Differences in Multimodal EEG and Clinical Correlations Between Alzheimer's Disease and Frontotemporal Dementia

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Research

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Abstract

Background. Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the two main types of dementia. We aim to investigate the difference between AD and FTD by use of multimodal EEG analyses. Additionally, the difference in correlations between EEG and clinical data was also investigated.

Methods. Thirty-one patients diagnosed with AD and 15 patients with FTD were recruited (2008.1-2020.2), along with 24 healthy controls. Clinical data were reviewed. EEG microstate analysis, spectral analyses, and connectivity analysis were performed.

Results. Microstate duration was increased in AD for microstate B and increased in FTD for microstate A compared to controls. Correspondingly, microstate C occurrence was decreased in both dementia groups, compared to control group. After divided into early onset and late onset AD, increased mean duration and reduced mean occurrence were observed in early onset AD, compared to late onset AD, with no significant difference in visual EEG score. CSF $A\beta_{42}$ was correlated to microstate B coverage in AD (r = -0.833, P = 0.010), and microstate D occurrence in FTD (r = 0.786, P = 0.021). ADL and MMSE were also related to visual EEG score and microstate, but for different variables in the two dementia groups. Spectral analysis revealed decreased power in 8-30 Hz and increased power in delta band in both dementia. AD had higher spectral power in the temporal region, compared to FTD. Reduced alpha and beta coherences were demonstrated in AD in bilateral frontal, fronto-temporal, and fronto-occipital connections, and in FTD in the right frontal and fronto-temporal connections.

Conclusions. Multimodal EEG analyses show different results between AD and FTD. Reduced coherence is across more brain areas in AD, including intra-anterior and anterior-posterior regions, compared to FTD, which only had frontal-temporal connectivity involved. Spectral analysis revealed a general EEG slowing. Increased microstate duration and decreased occurrence may be attributed to EEG slowing, for different classes in different types of dementia. Microstate may be more sensitive than visual EEG inspection. The correlations with clinical severity and biomarkers indicate that EEG is a potential biomarker for diagnosis and disease assessment.

Background

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60 to 80 percent of cases [1]. The most essential and often earliest clinical manifestation of AD is selective memory impairment. Accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neural tangles are causally related to neurodegenerative processes [2]. Aβ is thought to be the trigger of the disease process. Tau is a prerequisite for diagnosis of AD, but also can act independently without amyloid plaques to cause neurodegeneration in other disease, like frontotemporal dementia (FTD) [1]. FTD accounts for approximately 10% of all dementias [3], characterized by prominent changes in social behavior and personality or aphasia accompanied by pathological changes in the frontal and/or temporal lobes. TAR DNA-binding protein 43, tau, and fused-in-sarcoma protein were the three major

disease proteins in the neuropathology of FTD [4]. It can be difficult to distinguish clinically between AD and FTD, as AD may manifest with behavioral disturbances, and memory disturbances may manifest in FTD. Cerebrospinal fluid (CSF) biomarkers Aβ, total tau (t-tau), and phosphorylated tau (p-tau) have good accuracy in predicting AD [5, 6]. Low $A\beta_{42}$ levels, high concentrations of t-tau and p-ta, and the ratio of tau/$A\beta_{42}$ help to discriminate AD from healthy controls and other dementias [6, 7]. Moreover, electroencephalography (EEG) is increasingly considered to be a potential biomarker for dementia differentiation recently.

EEG is a relatively cost-effective, non-invasive technique. It provides in vivo data on electrical activity with high temporal resolution. Several characteristics of the EEG have been put forward as biomarkers in AD and might be useful in the early recognition of neural signatures of dementias and differential diagnosis [8]. EEG microstates are defined as quasi-stable brief patterns of coordinated electrical activity on the cortical surface, which was first described by Lehman D et al.[9, 10]. The topographies remained transiently stable for 60–150 ms before rapidly transitioning into a new state. These microstates have been shown to influence cognition and perception [11, 12]. Moreover, changes in consciousness state have been related to microstates changes [13]. Britz et al. reported that different cognitive functions were associated with specific microstates [14]. Previous studies have investigated microstates changes in cognitive disorders [10, 15–19]. More researches are required to get more convincing conclusions. Studies on the difference in microstate and the correlation between CSF biomarkers and microstates between AD and FTD are limited. The current study was set to investigate EEG microstate' characteristics in AD and FTD, along with EEG spectral and connectivity analysis, and the correlations between EEG and clinical data. The differences in EEG and clinical data were then analyzed to test the utility of EEG as a biomarker for clinical evaluations and differential diagnosis.

Methods

2.1 Patients

The study population consisted of patients with cognition impairment in Peking Union Medical College Hospital between June 2015 and October 2019. Patients were diagnosed based on information obtained from an extensive clinical history, physical examinations, and excluded mood disorders and schizophrenia. Clinical assessment scales included the Mini Mental State Examination (MMSE) [20], the Montreal Cognitive Assessment (MoCA) [21], and activities of daily living (ADL) score. Patients who had complications of other neurological or psychiatric disorders, and severe systemic diseases that may influence the cerebral nervous system, were also excluded. For FTD diagnosis, the Neary and Snowden et al. or the Mckhann et al. criteria were employed [22, 23]. The National Institute on Aging-Alzheimer's Association (NIA-AA) criteria were used to diagnose patients with dementia due to AD [24]. Dementia diagnoses were performed independently by two experienced clinicians.

2.2 Biomarkers assessments

CSF t-tau, p-tau and $A\beta_{42}$ were measured using an enzyme-linked immunosorbent assay (Fujirebio, Ghent, Belgium). Samples were handled by experienced senior laboratory technicians blinded to patients' information.

2.3 EEG examination and data preprocessing

EEG monitoring was performed using a 19-channel video-EEG monitoring system (NIHON KOHDEN, EEG-1200C). Recording electrodes were placed according to the international 10–20 system with a sampling frequency of 500 Hz. The degree of visual EEG abnormality was scored as follow: (1) 0 = normal; (2) 1 = mild abnormal: mild asymmetry background activities (< 50%), or irregular alpha rhythm, or excess beta activities with amplitude more than 50 μV, or excess theta activities mainly over the frontal region, or mild excess delta activities; (3) 2 = moderate abnormal: 7–8 Hz alpha rhythm, or no certain occipital alpha rhythm, asymmetry (> 50%), or moderate excess delta activities, or sporadic epileptiform discharge; (4) 3 = severe abnormal: low-voltage or electric silence, or periodic waves, or delta or theta activities are the dominated activities in the background, or rhythmic epileptiform discharge.

