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Gamma network topology and pathological changes in drug-resistant temporal lobe epilepsy with cognitive deficits

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October 19, 2022

Abstract

Temporal lobe epilepsy (TLE) is the most common form of adult epilepsy, frequently accompanied with cognitive deficits. The present study aims to investigate functional network alterations affected by cognitive impairments in drug-resistant TLE. Patients with drug-resistant TLE were divided into normal cognition (NC) and abnormal cognition (AC) groups based on their primary medical history and completed the Wechsler intelligence scale. Thirty-one patients in the NC group and 30 in the AC group had mean intelligence quotients (IQ) of 107 (96-137) and 71 (60-85), respectively. Eighteen controls were enrolled in the study. Graph theory analysis showed decreased alpha small world index (SWI) in the AC group compared to that in the NC group and controls. Increased SWI in the fast rhythm was observed in both TLE groups compared with controls. But the gamma SWI in the AC group declined and was significantly lower than in the NC group at 50–70 Hz. A lower IQ is associated with a decreased SWI in alpha and 50-70Hz. Spectral analysis revealed reduced alpha power and increased delta power in the TLE groups compared to the controls. Immunofluorescence analysis revealed more severe amyloid-β (Aβ) and phosphorylated Tau (p-Tau) loads in the resected hippocampus of the AC group than that of NC group. Cognitive deficits in drug-resistant TLE are associated with general EEG activity slowing, loss of efficiency in gamma connectivity, and increased Aβ and p-Tau expression. These alterations are potential markers and intervention targets for concomitant cognitive decline in drug-resistant epilepsy.

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Running title : cognitive deficits affect EEG and pathology in TLE

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Data availability statement :

The data that support the findings of this study are available from the corresponding author (QL) upon reasonable request

Acknowledgments

Funding: This work was supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) [Grant number: 2021-I2M-1–034, 2021-I2M-1–018, 2016-I2M-1–002], the Fundamental Research Funds for the Central Universities [grant number: 3332021011], National Natural Science Foundation of China [NSFC; grant numbers 81971293, 81788101], National Key Research and Development Program of China [Grant number: 2016YFC0905100], Research Fund from CAAE [UCB-2018029, CU-A-2021-21], the National Key Research and Development Project [grant number: 2018YFC2000803], and Hygiene and Health Development Scientific Research Fostering Plan of Haidian District Beijing [HP2021-03-50801].

Conflict of interests: None of the authors have potential conflicts of interest to be disclosed.

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Abstract

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Keywords: EEG; cognitive deficits; drug-resistant temporal lobe epilepsy; graph theory; pathology.

Acknowledgments

Funding: This work was supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) [Grant number: 2021-I2M-1–034, 2021-I2M-1–018, 2016-I2M-1–002], the Fundamental Research Funds for the Central Universities [grant number: 3332021011], National Natural Science Foundation of China [NSFC; grant numbers 81971293, 81788101], National Key Research and Development Program of China [Grant number: 2016YFC0905100], Research Fund from CAAE [UCB-2018029, CU-A-2021-21], the National Key Research and Development Project [grant number: 2018YFC2000803], and Hygiene and Health Development Scientific Research Fostering Plan of Haidian District Beijing [HP2021-03-50801].

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Introduction

Epilepsy is a prevalent neurological disorder that affects approximately 50 million people worldwide (Meyer et al., 2010). Temporal lobe epilepsy (TLE) is the most common form of localization-related epilepsy in adults. Hippocampal onset accounts for at least 80% of all temporal lobe seizures (Tatum, 2012). The temporal lobe is involved in learning, memory, and affective behavior (Gilliam et al., 2003). Damage to this structure as a result of recurrent spontaneous seizures can result in cognitive impairment (Helmstaedter, 2002), which has been frequently described as a potential comorbidity of TLE (Meador, 2002).

