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An analysis for Alzheimer's disease using cross-correlation and averaged frequency of EEG data

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***Abstract*— A survey by Japan's Ministry of Health, Labour and Welfare shows that the number of people with dementia will increase to 7 million individuals by 2025. This means that about one in five people who are 65 years of age or older will develop dementia. In addition, the number of traffic accidents involving older drivers has become an issue recently. Therefore, we considered that if there were a technique that allowed individuals to determine the presence of dementia by themselves, it could be detected at an earlier stage. Our proposed method employs averaged frequency and triple correlation techniques to detect the presence of Alzheimer's disease using only three electrodes and a short data acquisition period.**

***Index Terms*—Alzheimer's disease, EEG, phase, cross-correlation, averaged frequency**

I. Introduction

The number of elderly drivers who cause traffic accidents is increasing in Japan. In March 2017, the revised Road Traffic Law, which required more rigorous cognitive function tests for those over 75 years old, began to be enforced. Since this law came into effect, it was reported that there were about 30,000 people judged to have dementia [1]. Positron emission tomography (PET) and a biomarker test of cerebrospinal fluid are the major diagnostic methods for dementia, in addition to a dementia-related interview. Recently, the idea of diagnosis using electroencephalography (EEG) has also attracted considerable attention [2]. Therefore, it is hoped that an easy-to-use EEG inspection system might lead to the prevention of traffic accidents. Indeed, it may be possible to develop an economical EEG system for the detection of Alzheimer's disease (AD) with a simple algorithm. If such a system were to become commercially available, people could use it at home, detect signs of AD at an early stage, and begin treatment earlier.

The diagnosis of AD using EEG signals is commonly performed using spectral analysis focused on frequency characteristics. This technique capitalizes on the phenomenon of decreasing frequency and an increase in the measured amount of slow α waves in AD patients [3]. The normal frequency for α waves is in the 8–13 Hz range; 8 Hz is considered to be slow for α waves and may be indicative of extremely mild abnormality of brain function [4]. In addition, when calculating the proportion of subjects whose basal waves are less than 9 Hz among AD and control subjects, it was reported that the AD group was significantly larger than the control group [5] Thus, many studies of patients with AD have been carried out by monitoring the frequency decrease of α waves and the increase of slow waves [4]. For example, the correct diagnosis rate has been reported to be 80% [6]. However, despite the dramatic increase in patients suffering from age-related dementia, the data used for verification are limited to younger subjects (in their 60s), and there is currently no verification for elderly people. It has been reported that slow wave activity occurs not only in AD patients but also in normal elderly people [7]; therefore, it is unknown whether the method presented in this report is effective for the elderly. It is possible that normal elderly people and AD patients may not be differentiated. Therefore, we propose a method that is largely unaffected by age. To evaluate the proposed method, we used data from both young and old age groups in order to realize an estimation method that avoids an age bias. The triple correlation value

method can be easily estimated, but the correct diagnosis rate is only about 75% when classifying normal control (NLC) subjects and AD patients. Therefore, further improvement in accuracy is required. This method is not affected by age differences. On the other hand, we found that the method using frequency features showed a large discrepancy between young NLC subjects and AD patients. We considered that it might be possible to reduce the rate of false positives in NLC subjects by using the method with frequency features. In this study, we aimed to further improve accuracy by employing these two methods. We applied these methods to clinical EEG data obtained at two medical institutions to evaluate their feasibility.

II. Alzheimer's Disease Estimation Method

A. Linear combination of averaged frequency and triple correlation vale

The averaged frequency f value and the triple correlation value d are calculated from the characteristics of the frequency and triple correlation value respectively (details are provided in the next chapter). When calculating the discriminant function by linear discriminant analysis of the two feature quantities, the index value FD is defined by the following equation. The coefficients α and β are determined by linear discriminant analysis

$$\mathrm{FD} = \alpha f + \beta d \tag{1}$$

B. Calculation of averaged frequency

In order to quantitatively evaluate the characteristics of the slow wave formation, the individual peak frequency is calculated from the power spectrum value for each individual.