EEG data without excessive noise or artifacts from subjects were preprocessed with EEGLAB (R13_6_5b) in MATLAB R2017a. An independent component analysis was used for further artifact removal. Data were band-pass filtered into the range of 0.1–40 Hz and were recomputed against the average reference. Resting state EEG data were split into non-overlapping epochs of two seconds. Patients with less than 25 epochs were excluded. It resulted in 27 patients with AD, 21 with FTD, and 24 age-matched healthy controls (HC) for further analyses. Frequency spectral and EEG coherence analyses were performed in the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz).

2.4 Microstate analysis

The microstate analysis was conducted using the EEGLAB plugin Microstate 0.3 in MATLAB R2017a. EEG data were further band-pass filtered into the 1–20 Hz range for microstate analysis. The overall variances across all electrodes were quantified by measuring the global field power (GFP). EEG topographies tend to be stable during periods of high GFP [9]. The scalp maps at the momentary peaks of the GFP were extracted and clustered using a modified k-means spatial cluster analysis [18]. Previous studies revealed that the optimal number of microstate classes belonged to 2–6 classes (mean 3.7 classes), according to the agglomerative clustering procedure [25–27]. The current study used a cross-validation criterion and the Krzanovski-Lai criterion by the Cartool software [28] to determine the optimal number of microstate classes, testing the entire range of 1 to 12 classes.

The cluster analysis resulted in mean microstate topographies for each class. Group model maps were created based on individual model maps. The resulting class-labeled group microstate maps were then fit back to the templates to assign model maps to each participant.

Microstate topographies of each microstate class were compared between groups using a non-parametric randomization test (TANOVA, topographical analysis of variance), as implemented in the Ragu software [29]. Microstate duration (ms), frequency of occurrence of each microstate (/s), the

percentage of total analysis time covered by each microstate (%), and transition probabilities were calculated.

2.5 Frequency spectral analysis

Frequency spectral analysis was performed using a fast Fourier Transform (FFT, 1000-point) algorithm. The absolute power spectral density (PSD, dB, $10\log_{10}(V^2/Hz)$) for each channel based on the periodogram was calculated. Relative PSD (rPSD) was computed by normalizing the total power in the whole frequency range. The absolute and relative PSDs were averaged across channels within groups to obtain a measure for global comparisons between groups in each frequency band.

2.6 EEG connectivity analysis

The EEG coherence analysis was conducted in MATLAB R2017a. EEG coherence assesses the linear relationship between two signals at each frequency band, derived by FFT [30]. High coherence reflects a linear correlation between two cortical areas, indicating functional coupling between these cortical areas. EEG coherences were calculated for the twenty intrahemispheric electrode pairs Fp1-F3, Fp2-F4, F3-C3, F4-C4, C3-P3, C4-P4, P3-O1, P4-O2, O1-T5, O2-T6, T5-F7, T6-F8, F7-Fp1, F8-Fp2, F7-C3, F8-C4, T5-C3, T6-C3, Fp1-O1, Fp2-O2, and five interhemispheric electrode pairs F3-F4, T5-T6, C3-C4, P3-P4, O1-O2 in each frequency band. Coherence values were log transformed prior to statistical analyses to approximate the normal distribution. Two-tailed unpaired t-tests were used for group comparisons. To compensate for the effects of multiple testing, a Bonferroni correction was applied for each group of tests in each frequency band. The p-value of group comparisons in EEG coherence was multiplied by 25 (20 + 5 electrode pairs).

2.7 Statistics analyses

Relatively symmetrical data distribution of microstate, rPSD and absolute PSD was shown in the boxplots (Supplementary 1). Although there were outliers, it intuitively conformed to the normal assumption. Multivariate analysis of variance (MANOVA) was therefore performed to assess group differences of microstate variables. When overall significant effects were found, univariate ANOVAs followed by post hoc analyses with Bonferroni correction were performed. A Spearman correlation test was used for the correlation analysis. Continuous non-normal data were examined using a Kruskal-Wallis test for group comparisons. Chi square test was used for group comparison of categorical data. The level of significance was set at 0.05. Statistics analyses were performed using IBM SPSS Statistics v22.

Results

Clinical and demographics data between dementia and control groups were presented in Table 1. HC, AD and FTD participants had no difference in age. FTD group had higher proportion of male, and AD group had more females than males. The difference in gender between three groups was not significant. FTD group was significantly less impaired in terms of MMSE than the AD group ($P = 0.015$). Additionally, the two dementia groups did not differ significantly in terms of dementia duration, ADL, and MoCA. The

percentage of patients taking cholinesterase inhibitors (AChEIs) did not differ between the two dementia groups.

CSF biomarker tests were performed in 8 patients with AD and 8 with FTD. As expected, AD group had lower $A\beta_{42}$ and higher levels of t-tau and p-tau than FTD group. The differences were not significant. The ratio of p-tau to $A\beta_{42}$ was shown to be significantly higher in AD, compared to FTD ($P = 0.028$). 44.4% (8/18) subjects in AD group were APOE ε4 carriers, 11.1% (2/18) had two copies. For FTD group, 50% (4/8) of patients were carriers of the APOE ε4 genotype, and no one was APOE ε4 homozygotes.

Overall, 18 AD patients had normal EEG results, 5 had visual EEG scores of 1, and 16 had scores of 2. For FTD group, eight patients scored 0, 3 scored 1, and 4 scored 2. No participant had severe abnormal EEG results. The main EEG visual signs were abnormal or disappeared posterior dominant alpha rhythm and anterior dominant or diffuse slowing. Chi test showed no significant group difference in visual EEG severity.

Table 1
Demographic and clinical data in dementia and control groups.

	HC (n = 24)	AD (n = 39)	FTD (n = 15)	P
Age (mean, range)	57 (44–74)	59 (41–74)	60 (47–74)	0.523
Gender (M:F)	14:15	16:23	10:6	0.392
Disease course (mean, range, /y)	--	3.3 (0.25-13)	2.7 (0.5-6)	0.603
AChEI	--	19 (48.7%)	5 (31.3%)	0.37
MMSE (mean, range	--	12 (1–27, n = 38)	20 (6–27, n = 9)	0.015
MoCA (mean, range)	--	13 (6–21, n = 10)	18 (12–19, n = 6)	0.093
ADL (mean, range)	--	36 (20–54, n = 14)	25 (0–39, n = 6)	0.274
CSF biomarkers	--	n = 8	n = 8	0.065
(pg/ml, mean, range)		420 (281–550)	658 (287–870)	
$A\beta_{42}$				
T-tau		445 (94-1573)	261 (117–587)	0.505
P-tau		69.2 (40.9–122)	47.3 (26.7–71)	0.13
T-tau/$A\beta_{42}$		1.18 (0.20–4.59)	0.46 (0.15–1.09)	0.083
P-tau/$A\beta_{42}$		0.18 (0.11–0.36)	0.09 (0.03–0.20)	0.028
APOE ε4 0 1 2	--	10/18 (55.6%)	4/8 (50%)	0.692
		6/18 (33.3%)	4/8 (50%)	
		2/18 (11.1%)	0	
Visual EEG score	24 (100%)	18 (46.2%)	8 (53.3%)	0.459
0		5 (12.8%)	3 (20%)	
1		16 (41%)	4 (26.7%)	
2		0	0	
3				

HC: healthy controls. AD: Alzheimer disease; FTD: frontotemporal dementia.

