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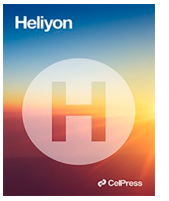

Early detection of Parkinson's disease: Systematic analysis of the influence of the eyes on quantitative biomarkers in resting state electroencephalography☆

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ABSTRACT

While resting state electroencephalography (EEG) provides relevant information on pathological changes in Parkinson's disease, most studies focus on the eyes-closed EEG biomarkers. Recent evidence has shown that both eyes-open EEG and reactivity to eyes-opening can also differentiate Parkinson's disease from healthy aging, but no consensus has been reached on a discriminatory capability benchmark. The aim of this study was to determine the resting-state EEG biomarkers suitable for real-time application that can differentiate Parkinson's patients from healthy subjects under both eyes closed and open. For this, we analysed and compared the quantitative EEG analyses of 13 early-stage cognitively normal Parkinson's patients with an age and sex-matched healthy group. We found that Parkinson's disease exhibited abnormal excessive theta activity in eyes-closed, which was reflected by a significantly higher relative theta power, a higher time percentage with a frequency peak in the theta band and a reduced alpha/theta ratio, while Parkinson's patients showed a significantly steeper non-oscillatory spectral slope activity than that of healthy subjects. We also found considerably less alpha and beta reactivity to eyes-opening in Parkinson's disease plus a significant moderate correlation between these EEG-biomarkers and the MDS-UPDRS score, used to assesses the clinical symptoms of Parkinson's Disease. Both EEG recordings with the eyes open and reactivity to eyes-opening provided additional information to the eyes-closed condition.

We thus strongly recommend that both eyes open and closed be used in clinical practice recording protocols to promote EEG as a complementary non-invasive screening method for the early detection of Parkinson's disease, which would allow clinicians to design patient-oriented treatment and improve the patient's quality of life.

1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease, is characterized by progressive motor symptoms

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over time. PD patients may also present non-motor manifestations such as cognitive dysfunction, depression, hallucinations, sleep disturbance and constipation, among others. Its prevalence amounted to over 8.5 million people worldwide in 2019 [1], with a higher incidence in men than women [2]. The disease affects 1–2 per 1000 of the general population and about 1% of those over 60 years [3], with a currently rising trend due to population aging. It is estimated that there were 4.94 million PD patients in China in 2030 [4]. A comprehensive study in the US found that the gross annual social economic burden attributed to Parkinson was $51.9 billion, with approximately 1 million PD patients in 2017 [5]. PD prevalence is expected to exceed more than $1.6 million with the total economic burden passing $79 billion by 2037 [5].

From the neuropathological point of view, the stereotypical and topographical patterns of neurodegenerative disease progression in the central nervous system may be explained by a "prion-like" transsynaptic or transneuronal spreading of misfolded proteins between the different brain regions over the years [6]. These pathological changes lead to impaired neural function, which gradually turns into clinical syndromes as the disease progresses [7], i.e. the neuropathological changes may precede the clinical symptoms by up to a decade [8], giving rise to the prodromal phase with various symptoms that are not yet sufficient to define the disease or to meet the established diagnostic criteria [9,10]. Indeed, the hyperechogenicity of the substantia nigra as well as olfactory and autonomic dysfunction, depression, rapid eye movement sleep disorders and neuropsychological impairment may occur several years before clinical manifestations [11]. Early detection is thus a key factor in helping clinicians to design a neuroprotective disease-modifying therapeutic program, even in the early prodromal phase to prevent or slow down its development and provide the patients with additional years of a higher quality of life.

Numerous genetic, biochemical, neuroimaging and neurophysiological biomarkers have been associated with PD vulnerability, although no single biomarker is as yet specific enough for routine use in diagnostic or prognostic evaluation in clinical practice [12]. Electroencephalography (EEG) has emerged as a non-invasive, low-cost, and highly sensitive screening method for objectively monitoring of the disease's progression thanks to its high temporal resolution [13]. From a theoretical perspective, the EEG-based neurophysiological biomarker is a functional marker of neuronal and synaptic integrity, which may be sensitive to the subtle changes that precede the structural alterations of neurodegenerative diseases [14]. Both spectral, non-linear dynamic and brain functional connectivity analysis from resting state EEG have been shown to successfully characterize neuropathological EEG changes in PD and correlate with its degree of severity [15–21], thus constituting its most faithful signature. In this work, we preferred to focus on spectral quantitative EEG (qEEG) measures rather than other more complex measures due to their simplicity and ease of interpretation by clinicians, to be able to design software for use in clinics in real time for early prediction of the risk of suffering from the disease.

Since it is associated with slowing down cortical activity, the basic EEG rhythm has been shown to decrease, even in its early stages, shifting from the alpha to the theta and delta bands according to the disease severity [22–24]. It has also been shown that the relative power of higher frequency activity is reduced in Parkinson's disease, while the slower oscillatory activity increases [21,25–31]. However, controversial results on the statistical significance have been reported for different frequency bands. The design of the studies in the literature is highly diverse; most seek to determine EEG features for early PD detection with eyes closed (EC), due to the lower influence of the electrooculogram [16,22,28,30,32–36]. In eyes open (EO), the differential patterns of change in the oscillatory brain activity were similar [37–39]. Recent studies have shown that resting-state EEG with eyes open can better differentiate PD and control subjects than eyes closed [40–42]. Schumacher et al. found that alpha reactivity to eye-opening (from eyes closed-to-open, REO) may provide a differential diagnosis between Alzheimer, Lewy body dementia and Parkinson patients [43]. Alpha REO was much reduced in the demented PD group [44]. Theta and alpha reactivity were also found to enhance the multiple regression model performance for discriminating Alzheimer's disease from control groups [45]. There is so far no evidence to assess the discriminatory ability between PD and control subjects of either EC, EO or its REO for different EEG frequency bands.

There is a growing body of evidence that shows that the EEG signal's non-oscillatory activity may also provide relevant information on the neural dynamics on different temporal scales, playing a complementary role with oscillatory activity [23,46]. The non-oscillatory phenomenon typically produces a broadband effect which obeys the 1/f power-law due to the longer duration of the lower components' deflections favouring their combination in the EEG spectrum [47]. The spectral slope and the offset are normally used to assess the non-oscillatory activity. Physiologically, the spectral slope is associated with the integration of the underlying synaptic current, whose fluctuation can be modelled by a combination of both excitatory and inhibitory activities with different decay rates [48]. The balance of synaptic excitatory and inhibitory current plays an essential role in neural computation, information transfer and neural oscillations [48]. Previous studies showed that broadband activity is not only age-dependent [49,50] but also dynamically changes with task demands and cognitive states and its impairment [49]. Both the offset and slope of non-oscillatory activity were significantly reduced by the nigrostriatal lesion in hemiparkinsonian rats, and the offset was reverted by acute levodopa treatment [46]. Few studies have focused on the feasibility of non-oscillatory activity as a biomarker to detect PD disease and have had inconsistent results [23,51,52].

The aim of this work was thus to determine the ability of resting state EEG-biomarkers to discriminate PD from healthy aging under both EC, EO and REO. We specifically focused on a simple quantitative analysis suitable for real-time applications to promote the clinical use of EEG as a complementary screening method for early PD detection, including the prodromal phase, before the appearance of clinical symptoms and to objectively monitor the disease progression and/or evaluate the effectiveness of modifying therapies.

2. Materials and methods

2.1. Participants

For the study we used a public database consisting of 40 participants distributed between 20 PD patients and 20 age-matched controls [53]. 13 of the 20 PD patients underwent a medication break (OFF) at least 12 h before the acquisition. To avoid the possible confounding effect of the medication, we only used the 13 PD OFF patients. Table 1 gives a brief description of the database, which includes demographical information and clinical and neuropsychological measurements. There was no statistically significant difference in age or sex. PD patients were cognitively normal with a similar mini-mental state score to the control group. The Beck's depression score of the PD patients was slightly higher than the control, without any significant difference. As expected, the PD patients presented a significantly higher MDS-Unified Parkinson's Disease Rating Scale (UPDRS) than the control subjects.

2.2. EEG acquisition and preprocessing

EEG was acquired using 64-channel with the NeurOne Tesla amplifier and sampled at 500 Hz. Two EOG channels were measured. Raw data are available in Ref. [54]. The 2-min of EEG recordings were conducted during the awake resting state with eyes closed followed by another 2-min of signals with eyes open. Preprocessing was done by EEGLAB on Matlab. The EEG was first high-pass filtered (hamming window FIR filter) with a cut-off frequency at 1 Hz to remove baseline fluctuations. We used the default configuration of fully automated statistical thresholding for EEG artifact rejection (FASTER) toolbox to automatically detect bad channels [55] and then interpolated with adjacent channels using spherical interpolation (z-score$\geq$3). We divided continuous EEG into 2-sec epoch data, and then used the FASTER toolbox to discard bad epochs (default configuration with z-score$\geq$3). We then carried out an independent component analysis of EEG epochs, and visually inspected them to further discard any remaining interference such as cardiac, muscle and motion artifacts. Finally, we projected back to the original space to obtain clean EEG epochs. Table S1 of Supplementary Materials shows the number of interpolated channels per subject, total number of epochs per subject, and number of additional epochs discarded in the visual inspection process.

2.3. Data analysis

Our aim was to compare the sensitivity of quantitative measures in detecting PD from control subjects for both EC, EO and REO, this latter being defined as the difference between eyes open and eyes closed. We worked out the following quantitative measures to characterize the EEG signals: the time percentage that a frequency peak is within the theta or alpha band, the relative powers of the delta, theta, alpha, beta and gamma bands, and the spectral exponent.

We first computed the power spectral density (PSD) of each clean epoch for each electrode and subject using the Hanning multitaper frequency transformation ($\delta f = 0.5$ Hz) to determine the frequency peak of each PSD within 4–13 Hz and then computed the time percentage that its frequency peak falls into theta ($\%t_\theta$) and alpha ($\%t_\alpha$) bands for the electrodes and subjects.

