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Quantitative EEG biomarkers of cognitive performance in drug-resistant temporal lobe epilepsy

Authors:

Sofia Lallana^{1,2}, Samuel López-Maza^{1,2}, Gemma Ortega^{3,4}, Elena Fonseca^{1,2}, Manuel Quintana^{1,2}, Laura Abaira^{1,2}, Enric Bellido^{1,2}, Daniel Campos-Fernández^{1,2}, Estevo Santamarina^{1,2}, Agustín Ruiz^{3,4}, Lluís Tárraga^{3,4}, Mercè Boada^{3,4}, Manuel Toledo^{1,2}

¹ Epilepsy Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain

² Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain

³ Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya, 08028, Barcelona, Spain

⁴ Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED). Instituto de Salud Carlos III, 28029, Madrid, Spain

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Corresponding author:

Dr. Elena Fonseca, MD, PhD

Epilepsy Unit, Neurology Department. Hospital Universitari Vall d'Hebron.

Passeig de la Vall d'Hebron 119-129. Barcelona, 08035, Spain

E-mail address: elena.fonseca@vallhebron.cat

ABSTRACT

Background

This study aimed to explore quantitative electroencephalography (qEEG) biomarkers of cognitive performance in drug-resistant temporal lobe epilepsy (TLE) and analyze their relationship with clinical characteristics.

Methods

Cross-sectional study including adult patients with drug-resistant TLE and a control group. Resting-state, eyes-closed qEEG samples were analyzed using the fast Fourier transform approach. Power spectral density was calculated for four frequency bands: delta (1–3.9Hz), theta (4–7.9Hz), alpha (8–12.9Hz), and beta (13–18Hz). Neuropsychological tests were administered to TLE patients.

Results

Twenty-nine TLE patients (mean age 42 ± 8.2 years; 44.8% women) and 23 age- and sex-matched controls were enrolled. Clinically significant cognitive impairment was found in 86.2% of patients (58.6% amnesic). Compared to controls, TLE patients showed increased ipsilateral power spectral density for the theta ($p=.045$), alpha ($p=.023$) and beta bands in the anterior region ($p=.029$) and for the delta band in the posterior region ($p=.03$). Alpha/theta ratio (ATR) was lower in the posterior quadrant of the epileptogenic hemisphere ($p=.013$), and higher seizure frequency correlated with a lower ATR in the ipsilateral temporal region ($r: -.425$; $p=.021$). Patients with amnesic cognitive impairment exhibited higher power spectral density across most frequency bands ($p<.005$). Impaired verbal memory and executive function were associated with increased power density.

Conclusion

Increased power spectral density was evident in all frequency bands in the epileptogenic hemisphere, particularly in those patients with amnesic cognitive impairment. Moreover, higher seizure frequency correlated with a lower ATR in the temporal region. Power spectral analysis can provide useful information in drug-resistant TLE patients.

KEYWORDS: electroencephalography, brain waves, neurocognitive disorders, drug resistant epilepsy, temporal lobe epilepsy

1. Introduction

Quantitative electroencephalography (qEEG) is defined as “the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison”[1].

To date, qEEG has shown its value primarily in critically ill patients, proving useful for detecting electrographic seizures and nonconvulsive status epilepticus, as well as for monitoring delayed cerebral ischemia in cases of subarachnoid hemorrhage [2]. More recently, quantitative EEG biomarkers based on seizure onset dynamics have been utilized to optimize preoperative assessments in epilepsy patients by delineating the epileptogenic zone [3,4].

Several qEEG parameters have been used to characterize the autistic brain and study attention deficit hyperactivity disorder [5,6]. Patients with these pathologies exhibit several differences in power spectra, coherence, and symmetry measures compared to controls, which could help link behavior with brain activity and quantitatively evaluate patient evolution and treatment efficacy. In addition, baseline qEEG changes have been described as biomarkers for cognitive prognosis in neurodegenerative conditions, such as Alzheimer’s disease, Parkinson’s disease, and Lewy body dementia [7–10]. Global EEG slowing is a marker of overall cognitive impairment in patients with an initial presenile cognitive decline and in non demented patients with Parkinson’s disease.

