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Comparison of Brain Activity between Patients with Parkinson Disease Dementia and Patients Affected by Dementia with Lewy Body through EEG Analysis

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Abstract

Objective: Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB) are two syndromes categorized under synucleinopathy, sharing comparable symptoms. The identification of biomarkers would offer an accurate approach for improved diagnosis, treatment, and monitoring of treatment efficacy for these distinct forms of dementia.
Method: This study utilized spectral analysis and nonlinear dynamic analysis to compare electroencephalogram (EEG) characteristics between PDD and DLB patients. EEG data was collected from 30 PDD patients, 36 DLB patients, and 36 healthy subjects at rest. Following a conditioning phase to minimize noise and eliminate artifacts, we derived spectral and complexity features using Welch's method and sample entropy. Analysis of variance with repeated measures was performed to compare spectral features and nonlinear dynamics of brain activity between the groups.
Results: Post hoc comparison showed that in the control group, the power of delta and theta bands was lower and the power of alpha and beta bands was higher than in patients with PDD and DLB. ($P < 0.05$). In the theta and alpha bands, the PDD group showed greater power than the DLB group ($P < 0.05$). Furthermore, there was a significant main effect of diagnosis ($F = 4.67$, $P = 0.007$), and also the diagnosis by region interaction for complexity values ($F = 4.58$, $P = 0.009$). Post hoc analysis showed that the EEG complexity of the control group was significantly higher than that of the PDD and DLB groups in the frontal, central, temporal and parietal regions ($P < 0.05$). Moreover, the EEG complexity of the PDD group was significantly higher than that of the DLB group in the central, temporal and parietal regions ($P < 0.05$).
Conclusion: Although both PDD and DLB had almost similar patterns compared to the control group, they showed differences in the EEG power spectrum and its nonlinear dynamics. Our findings indicated marked diffuse slowing and lower cortical complexity or activity in DLB patients compared to PDD in all regions, especially in the central, temporal and parietal areas.

Key words: *Brain; Complexity Analysis; Electroencephalogram; Lewy Body Dementia; Parkinson's Disease*

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Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are two common forms of dementia that are clinically and neuropathologically related to Parkinson's disease (PD). Both diseases are described by cognitive impairment, behavioral changes, and motor symptoms, presenting significant challenges for patients, caregivers, and healthcare providers (1). Understanding the underlying neurophysiological differences between PDD and DLB is crucial for developing accurate diagnostic tools and targeted treatment strategies. DLB and PDD are two types of degenerative dementia conditions that are often considered to be part of a single disease spectrum due to their overlapping symptom profiles, shared underlying neuropathology characterized by the accumulation of alpha-synuclein, overlapping patterns of cortical and subcortical atrophy, as well as alterations in neurotransmitter systems, such as dopaminergic and cholinergic pathways, and similar responses to treatment (2, 3). The main clinical features of both syndromes include a combination of Parkinsonian symptoms and dementia. PDD is often characterized by more prominent motor symptoms, such as rigidity, bradykinesia, and tremors, which are core features of Parkinson's disease (4). In contrast, DLB features more prominent visual hallucinations and fluctuating cognition. Also motor symptoms seen in Parkinsonism may develop later in the disease course compared to PDD (5). To aid clinical practice, a guideline has been proposed suggesting that PDD should be diagnosed if motor symptoms related to movement control precede cognitive impairment by more than one year, while DLB should be diagnosed if cognitive decline occurs before or at the same time as the initial motor symptoms (6). However, these distinctions are somewhat arbitrary, and it can be challenging to determine which symptoms appeared first, particularly in cases of PDD with early onset of cognitive issues. As a consequence, individuals who exhibit motor signs along with cognitive symptoms may be diagnosed with Parkinson's disease (PD), even if dementia is also present (7). Additionally, differentiating between minimal cognitive impairment (MCI) and dementia in older adults poses challenges, especially considering the limitations of current neuropsychological assessment tools (8). In summary, while PDD and DLB share several clinical and neuropathological features, they also exhibit distinct characteristics that have implications for diagnosis, treatment, and understanding of their underlying neurophysiological mechanisms. This underscores the importance of a tailored approach to managing each condition based on its unique clinical presentation and pathophysiological features.