3.1 EEG Microstates

The median optimal number of microstate classes in AD and control groups was four, while the median in FTD was five. The overall median optimal number in the entire dataset was four. The number of microstate classes was therefore set to four for further analyses, which was also commonly used in most researches, labeled as A, B, C, and D [26, 31]. The mean global explained variance (standard deviation, SD) of four microstates in each group was 79.8% (3.3%) for controls, 74.1% (2.3%) for AD, 77.0% (4.4%) for FTD.

Across all microstate classes, the mean microstate duration was 68.1 ms in controls, 75.1 ms in AD patients, and 76.6 ms in FTD patients. The mean duration in dementia groups tended to be increased compared controls, without statistical significance (Table 2). The mean number of unique microstate occurrence per second was reduced in AD, compared to HC ($P = 0.0021$).

Table 2
EEG microstate data in dementia and control groups.

Duration /ms (Std)	HC (n = 24)	AD (n = 39)	FTD (n = 15)	ANOVA (2,75)	P_{HC-AD}	P_{AD-FTD}	P_{HC-FTD}
A	64.7 (8.4)	69.0(7.2)	74.9 (14.6)	F = 5.447 0.006	0.247	0.127	0.004
B	65.1 (7.4)	73.2 (11.5)	70.8 (16.1)	F = 3.728 0.029	0.024	1	0.401
C	71.6 (17.9)	74.9 (14.5)	75.1 (24.2)	F = 0.300 0.742			
D	63.4 (14.9)	74.8 (20.5)	74.2 (18.8)	F = 3.011 0.055			
Mean Duration	68.7 (8.9)	75.1 (10.2)	76.6 (14.5)	F = 3.418 0.038	0.076	1	0.087
Occurrence /s (Std)	HC	AD	FTD	ANOVA (2,75)	P_{HC-AD}	P_{AD-FTD}	P_{HC-FTD}
A	3.74 (0.81)	3.41 (0.74)	3.64(0.94)	F = 1.398 0.254			
B	3.89 (0.82)	3.50(0.53)	3.57(0.70)	F = 2.696 0.074			
C	4.35 (0.67)	3.66(0.70)	3.33(0.43)	F = 13.420 < 0.001	< 0.001	0.285	< 0.001
D	3.22 (0.65)	3.34(0.75)	3.39(1.10)	F = 0.227 0.798			

HC: healthy controls. AD: Alzheimer disease; FTD: frontotemporal dementia.

Duration /ms (Std)	HC (n = 24)	AD (n = 39)	FTD (n = 15)	ANOVA (2,75)	P_{HC-AD}	P_{AD-FTD}	P_{HC-FTD}
Mean Occurrence	3.80 (0.40)	3.47(0.45)	3.48(0.55)	F = 4.221 0.018	0.021	1	0.111
Coverage (Std)	HC	AD	FTD	ANOVA (2,75)	P_{HC-AD}	P_{AD-FTD}	P_{HC-FTD}
A	0.24 (0.062)	0.23(0.044)	0.26(0.068)	F = 2.190 0.119			
B	0.25 (0.063)	0.25(0.043)	0.24(0.059)	F = 0.083 0.921			
C	0.30 (0.074)	0.27(0.071)	0.24(0.071)	F = 3.200 0.046	0.336	0.569	0.045
D	0.21(0.078)	0.25(0.100)	0.25(0.12)	F = 1.526 0.224			
HC: healthy controls. AD: Alzheimer disease; FTD: frontotemporal dementia.							

Group microstate maps were illustrated in Fig. 1. TANOVAs for each microstate class showed that the AD maps were different from controls maps for class B, FTD maps were different from AD and control maps for class A. There were no significant group differences in model map topography for class C and D.

Microstate analysis results were presented in Table 2 and Fig. 2. There're no significant differences between AD and FTD groups. Compared to controls, microstate A duration in FTD and microstate B durations in AD were increased. Microstate C occurrence was reduced in both dementia groups compared to controls, with no significant difference between AD and FTD groups. Coverage of microstate C was reduced in FTD, compared to controls. The transition to microstate C from A was reduced in AD group, compared to control group (0.081 vs 0.097, $P = 0.031$). Other microstate transition probabilities were shown no group difference (Supplementary 2).

3.2 Relation between microstate and clinical data

We found that the degree of visual EEG abnormality was negatively correlated to MMSE score ($r = -0.363$, $P = 0.025$) in AD, and positively correlated to the ratio of t-tau to $A\beta_{42}$ ($r = 0.756$, $P = 0.030$) and the ratio of

p-tau to $A\beta_{42}$ (r = 0.756, P = 0.030).

In the AD group, microstate B coverage was negatively correlated to the concentration of CSF $A\beta_{42}$ (r = -0.833, P = 0.010), and was positively correlated to the ADL score (r = 0.691, P = 0.006). Additionally, CSF $A\beta_{42}$ concentration was negatively related to transition probability from A to B (r = -0.714, P = 0.047), and p-tau concentration was negatively related to transition probability from A to C (r = -0.738, P = 0.037). MMSE score was negatively related to microstate C duration (r = -0.357, P = 0.028), and positively related to microstate A occurrence (r = 0.360, P = 0.026) and contribution A (r = 0.363, P = 0.025).

In the FTD group, the CSF $A\beta_{42}$ level was positively related to microstate D occurrence (r = 0.786, P = 0.021) and transition probability from D to A (r = 0.714, P = 0.047). There was a negative correlation between the mean occurrence and CSF t-tau concentration (r = -0.714, P = 0.047). ADL was negatively related to transition probability from D to B (r = -0.886, P = 0.019).

The microstate variables were not significantly correlated to MoCA scores, ratios of tau to $A\beta_{42}$, the number of APOE ε4 copies in both groups. The spearman correlations with a relatively high significance level (P < 0.040) were illustrated in Fig. 3. The correlations with p-value > 0.040 required a larger sample to be confirmed.

3.3 EEG microstate in early and late onset AD

Thirty-nine patients with AD were divided into two subgroups: early onset AD (EOAD, age < 65, n = 30) and late onset AD (LOAD, age > = 65, n = 9). Demographics data and clinical assessment scales were presented in Table 3. There're no significant differences between two subgroups in termS of gender, MMSE, MoCA, ADL, and visual EEG score.

