MEASUREMENT TOOLS FOR CLINICAL ASSESSMENT, CHARACTERIZATION AND NEUROREHABILITATION OF PARKINSON'S DISEASE

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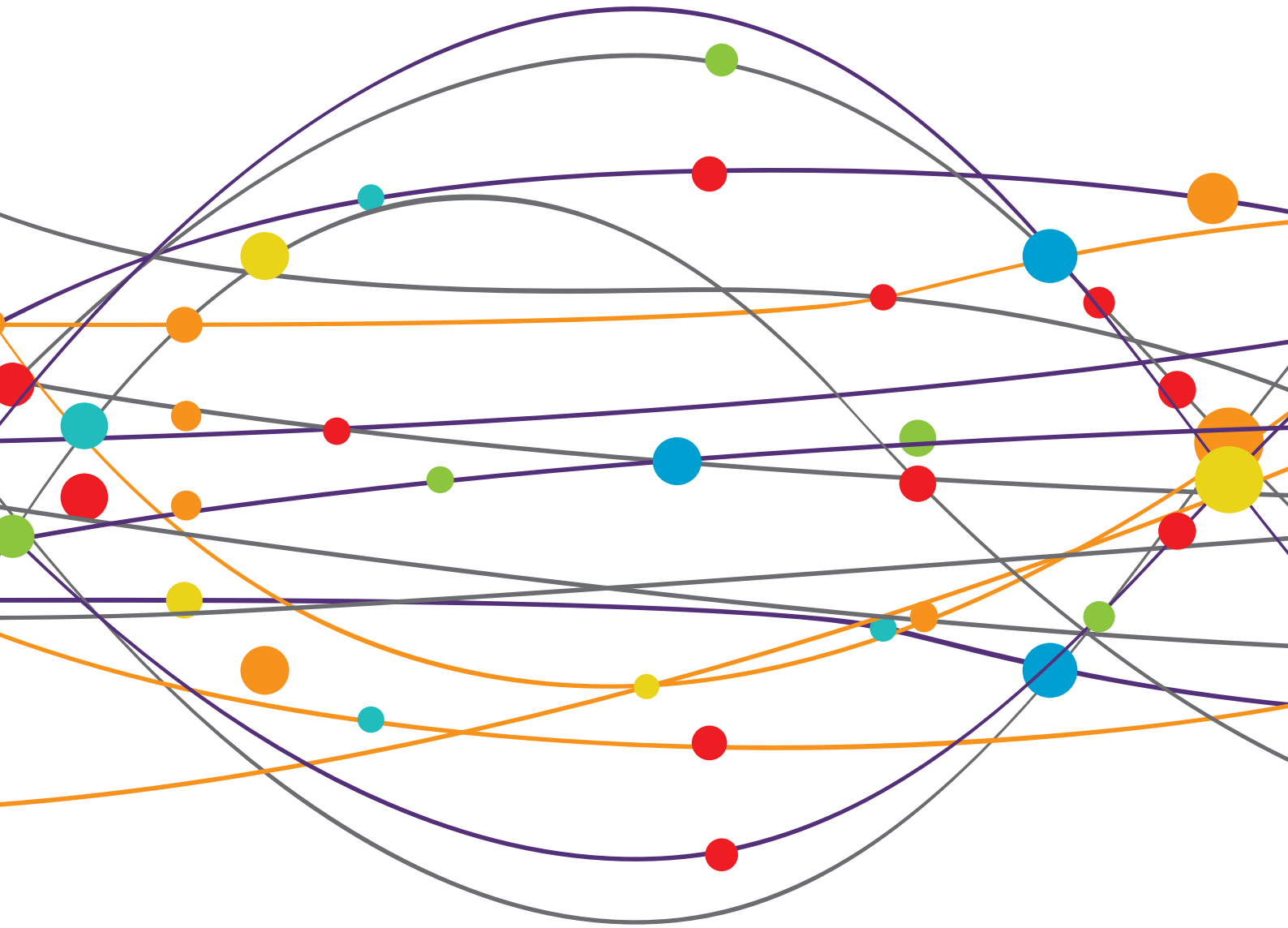
PUBLISHED IN: Frontiers in Neurology



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frontiers

ISSN 1664-8714
ISBN 978-2-88971-061-4
DOI 10.3389/978-2-88971-061-4

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MEASUREMENT TOOLS FOR CLINICAL ASSESSMENT, CHARACTERIZATION AND NEUROREHABILITATION OF PARKINSON'S DISEASE

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Dr. Carmen Rodriguez-Blazquez received support from AbbVie for attending two scientific congresses. Prof. Mayela Rodriguez-Violante received honorariums from Medtronic and Everneuropharma.

Citation: Rodriguez-Blazquez, C., Forjaz, M. J., Rodríguez-Violante, M., eds. (2021). Measurement Tools for Clinical Assessment, Characterization and Neurorehabilitation of Parkinson's Disease. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88971-061-4

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frontiers in Neurology

EDITORIAL
published: 28 May 2021
doi: 10.3389/fneur.2021.700581

Editorial: Measurement Tools for Clinical Assessment, Characterization and Neurorehabilitation of Parkinson's Disease

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Keywords: Parkinson's disease, assessment, neurorehabilitation, endpoint, digital

Editorial on the Research Topic

Measurement Tools for Clinical Assessment, Characterization and Neurorehabilitation of Parkinson's Disease

INTRODUCTION

As editors of this Research Topic on Measurement Tools for Clinical Assessment, Characterization and Neurorehabilitation of Parkinson's Disease, we are delighted to introduce the final collection of papers featured in this Research Topic.

In recent years, a wide variety of measurement tools have been developed for assessing motor and non-motor manifestations of Parkinson's disease (PD). Rater-based interviews and patient self-assessments provide an approximation to subjective and non-observable aspects of PD. The goal of this Research Topic is to offer a review on the recent advances in subjective and objective measurement tools for clinical assessment, characterization and neurorehabilitation of PD.

The topic is divided into four broad categories. The first one covers methodological studies on the psychometric properties of rating scales and questionnaires for clinical assessment, characterization and neurorehabilitation of PD. The second category comprises studied on validation of digital endpoints for clinical assessment, characterization, and neurorehabilitation of PD. The third category included studies on new developments and application of subjective and objective tools. Lastly, the fourth category is related to studies about the responsiveness and interpretation of change of measurement tools.

The final collection is comprised of 20 high-quality papers including 11 original research manuscripts, four systematic reviews, one review, and four brief research reports.

STUDIES ON METHODOLOGICAL ISSUES

Concerning non-motor aspects of PD, Fleury et al. presented a new scale to assess embarrassment and shame of people with PD. The SPARK scale, validated in a sample of 102 PD patients, provides valid and reliable data that may be of great usefulness to assess the social impact of PD.

Cognitive impairment is a common disabilitating non-motor PD, and two Spanish teams presented results from their research that can guide diagnosis and treatment. Specifically, the

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Edited and reviewed by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *26 April 2021*
Accepted: *27 April 2021*
Published: *28 May 2021*

Citation:
Rodriguez-Blazquez C, Forjaz MJ and Rodriguez-Violante M (2021) Editorial: Measurement Tools for Clinical Assessment, Characterization and Neurorehabilitation of Parkinson's Disease. Front. Neurol. 12:700581. doi: 10.3389/fneur.2021.700581

study by Horta-Barba et al. shows that, in a sample of 114 PD patients and 41 healthy controls, encoding and retrieval deficits are an important characteristic of mild cognitive impairment in PD patients, and it is associated with damage in specific brain areas. According to the study by Simon-Gozalbo et al., cognitive impairment in PD is associated with a more advanced disease stage and impact in psychosocial and quality of life outcomes.

Smell deficits and anosmia is one of the most common non-motor symptoms in PD, and could precede the onset of the motor symptoms. Zhao et al. explored the discriminatory power of the olfactory tests for the early diagnosis of PD, using Sniffin' Sticks test. The use of the identification domain test alone for assessing olfactory deficits in PD has great implications for clinical practice and research.

Gan et al. have studied the prevalence and clinical features of freezing of gait (FOG) in a sample of 838 PD patients. This study highlights the need of regularly assess gait and balance in PD patients, optimize the pharmacological treatment and implement early gait rehabilitation training.

STUDIES ON DIGITAL ENDPOINTS

In 16 consecutive patients, Béreau et al. showed that the software model was of limited use and results favored the clinical testing to select stimulation parameters. A review of technology-enabled care in PD presents it as a field with a lot of potential to provide comprehensive care and reduce health inequalities, although it also faces some challenges, such as the lack of standards of validation (Luis-Martínez et al.). An example of telerehabilitation intervention is provided by Isernia et al. with promising results.

A study by Wang et al. indicates that PD developed from essential tremor has specific characteristics, such as the presence of hyposmia and electrophysiological biomarkers, including postural tremor frequencies and amplitudes. In the treatment of PD, subthalamic nucleus deep brain stimulation requires determination of thresholds that can be clinically or software-guided.

STUDIES ON NEW DEVELOPMENTS

The issue contains studies on new developments and application of subjective and objective tools. Temporiti et al. shares a systematic review on the Action Observation Therapy (AOT) based on the mirror neuron system. Overall, seven studies were included revealing that AOT is effective in improving walking ability, freezing of gait and bradykinesia. Nevertheless, study heterogeneity should be considered.

Sanderson et al. address the use of goal-directed tablet-based task to characterize the motor features of PD. The authors developed a touchscreen tablet-based motor task with continuously-moving target designed to capture goal-directed movement. Their tablet-based task and analysis protocol correlated strongly with expert clinical assessments using the MDS-UPDRS-III.

Knudson et al. provide a study aimed at comparing objective and subjective measures using the tool Parkinson's KinetiGraph (PKG). They included 34 patients who wore the PKG for 6 days during the normal daily activities and then used the data collected to build a regression model to predict the MDS-UPDRS II score achieving a significant correlation.

This section includes three papers on potential biomarkers. Ohmichi et al. assessed caffeine concentrations in serum and plasma as a potential blood-based biomarker for PD. They included persons with PD, persons with other parkinsonism, and healthy controls. They found decreased blood concentrations of caffeine in PD compared to controls with a similar trend in the multiple system atrophy group, which warrants further study.

Maycas-Cepeda et al. assessed the role of amimia as a potential marker of other motor and non-motor features of the disease. They included 75 persons with PD and correlated their UPDRS sub scores. They report that amimia correlates with axial symptoms and cognitive situations in PD.

Ramezani et al. analyzed the association between the p.Val66Met, a polymorphism in the BDNF gene, and mild behavioral impairment. Met carriers had a 2-fold likelihood of having mild behavioral impairment than Val carriers suggesting this allele is associated with a higher neuropsychiatric burden in PD.

STUDIES ON RESPONSIVENESS AND INTERPRETATION OF CHANGE

Finally, a group of papers focused on studies about the usefulness, responsiveness, and interpretation of change, due to either time or treatment, of measurement tools used in clinical assessment and characterization and neurorehabilitation of PD.

Wang et al. analyzed how deep brain stimulation (DBS) modulates the intraoperative neuromuscular pattern of resting tremor in 39 PD patients. They identified three intraoperative biomarkers that allow to quantify and predict the efficacy of DBS in PD patients with resting tremor in a quick and efficient way.

Balance dysfunction in PD is usually not respondent to pharmacological or surgical treatment. Hasegawa et al. have assessed the efficacy of a specific intervention for balance deficits, using objective (wearable sensors) and clinical and subjective measures. The authors recommend the use of the objective measures for assessing the efficacy of exercise in improving the balance deficits.

The study of the changes in echogenicity in brainstem raphe (BR) detected by transcranial parenchymal sonography (TCS) and their association with motor and non-motor symptoms in PD patients is the aim of the work by Bei et al. Their findings support the hypothesis of a pathogenetic link between depression and, combined with substantia nigra hyperechogenicity, might be useful to detect individuals at risk for developing PD.

The ability of neurovestibular laboratory tests to predict future falls in patients with PD or atypical parkinsonism (AP) was explored by Venhovens et al. Accurate determination of the risk factor of falls could reduce their incidence and the associated disease burden. Cervical and ocular vestibular evoked myogenic potentials (VEMP) combined with clinical tests for postural

imbalance predicted future fall incidents in both PD and AP groups with a sensitivity of 100%.

Bouça-Machado et al. paper aimed at identifying which kinematic and clinical outcomes changes predict functional mobility (FM) changes in PD patients as a result of a specialized multidisciplinary program. These findings support the use of kinematic outcome measures to evaluate the efficacy of multidisciplinary interventions for FM in PD patients.

CONCLUSIONS

In this collection of articles, authors have presented important developments and applications in objective and subjective measurement tools for PD. The development of new treatments for PD requires reliable and sensitive measurements of patients' health status and abilities of daily living. Validated rating scales and questionnaires are being adapted to digital devices that allow a constant monitoring of the clinical condition. Mobile or residential technology is implemented for remote assessment of health-related parameters or for rehabilitation purposes, and digital endpoints are being used in clinical trials. This field of research is constantly evolving and we will see further advances in the future.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 February 2020
doi: 10.3389/fneur.2020.00142

Electromyography Biomarkers for Quantifying the Intraoperative Efficacy of Deep Brain Stimulation in Parkinson's Patients With Resting Tremor

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 26 October 2019
Accepted: 07 February 2020
Published: 26 February 2020

Citation:
Wang K-L, Burns M, Xu D, Hu W, Fan S-Y, Han C-L, Wang Q, Michitomo S, Xia X-T, Zhang J-G, Wang F and Meng F-G (2020) Electromyography Biomarkers for Quantifying the Intraoperative Efficacy of Deep Brain Stimulation in Parkinson's Patients With Resting Tremor. Front. Neurol. 11:142. doi: 10.3389/fneur.2020.00142

Introduction: Deep brain stimulation (DBS) is an effective therapy for resting tremor in Parkinson's disease (PD). However, quick and objective biomarkers for quantifying the efficacy of DBS intraoperatively are lacking. Therefore, we aimed to study how DBS modulates the intraoperative neuromuscular pattern of resting tremor in PD patients and to find predictive surface electromyography (sEMG) biomarkers for quantifying the intraoperative efficacy of DBS.

