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ORIGINAL ARTICLE

Frequency power and coherence of electroencephalography are correlated with the severity of Alzheimer's disease: A multicenter analysis in Taiwan

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Background/Purpose: Slowing of average electroencephalography (EEG) frequency in Alzheimer's disease (AD) is well established, but whether EEG changes are able to reflect the severity of AD is uncertain. We attempt to establish quantitative EEG parameters that are suitable for evaluating AD in clinical practice.
Methods: Ninety-five patients with newly diagnosed AD at different stages from four neurologic institutes were enrolled for the study. Standard scalp resting EEG data were collected for quantitative analysis. Global band power ratio and interhemispheric alpha band coherence were calculated.
Results: Patients with advanced AD had a greater slow-to-fast wave power ratio. Among several power ratio parameters, global theta and delta to alpha and beta band power ratio showed the best correlation with stages of AD ($p < 0.05$ between any two patient groups). Patients with advanced AD had decreased coherence in multiple brain regions. The phenomenon was most prominent in the centroparietal region ($p < 0.05$ between any two patient groups).
Conclusion: Increased global slow-to-fast power ratio and decreased centroparietal interhemispheric alpha band coherence are strongly correlated with disease progress in AD

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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patients. These two quantitative EEG parameters may help evaluate AD patients in daily clinical practice. Global power ratio changes may suggest a shift of dominant frequency, and decreased interhemispheric alpha band coherence may suggest functional disconnection and corpus callosum abnormalities in AD patients.

Introduction

Electroencephalography (EEG) is a traditional method of evaluating cortical activities. Typical EEG findings in patients with Alzheimer's disease (AD) are increased slow wave and decreased fast wave activities, but these changes are not specific.[1] EEG spectral profile study showed a shifted-to-the left spectral profile in early AD, and the effect involves mainly EEG signal of 10—11.5 Hz.[2] Modern linear EEG analysis in dementia usually involves methods of spectral band power and coherence.[3] Bennys et al[4] used two EEG power ratio parameters to differentiate between individuals with normal control and AD patients, with good results. In addition, their data showed correlations between the power ratio and different stages of AD in all brain regions except the frontal areas. EEG coherence, defined as the normalized cross-power spectrum per frequency of two signals recorded simultaneously at different sites of the scalp, is a sensitive method for assessing the integrity of structural connection between brain areas.[5,6] Previous studies showed its potential in differentiating vascular dementia from AD and also normal control from AD.[7—11]

Atrophy of the corpus callosum (CC) is present in different neurodegenerative diseases, including AD, frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration.[12] Callosal abnormalities in AD have been demonstrated microscopically[13] and by various *in vivo* imaging techniques, including region of interest, voxel-based morphometry, diffusion-weighted imaging, and diffusion tensor imaging.[14] A correlation between degree of callosal atrophy and dementia severity in AD is evident from previous studies.[12,15—19] A recent study using multimodal magnetic resonance imaging (MRI) analysis showed early changes in the CC in mild cognitive impairment (MCI) and mild AD.[20] The authors proposed two different mechanisms for the white matter changes in mild AD: Wallerian degeneration in posterior subregions of the CC and a retrogenesis process in the anterior callosal subregions.

The CC interconnects the cerebral hemispheres and has an important role in integrating information between homologous association cortices in the bilateral cerebral hemispheres.[21] We suggest that CC abnormalities in AD patients lead to decreased functional connectivity between bilateral cerebral cortices, and there is electrophysiological evidence in favor of such changes. Previous studies showed an association between interhemispheric EEG coherence and size of the CC in patients with callosal agenesis and AD.[22—24] Therefore, we suppose that interhemispheric EEG coherence is decreasing with advancing AD.

In our study, we retrospectively analyzed EEG data of 95 nonmedicated patients with AD at different stages from four neurologic institutes. For power ratio analysis, we modified Bennys et al's method[4] to use global field (including frontal electrodes) slow-to-fast power ratio as a single parameter in each participant for comparison. We examined the selected epochs carefully by visual inspection to avoid the influence of eye movement artifact on frontal signals. For interhemispheric coherence analysis, we compared alpha band coherence values for (1) dominant frequency at rest and (2) EEG profile change in early AD.[2] Correlation of these two EEG parameters with the severity of AD is studied.