Gamma activity (30–100 Hz) has been linked to memory access (Gruber & Müller, 2005; Gruber et al., 2002; Herrmann et al., 2004; Kaiser et al., 2003). Previous studies have reported suppressed synchronization of gamma frequency in cognition disorders, such as Alzheimer's disease (Politoff et al., 1996; Stam et al., 2002; Wang et al., 2020). Since gamma alternation occurs early in disease progression, it may be involved in the pathological processes of dementia. Modulation of the gamma band is a promising intervention for cognitive improvement in Alzheimer's disease (Park et al., 2020; Tian et al., 2021). Increased gamma band power has been reported in idiopathic general epilepsy (Pegg et al., 2020; Willoughby et al., 2003). However, EEG variations in gamma frequency in patients with TLE with cognitive impairment remain poorly understood.

We established a retrospective cohort of patients with drug-resistant TLE with and without cognitive deficits. Using this cohort we evaluated the characteristics of interictal resting-state EEG data in gamma frequency and pathological changes in the resected hippocampus of the patients. Spectral analysis, functional connectivity, and graph theoretical analysis were used in the current study to quantify the brain's functional system. We observed changes in small-world topology in the gamma band, and elevated amyloid-β (Aβ) and phosphorated Tau (p-Tau) deposition in TLE patients with cognitive dysfunction.

Materials & Methods

Patients

The study population consisted of patients with drug-resistant TLE treated between June 2012 and September 2021. The diagnosis of TLE was made by experienced epilepsy specialists according to criteria from the International League Against Epilepsy (ILAE) classification of epilepsies and epileptic syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 2017). All patients underwent EEG recordings and brain magnetic resonance imaging (MRI). Seizure origin was confirmed using EEG in all patients. Drug-resistant epilepsy was defined as the failure of two tolerated and appropriately chosen anti-seizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure inhibition (Kwan et al., 2010). The exclusion criteria were as follows: (1) epileptiform discharges over other regions except the temporal lobe on EEG; (2) concomitant seizures originating in non-temporal regions; (3) brain MRI revealing obvious lesions in non-temporal areas, which may influence seizure type or cognition; and (4) complications of other neurological disorders that may influence seizure or cognition, including

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tumor, trauma, stroke, mental retardation, neurodegenerative disease, and inherited neurological diseases, such as tuberous sclerosis.

Patients who met the following criteria were included in the abnormal cognition (AC) group: (1) complaints of cognitive decline, which interfered with daily routines and work performance; (2) declined calculation ability (< four correct, subtract 7 from 100, continued five times); and (3) impaired memory ability (< 2 points, recall the names of three objects learned earlier). The criteria of normal cognition (NC) group were as follows: (1) no complaints of cognitive dysfunction, qualified for job, and (2) normal calculation and memory abilities. The Wechsler Intelligence Scale (WIS) was used in 30 patients in the AC group and 31 patients in the NC group. All patients underwent video EEG monitoring using a 40-channel video-EEG monitoring system (Nicolet, USA) at the hospital for over 24 h. We also enrolled 18 sex- and age-matched healthy controls (HC). Recording electrodes were placed according to the international 10–20 system, densely in the bilateral temporal regions based on the international 10–10 system, with a sampling frequency of 512 Hz. The 40 electrodes included Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, T7, T8, P3, Pz, P4, P7, P8, O1, Oz, O2, AF7, AF8, F9, F10, FC5, FC6, FT7, FT8, FT9, FT10, C5, C6, T9, T10, CP5, CP6, TP7, TP8, TP9, TP10.

Hippocampal tissue was available from seven patients who underwent surgery. There were four patients in the AC group and three in the NC group. The mini-mental state examination (MMSE) was performed in these patients for cognitive evaluation. Hippocampal sclerosis was observed in all the pathology reports.

EEG examination and data preprocessing

Resting-state EEG data without excessive noise, muscle artifacts, or epileptiform discharges were extracted and preprocessed using EEGLAB (R13_6_5b) in MATLAB R2017b. An independent component analysis was used for further artifact removal, particularly for muscle artifacts. EEG data were resampled at 500 Hz and recomputed against the average reference. A 50 Hz notch filter was applied to attenuate the contamination from the alternating current. The bandpass filter was set to 0.1–100 Hz. The EEG data were split into non-overlapping epochs of two seconds. Each participant underwent 60–120 epochs.

