Quantitative EEG in Mild Cognitive Impairment and Alzheimer's Disease by AR-Spectral and Multi-scale Entropy Analysis

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Abstract

To assist effective and precise diagnosis for mild cognitive impairment (MCI) and Alzheimer's disease (AD), Electroencephalograph (EEG) has been widely used in clinical research of patients with AD at MCI state. To study the linear and nonlinear abnormality of EEG in AD and MCI patients, multiple characteristics was applied to distinguish AD and MCI patients from the normal controls (NC). EEG signals was recorded from 28 subjects, including 10 AD patients, 8 MCI subjects and 10 healthy elderly people. EEG signals in all channels was computed by auto-regressive model and multi scale entropy (MSE) to obtain relative power spectral density (PSD) value of each frequency band and entropy value in different time scales. Area under Receiver operating characteristic curve (AUC) was used to compare the classification ability of the two method. The ratio Alpha/theta of MCI group in left frontal area can distinguish MCI from NC subjects. Also the long scale entropy value in left frontal-central area manifests a better accuracy in distinguish AD and MCI from NC group. In addition, the combined feature from alpha/theta and long scale entropy in the left frontal central area can discriminate AD from NC group with higher AUC reaching 0.89. This indicated that combined PSD and MSE can be taken as a potential measure to detect AD in early state.

Keywords

Nonlinear • Multi-scale entropy • Alzheimer's disease Mild cognitive impairment

1 Introduction

Alzheimer's disease is a degenerative diseases of the central nervous increasingly affects the elderly people, causing loss in cognition, memory, even language function [1]. About 10–15% of MCI elderly people each year developed into AD, effective diagnosis and treatment for MCI is very important [2]. The clinical detection of MCI and AD is mainly based on subjective neuropsychological test [3]. The imaging method was used to study the brain structure changes of MCI and AD, but its specificity is not high in the early stage of AD [4]. Also the detection based on biomarkers is invasive [5]. EEG can reflect the physiological activities of the brain, and because of its low-cost, non-invasive and high time resolution, it has been widely used in clinical research of patients with AD at the MCI stage [6].

Quantitative EEG recordings in rest state provide an ideal methodology of the rapid detection in MCI and AD [7]. Babiloni et al. [8] presented the hippocampus volume is related to the loss of alpha rhythms in AD. Moretti et al. [9] found the alpha relative power of MCI in the frontal area was decreased, and power in theta band was increased. Compared with traditional spectrum estimation, the parameter estimation based on AR model performs better, it has been used to calculate PSD of EEG in MCI studies [10].

Although linear analysis is important to quantify the abnormal EEG rhythm of patients with MCI or AD, considering the non-stationarity and randomicity of EEG signal, complexity measures such as entropy were widely used to analysis EEG in AD patients. Abasolo et al. [11] showed the entropy of AD patients in the parietal area is lower than health elderly. Hogan et al. [12] found that the entropy of MCI subjects was reduced. MSE analysis base on entropy

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can measure the probability of producing new information for sequences under different scales size, it has been used in cognitive neuroscience. Mizuno et al. [13] found large scale entropy of AD patients in whole brain areas was higher than healthy elderly. Previous studies suggested the complexity changing of EEG signals related to cognitive impairment may be inconsistent in different time scales.

In this work to further quantify both linear and nonlinear comprehensive abnormality of EEG in MCI and AD patients, the PSD and MSE method was adopted to analysis the MCI, AD and normal elderly. Then we compared the accuracy of PSD value, MSE value and combined index in distinguishing AD and MCI from healthy elderly.

2 Subject and Experiment

2.1 Participants

Ten hospitalized AD patients from the department of neurology, JiangBin Hospital in NanNing, GuangXi province (China), and 18 volunteers over 60 years old were recruited. All subjects were right-handness, after clinical evaluation and neurological examinations, eight subjects whose MMSE score were ranged from 24 to 27 composed to be MCI group, other subjects composed to be NC group. Table 1 gives the information of subjects. '*' means difference of MMSE in three groups was significant. The difference in age, gender and education level are not significant.

2.2 EEG Recording

The data collected by the NicoletOne EEG acquisition instrument with 16 channels, sampling rate is 250 Hz. During the experiment the electrode impedance was kept under in 5 KΩ, acquisition channel concludes Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6. Five minutes EEG signal was collected in rest state with eyes closed. Five segment of 5 s which has no obvious interference in all channels was selected for subsequent processing. EEG signal was preprocessed by 0.05–40 Hz band pass filter, all data was processed in MATLAB (R2012a).

3 Method

3.1 Power Spectrum Density (PSD)

PSD analysis for each segment is estimated using AR Burg method, which is one of the most frequently used parametric method. AR model is based on modeling the data sequence as the output of a causal and discrete filter whose input is white noise. Thus the AR model of order p is expressed by the difference equation. AR parameters was estimated by the Burg algorithm, and the optimal order of AR model was estimated by the final prediction error criterion (FPE). The PSD in each frequency band was normalized to obtain the relative PSD, where the sub-band was selected as delta band in 0.5–4 Hz, theta band in 4–8 Hz, alpha band in 8–13 Hz and beta band in 13–30 Hz. And alpha/theta which shows the ratio of PSD in alpha band versus theta band was computed.

