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Analysis for Alzheimer's disease using cross-correlation of EEG data

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***Abstract*—As the elderly population grows, the number of people with dementia is also increasing. If dementia is detected at an early stage, it is possible to slow its progression. Patients with Alzheimer's disease, a type of dementia, show some specific EEG patterns, and we have therefore been investigating EEG analysis to detect Alzheimer's disease. In this paper, we propose a method that evaluates the phase relation between three electrodes. This method enables estimation of the dynamical behavior of an assumed dipole in the deep brain to potentially detect Alzheimer's disease, depending on the disease progression. This method requires only three electrodes and a short period of data collection (1 min). Experimental results show that Alzheimer's disease is identified with over 70% accuracy. Therefore, this Alzheimer's disease detection system appears to be feasible.**

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

I. Introduction

The number of elderly people with dementia is increasing with aging of the population in Japan. Among several types of dementia, Alzheimer's disease (AD) affects the largest number of patients. If AD can be detected at an early stage, it is possible to delay its progression with medications and appropriate care. Positron emission tomography (PET) and a cerebrospinal fluid test using biomarkers are the major diagnostic methods for AD, in addition to an interview using a dementia test. Recently, the idea of diagnosis using electroencephalography (EEG) has also attracted considerable attention [1]. EEG devices are inexpensive compared with other brain monitoring systems and can be purchased by individuals, so it may be possible to develop an economically reasonable EEG system for detection of AD with a simple algorithm. If such a system becomes commercially available, people could use it at home, detect signs of AD at an early stage, and begin treatment earlier.

Therefore, we aimed to develop an EEG-based diagnosis system for detecting AD. Although conventional EEG research requires many electrodes, we aimed to minimize the number of electrodes necessary for this system. In this paper, we propose a method to detect dementia from cross-correlation values between three electrodes while the patient is awake. We apply this method to clinical EEG data obtained at two medical institutions to evaluate its feasibility.

II. Proposed Method

A. Overview

There is a strong correlation between EEG potentials recorded from any three electrodes [2]. This phenomenon is similar to that of seismic waves. When the hypocenter of an earthquake is located near the surface, the observed seismic waves differ greatly from one observation point to the next. However, when the hypocenter is located in a deeper layer, P waves, a type of seismic wave, have similar amplitude and phase at all points. Likewise, the neural activity in deeper parts of the brain can be estimated through the analysis of EEG data recorded from three electrodes. Assume a region in the shape of a triangular pyramid, formed by a signal source point in the brain and the three electrodes. When the three electrodes are located the same distance from the source point, the recorded signals would have the same phase and would reflect the neural activity at the source point. By analyzing the time series of

EEG data observed at the three electrodes, it may be possible to classify AD patients (AD group) and elderly adults with normal cognitive function (control group). We have named this method Deep Neuronal Activity Topography (dNAT) [3].

We performed a pilot experiment to investigate appropriate electrode positions, examining regions such as the frontal and temporal regions. The results revealed significant differences between the AD and control groups in the occipital region, which was surrounded by three electrodes: P3, P4, and Oz in the International 10-20 System (Fig. 1).

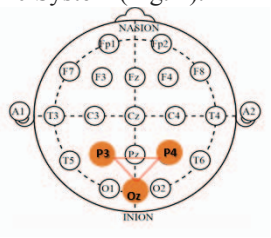

Fig. 1. Electrode sets located at P3, P4, and Oz in the International 10-20 EEG System

During the progression of AD, the frequency of alpha waves decreases in the awake and resting state with eyes closed, and the power of slow waves increases [4]. Waves with frequency of 8 Hz are known as slow alpha waves and are considered a potential marker of extremely mild brain dysfunction [5]. On the basis of these past research results, we decided to use a frequency band of 6–13 Hz in the awake and resting state with eyes closed, which is slightly lower than the alpha wave band 8–13 Hz. The EEG was recorded for 1 min at a sampling frequency of 200 Hz per channel. After the recording, the data were band-pass filtered in order to pick out signals in the frequency range 6–13 Hz.

It has been reported that the percentage of people whose dominant frequency of background activity is less than 9 Hz is significantly higher in AD patients than in healthy controls [6]. Furthermore, a negative correlation has been reported between age and fundamental frequency in elderly people with normal cognitive function, and slow waves become dominant due to aging [2]. Thus, when extracting EEG features, a method is needed for distinguishing between normal aging and AD because they have similar frequency characteristics. To confirm this, we examined using data of facilities with normal elderly person. To investigate this, we analyzed data of AD patients and elderly adults with normal cognitive function collected at two facilities.

