

# Electroencephalography-based machine learning for cognitive profiling in Parkinson's disease

Citation for published version (APA):

Betrouni, N., Delval, A., Chaton, L., Defebvre, L., Duits, A., Moonen, A., Leentjens, A. F. G., & Dujardin, K. (2019). Electroencephalography-based machine learning for cognitive profiling in Parkinson's disease: Preliminary results. *Movement Disorders*, 34(2), 210-217. <https://doi.org/10.1002/mds.27528>

## Document status and date:

Published: 01/02/2019

## DOI:

[10.1002/mds.27528](https://doi.org/10.1002/mds.27528)

## Document Version:

Publisher's PDF, also known as Version of record

## Document license:

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## RESEARCH ARTICLE

# Electroencephalography-Based Machine Learning for Cognitive Profiling in Parkinson's Disease: Preliminary Results

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**ABSTRACT: Background:** Cognitive symptoms are common in patients with Parkinson's disease. Characterization of a patient's cognitive profile is an essential step toward the identification of predictors of cognitive worsening.

**Objective:** The aim of this study was to investigate the use of the combination of resting-state EEG and data-mining techniques to build characterization models.

**Methods:** Dense EEG data from 118 patients with Parkinson's disease, classified into 5 different groups according to the severity of their cognitive impairments, were considered. Spectral power analysis within 7 frequency bands was performed on the EEG signals. The obtained quantitative EEG features of 100 patients were mined using 2 machine-learning algorithms to build and train characterization models, namely, support vector machines and k-nearest neighbors models. The models were then blindly tested on data from 18 patients.

**Results:** The overall classification accuracies were 84% and 88% for the support vector machines and k-nearest algorithms, respectively. The worst classifications were observed for patients from groups with small sample sizes, corresponding to patients with the severe cognitive deficits. Whereas for the remaining groups for whom an accurate diagnosis was required to plan the future healthcare, the classification was very accurate.

**Conclusion:** These results suggest that EEG features computed from a daily clinical practice exploration modality in—that it is nonexpensive, available anywhere, and requires minimal cooperation from the patient—can be used as a screening method to identify the severity of cognitive impairment in patients with Parkinson's disease. © 2018 International Parkinson and Movement Disorder Society

**Key Words:** characterization models; cognitive deficits; machine learning; quantitative EEG.

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The median age-standardized annual incidence rate in high-income countries has been estimated to be 14 per 100,000 people in the general population and 160 per 100,000 in people aged 65 years or older.<sup>1</sup> Apart from

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**Funding agencies:** A part of the study was supported by the Michael J. Fox Foundation for Parkinson's Research.

**Relevant conflicts of interests/financial disclosures:** Nothing to report.

**Received:** 2 April 2018; **Revised:** 25 August 2018; **Accepted:** 3 September 2018

Published online 21 October 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27528

the hallmark motor symptoms of bradykinesia, rigidity, and rest tremor, patients often have nonmotor symptoms, such as cognitive deficits. On average, 26.7% (range 18.9–38.2%) of PD patients meet the criteria for mild cognitive impairment (MCI).<sup>2</sup> Even in PD patients without dementia, cognitive impairment is associated with changes in instrumental activities of daily life,<sup>3</sup> poorer quality of life,<sup>4,5</sup> and increased healthcare costs.<sup>6</sup> Because MCI may progress to dementia,<sup>7</sup> it is clinically relevant to identify markers of cognitive decline. However, such markers are not easy to identify because of the heterogeneity of cognitive profiles in PD. This heterogeneity has been described in different ways, including striato-frontal versus posterior-cortical dysfunction,<sup>8</sup> MCI versus non-MCI,<sup>2</sup> and MCI versus dementia. Recently, we used a data-driven approach, which resulted in a spectrum of cognitive impairment