Source analysis and functional connectivity

An EEG cortical source analysis was performed using exact low-resolution electromagnetic tomography (eLORETA) software (Pascual-Marqui et al., 2011; Vecchio et al., 2021) (publicly available at*http://www.uzh.ch/keyinst/NewLORETA/LORETA01. htm*). This is a linear source imaging method used in resting-state EEG studies to estimate the current source densities of EEG rhythms in different frequency bands. Regions of interest (ROIs) were defined according to the Brodmann areas: 41 ROIs (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48), for each hemisphere. A lagged linear coherence between all pairs of the 82 ROIs was extracted by "all nearest voxels" for seven frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), gamma 1 (30–50 Hz), gamma 2 (50–70 Hz), and gamma 3 (70–90 Hz).

Graph theoretical analysis

Graph theoretical analyses were performed by GRETNA (Wang et al., 2015) in MATLAB R2017b. Graph theory is the study of graphs, which are mathematical structures used to model pairwise relations between objects. The graph is made up of nodes and edges. In the current study, nodes represent ROIs, while edges represent functional connectivity, which is the lagged linear coherence calculated using eLORETA, which was used for graph theory in a previous study (Vecchio et al., 2021). The small world index (SWI) calculated from graph theoretical analysis was used for further analysis due to the association with cognition (Vecchio et al., 2014; Zeng et al., 2015). A previous study reported that increased hippocampal volume reflected increased small-world characteristics in gamma frequency band of connectivity in Alzheimer's disease (Vecchio et al., 2017). The study by Vecchio et al. reported higher gamma small world characteristics during the resting state and better performance in short-term memory (Vecchio et al., 2016). The small world network combines high levels of local clustering among nodes and short path length (Bullmore & Sporns, 2009). SWI was defined

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as the ratio of the normalized clustering coefficient (Cw) and the normalized path length (Lw) (Rubinov & Sporns, 2010; Vecchio et al., 2018). Brain networks have a small world property (Bassett & Bullmore, 2006). The density threshold was set from 0.15 to 0.50, with a 0.05 interval. The upper limit of the density threshold was defined by the size of the connectivity matrix (82, 82) (Supplemental Method 1). SWI in 0.30–0.50 thresholds showed similar trends in each group (Supplemental Fig. 1). We chose the data at a density threshold of 0.45 for further analyses.

Frequency spectral analysis

Frequency spectral analysis was performed using a fast Fourier transform (1000-point) algorithm. The absolute power spectral density (PSD, dB, $10\log10(V^2/Hz)$) for each channel was calculated based on the periodogram. Relative PSD (rPSD) was computed by normalizing the total power over the entire frequency range. The absolute and relative PSDs were averaged across channels within groups to measure the global comparisons between groups in each frequency band. A group comparison of the PSDs for each channel was also performed.

Immunohistochemistry

Formalin-fixed paraffin-embedded hippocampal tissue blocks were sectioned at 5 mm thickness and subjected to fluorescence immunohistochemistry. Tyramide signal amplification (TSA) was used for double fluorescence immunostaining of the same tissue section (Tóth & Mezey, 2007). Double staining was used in combination with antibodies against neuron-specific nuclear protein (NeuN; Cell Signaling Technology, #24307) and Aβ peptide 1-42 (Abcam, ab201061), and a combination of antibodies against microtubule association protein-2 (MAP2, MILLIPORE, #1990899) and p-Tau (phosphor T231, Abcam, ab151559). All samples were processed using standard protocols and solutions (Tóth & Mezey, 2007).

Aβ and p-Tau depositions were quantified using an image analysis system (AON-STUDIO, 2021) based on the contrast between the stained and unstained regions. In each case, images were captured, and a threshold optical density was obtained that differentiated positively stained tissue from the background. Image analysis was performed while blinded to the identity of each patient. Three regions (×200) of the hippocampus were randomly sampled from each patient. The final measurement was obtained by dividing the area of the immune-positive plaques by the total sampling area. Data from all sampled areas were used for group comparisons. The significance of group differences was determined using the Mann-Whitney U test.

