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Differentiating neurodegenerative diseases based on EEG complexity

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Neurodegenerative diseases are common causes of impaired mobility and cognition in the elderly. Among them, tauopathies and α-synucleinopathies were considered. The neurodegenerative processes and relative differential diagnosis were addressed through a qEEG non-linear analytic method. Study aims were to test accuracy of the power law exponent β applied to EEG in differentiating neurodegenerative diseases and to explore differences in neuronal connectivity among different neurodegenerative processes based on β. *N* = 230 patients with a diagnosis of tauopathy or α-synucleinopathy and at least one artifact-free EEG recording were selected. Periodogram was applied to EEG signal epochs from continuous recordings. Power law exponent β was determined by the slope of the signal power spectrum versus frequency in logarithmic scale. A data-driven clustering based on β values was performed to identify independent subgroups. Data-driven clustering based on β differentiated tauopathies (overall lower β values) from α-synucleinopathies (higher β values) with high sensitivity and specificity. Tauopathies also presented lower values in the correlation coefficients matrix among frontal sites of recording. In conclusion, significant differences in β values were found between tauopathies and α-synucleinopathies. Hence, β is proposed as a possible biomarker of differential diagnosis and neuronal connectivity.

Keywords Degenerative diseases, Tauopathies, α-Synucleinopathies, Quantitative EEG, Spectrum power-law decay exponent

Neurodegenerative diseases are characterized by the progressive loss of populations of vulnerable neurons. They are more common in people in advanced age, being a predominant cause of cognitive and motor impairments in the elderly. Individual neurodegenerative disorders are heterogeneous in their clinical presentation, manifesting overlapping clinical signs and symptoms. In particular, α-synucleinopathies and tauopathies categories are intimately intertangled and among the most frequent diseases in this field[1,2].

Tauopathies are disorders characterized by pathological accumulation of tau protein in glia and neurons, while in α-synucleinopathies a pathological aggregation of pre-synaptic protein α-synuclein is detected[1]. Tauopathies are diseases prominently characterized by cognitive decline, including Alzheimer's Disease (AD), Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)[1]. In the context of α-synucleinopathies, syndromes with prominent parkinsonism are included, such as Parkinson's Disease (PD) and Multiple System Atrophy (MSA)[1]. However, clinical overlapping between the two groups exists, with parkinsonian features detectable in the context of cognitive decline among tauopathies and cognitive decline in the context of parkinsonism among α-synucleinopathies[1,3].

At present, diagnosis in living patients is possible only when clinical symptoms are manifested and the disease is already progressing, through criteria of "probability" and "possibility"[2]. In addition to the clinical features, neuroimaging data may represent supportive information for the diagnosis, including both structural and functional imaging[2].

Electroencephalography (EEG) offers a non-invasive and cost-effective method to measure electrical brain activity with excellent temporal resolution. EEG reveals real-time functioning of brain synapses[4]. Recognizing specific neural oscillation patterns can be helpful to define possible network impairment involved in neurodegeneration and its progression over time[5,6] However, EEG as it is actually used in clinical approach only relies on periodic rhythms.

Quantitative EEG (qEEG) is the mathematical process to extract quantitative parameters otherwise usually deduced by experienced electroencephalographers in an only visual and unaided manner. In order to extract

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meaningful features, EEG data has to be digitalized and cleared of artifacts[7]. Different kinds of analysis using this technique are currently being investigated[8–13].

Modern analyses of qEEG propose to address neurodegenerative diseases and relative patterns through the study of neuronal electrical discharge[5,9,13,14] Overall exposed qEEG techniques are based on the spectral analysis of the electrocortical signal. The use of such method to identify biomarkers of specific neurodegenerative processes is still limited, as well as its use in differential diagnostics between various neurodegenerative pathologies[5,15–19].

Spectral analysis only addresses fixed periodic components of the signal while the aperiodic activity is often ignored, considered as simple noise or background activity[4,20]. In neural data, this aperiodic activity has a specific distribution, with an inversely proportional relationship between power and its frequency[4]. This behavior can be expressed by the power law exponent β, which describes how signal is modulated over the frequency spectrum, representing a quantitative estimation of signal complexity[21]. β value should not be confounded with the well know "β band" of EEG. Analysis based on β computation allows to define if the signal follows a random or a deterministic behavior, typical of a fractal-like phenomenon in which the whole process has the same behavior as its parts; this property is called "self-similarity"[4,10–13]. However, the study of the intrinsic behaviors of neural oscillatory activities in neurodegenerative diseases remains still partly theoretical and poorly explored[11,22–26], despite its relevant potential application in clinical context.

