Clinical Neurophysiology 130 (2019) 1937–1944

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Phase lag index and spectral power as QEEG features for identification of patients with mild cognitive impairment in Parkinson's disease

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ARTICLE INFO

Article history:
Accepted 15 July 2019
Available online 25 July 2019

Keywords:
Parkinson's disease
QEEG
Connectivity
Spectral power
Mild cognitive impairment
Machine learning

HIGHLIGHTS

- EEG connectivity measures classify Parkinson patients with mild cognitive impairment (MCI-PD) from non-MCI PD better than spectral power.
- Connectivity in theta and delta bands (PLI) differs between MCI and non-MCI PD patients.
- Memory domain is highly correlated with connectivity measures in theta band.

ABSTRACT

Objectives: To identify quantitative EEG frequency and connectivity features (Phase Lag Index) characteristic of mild cognitive impairment (MCI) in Parkinson's disease (PD) patients and to investigate if these features correlate with cognitive measures of the patients.
Methods: We recorded EEG data for a group of PD patients with MCI ($n = 27$) and PD patients without cognitive impairment ($n = 43$) using a high-resolution recording system. The EEG files were processed and 66 frequency along with 330 connectivity (phase lag index, PLI) measures were calculated. These measures were used to classify MCI vs. MCI-free patients. We also assessed correlations of these features with cognitive tests based on comprehensive scores (domains).
Results: PLI measures classified PD-MCI from non-MCI patients better than frequency measures. PLI in delta, theta band had highest importance for identifying patients with MCI. Amongst cognitive domains, we identified the most significant correlations between Memory and Theta PLI, Attention and Beta PLI.
Conclusion: PLI is an effective quantitative EEG measure to identify PD patients with MCI.
Significance: We identified quantitative EEG measures which are important for early identification of cognitive decline in PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting 1–2% of the population older than 60 years (Poewe et al., 2008; Sveinbjornsdottir, 2016; Tysnes and Storstein, 2017). Cognitive impairment, whether without dementia or dementia itself, is a critical non-motor symptom of PD, which limits treatment options, and worsens outcomes and life expectancy of the patients (Emre, 2003; Levy et al., 2002; Watson and Leverenz, 2010).

At the same time, cognitive course of PD is heterogeneous and clinical manifestation of dementia is preceded by subtle functional changes. Mild Cognitive Impairment (MCI) is the intermediate condition between non-altered cognition and Parkinson's disease dementia (PD-D). A study showed prevalence of MCI in about 40% of newly diagnosed PD patients (Monastero et al., 2018). MCI can be a stable stage for many patients, as is demonstrated in a longitudinal study over 3 years (Lawson et al., 2017) while some studies have reported the progression rate of MCI to PD-D over 4–12 years to be 40–60% (Pedersen et al., 2017; Weil et al., 2018; Williams-Gray et al., 2013; Wood et al., 2016). As the clinical symptoms appear much later than the onset of cognitive impair-

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https://doi.org/10.1016/j.clinph.2019.07.017
1388-2457/

ment or neuro-degeneration, having methods of early identification of cognitive impairment in PD patients are of major importance for clinicians and researchers and can help improve the quality of life of patients.

Quantitative electroencephalography (qEEG) is a non-invasive and cost-effective technique that records the electrical activity of the brain (Rana et al., 2017). It provides quantitative information on brain functions, e.g. spectral power or connectivity and has been used to investigate different types of dementia (Al-Qazzaz et al., 2014) while also being routinely used in clinics for detecting epilepsy (Rosenow et al., 2015). Spectral powers measure the amplitude of the neuronal oscillations and phase denotes where an oscillation is in its cycle (Handy, 2009).

Increase of qEEG spectral powers in frequency range below 8 Hz and decrease of spectral power in ranges above 8 Hz are associated with a risk of cognitive decline in PD (Klassen et al., 2011; Dubbelink et al., 2014; Caviness et al., 2016; Babiloni et al., 2011; Stoffers et al., 2007). Brain connectivity alterations are also found to be associated with cognitive deterioration in PD (Bertrand et al., 2016; Gao and Wu, 2016; Hassan et al., 2017). Studies investigating PD patients have reported early changes in frontal inter-hemispheric coupling (Carmona et al., 2017) and indicate network decentralization to progress over time in these patients. Such network changes could be potential markers of disease progression (Olde Dubbelink et al., 2014).