Statistics analyses

The SWI and PSD data were normally distributed according to normality Q-Q plots. An analysis of variance (ANOVA) was performed to assess group differences in SWI and PSD, followed by post-hoc analyses with false discovery rate (FDR) correction when overall significant effects were observed. An independent t-test was used for AC and NC group comparisons of SWI. Spearman's correlation test was used for the correlation analysis between the SWI and cognition scales. Continuous non-normal data were examined using the Kruskal-Wallis or Mann-Whitney U-test for group comparisons. The chi-squared test was used for group comparisons of categorical data. The level of significance was set at $p< 0.05$. Analyses of SWI and PSD were performed for each frequency band. p -values were FDR-corrected for multiple comparisons. Group comparisons of functional connectivity were corrected using network-based statistic (NBS) (Zalesky et al., 2010). Statistical analyses were performed using IBM SPSS Statistics v22.

Results

WIS was performed in 61 patients with drug-resistant TLE (68.9% were male, median age 31, range 12–53). At the time of the EEG recordings, the median disease course was 13 years (0.5–35 years). There were no group differences in terms of age and sex between the TLE and HC groups (Table 1). Forty-four patients presented with temporal lesions. Anterior temporal lobectomy or lobotomy was performed on 50 patients. Pathology reports were available for thirty-six patients, including focal cortex dysplasia (n=28), hippocampal sclerosis (n=15), and tumors (n=3). Radiofrequency thermocoagulation was performed in two patients, and

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vagus nerve stimulation (VNS) was performed in one patient. Operations were performed in more patients with cognitive impairment than in those with normal cognition ($p = 0.005$). The mean IQ and memory quotient (MQ) in the NC group was 107 (range 93-137) and 101 (range 72-122), respectively. In the AC group, the mean IQ was 71 (50–85) and the mean MQ was 64 (40–83).

Graph theory analysis

In the current study, TLE patients with WIS scores in the NC ($n = 31$), AC ($n = 30$), and HC ($n = 18$) groups were included for further analyses. The results of the graph theory are presented in Table 1 and Figure 1. SWI in the AC group tended to be increased in delta and theta frequency but decreased in alpha frequency compared to that in the NC group and controls. Group differences were significant for alpha ($p_{\text{NC-AC}}$=0.006). Increased SWI in the fast rhythm was observed in both TLE groups compared with controls. However, in the gamma frequency, SWI in the AC group declined to the level of SWI in controls. SWI in the AC group was significantly lower than that in the NC group at 50–70 Hz ($p_{\text{NC-HC}}$=0.031,$p_{\text{NC-AC}}$=0.031) after applying the FDR correction.

Spearman's correlations between the WIS and SWI were tested in each frequency band (Supplemental Table 1). After applying a multiple test correction, the results showed that SWI in alpha and 50–70 Hz was positively correlated with IQ (alpha: $r = 0.434$, $P = 0.003$; 50–70 Hz: $r = 0.352$, $p = 0.021$) and MQ (alpha:$r = 0.373$, $P = 0.010$; 50–70 Hz: $r = 0.412$,$p = 0.007$) (Figure 2). The results of Spearman's correlation analysis of the SWI and cognition scores are summarized in Supplemental Table 1.

Group comparisons of functional connectivity between all ROIs were performed using EEG data from 40-channel EEG recordings. After applying NBS, no significant differences were observed.

Spectral analysis

The cross-channel grand average of the global EEG, PSD, and rPSD was calculated (Figure 3 A and B and Supplemental Table 2). After FDR correction, absolute PSD in slow rhythms was significantly increased in the TLE groups compared to controls (delta:$p_{\text{HC-NC=}}$0.012,$p_{\text{HC-AC}}$=0.012; theta:$p_{\text{HC-NC=}}$0.019,$p_{\text{HC-AC}}$=0.012). Group differences in rPSD were also detected for delta ($p_{\text{HC-NC}}$=0.003,$p_{\text{HC-AC}}$=0.002) and alpha ($p_{\text{HC-NC}}$=0.002,$p_{\text{HC-AC}}$<0.001). The results revealed that the general EEG activity slowed in drug-resistant TLE. No significant group differences in the absolute and relative PSDs were observed for gamma.