Numerous studies have demonstrated parallels between DLB and PDD in terms of clinical symptoms (9), neuropsychological assessments (10), neurochemical alterations (11), neuroimaging (12), and electrophysiological markers (13), indicating that these conditions could potentially represent different expressions of the same underlying condition (14). Nevertheless, recent findings have brought attention to differences, especially concerning the progression of motor and cognitive symptoms over time (15), cognitive profiles (16), distribution of neurotransmitters (17), neuropathological patterns (18), and electrophysiological measures (19). These findings suggest that PDD and DLB might either be distinct diseases that converge into a common pathway or independent conditions with shared genetic predispositions with PD and Alzheimer's disease (20).

The most common finding in nearly all forms of dementia is widespread slowing of the electroencephalogram (EEG), which tends to worsen as cognitive function declines (21). This slowing pattern is more evident in DLB compared to Alzheimer's disease and typically emerges earlier in the disease process (22). Similarly, PD patients exhibit EEG slowing when compared to age-matched healthy individuals (23). Moreover, most PD people develop PDD within the course of their motor disease (24). The identification of reliable biomarkers could offer a precise approach for enhancing the diagnosis, treatment selection, and monitoring of therapeutic responses across different types of dementia (25). EEG provides a cost-effective and non-invasive means for assessing brain activity and is widely available as an equipment in most primary care settings (26-30). Consequently, various EEG measurements have been extensively utilized in evaluating dementia and its differential diagnosis (31).

Most previous EEG studies have only focused on spectral analysis and ignored the nonlinear dynamics of brain signals, while various studies have proven the importance of these nonlinear dynamics in increasing our insight into various conditions. Therefore, the main goal of this research is to employ spectral and complexity EEG analyses to investigate brain activity patterns in patients with PDD and DLB. We will investigate alterations in specific EEG frequency bands, including delta, theta, alpha, and beta rhythms, as well as measures of EEG complexity, such as entropy and fractal dimension. By elucidating the differences in brain activity patterns between PDD and DLB, we seek to contribute to the refinement of diagnostic criteria and the development of targeted interventions tailored to the distinctive neurobiological underpinnings of each condition.

Materials and Methods

Participants

From June 2020 to February 2024, we retrospectively reviewed the EEG data recorded at a neurology clinic in Karbala, Iraq. We included people with DLB who fulfilled the revised criteria for probable DLB (32) and people with PDD who fulfilled the criteria for probable PDD (33). EEG records with mixed or overlapping

diagnoses were excluded. Also, signals with poor quality were discarded. Finally, EEG data of 36 DLB (72.2% male) and 30 PDD (76.5% male) patients were recruited in this research project. In addition, the Mini-Mental State Examination (MMSE) scores of the patients were obtained from their records. The MMSE is a widely utilized instrument for evaluating cognitive function. It comprises of tasks and questions that assess various cognitive abilities, including memory, attention, language, and spatial skills. The MMSE is considered both valid and reliable for assessing patients with dementia (34). The demographic information and clinical features of the patients are presented in Table 1. In addition, the EEG signal of 36 age-matched healthy volunteers (66.7% male) from among the companions referred to the neurology clinic was recorded by our research team as a healthy control group. The people of the control group were examined by a clinician for the absence of neurological and psychiatric diseases and the absence of drugs affecting brain waves. The research was approved by the Ethics Committee at the Faculty of Medicine of Karbala University.