Cognitive impairment is common in patients with epilepsy, particularly in those with drug-resistant temporal lobe epilepsy (TLE) [11,12]. Although the underlying pathological mechanisms are not fully understood, it is believed that epileptiform activity in the hippocampal region may contribute to cognitive deficits in TLE patients [13]. Furthermore, it has been suggested that TLE could share common pathways with neurodegenerative diseases like Alzheimer's disease, which often presents with epileptic seizures at onset [14].

Despite growing interest in studying baseline qEEG activity in TLE, few reports have characterized the findings[15,16] or examined their relationship with cognition or other clinical aspects [17–19]. In this exploratory study, we aimed to evaluate baseline qEEG biomarkers of cognitive performance in patients with drug-resistant TLE. Additionally, we investigated the relationship between qEEG parameters and clinical characteristics of the disease.

2. Materials & methods

2.1. Study design and participants

This cross-sectional study was conducted from January 2020 to November 2022 in a specialized epilepsy unit of a tertiary hospital. It included adult patients with drug-resistant TLE and a control group of patients with non-epileptic events who were admitted to the epilepsy monitoring unit. The TLE patients were part of a prospective cohort from our research group. The study was approved by the local ethics committee (PR(AG)19/2020). Consecutive patients with drug-resistant TLE and no structural lesions on neuroimaging (except mesial temporal sclerosis) were selected from our unit's

database. The TLE diagnosis was established following the International League Against Epilepsy (ILAE) diagnostic criteria and classification [20,21], based on seizure semiology, along with interictal and ictal electroencephalography findings. Epilepsy lateralization was determined through ictal/interictal epileptiform activity recorded on video-EEG. Drug resistance was defined according to the ILAE task force guidelines [22]. EEG acquisition and neuropsychological evaluations were performed within a maximum of 24 months.

We excluded structural epilepsy etiologies other than mesial temporal sclerosis to avoid bias due to focal slowing secondary to brain lesions. Patients were also excluded if they did not have a definite diagnosis of TLE, had previously undergone epilepsy surgery, or had intellectual disability, diagnosed dementia, or another neurodegenerative disease. Additionally, patients older than 55 years were excluded to rule out late-onset epilepsy possibly linked to underlying neurodegenerative conditions [23].

Demographic and clinical variables, including age at onset, epilepsy duration, and antiseizure medications (ASMs), were recorded from the patients' electronic medical history. Seizure frequency was documented using self-reported seizure diaries over a 12-month period prior to inclusion in the study.

For the control group, we retrospectively selected patients from our monitoring unit database who were diagnosed with non-epileptic events and had a normal visual video-EEG analysis. A diagnosis of epilepsy or any other neurological disorder that could affect baseline EEG activity was reasonably excluded based on medical history, the clinical

characteristics of the events, neurological examination, video-EEG results, and neuroimaging findings.

2.2. EEG acquisition and analysis

EEG data were acquired using a 64-channel digital XLTEK EEG system (Natus Medical Inc.), with scalp electrodes placed according to the international 10–20 system (Fp1-2, F3-4, F7-8, C3-4, T3-4, P3-4, T5-6, O1-2, Fz, Cz, Pz). Electrode impedance was kept below 5 k Ω . The sampling rate was 512 Hz, with a bandpass filter set between 0.3 and 70 Hz, and a notch filter applied at 50 Hz. The raw EEG data were reviewed by two independent epileptologists. For the quantitative analysis, 5-minute representative samples of baseline resting, closed-eye wakefulness EEG were selected. Baseline EEG samples were obtained during the first 24 hours upon admission to the epilepsy monitoring unit, before ASM medication withdrawal and ensuring there were no seizure recording during, at least, the following 6 hours.

