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Short Communications

A pilot study of machine learning of resting-state EEG and depression in Parkinson's disease

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ABSTRACT

Introduction: Depression is a non-motor symptom of Parkinson's disease (PD). PD-related depression is difficult to diagnose, and the neurophysiological basis is poorly understood. Depression can markedly affect cortical function, which suggests that scalp electroencephalography (EEG) may be able to distinguish depression in PD. We conducted a pilot study of depression and resting-state EEG in PD.
Methods: We recruited 18 PD patients without depression, 18 PD patients with depression, and 12 demographically similar non-PD patients with clinical depression. All patients were on their usual medications. We collected resting-state EEG in all patients and compared cortical brain signal features between patients with and without depression. We used a machine learning algorithm that harnesses the entire power spectrum (linear predictive coding of EEG Algorithm for PD: LEAPD) to distinguish between groups.
Results: We found differences between PD patients with and without depression in the alpha band (8–13 Hz) globally and in the beta (13–30 Hz) and gamma (30–50 Hz) bands in the central electrodes. From two minutes of resting-state EEG, we found that LEAPD-based machine learning could robustly distinguish between PD patients with and without depression with 97 % accuracy and between PD patients with depression and non-PD patients with depression with 100 % accuracy. We verified the robustness of our finding by confirming that the classification accuracy gracefully declines as data are randomly truncated.
Conclusions: Our results suggest that resting-state EEG power spectral analysis has the potential to distinguish depression in PD accurately. We demonstrated the efficacy of the LEAPD algorithm in identifying PD patients with depression from PD patients without depression and controls with depression. Our data provide insight into cortical mechanisms of depression and could lead to novel neurophysiological markers for non-motor symptoms of PD.

1. Introduction

Depression is a prominent non-motor symptom of Parkinson's disease (PD) [1]. PD-related depression affects ~20 %–40 % of PD patients, which is more than twice the expected prevalence in the general population [2,3]. Importantly, physicians often miss this aspect of PD, contributing to morbidity and decreased quality of life [4–7]. Despite its significance and impact [8], it is unclear which brain circuits contribute to PD-related depression [9]. Determining which brain circuits are involved could lead to the development of new diagnostic tools to

identify PD-related depression and targeted treatments such as neuromodulation [10]. A fast and accurate neurophysiological diagnostic tool may also facilitate neuromodulation. In addition, a better understanding of depression in PD may help us illuminate the fundamental mechanisms of both diseases.

PD and depression involve several overlapping circuits and associated neurotransmitters, including dopamine and serotonin [11]. These projection systems affect cortical physiology [12,13]. Cortical regions can be profoundly dysfunctional in PD [14] and in depression [15]. One particularly well-suited technique to capture cortical neurophysiology is

electroencephalography (EEG). EEG uses scalp electrodes to record activity from the cortex via an array of scalp electrodes. EEG has been rigorously used to predict anxiety and depression in large sample sizes [16], including out-of-sample validation [17]. An early EEG study comparing depressed and non-depressed PD patients found widespread differences in alpha bands (8–12 Hz) in posterior and frontal sites [8]. Similar findings have been found for anxiety in PD with a large sample size [18]. Quantitative EEG (qEEG) studies have found spectral differences that distinguished PD vs depression [19]. We recently developed a non-Fourier machine learning algorithm that holistically captures the power spectra of neurophysiological data [20]. This algorithm leverages linear predictive coding-based EEG algorithms for PD (LEAPD) and can distinguish PD from controls with high accuracy in out-of-sample tests [21]. We tested the hypothesis that LEAPD can distinguish depression in PD based on this prior work.

We conducted a proof-of-principle study to test this hypothesis. We collected resting-state scalp EEG in PD patients with and without depression. We compared these data with control patients with depression but without PD. We report three main results. First, PD patients with depression had globally attenuated alpha (8–13 Hz) rhythms, as well as attenuated central beta (13–30 Hz) and gamma (30–50 Hz) rhythms relative to PD patients without depression. Second, PD patients with depression had noteworthy global differences in gamma rhythms relative to non-PD patients with depression. Third, LEAPD-based classification accurately identified PD patients with depression relative to PD patients and non-PD depressed patients. Collectively, these data implicate cortical rhythms in PD-related depression, which could lead to novel targeted therapies or new diagnostic neurophysiological markers for this important non-motor aspect of PD.