Table 3
Clinical and EEG microstate data in early and late onset AD and age matched controls

	HC		AD		
	Younger(1) n = 16	Older(2) n = 8	Younger(3) n = 30	Older(4) n = 9	
Age (mean, range)	53 (44–62)	71 (68–74)	55 (41–64)	69 (65–75)	
Gender (M:F)	5:3	9:12	11:19	5:4	P = 0.525
Disease course (mean, range, /y)			3.4(0.25-13.0)	3.0(1.0–6.0)	P = 0.844
AChEI			16:23	3:6	P = 0.726
MMSE (mean, range			12(1–25)	14(3–27)	P = 0.493
MoCA (mean, range)			13(8–21)	11(6–15)	P = 0.831
ADL (mean, range)			33(20–50)	35(22–54)	P = 0.524
Visual EEG score			0 (n = 13) 1 (n = 3) 2 (n = 14)	0 (n = 5) 1 (n = 2) 2 (n = 2)	P = 0.327
Duration /ms (Std)	1	2	3	4	ANOVA (3,59)
A	64.7 (9.1)	64.9 (6.7)	70.3 (6.9)	64.9 (6.7)	F = 2.913 P = 0.042
B	64.6 (8.1)	66.45 (5.3)	75.7 (10.7)	64.9 (10.6)	F = 7.042 P < 0.001 P_{1-3}=0.001, P_{3-4} =0.024
C	66.8 (9.7)	86.0 (28.6)	78.3 (13.9)	63.5 (10.5)	F = 3.322 P = 0.026
D	63.0 (14.3)	64.8 (17.9)	77.5 (21.8)	65.7 (12.5)	F = 2.999 P = 0.038 P_{1-3}=0.043
Mean Duration	66.9 (5.8)	74.1 (14.4)	77.8 (9.3)	66.0 (7.9)	F = 7.401 P < 0.001 P_{1-3}=0.001, P_{3-4} =0.005
Occurrence /s (Std)	1	2	3	4	ANOVA (3,59)

	HC		AD		
	Younger(1) n = 16	Older(2) n = 8	Younger(3) n = 30	Older(4) n = 9	
A	3.82 (0.64)	3.52 (1.23)	3.18 (0.57)	4.19 (0.73)	F = 6.899 P < 0.001 P_{1-3}=0.008, P_{3-4} =0.002
B	3.95 (0.79)	3.72 (0.96)	3.35 (0.47)	3.99 (0.43)	F = 4.316 P = 0.008 P_{1-3}=0.032
C	4.31 (0.72)	4.47 (0.54)	3.62 (0.71)	3.79 (0.70)	F = 4.961 P = 0.004 P_{1-3}=0.005
D	3.38 (0.65)	2.75 (0.38)	3.21 (0.76)	3.75 (0.59)	F = 1.746 P = 0.167
Mean Occurrence	3.87 (0.31)	3.61 (0.59)	3.34 (0.36)	3.93 (0.46)	F = 9.435 P < 0.001 P_{1-3}<0.001, P_{3-4} =0.001
Coverage (Std)	1	2	3	4	ANOVA (3,59)
A	0.25 (0.06)	0.22 (0.07)	0.22 (0.04)	0.26 (0.04)	F = 3.2 P = 0.030
B	0.25 (0.07)	0.25 (0.06)	0.25 (0.04)	0.25 (0.04)	F = 0.16 P = 0.923
C	0.28 (0.07)	0.35 (0.07)	0.28 (0.07)	0.24 (0.05)	F = 1.867 P = 0.145
D	0.22 (0.08)	0.18 (0.06)	0.25 (0.11)	0.24 (0.06)	F = 0.999 P = 0.400

Microstate B and mean durations were significantly increased, and microstate A and mean occurrences were decreased in EOAD, compared to age matched controls and LOAD. Additionally, increased microsite D duration and reduced mean occurrences and occurrences for microstate B and C were revealed in EOAD, compared to controls. A preferential transition to microstate A from D was revealed in LOAD, compared to age matched controls (0.090 vs 0.047, P = 0.02). There are no significant differences by post hoc analyses in other variables.

3.4 Frequency spectral analysis

The across-channel grand average of global EEG PSD in each group was illustrated in Fig. 4A&C. Means of the absolute PSD in control group were higher compared to dementia groups in alpha and beta bands

with significance (Table 4 & Fig. 4A). As shown in the Fig. 4C and Table 4, the global relative PSD in dementia groups was significantly reduced in alpha and beta bands, and increased in delta bands, compared to controls. The topographies calculated from the global absolute and relative PSDs over frequency bands were illustrated in Fig. 4B&D. The topographies revealed that PSD changes were presented in the whole scalp regions.

There was no significant difference between the two dementia groups for both absolute and relative PSDs. The rPSD of three separated scalp regions (anterior: Fp1, Fp2, F3, F4, C3, C4, Fz, Cz; posterior: P3, P4, O1, O2, Pz; temporal: F7, F8, T3, T4, T5, T6) was calculated and compared among groups. The rPSD in each region in dementia groups was markedly reduced in alpha and beta bands and increased in theta band, compared to controls. Moreover, the rPSD level in the temporal region in AD groups was significantly higher than rPSD level in FTD groups in delta band ($P = 0.034$) (Supplement 3).

Table 4
Power spectral density in dementia and control groups

PSD (dB) (mean, std)	HC	AD	FTD	MANOVA (2, 75)	P_{HC-AD}	P_{AD-FTD}	P_{HC-FTD}
1-4Hz	2.11 (7.13)	1.51 (2.94)	0.65 (3.22)	F = 0.454 0.637			
4-8Hz	-0.55 (7.49)	5.22(2.77)	-2.90(2.87)	F = 1.124 0.330			
8-12Hz	2.77 (7.75)	-3.25 (3.41)	-3.29(3.79)	F = 11.199 < 0.001	< 0.001	1	0.002
12-30Hz	-5.27 (7.51)	-10.75(2.47)	-10.82 (2.47)	F = 11.661 < 0.001	< 0.001	1	0.002
rPSD (%, mean, std)	HC	AD	FTD	MANOVA (2,75)	P_{HC-AD}	P_{AD-FTD}	P_{HC-FTD}
1-4Hz	1.02 (0.4)	2.06 (0.58)	1.66 (0.79)	F = 23.745 < 0.001	< 0.001	0.079	0.004
4-8Hz	1.24 (0.7)	1.35 (0.37)	1.28 (0.62)	F = 0.324 0.724			
8-12Hz	1.94 (0.73)	1.00 (0.66)	1.22(0.92)	F = 12.398 < 0.001	< 0.001	0.946	0.012
12-30Hz	0.32 (0.10)	0.19 (0.11)	0.21(0.09)	F = 12.081 < 0.001	< 0.001	1	0.005