Methods: Intraoperative sEMG of 39 PD patients with resting tremor was measured with the DBS on and off, respectively, during the intraoperative DBS testing stage. Twelve signal features (time and frequency domains) were extracted from the intraoperative sEMG data. These sEMG features were associated with the clinical outcome to evaluate the efficacy of intraoperative DBS. Also, an sEMG-based prediction model was established to predict the clinical improvement rate (IR) of resting tremor with DBS therapy.

Results: A typical resting tremor with a peak frequency of 4.93 ± 0.98 Hz (mean ± SD) was measured. Compared to the baseline, DBS modulated significant neuromuscular pattern changes in most features except for the peak frequency, by decreasing the motor unit firing rate, amplitude, or power and by changing the regularity pattern. Three sEMG features were detected with significant associations with the clinical improvement rate (IR) of the tremor scale: peak frequency power ($R = 0.37$, $p = 0.03$), weighted root mean square ($R = 0.42$, $p = 0.01$), and modified mean amplitude power ($R = 0.48$, $p = 0.003$). These were adopted to train a Gaussian process regression model with a leave-one-out cross-validation procedure. The prediction values from the trained sEMG prediction model (1,000 permutations, $p = 0.003$) showed a good correlation ($r = 0.47$, $p = 0.0043$) with the true IR of the tremor scale.

Conclusion: DBS acutely modulated the intraoperative resting tremor, mainly by suppressing the amplitude and motor unit firing rate and by changing the regularity pattern, but not by modifying the frequency pattern. Three features showed strong robustness and could be used as quick intraoperative biomarkers to quantify and predict the efficacy of DBS in PD patients with resting tremor.

Keywords: Parkinson, DBS, efficacy quantifying, resting tremor, EMG

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by certain typical motor symptoms: resting tremor, rigidity, and bradykinesia (1–3). In recent years, deep brain stimulation (DBS) has been established as an effective treatment for PD, especially for the motor symptoms. DBS modulates the basal ganglia circuits through high-frequency electrical stimulation (4). The most commonly used and approved targets for PD-DBS include the subthalamic nucleus (STN), the globus pallidus internus (GPi) and the ventral intermediate (VIM). Other DBS experimental targets include the pedunculopontine nucleus (PPN), nucleus of the thalamus, the caudal zona incerta (cZI), centromedian, and parafascicular nuclei (CMPf) (5, 6). Neurosurgeons and the neurologist together choose the optimal targets according to the symptoms that primarily affect the patient's life and how the patient responded to DBS therapy. To achieve optimal stimulation efficacy, the targets for some patients would be changed one, two, or even more times with rescue or replacement operations or with repeat multiple-pass mapping through the use of microelectrode recording during the DBS testing stage (7–9). Furthermore, the currently established evaluation methods for DBS efficacy mostly depend on the neurosurgeon's or neurologist's experience, intraoperative patients' self-response, and post-operative assessment of a clinical scale (UPDRS, Unified Parkinson's Disease Rating Scale) (10, 11). Two major weak points of this evaluation system are the subjectivity of symptom assessment and the time delay before the surgery for target replacement (7, 12). Therefore, an intraoperative and objective evaluation method is crucial for determining the efficacy of DBS in PD patients with resting tremor.

More and more studies have indicated that PD patients show aberrant kinetic functioning patterns of discharge in motor units (MUs), which can be measured by surface electromyography (sEMG) (13–17). sEMG signals are usually considered as an accumulation effect of activated MUs under the electrodes and are often used to evaluate the activity of the neuromuscular system. Therefore, sEMG enables the objective quantification of neuromuscular function and movement and could be adopted as a biomarker to assess the disrupted neuromuscular system in PD patients and even the treatment effect of DBS and drugs (14). As previous studies have reported, DBS might exert its therapeutic action through altering sEMG characteristics like amplitude, duration, domain tremor frequency of muscular burst, rhythmicity or regularity, and tremor-electromyogram coherence (18, 19). However, all of these quantitative metrics are measured a long time after DBS operation and not during the operation. Therefore, no intraoperative biomarker for quantifying and predicting the efficacy of DBS in PD patients with resting tremor is available.

The purpose of the current study is to investigate how and to what extent the neuromuscular pattern of resting tremor in PD patients could be modulated by intraoperative DBS through measuring sEMG characteristics. Furthermore, given the lack of quick biomarkers, we also aimed to explore robust sEMG biomarkers for quantifying and predicting intraoperative DBS efficacy.

SUBJECTS AND METHODS

Study Subjects

As one of the three cardinal clinical symptoms in PD, resting tremor is the most common symptom and the easiest to observe. It is also the symptom that responds the most rapidly to DBS treatment and is easy to observe, usually within several seconds to a few minutes. In contrast, the effects of DBS treatment on rigidity and bradykinesia are more difficult to observe. Both should be evaluated over the long term with regular DBS programming and are not easy to assess quickly during the operation (17, 20). Therefore, resting tremor could be a suitable clinical symptom for measuring the acute effects of the intraoperative DBS treatment. Furthermore, good tremor control is also the minimum aim for DBS in PD patients.

In the current study, we included PD patients with visible resting tremor as study subjects. Thirty-nine patients (22 male and 17 female; aged 60.51 ± 8.96 years, mean ± SD) with visible resting tremor were enrolled in the study. The patients were evaluated by a multidisciplinary team at Beijing Tiantan Hospital, as shown in **Table 1**. The diagnosis of advanced PD was based on clinical criteria (21, 22). Informed written consent was obtained from all patients, and all procedures were approved by the ethics committee and the neuromodulation committee at Beijing Tiantan Hospital.

The DBS surgical procedures were performed in three stages (23): the (i) electrode implantation stage, (ii) quick testing stage, and (iii) implantable pulse generator (IPG) implantation stage. For the first stage (i), the electrodes were implanted under local anesthesia using the Leksell Stereotactic System (Elekta Instrument AB, Sweden). Intraoperative single-unit recordings were used to localize the motor subregion of the chosen target. Permanent quadripolar electrodes (3,387 Medtronic, Minneapolis, MN, USA for the GPi and 3,389 Medtronic,

TABLE 1 | Demographic and clinical information of patients.

Variable	Value (Mean ± SD)
Number of patients	39
Gender (male/female)	22/17
Course of disease (Years)	8.26 ± 6.17
Age at surgery (Years)	60.51 ± 8.96
Hoehn-Yahr stage (Number)	
2	2
2.5	14
3	19
4–5	4
DBS target (STN/GPi)	35/4

GPi, globus pallidus interna; STN, subthalamic nucleus.

Minneapolis, MN, USA for the STN) were positioned in the motor subregions of the respective stimulation targets. We then performed the intraoperative quick testing stage (ii) to examine the efficacy of DBS treatment. Usually, we adopted an initial DBS programming setting of voltage (0.5 V), frequency (130 Hz), and pulse width (PW 90 μs). The frequency and the pulse width were fixed, and the voltage was increased to 5 V with a step size of 0.1 V until the optimal balance between symptom control and side effects was achieved. Two DBS-experienced neurologists evaluated the quick intraoperative clinical efficacy of DBS stimulation. Once satisfactory efficacy was achieved, the third stage (iii) was started. Otherwise, the stimulation coordinates of the targets were modified (or other targets were tested). For the third stage, the electrodes were connected to an IPG implanted in the subclavicular area under general anesthesia. After that, post-operative CT was performed to exclude intracranial hemorrhage and to verify the exact location of the electrodes through the fusing of the CT images with the preoperative MR images. The IPG was turned on 1 month after the operation, and DBS programming was followed. All post-operative adjustments of DBS parameter settings were performed while subjects were in an off-medication state.

sEMG and Clinical Outcome Measurements

During the second stage (ii) of intraoperative testing, the sEMG was recorded using a Nicolet multiparameter electrophysiological instrument (Nicolet Corporation, Madison, Wisconsin, USA) with a sampling rate of 512 Hz. Bipolar electrodes (one over the belly of the muscle and one for the tendon with an at least 3 cm inter-electrode spacing) were attached to the limbs with obvious tremor symptoms using disposable Ag/AgCl electrodes as described in previous studies (12, 17): the extensor digitorum and the flexor digitorum superficialis for the forearms and the tibialis anterior muscle and the gastrocnemius muscle for the lower legs.

During all phases of sEMG recording, the patients' extremities with tremor were kept in an absolutely relaxed and resting position, fully supported against gravity. Continuous sEMG data were measured at two time-points during the quick testing stage (ii). The first one was the baseline (DBS-off state, after DBS lead implantation) sEMG data and was recorded before the DBS was turned on, when the lead reached the pre-planning stimulation position. The second time point was the stimulation-on (DBS-on) sEMG data. The patient's symptoms changed when the stimulation voltage was increased. Once a satisfactory therapeutic effect was achieved and reported via the intraoperative patient's self-response and observation, rapid motion activity, or the neurologists' experience and when resting tremor could not be evoked by limb movements, the programming parameter setting was fixed. Then the patient's second sEMG was recorded. At least 60 s of stable sEMG was recorded for each trial.

The patients' clinical outcomes were assessed using the motor section (part III) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (10) and the tremor subscale (item 15–18) of the MDS-UPDRS 1 month after the DBS surgery when the stimulator was turned on. All the clinical outcomes were evaluated in the off-medication state.

Pre-processing of Signals and Feature Analysis

The sEMG data were pre-processed before feature computations. Briefly, all sEMG signals of PD patients were first visually inspected by two experienced sEMG experts to remove non-resting motor-related signals with high peaked artifacts. Second, the sEMG signal was band-pass filtered between 20 and 200 Hz with a self-adapting-order Butterworth filter. As recommended in previous studies (24), the sEMG signals were segmented into small 1 s segments and the features were averaged across all segments, as shown in **Figure 1**.

For the tremor burst detection, the pre-processed sEMG signals were full-wave rectified to increase the signal-to-noise ratio (24). Since tremor was driven by rhythmic MU spike firing, the traditional Fourier-transform based methods were limited to extracting the burst signals directly (25, 26). Here, we adopted the Matlab built-in envelop function to detect the tremor burst, which searched for the root-mean-square envelopes of input signals, as shown in **Figures 1**, **2**.

The following time-domain and frequency-domain features were measured from the pre-processed sEMG signals [the feature formulae have been described in detail in previous studies (27, 28)]. All signal analyses were performed using MATLAB (Math Works, Natick, MA, USA).

Time domain:

- Weighted Root Mean Square (wRMS): RMS value for each second (segment)
- Modified Mean Absolute Value (MMAV1 and MMAV2): estimated the mean absolute value of the sEMG
- Waveform Length (WL): measured the cumulative length of the waveform over the segment
- Zero Crossings (ZC): measured the times the waveform crosses zero, namely the number of times when the waveform changes its sign
- Slope Sign Changes (SSC): also measured the number of times the slope changed its sign

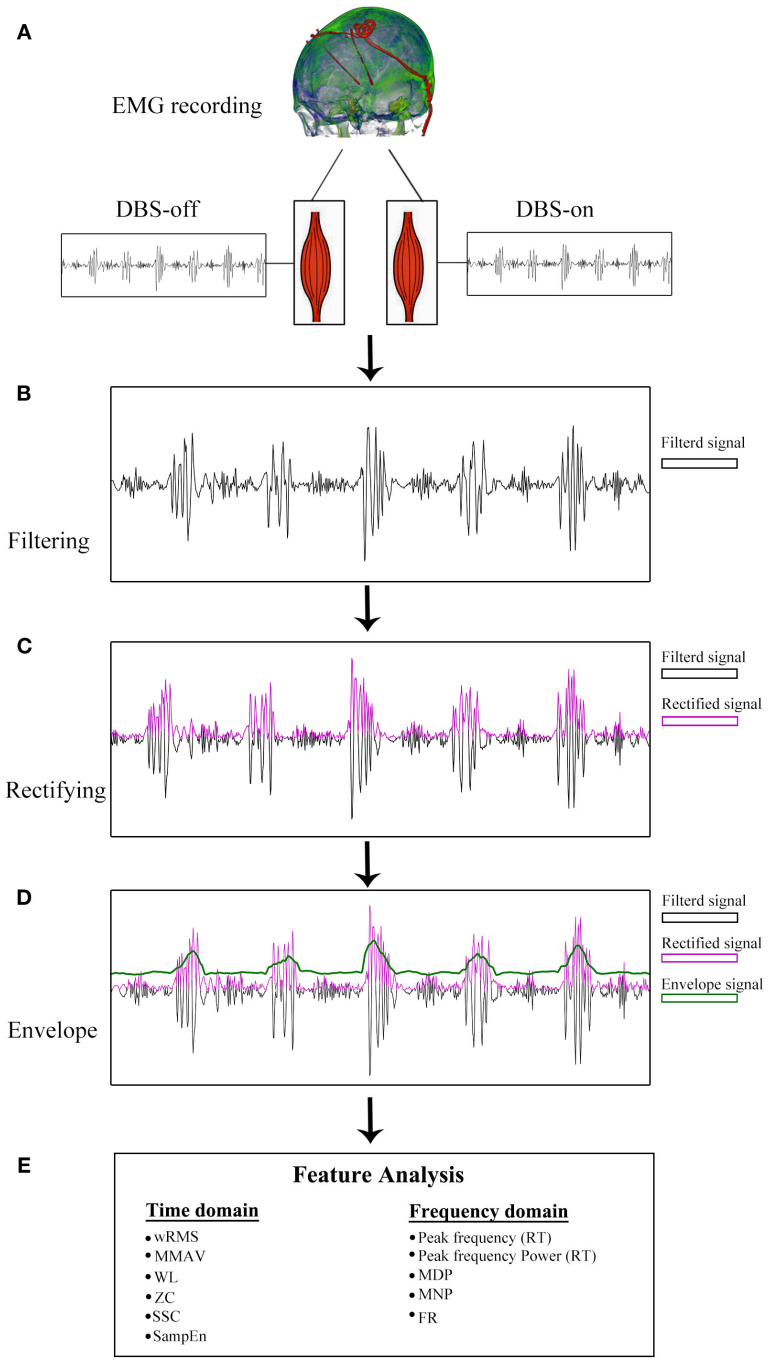

FIGURE 1 | sEMG signal pre-processing diagram. **(A)** sEMG data recording with DBS-on and DBS-off. **(B)** Filtered signals between 20 and 200 Hz. With respect to the resting tremor (RT) burst detection, the filtered signals were full-wave rectified **(C)** and enveloped **(D)**. **(E)** Twelve features were analyzed based on pre-processed sEMG signals.