2. Methods

2.1. Participants

36 PD patients (11 women; Table S1) were recruited from clinics at the University of Iowa. A movement-disorders physician examined all PD patients to verify that they met the diagnostic criteria recommended by the United Kingdom PD Society Brain Bank criteria. Depression was quantified using the Geriatric Depression Short Form Scale in PD patients [22]; a score of 5 to 15 was considered depressed). In addition, the motor Unified Parkinson's Disease Rating Scale (UPDRS) was administered to all PD patients by a qualified rater, along with other clinical metrics, such as the Montreal Cognitive Assessment (MOCA) and behavioral assays. Data were collected with patients taking all prescribed medications and PD patients were in the "ON" state. See our prior work for details of cognitive assessments [23]. Demographics and other clinical details are presented in Table S1 and were compared between groups by non-parametric Wilcoxon tests.

We recruited 12 demographically-matched depressed patients without PD (5 women, Table S1) from the University of Iowa's depression and neuromodulation clinic. These patients were diagnosed with depression by the Patient Health Questionnaire-9, with a value of 9 to 25. A psychiatrist evaluated all patients, and patients took their medications as prescribed.

According to the University of Iowa's Institutional Review Board (IRB), we obtained written informed consent from all participants. Demographics of patients and control subjects are summarized in Table S1.

2.2. EEG recording and analysis

Resting-state EEG was collected from patients sitting in a quiet room with their eyes open for two minutes. Scalp EEG signals were collected from 64 channels of an EEG actiCAP (Brain Products GmbH) using a high-pass filter with a 0.1-Hz cutoff and a sampling frequency of 500 Hz. Electrode Pz was used as a reference, and electrode FPz was used as the ground. We used recording methods described previously in detail using

a custom EEG cap with Iz, I1, and I2 leads in place of FT9, PO3, and PO4 leads; these leads were not analyzed [21,23,24]. We also removed FP1, FP2, FT10, TP9, and TP10 channels as these channels are often contaminated by artifacts, resulting in 56 channels for pre and post-processing. EEG activity at the reference electrode Pz was recovered by computing the average reference. Bad channels and bad epochs were identified using the FASTER algorithm and the *pop_rejchan* function from EEGLAB and were then interpolated and rejected, respectively. Eye blinks were removed using independent component analysis (ICA). All channels were low pass filtered at 100 Hz. Power was calculated using the *pwelch* function and was normalized to the mean power between 0 and 100 Hz for each channel. Scalp topography was plotted using *topoplot* from EEGLAB in delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–80 Hz; Fig. 1) bands.

2.3. Machine learning using linear predictive coding algorithms for PD (LEAPD)

LEAPD is an algorithm for binary classification of the spectral content of EEG signals. This approach was developed by Anjum et al. [19,20] to distinguish between PD patients and control participants. We implemented LEAPD to compare PD patients with depression (PDDEP) vs PD patients without depression (PD) and PDDEP vs depressed patients without PD (DEP). A LEAPD index between 0 and 1 is generated for each EEG recording using the procedure outlined below. In each of the two problems, a threshold of 0.5 is used to distinguish between two groups. For example, if the LEAPD index for an EEG recording is below 0.5, it is in Group B. If above 0.5, it is classified as belonging to Group A.

In LEAPD, an EEG time series from a channel is processed using linear predictive coding (LPC) to encode the signal into an autoregressive model's coefficients that minimize the prediction error's mean square [25] for that time series. Specifically, with $x(k)$ the k-th sample of the filtered EEG time series, an n-th order LPC determines the LPC coefficients $a_1, \cdots, a_n$ by minimizing the mean square error between $x(k)$ and $\sum_{i=1}^{n} a_i x(k-i)$. In LEAPD, these LPC coefficients are placed in an LPC vector which is the vector of these coefficients minus their mean. These coefficients can be determined by high-speed processing and can be viewed as the encoding of the EEG time series.

Each LPC vector is viewed as a point in n-dimensional space. LPC vectors of each group approximately lie on distinct affine subspaces. For example, those for PDDEP roughly lie on one affine subspace while those of PD on another. An affine subspace is the generalization of a one-dimensional line or a two-dimensional plane in larger dimensions. These affine subspaces are determined in the training phase for each EEG electrode using Principal Component Analysis (PCA) as described below.