B. Calculation of Triple Correlation Value

In evaluating the correlation of brain potentials at each electrode position, we calculated the triple correlation value (1). The triple correlation value is obtained by multiplying the potential signals *EVA(t), EVB(t),* and *EVC(t)* from the three electrodes, and applying time shifts of τ1 and τ2 with respect to the potential signal from each electrode and then integrating over time. $S_i(\tau_1,\tau_2)=\frac{1}{N}\int_i^{i+1}\left|\mathrm{EVA}(t)*EV\mathrm{B}(t-\tau_1)*EV\mathrm{C}(t-\tau_2)\right|dt$

(1)

To limit the rotation plane of the equivalent dipole assumed in the deep brain, we calculated the triple correlation only when the three potentials had the same sign. In (1), the number of times this occurred is represented by *N*. When this calculation is performed at a 1-s resolution, the triple correlation value is plotted on the feature space formed by the two time-delay parameters (t1, t2). As shown in Fig. 2, when comparing the distribution of triple correlation values between 52 normal controls and 20 AD patients, the distribution with respect to the time axis was more irregularly aligned in the AD patients than in the normal controls (Fig. 2 (b)). Viewing the triple correlation value as a forest, we found that the trees of the AD group seemed to be growing sparsely. On the other hand, the trees of the control group seemed to be growing regularly (Fig. 2 (a)). By evaluating the variation of the triple correlation value and the degree of dispersion in the time axis direction, it is possible to quantitatively classify differences in the characteristics of individuals.

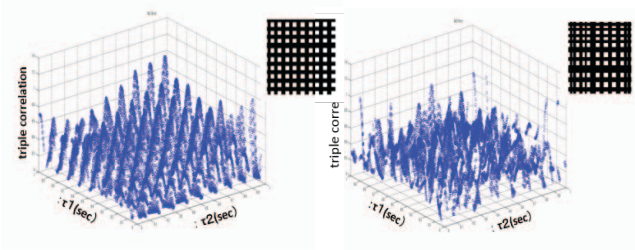

Fig. 2. Distribution of triple correlation values
a) Normal triple correlation b) AD triple correlation

C. Calculation of Index Value

In the previous section, we showed that the fluctuation of triple correlation values differed greatly between the normal controls and AD patients. However, this feature may not be seen in some distribution areas for the triple correlation. Thus, in some cases, it is not possible to classify AD by evaluating only the variation of the entire triple correlation value. To mitigate this, we calculated the maximum value of the triple correlation value at the delay parameter (τ1, τ2) for each rectangular region of 0.2 s × 0.2 s, which is the triple correlation value created every second calculated by (2). 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, …, 10 s. 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* (2).

$$ave\_S=\overline{std\_S_i}$$

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

$$S = ave\_S / std\_S \quad (2)$$

Next, we defined an index indicating the degree of variation in the time axis direction. First, when comparing the distribution of triple correlation values with trees, the upper right figure of Fig. 2 shows the state of the plane surrounded by τ1 and τ2 as seen from the top. The figure of black and white grid points is a view of the three-dimensional representation from the top, and the region where the three brain potentials take the same sign is displayed in white. Other areas are black. As shown in Fig. 3, dx_i (i = 1, 2, …, m) and dy_j (j = 1, 2, …, n) are the distances between the white rectangles in the horizontal and vertical directions, respectively. We considered whether dx_i and dy_j are evenly aligned in the length and breadth of the white rectangles in the τ1 and τ2 directions or whether the white squares are arranged in a disordered manner. When comparing normal controls and AD patients, one of τ1 and τ2 tended to show large bias in AD patients. Because the rectangles were regularly arranged in both the τ1 and τ2 directions in both normal controls and AD patients, we inferred that both τ1 and τ2 could quantitatively evaluate the distance between adjacent white squares at arbitrary times. Specifically, as shown in (3), we calculated the standard deviation *Std_dx* of m number of dx_i and the standard deviation *Std_dy* of n number of dy_j, and the average value of the two standard deviations was defined as the index value *SD*.

$$std\_dx = \sqrt{\frac{1}{m}\sum_{i=1}^{m}(dx_i - \overline{dx})^2}, \overline{dx} = \frac{1}{m}\sum_{i=1}^{m} dx_i$$

$$std\_dy = \sqrt{\frac{1}{n}\sum_{j=1}^{n}(dy_j - \overline{dy})^2}, \overline{dy} = \frac{1}{n}\sum_{j=1}^{n} dy_j$$

$$SD = \left|(std\_dx + sfd\_dy)/2\right| \quad (3)$$

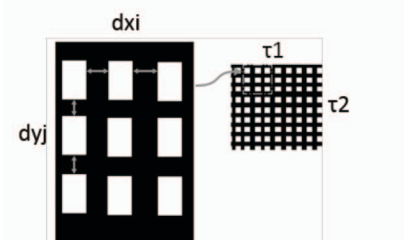

Fig. 3. Interval of the temporal fluctuation
(x-direction interval: dx_i; y-direction interval: dy_i)

Then, we defined a new index dNAT using this *SD* value and the *S* value calculated from (2). We refer to this as the dNAT value below.

$$dNAT = S + SD \quad (4)$$

The greater the difference between the triple correlation value and the variation in the time axis direction—in other words, the greater the dNAT value—the greater the likelihood of AD.