EEG Data and Conditioning

EEG signals were collected using same 19 Ag/AgCl disc scalp electrodes following the international 10-20 system. Specific electrode placements included Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, T3, T4, T5, T6, O1, and O2 channels, with additional electrodes positioned at A1 and A2 for reference. Electrode impedance was maintained below 5 kΩ during signal recording. Filtering parameters were set to a low-pass filter at 0.5 Hz and a high-pass filter at 70 Hz with a sampling frequency of 256 Hz. The EEG signals were continuously recorded for a duration of 10-15 minutes while the participants rested in a calm, quiet environment with eyes open. The first two minutes of the recorded signals were discarded to allow the participant to adapt to the environment. The captured data underwent visual examination by an experienced neurologist to identify any clinical significance or to detect artifacts. A FIR Butterworth band-pass filter (order 4) with cutoff frequencies at 0.5 Hz and 50 Hz was implemented to minimize EEG noise, and a 50 Hz notch filter was employed to eliminate power line interference. The electrode configuration was adjusted to linked ears, and a 50- to 60-second segment of artifact-free EEG was chosen for each subject.

Spectral Analysis

As brain functions and their underlying mechanisms are linked to EEG oscillations, the Welch technique was employed to identify the four standard frequency bands (35, 36): delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-34 Hz). The Welch technique is a widely utilized approach for calculating the power spectrum density (PSD) of a time series. This method entails using a sliding window of specific length and overlap to divide the signal into successive time segments. For each segment, a periodogram is created, and these periodograms are then averaged over time to estimate the PSD (37, 38). In this research, a Hanning window lasting one second, with an overlap of 0.5 seconds, was utilized in the Welch method. Following PSD calculation through the Welch algorithm and identification of the frequency bands, the relative power was derived from the PSD of each EEG band.

Complexity Analysis

In this research, sample entropy was calculated from the EEGs to estimate the complexity of brain activity in different brain sites. Sample entropy is a measure used in the analysis of time series data like EEGs to quantify the regularity or predictability of the data. It provides a way to assess the complexity of a signal by measuring the likelihood that similar patterns of data points will remain close together as the length of the patterns being considered increases (39). One advantage of sample entropy is its ability to detect subtle changes in the underlying dynamics of a time series, even in the presence of noise or other sources of variability. This makes it a valuable tool for identifying changes in brain activity and dynamics, as it can capture changes in the regularity and complexity of EEG signals that may be indicative of different cognitive states, neurological conditions, or responses to stimuli (40, 41). Sample entropy finds applications in EEG analysis for various purposes, such as investigating cognitive processes, monitoring brain function in clinical settings, and exploring the effects of interventions or treatments on brain activity. By quantifying the irregularity and complexity of EEG data, sample entropy can help researchers and clinicians to identify patterns and trends that may not be apparent through visual inspection alone. This can lead to deeper insights into brain function and dynamics, aiding in the understanding of neural processes and neurological conditions.

Statistical Analysis

First of all, it should be noted that analysis of EEG data was done based on signals derived from different brain regions different brain regions with the following definition: frontal (Fz, Fp2, F7, Fp1, F3, F4, F8), central (Cz, C3, C4), parietal (Pz, P3, P4), temporal (T3, T4, T5, T6) and occipital (O1, O2). Prior to this, we calculated a natural logarithm transformation for all EEG power and complexity measurements. Subsequently, we combined data from individual electrodes to generate an average for the specified regions. Any features extracted from EEGs that had values surpassing three times the interquartile range of the overall average in every diagnostic class (either relative power or sample entropy) in any region were excluded from subsequent analysis. Differences between groups in resting EEG features were investigated using repeated-measures ANOVA for delta, theta, alpha, and beta band powers as well as for sample entropy. Each overall ANOVA contained a factor for diagnosis (PDD, DLB, and control) and a factor for regions (frontal, central, parietal, temporal, and occipital). For significant

interactions, subsequent one-way ANOVAs were performed for every area. Significant main effects were further explored with post-hoc pairwise comparisons, adjusted through a Bonferroni correction. If the assumption of sphericity was violated, Greenhouse-Geisser estimates were utilized. All statistical analyses were carried out using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered for significance level in the analysis. Furthermore, one-way ANOVA was used to analyze demographic information.