3.5 Connectivity analysis

Mean coherence data in all groups were presented in Supplementary 4. The significant coherence changes were illustrated in Fig. 4. After application of the Bonferroni correction, there was a significant reduction of alpha and beta coherences for frontal region (Alpha: P_{Fp1-F3} <0.001, P_{Fp2-F4} <0.001; Beta: P_{Fp1-F3} <0.001, P_{Fp2-F4} <0.001), remote electrode pairs (Alpha: P_{Fp1-O1} = 0.002; Beta: P_{Fp1-O1} = 0.002, P_{Fp2-O2} = 0.005) and fronto-temporal electrode pairs (Alpha: P_{Fp1-F7} = 0.026, P_{Fp2-F8} = 0.009; Beta,

P_{Fp2-F8} = 0.006) in AD group, compared to control group. Additionally, coherence for the electrode pair F3-C3 was decreased in beta (P_{F3-C3} = 0.042) and theta bands (P_{F3-C3} = 0.027). Alpha coherence reductions were also shown in pairs F8-C4 (P_{F8-C4} = 0.042).

In the FTD group, alpha and beta coherences for the electrode pair Fp2-F8 were significantly decreased (Alpha: P_{Fp2-F8} = 0.015; Beta, P_{Fp2-F8} = 0.018), compared to controls. There was a reduction of beta coherence for the Fp2-F4 pair (P_{Fp2-F4} = 0.043). There're no significant coherence differences between AD and FTD groups.

Discussion

The current study investigated microstate's changes, power spectral density, and EEG connectivity in Alzheimer's disease and frontotemporal dementia. The correlation between EEG microstate and clinical severity and CSF biomarkers in the two dementia groups was also analyzed.

Cognitive scores and CSF biomarkers were different between FTD and AD as expected. Previous study reported that FTD was associated with greater impairments in ADLs than AD [32]. We found that the two groups had similar ADL scores, but significant higher MMSE score in FTD than AD were revealed. It indicated that FTD needs a higher MMSE score to get the same ADL with AD. The present study revealed lower $A\beta_{42}$ levels and higher tau levels in AD than FTD. The ratio of p-tau to $A\beta_{42}$ was significantly increased in AD compared to FTD. These results are in line with previous studies [5, 33].

The visual EEG severity was negatively correlated to the MMSE score. Previous studies reported the positive correlation between visual EEG scores and clinical severity [34, 35], which was also confirmed in the present study. We didn't find the correlation between CSF biomarkers and cognition scales, consistent with earlier study [36]. However, visual EEG scores were positively related to the ratios of t-tau to $A\beta_{42}$ and p-tau to $A\beta_{42}$ in AD group.

EEG microstate topographies in AD and FTD significantly deviate from controls. Microstate B map was different between AD and control, while class A map differed between FTD and control. Previous studies revealed very different results. Two studies revealed no topography differences between AD and controls [19, 37], but topographies of classes B and C in semantic dementia, a variant of FTD, were different from maps in control [37]. Schumacher et al. reported that all five classes (A-E) maps were different between AD and control groups [10]. Another study reported that AD had different topographies of classes A and D compared to control group [15].

Microstate variables changes were also different in FTD and AD. We found increased durations of class B in AD and class A in FTD. Microstate C occurrence was decreased in both dementia groups. Some studies revealed that microstate durations were decreased in patients with dementia or cognitive impairment [18, 19, 38, 39]. However, more recent studies reported increased durations [10, 15, 16], and reduced occurrences [10, 15] in AD. Consistent with the atter researches, increased durations were also

demonstrated in our study. The increased duration and reduced occurrence reflect the loss of microstate dynamics, which may be related to the EEG slowing [10].

Moreover, after divided into EOAD and LOAD, marked increased microstate duration and decreased occurrence for class A-C were observed in EOAD, as well as mean duration and occurrence. Earlier studies reported that visual EEG abnormalities were more severe in EOAD [34, 40]. Since visual EEG results showed no difference between the two subgroups, our results indicate that loss of microstate dynamics may be more sensitive than visual EEG slowing.

Microstate B was significantly different in AD for topography and duration, and correlated to CSF $A\beta_{42}$ and ADL score, with a high spearman's rank coefficient. These class B alterations were not presented in FTD. Previous studies revealed that microstate B was correlated with the bilateral occipital cortex [14]. In our study, EEG connectivity analyses demonstrated that fronto-occipital far coherence in alpha and beta bands were reduced in AD compared to controls, which was not detected in FTD group. AD patients have more atrophy in the occipital gyrus and precuneus than FTD patients [41]. The reduced fronto-occipital far coherence and prefer occipital atrophy may partially explained the difference of microstate B alteration between AD and FTD. For microstate A change in FTD, class A was correlated with superior and middle temporal lobe [14], consistent with the frontotemporal pathologic abnormalities in FTD.

Microstate correlation analysis demonstrated that microstate C duration was negatively correlated to MMSE score, while a positive correlation was revealed in microstate A occurrence and MMSE score in AD. We also found that CSF biomarkers were related to microstate. $A\beta_{42}$ level was related to microstate B coverage positively in AD and to microstate D occurrence negatively in FTD. CSF $A\beta_{42}$ and tau have high diagnostic accuracy. The correlation between biomarkers and EEG microstate and visual scores indicated that EEG could be a potential diagnostic method for dementia. Since EEG is a noninvasive and convenient examination, the diagnostic value of EEG for dementia is worthy of further work.

The spectral analysis demonstrated that FTD and AD had lower rPSD in alpha and beta bands, higher rPSD in delta bands, indicating the general EEG was slowing. It further suggests that loss of microstate dynamics may be attributed to EEG slowing. A diffuse slowing with reduction of power in faster rhythm and increased power in slow rhythm have been observed in AD [42, 43] and FTD [44]. But the power in delta band was lower in FTD than AD [44, 45]. The rPSD in slow rhythm tended to be lower in FTD than AD in the current study, with no significance. But a significant temporal delta power increase was detected in AD compared to FTD, indicating functional temporal impairment may be more severe in AD. Our study didn't evaluate memory function but revealed that AD had lower MMSE than FTD.

Finally, we found that AD had more reduced coherence, compared to FTD. Fronto-temporal coherence in alpha and beta bands was reduced in the left hemisphere in FTD, but bilateral sides in AD. Moreover, AD had reduced fronto-central, fronto-occipital and temporal-central connectivity in alpha, beta and delta bands, compared to controls. The previous study demonstrated that major coherence reductions were in the alpha band, while delta coherence results were conflicting [8]. Caso et al. revealed decreased fast

rhythm values in central/temporal regions in AD, compared to FTD, by use of sLORETA [45]. The findings in our study were consistent with the earlier studies. The frontal lobe and corpus callosum were vulnerably damaged [46], which may partially explained reduced connectivity to frontal and central areas in AD.