LEAPD constructs two matrices, one for each group. LPC vectors of each group form the rows of the corresponding matrix. A singular value decomposition (SVD) is performed on each matrix. The left eigenvectors corresponding to the M largest singular values form the basis for the corresponding M-dimensional affine subspace. Parameters used to learn these affine subspaces are: (1) the cutoff frequencies of the filter used to process the EEG data; (2) the LPC order; and (3) the dimension of the affine subspace.

For each new EEG recording, one obtains its LPC vector and generates its LEAPD index as its relative distance from each affine subspace: With D_A the distance of a recording's LPC vector from the affine subspace of group A and D_B the distance from the affine subspace of the group B, one obtains.

$$LEAPD\,Index = \frac{D_B}{D_B + D_A}.$$

A LEAPD index between 0 and 0.5 places the recording nearer to the affine subspace for group B leading to the recording being classified as being in group B. Likewise, an index between 0.5 and 1 classifies in group A. The distances are computed using standard projection methods
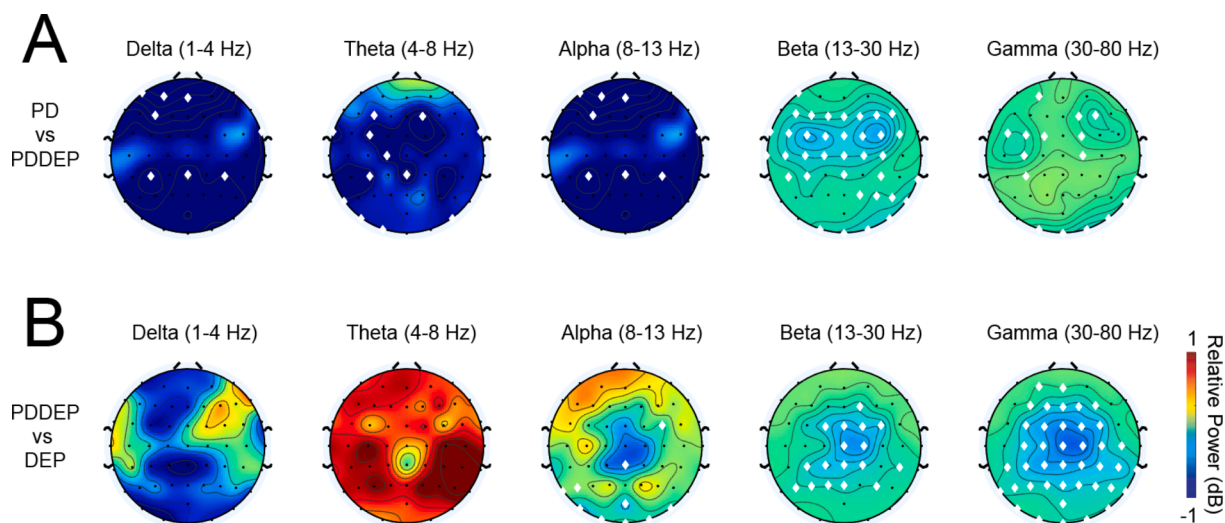
Fig. 1. Scalp topography of relative EEG power in PD patients with depression. A) Relative power in PD patients with depression (PDDEP) compared to PD patients without depression for delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30 Hz). B) Relative power in PDDEP compared to non-PD patients with depression (DEP). Electrodes are indicated by black dots; electrodes with significant differences between groups via ranksum testing are shown with white diamonds. Data from 18 PD, 18 PDDEP and 12 DEP.

for finding the distance of a point from an affine subspace [26].

We quantified differences between LEAPD values for each channel using non-parametric Wilcoxon rank-sum tests. In addition, we computed the LEAPD index for each recording to calculate the accuracy of PD vs PDDEP and DEP vs PD at each channel. Two-channel LEAPD values were computed by taking each channel's geometric mean of the LEAPD indices. We then used a classifier on all two-channel combinations and presented results only from selected high-performing combinations.

As the dataset was small, we could not perform out-of-sample prospective tests to validate the model's accuracy. However, we tested the robustness of the results by examining LEAPD performance on truncated data, in which a random subsequence of a desired smaller data length is selected over all participants. Truncation is shown across all electrodes. In all instances, leave-one-out cross-validation (LOOCV) was used to quantify performance. LOOCV uses the entire dataset without one test sample to predict each test sample, which protects against the overfitting common with small datasets. We report data from individual channels and combinations of channels that yielded the a) highest accuracy in discriminating PD vs PDDEP and PDDEP vs DEP, and b) were the most robust on truncated data.