Results

As shown in Table 1, the demographics and clinical information of subjects (30 with PDD, 36 with DLB, and 36 healthy controls) underwent further analysis. The three groups did not display any significant differences in terms of gender, age and educational level ($P > 0.05$). Although the PDD group reported a slightly longer disease duration than the DLB group, there was no significant difference in terms of disease duration ($P > 0.05$). In addition, despite the observed differences between the two groups in terms of MMSE score and clinical symptoms, no significant difference was observed between the two groups of patients ($P > 0.05$).

Table 1. Comparison of Baseline Characteristics of the Subjects in Each of the Parkinson's Disease Dementia (PDD), Dementia with Lewy Bodies (DLB) and Control Groups.

Variable	PDD (n = 30)	DLB (n = 36)	Control (n = 36)	P-value
Age, year (m ± SD)	70.46 ± 3.81	71.12 ± 4.23	69.77 ± 4.65	0.409
Gender, % Male	76.50	72.20	66.70	0.314
Educational level, year (m ± SD)	8.71 ± 2.12	9.00 ± 2.57	9.22 ± 3.04	0.735
Duration of disease, months (m ± SD)	57.51 ± 12.82	53.86 ± 11.95	-	0.236
Mini Mental State Examination (MMSE)	21.11 ± 2.90	20.32 ± 3.14	-	0.296
Symptoms (cognitive decline), n (%)	27 (90.00)	33 (91.67)	-	0.724
Symptoms (cognitive fluctuation), n (%)	16 (53.33)	21 (58.33)	-	0.210
Symptoms (Parkinsonism), n (%)	30 (100)	29 (80.55)	-	0.124
REM sleep behavior disorders, n (%)	18 (60.00)	23 (63.88)	-	0.423

Figure 1 illustrates 10 gradient-colored head spatial maps of the mean frequency represented in one second consecutive epochs in one PDD patient, one DLB patient and one healthy control. As can be seen, PDD and DLB patients showed an erratic rhythm of cortical activation through the scalp, with a variable mean frequency mostly in the pre-alpha and theta ranges. However, the normal subject showed a stable pattern of alpha activity.