The aim of this work is to understand through the analysis of β of the EEG spectrum if there is a fractal-like behavior with a higher level of neuronal organization in specific areas of the brain that varies between major neurodegenerative diseases (tauopathies vs. α-synucleinopathies). For these purposes, a data-driven approach has been applied. Therefore, the study aims were: (a) to test accuracy of the power law exponent β in differentiating neurodegenerative diseases; (b) to explore differences in neuronal connectivity among different neurodegenerative processes based on β.

Materials and methods

Study population and design

Clinical and electrophysiological data from patients referred for cognitive and motor complaints, who had undergone standardized EEG assessment attending the Neurologic Clinic at the University of Catania, Italy, were retrospectively selected over a fourteen-years period of time (2006–2020). Inclusion criteria for the study were: (a) a diagnosis of neurodegenerative disease based on standardized diagnostic criteria and confirmed by follow-up visits; (b) a comprehensive clinical and neuropsychological assessment at the time of the EEG; (c) at least one artifact-free complete EEG recording. Patients with diagnosis of tauopathy (Alzheimer's disease, Progressive Supranuclear Palsy, Corticobasal Degeneration) or α-synucleinopathy (Parkinson's Disease, Multiple System Atrophy) were included. Patients with mild-cognitive impairment (MCI) were also included. Parkinson's disease patients were differentiated into patients with normal cognition (PDNC), MCI (PDMCI) or dementia (PDD) based on previously performed operating protocol[27]. Standardized diagnostic criteria were used to clinically characterize study patients at the time of assessment[28–35]. We also selected EEG recordings from healthy subjects group-matched by age who referred no cognitive complain at the time of exam.

Clinical data collection was performed by independent operators for each group. All patients underwent clinical, neuropsychological and instrumental assessments as part of the routinely diagnostic work-up performed at the time of their admission to the Neurologic Clinic. Mini-Mental State Examination (MMSE) was used as screening tool to assess cognition in all study subjects[36]. Study protocol was approved by local ethics committee (Comitato Etico Catania 1). Informed consent was obtained from study subjects. All methods were performed in accordance with the relevant guidelines and regulations.

EEG recordings

For both patients and controls groups, EEG signals were recorded from homologous pairs of electrodes placed over each hemisphere according to the 10:20 system with unipolar derivation and common reference (G2) and using a pre-cabled headcap (data acquisition system: SystemPLUS ver. 1.02.1109 for BRAIN-QUICK BQ132 S, Micromed). In particular, the mid/frontal (F3/4), lateral/frontal (F7/8), anterior-temporal (T3/4), mid-parietal (P3/4) and occipital (O1/2) sites signals were acquired during resting state. The sampling rate of recordings was equal to 256–512 Hz. The impedance of EEG signals was kept between 2 and 10 kΩ at the homologous sites. Signals were band-pass filtered (1.6–30 Hz) and digitized using default sampling rate according to a standardized protocol[19,27]. 5-seconds artifacts-free signal epochs (voltage unit: μV) during eyes-closed task were visually selected off-line from 2-minutes continuous EEG recordings. Five different NOTCH-filtered samples for each site were selected for each study subject to be analyzed.

qEEG analysis and β index computation

A Welch's periodogram (50% overlap between 1-s Hamming windowed segments) was applied to each 5-s artifacts-free EEG signal epoch recorded in sites and states mentioned in the previous paragraph; this process was based on a standardized protocol[19]. Welch's method was applied in order to perform spectral analysis and compute the power spectral density [PSD (μV^2/Hz)][37,38], a function that defines the relationship between EEG signal power and the frequency of the signal[11,19,27].

EEG signal analysis for all selected epochs was performed through the implementation of an ad-hoc-created Scilab script (ver. 5.4.1, Scilab Enterprises 2011–2013). The power law exponent β was calculated for each coordinate as minus the slope of the PSD versus frequency in a Log-Log scale in order to estimate self-similarity of the detected electrocortical signal. Self-similarity of a dynamic process, and thus related fractal properties, can be studied by analyzing the power law relationship between frequency and size of the process variation (Supplemental material Fig. S1). In stochastic signal, fractal properties are maintained for $1 < \beta < 3$,

with more pronounced self-similarity for β closer to 1[39–41]. Mean values of power law exponent β were obtained by analyzing five EEG samples for each site of recording.

By summarizing step-by-step analytic process:

(a) $N=5$ 5-seconds EEG signal epochs from each sites of recording were selected to be analyzed;
(b) Spectral analysis of signal epochs was performed;
(c) For each signal epoch, β values were computed;
(d) For each site of recording, we used the average β values obtained from the captured $N=5$ signal epochs.

