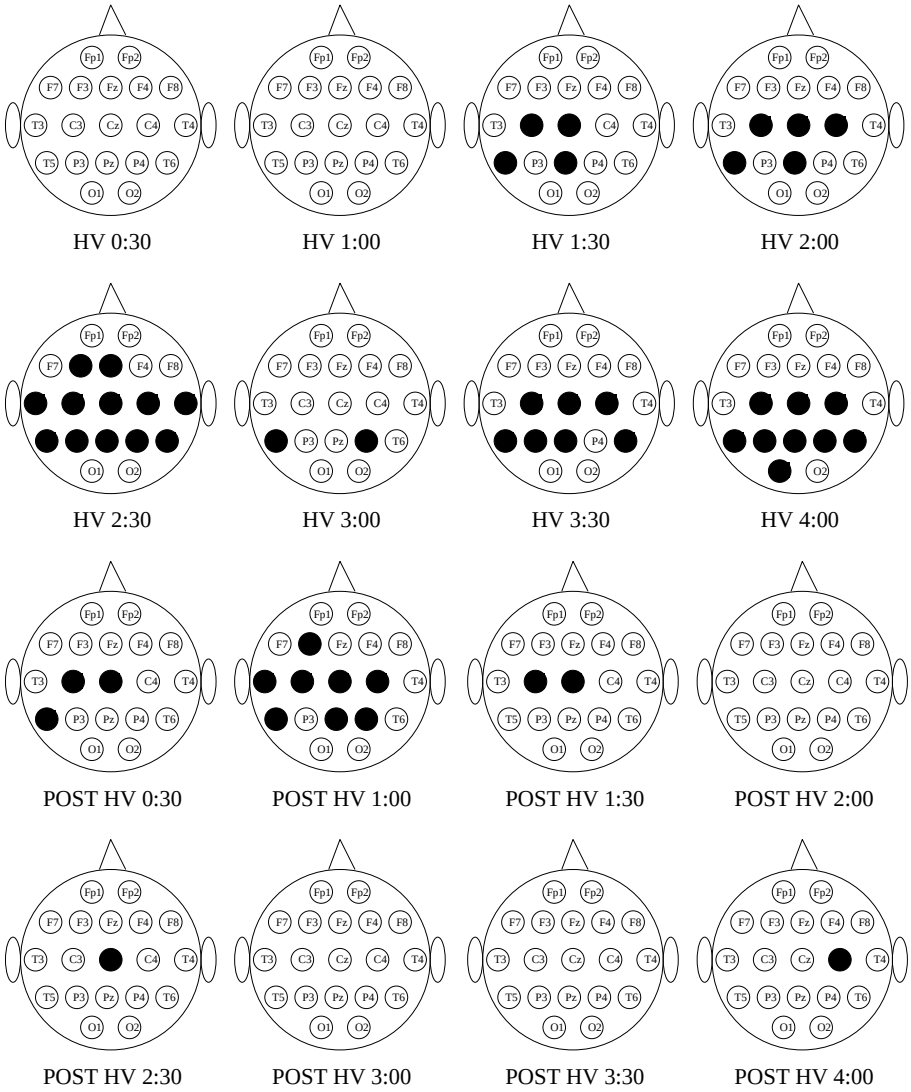


FIGURE 2. Electrodes with significant difference between healthy subjects and epilepsy patients in the theta band. (Horizontal unit shows the minutes.)