Limitations

The present study has some limitations. First, part of patients with dementia were taking AChEIs which can influence EEG data [47]. There was no difference in the number of patients taking AChEIs between FTD and AD. However, group comparisons between dementia and control groups may be required further work to confirm without AChEI influence. In addition, the sample size of patients who had CSF biomarkers was small. Therefore, the correlation analysis results with low spearman's rank coefficient and significance level were not strong enough. A larger sample will draw more convincing conclusions.

Conclusions

The current study demonstrated that EEG data of AD and FTD were different by use of microstate analysis, spectral analysis, and coherence analysis. More EEG changes and more areas involved were detected in AD, compared to FTD. The two disorders both had correlations with clinical severity and biomarkers, but for different microstate variables. It indicated that EEG data could be a potential marker for dementia diagnosis and clinical severity evaluations. However, EEG analyses can produce numerous variables. Some variables, like topography, had poor consistency, while some variables, like durations, which were not specific to one class, showed the similar characteristics in recent studies. More work to identify which EEG variables are useful for disease diagnosis and evaluations is required.

Abbreviations

amyloid beta	Aβ
Alzheimer disease	AD
activities of daily living	ADL
Cerebrospinal fluid	CSF
electroencephalography	EEG
early onset Alzheimer disease	EOAD
fast Fourier Transform	FFT
frontotemporal dementia	FTD
global field power	GFP
healthy controls	HC
late onset Alzheimer disease	LOAD
Multivariate analysis of variance	MANOVA
Mini Mental State Examination	MMSE
Montreal Cognitive Assessment	MoCA
phosphorylated tau	p-tau
power spectral density	PSD
standard deviation	SD
total tau	t-tau
topographical analysis of variance	TANOVA

Declarations

Ethics Statement and consent to participate

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was carried out in accordance with the recommendations of the Ethics Committee of Peking Union Medical College Hospital with written informed consent from all subjects in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Because this is a retrospective study, and there were no interventions performed outside routine clinical care for all patients. No formal research ethics approval was required.

Consent for publication

Written informed consent was obtained from all the participants for the publication of this article.

Competing Interest

The authors declare that they have no competing interests.

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Availability of data and materials

The data used during the current study are available from the corresponding authors on reasonable request.

Authors' contributions

NL analyzed and interpreted the data, wrote the original manuscript. JG analyzed the data and diagnosed the patients, revised the manuscript. QL and CLY conceived the study, revised the manuscript. CHM acquired the data, diagnosed the patients. HYS performed EEG recordings, analyzed visual EEG data. All authors read and approved the final manuscript.

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Figures

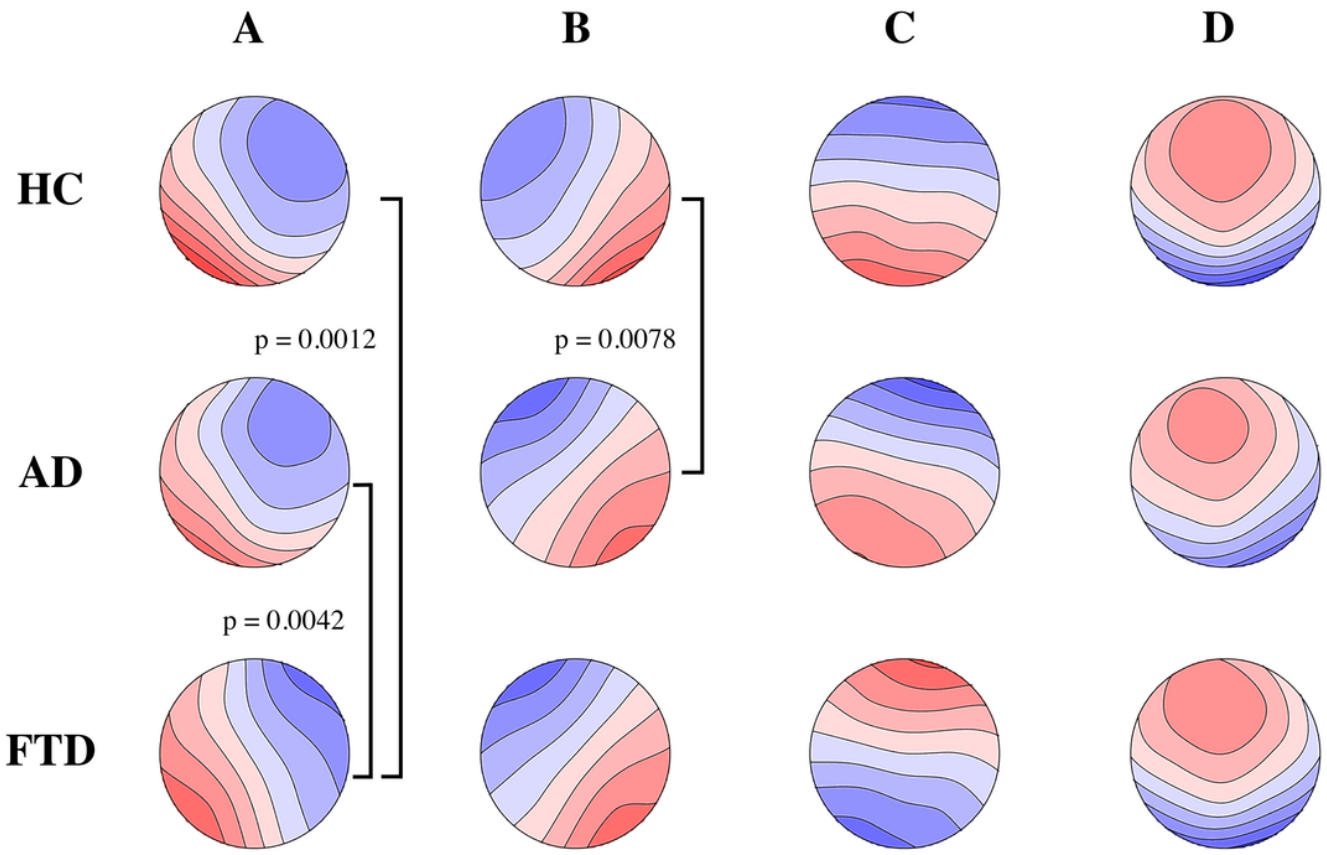

Figure 1

Microstate class topographies. Group comparisons used by TANOVA. Significant p-values after Bonferroni correction are illustrated. FTD had different microstate A map from HC and AD. Microstate B map was different in AD, compared to HC. FTD: frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls.