In recent years, increasing number of reports show that a combination of methods, sometimes referred to as "composite marker", can predict cognitive decline in Parkinson's disease significantly better than a single method (Anang et al., 2014; Liu et al., 2017). Moreover, information obtained by each of the component methods of such composite markers should be non-redundant, reflecting some independent processes (Aarsland et al. 2017).

The aims of this study were: (a) to identify spectral and connectivity qEEG measures potentially characteristic of MCI in PD patients; (b) to compare the predictive performance of spectral and connectivity qEEG measures; (c) to check for correlation between cognitive domains and EEG features.

2. Methods

2.1. Subjects

We selected patients at the out-patient movement disorders clinic of the University Hospital Basel (Switzerland) on the following criteria: PD according to UK PD Brain Bank (UPDRS, 2003), Mini-Mental Score Examination (MMSE) above 24/30, no history of vascular and/or demyelinating brain pathology, sufficient knowledge of German language. The study was approved by the local ethics committees (Ethikkommission beider Basel, Basel; Switzerland; EK 74/09) and all participants gave written informed consent before study inclusion.

2.2. Clinical neurological and neuropsychological assessments

Basic neurological examination was carried out in all individuals. All patients underwent comprehensive neuropsychological examinations. A series of 23 neuropsychological tests was carried out, resulting in aggregate five cognitive scores (domains): Memory, Attention + Working Memory, Executive Function, Language and Visual-Spatial Function. Overall test variables comprised an aggregate "overall cognitive score". MCI diagnosis was set on the grounds of Litvan 2012 level II criteria (Litvan et al., 2012). We identified 27 PD patients with MCI (MCI group) and 43 PD patients without MCI (non-MCI group). The individual tests grouped into domains are shown in Table 1. This grouping follows the same classification as used for the MCI categorization.

Table 1
Psychological tests grouped into 5 cognitive domains.

Domain	Neuropsychological tests
Memory	California Verbal Learning Test (Delis et al., 1987): (1) trial 1; (2) trial 5; (3) savings; (4) discriminability Rey-Osterrieth Complex Figure (Spreen and Strauss, 1998): savings (immediate recall divided by copy)
Executive Function	Five-Point Test (Regard et al., 1982): correct answers Semantic verbal fluency test (Isaacs and Kennie, 1973): correct answers Phonemic verbal fluency (Thurstone, 1948): correct answers Trail-Making Test (Reitan, 1955): time for part B divided by time for part A
Attention and Working Memory	Test of Attentional Performance (TAP) – Alertness (Zimmermann and Fimm, 2007): (1) reaction time with alerting sound; (2) reaction time without alerting sound TAP – Divided Attention: (1) reaction time to auditive stimuli (2) reaction time to visual stimuli (3) number of omissions Trail-Making Test: time for part A Digit span from the German version of the Revised Wechsler Memory Scale (Härtig et al., 2000): (1) correct forwards (2) correct backwards Corsi blocks from the German version of the Revised Wechsler Memory Scale (Härtig et al., 2000): (1) correct forwards; (2) correct backwards
Visuo-Spatial Function	Rey-Osterrieth Complex Figure: copy Block Design Test (Härtig et al., 2000): sum score
Language	Boston Naming Test (Morris et al., 1989): correct answers Similarities from the German version of the Revised Wechsler Memory Scale (Härtig et al., 2000): correct answers

2.3. EEG recording and processing

We recorded 12 min of EEG in resting-state eyes-closed condition, using a 256-channel EEG System (Netstation 300, EGI, Inc., Eugene, OR). EEG recordings were done in the afternoons and patients were seated comfortably in a relaxing chair, instructed to close their eyes. A technician present in the recording room controlled for vigilance of the patients. Before the EEG recording, patients were also asked to self- rate their sleepiness level from 1 to 9 using the Karolinska Sleepiness Scale (Åkerstedt and Gillberg, 1990; Kaida et al., 2006; Miley et al., 2016).