When quantified, the peak frequency decreases with the slow wave formation. Specifically, assuming that the lower limit frequency is l (Hz), the upper limit frequency is h (Hz), and the power of each frequency is Pi, the average frequency $fpeak$ is calculated using the following equation. (Equation 2)

$$f_{peak} = \frac{\sum_{i=l}^{h} iP_i}{\sum_{i=l}^{h} P_i} \tag{2}$$

C. Calculation of triple correlation value

There is a strong correlation between the EEG potentials recorded from any three electrodes This phenomenon is similar to that of seismic waves. When the epicenter is located close to the surface, an observed seismic wave differs greatly at each observation point. On the other hand, when the epicenter is located in the deeper layer, P waves, which are a type of seismic wave, have similar amplitude and phase in all places. Likewise, neural activity in the deeper part of the brain can be approximately estimated through the analysis of EEG data recorded from three electrodes, forming a triangular pyramidal region made up of a signal source point in the brain and the three electrodes. When the three electrodes are located at the same distance from the source point, the recorded signals would have the same phase, and reflect the neural activity at the source point. By analyzing the time series of EEG data observed at three electrodes, we may classify AD patients and NLC subjects. By evaluating the correlation between brain potentials at each electrode position, the triple correlation value is calculated (1). The triple correlation value is obtained by multiplying the potential signals *EVA (t)*, *EVB (t)*, and *EVC (t)* from the three electrodes, with each signal having the time shift of $\tau 1$, $\tau 2$ with respect to the potential signal from each electrode. (Equation 3)

$$S_i(\tau_1, \tau_2) = \frac{1}{N} \cdot \int_i^{i+1} |EVA(t) \cdot EVB(t-\tau_1) \cdot EVC(t-\tau_2)| dt \tag{3}$$

Here, to limit the rotational plane of the equivalent dipole inside the body, a calculation object is taken only when the three potentials have the same sign. N in Equation 3 is the number of times that the signs of three potentials are the same. When this calculation is performed every second, the triple correlation value is plotted on the feature space formed by the two time-delay parameters ($\tau 1$, $\tau 2$). As shown in Fig. 1, when comparing the distribution of triple correlation values between NLC subjects (n = 52) and AD patients (n = 20; see below), the distribution of AD patients is irregularly aligned compared to NLC subjects with respect to the time axis (Fig. 1-right). In other words, if one were to view the triple correlation values as a forest, the trees representing the AD patients would appear sparsely distributed. By contrast, the trees representing the NLC group appear to be well distributed and healthy (Fig. 1-left). By evaluating the variation in the triple correlation values and the degree of dispersion in the time axis direction, it is possible to quantitatively classify differences in characteristics among individuals.

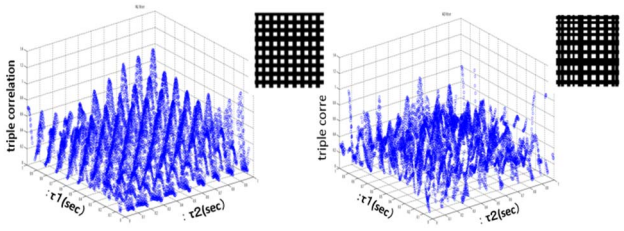

Fig. 1 The distribution of triple correlation values.
Normal triple correlation (left), AD triple correlation (right)

Although we found that the fluctuation of triple correlation values differs greatly between the NLC group and AD patients, this feature may not be seen in some areas. There are cases in which it is not possible to successfully classify subjects using only the evaluation of triple correlation variation. Therefore, the maximum triple correlation value at the delay parameter ($\tau 1$, $\tau 2$) is calculated for each rectangular region of 0.2 s × 0.2 s, which is the triple correlation value determined every second, as calculated in Equation 3. This equation calculated the standard deviation *std_Si* of the maximum value. Then, we calculated the average value *ave_S* of 10 standard deviations up to $i = 1, 2, \ldots,$ 10 sec. The size of the rectangular region of 0.2 s and the interval of calculating the triple correlation value of 10 s were

determined by adjusting several parameters. Next, we calculated the standard deviation *std_S* of the 10 standard deviations, and the ratio between the standard deviation and the average value was defined as the *index S* (Equation 4).

$$ave\_S = \overline{std\_S_i}$$
$$std\_S = \sqrt{\frac{1}{10}\sum_{i=1}^{10}(S_i - \overline{std\_S_i})^2}, \overline{std\_S_i} = \frac{1}{10}\sum_{i=1}^{10} std\_S_i$$
$$S = ave\_S / std\_S \quad (4)$$