The EEG recordings were systematically analyzed offline using the Persyst 14 EEG System Integration Software (Solana Beach, CA). Spectral analysis was performed on a longitudinal bipolar montage, employing the Fast Fourier Transform (FFT) algorithm with 2-second epochs. The results were averaged over the selected period. Mean values were obtained for the delta (1-3.9 Hz), theta (4-7.9 Hz), alpha (8-12.9 Hz), and beta (13-18 Hz) frequency bands. The mean absolute power spectral density ($\mu\text{V}^2/\text{Hz}$) for each band was calculated for both hemispheres (left: Fp1-F7, F7-T3, T3-T5, T5-O1 Fp1-F3, F3-C3, C3-P3, P3-O1; right: Fp2-F8, F8-T4, T4-T6, T6-O2 Fp2-F4, F4-C4, C4-P4, P4-O2), both anterior quadrants (left: Fp1-F7, F7-T3, Fp1-F3, F3-C3; right: Fp2-F8, F8-T4, Fp2-F4, F4-C4), both posterior quadrants (left: T3-T5, T5-O1, C3-P3, P3-O1; right: T4-T6, T6-O2, C4-P4, P4-O2), and temporal regions (left: T3-T5; right: T4-T6).

Additionally, relative power ratios (ADR, alpha-delta ratio; ATR, alpha-theta ratio) were calculated for all regions.

EEG data from the left and right hemispheres were classified as ipsilateral or contralateral based on epilepsy lateralization. For the control group, EEG measures were calculated as the mean values from both hemispheres, under the assumption of no significant interhemispheric asymmetries. In patients with bilateral interictal epileptiform abnormalities, the hemisphere with a higher prevalence of epileptiform abnormalities, or the one where seizures originated (if recorded), was considered ipsilateral for the statistical analysis.

2.3. Cognitive assessment

TLE patients were evaluated by a trained neuropsychologist who was blinded to the qEEG data. Cognitive complaints were reported during clinical interviews and in the cognitive functioning section of the Quality of Life in Epilepsy Inventory (QOLIE-31). The neuropsychological assessment protocol evaluated cognitive functions commonly impaired in TLE patients, including attention and executive functions, verbal and visual memory, language, visuoconstructive praxis, and visuoperception.

The following tests were administered: Phonetic Verbal Fluency (words beginning with “P” in one minute), Semantic Verbal Fluency (“animals” in one minute), the Trail Making Test (A and B), the Stroop test, the Digit Span forward and backwards subtests of the Wechsler Adult Intelligence Scale (third edition), the Free and Cued Selective Reminding Test (FCSRT) (learning, delayed recall, and recognition), the Boston Naming Test (BNT), the Rey–Osterrieth Complex Figure (ROCF) (copy and delayed recall), and Benton’s

Judgment of Line Orientation test (JLO). Normative data for each test were provided in accordance with the NEURONORMA Project [24]. All scores were adjusted for age, sex, and education level, and then converted to T scores. Tests results were combined to obtain indexes for each cognitive function. Impaired performance in each cognitive domain was established as a T score below -1.5.

Following the neuropsychological assessment, clinically significant cognitive impairment was defined following Petersen's criteria [25], which included subjective memory complaints, the absence of dementia, and measurable impairment in one or more cognitive functions. Amnestic and non-amnestic subtypes were categorized based on the presence of impaired memory function, with or without deficits in other cognitive domains [26,27].

2.4. Statistical analysis

Descriptive and frequency statistical analyses were performed using the IBM SPSS Statistics 25.0 software. Categorical variables, including demographic characteristics, are reported as frequencies (percentages) and continuous variables as the mean $\pm$ standard deviation (SD) or median and interquartile range [IQR], as appropriate. QQ plots were performed to determine whether quantitative data followed a normal distribution.