All data were segmented and processed in an automated way using a Matlab based in-house software (TAPEEG, https://sites.google.com/site/tapeeg/) (Hatz et al., 2015). EEG's were filtered (Firls: 0.5–70 Hz, 50 Hz notch) at a sampling rate of 1000 Hz and an inverse Hanning window was used to stitch together shorter segments, to have at least 3 min of cleaned EEG data. Artefacts like eye movements, traces of sleep, blinking, ECG etc. were detected and removed. After performing automated bad-channel detection (Hatz et al., 2015), the average of all 'good' channels was used to re-reference the EEG to a common average montage.

The independent component analysis implementation of EEGLAB (Delorme and Makeig, 2004) ("runica" with default settings) was used to remove further artefacts. Electrodes placed on the neck, ears, cheeks were excluded to remove spurious signals, and 214 electrodes were mapped to ten regions of interest: frontal left/right, central left/right, parietal left/right, temporal left/right, and occipital left/right (Figure S1).

2.4. EEG features: Spectral (frequency) and connectivity analyses

2.4.1. Frequency – spectral power

Spectral analysis is a process used for quantifying EEG. It is used to decompose a complex EEG signal into its component frequencies by applying Fourier Transformation (Walczak and Chokroverty, 2009, p. 12). A power spectrum reflects "the amount of activity" in frequency bands (Cozac, 2017). Relative power is used to assess the relative contribution of a particular frequency to the EEG signal (Heisz and McIntosh, 2013) and is calculated by dividing the absolute power in a given frequency band by the total power. We calculated median relative spectral powers in the following frequency ranges (Hz): 1–4 (delta), 4–8 (theta), 8–10 (alpha1), 10–13 (alpha2), 8–13 (alpha), and 13–30 (beta).

Spectral power can be assessed globally (over the whole scalp) and over definite scalp regions. Using a high density electrode system enables us to aggregate nearby signals, thus potentially reducing noise. We obtained the spectral powers for the ten regions of interest and also assessed spectral power globally. Thus, we analysed features in 6 frequency ranges and 11 locations, obtaining a total of 66 spectral features.

2.4.2. Connectivity – phase lag index

We used Phase Lag Index (PLI) as a measure of functional connectivity. PLI is calculated from the asymmetry of the distribution of instantaneous signal phase differences between two brain regions. (Cozac, 2017). It is based on the idea that a consistent phase lag translates to a time lag between two time series (Bastos and Schoffelen, 2016). In other words, PLI reflects the degree of synchronization between couples of signals; it denotes functional connection between regions of the brain, mentioned above (for instance, PLI in theta frequency range for connection between temporal left and temporal right regions reflects the level of synchronization of oscillations in 4–8 Hz in these 2 regions, from "chaotic" (lower PLI) to synchronized (higher PLI)). The main approach is to disregard phase differences which centre around 0 mod π (Stam et al., 2007).

It is calculated as:

$$PLI = |< sign[sin(\Delta\Phi(t_k))] >|$$

where $\Delta\Phi$ is the phase difference at time point t_k between two time series, calculated for all time-points per epoch (4096 in our case), *sign* stands for signum function, < > denotes the mean value and || indicates the absolute value. The instantaneous phases were estimated with the Hilbert transform using a 50% overlapping sliding window approach.

PLI values range between 0 and 1, where 0 can indicate possibly no coupling and 1 refers to perfect phase locking. We mapped the 214 electrodes to the ten anatomically defined regions. For each region, the average connectivity of all its electrodes to all other regional groups of electrodes was determined (Hardmeier et al., 2014). The connectivity between all pairs of regions was calculated, including the connectivity within a region. This resulted in 55 PLI measures for 6 frequency bands, totalling to 330.

2.5. Statistical analysis

2.5.1. Checking for normal distribution and standardization of measures

We compared the demographic and clinical features between MCI and non-MCI groups: age, sex, total education, UPDRS III, MMSE, Hoehn and Yahr Scores, using Wilcoxon non-parametric tests to test if the groups were comparable and for any apparent biases that might be visible. We also compared the global EEG frequency and PLI measures in both groups for a first overview of differences in EEG features in PD-MCI and Non-MCI and adjusted the p-values for multiple testing.

For statistical calculations we used R version 3.4.1 and RStudio version 1.0.143 (R Core Team, 2018).