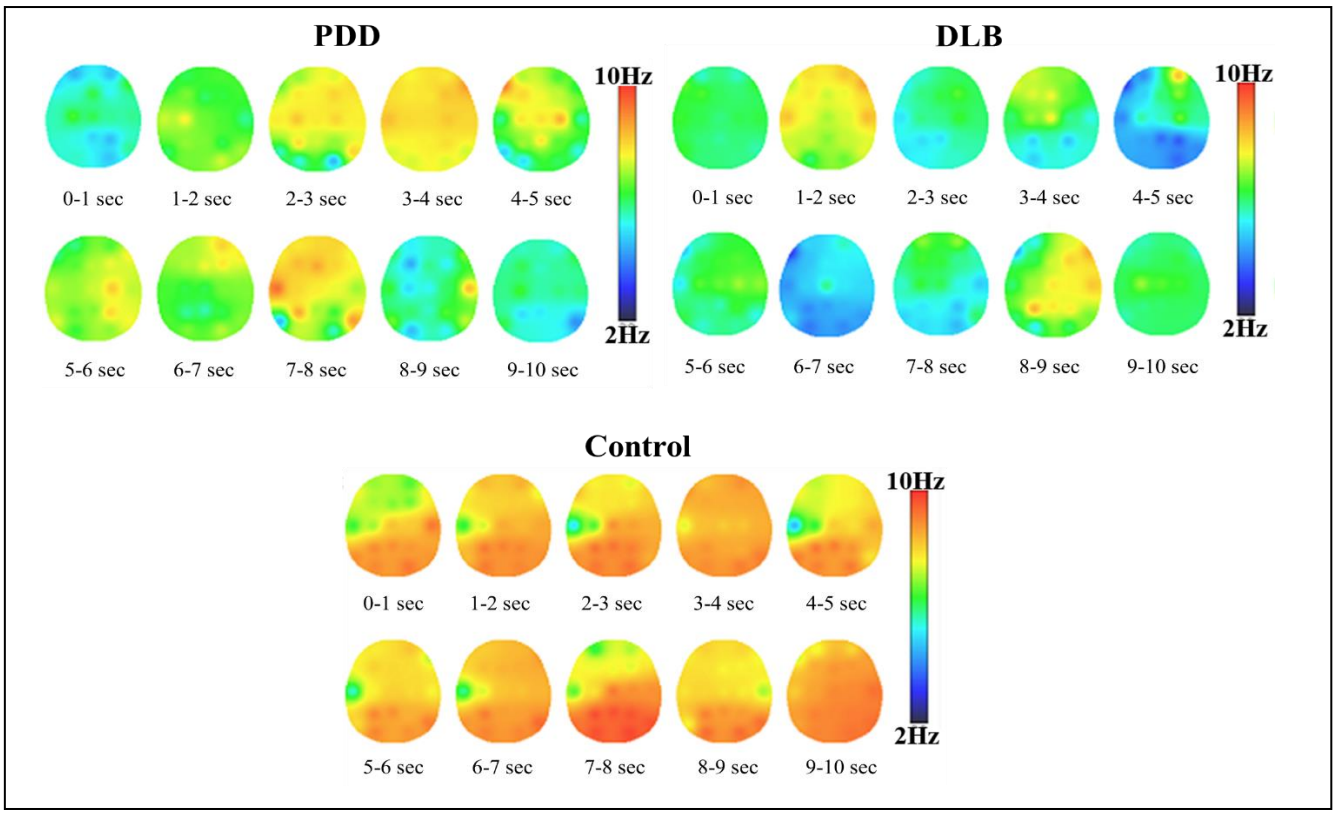

Figure 1. Gradient-Colored Head Spatial Maps of the Mean Frequency Represented in One Second Consecutive Epochs in One PDD Patient, One DLB Patient and One Healthy Control. Color Scales Represent Frequency Ranges. Note: PDD = Parkinson's Disease Dementia and DLB = Dementia with Lewy Bodies.

The outcomes of the comprehensive repeated measures ANOVAs for every frequency band can be found in Table 2. A significant main effect of region was observed across all frequency bands. As a result, an omnibus ANOVA encompassing all frequencies showed a substantial main effect of region ($F = 12.84$, $P < 0.001$). Table 3 shows the post hoc comparison of relative band powers in four frequency bands between PDD, DLB and Control groups. The power of the delta and theta bands in the control group was lower than that of the PDD and DLB patients. However, there was no significant difference in the delta band between the PDD and DLB groups. In the theta band, the PDD group showed greater power than the DLB group. In addition, the power of the alpha and beta bands in the control group was higher than that of the PDD and DLB patients. Also, in the alpha band, the PDD group showed greater power than the DLB group.

Table 2. Repeated Measures Analysis of Variance of Electroencephalogram Band Powers among Parkinson's Disease Dementia (PDD), Dementia with Lewy Bodies (DLB) and Control Groups.

Frequency Band		DF	F-Value	P-Value
Delta	Diagnosis	685	4.59	0.010
	Diagnosis × Region	17917	3.72	0.004
Theta	Diagnosis	685	5.96	0.006
	Diagnosis × Region	17917	4.11	0.021
Alpha	Diagnosis	685	6.06	0.001
	Diagnosis × Region	17917	5.82	0.008
Beta	Diagnosis	685	3.51	0.032
	Diagnosis × Region	17917	1.25	0.282

Table 3. Post Hoc Comparison of Relative Band Powers in Four Frequency Bands between Parkinson's Disease Dementia (PDD), Dementia with Lewy Bodies (DLB) and Control Groups.