The average PSD per electrode per subject was then computed to obtain the relative power of the typical EEG components without separating oscillatory and non-oscillatory activity: delta (2.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–45 Hz), total power being defined in the bandwidth 2.5–45 Hz. We also calculated the alpha/theta ratio, since this resting-state/EEG ratio has been shown to be linked to neuropsychological test performance in PD [15].

We also estimated the slope of the non-oscillatory activity from the average PSD (frequency range 2.5–45 Hz) for each electrode and subject using the three-step regression method proposed by Colombo [56], which has been used to characterize PD non-oscillatory activity [52]. This method consists of a least-square linear fitting of the PSD to determine oscillatory activity in the residual components. The positive residuals of the linear fitting larger than 1 median absolute deviation of the distribution were considered oscillatory peaks. Both oscillatory peaks and their contiguous frequency bins were removed to estimate the slope of the non-oscillatory activity by a second least-square fitting.

Since we sought to compare the sensitivity of different recording conditions in detecting PD, we conducted the *t*-test statistical analysis to determine the quantitative measures' sensitivity to differentiate PD from control subjects for both EC, EO as well as REO ($\alpha = 0.05$, two-tailed). Given the spatial dependence between the different electrode positions (64 electrodes/subject), we systematically evaluated two methods widely used to control family-wise error rate in multiple comparison issues. FDR (False Discovery Rate) is a

Table 1
Description of the demographical information and clinical and neuropsychological measurements of the database. The statistics used for each variable are the t statistic for continuous variables and Chi-squared statistic for categorical variables.

	Control (N = 20)	PD (N = 13)	Test statistic	p-value
Sex (male/female)	8/12	6/7	0.05	0.82
Age (mean±SD)	68 (6.0)	68 (7.4)	−0.2	0.84
Disease duration, years (mean±SD)	n/a	5 (4.3)	n/a	n/a
Mini-mental state score (mean±SD)	28 (2.0)	28 (1.4)	−0.63	0.54
Beck's depression inventory	5 (3.0)	8 (5.6)	−1.62	0.12
MDS-UPDRS, motor (mean±SD)	5 (3.0)	29 (15.6)	−5.14	<0.001

powerful method of correcting multiple comparison and provides meaningful control of false discoveries in both the time, spatial and frequency domains [57] using the two stage FDR method proposed by Benjamini, Krieger and Yekutieli (FDR BKY) [58], which is a more accurate and less conservative version than those proposed by Benjamini and Hochberg [59] and Benjamini and Yekutieli [60].

We also included the cluster-based permutation test, which is another common approach used to perform statistical tests on EEG data [61]. The spatial neighbour data samples that showed a significant difference between PD and control subjects at first-level univariate statistics ($\alpha = 0.05$) were grouped with a minimum cluster size of 2. Based on the assumption that the identified cluster effect is interchangeable between the conditions (PD vs. control), permutation tests were then used to perform statistical inference for the clusters (second-level). We computed the maximum of cluster-level statistics by adding the univariate t-statistics of the cluster for 5000 random partitions and obtained the Monte-Carlo p-value, which is the proportion of random partitions with a higher effect size than that observed. Monte-Carlo p-values less than $\alpha_{cluster}$ means significant difference between conditions at cluster level.

We also computed the average Cohen's effect size of each cluster with significant differences between groups, which measures the magnitude of the effect rather than its existence.

We also analysed the relationship between EEG changes with clinical Parkinson symptoms. Since we found that the Spearman's correlation varies little across different regions (results not shown), we computed the Spearman's correlation between the average qEEG of the whole brain (64 electrodes) and the MDS-UPDRS score – an assessment of clinical Parkinson motor and non-motor symptoms [62] to detect the existence of a relationship ($\alpha = 0.05$) as well as its magnitude.

3. Results

This section only gives the relevant results that can be used as biomarkers to detect the disease. Those obtained for basic rhythm, delta and gamma relative power with no statistical difference between the groups can be found in the Supplementary Material.

Fig. 1 show the average topographic map of $\%t_\theta$ for both control, PD as well as the group difference under different recording conditions. Significant differences between the groups for the cluster-based permutation test and FDR BKY correction method are marked by '+' and 'x' respectively, and '*' means a significant difference for both methods. Blue and yellow represent the increasing and decreasing trend in the PD group. In both EC and EO, PD subjects showed an overall increase of $\%t_\theta$ over control. This effect is much more noticeable in EC, giving rise to a diffuse significant increase in PD when compared to the control group, regardless of the

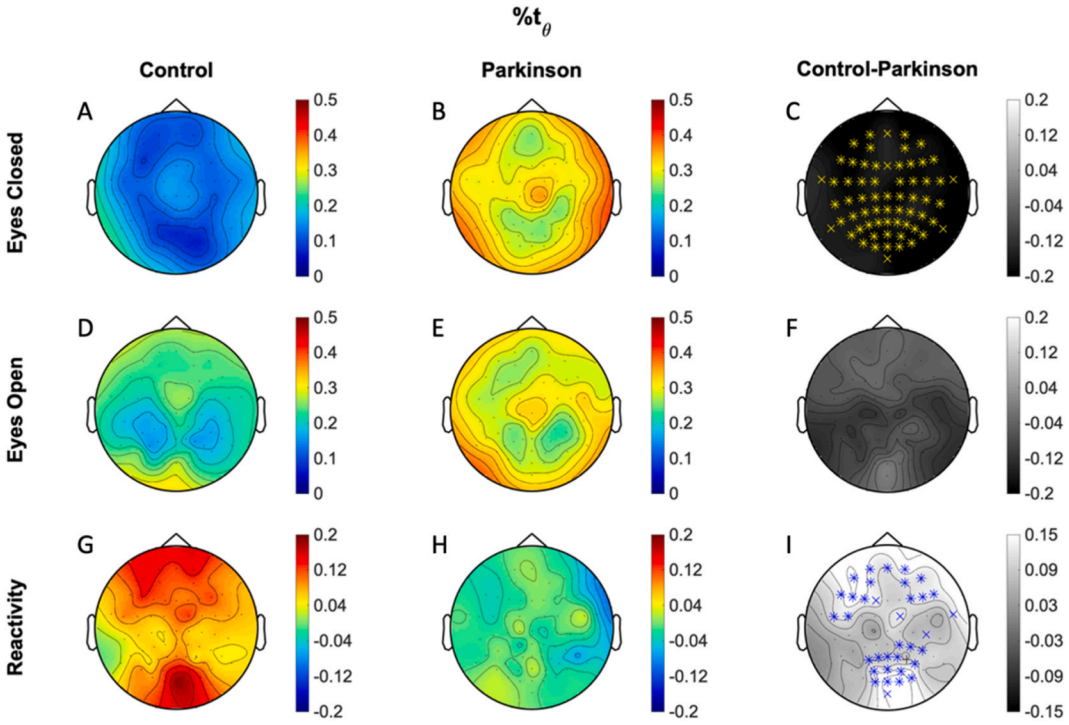

Fig. 1. Average topographic maps of $\%t_\theta$ for control and Parkinson subjects and the difference between these groups under different recording conditions: EC, EO and REO: map of the control group in EC (A), map of the PD group in EC (B), map of the differences between both groups in EC (C), map of the control group in EO (D), map of the PD group in EO (E), map of the differences between both groups in EO (F), map of the control group in REO (G), map of the PD group in REO (H), and map of the differences between both groups in REO (I). Statistical differences are marked on the group difference topographic map, where '+' and 'x' mean significant difference obtained by the cluster-based permutation test and FDR BKY correction respectively, '*' means significant difference were obtained by both methods. The increasing and decreasing trend in PD is marked in blue and yellow, respectively.

statistical method. No significant difference was found in EO. For the control subjects, eyes opening is associated with a remarkable overall increase of $\%t_\theta$, especially in the frontal, central and occipital channels, while this phenomenon is barely appreciated in PD subjects. Both cluster-based permutation test and FDR BKY showed that PD subjects had significantly less eyes-opening reactivity than the control group in the frontal, parietal and occipital electrodes. It should be noted that $\%t_\alpha$ obtained the same statistical result, but with a decreasing trend in PD, which we did not show.

Figs. 2–5 give the average topographic of relative power of theta, alpha, alpha/theta ratio and relative beta power.

The PD group again showed an overall increase of theta relative power over the control in both conditions (see Fig. 2), although to a lesser degree in EO. Statistical differences were found in the left frontal, central, parietal, right temporal, and occipital electrodes by the cluster-based permutation test and in almost all the electrodes except in the left temporal with the FDR BKY method in EC. In EO, we found a significant difference in central, parietal, and right temporal channels with the cluster-based permutation test, but not for the FDR BKY method. Eyes opening (REO) is associated with increasing theta relative power in frontal and occipital channels in control subjects, while the PD group exhibited a slightly decreasing trend. Neither of the two statistical methods obtained significant differences between PD and control groups for REO.

In the alpha band (see Fig. 3), the PD group showed overall less relative power than the control in EC with no statistical differences. No noticeable changes between the groups were found in EO. Although both groups showed reduced alpha relative power when opening the eyes, the PD group had significantly less reactivity to eyes opening than the control subjects.

In the alpha/theta ratio (see Fig. 4), in EC the PD group showed significantly lower values than the control in frontal, central, parietal, temporal, and right occipital electrodes by both statistical methods, while no significant difference was found in EO. REO was linked to a lower alpha/theta ratio in the control group and no remarkable changes were found in the PD group, obtaining significant differences only in frontal and right occipital electrodes in the cluster-based permutation test.

As can be seen in Fig. 5, PD had a similar beta relative power to control in EC, while in EO the beta relative power of the PD group was slightly lower than the control group. Statistical differences were found in the right occipital electrodes in EO by the cluster-based permutation test. REO was associated with increased beta relative power. In comparison to control group, PD showed less beta relative power reactivity than control. We found statistical differences in all electrodes for FDR BKY and in left frontal, central, right parietal, and right occipital in the cluster-based permutation test.