3.2 Multi-scale Entropy (MSE)

MSE is a method which measure the complexity of a finite length time series to quantify the probability of generating new information on different time scales. MSE method based on sample entropy of different scales was calculated as the following steps [13]: Firstly, for EEG time series X, construct a coarse-grained time series Y according to a scale factor, the length of reconstruction time series is M, in this work set m = 2 to get the new time series Y_m. Secondly, quantify the sample entropy of each coarse-grained time series, the distance between each Y_m was computed. Set a threshold, r = 0.25, the number of the distance less than r was calculated as B, then obtain the average ratio of this number to the total number of vectors. Lastly, for the next number of dimensions m + 1, repeat the above steps to obtain the sample entropy of each scale from 1 to 20.

3.3 Statistical Analysis

Comparison between groups (NC and MCI, MCI and AD, NC and AD) was made using the independent samples

Table 1 Information of subjects

Heading level	NC (N = 10)	MCI (N = 8)	AD (N = 10)	ANOVA P
Sex (female/male)	6/4	4/4	4/6	0.38
Age (years)	74.4 ± 9.6	79.1 ± 8.7	80.6 ± 6.7	0.25
Education (years)	8.5 ± 2.1	8.5 ± 1.4	8.0 ± 0.1	0.69
MMSE	28.9 ± 1.2	24.6 ± 0.7	16.9 ± 1.5	0.00*

T-test. ROC curves was used to estimate the discriminating ability of PSD and MSE. Area under curve (AUC) of ROC near the upper left corner indicate diagnostic capabilities. Statistical procedures was performed using SPSS 19.0.

4 Results

4.1 MSE in Different Scales

The sample entropy value on 1–20 scales in each channel of AD, MCI and NC group was shown in "Fig. 1". For each scale we compared the difference between AD and NC group. The red box indicated that within this range of scales, differences was statistically significant between AD and NC group. The long scale entropy of AD group was greater than MCI group, and the value of MCI group was greater than NC group, especially for scales more than 12, there was significant differences in each channel of the left side brain areas.

The average entropy from 13 to 20 were computed as the long scale entropy value. "Figure 2" shows the long scale entropy in left frontal, left occipital, left parietal occipital, left temporal, right frontal, right occipital, right occipital area and right temporal areas, differences between AD and NC group were analyzed by t test. The long scale entropy value of AD group was greater than MCI group, and the value of MCI was greater than NC group. Especially the difference between AD and NC group in the left frontal, left frontal-central and left parietal-occipital areas was significant.

4.2 PSD in Different Band

The average PSD value of different frequency band in each channel of the three group was shown Table 2, '*' means difference between AD and NC group was significant, and '+' means difference between AD and MCI group was significant.

For Alpha/Theta, difference between groups on left and right side of four brain areas were also analyzed by t test. As shown in "Fig. 3", the line means $p < 0.05$, the difference was significant. There was significant difference of the alpha/theta value in left frontal, left temporal, right temporal and right parietal occipital areas. There was significant difference of the alpha/theta value in left frontal area of MCI and NC group. And there was significant difference of the alpha/theta value in right parietal occipital area of MCI and AD group.

4.3 ROC Analysis

AUC was used to assess the ability of index in discriminating AD and MCI from NC group, the AUC of alpha/theta and long scale entropy in eight areas was computed, as Table 3 shows, '*' means AUC is more than 0.7. The results