Methods

Participants

Patients newly diagnosed with clinically probable AD (according to the NINCDS-ADRDA criteria)[25] from separate dementia registry database in four neurologic institutes, Taipei Medical University-Shuang Ho Hospital (2007—2009), Renai branch of Taipei City Hospital (2000—2005), Taipei City Psychiatric Center, Taipei City Hospital (2000—2005), and Pojen General Hospital (2000—2005), were recruited for baseline (pretreatment) standard scalp EEG study. Medical charts of all candidates were reviewed carefully to record patients' age of diagnosis, sex, Clinical Dementia Rating (CDR),[26] Mini-Mental State Examination (MMSE),[27] comorbidity, and concurrent medication use. Patients in whom CDR was performed 2 weeks after EEG recording; those with concurrent use of cholinesterase inhibitors, NMDA receptor antagonist, antipsychotics, antidepressants, and benzodiazepine; and those with major systemic diseases were excluded. All candidates who fulfilled our inclusion criteria were recruited and classified into four groups according to their disease severity. Patients with CDR values of 0.5, 1, 2, and 3 were classified as Groups CDR0.5, CDR1, CDR2, and CDR3, respectively. To overcome bias the number of candidates in Groups CDR2 and CDR3 was less than in other groups, candidates in Groups CDR2 and CDR3 were grouped together into a new group CDR$\geq$2 for the purpose of statistics.

EEG recording

EEG was recorded in specialized shielded rooms in each neurologic institute. Procedures were performed between 9 AM and 5 PM on weekdays. All participants were instructed not to stay up late prior to examination. During recording sessions, they sat on a tall-backed chair with eyes closed. Activation maneuvers, including opening of eyes, hyperventilation, or photic stimulation, could be performed under instruction by technicians. The events were also marked on the EEG recordings. Tin electrodes with

electrode caps were positioned in 19 scalp sites (FP1, FP2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2) according to the international 10–20 system and were referenced to electronically linked earlobes (A1 and A2). All electrode impedances were kept below 5 kΩ. Concurrent surface Electromyography and Electrocardiography were also recorded for reference but were not included in the EEG analysis. Five EEG recording systems, including Grass Comet XL, Nihon Kohden Neurofax 1200, and Stellate Harmonie, shared unified settings of sampling rate at 200 Hz, bandpass at 1–70 Hz, notch filter at 60 Hz, and total recording duration between 10 minutes and 15 minutes.

EEG analysis

A unified monopolar montage of 16 scalp electrodes (FP1, FP2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, and O2) referenced to electronically linked earlobes (A1 and A2) was used in five EEG recording systems. Signals on left scalp electrodes (FP1, F3, F7, C3, T3, T5, P3, and O1) were referenced to A1 and those on right scalp electrodes (FP2, F4, F8, C4, T4, T6, P4, and O2) to A2. All EEG data were reviewed by experienced electroencephalographers by direct visual inspection to evaluate the recording quality. For each dataset, epochs of at least 10 seconds of awake, resting, eye-closed, and artifact-free continuous EEG data were collected. Raw EEG data were exported to Matlab to perform fast Fourier transform and spectral analysis. The spectral analysis was performed using Welch's averaged periodogram method with a window length of 800 points and an overlap of 400 points. A Hanning window was used to reduce noise. Four standard frequency bands were defined as delta (2–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–32 Hz).

For each EEG dataset, several EEG parameters were computed. Absolute global band power is defined as averaged power density from 16 scalp electrodes of four standard frequency bands. Global band power ratio is defined as the ratio of slow wave power to fast wave power. We modified the indices proposed by Bennys et al.[4] In our study, we calculated the following band power ratios: theta to alpha (T/A), theta and delta to alpha and beta (TD/AB), theta to alpha and beta (T/AB), and theta and delta to alpha (TD/A). In this study, coherence was defined as the magnitude squared coherence of two signals using Welch's averaged, modified periodogram method. The magnitude squared coherence is a function of the power spectral densities [$P_{xx}(f)$ and $P_{yy}(f)$] of x and y, and the cross power spectral density [$P_{xy}(f)$) of x and y, as shown in equation (1):

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f) \cdot P_{yy}(f)} \quad (1)$$

Interhemispheric alpha band coherence is defined as alpha band coherence between two symmetrically located paired electrodes. In our study, eight paired electrodes were chosen: FP1–FP2, F3–F4, F7–F8, C3–C4, T3–T4, T5–T6, P3–P4, and O1–O2. Eight coherence values in each dataset were averaged to obtain the average interhemispheric alpha band coherence. Due to the major contribution of alpha rhythm in posterior head, interhemispheric centroparietal alpha band coherence, defined as averaged C3–C4 and P3–P4 coherence, was computed in each dataset to represent functional connection between bilateral centroparietal region.