Cognitive test variables were standardized ("normalized") with reference to a normative data base of 604 healthy individuals from the Memory Clinic, Felix Platter Hospital of Basel, Switzerland (Berres et al., 2000).

Spearman correlation coefficients were computed to check for significant correlations between the cognitive domains and PLI measures in each power band. The p-values and confidence intervals for correlations between the cognitive domains and all PLI global measures were obtained using the Psych (Revelle, 2018) package. The probability values were adjusted using the Holm correction method implemented in the package.

The ggcorrplot (Kassambara, 2018) package was used for visualizations.

2.5.2. Random Forest

Random Forest is a widely used ensemble machine learning method based on decision trees (Breiman, 2001). It has been reported to be successfully used in several classification and regression studies related to neurology, such as, for predicting disease progression or classifying patients based on different features in the case of Alzheimer's disease (Dimitriadis et al., 2018; Dimitriadis and Liparas, 2018; Sarica et al., 2017), Parkinson's disease (Açıcı et al., 2017; Chaturvedi et al., 2017) and Multiple Sclerosis(Lötsch et al., 2018; Zhang et al., 2018).

The method works by constructing several decision trees, selecting subsets of features randomly with replacement, evaluating the best features based on majority voting and then getting predictions based on these measures. The hyper parameters can be tuned to obtain models with high predictive performance. Each variable included in the model is evaluated based on its effect on the overall accuracy of the model and a measure called 'Mean Decrease Accuracy' reflects the importance of the predictor.

It is advantageous to use Random Forest as it combines decision trees with bagging, reduces overfitting, handles large number of predictor variables and ranks variables on the basis of their importance. This makes it more effective in feature selection.

In this analysis, Random Forest was applied with the standard implementation in R. Data were split into training (70%) and test sets (30%) and 5 fold Cross-Validation (Refaeilzadeh et al., 2009) was repeated 20 times. Area-under-the-curve (AUC) measures were obtained for Receiver Operating Characteristics (ROC)-curves. Classification models were built using frequency measures, PLI measures and frequency combined with PLI measures respectively. As a 5 fold Cross-Validation run resulted in 5 AUC values, the 20 times repeated 5 fold cross validation resulted in a total of 100 AUC values for each of the three types of classification models. We then obtained a ranked list of the top features important for the accuracy of the classification model.

To test whether the AUC values were significantly different while using frequency and PLI measures for classification, we carried out the Friedman test (Friedman, 1940), followed by post-hoc testing to see which of the groups had significant differences (Demšar, 2006). This showed us if the AUC values significantly differed between the three groups, and if so, between which pairs.

The following packages were used: Random Forest (Liaw and Wiener, 2002), caret (Kuhn, 2008), ROCR (Sing et al., 2005), PMCMR (Pohlert, 2014).

3. Results

3.1. Participant characteristics

For the first part of the study, we wanted to check if the data set was free from any apparent bias due to differences in demographic features and also if the EEG patterns corroborated with our previous findings. Table 2 shows the demographics the patients stratified according to the diagnosis of MCI. MCI and non-MCI patients did not differ in their age, education, UPDRS III and Hoehn and Yahr scores. UPDRS III scores recorded reflect the condition of patients under medication. The disease duration was also similar in both groups; so all patients were at a relatively early stage of the disease. As expected, they had significant differences in their MMSE scores. Self- reported sleepiness scores indicated alertness for majority of the patients, with median value 3 on the 1 to 9 sleepiness scale.

3.2. EEG features in PD-MCI and non-MCI patients

While inspecting the differences in the global EEG features in the two groups, relative median spectral power in theta ($p < 0.05$) and beta bands ($p < 0.05$) differed significantly between MCI and Non-MCI patient groups as did PLI in theta band ($p < 0.05$) (Fig. 1). This aligned with our previous understanding of theta power being highly associated with cognitive decline.

3.3. Classifying PD patients according to MCI using PLI and spectral measures

We proceeded to carry out the classification between the two groups and obtained the ROC-curves using PLI and frequency measures, separately and in combination. The demographics and clinical features assessed earlier were also included, to verify yet again if any of these features would be ranked as highly influential in the classification. The mean AUC values obtained for frequency measures after cross-validation (0.64 ± 0.15) were lower than those obtained for PLI (0.74 ± 0.17) and for the combination of Frequency, PLI (0.73 ± 0.16). The range of all 100 AUC values in these three cases is depicted in Fig. 2.