Statistical analysis

Data are presented as mean ± standard deviation for scalar variables, frequency and percent value for categorical variables. Differences in scalar measures between groups were tested using t-test with Bonferroni correction for pairwise comparisons. Differences in proportions between groups were tested using the z-test. A non-hierarchical cluster analysis using k-means method was performed based on β values detected among the homologous sites of recordings in all diagnostic groups. The Calinski-Harabasz pseudo F index stopping-rule was used to evaluate the optimal number of clusters to be tested using statistical inference. Receiver Operating Characteristic (ROC) curve analysis was performed to obtain optimal discriminant cut-off values for EEG parameters between the identified clusters. ROC Area Under Curve (AUC), Standard Error (S.E.) of AUC, cut-off values by Youden method and their performance in terms of sensitivity and specificity with 95% Confidence Intervals (95%CI) were provided. Correlation analysis between scalar measures was performed using Pearson's r to obtain correlation matrixes among β values recorded over the selected sites. Multivariate analysis was also performed after adjustment for principal confounding variables. Significance level was set up at p-values < 0.05.

Results

$N=230$ patients affected by cognitive complaints due to neurodegenerative diseases (tauopathies or α-synucleinopathies), who were studied with a resting EEG, were identified. Patients distribution per diagnostic group based on available criteria was: AD, $N=24$ [10.4%, of which 12 (50%) women]; MCI due to AD (MCI), $N=21$ [9.1%, of which 15 (71.4%) women]; PSP, $N=15$ [6.5%, of which 4 (26.7%) women]; CBD $N=27$ [11.7%, of which 15 (55.6%) women]. These patients were considered as having tauopathies. Moreover, other patients were considered as having instead α-synucleinopathies: PDD, $N=8$ [3.5%, of which 3 (37.5%) women]; PDMCI, $N=45$ [19.6%, of which 20 (44.4%) women]; PDNC, $N=56$ [24.3%, of which 27 (48.2%) women]; MSA, $N=34$ [14.8%, of which 12 (35.3%) women]. Clinical characteristics of study subjects as well as β values detected among the selected sites of recording are shown in Table 1. Patients did not differ by age at the time of EEG evaluation among groups, while disease duration was longer for PDD patients with respect to the other groups, as expected. MMSE score was lower for AD, CBD and PDD groups.

In all groups, β values presented a crescent gradient from anterior to posterior homologous sites. We observed significant lower β values in atypical parkinsonisms PSP and CBD with respect to age-matched controls [$N=37$, of which 26 (70.3%) women], where differences were observed among overall sites of recording. Differences with controls were also observed for MSA in frontal-temporal and occipital regions as well as for AD in frontal-temporal regions as well (Table 1).