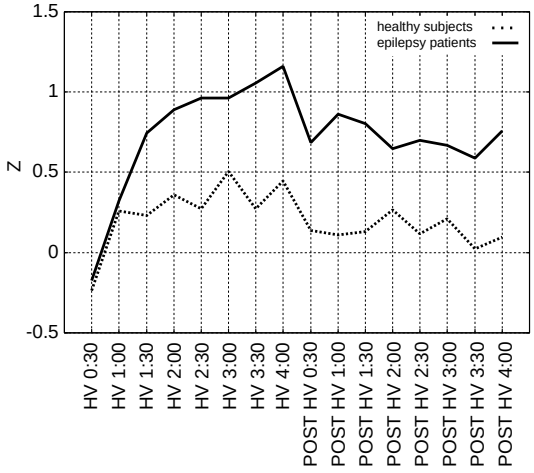


FIGURE 3. Temporary change of Z-score at C_z

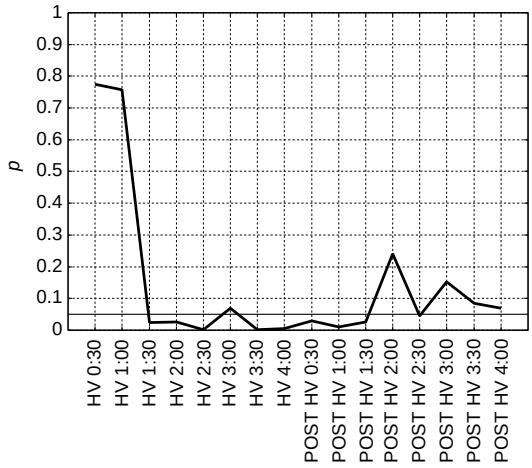
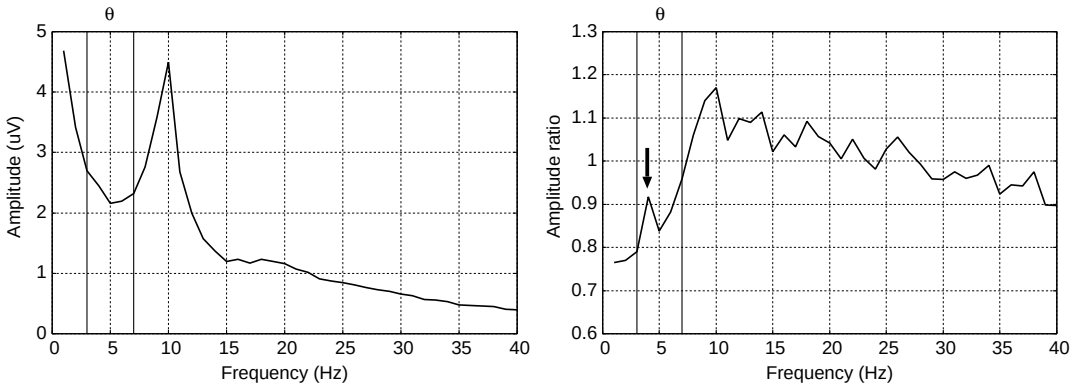


FIGURE 4. Temporary change of p value by t-test at C_z. (Horizontal line at 0.05 indicates the standard for a statistically significant difference.)

4. **Discussion.** In the present study, we determined that the theta band, C_z and the period from 1 min from the start of HV to 1.5 min after ceasing HV were the optimal EEG frequency band, electrode, and period to discriminate epilepsy patients from healthy subjects. It is well known that HV induces a change called 'build up', which involves the slowing of EEGs (i.e., an increase of low frequency components such as delta and theta waves). Gibbs et al. [13] reported that after 20 years of age, more than 40% of epilepsy patients showed diffuse EEG slowing, whereas it was seen in less than 10% of normal subjects. Diffuse slowing usually disappears rapidly after ceasing HV; it may persist for up to 30 s in normal adults [3]. Delta waves tend to appear in the posterior regions and spread forward in younger age subjects, whereas they tend to appear in the frontal regions and spread backwards in older subjects [14]. In our results by using Z-score, the theta wave showed the largest difference between healthy subjects and epilepsy patients. There are a few studies that have focused on the delta wave in epilepsy patient's [14]. However, the theta wave is also categorized as a slow wave, and delta and theta waves are typically considered together, with an increase considered as slowing of the EEG. The delta wave has a risk of contamination of artifact due to electrooculogram (EOG) and motion, while the potential for this contamination is smaller in the theta band.

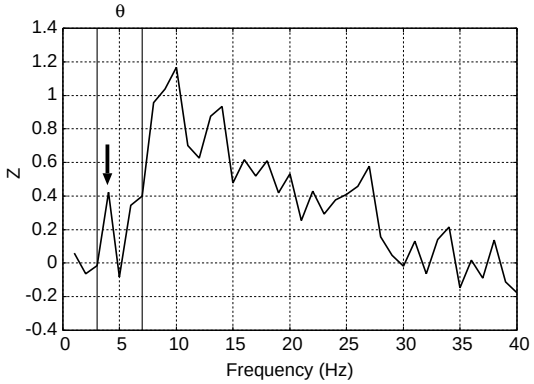
The best electrode for determining epilepsy in our study was C_z, as shown in Figure 2. The theta wave appears dominantly from the frontal to central regions. It is therefore considered that C_z included in the central area is an appropriate electrode for the epilepsy discrimination. With respect to the appropriate period for clinical discrimination, an understanding of the time course is important. The appearance of the theta wave is considered to have a close relationship with PCO_2 in the body. Yamatani et al. measured cerebral blood flow in the right carotid artery during HV, and reported that decreased PCO_2 and cerebral blood flow were the fundamental factors causing EEG slowing [15]. This report indicates that appearance of EEG slowing or theta wave increases temporally with decreasing PCO_2, as carbon dioxide is eliminated from the body by HV and then PCO_2 decreases. According to the report by Achenbach-Ng et al. [16], PCO_2 rapidly decreases from start of HV, and then takes a minimum at 30 s after HV before it gradually returns to the initial level by approximately 5 min after HV. The best period obtained by our results corresponds to this finding.