III. Data Used to Evaluate the Proposed Method

Data from two medical institutions were used to evaluate the proposed method. Based on the findings of specialists using tools such as cognitive tests, interviews, magnetic resonance imaging (MRI), and PET, subjects at each institution were classified into a normal control group and an AD group [9]. Details of the data are shown in Tables 1 and 2.

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

To estimate the prevalence of AD among the elderly throughout Japan, we selected a site in Tone Town, Ibaraki Prefecture, from the unified surveys of seven locations in 2009. In total, 612 residents aged 65 year or older participated in the interview survey. According to the process of "Dementia prevalence survey in the elderly," a specialist performed cognitive screening and conducted a structured interview, neurological diagnosis, and other means, in order to diagnose dementia and psychoneurotic diseases. For cognitive screening tests, The Mini Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) were used. In addition, 397 subjects underwent brain MRI scans. This prevalence survey was approved by the ethics committee of the University of Tsukuba [10].The 402 subjects who consented to additional examinations at the time of the survey underwent EEG examination and the doctors visually inspected the EEG results [6]. The 52 subjects in the control group had no memory or cognitive impairment and no abnormal findings on brain MRI or EEG. This study analyzed the following two groups based on their classifications at the time we reviewed the above-mentioned EEG results (Table 1).

- 52 normal controls (Tone_NC)
- 20 AD patients (Tone_AD)

Table 1. Characteristics of subjects at Town [1]

Data①	NLC	AD	P-value
n	52	20	
age (m±SD)	71.9 ± 5.9	84.4 ± 6.3	P<0.05*
MMSE (m±SD)	27.4 ± 1.9	26.0	P<0.01**
CDR m ± SD	0.0 ± 0.0	1.1 ± 0.7	P<0.01**

(2) Data acquired at Tokyo Metropolitan Institute of Gerontology

The normal controls were selected from elderly people who volunteered to undergo annual FDG-PET examination (PET examination showing brain activity using ^{18}F-labeled fludeoxyglucose) at the Tokyo Metropolitan Institute of Gerontology (TMIG). Among the volunteers, those who exhibited good PET results (rated A out of grades A, B, and C) were classified as the normal control group [6][7]. The diagnostic criteria for AD [8] were met by 22 patients whose FDG-PET findings did not contradict a diagnosis of AD (Table 2).

- 50 normal controls (TMIG_NLC)
- 22 AD patients (TMIG_AD)

Table 2. Characteristics of subjects at TMIG [2]

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**

EEG data were recorded using an electroencephalograph (EEG-9100, Nihonkoden Co., Ltd.) and an electrode helmet without paste (Brain Function Laboratory Co., Ltd.) in both settings. Data were recorded for just 1 min while subjects were awake. The filter at the time of recording was 0.08 to 300 Hz, and 21 electrodes were placed according to the International 10-20 system. For this analysis, we used data from only three electrodes (P3, P4, and Oz) with a reference electrode placed on the right earlobe and we used only 1 min of data from the start of the measured data. The sampling frequency at the time of analysis was 200 Hz.

IV. Results

Two-dimensional distributions of the two index *S* values and *SD* values in the AD group and the control group at each institution are shown in Fig. 4. The results show that the control group is distributed in the area below the straight line and the AD group is distributed in the area above the straight line. However, since the distributions are clustered in the vicinity of the straight line, it is difficult to clearly separate the AD group and the control group by only the two-dimensional distribution of the *S* and *SD* values.

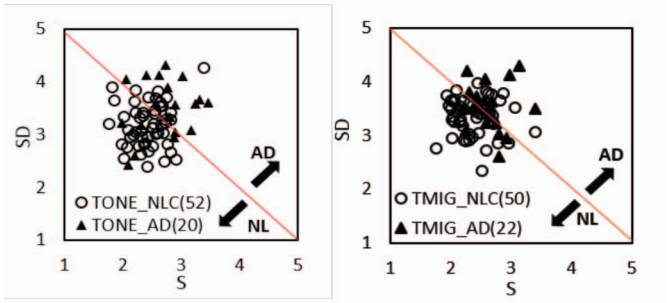

Fig. 4. *S* value and *SD* value in Tone town
(Left: Tone town, Right: TMIG)

Next, evaluation was performed using the value of the index dNAT obtained by linearly combining the *S* value and the *SD* value, as shown in (4). Fig. 5 shows that the dNAT value increases with decreasing MMSE for subjects at both medical institutions. 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 normal control groups could be clearly distinguished.