Moreover, group comparisons of PSDs were performed in each channel (Figure 3 C&D and Supplemental Table 3 & 4). As shown in Figure 3, powers in slow rhythm in the TLE groups were significantly increased mainly over the anterior regions, particularly the anterior and middle temporal lobes, compared to controls. The absolute PSD in alpha showed no difference in the group comparison. However, the relative PSD revealed that the percentage of alpha power decreased in both TLE groups over the entire head compared to controls. For gamma frequencies, the rPSD over the central, frontal, and temporal lobes was lower in the TLE groups than in the controls.

Pathology in hippocampus of drug-resistant TLE

Hippocampal tissues were available in seven patients with drug-resistant TLE, four in the AC group, and three in the NC group. The mean disease course was 13 years from seizure onset (5–23 years) in the NC group and 17 years (17–23 years) in the AC group. There were no significant differences in disease course, sex, or age. All patients underwent MMSE (Table 2). The mean MMSE score was 28 (28–29) in the AC group and 20 (17–23) in the NC group. Immunofluorescence revealed Aβ and p-tau deposits in both the NC and AC groups (Figure 4A and B). Three sampled regions (×200) were randomly selected from the hippocampus of each patient. The percentage of each sampled area with positive Aβ and p-Tau immunofluorescence was calculated using a quantitative analysis (Table 2). The mean percentage of Aβ in the sampled regions was 0.13% (0.03%–0.26%) in the NC group and 0.26% (0.01%–0.67%) in the AC group. The mean p-Tau load was 0.61% (0.25%–1.25%) in the NC group and 1.20% (0.58%–2.33%) in the AC group. As shown in Table 2 and Figure 4C, there was a significant difference in the severity of Aβ and p-Tau load between the NC and AC groups (Aβ: $p_{\text{NC-AC}} = 0.034$; p-Tau: $p_{\text{NC-AC}} = 0.012$).

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Discussion

Graph theory has been proposed for detailed understanding of structural connectivity between cortical areas (Sporns et al., 2005). In this study, graph theory revealed that SWI in drug-resistant TLE increased from beta frequency and had a markedly high level in gamma frequency. A recent study also found that in patients with focal epilepsy, SWI tended to increase in gamma frequency (30–45Hz) (Hatlestad-Hall et al., 2021). Our study presented all the SWI trends from delta to gamma (30–90Hz) in TLE patients. SWI is used to describe the balance between the local connectedness and the global integration of a network. Small-world organization is intermediate between random networks, short overall path length associated with a low level of local clustering, regular networks or lattices, and the high-level of clustering, which is accompanied by a long path length (Vecchio et al., 2014). Hypersynchronous neuronal activity associated with epilepsy could cause widespread functional network alterations. The elevated beta and gamma SWI in drug-resistant TLE may reflect increased post-synaptic activity of local neurons. Increased neuronal activity changes the ionic environment of neurons and leads to increased burst firing of neurons (Heinemann et al., 1986; Jensen et al., 1994). Intensified gamma networks may be related with the epileptic characteristics and cortical neuron excitation.

Interestingly, we showed that SWI increased at beta frequency in patients with TLE and cognitive deficits and then markedly declined at gamma frequencies. The change was significant at 50-70 Hz, compared to that in patients with normal cognition. The correlation between gamma-SWI and cognition has been demonstrated in previous studies (Vecchio et al., 2017; Vecchio et al., 2016), that lower gamma SWI in AD is associated with better short-term memory and a smaller hippocampal volume. Graph analysis suggests less efficient interaction and disconnection between brain regions in patients with Alzheimer's disease, and gamma activity is closely correlated with cognitive functions (Engel et al., 2001). Our study showed that gamma SWI could be influenced by focal epilepsy, but a comparison between patients with drug-resistant TLE to eliminate the influence of epilepsy revealed that gamma SWI was positively correlated with cognition level, especially in high gamma. Moreover, TLE patients with cognitive deficits may have reduced efficiency of network communication in gamma bands in the context of hypersynchronous neuronal activity. Additionally, the alpha SWI in both TLE groups was not significantly different from that in the healthy controls, may due to the small sample and multiple test correction. However, alpha SWI in TLE showed a positive association with IQ and MQ scores.

