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Mean Phase Coherence as a Supplementary Measure to Diagnose Alzheimer's Disease with Quantitative Electroencephalogram (qEEG)

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Abstract

Noninvasive detection of patients with probable Alzheimer's disease (AD) is of great importance for assisting a medical doctor's decision for early treatment of AD patients. In the present study, we have extracted quantitative electroencephalogram (qEEG) variables, which can be potentially used to diagnose AD, from resting eyes-closed continuous EEGs of 22 AD patients and 27 age-matched normal control (NC) subjects. We have extracted qEEG variables from mean phase coherence (MPC) and EEG coherence, evaluated for all possible combinations of electrode pairs. Preliminary trials to discriminate the two groups with the extracted qEEG variables demonstrated that the use of MPC as a supplementary or alternative measure for the EEG coherence may enhance the accuracy of noninvasive diagnosis of AD.

Key words : Alzheimer's disease (AD), dementia, EEG coherence, mean phase coherence (MPC), quantitative electroencephalogram (qEEG)

I. INTRODUCTION

Quantitative electroencephalogram (qEEG) has been a useful tool in clinical neuropsychiatry, which can be potentially used to assess electrophysiological changes associated with various psychiatric diseases such as dementia, schizophrenia, depression, and so on [1-4]. Recently, among various classical qEEG variables such as relative power at a specific frequency band for an electrode, bipolar asymmetry at central or anterior electrodes, and so on, EEG coherence between two electrodes at a specific frequency band is becoming of importance since it can efficiently quantify the modifications in the cortico-cortical connections of a subject [5].

Although considerable efforts have been made to build standard databases of important qEEG variables including the EEG coherence [1] and to characterize specific psychiatric diseases [2-5], the general applicability of their databases has not been proven sufficiently because the qEEG variables may be affected by various aspects such as sensitivity of the recording system, experimental conditions, and so on. Therefore, we tried to extract the qEEG variables from our own data sets. In the present study, we have collected eyes-closed resting EEG data sets from patients with Alzheimer's disease (AD) and age-matched normal control (NC) subjects, and tried to extract important qEEG variables which can be potentially used for the diagnosis of AD. We have calculated EEG coherence values between all possible combinations of electrode locations for 8 frequency bands and investigated statistical difference between the two groups. We have selected electrode pairs and frequency bands which showed statistically meaningful differences ($p < 0.01$) between the two groups. In addition, we also applied the same procedures to another measure called mean phase coherence (MPC) [6,7], which quantifies the synchronization of phase in a pair of time series. To the best of our knowledge, the use of MPC for the diagnosis of AD has not been reported. In the present paper, we investigated if the MPC can be an alternative or supplementary measure to diagnose AD.

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II. METHODS

A. EEG Recording

EEG was recorded for 22 AD patients (3 Males and 19 Females, Age 73.8y ± 7.6y, Symptom duration 22.4 ± 19 months) and 27 age-matched NC subjects (14 Males and 13 Females, Age 72.8y ± 4.5y) in relaxed states with eyes closed for 15 min each from 18 scalp electrode locations (Fp1, F3, C3, P3, Fp2, F4, C4, P4, F7, T3, O1, F8, T4, T6, O2, T1, T2), using the international 10 - 20 system with a ear reference. The AD group fulfilled the DSM-IV criteria of dementia of Alzheimer's type. Patients with other medical conditions known to cause dementia were excluded by means of neurological, serological and imagery tests, including computed tomographic imaging scan (CT-scan) and magnetic resonance imaging (MRI). The symptom severity of AD was assessed by mini mental status exam (MMSE). Their mean MMSE score was 19.2 ± 3.6. The control group had no personal history of psychiatric or neurological abnormalities. Their mean MMSE score was 27.37 ± 1.1, which was statistically different from that of the AD group ($p < 0.001$).