Interhemispheric power spectral density asymmetries were assessed using paired-samples *t*-tests. Ipsilateral power spectral density in TLE patients were compared with the control value means (left+right/2) using Student's *t* test. Correlations between power spectral density values and other quantitative variables (age, seizure frequency, epilepsy duration)

were assessed with Pearson's or Spearman's correlation coefficients, according to the distribution of each variable.

Associations with amnesic cognitive impairment and impaired cognitive domains were assessed using Student's *t* test. A heat map was generated to summarize the significance levels of comparisons between power spectral density values in the various brain locations and impairment for each cognitive domain.

P-values < 0.05 were considered statistically significant.

3. Results

Twenty-nine TLE patients who met the inclusion criteria during the study period were included, along with 23 controls with non-epileptic events.

3.1. Demographic and clinical characteristics

The mean age of TLE patients was 42 ± 8.3 [24-55] years, with 13 (44.8%) being women. The control group had a similar mean age (42 ± 18.3 years), with 15 (65.2%) being women. The diagnoses of the 23 control patients were as follows: functional seizures in 15 patients (65.2%) syncope in 5 patients (21.7%), a single paroxysmal event in 2 patients (8.7%), and no-REM parasomnia in 1 patient (4.3%). Among TLE patients, the median age at epilepsy onset was 29 [16.3-36.5] years, and the median duration of epilepsy was 9 [3.5-21.5] years. The etiology of epilepsy was unknown in 22 (75.9%) patients, while mesial temporal sclerosis was detected on MRI in 5 (17.2%) patients. Seizure frequency was reported as daily in 5 (17.2%) patients, weekly in 14 (48.3%), monthly in 6 (20.7%),

and yearly in 4 (13.7%). Demographic and clinical characteristics of the TLE patients are summarized in **Table 1**.

Clinically significant cognitive impairment was detected in 25 (86.2%) patients, with 17 (58.6%) classified as having amnesic impairment and 8 (27.6%) as non-amnesic. The remaining 4 (13.8%) patients reported subjective memory complaints. Those patients with amnesic cognitive impairment had a median of 3 impaired cognitive domains (IQR 2-6), while patients with non-amnesic cognitive impairment had a median of 1 cognitive domain impaired (IQR 1-1). This difference was statistically significant ($p = 0.019$). In terms of specific cognitive domains, deficits in verbal fluency and processing speed were observed in 8 (27.6%) patients and attention deficits in 4 (13.8%) patients. Regarding verbal memory, learning was impaired in 11 (37.9%) patients, delayed recall in 16 (55.2%) patients, and recognition in 6 (20.7%) patients. Visual memory impairments were documented in 4 (13.8%), visuoperception deficits in 10 (34.5%), visuoconstructive praxis difficulties in 2 (6.9%), and language deficits in 6 (20.7%) patients. The cognitive status and neuropsychological performance of TLE patients in each cognitive domain are summarized in **Table 2**.

3.2. qEEG differences between TLE patients and controls

Power spectral density bands showed no significant interhemispheric asymmetries in the control group ($p > .05$ for all absolute values and ratios). In contrast, TLE patients exhibited asymmetries between the epileptogenic and non-epileptogenic hemispheres. Specifically, the TLE group showed increased temporal theta power spectral density ($p = .023$), and lower ADR ($p = .043$) and ATR ($p = .045$) in the epileptogenic hemisphere.

Compared to controls, TLE patients had higher ipsilateral power spectral density for the theta ($p = .045$), alpha ($p = .023$), and beta bands ($p = .029$) in the anterior region, as well as increased delta band activity ($p = .03$) in the posterior region. Additionally, ATR was lower in the epileptogenic hemisphere, particularly in the posterior quadrant ($p = .013$). Differences in absolute power spectral density values between patients and controls are shown in **Fig. 1**.