Statistical analysis

One-way analysis of variance (ANOVA) with *post hoc* comparisons was used to examine EEG parameters in three groups: CDR0.5, CDR1, and CDR≥2. Further comparisons between Groups CDR2 and CDR3 were made by Mann–Whitney *U* test because of a relatively smaller number of candidates in these two groups. All the analyses were performed using SPSS version 17 for windows (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

Results

Participants and EEG data

Ninety-five newly diagnosed AD patients (48 males and 47 females) who fulfilled the inclusion criteria were enrolled. Their EEG data were collected retrospectively. According to patients' CDRs, EEG datasets were classified into four groups: CDR0.5, CDR1, CDR2, and CDR3 (Table 1).

Global band power ratios

In Groups CDR0.5, CDR1, and CDR≥2, T/A, mean [standard deviation (SD)], were 0.72 (0.35), 0.89 (0.56), and 1.86 (1.02); T/AB, mean (SD), were 0.34 (0.19), 0.50 (0.31), and 1.00 (0.57); TD/A, mean (SD), were 1.68 (1.09), 2.01 (1.47), and 4.27(2.67); and TD/AB, mean (SD), were 0.72 (0.34), 1.06 (0.54), and 2.16 (1.35), respectively. Patients of advanced AD had a greater slow-to-fast-wave power ratio, using T/A, T/AB, TD/A, or TD/AB as the power ratio parameter (Fig. 1). ANOVA of three AD groups showed strong statistical significance between all groups using TD/AB as the power ratio parameter ($p < 0.01$). A further comparison between Groups CDR2 and CDR3 by Mann–Whitney *U* test also showed statistical significance when TD/AB or T/AB was used as the power ratio parameter (Table 2).

Table 1 Demographic and clinical characteristics of AD patients in different groups.

	CDR0.5	CDR1	CDR2	CDR3
N	35	34	17	9
Age, y	76.4 (6.9)	78.9 (8.1)	80.2 (6.5)	81.4 (9.7)
Male	11	25	7	5
MMSE	21.0 (4.2)	17.7 (5.2)	12.3 (4.8)	8.1 (4.7)

Data are presented as mean (SD) or *n*.
AD = Alzheimer's disease; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; SD = standard deviation.

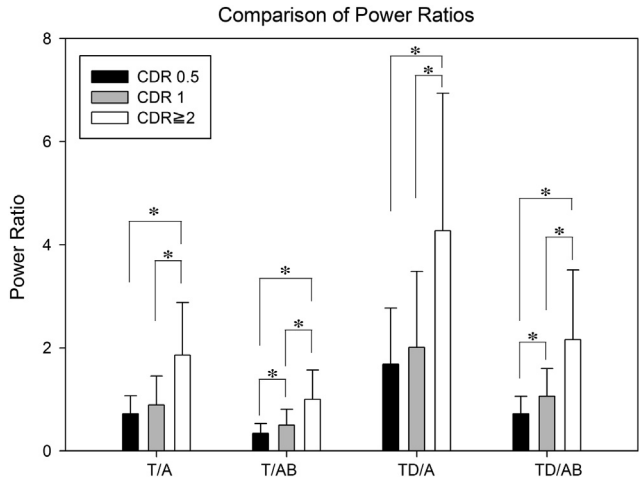

Figure 1 Comparison of power ratios between different groups. * Indicates significant difference in that comparison.

Interhemispheric alpha band coherence in each electrode pair.

A trend of decreasing coherence in advanced AD could be observed in F3—F4, F7—F8, C3—C4, P3—P4, T5—T6, and O1—O2 pairs. Among the eight electrode pairs, C3—C4 and P3—P4 coherence showed better correlation with disease severity (Table 3). A further comparison between Groups CDR2 and CDR3 by Mann—Whitney *U* test showed statistical significance in P3—P4 and O1—O2 pairs (Table 4).

Averaged interhemispheric alpha band coherence

The results show decreasing averaged interhemispheric alpha band coherence in advanced AD (Table 3). ANOVA of three AD groups shows statistical significance ($p < 0.05$) between CDR0.5—CDR≥2 and CDR1—CDR≥2. A further comparison of this parameter between CDR2 and CDR3 by Mann—Whitney *U* test did not reach statistical significance (Table 4).

Table 3 Global power ratio parameters in AD patients of groups CDR2 and CDR3.