Frequency Band	Brain Region	PDD (n = 30)	DLB (n = 36)	Control (n = 36)	Significant Difference (P < 0.05)
Delta	Frontal	0.23 ± 0.07	0.26 ± 0.08	0.18 ± 0.07	Control < PDD Control < DLB
	Central	0.19 ± 0.06	0.22 ± 0.08	0.17 ± 0.10	Control < DLB
	Temporal	0.18 ± 0.09	0.22 ± 0.10	0.17 ± 0.08	-
	Parietal	0.19 ± 0.08	0.22 ± 0.11	0.17 ± 0.10	-
	Occipital	0.18 ± 0.10	0.21 ± 0.09	0.17 ± 0.09	-
Theta	Frontal	0.18 ± 0.07	0.22 ± 0.06	0.15 ± 0.05	PDD < DLB Control < DLB
	Central	0.17 ± 0.06	0.23 ± 0.09	0.16 ± 0.06	PDD < DLB Control < DLB
	Temporal	0.18 ± 0.07	0.24 ± 0.10	0.17 ± 0.08	PDD < DLB Control < DLB
	Parietal	0.22 ± 0.09	0.24 ± 0.11	0.20 ± 0.12	-
	Occipital	0.21 ± 0.12	0.25 ± 0.14	0.21 ± 0.09	-
Alpha	Frontal	0.15 ± 0.06	0.12 ± 0.04	0.19 ± 0.05	DLB < PDD PDD < Control DLB < Control
	Central	0.19 ± 0.06	0.14 ± 0.05	0.20 ± 0.06	DLB < PDD DLB < Control
	Temporal	0.20 ± 0.08	0.15 ± 0.06	0.21 ± 0.06	DLB < PDD DLB < Control
	Parietal	0.21 ± 0.06	0.15 ± 0.07	0.30 ± 0.08	DLB < PDD PDD < Control DLB < Control
	Occipital	0.20 ± 0.08	0.16 ± 0.07	0.32 ± 0.08	PDD < Control DLB < Control
Beta	Frontal	0.14 ± 0.09	0.11 ± 0.05	0.24 ± 0.10	PDD < Control DLB < Control
	Central	0.15 ± 0.09	0.11 ± 0.08	0.24 ± 0.12	PDD < Control DLB < Control
	Temporal	0.15 ± 0.07	0.12 ± 0.06	0.18 ± 0.10	DLB < Control
	Parietal	0.14 ± 0.10	0.11 ± 0.08	0.16 ± 0.09	-
	Occipital	0.09 ± 0.04	0.07 ± 0.05	0.10 ± 0.07	-

After spectral analysis, EEG complexity analysis was performed. A significant main effect of region was observed across entropy values. According to the repeated measures analysis, there was a significant main effect of diagnosis ($F = 4.67$, $P = 0.007$), and also of the diagnosis by region interaction for complexity values ($F = 4.58$, $P = 0.009$). Post hoc analysis showed that the EEG complexity of the control group was significantly higher than that of the PDD and DLB groups in the frontal, central, temporal and parietal regions ($P < 0.05$). Moreover, the EEG complexity of the PDD group was significantly higher than that of the DLB group in the central, temporal and parietal regions ($P < 0.05$).