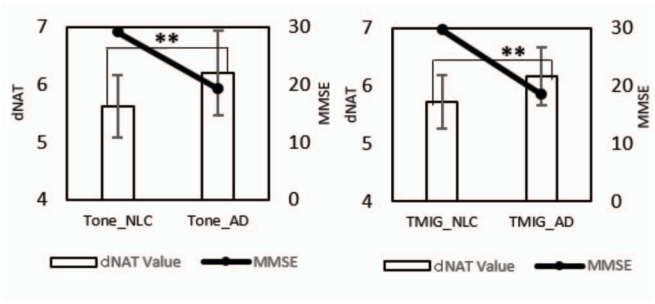

Fig. 5. dNAT value and MMSE
(Left: Tone town, Right: TMIG)

Next, we plotted as the ratio of the average dNAT value between the groups on the vertical axis versus the dNAT value on the horizontal axis; the result was called the sensitivity-specificity curve. Fig. 6 shows the sensitivity-specificity curves for the data of the two medical institutions, where the intersection of the curve of the normal control group and that of the AD group was defined as the boundary value. The sensitivity-specificity curve shows that the discrimination rate that can be determined when the boundary value is set as the threshold. As shown in Fig. 6, the normal control group and the AD group could be classified with a discrimination rate exceeding about 70% at both medical institutions. Furthermore, even if we compare data between different medical institutions, such as Tone_AD versus TMIG _NC and TMIG_AD versus Tone_NC, the results are as acccurate as when we compare data from the same medical institution. The data of the normal control groups in Tone Town and TMIG show almost identical characteristics, suggesting that the method is able to discriminate between elderly adults with normal cognitive function and those with AD.

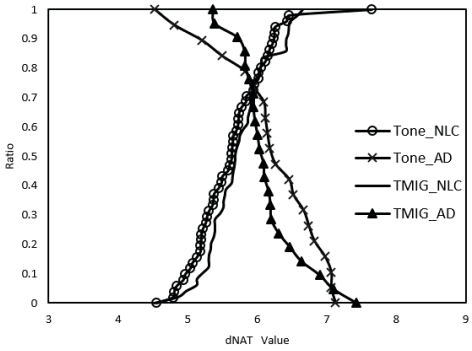

Fig. 6. Sensitivity-specificity curve for dNAT

V. Discussion

The proposed dNAT index is a method that we developed to classify AD patients and elderly adults with normal cognitive function based on feature quantities focusing on spatial and temporal fluctuations between three electrodes. Conventionally, many methods for detecting dementia using EEG are based on spectral analysis. These methods rely on observations that the frequency of the alpha wave decreases in the presence of dementia, and the power of slow waves increases. However, the power of slow waves also increases

with normal aging. Therefore, it may be difficult to distinguish between normal elderly people and AD patients.

In our dNAT method, it is possible to grasp the spatial and temporal characteristics of the triple correlation value by analyzing from the high theta band to the alpha band in order to take gradual waves into consideration. Using this method, we showed that it is possible to analyze data from different medical institutions with a discrimination rate exceeding about 70% between normal controls and AD patients. As shown in Tables 1 and 2, the normal control group of TMIG data was older than the normal control group from Tone Town, and the TMIG_AD group was younger than the Tone_AD group. However, since we observed a statistically significant difference between the normal control group and the AD group at each institution, we can conclude that the proposed method is not influenced by age. Furthermore, this method has a short measurement time and requires only a small number of electrodes. Therefore, the burden on the subject is small and the measurement can be easily performed without going to a medical institution.

VI. Conclusion

In this paper, we proposed a method to detect dementia using only three electrodes and 1 min of EEG data. Data were obtained from elderly residents in Tone Town, Ibaraki Prefecture, and at Tokyo Metropolitan Institute of Gerontology. Data from each institution were classified into a normal control group and an AD group based on findings such as cognitive tests, interviews, MRI, and PET conducted by doctors. The EEG data were sampled at 200 Hz per channel while subjects were awake and band-pass filtered to pick out signals in a frequency range of 6–13 Hz. Data were analyzed using only three electrodes (P3, P4, and Oz) out of the 21 electrodes of the International 10-20 System. We defined a dNAT index that quantifies the observation that both spatial and temporal fluctuations of the triple correlation values are disturbed due to dementia. Using this feature, we showed that normal controls and AD patients can be classified with a discrimination rate exceeding 70%.

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

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