**TABLE 1.** Demographic and clinical characteristics of the patients, according to the severity of cognitive impairment

Features	Total, n = 118					P
	Group 1, n = 28	Group 2, n = 33	Group 3, n = 43	Group 4, n = 5	Group 5, n = 9	
Age, y	60.54 ± 8.75	66.09 ± 6.65	67.04 ± 7.94	73.19 ± 5.29	67.56 ± 5.46	.002
Sex, F/M	8/20	9/24	16/27	3/2	0/9	
Education, y	13.61 ± 3.17	13.21 ± 4.17	11.63 ± 3.59	8.00 ± 1.41	10.56 ± 2.07	.002
Disease duration, y	7.75 ± 5.29	8.36 ± 7.49	8.81 ± 5.02	6.60 ± 3.58	12 ± 6.52	.14
Hoehn & Yahr stage	1.93 ± 0.4	2.14 ± 0.55	2.21 ± 0.59	2.40 ± 0.55	2.00 ± 0.93	.18
MDS-UPDRS3 score	26.00 ± 11.73	29.55 ± 12.22	28.74 ± 11.44	31.00 ± 12.79	29.00 ± 18.87	.73
Mattis DRS Score on 144	140.96 ± 3.02	139.73 ± 3.18	134.30 ± 5.39	129.80 ± 12.79	122.78 ± 8.23	<.0001
SDMT in 90 seconds	54.64 ± 7.15	43.33 ± 3.56	32.72 ± 7.01	21.00 ± 14.93	12.33 ± 5.89	<.0001
Alternating fluency: words in 60 seconds	25.71 ± 4.58	20.21 ± 3.24	14.74 ± 3.82	11.20 ± 8.04	9.33 ± 3.43	<.0001
Stroop errors	0.21 ± 0.50	1.00 ± 1.41	3.74 ± 4.45	36.00 ± 5.61	8.78 ± 4.94	<.0001

MDS-UPDRS3, Movement Disorders Society-Unified Parkinson's Disease Rating Scale-Part III (severity of motor symptoms); Mattis DRS, Mattis Dementia Rating Scale; SDMT, Symbol Digit Modalities Test.

severity levels rather than in specific profiles. A total of 5 clusters ranging from cognitively intact patients to patients with severe dysfunction in all cognitive domains were identified.<sup>9</sup> This was subsequently confirmed in a cross-sectional study.<sup>9,10</sup> Moreover, we showed that the identified clusters were associated with different patterns of functional connectivity using functional Magnetic Resonance Imaging (fMRI)<sup>11</sup> and high-density-EEG.<sup>12</sup> However, the identification of these different levels of cognitive deficits with easily available markers is needed.

The objective of the present study was to use data-mining techniques on quantitative EEG data to discover the best combination able to identify different levels of cognitive impairment in PD and especially the “at risk of cognitive decline” population, including patients with MCI that can progress to dementia.

## Material and Methods

### Clinical Sample

The data came from a previous cross-sectional observational study.<sup>10</sup> Patients were recruited from 2 European movement disorder centers in Lille, France, and Maastricht, The Netherlands. All patients met the United Kingdom Brain Bank criteria for idiopathic PD,<sup>13</sup> and none of them were suffering from any neurological diseases other than PD. Patients with moderate and severe dementia (defined as a score >1 on the Clinical Dementia Rating<sup>14</sup> and according to the Movement Disorders criteria<sup>15</sup> and those older than 80 years were excluded. All patients underwent a neuropsychological assessment.<sup>10</sup> A cluster analysis based on the test scores revealed the following 5 groups: G1 = cognitively intact patients (25.64%); G2 = cognitively intact patients with slight mental slowing (26.92%); G3 = patients showing mild cognitive deficits, particularly in executive

functioning (37.18%); G4 = patients with severe deficits in all cognitive domains, particularly executive functions (3.20%); and G5 = patients with severe deficits in all cognitive domains, particularly in working memory and recall in verbal episodic memory (7.05%). Of the 156 patients, 118 patients had a dense EEG recording. Their demographic and clinical characteristics are described in Table 1.