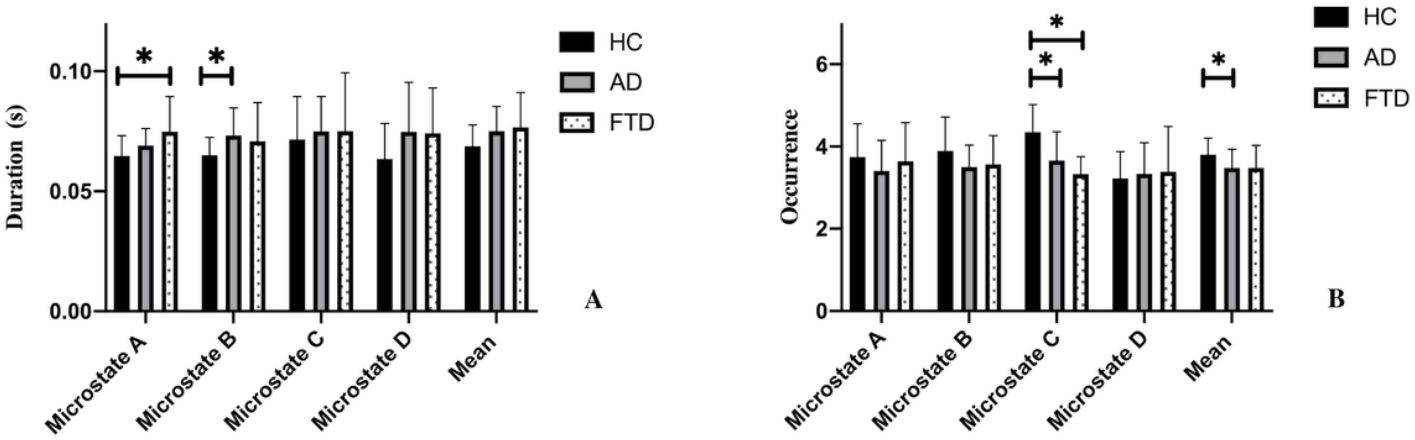

Figure 2

Microstate characteristics. Group comparison of microstate duration (A) and occurrence (B). P-values result from pairwise post hoc tests following univariate ANOVAs. *p<0.05. FTD: frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls.

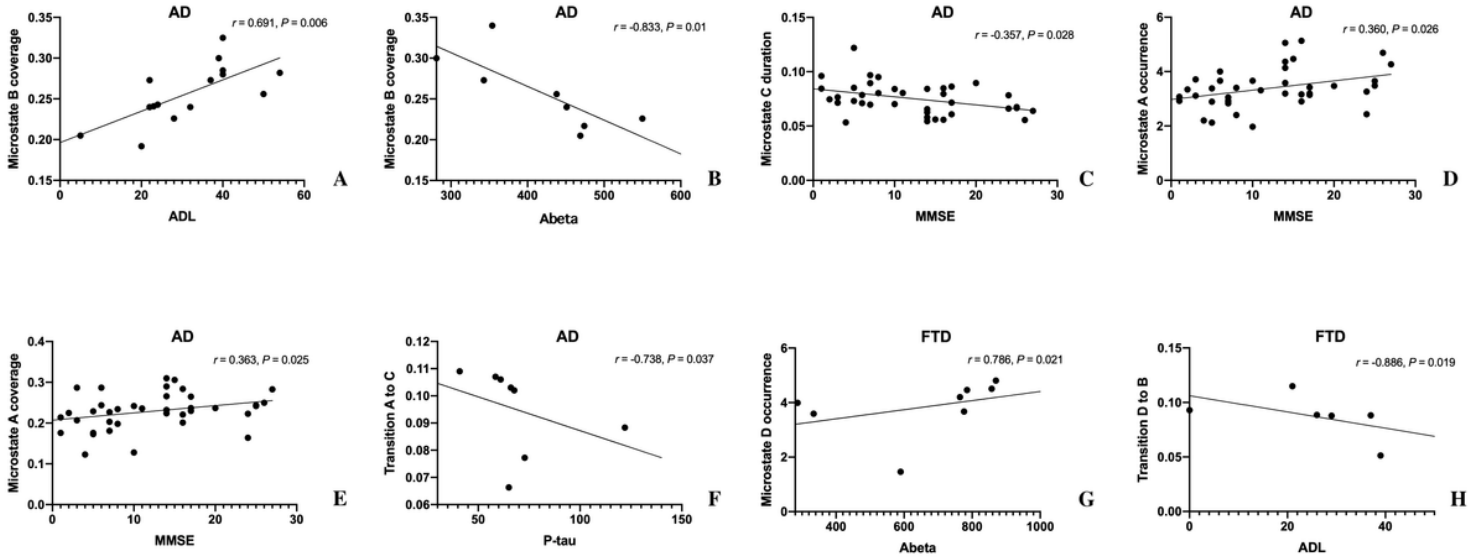

Figure 3

Correlations between microstate and clinical data. Spearman's correlations between microstate variables and clinical data, including cognitive scores and cerebrospinal fluid biomarkers levels. FTD: frontotemporal dementia; AD: Alzheimer's disease; ADL: activities of daily living; MMSE: Mini Mental State Examination.