- Sample Entropy (SampEn) (14): measured the degree of rhythmicity or regularity of the sEMG signal, a measure of the time-dependent structure of the signal.

Frequency domain:

- Peak Frequency [Peak(f)]: measured the dominant peak frequency of the tremor burst based on P-welch estimation
- Peak Frequency Power [Peak(f)PSD]: measured the power spectral density of the Peak frequency based on P-welch estimation
- Median Amplitude Power (MDP): measured the median amplitude spectrum in each segment
- Mean Amplitude Power (MNP): measured the mean amplitude spectrum in each segment

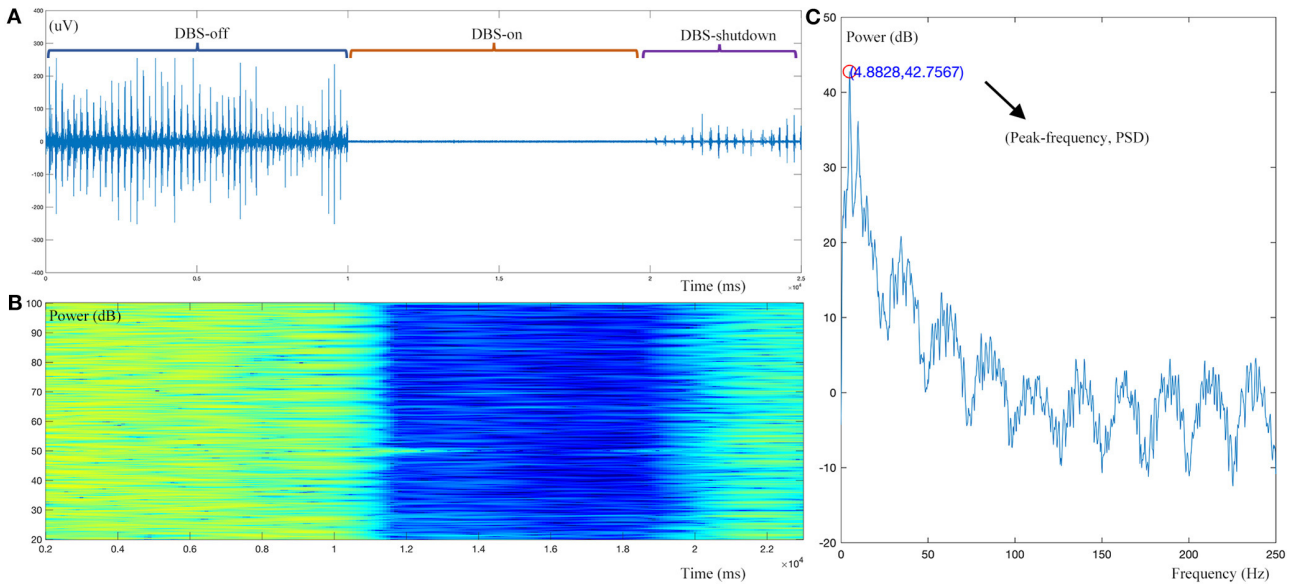

FIGURE 2 | Example dynamic changes in the sEMG signal during DBS operation. **(A)** Raw sEMG data during the DBS-off, DBS-on, and DBS-shutdown phases. **(B)** Time-frequency analysis of the pre-processed sEMG signal. **(C)** Resting tremor (RT) burst detection, showing a peak frequency of 4.88 Hz and peak frequency power [Peak(f)PSD] of 32.76 dB. As shown, this case has a typical resting tremor frequency of 4.88 Hz. With intraoperative DBS on, time-frequency analysis demonstrated that the amplitude or power of resting tremor was obviously decreased.

- Frequency Ratio (FR): the ratio of the lowest frequency in a segment to the highest frequency in the segment.

The above-described 12 features (27) can be divided into three categories; those that measured the frequency [Peak(f), MU firing rate (FR, ZC, SSC)], the amplitude or power [wRMS, MMAV1, MMAV2, Peak(f)PSD, WL, MDP, MNP], or the regularity (SampEn) of the sEMG signal.

Statistical Analysis

The basic characteristics and clinical outcome scores of PD patients were described as mean ± standard deviation (SD). The improvement rate (IR) was calculated between pre-operative scores and each post-operative follow-up as [100 [post-operative scores—pre-operative scores]/pre-operative scores]. Paired-*T*-tests were used to determine whether there was a significant difference between the clinical scale scores and sEMG features at baseline and stimulation-on. The robustness and inter-relationship between features were evaluated by co-correlation analysis based on Spearman correlation. Spearman correlation analysis was also employed to identify sEMG features associated with the tremor sub-scale of MDS-UPDRS.

The selected features that showed significant association with the tremor sub-scale of MDS-UPDRS were then used to create a machine-learning-based prediction model to predict the clinical tremor improvement with acute DBS stimulation. In general, datasets were divided into training sets and testing sets, which were optimized by a cross-validation algorithm using a leave-one-out cross-validation (LOOCV) iteration procedure to protect against model overfitting through partitioning of the data into folds (29–31). We then correlated the predicted values to the real IR of UPDRS-t and examined the correlation coefficient (*r*-value) and its significance. Furthermore, the significance of the prediction model established was tested through permutation testing (1,000 times). In brief, the PD patients' IR values of UPDRS-t were randomly permuted 1,000 times, and we compared the obtained *r*-value at each iteration with the true predictive *r*-value (true *r*-value). The number of permutations achieving a greater value than the true *r*-value was used to derive a *P*-value.

The statistical significance threshold was fixed at $p < 0.05$. Statistical analysis was performed with IBM SPSS (version 20.0; SPSS Inc, Chicago, IL, USA) and MATLAB (Math Works, Natick, MA, USA).

RESULTS

Demographic Results

The demographic characteristics of the PD patients are described in **Table 1**. The course of the patients' disease was 8.26 ± 6.17 years, and most patients were in Hoehn-Yahr stage 2.5 (14/39) or 3 (19/39). At the time of the surgery, patients were 60.51 ± 8.96 years old. Thirty-five patients were stimulated at the STN and four patients at the GPi, as described in **Table 1**.

Clinical Outcome

As measured by MDS-UPDRS (part III), the total motor score (off-medication UPDRS-III) was 63.42 ± 17.85 before the DBS stimulation, and the DBS-off sub-scale of the tremor part (off-medication UPDRS-t, items 15–18) was 15.60 ± 5.13 (mean ± SD). With stimulation on, the scores were significantly reduced to 31.19 ± 14.35 (UPDRS-III) and 3.71 ± 2.18 (UPDRS-t),

TABLE 2 | Clinical scores and EMG features between intraoperative DBS-off and DBS-on in PD patients.

Scores/features	DBS-off (Mean ± SD)	DBS-on	Improvement rate
Clinical scale			
UPDRS-III	63.42 ± 17.85	31.19 ± 14.35	0.52 ± 0.15 (*)
UPDRS-t	15.60 ± 5.13	3.71 ± 2.18	0.76 ± 0.15 (*)
EMG feature			
Frequency domain			
Peak frequency	4.93 ± 0.98	4.77 ± 2.81	0.03 ± 0.56 (ns)
Peak frequency	44.57 ± 11.06	11.30 ± 14.54	0.79 ± 0.41 (*)
PSD			
MDP	204.07 ± 191.34	21.66 ± 42.72	0.87 ± 0.16 (*)
MNP	500.09 ± 4.19	476.04 ± 29.32	0.05 ± 0.06 (*)
FR	0.15 ± 0.06	0.12 ± 0.07	0.16 ± 0.46 (*)
Time domain			
wRMS	4.21 ± 3.98	0.46 ± 0.57	0.84 ± 0.17 (*)
MMAV1	32.73 ± 25.62	3.93 ± 5.59	0.85 ± 0.15 (*)
MMAV2	22.79 ± 18.30	2.83 ± 4.23	0.84 ± 0.84 (*)
WL	1565.10 ± 1869.91	125.81 ± 263.30	0.86 ± 0.30 (*)
ZC	9.69 ± 6.54	2.20 ± 3.45	0.71 ± 0.52 (*)
SSC	12.63 ± 8.71	3.31 ± 4.77	0.65 ± 0.60 (*)
SampEn	0.64 ± 0.30	1.12 ± 0.40	−1.31 ± 1.63 (*)

The UPDRS-III and UPDRS-t were evaluated among 35 patients, and data for four patients were missing or not recorded.
*GPi, globus pallidus interna; STN, subthalamic nucleus; ns, non-significant, * Indicates $p < 0.001$.*

respectively. For UPDRS-III, the improvement rate was 0.52 ± 0.15 ($p < 0.0001$), and for UPDRS-t, the improvement rate was 0.76 ± 0.15 ($p < 0.0001$), as described in detail in **Table 2**.

sEMG Features

Except for peak frequency ($p = 0.7064$), the intraoperative sEMG features were significantly changed during intraoperative DBS-on, as shown in **Table 2** and **Figure 3**. Compared to the baseline, as to the amplitude or power-related features, wRMS, MMAV1, MMAV2, Peak(f)PSD, WL, MDP, and MNP all showed decreased values after DBS stimulation, indicating that DBS stimulation controlled the resting tremor through suppressing the aberrant tremor amplitude. For the regularity analysis, SampEn was significantly ($p < 0.01$) increased from 0.64 ± 0.30 (DBS-off) to 1.12 ± 0.40 (DBS-on), which demonstrated that the DBS-off regular (pathological) signals were restored to more random (normal) signals after intraoperative DBS stimulation.

For the features measuring the frequency characteristics (Peak(f), FR, ZC, and SSC), Peak(f) was used to assess the resting tremor frequency. The remaining features (FR, ZC, and SSC) were adopted to examine the related characteristics of the MU firing rate. Here, the detected resting tremor Peak(f) was 4.93 ± 0.98 Hz at the baseline (DBS-off) with a non-significant change with DBS stimulation (4.77 ± 2.81 Hz, $p = 0.71$). However, the features of FR, ZC, and SSC were significantly changed by DBS treatment. Tremor results from the accumulation effects of activated MUs. Therefore our results indicate that DBS only reduced the firing rate of the MUs but could not totally disrupt the pathological synchronization of the resting tremor in the MUs (i.e., DBS could not change the resting tremor frequency immediately or during the operation time without enough programming and stimulation time).

Correlation Analysis of sEMG Features and Clinical Scales

To test the robustness or reduce the redundancy or overlapping effects of sEMG features and find inter-relationships between features, we performed a co-correlation analysis between sEMG features. Briefly, 11 significant features were correlated "feature to feature" through Spearman correlation, as described in **Figure 4**. The feature of wRMS significantly correlated with all of the remaining 10 features. As described in **Figure 4**, Peak(f)PSD, WL, and ZC had nine correlated features. However, FR only significantly correlated with three features. The features wRMS, Peak(f)PSD, WL, and ZC might contain more components of other features and might contribute a higher accuracy as EMG biomarkers, as they could be interpreted as more comprehensive. In contrast, FR, MNP, and the other features correlated with fewer remaining features, which might reflect more "specific" roles in the sEMG characteristics, which cannot be explained and replaced by the "comprehensive" features.

It is well-established that feature reduction and selection is a very important procedure of model estimation for machine learning (32). To further explore the validity of all 12 sEMG features and find the most effective intraoperative biomarkers for quantifying the efficacy of DBS, we also performed correlation analysis between the improvement rate of the 12 sEMG features and the improvement rate of UPDRS-t. As described in **Figure 5**, Peak(f)PSD ($R = 0.37$, $p = 0.03$), wRMS ($R = 0.42$, $p = 0.01$), and MNP ($R = 0.48$, $p = 0.003$) showed a significant association with UPDRS-t.

Co-correlation analysis divided the 11 features into "specific" ones and "comprehensive" ones, and the association estimation between sEMG features and UPDRS-t detected three useful features among them for quantifying the intraoperative efficacy of DBS, namely Peak(f)PSD, wRMS, and MNP.

sEMG Prediction Model and Prediction Results

The three selected sEMG features (Peak(f)PSD, wRMS, and MNP) were inputted into the Gaussian process regression (GPR) model (using the Regression Learner App built-in to Matlab) to train the sEMG prediction model with the cross-validation algorithm of LOOCV. The predictive IR value showed a significant positive correlation with the true IR of UPDRS-t ($r = 0.47$, $p = 0.0043$). With 1,000 iterations of permutation testing, the sEMG prediction model with three robust features achieved a significant p-value of 0.003. The sEMG prediction model and prediction results are described in **Figure 6**. The Matlab codes for the sEMG prediction model in the current study have been made publicly available: https://github.com/kailiang-wang/sEMG-model-for-DBS-PD.