The record was performed by a conventional 32-channel EEG system (Nicolete Biomedical, Madison, WI, USA) in a dimly lit, soundproof, electrically shielded room. The horizontal eye movements were recorded across electrodes 1cm lateral to the outer canthus of each eye. The sensitivity was set at 7 μV, bandpass filter at 1Hz to 70Hz, and a sampling rate at 250Hz [8]. EEG segments with electrooculogram (EOG) artifacts were excluded in a semi-automatic manner and segments contaminated by the other artifacts were excluded by visual inspections. Then, five sets of 5 sec signals were randomly chosen from the processed EEG data and used for the present analysis.

B. Calculation of Coherence

EEG coherence represents the covariance of the EEG spectral activity at two electrode locations and can be considered as a measure of temporal synchronization of the EEG signals recorded at pairs of electrodes. Despite some known limitations, the coherence analysis of EEG data has become a basic tool available in practically all digital EEG machines used for clinical applications. In the present paper, coherence C was calculated by

$$C = |f_{xy}|^2 / (f_{xx} f_{yy}) \tag{1}$$

where f_{xy} denotes the power spectral estimate of two EEG signals x and y [9,10]. The numerator contains the cross spectrum for x and y, while the denominator contains the respective autospectra for x and y. This procedure returns a real number between 0 (no coherence) and 1 (maximum coherence).

C. Calculation of Mean Phase Coherence

Unlike the EEG coherence, MPC measures 'phase' synchronization between the two EEG signals, excluding their amplitude information [6,7]. Therefore, it is obvious that two signals with a high EEG coherence value also have a high phase coherence value, while high phase coherence does not always mean that their coherence value is high. Conceptually, MPC can be viewed as a similar measure with phase locking value (PLV) [11].

The mean phase coherence R can be evaluated by

$$R = \left(\left[\frac{1}{N} \sum_{j=0}^{N-1} \sin\left[\varphi_{x,y}(j\Delta t)\right] \right]^2 + \left[\frac{1}{N} \sum_{j=0}^{N-1} \cos\left[\varphi_{x,y}(j\Delta t)\right] \right]^2 \right)^{1/2} \tag{2}$$

where $\varphi_{x,y}$ represents phase difference between two EEG signals x and y (Mormann et al 2000) and Δt represents the interval of time samples. This procedure also returns a real number between 0 (no phase coherence) and 1 (maximum phase coherence). The phase angle $\varphi(t)$ of a signal $s(t)$ can be evaluated by

$$\varphi(t) = \arctan \frac{\tilde{s}(t)}{s(t)} \tag{3}$$

where $\tilde{s}(t)$ is the Hilbert transform of $s(t)$.

III. RESULTS

In the present study, we tried to extract meaningful qEEG variables which can be potentially used for the diagnosis of AD. We first calculated EEG coherence between all possible electrode pairs for each frequency band. Since the number of electrodes used for the recording was 18, coherence was evaluated for totally 18 × 17 / 2 = 153 electrode pairs. We divided the frequency domain of interest into 8 sub-frequency bands, which were delta(1-4 Hz), theta(4-8 Hz), alpha(8-12