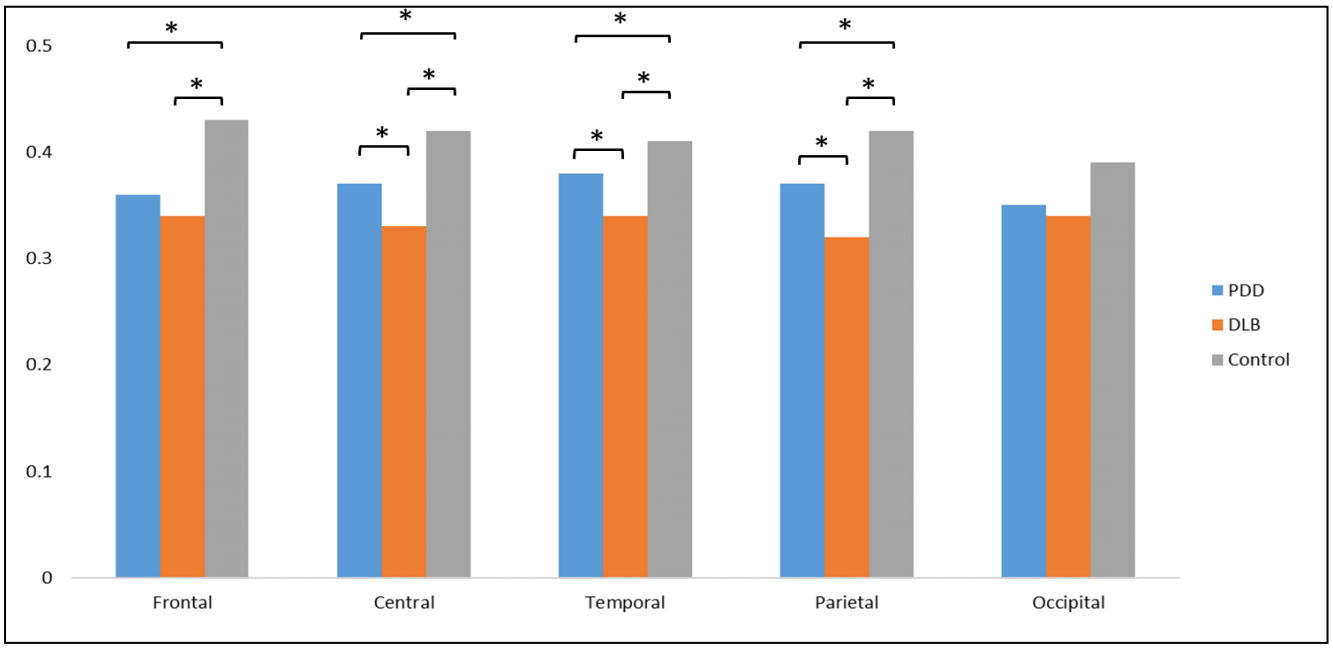

Figure 2. Comparison of Sample Entropy Values in Five Brain Regions between Parkinson's Disease Dementia (PDD), Dementia with Lewy Bodies (DLB) and Control Groups.

Discussion

This research compared brain activity between patients with PDD and patients affected by DLB through spectral and complexity analysis of EEG recordings. In people with DLB and PDD, there were changes in EEG frequency bands compared to normal matched individuals. These changes in EEG patterns can provide insights into the underlying neurophysiological differences associated with these conditions. Specifically, our findings showed that individuals with DLB and PDD exhibit increased delta and theta rhythms and reduced alpha and beta rhythms in contrast to normal individuals. This observation is in line with previous research (4, 16, 22). Moreover, this study revealed marked diffuse slowing in DLB patients compared to PDD in all regions regarding decrease in alpha and increase in the theta band in various brain areas. According to the high frequency band, the PDD group tends to show higher relative beta power than DLB patients. Many previous studies indicated a reverse relationship between EEG slowing and cognitive dysfunction in dementia (22, 42). Literature showed that EEG slowing is correlated with cholinergic dysfunction (43). DLB is associated with a significant decrease in cholinergic activity, which has been demonstrated to be more severe than in Alzheimer's disease (44), and also compared to PDD as shown in this study. This deficit tends to become manifest earlier in the progression of DLB (45). Research indicates a correlation between this cholinergic deficit and the degeneration of the cholinergic nucleus of Meynet (NBM) within the substantia innominate, which is part of the basal forebrain (46). Furthermore, this degeneration is more evident in DLB compared to Alzheimer's disease and PDD. These findings highlight the substantial impact of cholinergic dysfunction in DLB and its implications for disease progression. In our research, we observed that individuals with DLB exhibited greater EEG slowing and decreased relative alpha power in the front part of the brain compared to those with PDD. We believe that this difference may be due to the likelihood of more substantial damage to the cholinergic nucleus in the forebrain among individuals with DLB. Our findings interestingly indicated non-significant greater beta power in the PDD group compared to the DLB. The increased relative power of this fast wave in PDD compared to DLB could potentially explain the fundamental pathophysiological distinction between these two types of dementia. Nevertheless, further investigation is necessary to uncover the reasons behind this variability in the pattern of high frequency brain activity. In contrast to slow waves, fast waves have not received significant attention in studies examining EEG changes in dementia. Therefore, it seems crucial for high frequency brain wave patterns to be the focus of future research in this area.