We then wanted to test if AUC values obtained from these 3 groups have any significant differences, so as to understand if the classification performance would truly improve while using PLI measures instead of frequency. Friedman test showed overall group differences to be significant and then, the Friedman posthoc testing showed that the classification performance using PLI was statistically different than using frequency measures, but similar to performance obtained when combining frequency and PLI together. This is depicted in Table 3.

Table 2
Patient demographics, showing Median [Min, Max].

Parameters	PD patients ($n = 70$)		
	MCI ($n = 27$) (21 M, 6F)	Non-MCI ($n = 43$) (26 M, 17F)	p-value
Age	67[53,84]	67[46,82]	n.s.
Education	16[9,20]	15[9,21]	n.s
MMSE	29[24,30]	29[27,30]	0.02
UPDRS III	15[0,41]	15[0,36]	n.s.
Hoehn and Yahr	2[0,5]	2[0,4]	n.s
Disease duration (years)	5[0,23]	4[0,17]	n.s
Levadopa Dosage (mg/day)	650[0,1875]	525[0,2129.5]	n.s
Karolinska Sleepiness Scale	3[1,7.7]	3[1,7]	n.s.

On an external unseen test set, AUC values of 0.65, 0.65 and 0.71 were obtained respectively for the three cases.

With regards to identifying the most important variables to identify MCI in PD patients, more PLI measures than spectral measures were ranked amongst the most important ones. In the model constructed using PLI features, measures in theta, delta, beta bands, especially in the Temporal, Central and Parietal regions were ranked high. The clinical features were not ranked amongst the top 20 variables influential for the prediction accuracy of the model but Hoehn and Yahr stage came up as important feature while using frequency features alone. When considering all frequency and PLI measures together, theta powers in the parietal, central, regions and alpha1 power in central region were ranked at the top, together with PLI measures. Figures S2 and S3 in the Supplementary Material show the top 20 PLI and all frequency and PLI combined measures, ranked according to their effect on the accuracy of the model by Random Forest respectively.

These results indicate that PLI measures perform better while classifying MCI from Non-MCI patients. We found no added benefit in performance while adding on the frequency measures to the PLI features. So, for classification purposes, using this data, we can say that PLI would be the preferred choice of EEG measure over frequency. In line with our previous understanding and assumptions, theta, beta power bands and theta PLI showed the major differences in the two groups. We also observed Alpha frequency and Delta PLI measures amongst the top influential variables selected by Random Forest.

Additionally, we also investigated the effect of using all 256 electrodes, without mapping to corresponding anatomical brain regions, for the development of prediction models and classifying PD MCI from PD non-MCI patients. In this case, we retrieved 1278 frequency measures and 136,846 non-zero PLI measures. AUC values from the model developed using frequency measures during cross-validation (0.65 ± 0.15) did not differ much when using PLI measures (0.696 ± 0.145) or combining all frequency and PLI measures (0.7 ± 0.14) during cross-validation. There were no statistical differences in AUC's, as depicted in Table S1 in the Supplementary Material.

Figure S4 in the Supplementary Material shows the higher influence of Theta and Delta PLI in the classification using all PLI and frequency measures. Most of the electrodes ranked at the top corresponded to the Temporal, Parietal and Central Regions, aligned with our previous findings. The only frequency feature ranked amongst the top 20 variables corresponded to Theta power in the Temporal Right region. On an unseen external test, AUC values of 0.74, 0.85 and 0.875 were obtained for the three models respectively.

However, when comparing the runtime complexities for different models, we noted that using all PLI and frequency features without mapping to regions took maximum time (40,620.02 seconds or about 11 hours), while doing so with the mapped 10 regions took 64.45 seconds. The model using PLI features mapped to 10 regions took 53.79 seconds, while using all PLI features without mapping took 32,924 seconds. Models built using 256 electrodes in general took more runtime, which should be taken into consideration while building similar models in the future. Time taken by each of the six models can be seen in Table S2 of the Supplementary Material.