Spectral analyses revealed a reduction of spectral power in the alpha band and increased power in the delta and theta bands in patients with drug-resistant TLE, compared to healthy controls. Changes in patients with cognitive impairment were more pronounced. This indicated that the general EEG was slow in drug-resistant TLE. Increased delta power is mainly localized over the anterior head, especially in the temporal region. The results are corresponding to temporal lesions in TLE. Decreased gamma power was detected in the temporal, central, and frontal lobes; however, the average rPSD in the entire head was not significantly different. Previous studies have suggested reduced resting-state gamma power/synchronization in Alzheimer's disease (Koenig et al., 2005; Ribary et al., 1991; Stam et al., 2002). The present study revealed that interictal EEG without epileptiform discharges in TLE had lower gamma power in the temporal and frontal regions. No group differences of gamma power were detected between the TLE groups. But the gamma-communicating functional network was influenced by cognitive impairment in TLE.

Pathological changes were significant in epilepsy patients with cognitive deficits, including Aβ and p-Tau deposition in the resected hippocampus. The current study showed that amyloid and p-Tau loads were increased in TLE patients with cognitive deficits compared to patients with normal cognition. Both Aβ and p-Tau deposits have been documented in drug-resistant TLE tissue (Gourmaud et al., 2020; Tai et al., 2016). Increased Aβ1–42 peptide and hyperphosphorylated Tau in the hippocampus are associated with cognitive deficits and have been reported in temporal lobe epilepsy (Gourmaud et al., 2020). Aβ peptides play a key role in Alzheimer's disease pathogenesis (Karran et al., 2011). The findings of our and previous studies indicate that Aβ and p-Tau deposits may be correlated with impaired cognition in drug-resistant TLE. Gamma frequency entrainment can attenuate amyloid load and improve cognition in AD and wild-

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type animal models (Iaccarino et al., 2016; Park et al., 2020; Tian et al., 2021). Considering these data, we propose that alterations in gamma frequency may be a potential therapeutic target for drug-resistant TLE with cognitive deficits.

Limitations

The present study had limitations. First, the WIS scores were lacking in the control group, and would enable more robust conclusions from comparisons between controls and drug-resistant TLE patients. Nonetheless, a detailed medical history, especially concerning neurological diseases, was reviewed for healthy controls. Additionally, all controls passed the primary cognition test with calculation and memory abilities. Second, a larger sample size for the pathological analysis will further validate these data. Moreover, evaluating pathological factors directly reflecting the cause of impaired efficiency of brain connectivity, such as synapsis and myelination status may lead to more robust conclusions.

Conclusion

Overall, we demonstrated that cognitive deficits in drug-resistant temporal lobe epilepsy may lead to slowing of general EEG activity, loss of efficiency in gamma band connectivity, and increased Aβ and p-Tau expression. The EEG and pathological changes in these patients indicated that high frequency may be an evaluation marker and a potential therapeutic target for cognitive dysfunction.

Conflict of interests: None of the authors have potential conflicts of interest to be disclosed.

Ethics statement: The studies involving human participants were reviewed and approved by The Ethics Committee of Peking Union Medical College Hospital (No. JS3511). The patients/participants provided their written informed consent to participate in this study.

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Table1. Demographic data, cognition scales and small world index across gamma bands in drug-resistant temporal lobe epilepsy

	HC (n=18)	NC (n=31)	AC (n=30)	P
Age (mean, range)	33(16-58)	28(12-51)	33(13-53)	P=0.116
Sex (M:F)	10:8	22:9	20:10	P=0.541
Disease course /y (mean, range)		11.5(0.5-31)	15.0(1-35)	P=0.113
IQ		107(93-137)	71(50-85)	P <0.001
MQ		101(72-122)	64(40-83)	P<0.001
MRI temporal lesion		21(67.7%)	23(76.7%)	P=0.570
Operations		23(74.2%)	30(100%)	P=0.005
Lobectomy/lobotomy		20(74.2%)	30(100%)	P<0.001
Thermocoagulation		2(6.5%)	0	P=0.492
VNS		1(3.2%)	0	P=1.000
Small world index				ANOVA (2, 76)
1-4Hz	0.971 (0.029)	0.975 (0.026)	0.978 (0.021)	F=0.364, P=0.696
4-8Hz	0.985 (0.021)	0.982 (0.030)	0.990 (0.027)	F=0.598, P=0.645
8-12Hz	0.980 (0.016)	0.985 (0.022)	0.972 (0.015)	F=6.248, P=0.021 $P_{NC\text{-}AC}$=0.006
12-30Hz	0.995 (0.021)	1.012 (0.043)	1.008 (0.035)	F=1,468, P=0.415
30-50Hz	1.002 (0.038)	1.017 (0.042)	1.010 (0.033)	F=0.954, P=0.546
50-70Hz	1.006 (0.032)	1.031 (0.036)	1.009 (0.032)	F=4.543, P=0.049 $P_{NC\text{-}HC}$=0.031, $P_{NC\text{-}AC}$=0.031
70-90Hz	1.011 (0.043)	1.031 (0.047)	1.006 (0.033)	F=2.992, P=0.131