Fig. 6 shows the topographic map of the slope of non-oscillatory activity for the control and PD groups, also the group difference under different recording conditions. The non-oscillatory activity in the PD group showed a steeper slope than control in both EC and

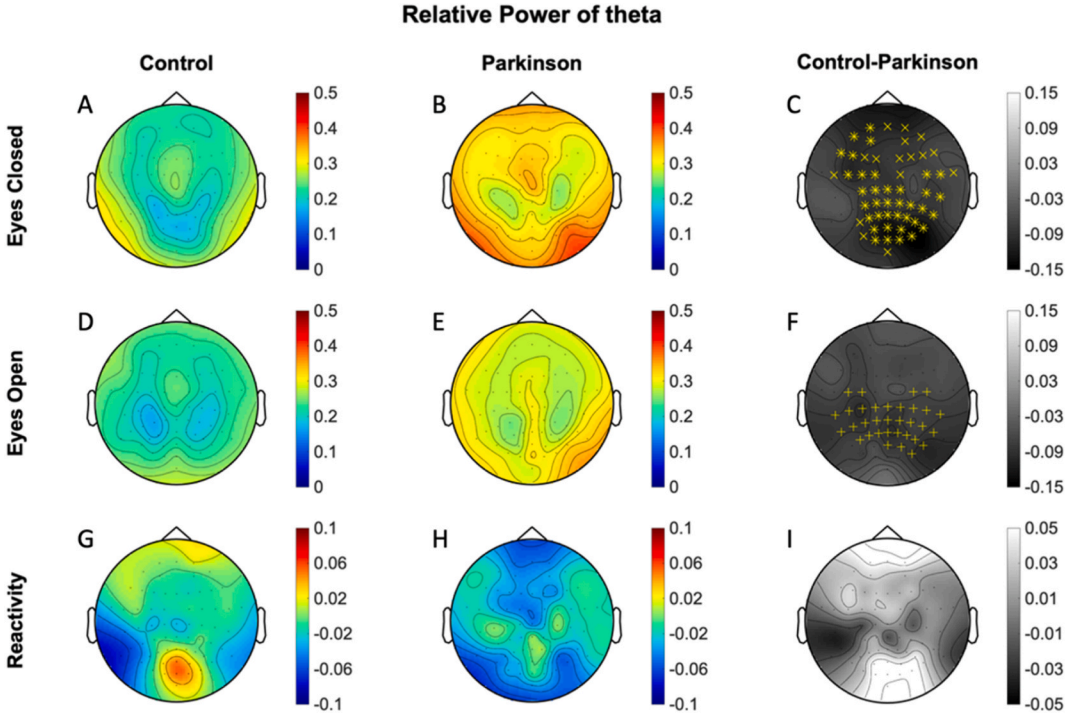

Fig. 2. Average topographic maps of theta relative power for control and Parkinson subjects and the difference between these groups under different recording conditions: EC, EO and REO: map of the control group in EC (A), map of the PD group in EC (B), map of the differences between both groups in EC (C), map of the control group in EO (D), map of the PD group in EO (E), map of the differences between both groups in EO (F), map of the control group in REO (G), map of the PD group in REO (H), and map of the differences between both groups in REO (I). Statistical differences are marked on the group difference topographic map, where '+' and 'x' mean significant differences obtained by cluster-based permutation test and FDR BKY correction, respectively, '*' means significant differences were obtained by both methods. The increasing and decreasing trend in PD is marked in blue and yellow, respectively.

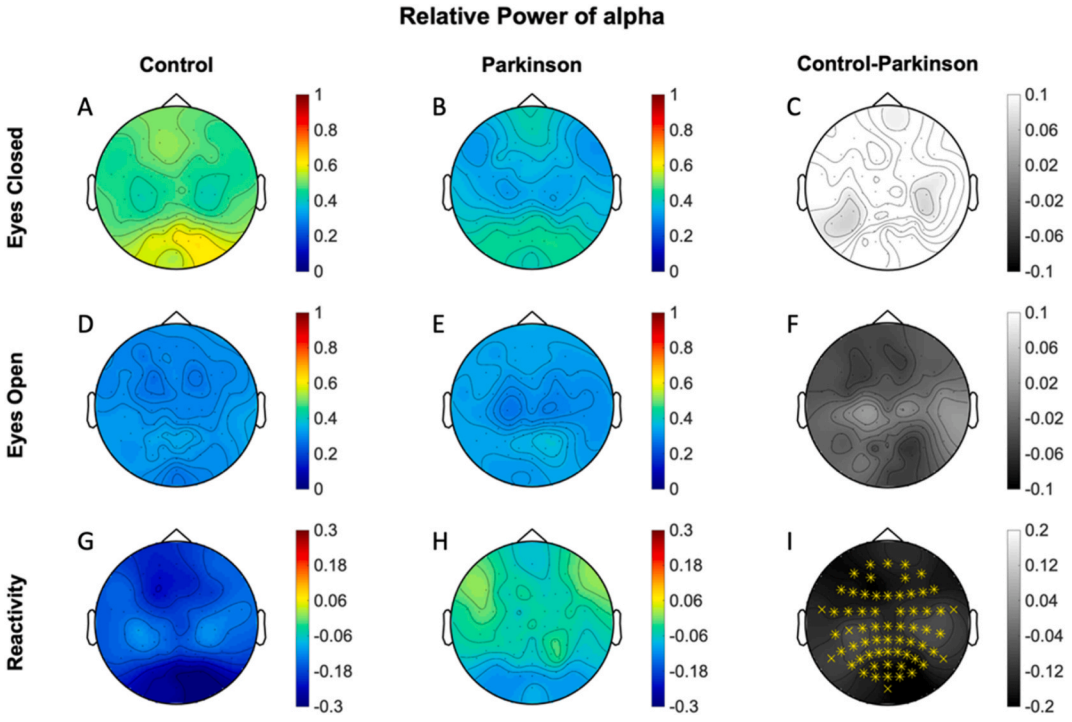

Fig. 3. Average topographic maps of alpha relative power for control and Parkinson subjects, as well as the difference between these groups under different recording conditions: EC, EO and REO: map of the control group in EC (A), map of the PD group in EC (B), map of the differences between both groups in EC (C), map of the control group in EO (D), map of the PD group in EO (E), map of the differences between both groups in EO (F), map of the control group in REO (G), map of the PD group in REO (H), and map of the differences between both groups in REO (I). Statistical differences are marked on the group difference topographic map, where '+' and 'x' means significant difference obtained by the cluster-based permutation test and FDR BKY correction respectively, '*' means significant difference were obtained by both methods. Increasing and decreasing trends in PD are marked in blue and yellow, respectively.

EO. No significant difference was found for the non-oscillatory activity slope in EC, while a diffuse significant difference was obtained for EO for both statistical tests. Eyes opening (REO) was generally related to a smoother slope of non-oscillatory activity, with no significant differences between the groups.

Table 2 shows a comparative summary of both statistical methods of differentiating between the PD and control groups under different recording conditions. Both methods in general have similar channel number and average effect size values. The FDR BKY correction provides significant differences in more channels for theta relative power in EC and beta reactivity (in bold) than the cluster-based permutation test. Theta and beta power in EO, and alpha/theta ratio in REO with relatively lower channel numbers (in italic) only obtained significant differences in the cluster-based permutation test. This could mean that the FDR BKY method has a more diffuse effect and is less sensitive when there is a local effect.

Table 3 shows the Spearman correlation between MDS-UPDRS score and the average qEEG of the whole brain under different recording conditions (EC, EO, and REO). In general, we found a significantly moderate correlation between qEEG parameters and MDS-UPDRS score that discriminate the PD subjects from the control group: $\%t_\theta$, relative θ power and α/θ ratio in EC, spectral slope in EO, and $\%t_\theta$-reactivity, α-reactivity and β-reactivity (grey-shaded Table 2). Surprisingly, a significant correlation with the MD-UPDRS score was also obtained for relative alpha power in EC, basic rhythm and relative beta and gamma power in EO, relative delta and gamma power and alpha/theta in REO.

4. Discussion

4.1. Physiological changes in PD patients

This study assessed the usefulness of quantitative resting-state EEG in distinguishing PD from control subjects in both EC, EO and REO. We found consistent trends for different EEG oscillations in PD with previous studies in both EC [21,25–31] and EO [44,63], with no significant differences between the groups for relative α-power. Regardless of the consistent trends, the statistical analyses reported in the literature are somewhat controversial [15,25,64] as well as the relationship between clinical symptoms and EEG biomarkers [23,51,65,66]. We believe that these controversial results are due to the disease's progressive nature, with the additional confusion of a different disease etiology. Also, relative band power is generally computed from clean EEG epochs without removing the 1/f aperiodic slope as in the present work. This may also have confounded the results that involve relative powers, such as the alpha/theta ratio

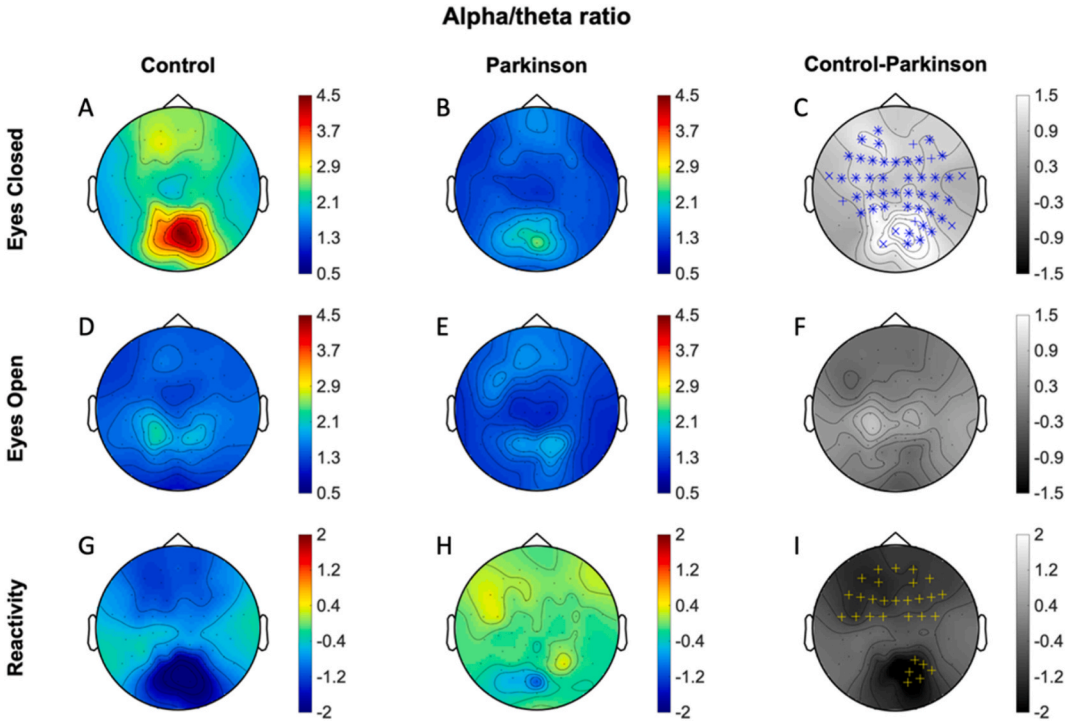

Fig. 4. Average topographic maps of alpha/theta ratio for control and Parkinson subjects and the difference between these groups under different recording conditions: EC, EO and REO: map of the control group in EC (A), map of the PD group in EC (B), map of the differences between both groups in EC (C), map of the control group in EO (D), map of the PD group in EO (E), map of the differences between both groups in EO (F), map of the control group in REO (G), map of the PD group in REO (H), and map of the differences between both groups in REO (I). Statistical differences are marked on the group difference topographic map, where '+' and 'x' means significant difference obtained using cluster-based permutation test and FDR BKY correction, respectively, '*' means significant difference were obtained by both methods. Increasing and decreasing trends in PD are marked in blue and yellow, respectively.