Furthermore, for the first time, our study investigated EEG complexity in these two syndromes and showed that cortical complexity is highly reduced in both PDD and DLB patients contrasted to the normal condition. This observation is consistent with previous research showing reduced cortical complexity in dementia (47, 48). Seker *et al*. conducted a study where they analyzed the permutation entropy of EEG recordings from 85

Alzheimer's patients and 85 individuals without the condition. Their findings indicated a decrease in EEG complexity among the patients (49). Similarly, Yang *et al*. investigated the multiscale entropy of EEGs from 15 Alzheimer's patients and 15 healthy controls, revealing a reduction in EEG complexity in patients when considering short-time scales (50). Additionally, although with a limited sample size (15 subjects per group), McBride *et al*. also observed corresponding outcomes when comparing individuals with Alzheimer's and healthy subjects using Lempel-Ziv complexity and sample entropy (51). This important observation indicates the presence of distinct dynamic systems in the brain that are influenced by dementia, such as PDD and DLB, providing evidence for the disconnectivity theory underlying dementia neuropathology (52). Furthermore, it enhances our comprehension of the atypical neural connections found in this condition. In fact, the decreased EEG complexity in people with PDD or DLB may indicate a transition in brain activity toward more foreseeable patterns (50). In addition, our findings showed that EEG complexity in DLB patients is significantly lower than that of PDD patients in the central, temporal, and parietal regions. This observation may indicate lower brain activity of DLB patients in these brain areas and express its specific neuropathology compared to PDD patients. Lewy bodies and Lewy neurites, which are abnormal protein deposits primarily composed of alpha-synuclein, have been found in these areas. These neuropathological changes are associated with the cognitive and motor symptoms observed in individuals with DLB.

Limitation

Although the study includes several participants, the sample size for either PDD or DLB group may be relatively small. A larger cohort could enhance the statistical power and generalizability of the findings. Moreover, this research uses a cross-sectional design, which limits the ability to draw conclusions about the progression of EEG changes over time. Longitudinal studies would provide more insight into how EEG characteristics evolve in both PDD and DLB patients. The analysis was conducted during rest periods, which may not fully capture the dynamic nature of brain activity. Incorporating tasks that engage cognitive functions could provide a more comprehensive understanding of the EEG differences between the groups. In addition, the study mainly focuses on spectral and complexity features of EEG data. Exploring additional EEG metrics, such as coherence or connectivity analysis, could uncover further distinctions between PDD and DLB.

Conclusion

In summary, this research showed obvious differences between PDD and DLB syndromes, which can be a sign of their different nature and different neuropathology. Although both PDD and DLB had almost similar patterns compared to the control group, they showed differences in the EEG power spectrum and its nonlinear dynamics. Our findings indicated marked diffuse slowing and lower cortical complexity or activity in DLB patients compared to PDD in all regions, especially in the central, temporal and parietal areas. According to our findings, it appears that PDD and DLB may represent separate conditions leading to a shared final outcome. Nevertheless, additional prospective and longitudinal investigations are necessary to make precise conclusions.

Conflict of Interest

None.

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