HC: healthy control; NC: normal cognition; AC: abnormal cognition

Table 2. Amyloid-β and phosphorated-Tau load (percentage of sampled area with positive immunohistochemistry) in hippocampus of drug-resistant temporal lobe epilepsy.

	Age	Sex	MMSE	Amyloid-β load (%)	p-Tau load(%)
NC-case1	31	Male	28	0.03 0.05 0.08	0.38 0.96 0.25
NC-case2	24	Male	29	0.08 0.21 0.11	0.32 1.25 0.83

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	Age	Sex	MMSE	Amyloid-β load (%)	p-Tau load(%)
NC-case3	33	Male	28	0.26 0.12 0.20	0.38 0.72 0.40
AC-case1	27	Male	17	0.01 0.27 0.42	1.97 0.58 1.45
AC-case2	39	Male	23	0.19 0.48 0.13	0.88 1.03 1.19
AC-case3	30	Male	20	0.30 0.14 0.12	0.64 0.63 1.05
AC-case4	52	Female	19	0.67 0.28 0.13	1.8 0.87 2.33
	$P_{\text{NC-AC}} =$ 0.629	$P_{\text{NC-AC}} =$ 1.000	$P_{\text{NC-AC}} =$ 0.057	$P_{\text{NC-AC}} =$ 0.034	$P_{\text{NC-AC}} =$ 0.012

NC: normal cognition; AC: abnormal cognition

Figure legends

Figure 1. Small world index (SWI) trends in drug-resistant TLE and control groups. SWI in the AC group decreased in alpha frequency compared to that in the NC group and controls. The SWI increased in beta frequency in both TLE groups, then declined in gamma frequency in AC group. TLE: temporal lobe epilepsy; NC: normal cognition; AC: abnormal cognition.

Figure 2. Association between cognitive scales and small world index (SWI) by Spearman's correlations. (A-D) SWI in alpha and gamma frequency bands (50-70Hz) showed positive correlation with intelligence quotient and memory quotient after FDR correction.

Figure 3. Frequency spectral analysis in drug-resistant temporal lobe epilepsy (TLE) patients. (A) & (B) Across-channel grand average of Power spectral density (PSD) showed increased delta power and decreased alpha power in drug-resistant TLE groups, compared to controls. **(C) & (D)** Increased delta power in TLE groups are mainly over the anterior regions. For gamma frequencies, the relative PSD over the central, frontal, and temporal areas was lower in the TLE groups than in the controls.

Figure 4. Αμψλοιδ-β (Αβ) ανδ πηοσπηορατεδ-Ταυ (π-Ταυ) ιμμυνοφλυορεσϲενϲε ιν η-ιππoϲαμπυϲ οφ δρυγ-ρεσιϲταντ ΤΛΕ. (A) Different Aβ expression between NC and AC groups is observed, with similar Neun expression. **(B)** The p-Tau deposition is more severe in AC group, compared with NC group, while the expression of MAP2 is similar in two groups. **(C)** Quantitative analysis showed substantial differences between NC and AC groups in Aβ and p-Tau expression. NC: normal cognition; AC: abnormal cognition.