[67–69]. In this regard, Wang et al. did not find a remarkable enhancement of the oscillatory activity extracted by the FOOOF algorithm to differentiate Parkinson's disease from healthy subjects than non-oscillatory activity and mixed power (without removing the 1/f aperiodic slope) [23]. Further studies are still needed to determine whether the relative power of the oscillatory activity can better discriminate between PD and control subjects.

We found that PD showed widespread and significantly lower α-reactivity in resting state EEG than control subjects, which outperformed both EC and EO. Our results suggest that α-reactivity could be used as a sensitive biomarker for early detection of PD, in agreement with previous studies [43,70,71], but also presented a high correlation with MDS-UPDRS. We believe that this enhanced discriminatory capacity could be due to the reduced biological variability since it measures the relative power changes between EC and EO under the same recording conditions. Physiologically, resting-state EEG α-reactivity not only reflects higher brain arousal and vigilance and promoted visual information processing in parietal, temporal, and occipital cortical regions, but also related to attention and cognitive performance [71]. The diminished α-reactivity in PD may be associated with the interaction of dementia with Lewy Bodies-related α-synucleopathy in the generation of resting state EEG alpha rhythm in posterior regions, altering the brain neural networks modulated by brainstem noradrenergic and dopaminergic neurons as well as forebrain cholinergic neurons [49]. Our results suggest that PD patients exhibit a marked deficit in the cholinergic system [63,72,73] causing degeneration of the nucleus basalis of Meynert [43].

We also found a widespread significant increase of relative theta power in both EC and EO with a significant correlation with MDS-UPDRS score, although the latter was less sensitive in differentiating PD from the control group. Our results agree with previous studies that proposed this measure as the most pronounced differences with the control group [24,40,74], besides its significant correlation in EC [75]. Theta activity is associated with a variety of cognitive and attentional processes involving both frontal and posterior cortical regions, including the periodic sampling of unattended visual information and navigation of the sensory environment [76]. This supports the idea that the PD group requires considerable cognitive and attentional resources for processing environmental information [77]. Caviness et al. hypothesised that the increase in theta power was related to the abnormal diffuse acetylcholine and monoamine pathway projection to broad neocortical areas and intrinsic cortical circuits in PD [78]. The increased theta power has been shown to correlate with progressive hippocampal volume loss [79,80]. For reactivity, we found the increased relative theta power from EC to EO exhibited a peak difference in the parietal cortex in the control group and local peaks in the occipital and frontal cortices, which agrees with Petro et al. [76]. By contrast, the increased theta power associated with eyes opening was not found in the PD group,

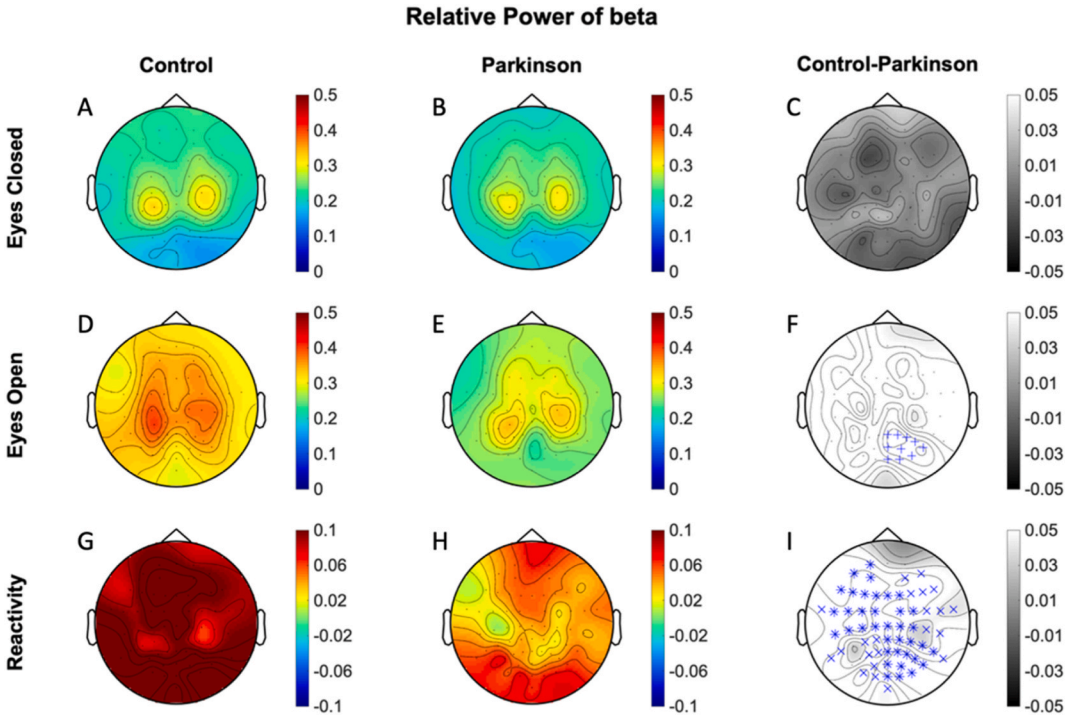

Fig. 5. Average topographic maps of beta relative power for control and Parkinson subjects and the difference between these groups under different recording conditions: EC, EO and REO: map of the control group in EC (A), map of the PD group in EC (B), map of the differences between both groups in EC (C), map of the control group in EO (D), map of the PD group in EO (E), map of the differences between both groups in EO (F), map of the control group in REO (G), map of the PD group in REO (H), and map of the differences between both groups in REO (I). Statistical differences are marked on the group difference topographic map, where '+' and 'x' means significant difference obtained by the cluster-based permutation test and FDR BKY correction, respectively, '*' means significant differences were obtained by both methods. Increasing and decreasing trends in PD are marked in blue and yellow, respectively.

but rather a downward trend in the frontal and occipital electrodes. No significant difference was found for theta reactivity between the groups.

We also found a significantly diffuse reduction of alpha-theta ratio in PD in EC. Indeed, the diffuse reduction alpha-theta ratio, especially in the posterior region was proposed as a consistent biomarker of visuospatial performance impairment in PD with EC, which indirectly mirrors a cholinergic deficit [15,64,81]. Although basic rhythm frequency lacked a significant difference between the groups, the shift from higher to lower rhythms was also reflected in a significantly higher $\%t_\theta$ in PD than in the control group, obtaining a significant positive correlation with the MDS-UPDRS score in EC, in agreement with Novak [22] and Vardy [82]. This result suggests that the $\%t_\theta$ is more sensitive than the average basic rhythm frequency in detecting early-stage PD, since EEG abnormalities may not be consistent across the recording session and may happen at isolated times rather than in the early stages of neurodegenerative diseases [7]. Our results also agree with Jaramillo et al. who found that the PD-related difference of the theta band using epoch-to-epoch approach was more reproducible across the 4 analysed databases than when computing average across epochs [83].

Beta activity plays a key role in controlling the information coding capacity across the motor loops of the cortical-basal ganglia circuit [84]. A great deal of evidence has shown their strong correlation with rigidity and bradykinesia at rest [85,86]. While cortical beta power significantly increased in PD [84,87], controversial results were obtained at the scalp level. Few studies found a significantly reduced relative beta power in PD in EC [25,44], while other studies reported no significant differences between PD and the control group in EC [16,28,88–91], which is consistent with our findings. Our results partially agree with Miladinović [75] and Neumann [92] who found a significant correlation between UPDRS-III, which is a subcomponent of the MDS-UPDRS score and low beta in PD under pharmacological treatment [75] which has been shown to reduce the low beta band and increase the high-beta [52,93,94]. We also found that beta reactivity is more sensitive in detecting PD than either EC or EO, obtaining a diffuse significant difference, as well as a strong correlation with the MDS-UPDRS score. As far as we know, this is the first time that beta reactivity has been reported as another potential EEG-biomarker in assessing PD.

Delta rhythm may be a reflection of an altered monoaminergic receptor in PD [95]. Whalen found that delta oscillations in the substantia nigra pars reticulata are a strong indicator of dopamine loss and akinesia [96]. Abnormally increased delta power has been associated with the cognitive dysfunction in PD patients [16,34,97]. In this work we did not find a significant difference between PD and the control group.