	CDR2 ($N = 17$)	CDR3 ($N = 9$)	Mann—Whitney *U* test *p*
T/A	1.58 (0.86)	2.38 (1.13)	0.05
T/AB	0.83 (0.53)	1.32 (0.54)	0.029*
TD/A	3.63 (2.40)	5.48 (2.89)	0.18
TD/AB	1.71 (1.06)	3.00 (1.49)	0.034*

Data are presented as mean (SD).
* $p < 0.05$.
AD = Alzheimer's disease; SD = standard deviation; T/A = global power ratio of theta to alpha band; T/AB = global power ratio of theta to alpha and beta band; TD/A = global power ratio of theta and delta to alpha band; TD/AB = global power ratio of theta and delta to alpha and beta band.

Interhemispheric centroparietal alpha band coherence

The results show decreasing interhemispheric centroparietal alpha band coherence in advanced AD (Table 3). ANOVA shows statistically significance ($p < 0.05$) between any two patient groups. A further comparison between CDR2 and CDR3 by Mann—Whitney *U* test did not reach statistical significance (Table 4).

Discussion

Our study shows increased global slow-to-fast power ratio and decreased interhemispheric alpha band coherence in

Table 2 Global power ratio parameters in three AD groups.

	CDR0.5 ($N = 35$)	CDR1 ($N = 34$)	CDR≥2 ($N = 26$)	ANOVA	*p*
T/A	0.72 (0.35)	0.89 (0.56)	1.86 (1.02)	CDR0.5—CDR1	0.355
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	<0.001**
T/AB	0.34 (0.19)	0.50 (0.31)	1.00 (0.57)	CDR0.5—CDR1	0.047*
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	0.001**
TD/A	1.68 (1.09)	2.01 (1.47)	4.27 (2.67)	CDR0.5—CDR1	0.635
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	0.001**
TD/AB	0.72 (0.34)	1.06 (0.54)	2.16 (1.35)	CDR0.5—CDR1	0.008**
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	0.001**

Data are presented as mean (SD).
* $p < 0.05$.
** $p < 0.01$.
AD = Alzheimer's disease; ANOVA = analysis of variance; SD = standard deviation; T/A = global power ratio of theta to alpha band; T/AB = global power ratio of theta to alpha and beta band; TD/A = global power ratio of theta and delta to alpha band; TD/AB = global power ratio of theta and delta to alpha and beta band.

Table 4 Interhemispheric alpha band coherence of eight electrode pairs and derived interhemispheric centroparietal alpha band coherence in three AD groups.

	CDR0.5 ($N = 35$)	CDR1 ($N = 34$)	CDR≥2 ($N = 26$)	ANOVA	p
FP1—FP2	0.55 (0.15)	0.56 (0.17)	0.48 (0.14)	CDR0.5—CDR1	0.933
				CDR0.5—CDR≥2	0.107
				CDR1—CDR≥2	0.093
F3—F4	0.54 (0.10)	0.48 (0.14)	0.43 (0.15)	CDR0.5—CDR1	0.062
				CDR0.5—CDR≥2	0.001**
				CDR1—CDR≥2	0.111
F7—F8	0.28 (0.14)	0.23 (0.13)	0.21 (0.09)	CDR0.5—CDR1	0.089
				CDR0.5—CDR≥2	0.036*
				CDR1—CDR≥2	0.598
C3—C4	0.45 (0.13)	0.39 (0.15)	0.31 (0.15)	CDR0.5—CDR1	0.098
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	0.039*
T3—T4	0.17 (0.08)	0.17 (0.09)	0.11 (0.06)	CDR0.5—CDR1	0.843
				CDR0.5—CDR≥2	0.008**
				CDR1—CDR≥2	0.014*
P3—P4	0.50 (0.12)	0.42 (0.13)	0.36 (0.13)	CDR0.5—CDR1	0.012*
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	0.057
T5—T6	0.27 (0.11)	0.23 (0.11)	0.19 (0.09)	CDR0.5—CDR1	0.133
				CDR0.5—CDR≥2	0.006**
				CDR1—CDR≥2	0.161
O1—O2	0.59 (0.14)	0.52 (0.15)	0.48 (0.19)	CDR0.5—CDR1	0.090
				CDR0.5—CDR≥2	0.009**
				CDR1—CDR≥2	0.290
Interhemispheric centroparietal alpha coherence	0.48 (0.12)	0.41 (0.13)	0.34 (0.13)	CDR0.5—CDR1	0.029*
				CDR0.5—CDR≥2	<0.001**
				CDR1—CDR≥2	0.036*