### Quantitative EEG Data

EEG activity was recorded in high resolution using 128 channels (Waveguard; ANT Software BV, Enschede, The Netherlands) with a resting-state protocol. All recordings were performed when the patients were in the “on drug” state after receiving their usual antiparkinsonian treatment. A total of 122 scalp electrodes were set up according to the standards of the international 10/05 system. Signal acquisition was performed with an analogic 0.1 to 100 Hz bandwidth filter at a frequency of 512 Hz. The obtained EEG data were then preprocessed with the Brain Analyzer software (Brain Products GMBH, Gilching, Germany). First, the data were expressed as an averaged common reference. Ocular artefacts were corrected by the Gratton and Coles method.<sup>16</sup> Then a 50-Hz filter was applied to remove the residual noise. Each EEG was visually checked to remove periods of drowsiness, and a semi-automatic artefact-rejection method was used to remove muscle activity. Finally, a 4-second epoch segmentation was performed. Only plots with at least 20 segments of 4 seconds at the end of preprocessing were kept for further analysis.

The signal processing consisted of a spectral power analysis using a fast Fourier transform with a 2-second duration and 50% overlap. The selected frequency bands were those usually recommended for the analysis of resting cortical rhythms in elderly individuals with

neurodegenerative pathology<sup>17</sup>: delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10.5 Hz), alpha2 (10.5-13 Hz), beta1 (13-20 Hz), and beta2 (20-30 Hz). Absolute and relative powers in each frequency band were computed from scalp electrodes. The relative power was the ratio of the absolute power in a frequency band to the power of the entire frequency spectrum from 2 to 30 Hz.

The 122 scalp electrodes were divided into 5 regions of interest (ROIs; frontal, central, parietal, occipital, and temporal), according to the cortical projections of the electrodes in Talairach space.<sup>18</sup> In each ROI, analyses were run with 2 densities of electrodes: high (12-20 electrodes by ROI), corresponding to dense EEG (ie, electrodes included in the 10-05 system) and low (2-5 electrodes/ROI), corresponding to the usual EEG acquisitions with electrodes included in the 10-20 system.<sup>19</sup> The mean absolute and relative powers in each frequency band were computed for each ROI and each density. Finally, the value of the peak frequency, which corresponded to the frequency associated with the maximum power of the EEG, as measured by the P3, P4, and Oz electrodes, was determined.

In total, 6 different configurations were considered: absolute global, absolute low density, absolute high density, relative global, relative low density, and relative high density.

## Statistical Analysis and Mining of the Quantitative EEG Data

### Features Selection

Before mining the data, the statistical dependence between the distribution of the patient groups and the QEEG features was investigated for the 6 configurations using analyses of variance, with the patient groups as the between-group factor and the QEEG features as the within-group factor. Age, gender, duration of formal education, and individual peak frequency were used as covariates. Model assumptions of normality and homogeneity were checked with conventional residual plots.

The first step in classification model building is dimensionality reduction, which aims to reduce the features number by selecting the most discriminative ones. Different techniques for dimensionality reduction exist. Here, we employed an adaption of the correlation feature selection method proposed by Hall.<sup>20</sup> The idea is to select the most correlated features with the patient groups and in the same time the least correlated between them. First, Pearson correlation tests were done for each configuration to measure the correlation between the QEEG data and the patient groups. Only features with significant correlations were considered. When different features exhibit close correlation scores, selection is done in a way to keep features from different frequency bands and from the considered anatomical regions to have a global representation of signal alteration in the brain.

### Classification

In this study, to highlight the efficiency of the selected features in separating the groups, 2 different supervised classifiers were considered: support vector machine (SVM) and k-nearest neighbor (KNN) classifiers.

**SVM.** The SVM algorithm can handle both linear and nonlinear problems. Basically, the main idea behind the method is to find the line (hyperplane in higher dimensions) that optimally separates the classes. Instead of measuring the distance to all points, SVMs look for the largest margin between only the points on either side of the decision line. This will be the line in which the distances from the closest point in each of the groups will be farthest away. The training samples that lie on the margin are referred to as support vectors and conceptually are the most difficult data points to classify.

SVMs use a clever technique to fit nonlinear data: the kernel trick. A kernel is a mathematical construct that can “warp” the space where the data are defined. The algorithm can then find a linear boundary in this warped space, making the boundary nonlinear in the original space.<sup>21</sup>

SVMs were originally designed for binary classification. To address the multiclass problem of this study, the one-versus-one approach was used. This pairwise decomposition approach evaluates all possible pairwise classifiers and thus induces  $k(k-1)/2$  (i.e.,  $k = 5$  in this work) individual binary classifiers. Each classifier is trained on data from 2 classes.