	AD ($N=24$)	MCI ($N=21$)	PSP ($N=15$)	CBD ($N=27$)	PDD ($N=8$)	PDMCI ($N=45$)	PDNC ($N=56$)	MSA ($N=34$)	CTRL ($N=37$)
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Age (years)	68.9 ± 9.1	65.6 ± 9.9	67.4 ± 6.0	69.6 ± 5.5	66.4 ± 5.2	66.2 ± 8.2	65.4 ± 8.8	63.9 ± 8.9	68.8 ± 6.2
MMSE score	$15.3 \pm 4.6^{a, b,c, d,e, f}$	25.1 ± 3.5^{a}	24.1 ± 6.9^{b}	$22.2 \pm 6.3^{c, g,h}$	$19.3 \pm 3.2^{i, j,k}$	$26.6 \pm 2.2^{d, g,i}$	$27.5 \pm 2.2^{e, h,j}$	$25.7 \pm 3.5^{f, k}$	–
Disease duration (years)	2.3 ± 1.3^{a}	1.6 ± 0.9^{b}	4.0 ± 3.1^{c}	3.2 ± 1.8^{d}	$14 \pm 8.2^{a, b,c, d,e, f,g}$	4.3 ± 4.1^{e}	2.8 ± 3.6^{f}	4 ± 2.3^{g}	–
F3 β	2.51 ± 0.34	2.62± 0.46	$2.21 \pm 0.28^{a, c}$	$2.34 \pm 0.29^{b, d}$	2.83 ± 0.28	$2.77 \pm 0.55^{c, d}$	2.53 ± 0.45	2.43 ± 0.55	$2.77 \pm 0.47^{a, b}$
F4 β	2.44 ± 0.37	2.53 ± 0.5	$2.23 \pm 0.27^{a, c}$	$2.33 \pm 0.33^{b, d}$	2.67 ± 0.34	$2.76 \pm 0.53^{c, d}$	2.54 ± 0.45	2.43 ± 0.55	$2.78 \pm 0.45^{a, b}$
F7 β	2.44 ± 0.39	2.46 ± 0.5	$2.16 \pm 0.43^{a, c}$	$2.22 \pm 0.43^{b, d}$	2.79 ± 0.29	$2.72 \pm 0.56^{c, d}$	2.5 ± 0.45	2.37 ± 0.52	$2.68 \pm 0.45^{a, b}$
F8 β	2.33 ± 0.42	2.49 ± 0.55	$2.13 \pm 0.38^{a, c}$	$2.22 \pm 0.41^{b, d}$	2.63 ± 0.46	$2.71 \pm 0.52^{c, d}$	2.54 ± 0.44	2.37 ± 0.59	$2.74 \pm 0.45^{a, b}$
T3 β	2.32 ± 0.39	2.45 ± 0.47	$2.15 \pm 0.35^{a, d}$	$2.25 \pm 0.5^{b, e}$	2.76 ± 0.37	$2.73 \pm 0.55^{a, b,c}$	2.6 ± 0.48	2.32 ± 0.58^{c}	$2.73 \pm 0.47^{d, e}$
T4 β	$2.35 \pm 0.49^{a, d}$	2.52 ± 0.41	$2.25 \pm 0.42^{b, e}$	$2.28 \pm 0.47^{c, f}$	2.72 ± 0.37	$2.74 \pm 0.51^{a, b,c}$	2.63 ± 0.42	2.46 ± 0.5	$2.81 \pm 0.45^{d, e,f}$
P3 β	2.94± 0.33	3.04 ± 0.41	$2.73 \pm 0.33^{a, c,e}$	$2.75 \pm 0.4^{b, d,f}$	3.23 ± 0.25	$3.17 \pm 0.43^{a, b}$	$3.13 \pm 0.29^{c, d}$	2.94 ± 0.43	$3.21 \pm 0.39^{e, f}$
P4 β	2.97± 0.29	3.04 ± 0.4	2.81 ± 0.24^{a}	$2.79 \pm 0.42^{b, c,d}$	3.24 ± 0.18	$3.21 \pm 0.38^{a, b}$	3.12 ± 0.33^{c}	2.97 ± 0.42	3.21 ± 0.38^{d}
O1 β	2.96 ± 0.35	3.06 ± 0.38	2.82 ± 0.28	2.76 ± 0.5^{a}	3.07 ± 0.34	3.05 ± 0.43	3.03 ± 0.35	2.84 ± 0.44^{b}	$3.22 \pm 0.34^{a, b}$
O2 β	2.94 ± 0.31	2.98 ± 0.41	2.80 ± 0.3	2.74 ± 0.48^{a}	3.11 ± 0.31	3.06 ± 0.4	3.02 ± 0.36	2.87 ± 0.41^{b}	$3.22 \pm 0.36^{a, b}$

Table 1. Clinical characteristics and qEEG parameters among different groups. Bonferroni-corrected sig. level for pairwise comparisons: $p=0.005$. For each table line, significant differences among two groups are indicated by similar superscript letters (i.e. MMSE score was different in AD vs. MCI – letter "a", AD vs PSP – letter "b", AD vs CBP – letter "c", etc.).

When we looked at differences between single diagnostic groups, we found that in bilateral frontal-temporal regions β values were significantly higher for PDMCI with respect to the atypical parkinsonisms PSP, CBD and MSA; differences remained significant in parietal regions only for PSP and CBD. In parietal regions, it was also observed higher β values for PDNC with respect to CBD and partially to PSP (Table 1).

Non-hierarchical cluster analysis using k-means method was then performed based on β values detected among the selected homologous sites of recordings in all diagnostic groups: F3, F4; F7, F8; T3, T4; P3, P4; O1, O2 ($N=10$ variables). Two independent groups of patients based on clustering parameters were identified (for $N=2$ to 8 clusters: $N=2$ pseudo $F=186.33^{*}$; $N=3$ pseudo $F=167.78$; $N=4$ pseudo $F=139.16$; $N=5$ pseudo $F=120.41$; $N=6$ pseudo $F=104.85$; $N=7$ pseudo $F=99.36$; $N=8$ pseudo $F=87.54$): Cluster A ($N=77$; 33.5%) and Cluster B ($N=153$; 66.5%). Distribution of diagnostic groups among the two identified clusters are shown in Table 2, together with statistically significant differences in evaluated clinical-instrumental variables.

Cluster A included more α-synucleinopathies with impaired cognition (PDMCI, PDD). Cluster B included instead more tauopathies with impaired cognition (PSP, CBD, AD) (Fig. 1). Patients in Cluster A presented younger age, longer disease duration, higher MMSE score and overall significant higher β values among all the homologous sites of recording with respect to Cluster B (Fig. 2). Differences in β values remained all significant after adjusting for principal confounding factors (age, disease duration, MMSE).

ROC curve analysis was applied to test accuracy of β in differentiating the two identified clusters based on a data-driven approach. Results are shown in Table 3. The parameters showed to differentiate the two clusters with high sensitivity and specificity over different recording sites.