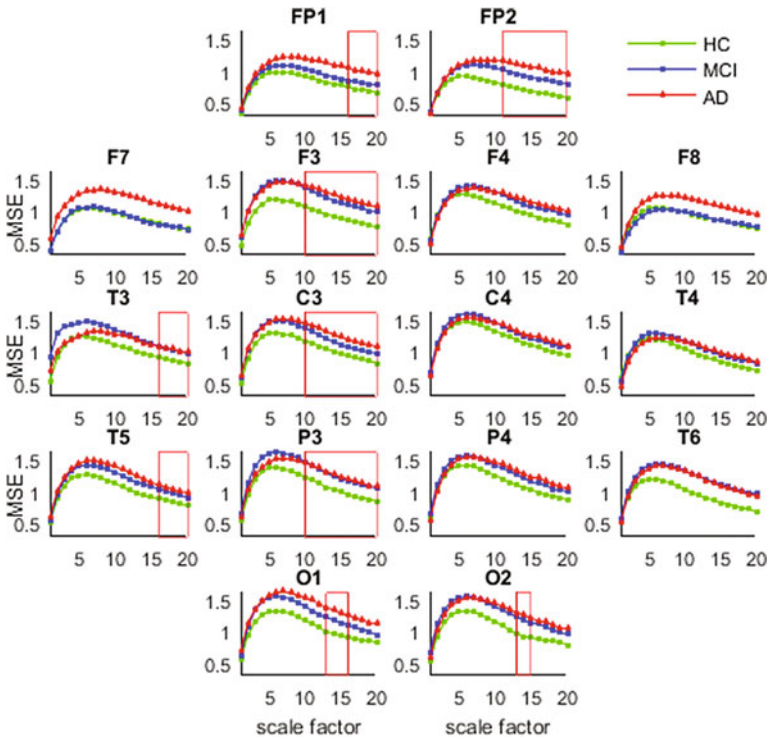

Fig. 1 MSE in different scales of different channel

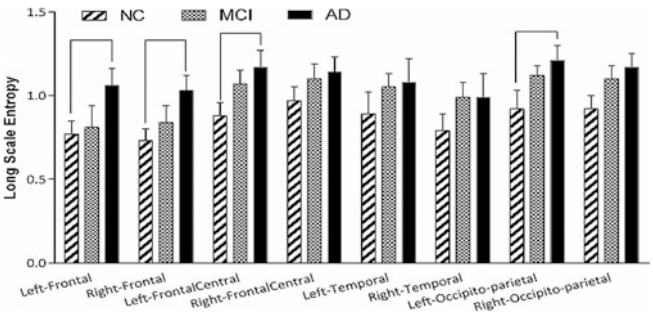

Fig. 2 Alpha/theta in different areas

Table 2 PSD index of different frequency band

	β	α	θ	δ	(β + α)/(θ + δ)	α/θ
NC	0.18 ± 0.03	0.41 ± 0.05	0.24 ± 0.02	0.16 ± 0.04	0.72 ± 0.34	2.91 ± 0.33
MCI	0.15 ± 0.02*	0.40 ± 0.06	0.28 ± 0.02*	0.16 ± 0.05	0.60 ± 0.33*	2.13 ± 0.31*
AD	0.12 ± 0.01*,+	0.33 ± 0.05*,+	0.37 ± 0.02*,+	0.19 ± 0.06*,+	0.28 ± 0.16*,+	0.95 ± 0.12*,+

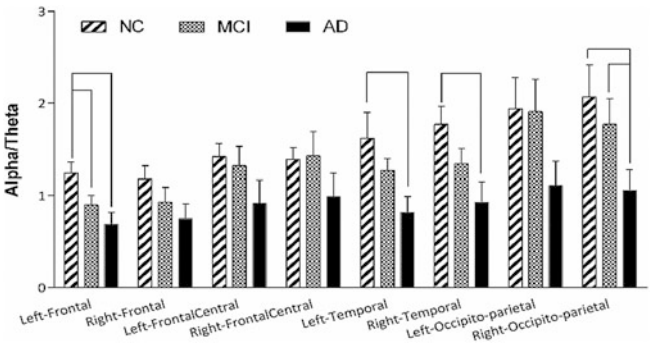

Fig. 3 Long-scale entropy in different areas

Table 3 AUC of alpha/theta and long scale entropy

Brain areas	AUC of alpha/theta		AUC of long scale entropy	
	AD and NC	MCI and NC	AD and NC	MCI and NC
L-Frontal	0.61	0.76*	0.77*	0.55
R-Frontal	0.68	0.56	0.80	0.54
L-FrontalCentral	0.75*	0.48	0.81*	0.73*
R-FrontalCentral	0.59	0.58	0.68	0.61
L-Temporal	0.56	0.69	0.65	0.58
R-Temporal	0.65	0.58	0.63	0.65
L Occipitoparietal	0.86*	0.55	0.74*	0.69
R Occipitoparietal	0.79*	0.74*	0.67	0.69

indicated that the two indexes in left frontal-central and occipito-parietal areas has certain accuracy in discriminating AD from NC group. AUC of linear and nonlinear index in the Left Frontal-Central area was all more than 0.7, with 0.75 and 0.81. We further combined those two value in left frontal-central area to distinguish AD from NC group, the AUC of combined index reached 0.89, which is higher than AUC from any single feature.

5 Discussion

In this study, linear and non-linear method, PSD and MSE analysis was employed to distinguish MCI and AD patients from normal elderly. Cognitive impairment is related to the spontaneous EEG activity rhythm, the abnormality of all the PSD index in MCI and AD patient was consistent with the

prior studies. The significant declined power of alpha band in AD patients was indicated, and these values of MCI subjects also has a downward trend compared with normal elderly. The alpha/theta ratio in left frontal and right occipito-parietal areas can be a typical feature of cognitive decline, which discriminated MCI from normal elderly significantly.

For MSE analysis, we determined the appropriate range of scale to obtain long scale entropy value, the complexity abnormality of MCI patients was consistent with prior studies. The long scale entropy in left frontal-central and ccipito-parietal areas provided better classification performance between AD patient and normal elderly. And in left frontal-central area it also provided good classification performance between the MCI and NC. This manifests EEG abnormality in dominant side brain areas of AD patients is more notable. The complexity of EEG from MSE analysis can provide more information which may benefit our understanding of cognitive impairment.

Since the brain is a complex system showing both linear and nonlinear features, combining PSD and MSE which can reflect the rhythmicity as well as complexity, to obtain effective multiple quantitative EEG index in rest state, can be taken as a potential measure in early screen of AD.

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Conflict of Interest The authors declare that they have no conflict of interest.

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