Finally, we tried to discriminate epilepsy patients from healthy subjects by classification techniques. By classifying them by support vector machine (SVM) using 9 dimensional Z-scores in the best period (HV 1:30 $\sim$ POST HV 1:30), we obtained an accuracy of 71.7%. In this analysis, we used R as statistical software and gaussian kernel in the classification by SVM. Moreover, to calculate accuracy, the one-leave-out cross-variation method was used. Here, the numbers of healthy and patient data are matched to 23 by picking healthy subjects data randomly, as the number of healthy subjects was much larger than that of patient data. Regarding the classification accuracy, to our knowledge there are no other reports of epilepsy classification rate using the HV test. Nevertheless, using an alternative algorithm for temporal lobe epilepsy (TLE) data, sensitivities ranging from 75.8% [17] to 100.0% [18] have been reported (true positive rate). However, we cannot directly compare our results with those epilepsy seizure studies, as those studies use more severe conditions (the HV test does not necessarily provoke prominent spikes). Although our result was close to the worst value of the TLE results, our data are comparable to results for EEG including spikes due to epileptic seizures. Thus, our method is useful to judge epilepsy using the HV test even if EEGs are not recorded during the seizure. Larsson et al. reported differences in alpha frequency variations in patients with epilepsy compared to a healthy group. According to their results, the epilepsy group showed a lower frequency and lower frequency variability [19]. However, classification rate was not mentioned.



(a) Frequency power spectrum during HV

(b) The amplitude ratio between before and during HV



(c) Z-score based on amplitude distributions before and during HV

FIGURE 5. Comparison of Z-score at C_z with conventional indices. (Vertical lines at 3 and 7 Hz indicates both ends of theta band.)

After classification, we inspected the EEG one by one for misclassified cases. Consequently, some epilepsy patients did not generate a low frequency component including theta wave with high amplitude, indicating large individual differences. However, our method can be used to detect the possibility of epilepsy as a screening test. Moreover, by considering other EEG routine examinations, the accuracy of screening will be improved.

In this study, we used the Z-score to evaluate EEGs with the HV test. We then show the advantages of this method compared with other conventional indices as follows. Frequency amplitude spectrum is a popular index and generally used for HV EEG analysis [9]. However, the prominent appearance of the theta wave cannot be seen, as shown in Figure 5(a). Using the power ratio between before and during HV, we can detect a small peak as indicated by an arrow in Figure 5(b). The peak of Z-score in Figure 5(c) was more prominent than the amplitude ratio. Z-score changes dynamically over the entire frequency range, and its sensitivity for detecting the occurrence of a required frequency component is high. Moreover, although the peak in the range of the theta band could be seen in Figure 5(b), the ratio at the peak was less than 1.0, indicating a decrease by HV. These data contrast with the previously reported increases of theta wave by HV [15]. We then considered that extremely large or low values at local analysis sections may affect the ratio. Nevertheless, the Z-score in Figure 5(c) showed a positive value. This indicates an increase by HV as the Z-score is obtained by using the rank-sum with the ability to reduce the effect of these outliers. These results suggest that our method is advantageous than more classical methods, leading to these stable results.

5. **Conclusions.** Herein, we proposed an analysis method for EEG using the HV test, a type of EEG routine examination. We previously reported the core analysis algorithm for this method. The objective of the present study was top determine the availability of our method in the HV test. The HV test in our study consisted of 4 min during HV and 4 min at rest after HV. Our analysis method introduced the Z-score index, which indicated the enhancement/suppression during HV or post HV compared with the section in pre HV. Here, the standard was obtained from EEG at 30 s before the HV test. Using this method, we investigated the optimal frequency band, electrode, and period in the HV test for discriminating epilepsy patients from healthy subjects. The best results were the theta wave, C_z, and the period 1 min from the HV start to 1.5 min after HV.

In 44 healthy subjects and 23 epilepsy patients, by classifying healthy subjects from epilepsy patient data by SVM using 9 dimensional Z-score data obtained in this optimal time period, and by evaluating the performance by the leave-one-out cross-variation method, we obtained a 71.7% accuracy. We examined the misclassified cases and found that some epilepsy patients did not generate the low frequency component, including a high amplitude theta wave. Thus, there is a large individual difference among epilepsy patients. It is feasible that epilepsy patients may be subclassable by the addition of different indices.