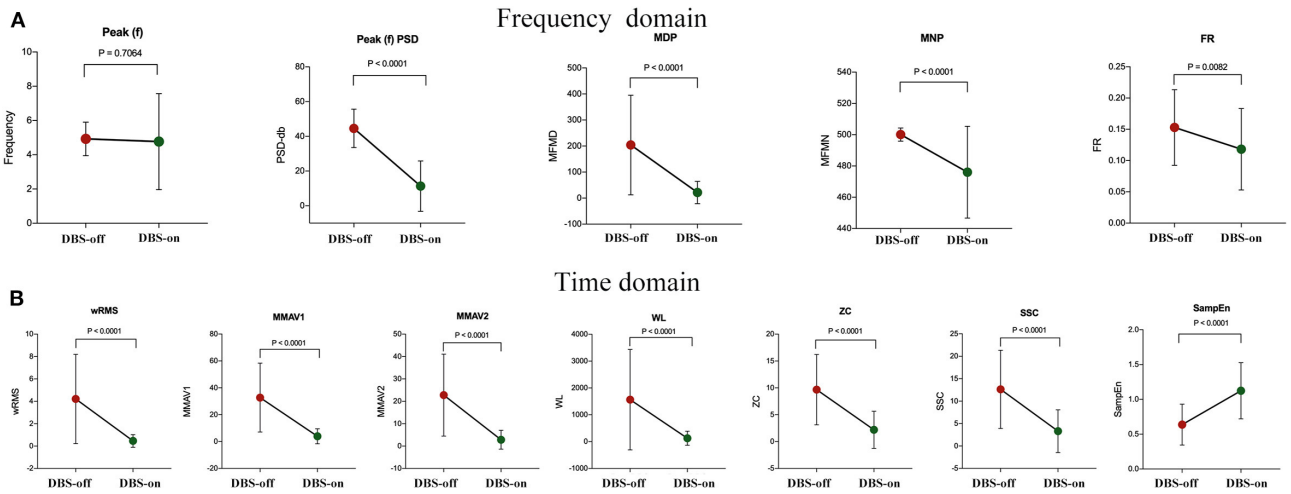

FIGURE 3 | sEMG signal feature analysis between intraoperative DBS-off and DBS-on. **(A)** Features of the frequency domain and **(B)** features of the time domain. As shown, except for the feature of peak frequency ($p = 0.7064$), the features changed significantly with intraoperative DBS-on. Compared to the baseline (DBS-off), in the frequency domain, Peak(f)PSD, MDP, MNP, and FR all showed significantly decreased values after DBS stimulation. In the time domain, wRMS, MMAV1, MMAV2, WL, ZC, and SSC were significantly decreased as well. For the regularity analysis, the SampEn value was significantly increased with DBS-on.

DISCUSSION

The purpose of the current study was (i) to explore the underlying mechanism by which DBS modulates the intraoperative neuromuscular pattern of resting tremor in PD patients with resting tremor and (ii) to find effective sEMG biomarkers for quantifying and predicting the intraoperative efficacy of DBS. Using sEMG data of DBS-on and -off states from PD patients with resting tremor during the intraoperative testing stage, we analyzed 12 sEMG features measuring the frequency or MU firing rate (4/12), amplitude or power (7/12), and regularity (1/12) of the sEMG signal. We revealed three important findings regarding intraoperative DBS. First, DBS exerts its intraoperative therapeutic effect mainly by suppressing neuromuscular amplitude and regularity patterns but not frequency. Second, DBS did not change the resting tremor frequency immediately but reduced the MU firing rate. Third, three useful and quantitative sEMG biomarkers were detected; Peak(f)PSD, wRMS, and MNP showed a significant association with the clinical scale and could be considered as predictive biomarkers for detecting the intraoperative efficacy of DBS for resting tremor. Our results provide new evidence of quantifying and predicting the intraoperative efficacy of DBS by exploring sEMG biomarkers that could be used to aid clinical DBS treatment.

sEMG Biomarkers for DBS

The assessment of the effectiveness of intraoperative DBS has always been challenging for DBS experts, although it is critical for surgical decision-making. Traditional subjective evaluation methods of repetitive passive movements or patient self-response are not sufficiently sensitive and precise to assess the real therapeutic effects in a variety of clinical settings (12). Therefore, biomarkers to represent and quantify the expected response need to be defined. In the past few years, sEMG has been proposed to discriminate patients from normal controls (14, 33). It was also used to distinguish between essential tremor and tremor of PD through spectrally based methods, such as amplitude analysis (14), wavelet-based approaches (34, 35), linear and non-linear parameters (33, 36), EMG-burst shape analysis (36, 37), and a principal component approach (12).

However, to our knowledge, only five studies have investigated sEMG biomarkers for quantifying the efficacy of DBS, as described in previous studies (12, 17, 36, 38). In line with previous studies, our results confirmed that sEMG features were sufficiently robust and sensitive to quantify the efficacy of DBS via three sEMG biomarkers: Peak(f)PSD, wRMS, and MNP. In addition, the present study includes the largest sample size for an sEMG study in DBS patients to date. On the other hand, the previous sEMG studies on DBS did not focus on the intraoperative assessment of the effects of DBS but tested the effects in post-operative patients, who might have been stimulated for a long time with proper programming and some of whom even showed a stable therapeutic effect. Our study, however, was designed to study DBS intraoperatively in a clinical setting. Compared to long-term DBS PD patients, the efficacy of DBS in intraoperative patients would be more challenging to evaluate because these patients were receiving DBS stimulation for the first time. The therapeutic effect of intraoperative DBS might not be stable, especially for rigidity, bradykinesia, gait problems, and non-motor symptoms, which depend on the long-term application of DBS, and even show a long time delay effect (4). The clinical manifestation of a rapid response that is easy to observe and addresses the main symptoms patients complain about is vital for capturing the immediate effectiveness of DBS treatment in the environment of the operating theater. The remaining symptoms can be treated gradually with the optimal and long-term DBS programming settings (20). For this reason, here, we chose PD patients with obvious resting

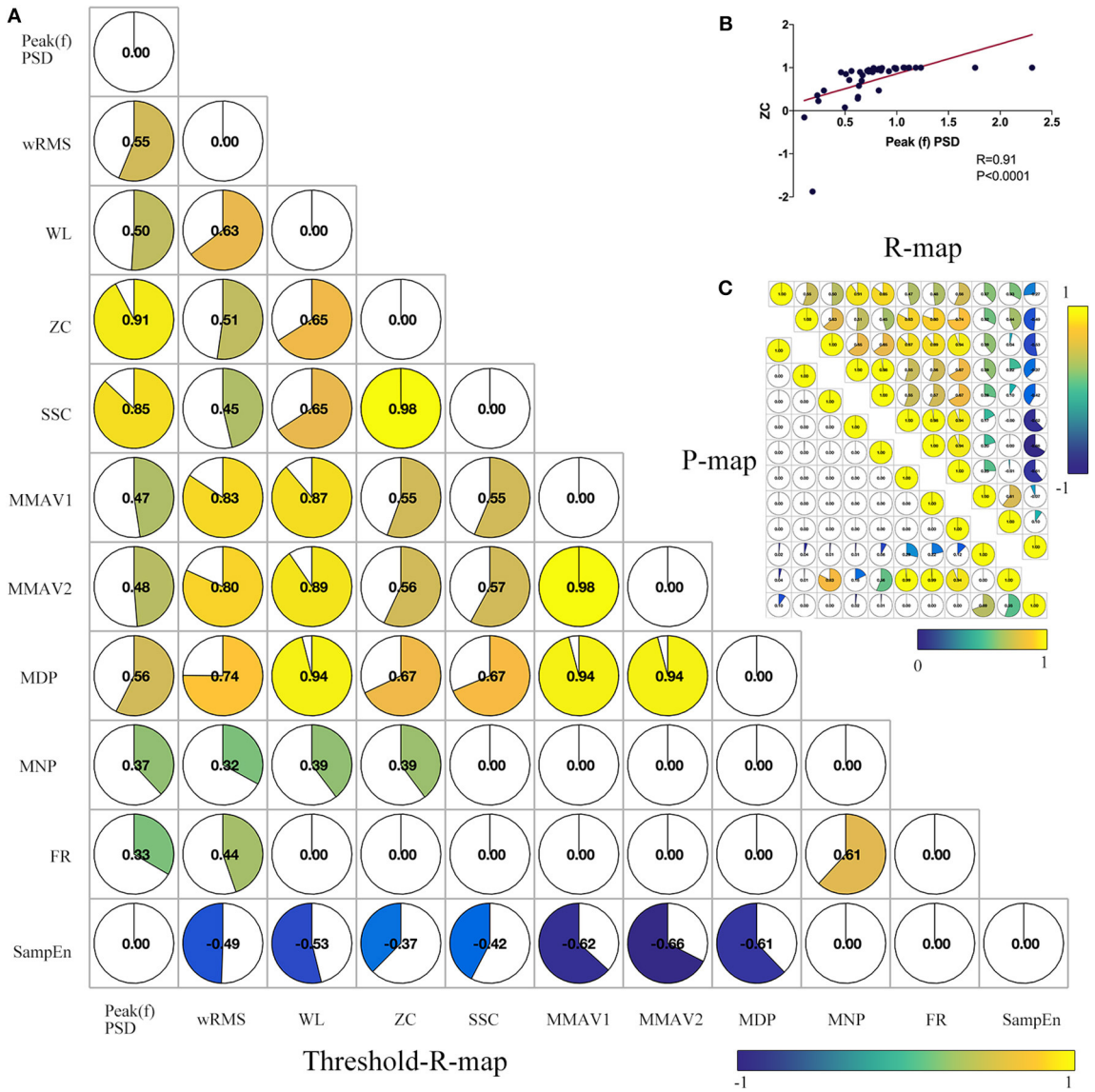

FIGURE 4 | Co-correlation analysis between significant sEMG signal features. **(A)** Combined correlation R-map under the threshold of $p < 0.05$ (without multiple correction). The value in the matrix indicates the significant correlation *R*-value with inter-feature Spearman correlation. **(B)** Example co-correlation analysis between feature ZC and Peak(f)PSD. **(C)** The upper triangular matrix represents the raw correlation R map, and the lower triangular matrix demonstrates the raw correlation P map. As shown, wRMS has 10 co-correlated features. Peak(f)PSD, WL, and ZC have three co-correlated features. SSC, MMAV1, MMAV2, and MDP have eight co-correlated features. SampEn, MNP, and FR have seven, five, and three co-correlated features, respectively.

tremor and used resting tremor as the main metric to measure the efficacy of intraoperative DBS. Our study showed that the sEMG features of resting tremor are the first preliminary biomarkers to evaluate and predict the efficacy of intraoperative DBS, including Peak(f)PSD, wRMS, and MNP, especially for the prediction effects of these sEMG biomarkers, which have been rarely reported in previous studies.

Mechanism of Intraoperative DBS Treatment for Resting Tremor

In the current study, our patients achieved a clinical improvement of 0.52 ± 0.15 UPDRS-III when the stimulation was on for the first time after the operation, which could be used to mimic the intraoperative stimulation. Our result was in line with the report in Kleiner-Fisman et al. (39) that an improvement of 52% was achieved based on 37 cohort studies. Hence, the intraoperative effectiveness of DBS in our study is as effective as in other studies (33–35). We also used items 15–18 of UPDRS-III to define the sub-scale of tremor and measured a tremor improvement of 0.76 ± 0.15 ($p < 0.001$). Although we only recorded and assessed the sEMG data based on the resting tremor, the total motor and tremor symptoms were both controlled well in our patients. Thus, the benefit of using intraoperative sEMG biomarkers for quantifying the efficacy

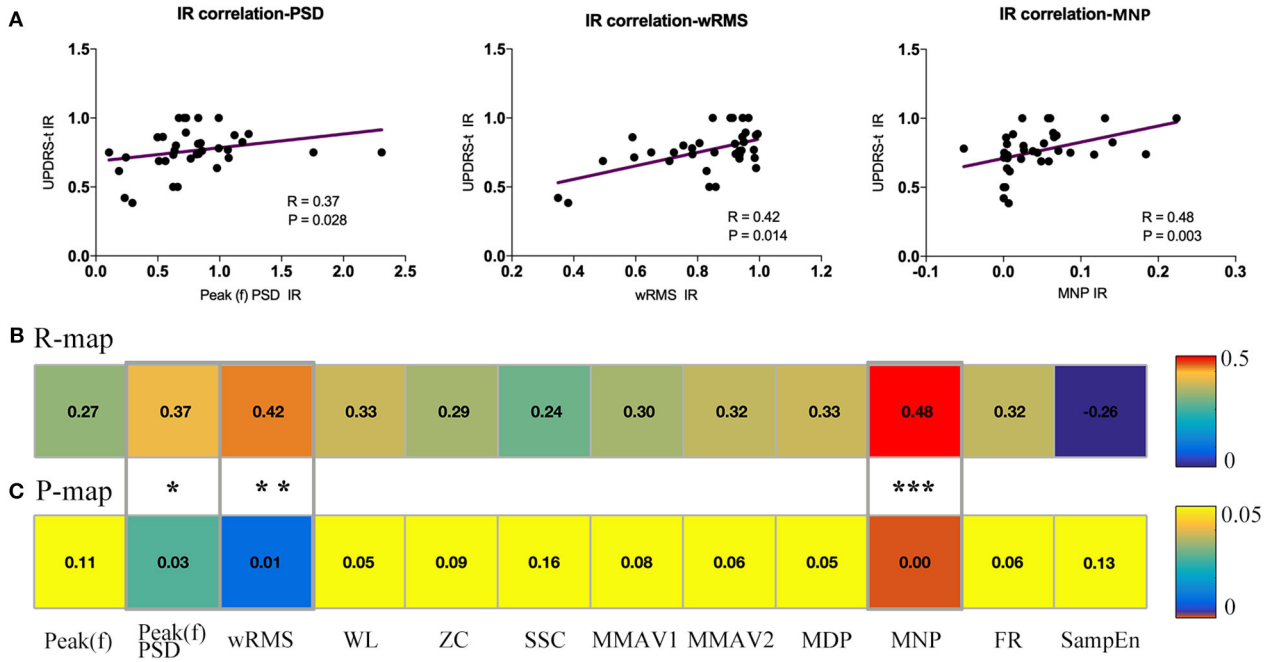

FIGURE 5 | Association analysis between sEMG signal features and UPDRS-t. All changing 12 sEMG features were correlated with the clinical improvement rate (IR) of UPDRS-t. **(A)** Three important sEMG features were detected to have significant correlation with the IR of UPDRS-t, including Peak(f)PSD ($R = 0.37$, $p = 0.03$), wRMS ($R = 0.42$, $p = 0.01$), and MNP ($R = 0.48$, $p = 0.003$). All raw correlation analyses are shown in **(B)** R map and **(C)** P map. *Indicates significant changes. **, ***Indicates *p*-values.