3. Results

PD patients with and without depression had similar age ($p = 0.23$), motor function as measured by UPDRS ($p = 0.22$), and cognitive profiles as measured by the MOCA ($p = 0.94$ value; Tables S1-S2). We collected resting-state EEG data and compared scalp topography of relative power for PD patients vs PD patients with depression (PDDEP) at delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma bands (30–80 Hz; Fig. 1A). We also compared scalp topography for PDDEP vs non-PD patients with depression (DEP; Fig. 1B). These data illustrate that band-specific differences can distinguish depression in PD.

Our machine learning approach, LEAPD, compresses power spectra into a set of autoregressive coefficients that holistically captures the shape of each power spectra with a few numbers [20,21]. Here, we used LEAPD to classify PD vs PDDEP and PDDEP vs DEP from single channels, as well as combinations of two channels (Fig. 2; Table S3).

We first used LEAPD to discriminate 18 PD from 18 PDDEP patients across all EEG electrodes (Fig. 3A). Single-channel accuracy for channel CP3 was 86 % and for TP8 was 86 % (Fig. 3A). Combining both CP3 and
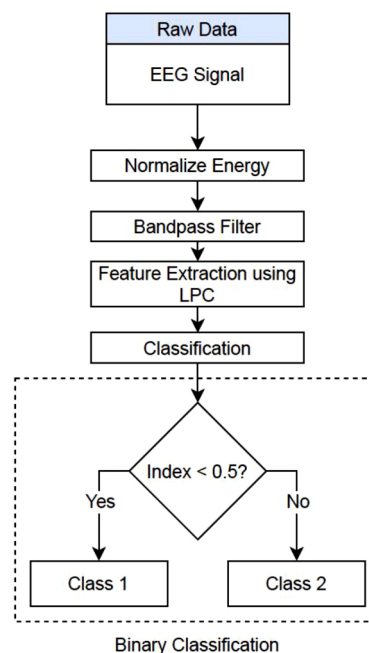

Fig. 2. LEAPD Classification approach: Flow chart of classification.

TP8 resulted in an overall LOOCV classification accuracy of 97 %. These channels had distinct LEAPD indices between PD and PDDEP (CP3: $p = 0.00009$, Cohen's d = 1.8; TP8: $p = 0.00004$, Cohen's d = 1.8; CP3 + TP8: $p < 0.001$; Cohen's d = 3.3). Of note, LEAPD outperformed traditional spectral analyses of the delta, theta, alpha, beta, and gamma rhythms.

Receiver-operator curves (ROCs) for these channels in predicting PD vs PDDEP are shown in Fig. 3B.