The index S_i of Equation 4 indicates the degree of variation in time axis direction and is defined as follows. According to the aforementioned forest metaphor, the distribution of triple correlation values is reflected in Fig. 1 as a "forest" of individual trees represented by $\tau 1$, $\tau 2$ data points in black. The three brain potentials that take the same sign (+ or −) are displayed in white. As shown in Fig.2, dx_i (i = 1, 2,…m) and dy_j (j = 1, 2,…n) represent the distances between the vertical rectangle and the horizontal direction of the white rectangle. We then consider whether *dxi* and *dyj* are evenly aligned in length and breadth in the white rectangle in both the $\tau 1$ and $\tau 2$ directions or whether the white squares are arranged in a disordered manner. When comparing NLC subjects and AD patients, there was a tendency for either $\tau 1$ or $\tau 2$ to be significantly biased in AD patients. Since rectangles from both NLC subjects and AD patients are regularly arranged in both $\tau 1$ and $\tau 2$ directions, we considered that both $\tau 1$ and $\tau 2$ could quantitatively evaluate the distance between adjacent white squares at an arbitrary time. Specifically, as shown in Equation 5, the standard deviation *Std_dx* of m number of dxi and the standard deviation *Std_dy* of n number of *dyj* are calculated, and the average value of the two standard deviations is defined as the index value *SD*.

$$std\_dx = \sqrt{\frac{1}{m}\sum_{i=1}^{m}(dx_i - \overline{dx})^2}, \overline{dx} = \frac{1}{m}\sum_{i=1}^{m} dx_i$$
$$std\_dy = \sqrt{\frac{1}{n}\sum_{j=1}^{n}(dy_j - \overline{dy})^2}, \overline{dy} = \frac{1}{n}\sum_{j=1}^{n} dy_j$$
$$SD = \left|(std\_dx + sfd\_dy)/2\right| \quad (5)$$

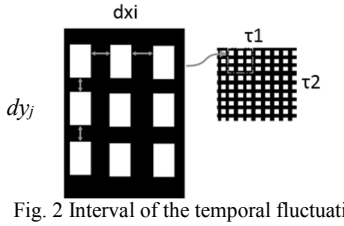

Fig. 2 Interval of the temporal fluctuation.
(*dxi*, x-direction interval; *dyi*, y-direction interval)

Then, a new index *d* is defined using this SD value and the S value calculated by Equation 6. We will refer to this as the d value. The coefficients a and b are determined by linear discriminant analysis.

$$d = aS + bSD \quad (6)$$

It is considered that the greater the difference between the triple correlation value and the variation in the time axis direction (higher *d* value), the greater the tendency toward dementia

III. Data Used to Evaluate the Proposed Method

Data from two medical institutions were used to evaluate the proposed method. Based on the findings from the cognitive test, interview, and magnetic resonance imaging (MRI) and PET scans, each subject was classified into an NLC or dementia group. Details of the data are shown below (Table 1, Table 2).

A. Data for elderly residents in Tone Town, Ibaraki Prefecture (Tone Town)

To estimate the prevalence of dementia among the elderly throughout the country, one site was selected from the unified surveys of seven locations in 2009. This was Tone Town, Ibaraki Prefecture, where 612 elderly residents aged 65 year or over participated in the survey. From that group, an MRI examination was performed on 397 subjects. In accordance with the process defined in the "Dementia prevalence survey in the elderly" cognitive function tests and structured interviews were performed by a specialist, as well as neurological tests, and dementia/psychoneurotic diseases were diagnosed. The Mini Mental State Examination (MMSE) was used to test cognitive function. This prevalence survey was approved by the ethics committee of the University of Tsukuba, and 402 patients who consented to the additional examination at the time of the survey were subjected to EEG examination and visually inspected by two doctors. Doctors classified the participants into a normal group, and an AD and other dementia group (AD group) based on the diagnosis resulting from the dementia prevalence survey. Then, the normal group was further classified into an NLC group following MRI examination. Thus, the following two groups of subjects (Tone_NLC, Tone_AD) were included in the analysis based on their classifications as determined by the EEG results (Table 1):

Table 1 Data used in Tone Town.

Tone	NLC	AD	P-value
n	52	20	
age(m ± SD)	71.9 ± 5.9	84.4 ± 6.3	P<0.05*
MMSE(m ± SD)	29.1 ± 1.1	19.1 ± 3.5	P<0.01**

B. Data aquired at Tokyo Metropolitan Institute of Gerontology (TMIG)

The NLC subjects were selected from normal, elderly individuals who voluntarily received a PET examination showing brain activity using radiopharmaceutical [F-18]-labeled fluorodeoxyglucose; FDG-PET) every year at the Tokyo Metropolitan Institute of Gerontology (TMIG). Among them, subjects who received "good" PET findings (judged A from three possible grades: A, B, C) were classified as NLC (TMIG_NLC) subjects [6][7]. Twenty-two patients were diagnosed with AD (TMIG_AD) by selecting cases in which the FDG-PET findings did not contradict the AD diagnosis,

satisfying the criteria of probable AD dementia in the core clinical criteria (Table 2):

Table 2 Data used at TMIG.