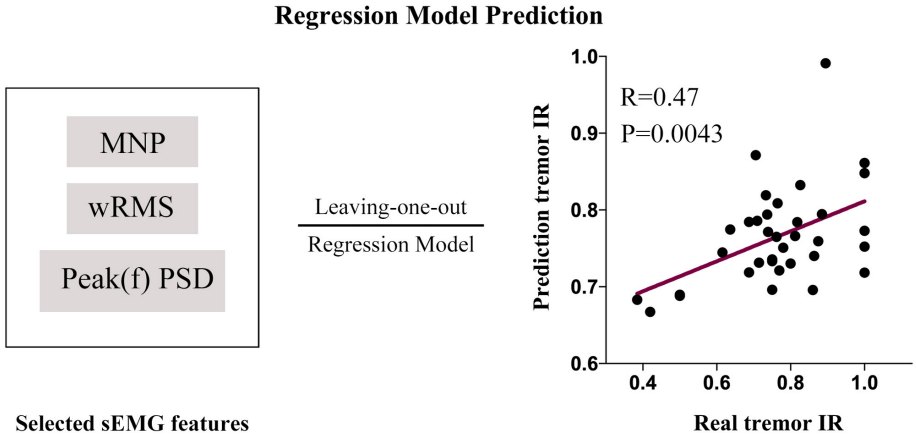

FIGURE 6 | An sEMG feature (Peak(f)PSD, wRMS and MNP)-based prediction model was established with a leave-one-out cross-validation procedure. The model was trained with the Gaussian process regression (GPR) model (1,000 iterations of permutation testing, $p = 0.003$). The predictive IR value showed a significantly positive correlation with the real IR of UPDRS-t ($r = 0.47$, $p = 0.0043$).

of DBS for resting tremor is also supported by the correlation analysis between sEMG features (Peak(f)PSD, wRMS, and MNP) and the tremor sub-scale of UPDRS-III (UPDRS-t).

The mechanisms responsible for the modulation of resting tremor by DBS remain unclear (2). Circuit models of the basal ganglia might provide a possible explanation (5). STN and GPi are both important nodes of this model, and stimulating both targets would change the neural activity, which is correlated with tremor, as suggested by animal models (40, 41) and functional connectome analysis (42–44). In the current study, three sEMG features were detected that were correlated to tremor modulation, namely Peak(f)PSD, wRMS, and MNP, which all measured the amplitude or power of tremor. The Peak(f)PSD measured the power of the typical resting tremor of 4.93 ± 0.98 Hz (45, 46), while wRMS and MNP evaluated the muscular power of the whole frequency band. Although the MU firing rate and regularity of resting tremor also changed, neither was found to be significantly associated with the UPDRS-t improvement rate.

One reason for this could be that intraoperative DBS has an immediate effect but that long-term (chronic) stimulation would produce a positive and significant effect on muscular activity and resting tremor. Thus, our study showed that only the amplitude or power feature could be considered as sEMG biomarkers for quantifying the intraoperative efficacy of DBS in PD patients with resting tremor.

There are several limitations to the present study. First, we did not include normal healthy people (NHP) as a control group to explore differences between PD patients and NHP or DBS-on patients and NHP. Furthermore, only intraoperative PD patients were studied. However, this was related to the purpose of our research, which was aimed at finding individual intraoperative sEMG biomarkers for quantifying the intraoperative efficacy of DBS instead of identifying PD patients from the normal population (33). In the future, an NHP group could be enrolled to study whether DBS restored the pathologic PD neuromuscular state to a normal state. Second, we only focused on the symptom of resting tremor to simplify the study design and find quick sEMG biomarkers, as mentioned above. However, as the results of UPDRS-III show, other symptoms were also controlled well in the current study. Future work will aim to find more sEMG biomarkers for quantifying and predicting the symptoms of rigidity, bradykinesia, and even non-motor symptoms for DBS-PD patients with chronic stimulation. Thirdly, although we recorded the sEMG data after the microlesioning effect had occurred, the clinical improvement of sEMG features with DBS-on might still mix with the microlesioning effect (47). However, it is still valid because the microlesioning effect could be considered a "stimulation" effect of intraoperative DBS, which often showed a "stimulation" effect with transient microhemorrhage, edema, gliosis proliferation, and synaptic plasticity from the stimulation tissue, which has already been proved to help predict motor benefit from DBS (47, 48).

CONCLUSION

In summary, for the first time, intraoperative sEMG biomarkers were studied for quantifying and predicting the intraoperative efficacy of DBS in PD patients with resting tremor. Three important sEMG biomarkers were reported: Peak(f)PSD, wRMS, and MNP. On the other hand, DBS played an acute role in modulating the intraoperative resting tremor, mainly through suppressing the amplitude, regularity, and MU firing rate pattern rather than the frequency pattern. The current study provides new evidence to elucidate a potential mechanism of DBS treatment for intraoperative PD and found three useful sEMG biomarkers for quantifying the clinical success of DBS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the medical ethics committee of IRB of Beijing Tiantan Hospital Affiliated to Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FW, K-LW, and F-GM: study concept and design. S-YF, QW, DX, C-LH, and SM: data collection. K-LW, MB, S-YF, WH, and X-TX: analysis and interpretation. K-LW: drafting of the manuscript. F-GM, MB, WH, and FW: critical revision of the manuscript. FW, F-GM, and J-GZ: study supervision.

FUNDING

This study was funded partly by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (Grant Code: XMLX201833) and partly by the Key Research and Development Program of Ningxia (2018BFG02007).

REFERENCES

1. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* (2016) 15:1257–72. doi: 10.1016/S1474-4422(16)30230-7
2. Elkouzi A, Vedam-Mai V, Eisinger RS, Okun MS. Emerging therapies in Parkinson disease — repurposed drugs and new approaches. *Nat Rev Neurol.* (2019) 15:204–23. doi: 10.1038/s41582-019-0155-7
3. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol.* (1999) 56:33–9. doi: 10.1001/archneur.56.1.33
4. Okun MS. Deep-brain stimulation for Parkinson's disease. *N Engl J Med.* (2012) 367:1529–38. doi: 10.1056/NEJMct1208070
5. DeLong MR, Wichmann T. Basal ganglia circuits as targets for neuromodulation in Parkinson disease. *JAMA Neurol.* (2015) 72:1354–7. doi: 10.1001/jamaneurol.2015.2397
6. Cernera S, Okun MS, Gündüz A. A review of cognitive outcomes across movement disorder patients undergoing deep brain stimulation. *Front Neurol.* (2019) 10:896–18. doi: 10.3389/fneur.2019.00419
7. Oyama G, Foote KD, Hwynn N, Jacobson CE IV, Malaty IA, Rodriguez RL, et al. Rescue leads: a salvage technique for selected patients with a suboptimal response to standard DBS therapy. *Parkinsonism Relat Disord.* (2011) 17:451–5. doi: 10.1016/j.parkreldis.2011.03.009
8. Ellis TM, Foote KD, Fernandez HH, Sudhyadhom A, Rodriguez RL, Zeilman P, et al. Reoperation for suboptimal outcomes after deep brain stimulation surgery. *Neurosurgery.* (2008) 63:754–61. doi: 10.1227/01.NEU.0000325492.58799.35
9. Okun MS, Rodriguez RL, Foote KD, Sudhyadhom A, Bova F, Jacobson C, et al. A case-based review of troubleshooting deep brain stimulator issues in movement and neuropsychiatric disorders. *Parkinsonism Relat Disord.* (2008) 14:532–8. doi: 10.1016/j.parkreldis.2008.01.001
10. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, 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.* (2008) 23:2129–70. doi: 10.1002/mds.22340
11. Ramaker C, Marinus J, Stiggelbout AM, van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord.* (2002) 17:867–76. doi: 10.1002/mds.10248
12. Rissanen SM, Kankaanpää M, Tarvainen MP, Novak V, Novak P, Hu K, et al. Analysis of EMG and acceleration signals for quantifying the effects of deep