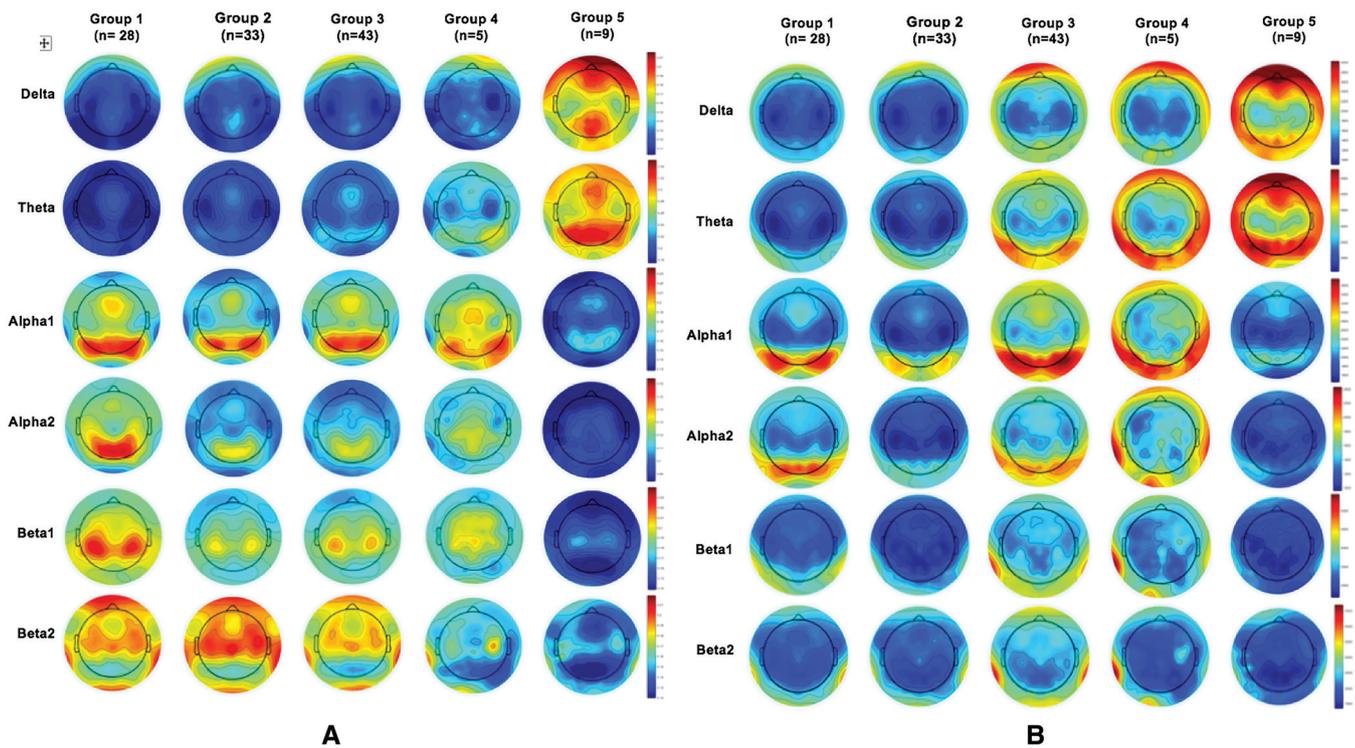
The open source SVM library (<http://www.csie.ntu.edu.tw/~cjlin/libsvm>) was used with a Gaussian kernel. As a pretreatment, the features were normalized using a z-score method.

**KNN.** The KNN algorithm is a nonlinear machine learning method. The basic idea is to classify a new data record by comparing it with similar records from the training set. Similarity is defined using usual metrics, such as the Euclidean distance and the Mahalanobis distance of the correlation.

When making predictions regarding new records, the algorithm finds the closest known record and assigns that class to the new record. This would be a 1-nearest neighbor classifier, as only the closest neighbor is considered. Usually, 3, 5, or 9 neighbors are used and pick the class that is the most common among the neighbors.