Finally, correlation coefficients matrix was built to test functional connectivity among closed sites of EEG recording using β. We observed differences in β-related connectivity among frontal sites of recording between the identified clusters. Specifically, Cluster B demonstrated weaker correlations, suggesting lack of functional connections among frontal networks (Fig. 3).

Discussion

The aim of this study was to test accuracy of the power law exponent applied to EEG to differentiate neurodegenerative diseases and to explore their neuronal connectivity. EEG is a widely available, non-invasive, cost-effective, generally safe and painless diagnostic method that provides direct insight into brain synaptic activity in real time. It has been proved how qEEG compliments and improves the currently established diagnostic work-up of patients along the progression of neurodegenerative diseases[11,22,42,43] Fewer works have also examined the background of aperiodic exponents in order to better understand aging[24], and cognitive function[22,23].

The first step of this study was the comparison of β values of single considered pathologies. While β values were higher over the occipital sites, a significant alteration could not be identified, probably due to the physiological behavior of the index[10]. Based on the range of detected β values, EEG signal behavior in diagnostic groups and controls was comparable to systems which seem apparently stochastic but are instead organized as fractal-like systems[39,41]. This means that electrocortical activity seems not randomly modulated but organized in oscillatory activities which may underlie functional networks.

Our findings indicated lower β values in frontal-temporal areas for PSP, CBD and MSA as opposed to PDMCI. Differences remained significant in parietal regions for PSP and CBD patients in contrast to PDMCI and PDNC. A relevant result of this study is that β values of α-synucleinopathies do not vary among themselves but they are different when compared to tauopathies such as PSP and CBD, because tauopathies presented overall lower β values than α-synucleinopathies. As previously mentioned, literature has already been trying to find new biomarkers for neurodegenerative diseases through qEEG[11,22,42,43] However, even if qEEG and power law exponent β are not new to literature, only single diseases at a time have been examined and there have not been any works comprehensive of all the field of neurodegenerative diseases.

Another major finding of this study is that β values presented high sensitivity and specificity to distinguish between tauopathies and α-synucleinopathies and thus it is proposed as a possible biomarker of differential diagnosis. In fact, with a maintained crescent gradient from anterior to posterior cortical sites, cut-offs were pinpointed with overall sensitivity of 87–95% and specificity of 71–88%. Both sensitivity and specificity proved to decrease proceeding from anterior to posterior cortical lobes, being maximum at frontal areas and minimum at occipital ones.

We finally found that possible differences in functional neuronal connectivity at frontal sites of recording between tauopathies and α-synucleinopathies. In particular, tauopathies seem to be characterized by loss of functional connections among frontal networks. This feature was tested through the analysis of β, which is then also proposed as a possible biomarker of neuronal connectivity in order to better investigate neurodegenerative processes.

Traditional quantitative analysis of EEG has been proposed as key tool to explore progression and potential intervention in neurodegenerative dementia, and several reliable features have been identified by expert panel, including abnormalities in peak frequency, power, and "interrelatedness" at posterior alpha (8–12 Hz) and widespread delta (< 4 Hz) and theta (4–8 Hz) rhythms[44]. Application of non-linear features of EEG signals in neurodegenerative diseases are instead still limited, also because pathophysiological interpretation of intrinsic characteristics of signal remained controversial[45]. By accredited hypothesis, β values may reflect activity of spiking neurons of cortical networks being modulated by excitatory and inhibitory inputs[46]. Pathological processes related to aging may be potentially explored by this tool. Indeed, aging is associated with a flattering of the power law relationship between EEG spectral density and frequency, allowing reduced EEG signal-to-noise ratio[24]. Following the "neural noise hypothesis", reduced signal-to-noise may reflect increased spontaneous baseline neural spiking activity altering neural networking[24]. It has been hypothesized that in dementia, pathological

	Cluster A (*N* = 77; 33.5%)		Cluster B (*N* = 153; 66.5%)		
	N	**Percent**	**N**	**Percent**	**p value**
AD	3	3.9%	21	13.7%	0.021*
MCI	9	11.7%	12	7.8%	n.s.
PSP	1	1.3%	14	9.2%	0.023*
CBD	3	3.9%	24	15.7%	0.009*
PDD	6	7.8%	2	1.3%	0.011*
PDMCI	26	33.8%	19	12.4%	< 0.001*
PDNC	20	26%	36	23.5%	n.s
MSA	9	11.7%	25	16.3%	n.s.
	N	**Mean ± S.D.**	**N**	**Mean ± S.D.**	**p value**
Age (years)	77	64.4 ± 8.4	153	67.4 ± 8.1	< 0.001*
MMSE score	77	25.9 ± 3.5	153	23.8 ± 5.9	< 0.001*
Disease duration (years)	77	4.8 ± 5.3	153	3 ± 2.7	< 0.001*
F3 β	77	3.03 ± 0.33	153	2.29 ± 0.31	< 0.001*
F4 β	77	2.99 ± 0.36	153	2.27 ± 0.32	< 0.001*
F7 β	77	2.97 ± 0.37	153	2.22 ± 0.34	< 0.001*
F8 β	77	2.93 ± 0.4	153	2.22 ± 0.38	< 0.001*
T3 β	77	2.99 ± 0.37	153	2.22 ± 0.38	< 0.001*
T4 β	77	2.98 ± 0.37	153	2.3 ± 0.36	< 0.001*
P3 β	77	3.37 ± 0.26	153	2.84 ± 0.33	< 0.001*
P4 β	77	3.4 ± 0.24	153	2.86 ± 0.31	< 0.001*
O1 β	77	3.27 ± 0.32	153	2.8 ± 0.36	< 0.001*
O2 β	77	3.26 ± 0.32	153	2.79 ± 0.33	< 0.001*