PD had a steeper spectral slope than the control group in both EC and EO, in agreement with Vinding et al. [51]. A flatter spectral

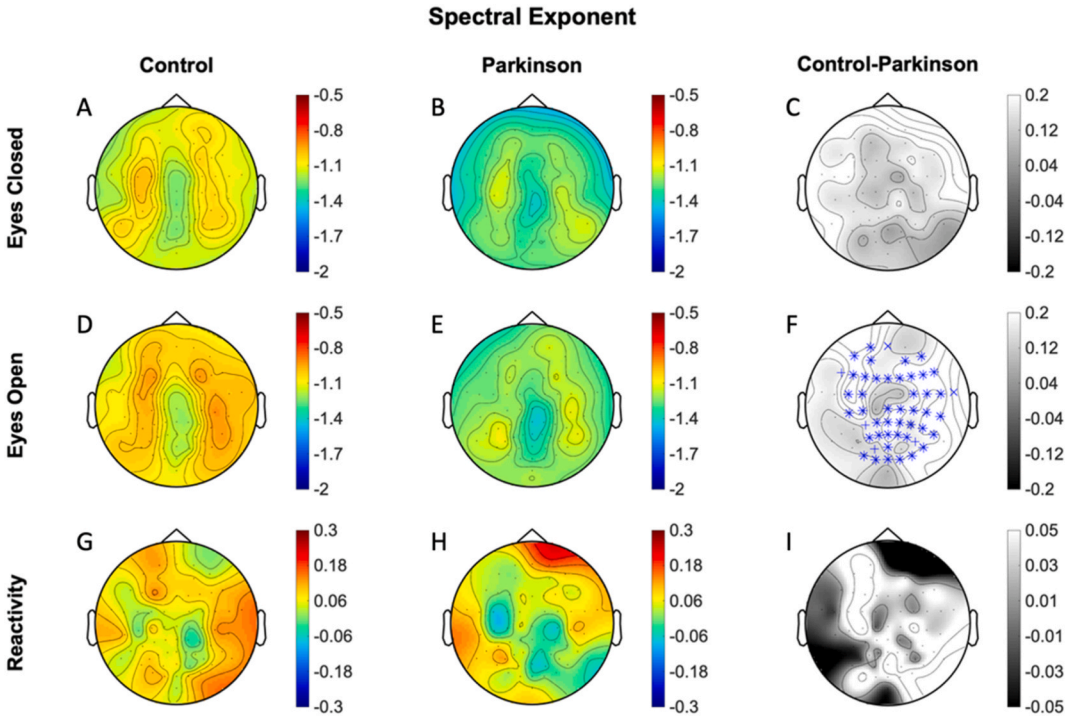

Fig. 6. Average topographic maps of the spectral exponent for control and Parkinson subjects and the difference between these groups under different recording conditions: EC, EO and REO: map of the control group in EC (A), map of the PD group in EC (B), map of the differences between both groups in EC (C), map of the control group in EO (D), map of the PD group in EO (E), map of the differences between both groups in EO (F), map of the control group in REO (G), map of the PD group in REO (H), and map of the differences between both groups in REO (I). Statistically significant differences are marked on the group difference topographic map, where '+' and 'x' means significant difference obtained by the cluster-based permutation test and FDR BKY correction, respectively, '*' means significant differences were obtained by both methods. Increasing and decreasing trends in PD are marked in blue and yellow, respectively.

Table 2
Summary of both FDR BKY and cluster-based permutation test for discriminating PD and control group under different recording conditions. 'Channel' indicates the channel number (maximum = 64) with a significant difference between PD and control group and 'ES' its corresponding average effect size. Grey shaded indicates significant difference between PD and control group for both statistical tests.

	FDR BKY						Cluster-Based Permutation Test					
	EC		EO		REO		EC		EO		REO	
	Channel	ES	Channel	ES	Channel	ES	Channel	ES	Channel	ES	Channel	ES
$\%t_\theta$	64	1.04	n.s	n.s	35	1.21	57	1.05	n.s	n.s	31	1.18
θ	**53**	**1.00**	n.s	n.s	n.s	n.s	**37**	**1.08**	*33*	*0.94*	n.s	n.s
α	n.s	n.s	n.s	n.s	64	1.34	n.s	n.s	n.s	n.s	58	1.33
β	n.s	n.s	n.s	n.s	**59**	**1.12**	n.s	n.s	*10*	*0.94*	**37**	**1.20**
α/θ	45	1.04	n.s	n.s	n.s	n.s	44	1.02	n.s	n.s	*29*	*1.03*
slope	n.s	n.s	45	1.23	n.s	n.s	n.s	n.s	47	1.22	n.s	n.s

slope is usually linked to a higher background rate of firing decoupled from an oscillatory carrier frequency driven by an increased excitation/inhibition ratio [48]. The atypically steep spectral slope of non-oscillatory activity in PD is the consequence of a pathological decoupling between the population spiking activity and low-frequency oscillatory neural fields [98] and could reflect a lower background neuron firing rate, giving rise to a lower and unbalanced excitatory-inhibitory ratio [48,56]. This is consistent with that PD patients exhibited reduced inhibition and hyperactivity of the subthalamic nucleus [99]. We also found that the EO spectral slope is more sensitive than EC and REO in discriminating PD from the control group as well as obtaining moderate correlation with MDS-UPDRS, which disagree with previous studies that analysed the utility of the non-oscillatory activity of resting state EEG to detect PD from control groups [23] as well as its relationship with clinical symptom [23,51,65,66]. The discrepancy could be associated with a different disease etiology and the algorithm used to estimate the parameters of the non-oscillatory activity: FOOOF algorithm [68] vs. three-step regression method [56]. Our result is in line with the EO spectral slope showing a declining trend as a function of age [100].

Table 3
Spearman's rho value between qEEG and the MDS-UPDRS score for different recording conditions (EC, EO and REO). Significant correlation is shown in bold ($\alpha = 0.05$). Grey shaded indicates those qEEG with significant difference between PD and control group for both cluster-based permutation test and FDR-BKY.

	EC	EO	REO
Basic Rhythm	-0.33	**-0.35**	-0.07
$\%t_\theta$	**0.55**	0.24	**-0.48**
δ	0.29	0.10	**-0.39**
θ	**0.47**	**0.48**	-0.14
α	**-0.40**	0.05	**0.61**
β	-0.003	**-0.37**	**-0.57**
γ	0.03	**-0.38**	**-0.63**
α/θ	**-0.53**	-0.26	**0.60**
Spectral slope	-0.28	**-0.51**	-0.25

We hypothesised that this phenomenon is related to the attentional or arousal levels between conditions [100], although its physiological meaning is still unclear. PD requires greater attentional resources to process the external environment information, leading to a reduced overall attention capacity, which may be more evident in EO, giving rise to major differences in background firing rate and spectral slope of non-oscillatory scalp activity. Regardless of its physiological meaning, the EO spectral slope may be another valuable biomarker for detecting pathological scalp activities in PD.

To sum up, in this work we not only confirmed the usefulness of existing EEG-biomarkers (relative θ-power, $\%t_\theta$ and α/θ ratio) in EC, but also found new sensitive biomarkers in EO (non-oscillatory activity' slope) and REO ($\%t_\theta$, α-reactivity and β-reactivity) for discriminating early-stage PD patients from control groups, something that has been given little consideration in the literature. We also found a significant moderate relationship between these EEG-biomarkers and the MDS-UPDRS score.

4.2. Multiple comparison corrections

Since we sought to determine the subtle difference between control and PD subjects, we used statistical methods well suited to small sample sizes or weak effects. Instead of Bonferroni or permutation tests, which provide a strong control of family-wise error rate [57], we systematically evaluated the two most commonly used statistical methods for EEG/MEG analysis: the cluster-based permutation test and a different implementation of FDR methods. We found that the FDR BKY method was more sensitive than the Benjamini and Hochberg method and the Benjamini and Yekutieli methods (results not shown), which is consistent with other authors who reported that the BKY method outperformed in terms of FDR control and power when the p-value is independent or has a positive type of dependence [57,101].

Both the cluster and FDR BKY methods showed broad and similar effects, although the reliability of these methods in providing the significant difference with a specific spatial location is disputed [57,61]. In contrast, we only found a less diffuse effect in EO theta power, beta reactivity and alpha/theta reactivity for the cluster-based permutation test. Our results are consistent with cluster-based permutation tests being remarkable at capturing broad effects, but they are also likely to miss narrowly distributed effects, since their cluster mass or size will not differ much from that of the noise cluster [57]. Since they provide a weak control of the family-wise error rate, cluster-based tests are possibly the most powerful high-sensitivity mass-univariate procedure for detecting the presence of such effects, while maximizing power by using the cluster structure of the data as its sole test statistic [57].

The relatively lower sensitivity of the BKY method may be due to the small size of the database, since a large sample size is usually required to achieve good power when controlling low-level FDR [102]. In this regard, in addition to reporting the statistical significance that only determines the existence of an effect, we also determined the effect size of the different biomarkers embedded in the EEG, which is an important factor in determining the statistical power that depends on effect size and sample size [103]. Although we found a large effect size (>0.8) in this work, this could have been overestimated due to the small sample size [104]. For a balanced design and effect size of around 1, simulation studies have shown that the statistical power is about 0.2 and 0.4 for a true null hypotheses rate of 0.8 and sample size of 10 and 20, respectively [102]. Underpowered studies tend to overestimate the size of the true effect [105]. It would be necessary to obtain approximately 80 samples to achieve a statistical power of 80% while controlling FDR at 0.05, which is much higher than the current sample size.

4.3. Limitations of the study

Despite identifying multiple EEG-biomarkers, this study is not exempt from limitations. As previously mentioned, our sample size was relatively small, giving rise to a low statistical power of below 0.4. A large database that includes different PD etiology is urgently needed by the technical/scientific community to serve as a platform for different methodology benchmarks and to identify more reliable EEG-biomarkers to monitor the disease's progression. Despite this limitation, we highly recommend including EO and REO in the clinical practice recording protocol, since they provide additional information that is not available in EC.

In this work, we only determined the discriminatory capability of these EEG-biomarkers between PD and control groups and did not analyse the mutual and/or complementary information between different EEG-biomarkers in detecting early-stage PD. The feasibility

of using these EEG-biomarkers for early detection of neuropathology in the prodromal phase before the symptoms appear and also to assess the progression of the disease remains unclear. In this regard, the 10-year longitudinal study of the general 50-60-year-old population could provide valuable information to determine the neuropathological EEG changes for neurodegenerative disease prevention.