This algorithm was used through the classification learner toolbox of Matlab (MathWorks, Natick, Massachusetts). After multiple tests, the 9-neighborhood and the Euclidean distance were retained as the configuration that enhanced the performances.

**Classification Scheme.** SVM and KNN require learning steps to optimize their models' parameters. As the quality of the learnt models can be impacted by the learning data, a k-fold cross-validation scheme was used for each algorithm. In this validation strategy, the



**FIG. 1.** Head plots of the distribution of mean power per frequency band. The warmer colors indicate higher relative power (scaled from minimum to maximum values of the total group): (A) relative powers; (B) absolute powers. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

data set is randomly split into  $k$  folds,  $k-1$  folds are used to train the models and the  $k^{\text{th}}$  fold is the testing set. Regarding the data size ( $n = 118$ ),  $k$  was set to 5. The global validation approach consisted in repeating the 5-fold validation 5 times and the global classification accuracy was expressed as mean  $\pm$  SD.

Furthermore and to define final classification model for each algorithm and to highlight the classification behaviors, a second line validation was carried out. The initial group of 118 patients was split into 2 sets, namely, a learning set of 100 patients and a testing set with the remaining 18 patients. Special attention was paid to G4 and G5, which had the smallest number of patients, that is, 5 in G4 and 9 in G5. To form the training set, 3 patients from G4 and 6 from G5 were included. The testing set was formed with 4 patients from G1, 4 patients from G2, 5 patients from G3 and 2 and 3 patients from G4 and G5, respectively.

## Results

### QEEG Data

Figures 1a and 2b depict the relative and absolute powers in each frequency band for the 5 groups. Increases in the delta and theta frequencies and decreases in the alpha and beta bands were observed with the worsening of cognitive decline, mainly for the relative powers.

### Relation Between the QEEG Features and the Patient Groups

The results of the analyses of variance between the distribution of the patient groups and the QEEG features are shown in Table 2. It revealed significant ( $P < .001$ ) interactions for the 6 considered features configurations.

### Mining the QEEG

The correlation analyses between the QEEG features and the patient groups revealed that the peak frequency is one of the most correlated features (Pearson correlation coefficient =  $-0.411$ ). Based on the complete

		Predicted classes				
		G1	G2	G3	G4	G5
True classes	G1	4	0	0	0	0
	G2	0	4	0	0	0
	G3	0	0	5	0	0
	G4	0	0	0	1	1
	G5	0	0	0	1	2

**FIG. 2.** Confusion matrix for the classification results using the  $k$ -nearest neighbors algorithm with the relative power low-electrode density. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 2.** Results of analyses of variance with the patient group as the between-group factor and the quantitative EEG features as the within-group factor, weighted by gender, age, education, and patient individual peak frequency

Scores	Relative			Absolute		
	Global	Low configuration	High configuration	Global	Low configuration	High configuration
$R^2$ , %	40.6	59.6	56.2	35.5	55	53
F value	6.595	2.95	2.638	2.638	2.588	2.40
P	<.0001	<.0001	<.0001	<.0001	<.0001	.001

correlation scores, the dimensionality reduction strategy allowed selecting the optimal features: the peak frequency was retained for all the configurations. For the absolute global configuration, theta, alpha1, and beta2 were retained, whereas for both configurations, the absolute low and high densities, frontal theta, temporal theta, central theta, and parietal theta were retained.

Regarding relative power, delta, alpha2, and beta1 were retained for the global power, whereas the theta and beta1 frequencies from frontal, temporal, central, and parietal regions were selected for configurations with both low and high densities.

Thus, for the classification, models were built by combining the demographic data with the selected QEEG features. After learning and validation using the 5-fold cross-validation scheme, the best classification accuracies were obtained with the relative, low density of electrodes configuration for both algorithms. The classification accuracies were about 86% ± 3.5 for SVM and 87% ± 2.8 for KNN.

The results for the second-line validation involving models learning on data from 100 patients and prediction on the remaining 18 patients are grouped in Table 3. The results are reported for the 6 considered configurations. Figure 2 shows the confusion matrix obtained using the KNN algorithm on features from the relative power with low electrode density configuration.