3.4. Correlation of cognitive domains and EEG features

Now that we determined PLI to be an effective measure for identifying PD patients with MCI, we wanted to assess correlations between each of the 5 cognitive domains and the Overall Cognitive Score (Attention + Working Memory, Executive Function, Memory, Visuo-Spatial Function, Language) and global PLI measures to get

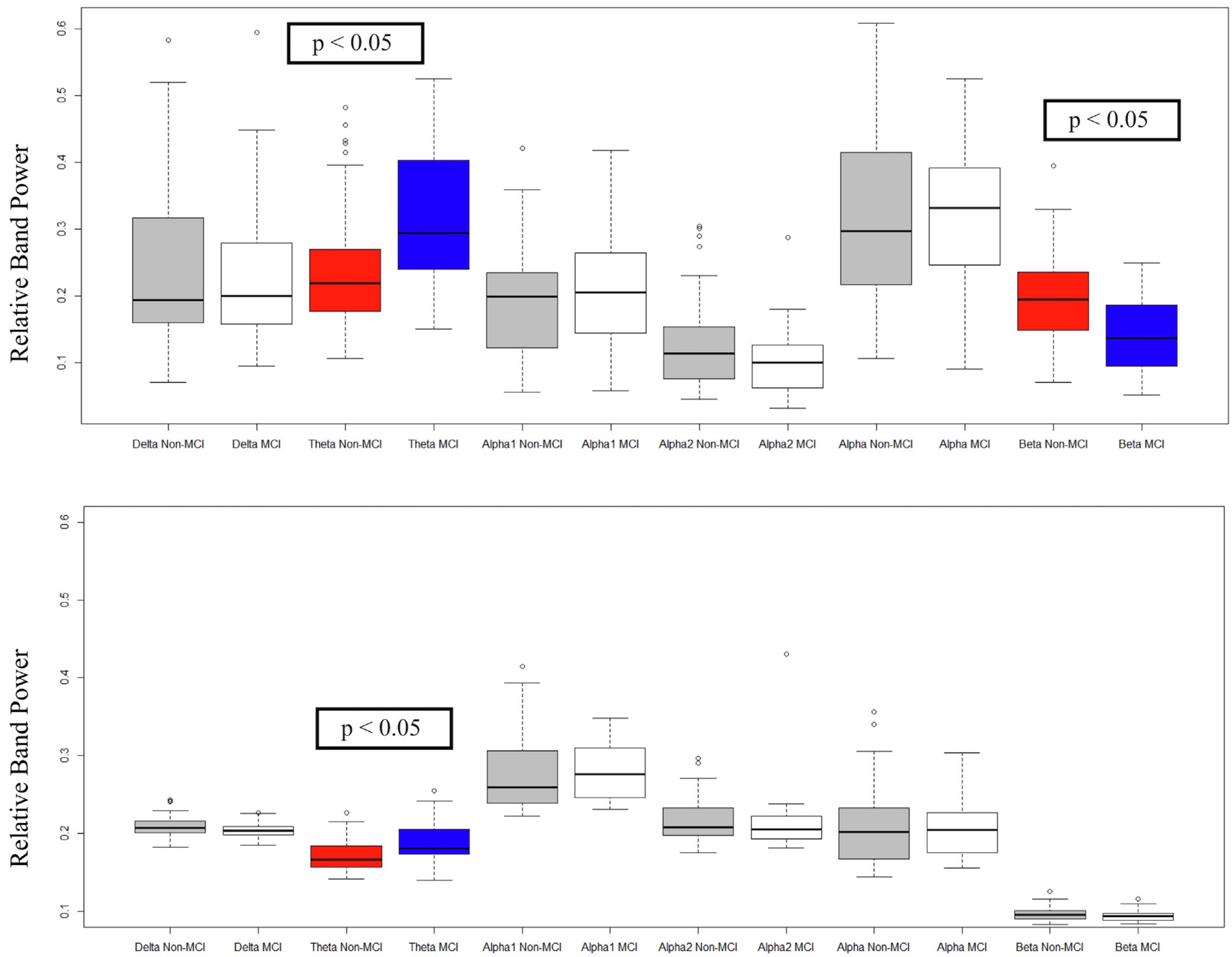

Fig. 1. (a and b): Global spectral powers and PLI measures in Delta, Theta, Alpha1, Alpha2, Alpha, Beta bands between PD Non-MCI and PD MCI patients. Theta, Beta global powers and Theta global PLI differed significantly in the two groups.