Data②	NLC	AD	P- Value
n	50	22	
age (m±SD)	73.5± 5.2	70.0± 9.3	P=0.13 P > 0.05
MMSE (m±SD)	29.7± 0.6	18.5± 6.9	P<0.01**

Among NLC subjects, the age of the TMIG_NLC group is higher than of the Tone_NLC group. By contrast, the AD group has a younger age pattern than the Tone_AD group.

EEG data for analysis were recorded using an electroencephalograph (EEG-9100, Nihonkoden Co., Ltd.) and an electrode helmet without paste (Brain Function Laboratory Co., Ltd.). EEG was recorded in alert subjects for a period of 60 s. The filter at the time of recording was 0.08 to 300 Hz, and the electrode distribution was 21 electrodes according to the international 10-20 system. The analysis used only three electrodes (P3, P4, and Oz) based on the right earlobe (see below), and used only 1 min of data. Them sampling frequency at the time of analysis was 200 Hz.

IV. Results

A. Averaged frequency

Using the frequency characteristics, the average frequency of the three electrodes of the occipital region (P3, P4, Oz) was calculated in the α band (8–11 Hz), as performed by C. Huang et al The results from Tone Town are shown in Fig. 3. As shown in Fig. 3 (left graph), the average frequency of the AD group was significantly lower than that of the NLC group. On the other hand, as shown in Fig. 4, when comparing ages 75 and over 75 in the NLC groups (since only one person under the age of 75 appeared in the AD group, only those individuals over 75 years old were described), the 75 and over group displayed frequency reduction even in NLC subjects. Therefore, in NLC subjects, the significant difference was smaller in the under 75 NLC group than in the AD group. However, as shown in Fig. 3 (right graph), since significant differences are seen between young NLC subjects and elderly AD patients, we considered that it might be possible to use the feature of frequency. As mentioned earlier, this is probably due to the influence of the slow waves in the α band, as also found in the AD group, because the TMIG_NLC group is older. For this, it was necessary to find a frequency band that could reflect the finding that the power of the θ band increases more in the AD group than in the NLC group. Therefore, not only the α band but also the θ and β bands, including nine patterns, were verified. Specifically, the optimal parameters were those with the highest average of the four correct diagnostic rates (Tone_NLC vs Tone_AD, Tone_NLC vs TMIG_AD, TMIG_NLC vs Tone_AD, and TMIG_NLC vs TMIG_AD) in the results of the NLC and the AD groups for the two medical institutions. After we evaluated the nine patterns, the frequency band of 6–13 Hz was determined to be the most promising, displaying the highest correct diagnostic rate (69%).

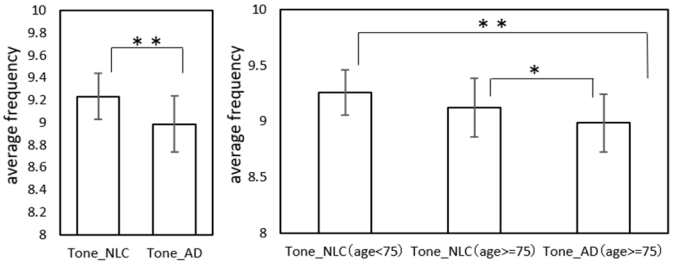

Fig. 3 Average frequency of the data in Tone Town.

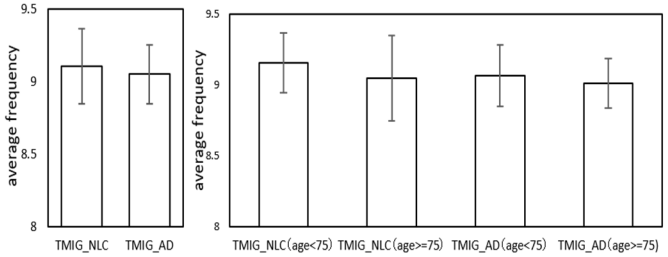

Fig. 4 Average frequency of the data at TMIG.

B. Triple correlation

To calculate triple correlation in Equation 6, linear discriminant analysis was performed using data from Tone Town, and the optimum discrimination coefficient was determined. The standardized discrimination coefficient was taken as the coefficient of the discriminant function. As a result, a = 0.69 and b = 0.61. Therefore, this coefficient was applied to Equation 6, and d = 0.7S + 0.6SD was defined as an evaluation function. Figure 5 shows the averaged d and MMSE values.