brain stimulation in Parkinson's disease. *IEEE Trans Biomed Eng*. (2011) 58:2545–53. doi: 10.1109/TBME.2011.2159380
13. Ruonala V, Pekkonen E, Airaksinen O, Kankaanpää M, Karjalainen PA, Rissanen SM. Levodopa-Induced changes in electromyographic patterns in patients with advanced Parkinson's disease. *Front Neurol*. (2018) 9:35 doi: 10.3389/fneur.2018.00035
14. Sturman MM. Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in Parkinson's disease. *Brain*. (2004) 127:2131–43. doi: 10.1093/brain/awh237
15. Perumal SV, Sankar R. Gait and tremor assessment for patients with Parkinson's disease using wearable sensors. *ICT Express*. (2016) 2:168–74. doi: 10.1016/j.icte.2016.10.005
16. Nishikawa Y, Watanabe K, Takahashi T, Orita N, Kimura H, Matsumoto M, et al. Spatial electromyography distribution pattern of the vastus lateralis muscle during ramp up contractions in Parkinson's disease patients. *J Electromyogr Kinesiol*. (2017) 37:125–31. doi: 10.1016/j.jelekin.2017.10.003
17. Rissanen SM, Ruonala V, Pekkonen E, Kankaanpää M, Airaksinen O, Karjalainen PA. Signal features of surface electromyography in advanced Parkinson's disease during different settings of deep brain stimulation. *Clin Neurophysiol*. (2015) 126:2290–8. doi: 10.1016/j.clinph.2015.01.021
18. Vaillancourt DE, Prodoehl J, Sturman MM, Bakay RAE, Metman LV, Corcos DM. Effects of deep brain stimulation and medication on strength, bradykinesia, and electromyographic patterns of the ankle joint in Parkinson's disease. *Mov Disord*. (2006) 21:50–8. doi: 10.1002/mds.20672
19. Vaillancourt DE, Newell KM. The dynamics of resting and postural tremor in Parkinson's disease. *Clin Neurophysiol*. (2000) 111:2046–56. doi: 10.1016/S1388-2457(00)00467-3
20. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. *Mov Disord*. (2006) 21:S284–9. doi: 10.1002/mds.20961
21. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424
22. Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease. *Eur J Neurol*. (2012) 20:16–34. doi: 10.1111/ene.12022
23. Zhang JG, Ge Y, Stead M, Zhang K, Yan SS, Hu W, et al. Long-term outcome of globus pallidus internus deep brain stimulation in patients with tourette syndrome. *Mayo Clin Proc*. (2014) 89:1506–14. doi: 10.1016/j.mayocp.2014.05.019
24. Vial F, Kassavetis P, Merchant S, Haubenberger D, Hallett M. How to do an electrophysiological study of tremor. *Clin Neurophysiol Pract*. (2019) 4:134–42. doi: 10.1016/j.cnp.2019.06.002
25. Xu FL, Hao MZ, Xu SQ, Hu ZX, Xiao Q, Lan N. Development of a closed-loop system for tremor suppression in patients with Parkinson's disease. *Conf Proc IEEE Eng Med Biol Soc*. (2016) 2016:1782–5. doi: 10.1109/EMBC.2016.7591063
26. Ayache SS, Al-ani T, Farhat WH, Zouari HG, Créange A, Lefaucheur JP. Analysis of tremor in multiple sclerosis using Hilbert-Huang transform. *Neurophysiol Clin*. (2015) 45:475–84. doi: 10.1016/j.neucli.2015.09.013
27. Rechy-Ramirez EJ, HHSOCS. *Stages for Developing Control Systems Using EMG and EEG Signals: A Survey. CES-513*. Colchester: University of Essex (2011).
28. Chen W, Zhuang J, Yu W, Wang Z. Measuring complexity using FuzzyEn, ApEn, and SampEn. *Med Eng Phys*. (2009) 31:61–8. doi: 10.1016/j.medengphy.2008.04.005
29. Shen X, Finn ES, Scheinost D, Rosenberg MD, Chun MM, Papademetris X, et al. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. *Nat Protoc*. (2017) 12:506–18. doi: 10.1038/nprot.2016.178
30. Abós A, Baggio HC, Segura B, García-Díaz AI, Compta Y, Martí MJ, et al. Discriminating cognitive status in Parkinson's disease through functional connectomics and machine learning. *Sci Rep*. (2017) 7:45347. doi: 10.1038/srep45347
31. Zhu Y, Yu Y, Shinkareva SV, Ji GJ, Wang J, Wang ZJ, et al. Intrinsic brain activity as a diagnostic biomarker in children with benign epilepsy with centrotemporal spikes. *Hum Brain Mapp*. (2015) 36:3878–89. doi: 10.1002/hbm.22884
32. Lu CF, Hsu FT, Hsieh KL, Kao YJ, Cheng SJ, Hsu JB, et al. Machine learning–based radiomics for molecular subtyping of gliomas. *Clin Cancer Res*. (2018) 24:4429–36. doi: 10.1158/1078-0432.CCR-17-3445
33. Kugler P, Jaremenko C, Schlachetzki J, Winkler J, Klucken J, Eskofier B. Automatic recognition of Parkinson's disease using surface electromyography during standardized gait tests. *Conf Proc IEEE Eng Med Biol Soc*. (2013) 2013:5781–4. doi: 10.1109/EMBC.2013.6610865
34. Hossen A. A neural network approach for feature extraction and discrimination between Parkinsonian tremor and essential tremor. *Technol Health Care*. (2013) 21:345–56. doi: 10.3233/THC-130735
35. Kramer G, van der Stouwe AMM, Maurits NM, Tijssen MAJ, Elting JWJ. Wavelet coherence analysis: a new approach to distinguish organic and functional tremor types. *Clin Neurophysiol*. (2017) 129:13–20. doi: 10.1016/j.clinph.2017.10.002
36. Ruonala V, Pekkonen E, Rissanen S, Airaksinen O, Miroshnichenko G, Kankaanpää M, et al. Dynamic tension EMG to characterize the effects of DBS treatment of advanced Parkinson's disease. *Conf Proc IEEE Eng Med Biol Soc*. (2014) 2014:3248–51. doi: 10.1109/EMBC.2014.6944315
37. Marusiak J, Andrzejewska R, Swiercz D, Kisiel-sajewicz K, Jaskólska A, Jaskólski A. Spike shape analysis of electromyography for parkinsonian tremor evaluation. *Muscle Nerve*. (2015) 52:1096–8. doi: 10.1002/mus.24903
38. Blahak C, Wöhrle JC, Capelle HH, Bäzner H, Grips E, Weigel R, et al. Tremor reduction by subthalamic nucleus stimulation and medication in advanced Parkinson's disease. *J Neurol*. (2007) 254:169–78. doi: 10.1007/s00415-006-0305-x
39. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord*. (2006) 21:S290–304. doi: 10.1002/mds.20962
40. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci*. (1990) 13:281–5. doi: 10.1016/0166-2236(90)90110-V
41. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science*. (1990) 249:1436–8. doi: 10.1126/science.2402638
42. Vanegas-Arroyave N, Lauro PM, Huang L, Hallett M, Horovitz SG, Zaghloul KA, et al. Tractography patterns of subthalamic nucleus deep brain stimulation. *Brain*. (2016) 139:1200–10. doi: 10.1093/brain/aww020
43. Accolla EA, Herrojo Ruiz M, Horn A, Schneider GH, Schmitz-Hübsch T, Draganski B, et al. Brain networks modulated by subthalamic nucleus deep brain stimulation. *Brain*. (2016) 139:2503–15. doi: 10.1093/brain/aww182
44. Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. Connectivity predicts deep brain stimulation outcome in Parkinson disease. *Ann Neurol*. (2017) 82:67–78. doi: 10.1002/ana.24974
45. Elias WJ, Shah BB. Tremor. *JAMA*. (2014) 311:948–7. doi: 10.1001/jama.2014.1397
46. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord*. (2017) 33:75–87. doi: 10.1002/mds.27121
47. Cersosimo MG, Raina GB, Benarroch EE, Piedimonte F, Alemán GG, Micheli FE. Micro lesion effect of the globus pallidus internus and outcome with deep brain stimulation in patients with Parkinson disease and dystonia. *Mov Disord*. (2009) 24:1488–93. doi: 10.1002/mds.22641
48. Sitburana O, Almaguer M, Ondo WG. A pilot study: microlesion effects and tremor outcome in the ventrointermediate deep brain stimulation (VIM-DBS). *Clin Neurol Neurosurg*. (2010) 112:106–9. doi: 10.1016/j.clineuro.2009.10.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 April 2020
doi: 10.3389/fneur.2020.00240

The Free and Cued Selective Reminding Test in Parkinson's Disease Mild Cognitive Impairment: Discriminative Accuracy and Neural Correlates

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Introduction: Memory alterations are common in Parkinson's disease (PD) patients but the mechanisms involved in these deficits remain poorly understood. The study aims to explore the profile of episodic memory deficits in non-demented early PD patients.

Methods: We obtained neurological, cognitive and behavioral data from 114 PD patients and 41 healthy controls (HC). PD participants were grouped as normal cognition (PD-NC) and mild cognitive impairment (PD-MCI) according to the Level II criteria of the Movement Disorders Society Task Force (MDS-TF). We evaluate the performance amongst groups on an episodic memory task using the Free and Cued Selective Reminding Test (FCSRT). Additionally, gray matter volume (GMV) voxel based morphometry, and mean diffusivity (MD) analyses were conducted in a subset of patients to explore the structural brain correlates of FCSRT performance.

Results: Performance on all subscores of the FCSRT was significantly worse in PD-MCI than in PD-NC and HC. Delayed total recall (DTR) subscore was the best at differentiating PD-NC from PD-MCI. Using crosstabulation, DTR allowed identification of PD-MCI patients with an accuracy of 80%. Delayed free and cued recall was associated with decreased GMV and increased MD in multiple fronto-temporal and parietal areas.

Conclusion: Encoding and retrieval deficits are a main characteristic of PD-MCI and are associated with structural damage in temporal, parietal and prefrontal areas.

Keywords: PD-MCI, Free and Cued Selective Reminding Rest, Parkinson's disease, memory, episodic memory

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico

Reviewed by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *19 November 2019*
Accepted: *12 March 2020*
Published: *21 April 2020*

Citation:
Horta-Barba A, Pagonabarraga J, Martínez-Horta S, Marín-Lahoz J, Sampedro F, Fernández-Bobadilla R, Botí MÁ, Bejr-Kasem H, Aracil-Bolaños I, Pérez-Pérez J, Pascual-Sedano B, Campolongo A, Izquierdo C, Gómez-Ansón B and Kulisevsky J (2020) The Free and Cued Selective Reminding Test in Parkinson's Disease Mild Cognitive Impairment: Discriminative Accuracy and Neural Correlates. Front. Neurol. 11:240. doi: 10.3389/fneur.2020.00240

INTRODUCTION

At the time Parkinson's disease (PD) diagnosis, up to 30% of patients meet diagnostic criteria for mild cognitive impairment (PD-MCI) (1–3). The rate of progression of PD-MCI is heterogeneous, with up to 36% of patients fulfilling diagnostic criteria for PD dementia (PDD) after 4 years after diagnosis, with cumulative PDD prevalence of 80% in 20 years long-term survivors (4–6). Thus, despite dementia is not an inevitable consequence of PD, it affects a significant proportion of patients for which treatments to ameliorate this entity are lacking.

Identifying early cognitive indicators suggestive of progression to dementia is a major need to stratify patients in different groups of risk and also to design interventions before PDD onset. In this sense, the addition of posterior-cortical type deficits -to the prototypical frontal-executive alterations seen in most PD patients- seem to characterize the transition from PD-MCI to PDD in this population. Accordingly, the development of language, memory and visuospatial/visuoperceptive alterations are indicative of a more aggressive progression of cognitive deterioration in PD (7, 8).

Episodic memory alterations are also found in PD and affects up to 45% of *de novo* PD patients. However, its role in the delineation of progression from PD-MCI to PDD and the mechanisms participating in these deficits has been scarcely studied (9). Attention and retrieval deficits -rather than storage and retention alterations- has been pointed to sub-serve episodic memory difficulties in PD (10). This is supported by the benefit commonly observed in retrieval when semantic or recognition cues are presented to PD patients. Accordingly, decreased performance in memory tasks in PD have been attributed to frontal-executive deficits rather than to hippocampal or medial temporal lobe alterations. However, difficulties in retrieving information even during recognition and cued-facilitated recall have also been described in PD (11). This suggests that in some patients amnestic difficulties may be associated to hippocampal alterations rather than been restricted to frontal-executive alterations. The role that this kind of deficits might play in PD-MCI and in the conversion to PDD is mostly unknown. However, exploring differences in episodic memory performance in non-demented PD patients with and without PD-MCI may help to delineate early cognitive changes with significant prognostic implications in terms of cognitive progression.

In the present study, we aimed to explore the profile of episodic memory deficits in non-demented early PD patients with normal cognition (PD-NC) and PD-MCI. To explore the extent of structural brain differences accompanying these deficits, we also conducted voxel based morphometry (VBM) and mean diffusivity (MD) analyses in a subset of participants. Gray matter volume (GMV) analyses through VBM is a macrostructural neuroimaging technique that has been widely used to characterize brain atrophy. In recent years, increases in MD both in white-matter and gray-matter tissues have been suggested to infer microstructural brain damage.

METHODS

Participants

We prospectively recruited 114 PD patients who fulfilled the UK Brain Bank Diagnostic Criteria for PD and regularly attending the Movement Disorders Unit at our center and a group of 41 age-matched and education-matched healthy controls. The study procedures included a neurological examination and the administration of a comprehensive neuropsychological assessment battery which was done to all participants, including patients and healthy controls. Presence of PDD according to consensus guidelines (12); having undergone deep brain stimulation surgery; brain abnormalities evidenced in imaging studies performed in the previous year; major depression; treatment with anticholinergic drugs; and any known causes of cognitive impairment other than PD defined exclusion criteria. Written informed consent was obtained from all participants and all procedures were performed in accordance with the standards of the local Ethic Review Board of the Sant Pau hospital in Barcelona, and with the 1964 Helsinki declaration and its later amendments.

Procedures

Data was collected during two separate visits. Data at screening included: age, educational level, current medications with dopaminergic drugs converted to levodopa equivalent daily dose (LEDD), formal application of the MDS criteria to exclude PDD, the MDS-Unified Parkinson's Disease Rating Scale part III (UPDRS-III) motor subscale, Hoehn, and Yahr (H&Y), and the Parkinson's Disease-Cognitive Rating Scale (PD-CRS), which is a screening instrument that addresses global cognition. On the second visit, a comprehensive neuropsychological examination that fulfilled the standards proposed by the MDS Task Force for the diagnosis of PD-MCI was completed (2).

Neuropsychological Assessment and Group Classification

PD participants were grouped as PD-NC and PD-MCI according to the Level II criteria of the Movement Disorders Society Task Force (MDS-TF) for the diagnosis of PD-MCI (1, 2). Thus, five cognitive domains (attention, language, memory, visuospatial skills, and executive functions) were examined using a comprehensive battery composed of two tests per domain. We applied cut-offs of 1.5 SD below normative values and PD-MCI was confirmed when any two (or more) impaired neuropsychological test were present (2, 13). The following standardized and recommended neuropsychological measures were used: Parkinson's Cognitive dementia rating scale (PD-CRS), forward and backward Corsi's block-tapping task, forward digit span task, phonetic and semantic verbal fluency, the Rey-Osterrieth complex figure test, the Boston Naming test, the Judgment of Line Orientation, and the number location subtest of the Visual Object and Space Perception Battery.

Episodic memory was assessed using the Free and Cued Selective Reminding Test (FCSRT). The FCSRT is a widely used episodic memory test which assesses immediate and delayed free-recall and cued-facilitated immediate and delayed recall. In

studies assessing memory performance in MCI in the general population, the FCSRT has shown to reflect hippocampal-mediated consolidation memory defects better than free-list learning tests. Moreover, the FCSRT performance predicts progression to dementia in close relationship with progressive atrophy of the medial temporal lobe and other neocortical temporal and parietal regions (10, 14–19). The FCSRT was administered using standard procedures as described by Grober and Buschke (20). Participants were shown a card with four words, and were asked to determine which one of the four corresponds to a particular category (e.g., cue; clothing, and the word "vest"). The participant should learn the four items on the four cards (total 16 words). Three recall trials were conducted, each one preceded by 20 s of counting backwards used as interference. For each trial, participants were asked to freely recall as many items as possible and category cues were provided for items not retrieved by total free recall. The same procedure of recalling (freely and cued) was done after a 30 min interval. Subjects were required to freely remember the words and category cues were provided for items not retrieved freely. The measures evaluated here were: total free recall-TFR (cumulative sum of free recall from the three trials; range 0–48), total recall-TR (cumulative sum of free recall + cued recall from the three trails, range 0–48), delayed free recall-DFR (free delayed recall, range 0–16), and delayed total recall-DTR (free delayed recall + cued delayed recall, range 0–16).

Both patients and healthy controls followed the same assessment.

Neuroimaging Acquisition

A subsample of 56 patients underwent 3-Tescla Magnetic Resonance Imaging (MRI) (Philips Achieva). T1-weighted MRI acquisition was performed using a dedicated axial T13D-MPRAGE MRI (TR/TE, 500/50 ms; flip angle, 8, field of view [FOV], 23 cm; with in-plane resolution of 256 × 256 and 1-mm slice thickness). Diffusion Tensor Imaging (DTI) scans were also obtained (FOV 220 mm, voxel size 2 mm, TR 8,000 ms, TE 80 ms, flip angle 90°, 32 directions, b-factor 1000). The neuropsychological and MRI scans were performed within a maximum of 3 months between procedures.