In addition, we found that LEAPD was highly accurate in differentiating 12 PDDEP patients (selected at random from 18 total) from 12 DEP patients, with 96 % single-channel signal accuracy for electrode CPz and 92 % for electrode CP4. Combining both channels resulted in 100 % classification accuracy (Fig. 3C-D). For these electrodes, LEAPD distinguished PDDEP vs DEP (Fig. 3D; CPz: $p = 0.00004$, Cohen's d = 4.3; CP4: $p = 0.0007$, Cohen's d = 2.0; CP4 + CPz: $p = 0.00004$; Cohen's
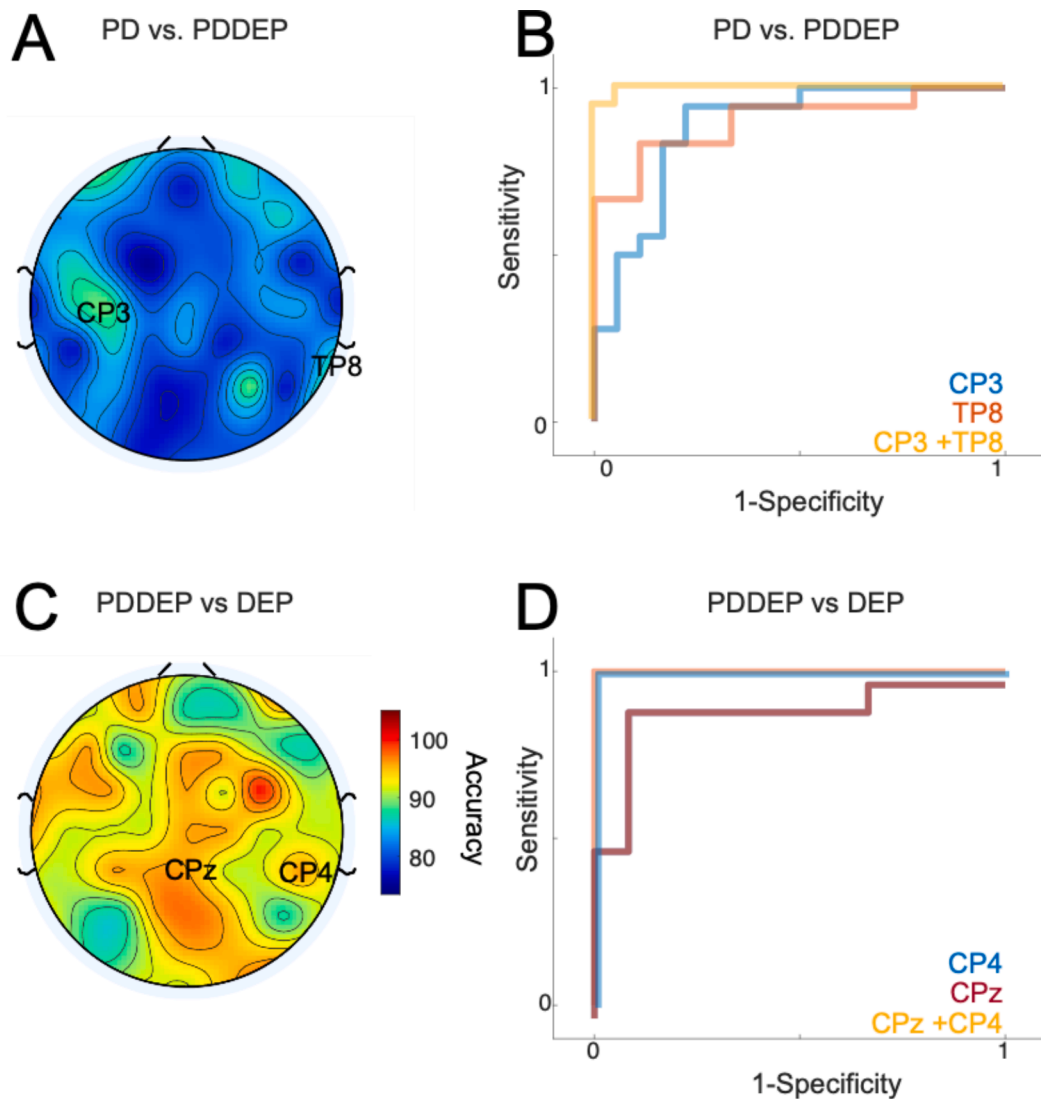
Fig. 3. Machine-learning classification of LEAPD. A) We constructed LEAPD indices from LPC coefficients from electrodes CP3 and TP8 for PD patients without depression (PD) vs PD patients with depression (PDDEP). B) Receiver-operating curves (ROC) for single-channel performance of CP3, TP8, and CP3 and TP8 (CP3 + TP8) combined. Data from 18 PD and 18 PDDEP patients. C) single channel performance across single electrodes and D) ROC curves and. Data from 12 PDDEP and 12 DEP patients.

d = 4.3).

Electrodes CP3 + TP8 were selected for the classification of PD vs PDDEP and CP4 + CPz for PDDEP vs DEP. To provide direct comparisons between classifications, we selected channels for classification between groups. We found that the combination of $P4 + C6$ was 97 % accurate for PD vs PDDEP and 100 % accurate for PDDEP vs PD. Furthermore, $P4 + C6$ was 72 % accurate in separating PD vs a combined dataset of PDDEP and DEP and 86 % accurate in separating DEP from a combination of PD and PDDEP. Our results show that LEAPD can accurately discriminate depression in PD from a single combination of two channels.

Additionally, we performed a truncation analysis of CP3, TP8, and CP3 + TP8 combined for PD vs PDDEP and of CPz, CP4, and CPz + CP4 combined for DEP vs PDDEP. Recorded EEG data were truncated from full-length samples to samples numbering a fraction of the original length. LEAPD analysis was then performed on the shortened signal using the same parameters as the original signal. Truncation samples were chosen as continuous non-overlapping subsets of the time-series signals and was split into subsamples dependent on the truncation fraction. For a given truncation fraction, subsamples were chosen with random start time offsets under the constraint that subsamples from a single subject may not overlap. A uniform distribution of possible start

values was used to generate the time offsets.