## Discussion

### EEG and Cognition in PD

PD is often associated with cognitive impairment and dementia.<sup>22</sup> The addition of these impairments to motor deficiencies increases disability and mortality. The development of predictive biomarkers of cognitive impairments is, therefore, a major challenge for the early initiation of care strategies. EEG could contribute to the

identification procedure because cognitive impairment has been associated with modifications of signal rhythms in neurodegenerative diseases. Several studies have described changes in PD patients with comparison to healthy subjects.<sup>17,23</sup> These changes increased with cognitive decline.<sup>24–26</sup> The results of the data-mining modeling approach, as proposed in this study, showed that the quantitative analysis of a 10-minute, resting-state EEG recording was able to characterize the severity of cognitive impairment in PD patients.

Dementia in PD is associated with a significant and diffuse slowing down of resting oscillatory brain activity in comparison with dementia-free PD patients and age-matched healthy subjects. Indeed, increases in power in the delta and theta bands and decreases in the alpha and beta bands were reported.<sup>23,27</sup> Moreover, a progression in the alteration of cortical EEG rhythms has been shown to correlate with the severity of cognitive decline.<sup>24,25</sup> However, these features were present at the group level and cannot be used to characterize cognitive impairment individually.

Most studies on cognitive phenotypes in PD have used a priori, limited definitions of patient groups, such as patients with versus without dementia or MCI versus non-MCI patients. Our study aimed to identify QEEG patterns associated with different cognitive profiles in PD and to use them in a classification model to build a screening strategy.

### Machine Learning for the Characterization

Different machine learning techniques were investigated in the study including unsupervised algorithms that do not require a learning step as well as supervised methods, but the best classification accuracies were obtained using SVM and KNN. As it was described in recent studies, these algorithms start to be investigated in EEG signal classification<sup>28–30</sup> for their capacities to

**TABLE 3.** Classification results obtained for data from the testing set (18 patients)

Classifiers	Relative			Absolute		
	Global	Low density	High density	Global	Low density	High density
SVM, %	70	84	79	44	75	73
KNN, %	72	88	81	48	76	70

KNN, k-nearest neighbors; SVM, support vector machine.

handle nonlinear problems. Moreover, the results from both algorithms were reported in our study because from a fundamental point of view, they rely on different mathematical principles and, thus, the classification accuracies they reached would highlight the effectiveness of the features used. Indeed, the models learned using these methods can be not intuitive to understand. Herein, the basic idea was that the selection and combination of the most discriminative QEEG features could build models for each phenotype and, thus, allow characterization of a patient at an individual level. Mainly, there are 3 strategies for feature selection algorithms: filter methods, wrapper methods, and embedded methods. The first category uses statistical measures to assign a scoring to each feature. Wrapper methods consider the selection of a set of features as a search problem, based on the learning algorithm, where different combinations are prepared and compared, whereas embedded methods select the features according to their contribution to the model accuracy.

The method used in the present study is based on correlation and belongs to the filter methods. Given, the nature of the data and the context, it appeared as a good approach to allow selecting the most accurate features while ensuring the incorporation in the model of meaningful features that represent the EEG signal variation in the different frequency bands and in different anatomical regions. Nevertheless, it will be interesting to evaluate the model produced by a wrapper method and to compare it with the current model.

The QEEG features consisted of values from 7 frequency bands. For the 6 considered configurations, the selection included slow (delta or theta frequency bands) and rapid (alpha or beta frequency bands) cortical rhythms. This result was consistent with those of previously reported studies that described an increase of power in the delta and theta bands as the severity of cognitive impairment increases.<sup>23,27</sup>

Once learned, the models were blindly tested and the overall classification accuracies were 84% and 88% for the SVM and KNN algorithms, respectively (Table 3). As expected, the worst classifications were observed for patients from G4 and G5. This was mainly a result of the small sample size of these groups. Moreover, if both patient groups were characterized by severe cognitive deficits, their cognitive profiles differed. Patients in G5 had predominantly memory deficits, whereas in G4, the dysexecutive syndrome was particularly severe (see ref.<sup>10</sup>). Furthermore, despite the fact that there was no group effect on disease duration, it appeared from the data that patients in G4 had faster disease progression (shorter disease duration for similar disease severity).