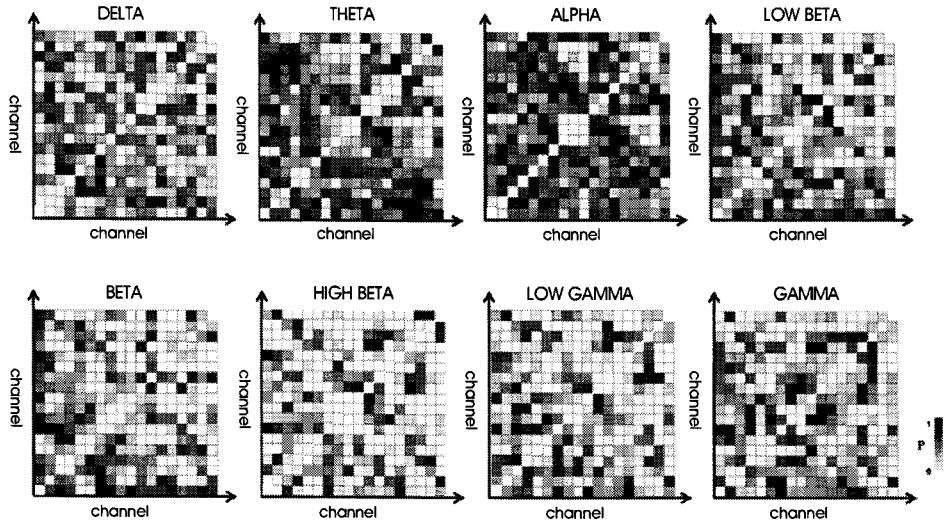

Fig. 1. Results of *p*-value evaluation. Coherence values that were evaluated for all possible combinations of electrode pairs at 8 different frequency bands were statistically compared between AD group and healthy control subject group. Bright colors represent small *p*-values. Channels in horizontal and vertical axes were Fp1, F3, C3, P3, Fp2, F4, C4, P4, F7, T3, O1, F8, T4, T6, O2, T1, and T2.

Hz), low beta(12-15 Hz), beta(15-18 Hz), high beta(18-30 Hz), low gamma(30-40 Hz), and gamma(40-50 Hz) band [12,13]. Therefore, the number of all candidates was $8 \times 153 = 1224$.

For each of the candidates, the difference between two groups (AD patients and normal controls) was estimated using a *p*-value obtained from paired *t*-tests. Fig. 1 shows the distribution of the *p*-values, where horizontal and vertical axes represent channels. Dark colors represent high *p*-value, which means that two groups do not show statistically significant difference, while bright colors represent small *p*-value, which means that two groups may be statistically different. Please note that this process was required just to extract potentially more meaningful qEEG parameters and we did not use the *p*-value elsewhere.

We then picked up two qEEG variables which showed smallest *p*-values among the candidate variables. The selected qEEG variables were alpha coherence between P4 and T1 electrodes and high beta coherence between C4 and T1 electrodes. Fig. 2 shows the scatter distribution of coherence values of every individual signal. It can be seen by the visual inspection of the figure that two groups are roughly discriminable. When a linear binary decision was applied to the two qEEG variables, maximum diagnostic accuracy reached to 85.7%.

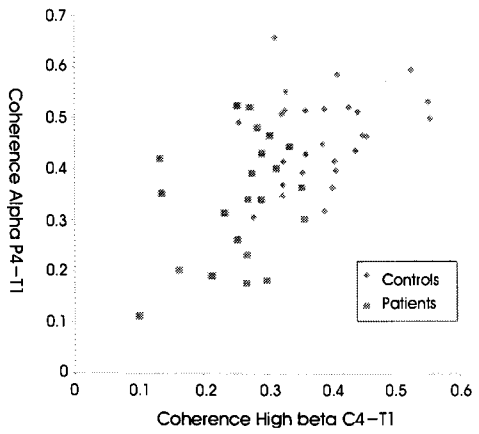

Fig. 2. Scatter distribution of selected qEEG variables evaluated for every individual signal. The selected qEEG variables were alpha coherence between P4 and T1 electrodes and high beta coherence between C4 and T1 electrodes.

Table 1. The number of significant qEEG variables of which the p-values are less than 0.01.

frequency bands	Coherence	MPC*
Delta	9	4
Theta	5	5
Alpha	7	2
Low beta	7	13
Beta	7	15
High beta	24	24
Low gamma	11	13
Gamma	7	3
Sum	77	79

*MPC represents mean phase coherence

We then evaluated MPC between all possible electrode locations for the 8 frequency bands used for the EEG coherence calculation and also estimated statistical difference between the two groups using paired *t*-tests. To show the difference in the numbers of potential qEEG variables, we counted the numbers of qEEG variables, of which the *p*-values are less than 0.01, from both coherence and MPC. Table 1 summarizes and compares the number of features extracted from coherence and MPC. We can see from the table that more potential features could be extracted from the coherence at lower frequency bands, while slightly more features could be extracted from MPC at higher frequency bands.