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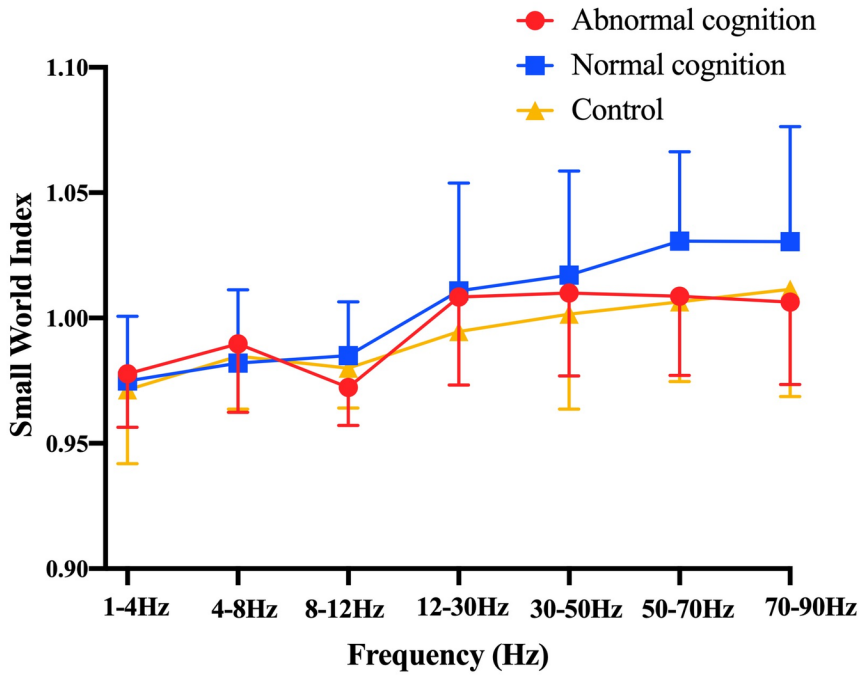

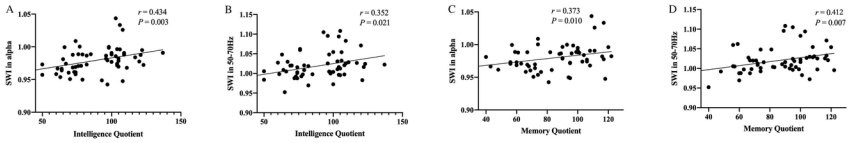

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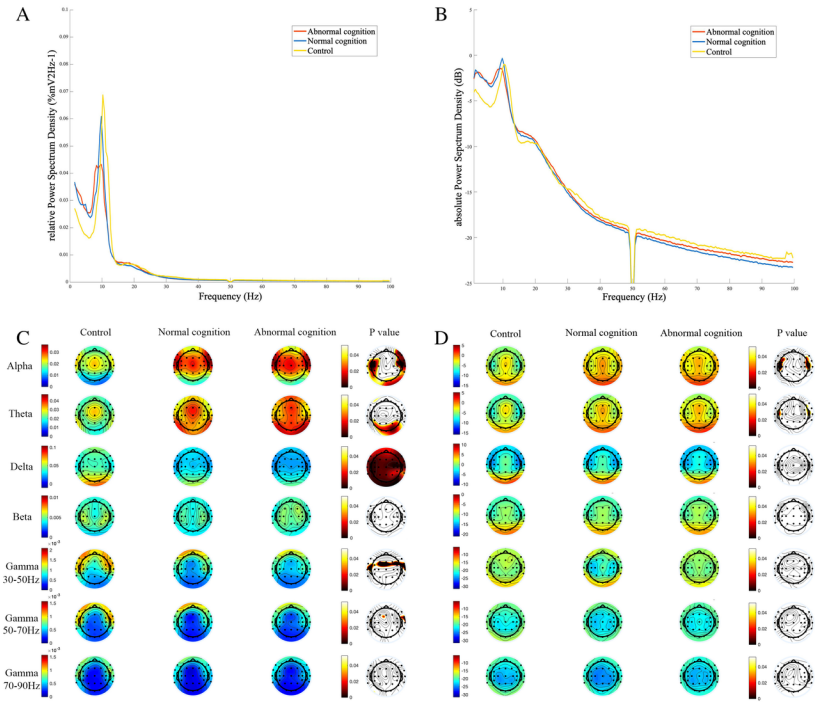

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