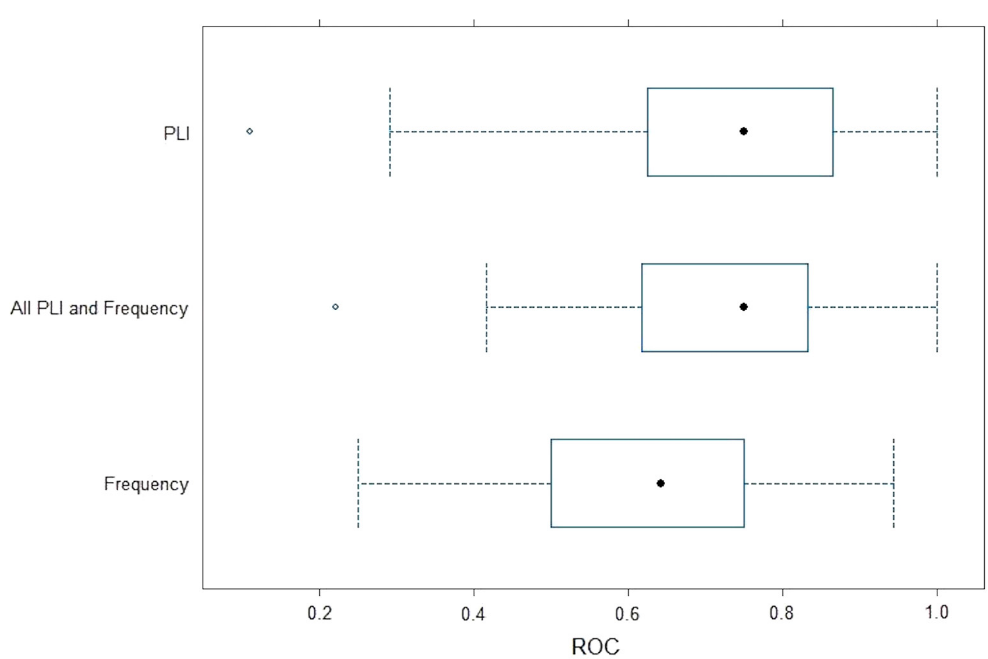

Fig. 2. AUC spreads showing model performance while using PLI, Frequency and a combination of PLI, Frequency measures mapped to 10 regions.

Table 3
Statistical significances between AUC measures obtained during classification using frequency, PLI measures and combining them together.

EEG features comparisons	p-value
PLI vs Frequency	7.7e–05
Frequency + PLI vs Frequency	0.0005
Frequency + PLI vs PLI	0.8

some additional insights into cognitive decline. The strongest correlations were seen for Theta PLI with Memory ($r = -0.4$), Attention ($r = -0.38$).

While checking for which of these correlations remain significant, we found alpha2 PLI to be correlated with Memory at $p = 0.05$, theta PLI with Attention + Working Memory at $p = 0.05$, alpha1 PLI with Visuo-Spatial Function at $p = 0.01$, beta PLI with Attention + Working Memory and theta PLI with Memory at $p = 0.001$ (Fig. 3). After adjusting the correlation p-values using Holm correction we identified the most significant correlation for Memory domain with: theta PLI ($p = 0.04$).

The p-values and confidence intervals for correlations between the cognitive domains and all PLI global measures can be seen in Table S3 of the Supplementary Material.

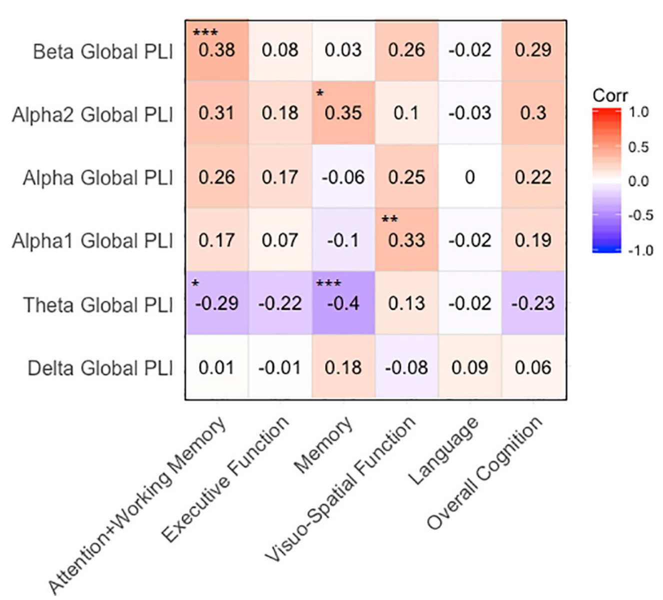

Fig. 3. Spearman rank correlations for cognitive domains and PLI measures in each power band. (* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$).