Statistical Analysis

Data are expressed as means ± standard deviation (SD) for the continuous variables and as mean range for the ordinal variables. Differences between groups were analyzed with independent two-tailed *t*-tests and analyses of variance (ANOVA) for continuous variables, the Mann-Whitney test for ordinal data, and the $\chi 2$ test for categorical variables. Comparison of clinical, demographic, and neuropsychological data between groups were done using One-Way ANOVA between the three groups, with additional Tukey *post-hoc* tests for more direct comparisons between each pair of groups.

Binary logistic regression analysis was performed to test the independent classification capacity of the different FCSRT subscores.To calculate the effect size of the differences observed between cognitive groups we used Cohen's *d* coefficient (d values: 0–0.3, small effect size; 0.3–0.6, moderate effect size; >0.6, large effect size). Receiver operator characteristic (ROC) curves were generated to explore the discriminative capacity of each FCSRT subscore. We used cross-tabulation to calculate diagnostic accuracy. Associations between demographic, clinical and cognitive variables were studied using Pearson's correlations. Significance was set at $p < 0.05$. All the statistical procedures were performed using the SPSS v16.0 statistical software package.

Neuroimaging Analysis

A voxel-based morphometry (VBM) analysis of gray matter volume (GMV) was performed using the Statistical Parametrical Mapping (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm/). T1-MRI images were segmented to obtain GMV probability maps, which were then normalized to the Montreal Neurological Institute (MNI) stereotactic space using DARTEL. The resulting images were smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM).

DTI images were preprocessed using FSL 5.0 software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). First, non-brain tissue was removed using the Brain Extractor Tool (BET). Second, motion and eddy current correction was performed using the FMRIB's Diffusion Toolbox (FDT). Diffusion tensors were then computed and mean diffusivity (MD) maps were obtained for each patient. These maps were then normalized to MNI space and smoothed using an isotropic filter of 6 mm FWHM.

The normalized GMV and MD images were entered into a voxel-wise multiple regression analysis to explore the brain correlates of the DFR and DTR scores in both modalities. Age, sex, education and total intracranial volume were used as covariates of no interest. Voxelwise imaging results showing $p < 0.005$ (uncorrected) and a minimum cluster extent size of $k = 100$ voxels was considered significant (21–23). Clusters surviving family-wise error (FWE) correction for multiple comparisons are reported in the corresponding cluster description table (**Table 4**). The MRIcron software tool (https://www.nitrc.org/projects/mricron) was used to represent the statistical voxelwise maps.

RESULTS

One hundred and fourteen PD patients (68.0 ± 8.3 years) and 41 healthy controls (HC; 66.3 ± 7.4 years) were included in the study. PD patients were in the early to mid-stages of the disease (disease duration 5.3 ± 3 years; H&Y stage 2.0 ± 0.2; UPDRS-III 25.2 ± 8.1). As seen in **Table 1**, PD patients and HC were matched for age, gender and education.

According to MDS-TF level II criteria for PD-MCI, using a detection threshold of −1.5 SD, 22 of the 114 patients (19.0%) were classified as having PD-MCI and all HC were classified in the range of normal cognition, following this same criteria. Looking at the different cognitive groups, those in the PD-MCI group were significantly older than PD-NC [$t_{(113)} = 3.174$; $p < 0.01$] and HC [$t_{(63)} = 3.78$; $p < 0.01$], have lower educational level than PD-NC [$t_{(113)} = -4.18$; $p < 0.01$] and HC [$t_{(63)} = -3.66$; $p < 0.01$], and had higher UPDRS-III score than PD-NC [$t_{(63)} = 3.10$; $p < 0.05$].

As depicted in **Table 2**, between-group comparisons showed significant differences in all the cognitive measures with the

TABLE 1 | Clinic and sociodemographic characteristics of the sample.

	Controls	PD total sample	PD-NC	PD-MCI	*P**	*P*†
Age (years)	66.3 ± 7.4	68 ± 8.3	67.5 ± 8.1	72.9 ± 4.9	0.251	0.012
Gender (m/f)	21/20	72/42	64/28	8/14	$\chi^2 = 0.125$	$\chi^2 = 0.004$
Education (years)	13.2 ± 4.8	12.2 ± 4.7	13 ± 4.4	8.7 ± 4.4	0.250	<0.001
Disease duration (years)	–	5.3 ± 3.4	5 ± 3.1	6.1 ± 4.2	–	0.278
MDS-UPDRS III[a]	1.2 ± 1.2	25.2 ± 8.1	24 ± 7.4	29.8 ± 9	<0.001	<0.01
H&Y[b]	–	2 ± 0.2	2 ± 0.2	2 ± 0.2	–	0.891
Total LEDD[c]	–	565 ± 312	571 ± 320	540 ± 282	–	0.680

[a]*Movement Disorders Society—Unified Parkinson's Disease Rating Scale part III.*
[b]*Hoehn and Yahr stage.*
[c]*Total levodopa equivalent daily dose.*
**P-values were determined with t-test for independent samples between healthy controls and PD.*
†*P-values were determined with t-test for independent samples between PD-NC, and PD-MCI.*

TABLE 2 | Level I and Level II assessment scores.

	Controls[a]	PD-NC[b]	PD-MCI[c]	*ANOVA*	*Turkey's*
PD-CRS Total score	101.2 ± 12.9	95 ± 15.4	73 ± 7.1	<0.001	[a–b]0.056; [b–c] <0.001
Frontal-subcortical	72.3 ± 12.1	66.4 ± 14.6	44.8 ± 7	<0.001	[a–b]0.057; [b–c] <0.001
Posterior-cortical	28.9 ± 1.7	28.5 ± 1.7	27.1 ± 2	<0.001	[a–b]0.594; [b–c] <0.005
Attention					
Corsi Forward	5.2 ± 0.9	5.2 ± 0.9	4.1 ± 1	<0.001	[a–b]0.987; [b–c] <0.001
Digit span forward	5.5 ± 1	5.5 ± 1.1	4.6 ± 0.7	<0.01	[a–b]0.947; [b–c] <0.005
Executive functions					
Phonetic fluency	15.4 ± 4.6	15.5 ± 4.9	8.7 ± 3.4	<0.001	[a–b]0.993; [b–c] <0.001
Corsi Backward	4.8 ± 0.9	4.7 ± 1	3.4 ± 0.9	<0.001	[a–b]0.878; [b–c] <0.001
Memory					
PD-CRS delayed memory total recall	6.6 ± 1.8	6.2 ± 2.4	4.5 ±1.7	<0.001	[a–b]0.660; [b–c] <0.001
ROCFT –30 min[1]	16.1 ± 5.8	13.3 ± 6.8	4.8 ± 5.3	<0.001	[a–b]0.076; [b–c] <0.001
Language					
BNT-60[2]	54.6 ± 6.7	54.7 ± 4.6	47.7 ± 5.2	<0.001	[a–b]0.685; [b–c] <0.001
Semantic fluency	20.6 ± 4.8	19 ± 5.5	12.1 ± 3.2	<0.001	[a–b]0.229; [b–c]0.001
Visuospatial					
JLOT[3]	23.3 ± 4.6	22.4 ± 5	15.1 ± 6.9	<0.001	[a–b]0.679; [b–c] <0.001
VOSP—number location[4]	19.7 ± 1	19.6 ± 0.9	19.3 ± 1.2	0.351	[a–b]0.907; [b–c]0.424

[1]*Rey-Osterrieth complex figure test –30 min delayed recall.*
[2]*Boston Naming Test –60 items.*
[3]*Judgement of line orientation test.*
[4]*Visual object and shape perception test.*
[a–b]*Controls vs. PD-NC.*
[b–c]*PD-NC vs. PD-MCI.*

exception of the number location subtest of the VOSP. *Post-hoc* comparisons showed no significant differences in cognitive performance between PD-NC and controls. Conversely, PD-MCI performed significantly worse than PD-NC in all cognitive measures with the exception of the number location subtest of the VOSP.

Looking at the FCSRT test performance, no differences were found between PD-NC and HC in any of the obtained FCSRT subscores. Conversely, performance of the patients in the PD-MCI group was significantly worse than performance of the HC and the PD-NC in all the subscores ($p < 0.001$). As reflected by Cohen's *d*, large effect sizes were found for TFR ($d = 1.09$), TR ($d = 1.23$), DFR ($d = 1.03$), and DTR ($d = 1.60$) when comparing PD-MCI with PD-NC. Large effects were also found when comparing PD-MCI with HC in all FCSRT subscores: TFR ($d = 1.31$), TR ($d = 0.94$), DFR ($d = 1.05$), and DTR ($d = 1.14$). When comparing PD-NC with HC with Cohen's *d*, we found small effects in all FCSRT subscores: TFR ($d = 0.29$); TR ($d = 0.11$); DFR ($d = 0.06$); and DTR ($d = 0.10$). We used stepwise logistic regression analysis (forward; conditional) to determine FCSRT subscores that independently differentiated PD-NC from PD-MCI. The variables found to be significantly different between cognitive groups in the one-way ANOVA were included in the analysis to assess their contribution to group

discrimination. From all the variables included in the model, the DTR ($r = 549$; $p < 0.001$) was the best differentiating PD-NC from PD-MCI independently on age, education or UPDRS-III score (see **Table 3**).

Discriminative Capacity of the FCSRT

Receiver operating characteristics (ROC) curves to discriminate between PD-MCI and PD-NC indicated that a cut-off of ≤ 20/21 points on the TFR score yielded sensitivity, 73%; specificity, 77% (AUC = 0.770; 95% confidence interval, 0.663–0.878, $p <$ 0.005). A cut-off score ≤ 38/39 points on the TR score showed sensitivity, 80%; specificity, 69% (AUC = 0.803; 95% confidence interval, 0.704–0.902, $p < 0.001$). A cut-off score ≤6/7 on the DFR score showed sensitivity, 80%; specificity, 70% (AUC = 0.760; 95% confidence interval 0.647–0.874, $p < 0.005$). The DTR score showed the best discriminative properties to differentiate PD-MCI from PD-NC using a cut-off ≤12/13 points, achieving sensitivity, 86%; specificity, 81% (AUC = 0.870; 95% confidence interval 0.804–0.936, $p < 0.001$). Using crosstabulation, we found DTR scores identified PD-MCI patients with 80% accuracy (see **Figure 1**).

Neuroimaging Data

Voxel-wise multiple regression analysis between GMV and DFR and DTR respectively showed significant positive associations between FCSRT performance and GMV in multiple fronto-temporal and parietal areas. Specifically, poorer DFR scores were associated with decreased GMV in the left mid temporal gyrus (BA 21), the paracentral gyrus and the superior temporal gyrus (BA 41) (FWE corrected $p < 0.05$). Less restrictive criteria (uncorrected $p < 0.005$; $k = 100$) showed positive associations with the right mid temporal gyrus, the right superior frontal gyrus and the left inferior parietal gyrus (BA 40). Performance in the DTR was significantly associated with GMV in the

TABLE 3 | Comparative FCSRT performance between PD-MCI, PD-NC and HC.

	Controls[a]	PD-NC[b]	PD-MCI[c]	*ANOVA*	*Turkey's*	*Cohen's d*[*]
FCSRT						
Total free recall	26.7 ± 7.5	24.5 ± 7	16.7 ± 7	<0.001	[a–b]0.300; [b–c] <0.001	1.09
Total recall	41.6 ± 6.7	42.8 ± 5.1	35.1 ± 9.1	<0.001	[a–b]0.872; [b–c] <0.001	1.23
Delayed free recall	9.6 ± 3.1	9.4 ± 3	6.4 ± 3	<0.001	[a–b]0.952; [b–c] <0.001	1.03
Delayed total recall	14.2 ± 2.6	14.4 ± 1.8	11 ± 3	<0.001	[a–b]0.878; [b–c] <0.001	1.60

[a–b] *Controls vs. PD-NC.*
[b–c] *PD-NC vs. PD-MCI.*
**Cohen's d for PD-NC vs. PD-MCI comparisons.*

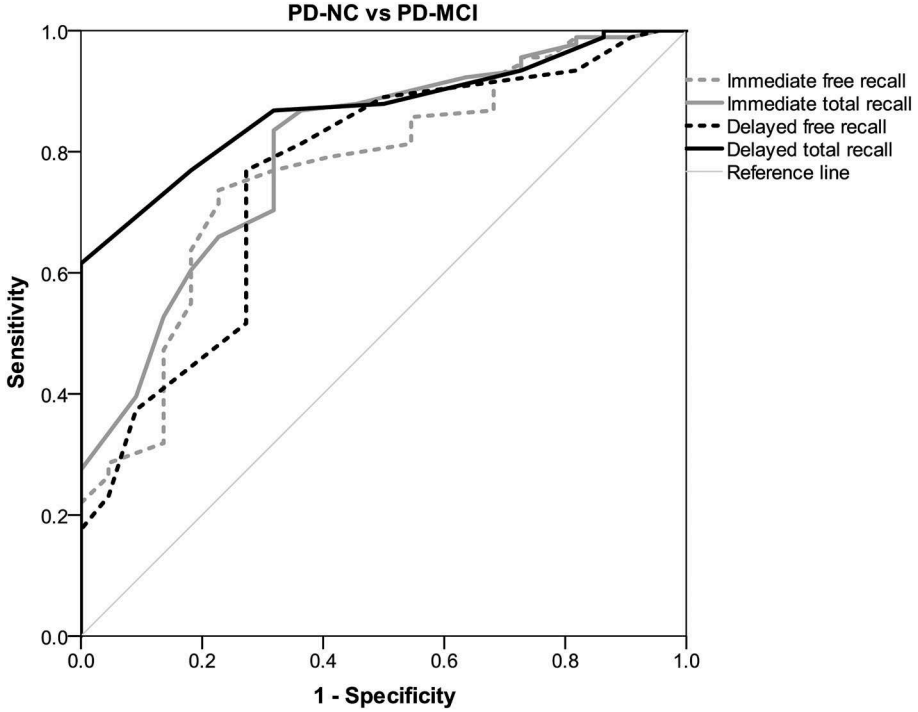

FIGURE 1 | Receiver operating characteristic (ROC) curves illustrating the discriminative properties of the FCSRT.