Table 2. Differences in diagnostic groups distribution and clinical-instrumental variables between identified clusters. t-test and z-test were applied to test differences between means and proportions respectively. *n.s.* not-significant. *Sig. p values.

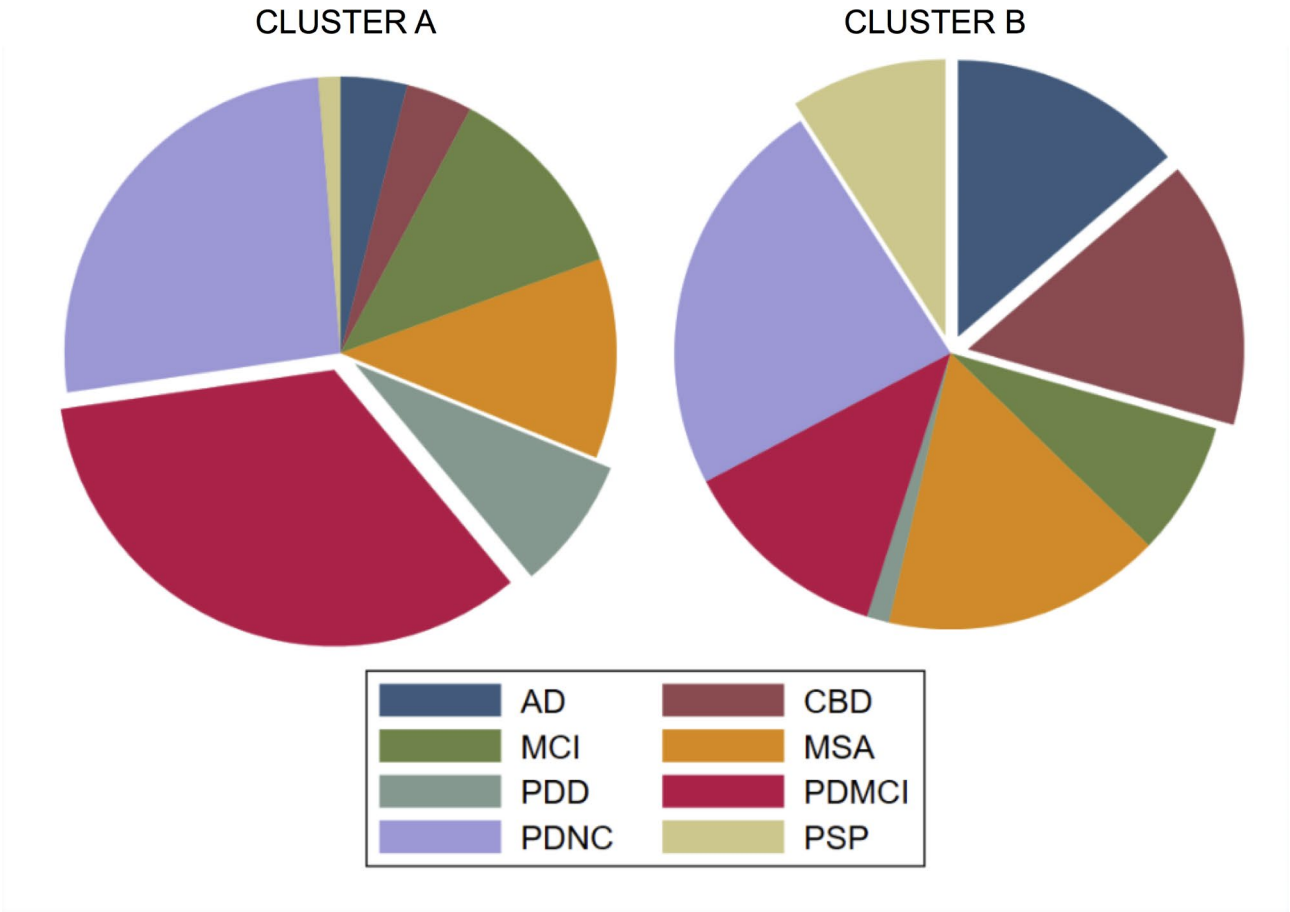

Fig. 1. Non-hierarchical clustering of neurodegeneration based on EEG power-law exponent β. ($N = 230$; 2 Groups by pseudo-F). LEFT: Cluster A: $N = 77$. RIGHT: Cluster B: $N = 153$. Cluster A presented overall sig. higher β values, including more α-synucleinopathies with impaired cognition (PDMCI, PDD). Cluster B presented overall sig. lower β values, including more tauopathies with impaired cognition (PSP, CBD, AD).

processes at molecular levels may converge in networks failure due to synaptic loss, leading to EEG thalamo-cortical "disconnection mode" and default mode network alteration[44,47,48].

Concerning application of β in AD, a single study based on a comprehensive review reported lower values with respect to controls in frontal and temporal regions, possibly reflecting topographic brain atrophy and loss of loco-regional connectivity[45,49]. Data on PD are less conclusive, even significant changes in aperiodic activity across the whole neocortex has been demonstrated[46]. No consistent data on the use of β in differentiating atypical parkinsonism as well as tauopathies vs α-synucleinopathies are available on literature.

Principal limitations of this study were: (1) small sample size adopted for single diseases, which was partially addressed by grouping them into clusters related to either α-synucleinopathies or tauopathies; (2) the retrospective design, which can lead to selection biases; (3) the uncertainty related to the adopted clinical criteria we used to diagnose the different groups of pathologies; (4) the limited set of adopted EEG channels[11,19], which may lead to a low spatial resolution.

In conclusion, statistically significant differences in β values were found between the two large groups of tauopathies and α-synucleinopathies. Even taking into consideration the aforementioned limitations, this is one of the first works to explore neurodegenerative diseases as a whole through the implementation of qEEG analysis and β. Power law exponent β was proved to be a high accurate index and a reliable score measure towards the improvement of diagnosis in this field.

Nonetheless, future large-scale longitudinal studies are needed in order to integrate qEEG analyses in different domains with topographical and temporal properties and produce robust qEEG measures to be utilized for neurodegenerative diseases assessments.