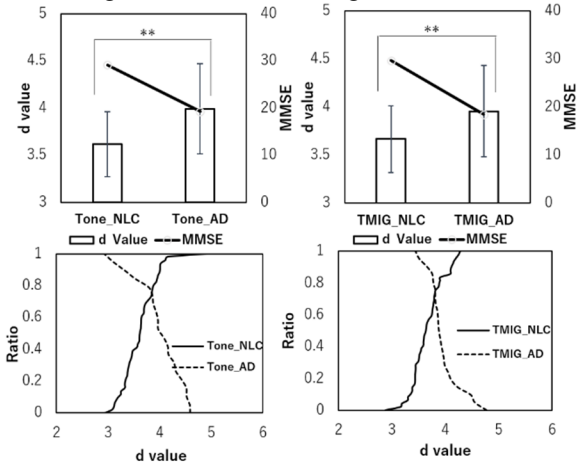

Fig. 5 *d*-values for Tone Town and TMIG.

At both medical institutions, the AD group had a lower MMSE score than the NLC group, whereas the d value was larger in the AD group than in the NLC group. The results of Wilcoxon's rank sum test indicate that Tone_NLC and Tone_AD as well as TMIG_NLC and TMIG_AD showed significant differences at $p < 0.01$. Therefore, the AD and NLC groups could be clearly distinguished. In addition, although there was a large difference in average age among medical institutions in the AD group, d value did not differ markedly.

This indicates that this feature is less affected by age than the frequency method. When the intersection of the RCD curves was taken as the threshold, the correct diagnosis rate was 75% for Tone Town and 72% for TMIG.

C. Averaged frequency and triple correlation

Linear discriminant analysis was performed using data from two medical institutions data on the f and d values to calculate coefficients of the discriminant function shown in Equation 1, resulting in $\alpha = 0.5769$ and $\beta = -0.7857$. $FD = 0.6f - 0.8d$ was defined as an evaluation function. We analyzed data from the two medical institutions using this discriminant function *FD* value and the results are shown in Fig. 8. The correct diagnosis rate was about 80% for both Tone_NLC and Tone_AD groups, and about 72% for the TMIG_NLC and TMIG_AG groups in Fig. 6 (left graph). Evaluation of the above three index values was performed using a receiver operating characteristic (ROC) curve in Fig. 6 (right graph),. We used area under the curve (AUC) to evaluate accuracy. Among the three index values, the AUC of the *FD* value was the highest (0.8). Therefore, it can be seen that *FD* is the optimal index. Furthermore, the statistical significance (p-value <0.01) between normal and AD of FD value is evaluated with the Mann-Whitney U-test.

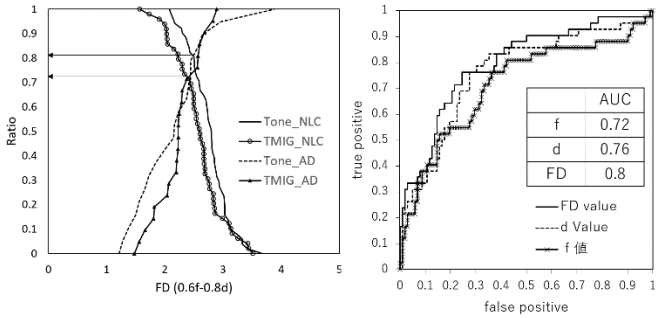

Fig. 6 RCD curve and ROC curve for Tone Town and TMIG.

V. Discussion

Compared with the brain waves of middle-aged adults, those of normal elderly people showed a frequency decrease in α waves and an increase in slow waves. Therefore, it was difficult to classify NLC subjects and AD patients using only frequency characteristics. However, since young NLC subjects show few characteristics of slow wave formation, a group of young NLC subjects from Tone town could be classified into about 80% of the Tone_AD group and about 76% of the TMIG_AD group.This can be considered a high correct diagnosis rate. Furthermore, the ROC curve showed that the accuracy improves when using an evaluation function created from the two indices rather than using only the average frequency and the index of the triple correlation value.

VI. Conclusion

The method shown herein requires a short measurement period and only a small number of electrodes. Therefore, our method aims to create a measurement system that individuals can utilize at home, without needing to go to a specialized medical facility.

In this study, we analyzed the EEG data from three electrodes (P3, P4, and Oz) out of the 21 electrodes from the international 10-20 System and we used a short data collection period (1 minute) in the frequency range 6–13 Hz. We propose an AD estimation method utilizing the phenomenon of slow wave formation in the α band along with determination of a triple correlation value.

In the future, we will study patients with mild dementia (also known as mild cognitive impairment; MCI) and analyze data from patients who have progressed from MCI to AD, as well as data from those who have progressed from normal cognitive function to MCI or AD. In this way, we aim to conduct further detailed analyses of dementia.

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