Additionally, the motion artifacted-epochs were mainly rejected by the FASTER toolbox and remanent artifacts were then discarded by expert supervision, which still involves a certain degree of subjectivity. This may also be one of the main barriers to transferring the EEG technique to clinical practice. The convolutional neural network has recently been proposed to automatically discard motion artifacts from the EEG signal, with promising results (accuracy~80%) [106–108]. Further benchmark studies of different network architectures are still needed to design a robust and generalizable real-time system for clinical use from a larger database without the assistance of technical staff. We believe that this may be the turning point to promote the EEG transferability to clinical practice.

Despite these limitations, we have not only provided new and relevant EEG-biomarkers that describe the neuropathological changes in PD but can also be further used for early detection in the prodromal phase and/or to assess its progression.

5. Conclusions

The quantitative EEG contains sensitive biomarkers that can early detect subtle pathological neural activity in PD-cognitively normal subjects under different recording conditions. In the eyes closed condition, the most consistent EEG-biomarker in detecting early-stage PD was the widespread and significantly higher relative theta power, which is also reflected in an increased $\%t_\theta$ and lower alpha/theta ratio. In contrast, the spectral slope of non-oscillatory activity was the most reliable biomarker in eyes open to discriminate PD from healthy aging, although the PD group also showed a significantly higher relative theta in the central, parietal, and right temporal electrodes and beta power in the right parietal electrodes. Our results also indicate that eyes-opening reactivity contains even more information for discriminating PD from the control group, which is reflected in different quantitative indicators such as a significantly lower $\%t_\theta$, reduced alpha and beta and reduced alpha/theta ratio.

These results suggest that different recording conditions may contain different complementary information to discriminate PD from healthy aging. These qualitative biomarkers could easily be implemented in real-time applications in clinical practice for early detection of the neuropathological changes in high-risk patients in the prodromal phase, also for objectively monitoring the disease's progress and/or evaluating the effectiveness of a disease-modifying therapy.

Author contribution statement

Guillem Gimenez-Aparisi, Enrique Guijarro-Estelles, Yiyao Ye-Lin: Conceived and designed the experiments; Performed the experiments; Analysed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Antonia Chornet-Lurbe, Sara Ballesta-Martinez, Mario Pardo-Hernandez: Conceived and designed the experiments; Analysed and interpreted the data; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at https://osf.io/pehj9/.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:G. Gimenez Aparisi reports financial support was provided by European Union - NextGenerationUE.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20625.

References

[1] Parkinson disease. https://www.who.int/news-room/fact-sheets/detail/parkinson-disease#. (Accessed 13 January 2023).
[2] W.-M. Liu, R.-M. Wu, J.-W. Lin, Y.-C. Liu, C.-H. Chang, C.-H. Lin, Time trends in the prevalence and incidence of Parkinson's disease in Taiwan: a nationwide, population-based study, J. Formos. Med. Assoc. 115 (7) (2016) 531–538, https://doi.org/10.1016/j.jfma.2015.05.014. Jul.

[3] O.-B. Tysnes, A. Storstein, Epidemiology of Parkinson's disease, J. Neural. Transm. 124 (8) (Aug. 2017) 901–905, https://doi.org/10.1007/s00702-017-1686-y.

[4] Z. Ou, et al., Global trends in the incidence, prevalence, and years lived with disability of Parkinson's disease in 204 countries/territories from 1990 to 2019, Front. Public Health 9 (2021), https://doi.org/10.3389/fpubh.2021.776847. Dec.

[5] W. Yang, et al., Current and projected future economic burden of Parkinson's disease in the U.S, NPJ Parkinsons Dis 6 (1) (2020) 15, https://doi.org/10.1038/s41531-020-0117-1. Jul.

[6] F. Agosta, M. Weiler, M. Filippi, Propagation of pathology through brain networks in neurodegenerative diseases: from molecules to clinical phenotypes, CNS Neurosci. Ther. 21 (10) (Oct. 2015) 754–767, https://doi.org/10.1111/cns.12410.

[7] A.H. Meghdadi, et al., Resting state EEG biomarkers of cognitive decline associated with Alzheimer's disease and mild cognitive impairment, PLoS One 16 (2) (Feb. 2021), e0244180, https://doi.org/10.1371/journal.pone.0244180.

[8] D.W. Dickson, Parkinson's disease and parkinsonism: neuropathology, Cold Spring Harb Perspect Med 2 (8) (2012), a009258, https://doi.org/10.1101/cshperspect.a009258. Aug.

[9] P. Mahlknecht, K. Seppi, W. Poewe, The concept of prodromal Parkinson's disease, J. Parkinsons Dis. 5 (4) (Oct. 2015) 681–697, https://doi.org/10.3233/JPD-150685.

[10] R.B. Postuma, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (Oct. 2015) 1591–1601, https://doi.org/10.1002/mds.26424.

[11] D. Berg, Biomarkers for the early detection of Parkinson's and Alzheimer's disease, Neurodegener. Dis. 5 (3–4) (2008) 133–136, https://doi.org/10.1159/000113682.

[12] U. Ganguly, et al., Alpha-synuclein as a biomarker of Parkinson's disease: good, but not good enough, Front. Aging Neurosci. 13 (2021), https://doi.org/10.3389/fnagi.2021.702639. Jul.

[13] N.N. Kulkarni, V.K. Bairagi, Electroencephalogram based diagnosis of alzheimer disease, in: Proceedings of 2015 IEEE 9th International Conference on Intelligent Systems and Control, ISCO 2015, Institute of Electrical and Electronics Engineers Inc., 2015, https://doi.org/10.1109/ISCO.2015.7282275. Sep.

[14] R.A. Cromarty, et al., Neurophysiological biomarkers for Lewy body dementias, Clin. Neurophysiol. 127 (1) (2016) 349–359, https://doi.org/10.1016/j.clinph.2015.06.020.

[15] A. Jaramillo-Jimenez, et al., Resting-state EEG alpha/theta ratio related to neuropsychological test performance in Parkinson's Disease, Clin. Neurophysiol. 132 (3) (Mar. 2021) 756–764, https://doi.org/10.1016/j.clinph.2021.01.001.

[16] J.N. Caviness, et al., Differential spectral quantitative electroencephalography patterns between control and Parkinson's disease cohorts, Eur. J. Neurol. 23 (2) (2016) 387–392, https://doi.org/10.1111/ene.12878.

[17] M. Bočková, I. Rektor, Impairment of brain functions in Parkinson's disease reflected by alterations in neural connectivity in EEG studies: a viewpoint, Clin. Neurophysiol. 130 (2) (Feb. 2019) 239–247, https://doi.org/10.1016/J.CLINPH.2018.11.013.

[18] J.N. Caviness, Pathophysiology of Parkinson's disease behavior-a view from the network, Parkinsonism Relat. Disorders 20 (1) (2014) 39–43.

[19] C.J. Stam, Nonlinear dynamical analysis of EEG and MEG: review of an emerging field, Clin. Neurophysiol. 116 (10) (Oct. 2005) 2266–2301, https://doi.org/10.1016/J.CLINPH.2005.06.011.

[20] S. Bhat, U.R. Acharya, Y. Hagiwara, N. Dadmehr, H. Adeli, Parkinson's disease: cause factors, measurable indicators, and early diagnosis, Comput. Biol. Med. 102 (Nov. 2018) 234–241, https://doi.org/10.1016/J.COMPBIOMED.2018.09.008.

[21] Q. Wang, L. Meng, J. Pang, X. Zhu, D. Ming, Characterization of EEG data revealing relationships with cognitive and motor symptoms in Parkinson's disease: a systematic review, Front. Aging Neurosci. 12 (2020) 373, https://doi.org/10.3389/FNAGI.2020.587396/BIBTEX. Nov.

[22] K. Novak, B.A. Chase, J. Narayanan, P. Indic, K. Markopoulou, Quantitative electroencephalography as a biomarker for cognitive dysfunction in Parkinson's disease, Front. Aging Neurosci. 13 (2022), https://doi.org/10.3389/fnagi.2021.804991. January.

[23] Z. Wang, et al., Separating the aperiodic and periodic components of neural activity in Parkinson's disease, Eur. J. Neurosci. 56 (6) (Sep. 2022) 4889–4900, https://doi.org/10.1111/ejn.15774.

[24] M. Moazami-Goudarzi, J. Sarnthein, L. Michels, R. Moukhtieva, D. Jeanmonod, Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients, Neuroimage 41 (3) (2008) 985–997, https://doi.org/10.1016/j.neuroimage.2008.03.032.

[25] C.X. Han, J. Wang, G.S. Yi, Y.Q. Che, Investigation of EEG abnormalities in the early stage of Parkinson's disease, Cogn Neurodyn 7 (4) (2013) 351–359, https://doi.org/10.1007/s11571-013-9247-z.

[26] L. Shirahige, M. Berenguer-Rocha, S. Mendonça, S. Rocha, M.C. Rodrigues, K. Monte-Silva, Quantitative electroencephalography characteristics for Parkinson's disease: a systematic review, J. Parkinsons Dis. 10 (2) (2020) 455–470, https://doi.org/10.3233/JPD-191840.

[27] K. Serizawa, et al., Comparison of quantitative EEGs between Parkinson disease and age-adjusted normal controls, J. Clin. Neurophysiol. 25 (6) (Dec. 2008) 361–366, https://doi.org/10.1097/WNP.0B013E31818F50DE.

[28] D. Stoffers, J.L.W. Bosboom, J.B. Deijen, E.C. Wolters, H.W. Berendse, C.J. Stam, Slowing of oscillatory brain activity is a stable characteristic of Parkinson's disease without dementia, Brain 130 (7) (2007) 1847–1860, https://doi.org/10.1093/brain/awm034.

[29] J.N. Caviness, et al., Longitudinal EEG changes correlate with cognitive measure deterioration in Parkinson's disease, J. Parkinsons Dis. 5 (1) (Jan. 2015) 117–124, https://doi.org/10.3233/JPD-140480.

[30] C. Babiloni, et al., Levodopa may affect cortical excitability in Parkinson's disease patients with cognitive deficits as revealed by reduced activity of cortical sources of resting state electroencephalographic rhythms, Neurobiol. Aging 73 (2019) 9–20, https://doi.org/10.1016/j.neurobiolaging.2018.08.010.