3.3. Relationship between qEEG parameters and cognitive performance in TLE patients

Patients categorized as having clinically significant amnesic cognitive impairment showed higher power spectral density than the non-amnesic group across all frequency bands, with statistically significant increases in theta, alpha, and beta frequencies ($p < .05$) (**Fig. 2**).

Analysis of the various cognitive domains separately showed that executive fluency and delayed verbal memory functions were those most strongly associated with a power spectral density increase (**Fig. 3**).

3.4. Relationship between qEEG parameters and epilepsy characteristics

Higher seizure frequency correlated with lower ATR in the ipsilateral temporal region ($r = -.425$; $p = .021$). Longer epilepsy duration correlated with higher ATR in the ipsilateral temporal region ($r = .537$; $p = .003$). No significant correlations were found between power spectral density values and age at epilepsy onset, number of ASMs, or use of benzodiazepines.

4. Discussion

In our sample, baseline qEEG activity analysis demonstrated higher absolute power spectral density across all frequency bands in TLE patients compared to controls, which was associated with the presence of an amnesic cognitive impairment and impaired verbal memory and executive functioning. Our findings aligns with previous research, which reported greater focal slowing and diffuse power increases in TLE patients during both wakefulness and sleep. It has been hypothesized that the increase of power in epilepsy patients may be attributed to a larger number of neurons oscillating synchronously, higher synchrony, or both [15–17].

When analyzing quantitative EEG in studies focused on brain-behavior analysis and cognition, the characterization of background EEG activity has been shown to provide the most valuable information [5,28]. Spectral power analysis involves transforming the EEG traces from time domain into frequency domain, providing information about the harmonic content of the signal. Additionally, power spectral density can be expressed as a ratio, obtained by dividing the absolute power between two bands (e.g., ATR: alpha-theta ratio). EEG power spectrums are regulated by anatomically complex homeostatic systems in the various frequency bands. Within the alpha frequency range, EEG power is positively related to cognitive performance and brain maturity in the normal brain, while the opposite holds true for the theta frequency range. Coherence measures the degree of coupling between signals generated by specific neuronal assemblies. In the normal brain, when a coherent oscillation occurs, these neural groups can communicate effectively because their communication windows for input and for output are open at the same time [29].

When investigating our qEEG findings in drug-resistant TLE patients in relation to cognitive syndromes, those with amnesic cognitive impairment exhibited significant increases in power spectral density across most frequency bands compared to patients with non-amnesic cognitive impairment. Most of our TLE patients presented with an amnesic cognitive impairment profile (58.6%), with these patients exhibiting a greater number of impaired cognitive domains to those with non-amnesic cognitive impairment (median of 3 versus 1 domain affected, $p = 0.019$). This greater severity of symptoms may influence the quantitative EEG findings.

In the analysis of the different cognitive domains in the study sample we found that verbal memory functions were those most frequently impaired. It should be noted that the majority of the included patients had epilepsy with left lateralization, presumably the dominant hemisphere, where verbal memory impairments are expected [30,31]. Additionally, executive functions were also impaired in a significant proportion of patients. Executive dysfunction has been reported in TLE patients, even at early stages of the disease [32], suggesting that the pathology may extend beyond the temporal lobe to involve larger brain networks. Verbal memory and executive deficits were both associated with higher power spectral density in our study. In a previous study conducted by Tedrus et al, associations were identified between increased interhemispheric delta coherence and impaired verbal fluency, as well as between elevated interhemispheric beta coherence and delayed visual recall [17]. These findings, along with ours, suggest that the hypersynchrony seen in epilepsy may manifest as increased power spectral density or as a pathologically increased coherence in epilepsy patients.