Truncation fractions of 0.23, 0.3, and 0.45 were tested 100 times each using the described random starting time offset method. The median performance was measured in Table S4. A boxplot of the runs is shown in Fig. 4. Although truncation reduced the channels' accuracy, each channel still retained significant discriminatory ability at shorter signal lengths. The performance degraded gracefully with truncation, indicating that the signals chosen are likely measuring a fundamental difference in EEG behavior between classes rather than an artifact of overfitting. Notably, an accuracy greater than 85 % was achieved from two minutes of resting-state EEG signals. Performance on truncated data is shown in Fig. 4 for all channels of interest for PD vs PDDEP (Fig. 4A) and PDDEP vs DEP (Fig. 4B). Collectively, these data suggest that spectral features of scalp EEG can distinguish depression in PD.

4. Discussion

We explored the cortical basis of depression in PD using resting-state scalp EEG. We found that PD patients with depression significantly differed in beta and gamma rhythms. We used LEAPD, a spectral machine learning approach, to detect differences in EEG signals from two
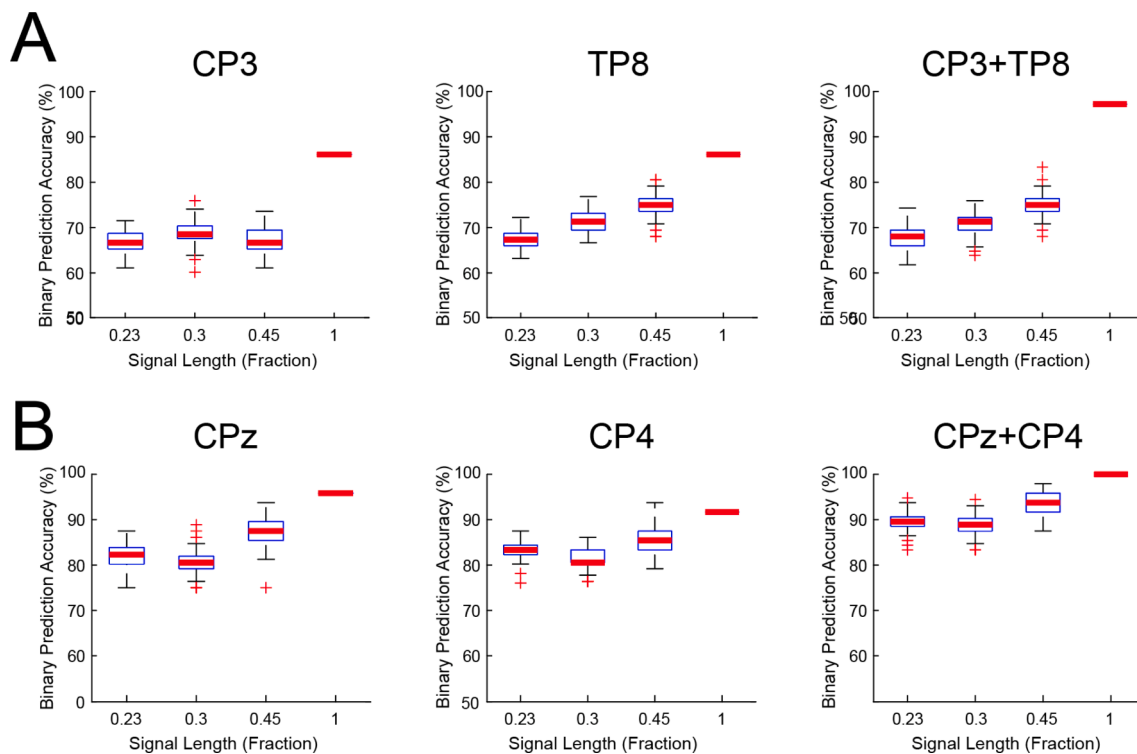
Fig. 4. Truncation analysis of LEAPD-based classification. A) Classification of PD vs PDDEP for CP3, TP8, and both CP3 + TP8 with truncated data lengths. B) Classification of PDDEP vs DEP for CPz, CP4, and both CPz + CP4 with truncated data lengths (truncation as in A).

minutes of resting-state data from a single electrode, achieving accuracies of 97 % for PD patients with and without depression and 100 % for PD vs non-PD patients with depression. These data indicate that PD patients with depression can be accurately differentiated from PD patients without depression and depressed non-PD patients using machine learning. Thus, we proposed that LEAPD parameters derived from LPC-based analyses of EEG power spectra could be a neurophysiological marker for depression in PD.