[31] D. Arnaldi, et al., Prediction of cognitive worsening in de novo Parkinson's disease: clinical use of biomarkers, Mov. Disord. 32 (12) (2017) 1738–1747, https://doi.org/10.1002/mds.27190.

[32] E. Maggioni, et al., Effective connectivity during rest and music listening: an EEG study on Parkinson's disease, Front. Aging Neurosci. 13 (April) (2021) 1–16, https://doi.org/10.3389/fnagi.2021.657221.

[33] K.T.E. Olde Dubbelink, D. Stoffers, J.B. Deijen, J.W.R. Twisk, C.J. Stam, H.W. Berendse, Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: a longitudinal study, Neurobiol. Aging 34 (2) (2013) 408–418, https://doi.org/10.1016/j.neurobiolaging.2012.02.029.

[34] A. Pal, N. Pegwal, M. Behari, R. Sharma, High delta and gamma EEG power in resting state characterise dementia in Parkinson's patients, Biomark Neuropsychiatry 3 (April) (2020), 100027, https://doi.org/10.1016/j.bionps.2020.100027.

[35] M. Hassan, et al., Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease, Neuroimage Clin 14 (2017) 591–601, https://doi.org/10.1016/j.nicl.2017.03.002.

[36] M. Conti, et al., Brain Functional Connectivity in de novo Parkinson's Disease Patients Based on Clinical EEG, Front. Neurol. 13 (2022), https://doi.org/10.3389/fneur.2022.844745. March.

[37] L.I. Boon, et al., A systematic review of MEG-based studies in Parkinson's disease: the motor system and beyond, Hum. Brain Mapp. 40 (9) (2019) 2827–2848, https://doi.org/10.1002/hbm.24562.

[38] M. Bayot, et al., Functional networks underlying freezing of gait: a resting-state electroencephalographic study, Neurophysiol. Clin. 000 (xxxx) (2022), https://doi.org/10.1016/j.neucli.2022.03.003.

[39] R.J. Barry, F.M. de Blasio, EEG differences between eyes-closed and eyes-open resting remain in healthy ageing, Biol. Psychol. 129 (April) (2017) 293–304, https://doi.org/10.1016/j.biopsycho.2017.09.010.

[40] H. Railo, I. Suuronen, V. Kaasinen, M. Murtojärvi, T. Pahikkala, A. Airola, Resting State EEG as a Biomarker of Parkinson's Disease: Influence of Measurement Conditions, bioRxiv, 2020.

[41] S.M. Keller, et al., Computational EEG in Personalized Medicine: A Study in Parkinson's Disease, 2018, pp. 1–6 [Online]. Available: http://arxiv.org/abs/1812.06594.

[42] A.H. Meghdadi, M.S. Karic, C. Berka, EEG analytics: benefits and challenges of data driven EEG biomarkers for neurodegenerative diseases, Conf Proc IEEE Int Conf Syst Man Cybern 2019-Octob (2019) 1280–1285, https://doi.org/10.1109/SMC.2019.8914065.

[43] J. Schumacher, et al., EEG alpha reactivity and cholinergic system integrity in Lewy body dementia and Alzheimer's disease, Alzheimer's Res. Ther. 12 (1) (2020) 1–13, https://doi.org/10.1186/s13195-020-00613-6.

[44] J.L.W. Bosboom, et al., Resting state oscillatory brain dynamics in Parkinson's disease: an MEG study, Clin. Neurophysiol. 117 (11) (2006) 2521–2531, https://doi.org/10.1016/j.clinph.2006.06.720.

[45] L.C. Fonseca, G.M.A.S. Tedrus, M.A. Fondello, I.N. Reis, D.S. Fontoura, EEG theta and alpha reactivity on opening the eyes in the diagnosis of Alzheimer's disease, Clin. EEG Neurosci. 42 (3) (Jul. 2011) 185–189, https://doi.org/10.1177/155005941104200308.

[46] J. Kim, J. Lee, E. Kim, J.H. Choi, J.C. Rah, J.W. Choi, Dopamine depletion can be predicted by the aperiodic component of subthalamic local field potentials, Neurobiol. Dis. 168 (Jun. 2022), 105692, https://doi.org/10.1016/J.NBD.2022.105692.

[47] C. Alain, et al., Spontaneous Alpha and Theta Oscillations Are Related to Complementary Aspects of Cognitive Control in Younger and Older Adults, 2021, https://doi.org/10.3389/fnhum.2021.621620.

[48] R. Gao, E.J. Peterson, B. Voytek, Inferring synaptic excitation/inhibition balance from field potentials, Neuroimage 158 (Sep. 2017) 70–78, https://doi.org/10.1016/J.NEUROIMAGE.2017.06.078.

[49] B. Voytek, et al., Age-related changes in 1/f neural electrophysiological noise, J. Neurosci. 35 (38) (2015) 13257–13265, https://doi.org/10.1523/JNEUROSCI.2332-14.2015.

[50] S. Martin, et al., Differential contributions of subthalamic beta rhythms and 1/f broadband activity to motor symptoms in Parkinson's disease, NPJ Parkinsons Dis 4 (1) (2018), https://doi.org/10.1038/S41531-018-0068-Y. Dec.

[51] A.C. Mikkel Vinding, et al., Changes in Non-oscillatory Features of the Cortical Sensorimotor Rhythm in Parkinson's Disease across Age, medRxiv, 2021, https://doi.org/10.1101/2021.06.27.21259592, 06.27.21259592, Jun. 2022.

[52] J. Zhang, A. Villringer, V.V. Nikulin, Dopaminergic modulation of local non-oscillatory activity and global-network properties in Parkinson's disease: an EEG study, Front. Aging Neurosci. 14 (2022) 381, https://doi.org/10.3389/FNAGI.2022.846017/BIBTEX. Apr.

[53] H. Railo, N. Nokelainen, S. Savolainen, V. Kaasinen, Deficits in monitoring self-produced speech in Parkinson's disease, Clin. Neurophysiol. 131 (9) (Sep. 2020) 2140–2147, https://doi.org/10.1016/j.clinph.2020.05.038.

[54] H. Railo, Jul, OSF | Parkinson's disease: Resting state EEG 15 (2021), https://osf.io/pehj9/. (Accessed 3 February 2023).

[55] H. Nolan, R. Whelan, R.B. Reilly, FASTER: fully automated statistical thresholding for EEG artifact rejection, J. Neurosci. Methods 192 (1) (Sep. 2010) 152–162, https://doi.org/10.1016/J.JNEUMETH.2010.07.015.

[56] M.A. Colombo, et al., The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine, Neuroimage 189 (Apr. 2019) 631–644, https://doi.org/10.1016/j.neuroimage.2019.01.024.

[57] D.M. Groppe, T.P. Urbach, M. Kutas, Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review, Psychophysiology 48 (12) (2011) 1711–1725, https://doi.org/10.1111/J.1469-8986.2011.01273.X.

[58] Y. Benjamini, A.M. Krieger, D. Yekutieli, Adaptive linear step-up procedures that control the false discovery rate, Biometrika 93 (3) (2006) 491–507, https://doi.org/10.1093/biomet/93.3.491.

[59] Y. Benjamini, Y. Hochberg, Controlling the false discovery rate: a practical and powerful approach to multiple testing, J. Roy. Stat. Soc. B 57 (1) (Jan. 1995) 289–300, https://doi.org/10.1111/J.2517-6161.1995.TB02031.X.

[60] R. February, I. Academy, THE control of the false discovery rate in multiple testing under dependency by yoav Benjamini 1 and daniel Yekutieli 2, Ann. Stat. 29 (4) (2001) 1165–1188.

[61] J. Sassenhagen, D. Draschkow, Cluster-based permutation tests of MEG/EEG data do not establish significance of effect latency or location, Psychophysiology 56 (6) (2019), https://doi.org/10.1111/PSYP.13335. Jun.

[62] C.G. Goetz, et al., Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (15) (Nov. 2008) 2129–2170, https://doi.org/10.1002/MDS.22340.

[63] P.T. Francis, E.K. Perry, Cholinergic and other neurotransmitter mechanisms in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies, Mov. Disord. 22 (S17) (Jan. 2007) S351–S357, https://doi.org/10.1002/MDS.21683.

[64] D. Eichelberger, et al., Correlation of visuospatial ability and EEG slowing in patients with Parkinson's disease, Parkinsons Dis 2017 (2017), https://doi.org/10.1155/2017/3659784.

[65] Y. Rosenblum, et al., Decreased aperiodic neural activity in Parkinson's disease and dementia with Lewy bodies, J. Neurol. (May 2023) 1–12, https://doi.org/10.1007/S00415-023-11728-9/FIGURES/2.

[66] D.L. Clark, T. Khalil, L.H. Kim, M.S. Noor, F. Luo, Z.H. Kiss, Aperiodic subthalamic activity predicts motor severity and stimulation response in Parkinson disease, Parkinsonism Relat. Disorders 110 (May 2023), 105397, https://doi.org/10.1016/J.PARKRELDIS.2023.105397.

[67] T. Donoghue, et al., Parameterizing neural power spectra into periodic and aperiodic components, Nat. Neurosci. 23 (12) (2020) 1655, https://doi.org/10.1038/S41593-020-00744-X. Dec.

[68] M. Gerster, et al., Separating neural oscillations from aperiodic 1/f activity: challenges and recommendations, Neuroinformatics 20 (4) (Oct. 2022) 991–1012, https://doi.org/10.1007/S12021-022-09581-8.

[69] T. Donoghue, J. Dominguez, B. Voytek, Electrophysiological frequency band ratio measures conflate periodic and aperiodic neural activity, eNeuro 7 (6) (2020), https://doi.org/10.1523/ENEURO.0192-20.2020.

[70] E.A. Barcelon, et al., Grand Total EEG score can differentiate Parkinson's disease from Parkinson-related disorders, Front. Neurol. 10 (APR) (2019) 1–11, https://doi.org/10.3389/fneur.2019.00398.

[71] C. Babiloni, et al., Reactivity of posterior cortical electroencephalographic alpha rhythms during eyes opening in cognitively intact older adults and patients with dementia due to Alzheimer's and Lewy body diseases, Neurobiol. Aging 115 (2022) 88–108, https://doi.org/10.1016/j.neurobiolaging.2022.04.001.