Although the etiopathological mechanisms explaining the relationship between increases in power spectral density and the cognitive manifestations of epilepsy are not fully understood, similar patterns have been observed in other neurodegenerative disorders, particularly in Alzheimer's disease. It has been traditionally noted that slow frequencies (delta, theta) increase, and fast frequencies (alpha, beta) decrease, in Alzheimer's [33]. However, recent studies suggest that these changes develop gradually, with the initial typical findings in patients with cognitive impairment due Alzheimer's disease being an increase in theta power band [34,35]. This progression could partly explain our findings, where the increase in theta power was more pronounced than the increase in delta, possibly because none of our patients had severe cognitive impairment. In relation to these findings in epilepsy, a study with similar characteristics to ours has been recently published [18] in which patients with MTLE were compared to healthy controls. This study revealed a correlation between impaired cognitive performance and a decrease in ATR (increase in theta power band). ADR was also decreased, though to a lesser extent. These findings support the idea that the power spectrum of qEEG shifts towards lower frequencies in MTLE patients compared to healthy controls, especially in those with cognitive symptoms.

Regarding the severity of cognitive impairment in our patients, it is worth noting that the median follow-up period for our patients since the onset of epilepsy was 9 years. Compared to similar cases in the literature - such as the study conducted by Bjorke et al [32] where patients were recently diagnosed but retrospectively had epilepsy symptoms starting 7 years earlier – statistically significant deficits in memory and executive function were observed in comparison to healthy controls. However, most patients did not meet

the criteria for significant cognitive impairment, as may be the case for some patients in our sample.

Concerning the clinical characteristics of our TLE patients, qEEG also provided interesting parameters that correlated with disease severity. Specifically, lower ATR in the ipsilateral temporal region was linked to higher seizure frequency. It has been hypothesized that seizures may induce synaptic plasticity [15], reflected by changes in delta power, which could partially explain these findings. Focal epilepsy has been linked to progressive cortical thinning [36,37] suggesting that synaptic dysfunction in long-standing epilepsy could result in greater slowing, measurable by qEEG.

The main limitation of this study is the small sample size, which hinders accurate representation of drug-resistant TLE and the associated cognitive states, and increases the likelihood of qEEG artifacts. Furthermore, by focusing solely on resting-state eyes-closed samples for the qEEG analysis, important data may have been missed, as EEG changes during sleep may also have an impact on cognition in these patients. Another important limitation of our analysis is that no correction for multiple comparisons was performed. This decision was made because the present study has an exploratory focus, aiming to generate hypotheses for future, more specific studies. However, it is important to note that the absence of such a correction increases the risk of obtaining falsely significant results, which could potentially invalidate some of our findings. To confirm these preliminary results, it will be necessary to conduct confirmatory analyses in future studies where appropriate statistical correction is applied. Nevertheless, this study supports existing evidence of increased power density in epilepsy patients and explores a new path

of research into the relationship between qEEG findings and cognitive impairment in epilepsy, which warrants further investigation.

5. Conclusion

This study shows that increased power spectral density across all frequency bands in the epileptogenic hemisphere can be detected by qEEG in patients with drug-resistant TLE. This finding was associated with amnesic cognitive impairment and impaired verbal memory and executive functioning. Additionally, a lower ATR in temporal regions correlated with higher seizure frequency. These findings suggest that qEEG parameters hold potential as biomarkers for both the clinical and cognitive aspects of drug-resistant TLE, although further long-term follow-up studies in this line are needed.

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DECLARATION OF COMPETING INTERESTS

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the journal's position on issues concerning ethical publication and affirm that this report is consistent with those guidelines.

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TABLES

Table 1. Demographic and clinical characteristics of the patients included in the study.

Demographic and clinical characteristics of TLE patients included in the study (n=29)		
Age, years, mean $\pm$ SD		42 $\pm$ 8.3
Sex, n (%)	Male	16 (55.2)
	Female	13 (44.8)
Age at epilepsy onset, years, median [IQR]		29 [16-36.5]
Epilepsy duration, years, median [IQR]		9 [3.5 – 21.5]
Epilepsy lateralization, n (%)	Left temporal	20 (69.0)
	Right temporal	9 (31.0)
Seizure frequency, n (%)	Daily	5 (17.2)
	Weekly	14 (48.3)
	Monthly	6 (20.7)
	Yearly	4 (13.7)
Number of ASMs, n (%)	1	2 (6.9)
	2	13 (44.8)
	3	9 (31)
	4	5 (17.2)

TLE, temporal lobe epilepsy; ASM, antiseizure medication.