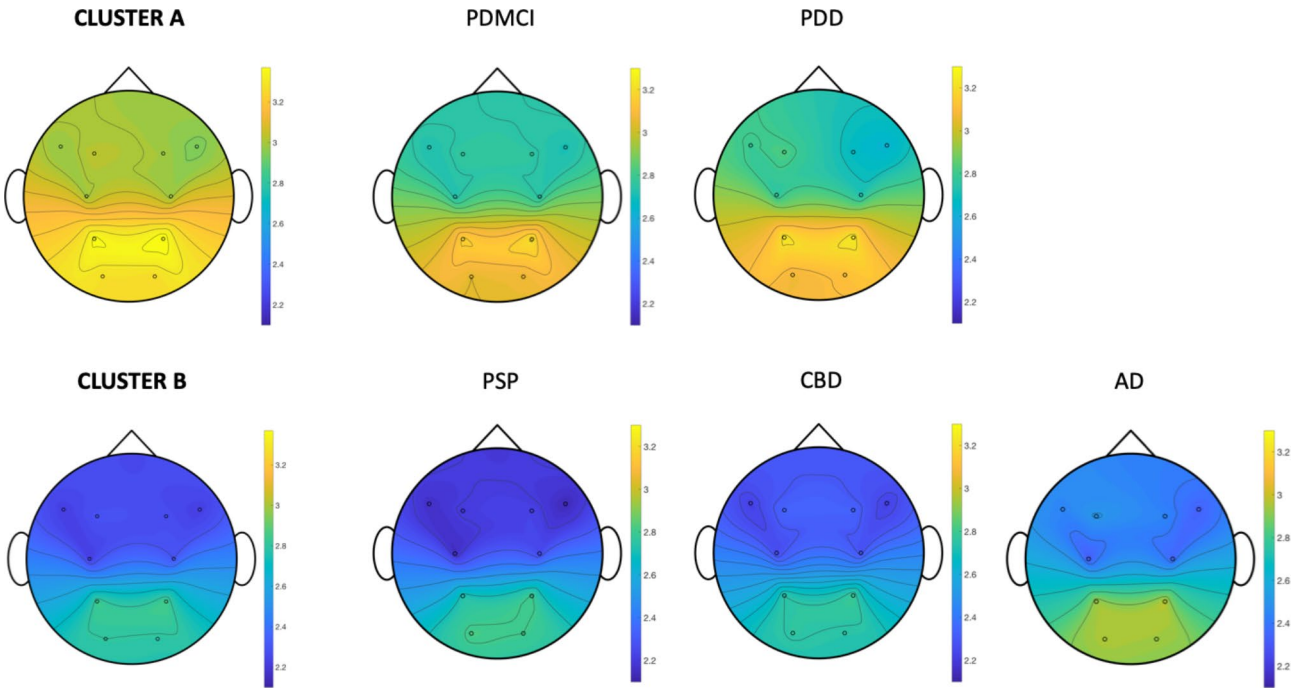

Fig. 2. Topoplot showing differences in topographical distribution of power-law exponent β based on selected sites of recordings between Cluster A and Cluster B as well as in principal included α-synucleinopathies (for Cluster A) and tauopathies (for Cluster B). Range colours based on β values from lower (blue) to higher (yellow).

	AUC	S.E.	Cut-off	Sensitivity (95%CI)	Specificity (95% CI)
F3 β	0.97	0.01	2.71	0.95 (0.91–0.98)	0.88 (0.79–0.94)
F4 β	0.94	0.02	2.62	0.88 (0.82–0.93)	0.88 (0.79–0.94)
F7 β	0.94	0.02	2.6	0.89 (0.84–0.94)	0.86 (0.76–0.93)
F8 β	0.90	0.02	2.72	0.92 (0.87–0.96)	0.73 (0.61–0.82)
T3 β	0.93	0.02	2.7	0.92 (0.87– 0.96)	0.78 (0.67–0.87)
T4 β	0.92	0.02	2.74	0.94 (0.89–0.97)	0.8 (0.7–0.89)
P3 β	0.91	0.02	3.27	0.94 (0.89–0.97)	0.71 (0.6–0.81)
P4 β	0.93	0.02	3.17	0.89 (0.83–0.93)	0.8 (0.7–0.88)