Our ultimate goal is to integrate all EEG routine examinations using one common analysis method and index, to support a final clinical decision by medical doctors.

REFERENCES

[1] T. Fukami, F. Ishikawa, B. Ishikawa and Y. Saito, Quantitative evaluation of photic driving response for computer-aided diagnosis, *J. Neural Eng.*, vol.5, no.4, pp.411-421, 2008.

[2] T. Fukami, F. Ishikawa, B. Ishikawa and Y. Saito, Quantitative evaluation of eye opening and closure with time variation in routine EEG examinations, *International Journal of Innovative Computing, Information and Control*, vol.7, no.9, pp.5529-5540, 2011.

[3] T. Takahashi and H. C. Keith, Activation methods, in *Niedermeyer's Electroencephalography*, D. L. Schomer and F. L. da Silva (eds.), Philadelphia, Lippincott Williams & Wilkins, 2010.

[4] S. R. Siddiqui, A. Zafar, F. S. Khan and M. Shaheen, Effect of hyperventilation on electroencephalographic activity, *J. Pak. Med. Assoc.*, vol.61, no.9, pp.850-852, 2011.

[5] A. Abubakr, I. Ifeayni and I. Wambacq, The efficacy of routine hyperventilation for seizure activation during prolonged video-electroencephalography monitoring, *J. Clinical Neuroscience*, vol.17, pp.1503-1505, 2010.

[6] A. M. Arain, P. G. Arbogast and B. W. Abou-Khalil, Utility of daily supervised hyperventilation during long-term video-EEG monitoring, *J. Clin. Neurophysiol.*, vol.26, no.1, pp.17-20, 2009.

[7] H. Angus-Leppan, Seizures and adverse events during routine scalp electroencephalography: A clinical and EEG analysis of 1000 records, *Clinical Neurophysiology*, vol.118, pp.22-30, 2007.

[8] A. Barker, J. Ng, C. D. Rittey, R. H. Kandler and S. R. Mordekar, Outcome of children with hyperventilation-induced high-amplitude rhythmic slow activity with altered awareness, *Dev. Med. Child Neurol.*, vol.54, no.11, pp.1001-1005, 2012.

[9] T. Konishi, The standardization of hyperventilation on EEG recording in childhood. II. The quantitative analysis of build-up, *Brain Dev.*, vol.9, no.1, pp.21-25, 1987.

[10] I. Petersen and O. Eeg-Olofsson, The development of the electroencephalogram in normal children from age 1 through 15 years – Nonparoxysmal activity, *Neuropaediatrie*, vol.2, pp.247-304, 1971.

[11] R. J. Oweis and E. W. Abdulhay, Seizure classification in EEG signals utilizing Hilbert-Huang transform, *Biomed. Eng. Online.*, vol.10, no.38, 2011.

[12] P. B. Pachori, Discrimination between ictal and seizure free EEG signals using empirical mode decomposition, *Research Letters in Signal Processing*, vol.13, 2008.

[13] F. A. Gibbs, E. L. Gibbs and W. G. Lennox, Electroencephalographic response to overventilation and its relation to age, *J. Pediatr.*, vol.23, pp.497-505, 1943.

[14] R. G. Bickford, Activation procedures and special electrodes, in *Current Practice of Clinical Electroencephalography*, D. W. Klass and D. D. Daly(eds.), New York, Raven Press, 1979.

[15] M. Yamatani, T. Konishi, M. Murakami and T. Okuda, Hyperventilation activation on EEG recording in childhood, *Epilepsia.*, vol.35, no.6, pp.1199-1203, 1994.

[16] J. Achenbach-Ng, T. C. Siao, N. Mavroudakis, K. H. Chiappa and L. Kiers, Effects of routine hyperventilation on PCO2 and PO2 in normal subjects: Implications for EEG interpretations, *J. Clin. Neurophysiol.*, vol.11, no.2, pp.220-225, 1994.

[17] J. Gotman, Automatic recognition of epileptic seizures in the EEG, *Electroencephalogr. Clin. Neurophysiol.*, vol.54, pp.530-540, 1982.

[18] I. Osorio, M. G. Frei and S. B. Wilkinson, Real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset, *Epilepsia*, vol.39, pp.615-627, 1998.

[19] P. G. Larsson and H. Kostov, Lower frequency variability in the alpha activity in EEG among patients with epilepsy, *Clin Neurophysiol.*, vol.116, no.11, pp.2701-2706, 2005.