Table 2. Cognitive status and neuropsychological performance of TLE patients in each cognitive domain.

Cognitive domain	T-score mean ($\pm$ SD)	Impaired, n (%)
Verbal fluency (executive)	-0.92 ± 0.88	8 (27.6%)
Processing speed	-0.82 ± 1.07	8 (27.6%)
Attention	-0.66 ± 0.80	4 (13.8%)
Learning (verbal memory)	-1.35 ± 0.92	11 (37.9%)
Recognition (verbal memory)	0.79 ± 2.19	6 (20.7%)
Delayed recall (verbal memory)	-1.51 ± 1.04	16 (55.2%)
Delayed recall (visual memory)	-0.035 ± 1.17	4 (13.8%)
Visuoperception	-0.72 ± 1.45	10 (34.5%)
Visuoconstructive praxis	1.44 ± 1.82	2 (6.9%)
Language	-0.58 ± 1.23	6 (20.7%)

FIGURES

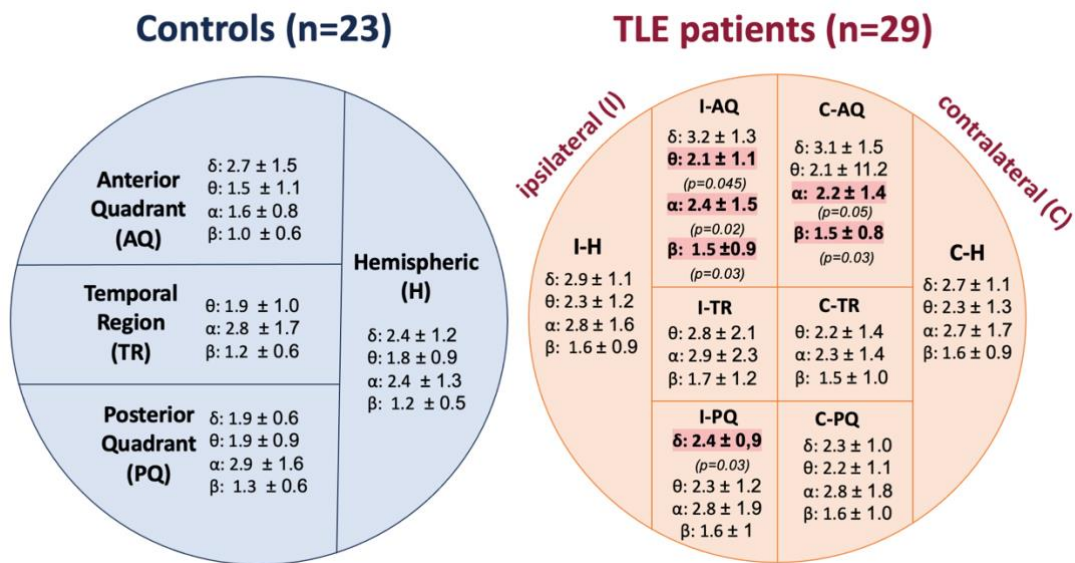


Figure 1. Absolute power spectral density values (mean $\pm$ SD) in controls and TLE patients. The frequency bands in which TLE patients exhibited a significant increase in power spectral density compared to controls are highlighted. Δ , delta; θ , theta; α , alpha; β , beta; AQ, anterior quadrant; TR, temporal region; PQ, posterior quadrant; H, hemispheric; I, ipsilateral; C, contralateral.