When considering the results of the characterization in G1, G2, and G3, 100% good accuracy was obtained. For G1 and G2, it was particularly striking because, when using post hoc tests to compare the powers in

different band frequencies, no differences were observed. We should, however, mention that G1 consisted of cognitively intact patients with high performance levels in all cognitive domains and G2 of cognitively intact patients, slightly slower than those in G1.

The best classification results were obtained using the relative powers. These values, computed as the ratio of the absolute power in a frequency band to the power of the entire frequency spectrum, allowed the intersubject variability to reduce and thus to enhance the intergroup differences.

In the same way, the best results were reached when low-density arrays were considered. Such results can be explained by the fact that power values computed by integrating the activity from focused with large inter-electrode distance sites in the anatomical region of interest is more specific in terms of patient characterization than values obtained by considering large sampling of the region implying the consideration of redundant information from close sources.

### Clinical Significance

Classically, patients' cognitive subtypes are characterized using neuropsychological assessment. In this study, starting from an initial characterization using this method, quantitative EEG features associated with each subtype were used to train supervised algorithms. Models were, thereafter, set up to define the cognitive profile of each patient. Regarding clinical considerations, such a tool could be very suitable for a preliminary screening of a patient's cognitive profile and, thus, to quickly steer the patient to more in-depth exams according to their condition.

It is important to stress the fact that the characterization performed with the proposed method is valid only at the EEG acquisition time and does not predict the cognitive course. Indeed, at the time of the study, no follow-up data were available. However, the methodological approach set up can be extended by integrating and learning from follow-up data to be able to predict patient progression. Recently, Arnaldi and colleagues<sup>31</sup> reported results to support this statement. In their study, a group of early-diagnosed, drug-naïve patients underwent clinical and neuropsychological assessments as well as Dopamine Transporter (DaT)-SPECT and QEEG at baseline. After an average 5-year follow-up, the authors found that combined QEEG and DAT-SPECT features were the best biomarkers for predicting cognitive decline. The authors also highlighted that QEEG is highly reproducible and automatically available on most clinical devices and machines.

### Limits and Future Trends

In its current form, our study suffers some limitations. Two are related to the patient cohort size. The

first concerns the small patient numbers in G4 and G5. The validity of the models built for these 2 groups is questionable. The obtained results for these groups were lower than those for the other groups, whose larger sample size allowed a better learning conditions for the algorithms. However, this limitation can be nuanced by the fact that the misclassifications observed (Fig. 2) concerned only patients from G4 and G5, those with severe cognitive impairment, whereas for the remaining patients for whom an accurate diagnosis was required to plan the future healthcare, the classification was very accurate. In an experiment where G4 and G5 patients were merged to obtain a group with a larger patient number, the classification reached 100% of accuracy.

The second limitation, related to the previous limitation, concerns the validation. Ideally, model training should be performed on a cohort and the validation should be performed in a prospective way on an independent group. In our study, although learning and classification were performed using separate patient data, the patients were included in the same cohort. This can be a limit of the method generalization. Finally, cognitive functions were assessed, and EEG were recorded only when the patients were in the “on drug” state, without comparison with the “off drug” state. By consequence, it is impossible to determine the effects of medication on the proposed models. However, our main objective was to use machine learning to determine whether a combination of quantitative EEG parameters was able to classify patients with PD according to their cognitive status, at an individual level, and in everyday clinical practice. Hence, the conditions of our data acquisition were very close to the clinical practice and favorable for a transfer to it.

In conclusion, the combination of QEEG analysis and machine-learning techniques appears to be a powerful approach for classifying patients into diverse cognitive conditions. The presented results suggested that this method can be used as a screening tool to identify the severity of cognitive impairment in patients with PD. The method could be extended to predict the progression of cognitive status by integrating follow-up data. However, further investigations involving additional patients are needed to confirm and validate the models. ■

**Acknowledgments:** The authors thank Dr. Lucie Plomhause for her help in neuropsychological assessment, Drs. Jean-Louis Bourriez and Christopher Leroy for their help in EEG data management and Professors Vivianne van Kranen Mastenbroek and Philippe Derambure for their help in clinical assessment.

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