Data are presented as mean (SD) or *n*.
* $p < 0.05$.
** $p < 0.01$.
AD = Alzheimer's disease; ANOVA = analysis of variance.

advanced AD, and the changes are closely correlated with the severity of disease. TD/AB among the proposed slow-to-fast power ratio parameters, and C3—C4 and P3—P4 among the proposed electrode pairs of interhemispheric alpha band coherence showed the best result. There is no significant difference between the power ratio method and the alpha band coherence method. Our study extends the notion of previous studies that EEG can differentiate AD patients from normal elderly or those with other types of dementia.[7—10]

The idea of slow-to-fast band power ratio is straightforward. Benefits of taking into consideration changes in both slow and fast waves simultaneously, while avoiding variation of absolute band power among individuals or on different machine settings, are obvious. Its significance in differentiating nondemented individuals from AD patients was documented by Bennys et al.[4] They also demonstrated an increased slow-to-fast band power ratio in advanced AD over all brain regions except the frontal area, which may be caused by contamination of EEG signal by eye movement. Based on the results of Bennys et al's work, we believe that power ratio can be used to reflect severity in AD during clinical practice. However, using multiple power ratio parameters in a single individual will make comparison across time or among individuals difficult. In addition, which frequency band should be included in power ratio analysis is still unknown.

In our study, we reduced the signal contamination of eye movement in frontal region by choosing epochs through direct visual inspection and used a single power ratio parameter in each participant for comparison. All proposed slow-to-fast power ratio parameters showed correlation with AD stages, reflecting a shift of dominant frequency to slower frequency in EEG of AD described in other literary works.[28,29] The finding that TD/AB showed the best result seems reasonable when we consider AD of all stages. This feature is consistent with the experience of traditional visual inspection of EEG.

Decrease of interhemispheric alpha band coherence in AD may suggest impaired interhemispheric dyssynchrony even in its early stage. On the basis of neurophysiology, dyssynchrony across the bilateral cerebral hemispheres probably arises from functional interruption in the CC. Decreased local EEG coherence in AD has been documented in a study, and decrease in alpha coherence is the most peculiar finding.[30] Findings of this study suggest decreased

corticocortical connections in AD patients. However, altered local alpha coherence gives no information on the CC neurophysiology. Another recent study of EEG coherence using a novel method, called global field synchronization (GFS), also confirmed the hypothesized disconnection syndrome in MCI and AD patients.[31] Changes in GFS values were observed in multiple frequency bands, with the most pronounced effects being found in the alpha band. Again, the CC may contribute only partly to the GFS.

In our study, decreased interhemispheric alpha band coherence has been remarkable across bihemispheric centroparietal region at the rest state. The distribution is roughly part of the default mode network (DMN) on functional MRI study in normal individuals.[32] DMN is believed to be related to episodic memory retrieval in normal individuals, and an altered pattern of DMN has been associated with MCI and AD.[33,34] The association between changes in interhemispheric alpha band coherence and DMN is speculated. Because P3—P4 alpha band coherence distinguishes Group CDR0.5 from Group CDR1 and C3—C4 alpha band coherence distinguishes Group CDR1 from Group CDR$\geq$2, we propose that interhemispheric dyssynchrony in AD follows a posterior to anterior fashion as disease progresses.

Our study has certain limitations. First, the number of participants in group CDR$\geq$2 is relatively small. The facts that early diagnosis of AD is the rule nowadays and multiple medications are often used in advanced AD made enrollment of patients with advanced AD in our study difficult. Second, special MRI techniques of the CC, such as voxel-based morphometry, diffusion-weighted imaging, and diffusion tensor imaging, were not used here to correlate with interhemispheric coherence. Most of our patients received routine axial brain CT or MRI scans for differential diagnosis of dementia. Third, aging effect on EEG was not excluded completely, although the difference in mean age between groups was rather small. MMSE scores were not used for correlation here because they should be adjusted according to patients' age and education to reflect the severity of dementia.[35] The rationality of direct comparison of MMSE scores among individuals is doubtful.

In conclusion, global slow-to-fast wave band power ratios and interhemispheric alpha band coherence are closely correlated with stages of AD. Decreased interhemispheric alpha band coherence may suggest functional disconnection of the CC. We recommend the use of TD/AB power ratio and averaged interhemispheric alpha band coherence in clinical practice to evaluate AD patients. Further investigations are needed to verify their role as longitudinal electrophysiologic biomarkers in AD.

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