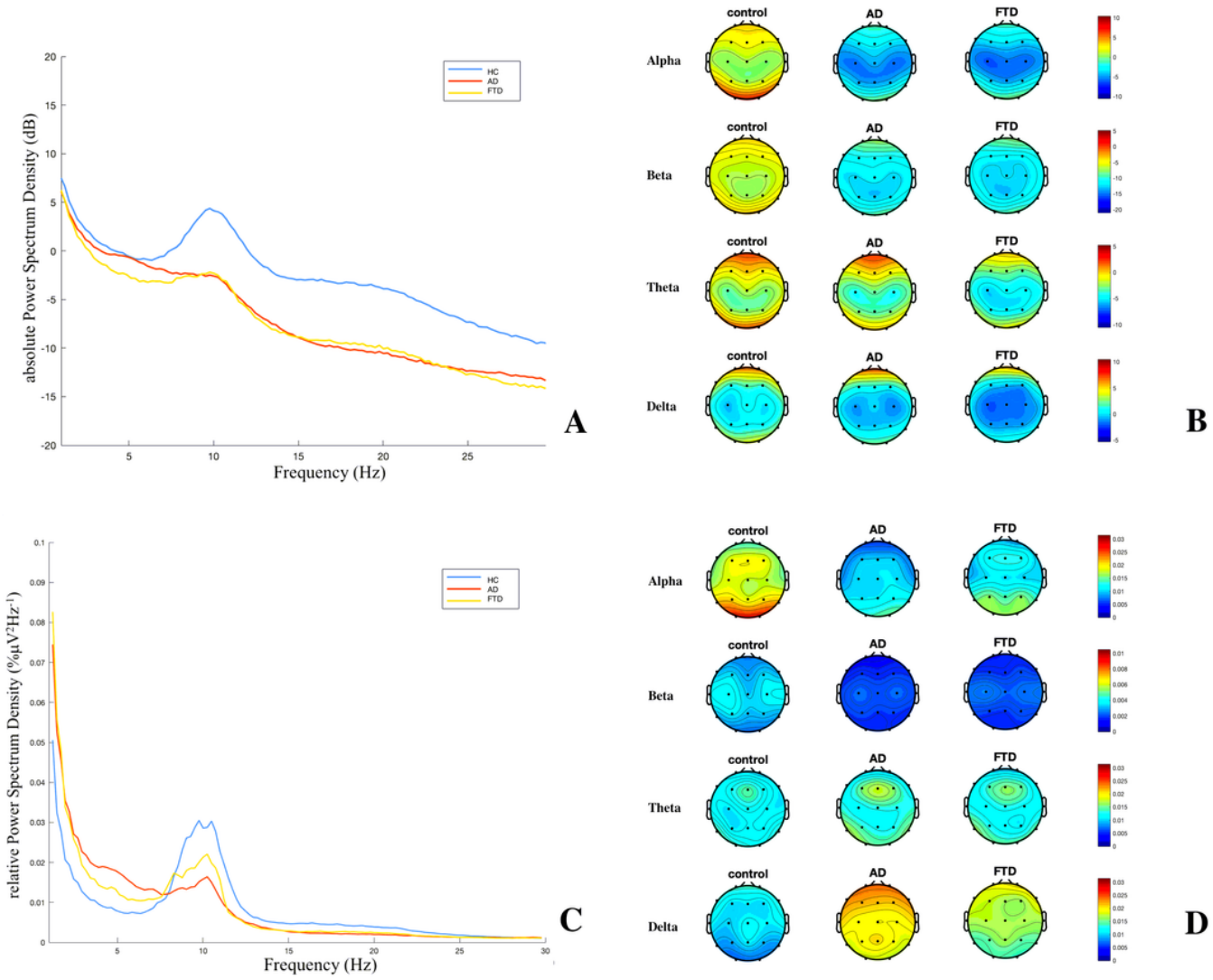

Figure 4

Frequency spectral analysis. Across-channels grand average of absolute power spectral density (PSD, dB) and relative PSD (%μV2Hz-1) over with frequency for each group are illustrated. The topographies were calculated from PSD in each frequency band. A general slowing EEG was presented in both FTD and AD groups. FTD: frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls.

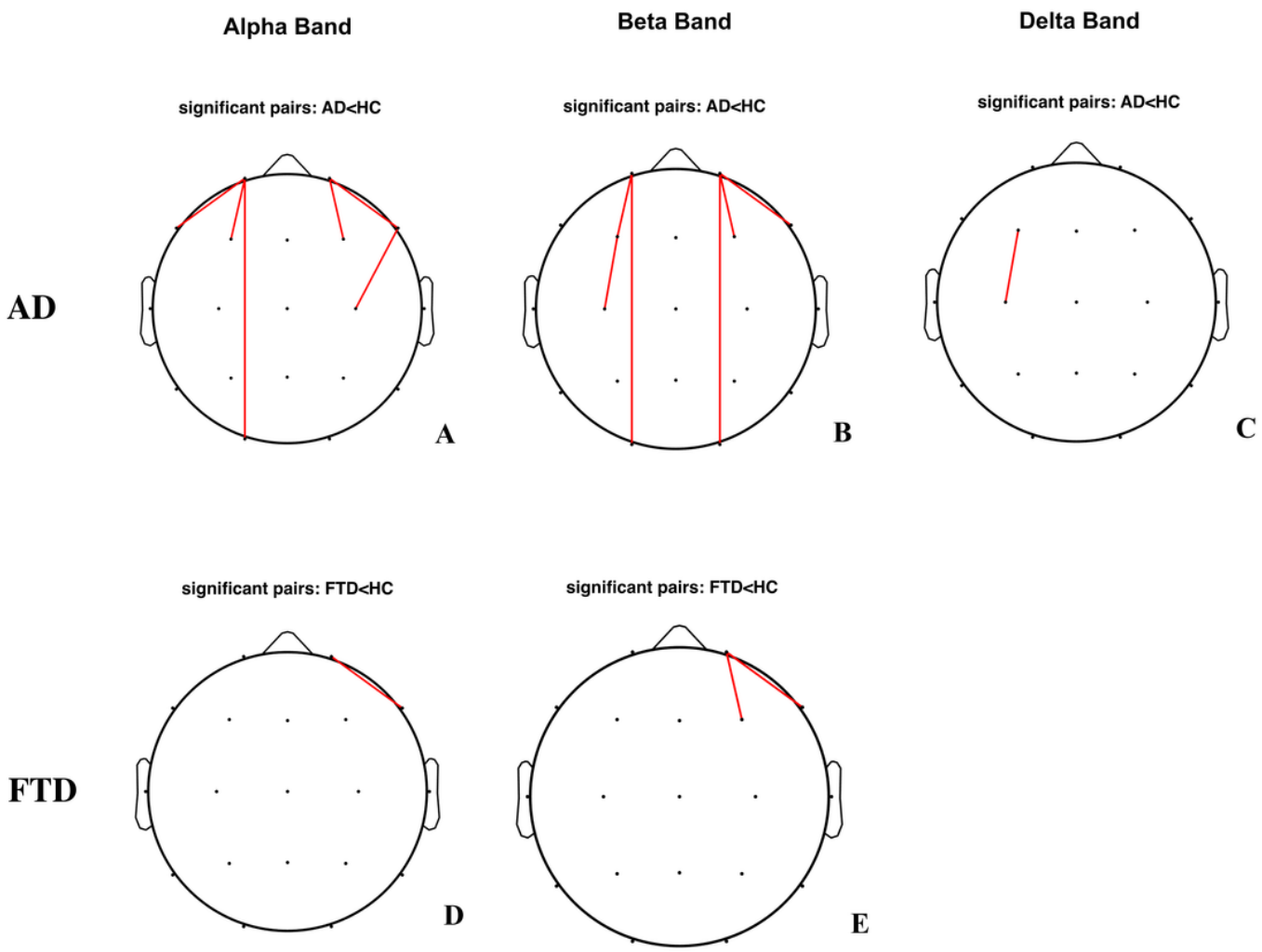

Figure 5

Connectivity analysis. The electrode pairs with significant reduce EEG coherences after Bonferroni correction are connected by red lines in AD and FTD groups, compared to HC. FTD: frontotemporal dementia; AD: Alzheimer's disease; HC: healthy controls.

Supplementary Files

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- Supplementary1.tiff