[72] L. Wan, et al., From eyes-closed to eyes-open: role of cholinergic projections in EC-to-EO alpha reactivity revealed by combining EEG and MRI, Hum. Brain Mapp. 40 (2) (2019) 566–577, https://doi.org/10.1002/hbm.24395.

[73] P. Tiraboschi, et al., Early and widespread cholinergic losses differentiate dementia with Lewy bodies from Alzheimer disease, Arch Gen Psychiatry 59 (10) (Oct. 2002) 946–951, https://doi.org/10.1001/ARCHPSYC.59.10.946.

[74] S.M. Keller, U. Gschwandtner, A. Meyer, M. Chaturvedi, V. Roth, P. Fuhr, Cognitive decline in Parkinson's disease is associated with reduced complexity of EEG at baseline, Brain Commun 2 (2) (2020) 1–13, https://doi.org/10.1093/braincomms/fcaa207.

[75] A. Miladinovic, et al., EEG changes and motor deficits in Parkinson's disease patients: correlation of motor scales and EEG power bands, in: Procedia Computer Science, Elsevier B.V., 2021, pp. 2616–2623, https://doi.org/10.1016/j.procs.2021.09.031.

[76] N.M. Petro, et al., Eyes-closed versus eyes-open differences in spontaneous neural dynamics during development, Neuroimage 258 (2022), 119337, https://doi.org/10.1016/j.neuroimage.2022.119337. January.

[77] G. Yogev-Seligmann, T. Krasovsky, M. Kafri, Compensatory movement strategies differentially affect attention allocation and gait parameters in persons with Parkinson's disease, Front. Hum. Neurosci. 16 (August) (2022) 1–11, https://doi.org/10.3389/fnhum.2022.943047.

[78] J.N. Caviness, et al., Both early and late cognitive dysfunction affects the electroencephalogram in Parkinson's disease, Parkinsonism Relat. Disorders 13 (6) (2007) 348–354, https://doi.org/10.1016/j.parkreldis.2007.01.003.

[79] R. Camicioli, M.M. Moore, A. Kinney, E. Corbridge, K. Glassberg, J.A. Kaye, Parkinson's disease is associated with hippocampal atrophy, Mov. Disord. 18 (7) (2003) 784–790, https://doi.org/10.1002/MDS.10444. Jul.

[80] M. Grunwald, A. Hensel, H. Wolf, T. Weiss, H.J. Gertz, Does the hippocampal atrophy correlate with the cortical theta power in elderly subjects with a range of cognitive impairment? J. Clin. Neurophysiol. 24 (1) (Feb. 2007) 22–26, https://doi.org/10.1097/WNP.0B013E31802ED5B2.

[81] F. Massa, et al., Utility of quantitative EEG in early Lewy body disease, Parkinsonism Relat. Disorders 75 (Jun. 2020) 70–75, https://doi.org/10.1016/J.PARKRELDIS.2020.05.007.

[82] A.N. Vardy, E.E.H. van Wegen, G. Kwakkel, H.W. Berendse, P.J. Beek, A. Daffertshofer, Slowing of M1 activity in Parkinson's disease during rest and movement - an MEG study, Clin. Neurophysiol. 122 (4) (Apr. 2011) 789–795, https://doi.org/10.1016/j.clinph.2010.10.034.

[83] A. Jaramillo-Jimenez, et al., Spectral features of resting-state EEG in Parkinson's Disease: a multicenter study using functional data analysis, Clin. Neurophysiol. 151 (Jul. 2023) 28–40, https://doi.org/10.1016/j.clinph.2023.03.363.
[84] S. Little, P. Brown, The functional role of beta oscillations in Parkinson's disease, Parkinsonism Relat. Disorders 20 (SUPPL.1) (2014) S44–S48, https://doi.org/10.1016/S1353-8020(13)70013-0.
[85] S. Little, A. Pogosyan, A.A. Kuhn, P. Brown, Beta band stability over time correlates with Parkinsonian rigidity and bradykinesia, Exp. Neurol. 236 (2) (2012) 383, https://doi.org/10.1016/J.EXPNEUROL.2012.04.024. Aug.
[86] C.C. Chen, et al., Complexity of subthalamic 13–35 Hz oscillatory activity directly correlates with clinical impairment in patients with Parkinson's disease, Exp. Neurol. 224 (1) (Jul. 2010) 234–240, https://doi.org/10.1016/J.EXPNEUROL.2010.03.015.
[87] C. Cao, D. Li, S. Zhan, C. Zhang, B. Sun, V. Litvak, L-dopa treatment increases oscillatory power in the motor cortex of Parkinson's disease patients, Neuroimage Clin 26 (April) (2020), 102255, https://doi.org/10.1016/j.nicl.2020.102255.
[88] P. Brown, Abnormal oscillatory synchronisation in the motor system leads to impaired movement, Curr. Opin. Neurobiol. 17 (6) (Dec. 2007) 656–664, https://doi.org/10.1016/J.CONB.2007.12.001.
[89] G.S. Yi, J. Wang, B. Deng, X. Le Wei, Complexity of resting-state EEG activity in the patients with early-stage Parkinson's disease, Cogn Neurodyn 11 (2) (2017) 147–160, https://doi.org/10.1007/s11571-016-9415-z.
[90] J.S. George, J. Strunk, R. Mak-Mccully, M. Houser, H. Poizner, A.R. Aron, Dopaminergic therapy in Parkinson's disease decreases cortical beta band coherence in the resting state and increases cortical beta band power during executive control, Neuroimage Clin 3 (Jan. 2013) 261–270, https://doi.org/10.1016/J.NICL.2013.07.013.
[91] N.C. Swann, C. De Hemptinne, A.R. Aron, J.L. Ostrem, R.T. Knight, P.A. Starr, Elevated synchrony in Parkinson's disease detected with electroencephalography, Ann. Neurol. 78 (5) (Nov. 2015) 742, https://doi.org/10.1002/ANA.24507.
[92] W.J. Neumann, et al., Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease, Mov. Disord. 31 (11) (Nov. 2016) 1748–1751, https://doi.org/10.1002/MDS.26759.
[93] A. Priori, et al., Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease, Exp. Neurol. 189 (2) (Oct. 2004) 369–379, https://doi.org/10.1016/J.EXPNEUROL.2004.06.001.
[94] P. Stanzione, et al., Quantitative EEG changes in non-demented Parkinson's disease patients before and during L-dopa therapy, Eur. J. Neurol. 3 (4) (1996) 354–362, https://doi.org/10.1111/J.1468-1331.1996.TB00229.X.
[95] C. Vakalopoulos, The EEG as an index of neuromodulator balance in memory and mental illness, Front. Neurosci. 8 (8 APR) (2014) 1–15, https://doi.org/10.3389/fnins.2014.00063.
[96] X.T.C. Whalen, A.M. Willard, J.E. Rubin, A.H. Gittis, Delta oscillations are a robust biomarker of dopamine depletion severity and motor dysfunction in awake mice, J. Neurophysiol. 124 (2) (2020) 312–359, https://doi.org/10.1152/jn.00158.2020.
[97] H. Bousleiman, et al., Power spectra for screening parkinsonian patients for mild cognitive impairment, Ann Clin Transl Neurol 1 (11) (Nov. 2014) 884–890, https://doi.org/10.1002/ACN3.129.
[98] W.J.F. Ae, J. Zhai, Simulated Power Spectral Density (PSD) of Background Electrocorticogram, ECoG), 2008, https://doi.org/10.1007/s11571-008-9064-y.
[99] C. Wiest, et al., The Aperiodic Exponent of Subthalamic Field Potentials Reflects Excitation/inhibition Balance in Parkinsonism: a Cross-Species Study in Vivo, 08.23.504923, bioRxiv, 2022, p. 2022 [Online]. Available: http://biorxiv.org/content/early/2022/08/23/2022.08.23.504923.abstract.
[100] A.T. Hill, G.M. Clark, F.J. Bigelow, J.A.G. Lum, P.G. Enticott, Periodic and aperiodic neural activity displays age-dependent changes across early-to-middle childhood, Dev Cogn Neurosci 54 (2022), 101076, https://doi.org/10.1016/j.dcn.2022.101076. October 2021.
[101] F. Liu, S.K. Sarkar, A new adaptive method to control the false discovery rate, in: Recent Advances in Biostatistics, WORLD SCIENTIFIC, 2011, pp. 3–26, https://doi.org/10.1142/9789814329804_0001.
[102] T. Tong, H. Zhao, Practical guidelines for assessing power and false discovery rate for a fixed sample size in microarray experiments, Stat. Med. 27 (11) (2008) 1960–1972, https://doi.org/10.1002/sim.3237.
[103] G. M. Sullivan and R. Feinn, "Using Effect Size-Or Why the P Value Is Not Enough", doi: 10.4300/JGME-D-12-00156.1..
[104] Z. Zhang, X. Xu, H. Ni, Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study, Crit. Care 17 (1) (Jan. 2013) 1–9, https://doi.org/10.1186/CC11919/TABLES/3.
[105] M. Perugini, M. Gallucci, G. Costantini, Safeguard power as a protection against imprecise power estimates, Perspect. Psychol. Sci. 9 (3) (2014) 319–332, https://doi.org/10.1177/1745691614528519.
[106] O. Komisaruk, E. Nikulchev, Neural network model for artifacts marking in EEG signals, Int. J. Adv. Comput. Sci. Appl. 12 (12) (2021) 2021, https://doi.org/10.14569/IJACSA.2021.0121204. *Article in.*
[107] W.Y. Peh, Y. Yao, J. Dauwels, Transformer convolutional neural networks for automated artifact detection in scalp EEG, in: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2022, pp. 3599–3602, https://doi.org/10.1109/EMBC48229.2022.9871916, 2022-July.
[108] S. Wang, B. Guo, C. Zhang, X. Bai, Z. Wang, EEG detection and de-noising based on convolution neural network and Hilbert-Huang transform, Proceedings - 2017 10th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics, CISP-BMEI 2018-January (2017) 1–6, https://doi.org/10.1109/CISP-BMEI.2017.8302146. Feb. 2018.