O1 β	0.86	0.03	3.14	0.88 (0.82–0.93)	0.75 (0.64–0.84)
O2 β	0.86	0.03	3.1	0.87 (0.8–0.92)	0.77 (0.66–0.86)

Table 3. ROC curve analysis of β values in differentiating clusters. *AUC* area under curve; *S.E.* standard error, *95% CI* 95% confidence intervals. AUC are all significant at $p < 0.001$. Cut-off estimation using Youden method.

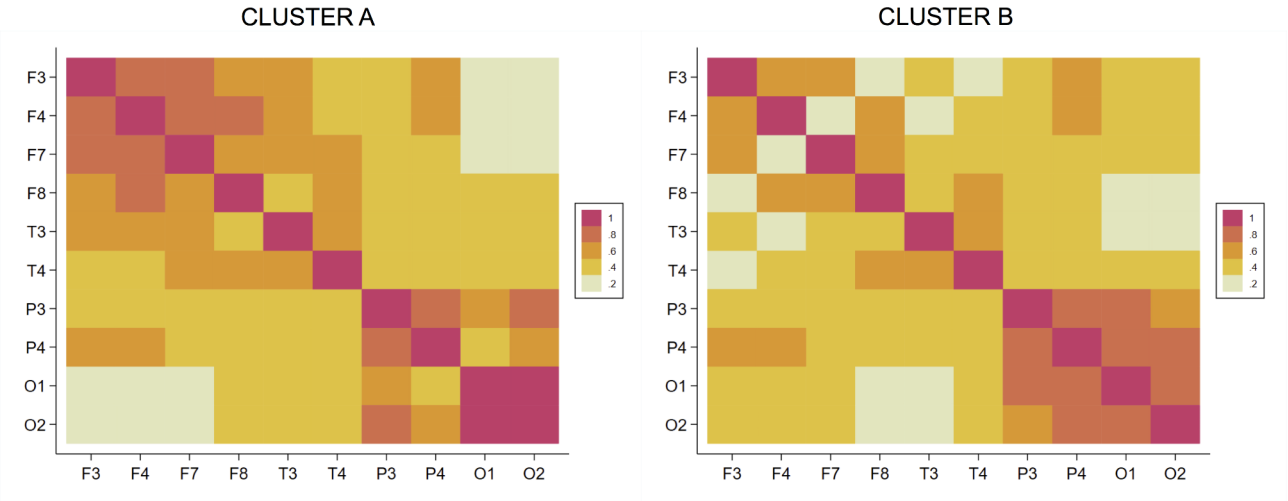

Fig. 3. Heatmap of correlation coefficients matrix showing differences in functional connectivity among frontal sites of recording between identified clusters (LEFT: Cluster A, $N=77$; RIGHT: Cluster B, $N=153$) based on β values. Range colours based on correlation r.

Data availability

Study dataset is available in anonymous format under specific request to the Corresponding Author.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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