4. Discussion

In this study, we analysed the capacity of quantitative EEG to identify MCI in patients with Parkinson's disease. It is considerable to note that though PD-MCI is a common condition, it could result from a mixture of complex pathophysiology, rather than being a distinct pathologic entity, as shown in some studies (Wen et al., 2017). Identifying clinical features or biomarkers associated with this condition can be useful in early risk assessment of dementia.

Patients with MCI in our study, in comparison to those without MCI, had statistically significant differences in the following frequency measures: higher theta spectral power, and lower beta power; and following connectivity measures: higher PLI in theta band. This corresponds to studies reporting higher theta and lower beta powers in PD-MCI patients (He et al., 2016). PLI measures in theta, delta bands came up ranked high as important variables while classifying PD-MCI from PD non-MCI patients.

When considering model performance with AUC as a criterion in this dataset, cross-validated classification performance was better with PLI than frequency and this was comparable to the performance obtained while combining PLI and frequency measures. This shows us that PLI features are not inferior to frequency measures and may contain additional information for understanding and detecting disease progression.

In a previous analysis, we had identified theta spectral power as predictor of general cognitive decline in a cohort of PD patients (Cozac et al., 2016), but we had not investigated connectivity measures (PLI) with regard to MCI. Considering the EEG features ranked high in the classification and looking at the correlations between EEG features and cognitive domains, we see that theta PLI is highly correlated with Memory cognitive domain. These results confirm previous findings of cognitive domains like memory being associated with EEG features like theta power (Han et al., 2017; Jacobs et al., 2006). They may also provide additional evidence to the concept of consecutive cognitive decline and as shown in several studies, MCI is a risk factor of progression to dementia in PD (Caviness et al., 2007; Hobson and Meara, 2015; Wood et al., 2016).

We also re-ran the classification analysis using signals from all electrodes, without mapping to ten regions of interest in the brain, although excluding the electrodes placed on neck, cheeks, and ear lobes. Using all PLI and frequency features, we found that the most important variables ranked at the top were those from Theta, Delta PLI, corresponding to Temporal, Parietal, Central regions and Theta power in the Temporal region. This aligned with results obtained from creating models with features mapped to regions, in which the number of features are much reduced. Through this analysis, we also saw how computationally expensive it can be to deal with vast amounts of data, as with more than 130,000 PLI features.

The limitations of this study arise due to the small number of patients, especially those diagnosed with MCI. However, the study also has some strengths. As this data was recorded at baseline and patients had mild cognitive impairment, they also had low dosages of medication which could not have had a substantial altering effect on the EEG. Patients at advanced stages of the disease can potentially be on medication for several issues such as sleep, bladder, etc. which could affect the EEG recordings. We also had extensive neuropsychological testing which served as reliable scores for overall cognition and the different domains. The EEG features identified in this study could be characteristic of cognitive impairment and help us investigate cognitive decline while following up with the patients in the next steps.

Declaration of Competing Interest

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

Acknowledgements

The authors thank all the patients, their families and caregivers for their participation in the study. The authors also thank the Memory Clinic, University Center for Medicine of Aging Basel, for developing and applying the neuropsychological assessment of patients with PD and are thankful to all the other group members of Department of Neurology, University Hospital Basel as well as Department of Mathematics and Computer Science, University Basel who supported and contributed to this study.

Funding

This study is based on work that has been supported by the Swiss National Science Foundation (Grant CR32I2_159682), Hedwig Widmer-Stiftung, Parkinson Schweiz, Jacques and Gloria Gossweiler Foundation, Freiwillige Akademische Gesellschaft BS, Botnar Foundation, Novartis Research Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.07.017.

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