Depression is a complex disorder [27] involving many brain networks; however, one consistent finding is abnormal cortical function [15,28]. Scalp EEG studies have found dysfunctional alpha rhythms in depressed patients [29,30], which we report here comparing PD patients with and without depression. Beta rhythms can be profoundly abnormal in PD [31], and our data here indicate that depression decreases resting-state beta, alpha, and gamma rhythms in PD. We find that many cortical regions are implicated in PD-related depression, including prefrontal and parietal regions that have been found in prior studies of depression [15,32].

These data suggest that EEG, which is relatively inexpensive and ubiquitously available, can identify PD patients with depression. This finding is important because depression can be missed in PD [4–6], and electrophysiological diagnostic tools may aid this effort. Nonetheless, we report that our approach can rapidly, robustly, and accurately identify EEG signals from PD patients with depression. Furthermore, LEAPD outperforms traditional spectral analyses based on the power in predefined bands. Performance degrades with data truncation; however, it may be that 2 min is close to the threshold required for accurate discrimination, particularly in the case of DEP vs PDDEP.

Our results are in line with previous efforts to use LEAPD to identify local field potentials from animal models of PD and EEG data recorded from PD patients and controls [20,21]. LEAPD-based techniques might have additional utility in settings where neurophysiology is common, such as during deep-brain stimulation surgeries, and they may be helpful for closed-loop control applications. Besides being robust and accurate, LEAPD is amenable to fast implementation and can serve as a trigger

mechanism for brain stimulation.

Our work is supported by prior qEEG studies describing that a single parameter can differentiate depression and dementia in PD [19]. An early study that averages across all EEG electrodes reported distinct scalp topography of depressed PD patients, focusing on alpha rhythms [8]. Our study supports these differences, and we can localize these results to the left frontal electrodes. In addition, we find broader differences over central electrodes in beta and gamma bands, which may have been averaged out in prior work that averaged EEG signals from multiple electrodes. Single-electrode and spectral band analyses reveal differences with depression in PD (Table S3). However, LEAPD has several advantages: 1) it holistically captures the entire power spectra, 2) it is robust to random truncation and captures spectral differences in a single parameter, and 3) it can be used for binary classification.

We used LEAPD to distinguish PD patients with depression from PD patients and non-PD patients with depression. Recent work has reported frontal differences in sleep in PD patients with depression [33] and differences between midline event-related potentials between PD patients with and without depression [34]. Our study extends these findings, helps define the spectral topography of resting-state EEG in PD patients with depression, and demonstrates the potential of machine learning for identifying PD patients with depression. We note that EEG is not routinely used in diagnosing or treating depression in PD or non-PD patients. Our data might contribute to a better understanding of the neurophysiological basis of depression in PD and possibly to the development of novel neuromodulatory treatments.

Our study has several limitations. First, our sample size was limited, although in line with prior EEG studies in PD patients with depression [33,34], as these patients can be challenging to diagnose. Indeed, this is the principal motivation of this paper. Second, all of our patients were medicated, and there is a possibility that medications could influence these EEG signals [35]. Third, our method of diagnosing depression and quantifying symptom burden in PD patients was distinct from the method used with non-PD patients, limiting comparisons between these groups. Critically, this only applies to PDDEP vs DEP, and the LEAPD

classifier still performed with >97 % accuracy in distinguished PD vs PDDEP when the same depression scale was used. Finally, our LEAPD approach did not include an out-of-sample prospective test (we note this is the largest resting-state EEG dataset of depression in PD that we are aware of). However, the truncation analysis does remove concerns of overfitting. These concerns suggest that our finding is a preliminary, proof-of-principle demonstration, and much further work is needed to investigate depression in PD and the effect of interventions. Despite these shortcomings, our findings describe spectral changes in PD patients with depression compared to PD patients without depression and non-PD patients with depression. We report that LEAPD-based machine learning approaches can identify EEG signals from PD patients with depression. These data could help illuminate the cortical neurophysiology of PD-related depression and could help lead to new neurophysiological markers or diagnostic tools.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2022.100166.

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