To demonstrate that the use of MPC along with the coherence can be advantageous, we picked two qEEG variables: one from the coherence and the other from MPC. The selected qEEG variables were high beta MPC between T1 and C4 electrodes and alpha coherence between P4 and T1 electrodes. Fig. 3 shows the scatter distribution of the selected qEEG variables evaluated for every individual signal. It can be seen by the visual inspection of the figure that the border between the two groups became much clearer than that shown in Fig. 2. When a linear binary decision was applied to the two qEEG variables, the diagnostic accuracy increased to be 91.8%.

We then applied multiple features (more than 2) extracted from the coherence and MPC analyses to the diagnosis of early dementia. For the classification, we used support vector machine (SVM) algorithm [14] implemented in MATLAB (Mathworks, Inc.) toolbox. Table 2 summarizes the test results when 3 and 4 features were used for the classification. In the table, 'Coherence' or 'MPC' represents the estimated classification accuracy when 3 or 4 features with smallest *p*-values were selected among either coherence values or MPC values. In the 'Coherence + MPC' case, 3 features were composed of

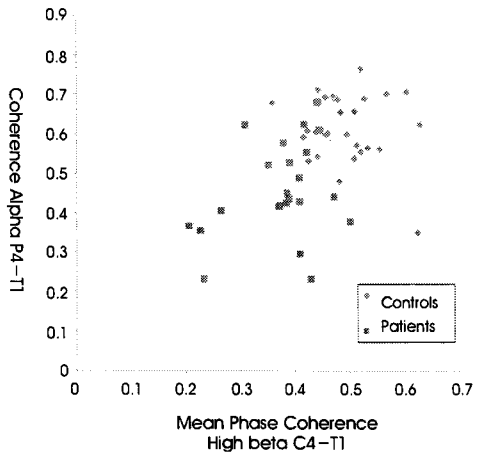

Fig. 3. Scatter distribution of selected qEEG variables evaluated for every individual signal. The selected qEEG variables were high beta mean phase coherence between T1 and C4 electrodes and alpha coherence between P4 and T1 electrodes.

Table 2. Classification results using multiple qEEG variables: The classification accuracy was evaluated by support vector machine (SVM).

# of features	3	4
Coherence	91.6%	91.6%
MPC*	91.6%	95.8%
Coherence + MPC*	95.8%	95.8%

*MPC represents mean phase coherence

2 coherence features and 1 MPC feature, and 4 features were composed of 2 coherence and 2 MPC features. We also evaluated the classification accuracy when 3 features were composed of 1 coherence feature and 2 MPC features, which resulted in the identical classification accuracy (95.8%). From the results, we could observe the following facts:

- The use of slightly more qEEG features may enhance the classification accuracy. When we tested the same process for more than 5 qEEG features, however, we couldn't get any more improvement in the classification accuracy.
- The use of MPC instead of EEG coherence showed slight improvement in the classification accuracy in the 4-dimensional case, but it could hardly be generalized.
- The combinational use of coherence and MPC showed some improvement in the classification accuracy, compared to the conventional EEG coherence results. The results are consistent with those of the previous 2-dimensional case study presented in Figs. 2 and 3.

In summary, the results of our study demonstrated that the complementary use of MPC together with the coherence may enhance the overall diagnostic accuracy, compared to that of the conventional EEG coherence. These preliminary results are thought to be meaningful since we can now try another promising measure other than EEG coherence in order to enhance the diagnosis accuracy of AD.

Ⅳ. CONCLUSIONS

In the present study, we extracted qEEG variables from MPC and EEG coherence evaluated for all possible combinations of electrode pairs. Some examples adopting the extracted qEEG variables demonstrated that the use of MPC as a supplementary or alternative measure may enhance accuracy of diagnosis of AD, which can provide us with more degrees of freedom when one chooses qEEG features.

In our case studies, we sometimes observed that the smaller p-value does not always guarantee the higher classification accuracy. Although the t-test between any two distributions is the most widely-used method to extract meaningful qEEG features, application of other measures which can reflect the separation more clearly might be needed for our future studies. In addition, validation and comparison of various classification algorithms, such as feed-forward neural network, partial least squares, and so on [14], with the extracted qEEG variables will be also performed in our future studies.

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