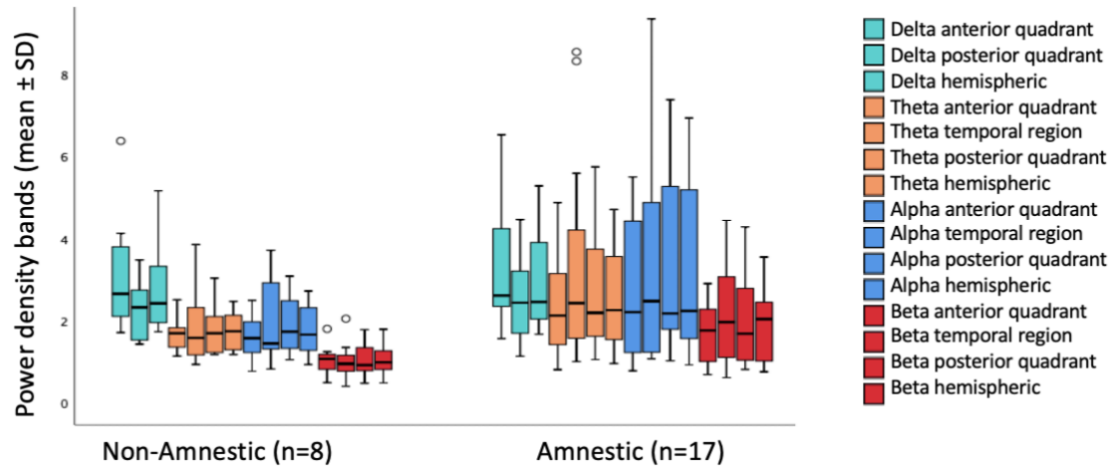


Figure 2. Absolute value distribution of power spectral density bands in TLE patients with amnestic vs non-amnestic cognitive impairment. An increase in theta, alpha, and beta frequencies directly correlated with amnestic cognitive impairment ($p < .005$).

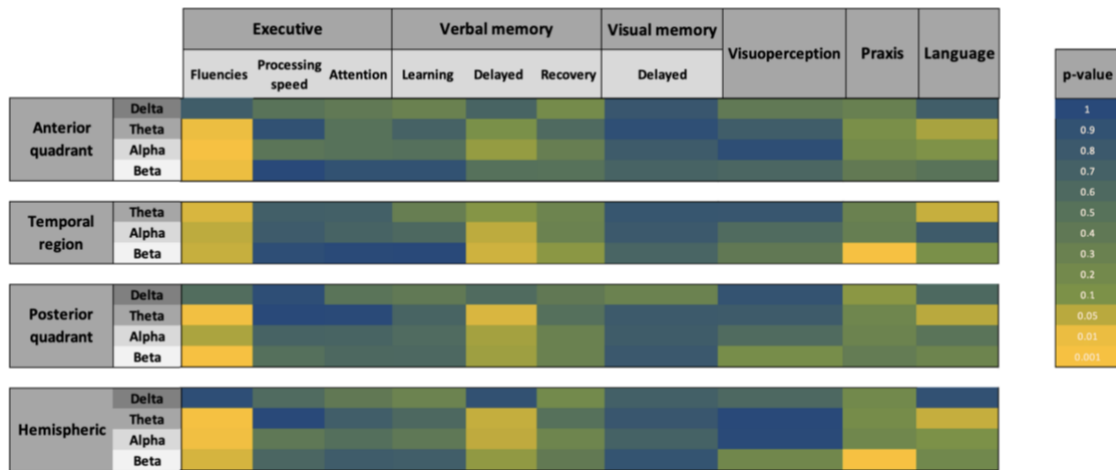


Figure 3. Heat map displaying the significance levels of comparisons between spectral power density values across different brain locations and impairments in each cognitive domain. Increases in power spectral density were most strongly associated with impairments in executive fluencies and delayed verbal memory ($p < .005$).