TABLE 4 | Results of the GMV voxel-based morphometry and MD-DTI analysis.

Anatomical region	Cluster size	*T* value	MNI coordinates (*x, y, z*)
VOXEL-BASED MORPHOMETRY ANALYSIS OF GMV			
FCSRT delayed free recall			
Left mid temporal (BA 21) / postcentral / superior temporal (BA 41)*	2,799	4.63	−60, −26, −5 −57, −21, 26 −57, −18, 8
Right mid temporal	551	3.25	60, −39, 9
Left inferior parietal (BA 40)	498	3.76	−47, −45, 45
Right superior frontal	371	3.55	21, 6, 59
FCSRT delayed total recall			
Right SMA / superior frontal (BA 6)*	1,832	4.44	17, 11, 66 21, 8, 60
Left mid temporal (BA 21)	606	3.90	−60, −26, −5
MD-DTI ANALYSIS			
FCSRT delayed free recall			
Left superior temporal (BA 22)	1,212	3.72	−46, −7, 1
Left inferior frontal (BA 47)	916	3.44	−40, 14, −5
Left hippocampus	884	4.41	−36, −21, −15
Left mid temporal	509	3.69	−56, −25, −5
Left middle temporal	246	4.23	−54, −59, 1
FCSRT delayed total recall			
Left inferior frontal*	4,158	4.04	−45, 12, 22
Left postcentral	2,307	3.70	−58, −11, 27
Left superior temporal	1,210	3.31	−62, −16, 1
Left inferior temporal	574	3.79	−40, −18, −19
Left superior temporal pole	553	4.12	−43, 13, −23

**Cluster level FWE corrected ($p < 0.05$).*

right supplementary motor area (SMA), in the right superior frontal gyrus (BA 6) (FWE corrected $p < 0.05$) and in the left mid temporal gyrus (BA 21) (see **Table 4**, **Figure 2** and **Supplementary Table 1**).

Voxel-wise MD multiple regression analysis with DFR and DTR showed a significant association between performance and MD in multiple fronto-temporal and parietal clusters predominantly located in the left hemisphere. Specifically, associations were found between worse DFR and increased MD in the left superior temporal gyrus (BA 22), the left inferior frontal gyrus (BA 47), the left hippocampus, the left mid temporal and the left middle temporal gyrus. Performance in the DTR was significantly associated with MD in the left inferior frontal (FWE corrected $p < 0.05$), the left postcentral, the left superior temporal gyrus, the left superior temporal pole, and the left inferior temporal gyrus (see **Table 4** and **Figure 3**).

Voxel-wise multiple regression analysis between GMV and MD with both IFR and ITR scores did not show any significant association surviving FWE correction.

DISCUSSION

In the present study we assessed performance in the FCSRT in non-demented PD and compared the performance in this task between PD-MCI and PD-NC. We also explored the discriminative properties of different subscores of the FCSRT and, in a subset of patients; we addressed the structural neuroimaging correlates of FCSRT performance by means of GMV-VBM and MD.

Our results show that, among other neuropsychological measures, PD-MCI patients perform significantly worse than PD-NC and healthy controls in the FCSRT. No significant differences were seen between PD-NC and healthy controls in this respect.

The FCSRT performance in the PD-MCI group was worse than that in PD-NC patients and controls in all the free and cued immediate and delayed recall conditions, suggesting difficulties at level of encoding, consolidation and retrieval. Interestingly, multiple measures of memory performance and specifically a single measure of episodic memory (DTR) correctly classified as PD-MCI up to 80% of the cases. These results emphasize the notion that beyond the prototypical frontal-executive deficits characterizing cognitive impairment in PD, amnestic difficulties are also inherent features of the cognitive changes observed in PD. Accordingly, this indicates that early to mid in the course of PD-MCI, not just frontal-executive, but also amnestic difficulties are present.

Neuroimaging data showed an association between widespread cortical (temporal, parietal and prefrontal) areas and FCSRT performance. Less GMV in mid temporal (BA 21),

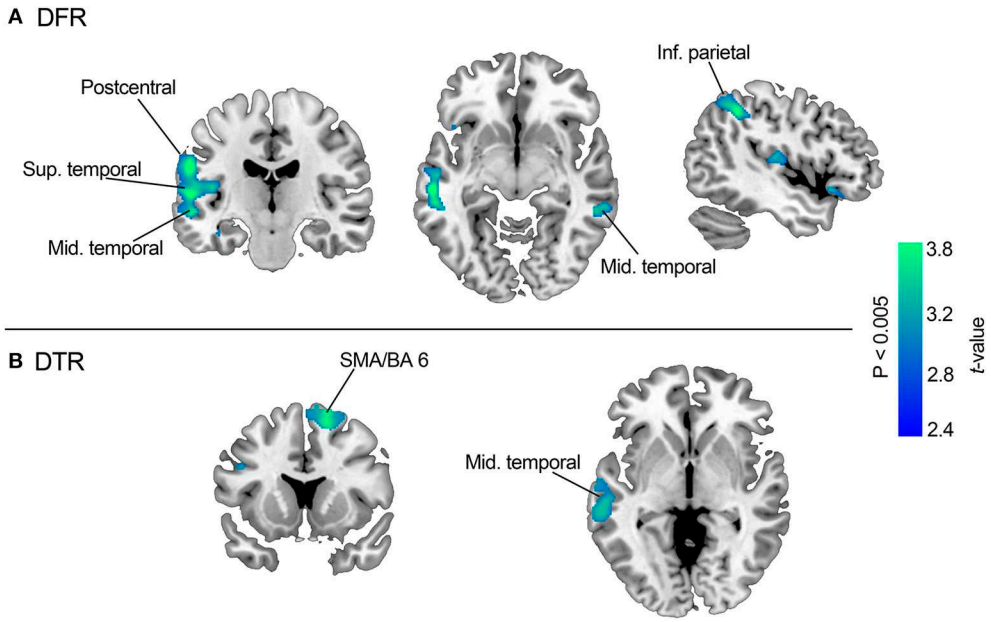

FIGURE 2 | Results of the VBM analysis. The slices show regions with significant GMV decreases in association with poorer FCSRT performance. Section **(A)** (top) depicts GMV associated with DFR performance; section **(B)** (bottom) depicts GMV associated with DTR performance. For depiction purposes results are showed with a $p < 0.005$ (uncorrected) and $k = 100$.

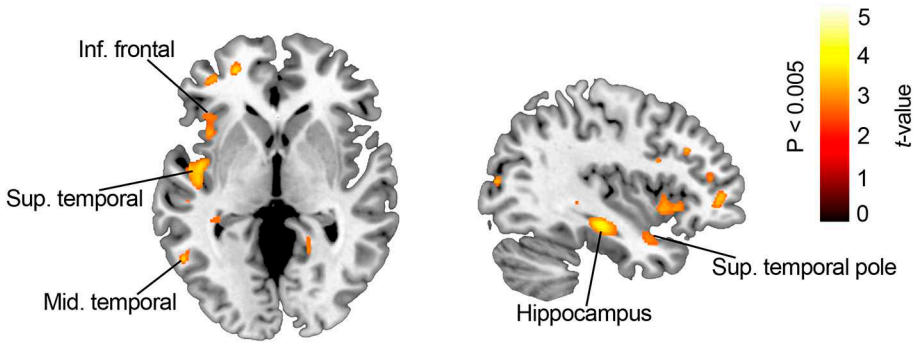

FIGURE 3 | Results of the voxelwise MD analysis. The slices show regions with significant MD increases in association with poorer FCSRT performance. For depiction purposes results are showed with a $p < 0.005$ (uncorrected) and $k = 100$.

the superior temporal, the supramarginal, the inferior parietal and the superior frontal gyrus was clearly associated with delayed free recall. Conversely, a more selective involvement of superior frontal regions was found for delayed total recall. All these areas have complex connections that can be grouped into (a) temporal and parietal areas more specialized in storage processes, and (b) prefrontal areas more specialized in retrieval processes (5, 24). Altogether, our results suggest that episodic memory deficits in PD-MCI are sub-served by dysfunction of parieto-temporal and prefrontal-related encoding, consolidation and retrieval processes. Similarly, MD-DTI analyses delineated the involvement of a set of fronto-temporal regions including the temporal pole and the hippocampus. All these regions are connected through the parahippocampal cingulum bundle, which extends along the parahippocampal gyrus, running from the anteromedial temporal lobe to the inferior parietal and occipital lobes (25). The parahippocampal cingulum bundle is closely linked to learning and episodic memory (26–28). Furthermore, microstructural white matter changes in this region have been consistently associated with episodic and recognition memory deficits in amnestic MCI and early AD patients (29–31).

In the only previous study that has analyzed the performance of FCSRT in PD patients with amnestic mild cognitive impairment, PD patients performed worse than healthy controls on delayed free recall, but no differences were found regarding delayed cued recall scores (10). This discrepancy could be explained by both the smaller sample size and the lack of

comparison between PD patients with and without MCI, as the study focused on comparing amnestic mild cognitive impairment with healthy controls and patients with amnestic mild cognitive impairment without PD. Although memory deficits in PD-MCI patients are widely considered to be caused by retrieval problems, studies using comprehensive neuropsychological batteries have shown that memory impairment in pre-dementia stages is also the consequence of encoding and storage failure (32). The ability of a memory test, such as the FCSRT, to assess both encoding and retrieval deficits would explain its appropriateness for screening PD-MCI accurately.

Recent studies in newly diagnosed and non-demented PD patients have also underlined the relevance and early development of cortical gray matter changes and DTI-MD alterations in hippocampal and parahippocampal structures as predictors of worsening cognition (33, 34).

This study has several limitations. First, there were fewer PD-MCI patients than PD-NC patients. However, the prevalence of PD-MCI is representative of the one observed in PD patients in the early to mid-stages of the disease. Second, we did not include in the study the measure "trial 1 free recall of the FCSRT" which would have given us more information about encoding. Third, the fact that we did not include patients with dementia limits our ability to see how this population performs on FCSRT. Fourth, not all the participants underwent neuroimaging, and although the number of PD patients with available neuroimaging was comparable to other VBM and DTI studies, imaging data was lacking for the healthy control group used in this study. And fifth, only a small subset of the clusters described in the neuroimaging analyses survived FWE correction.

To our knowledge, this is the first study to look for FCSRT cut-off scores in the screening of PD-MCI by using currently accepted MDS-TF criteria, providing evidence that this test is highly accurate for this purpose. Furthermore, we observed that FCSRT impairment correlates with structural changes in crucial areas of the semantic network and memory storage. The combination of these clinical and imaging findings supports the use of this test as an appropriate neuropsychological tool to detect PD-MCI patients with widespread cortical alterations.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité etico de Investigación Clinica—Sant Pau. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AH-B, JP, SM-H, and JK conception, design, data collection, data analysis, data interpretation, writing, and editing. JM-L, FS, RF-B, MB, HB-K, IA-B, JP-P, BP-S, AC, CI, and BG-A data collection and editing.

FUNDING

This work was partially supported by grants from La Marató TV3 (20142910, 2014/U/477); FIS (PI14/02058, PI15/00962); CIBERNED.

ACKNOWLEDGMENTS

The authors thank all the patients for their participation in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00240/full#supplementary-material

REFERENCES

1. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Move Disord.* (2011) 26:1814–24. doi: 10.1002/mds.23823
2. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. *Move Disord.* (2012) 27:349–56. doi: 10.1002/mds.24893
3. Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain.* (2007) 130:1787–98. doi: 10.1093/brain/awm111
4. Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain.* (2004) 127:550–60. doi: 10.1093/brain/awh067
5. Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci.* (2007) 8:976–87. doi: 10.1038/nrn2277
6. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney Multicenter Study of Parkinson's disease: the inevitability of dementia at 20 years. *Move Disord.* (2008) 23:837–44. doi: 10.1002/mds.21956
7. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol.* (2010) 9:1200–13. doi: 10.1016/S1474-4422(10)70212-X
8. Pagonabarraga J, Kulisevsky J. Cognitive impairment and dementia in Parkinson's disease. *Neurobiol Dis.* (2012) 46:590–6. doi: 10.1016/j.nbd.2012.03.029
9. Muslimović D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology.* (2005) 65:1239–45. doi: 10.1212/01.wnl.0000180516.69442.95

10. Costa A, Zabberoni S, Peppe A, Perri R, Fadda L, Iannarelli F, et al. Free and cued recall memory in Parkinson's disease associated with amnestic mild cognitive impairment. *PLoS ONE*. (2014) 9:e86233. doi: 10.1371/journal.pone.0086233
11. Das T, Hwang JJ, Poston KL. Episodic recognition memory and the hippocampus in Parkinson's disease: a review. *Cortex*. 113:191–209. doi: 10.1016/j.cortex.2018.11.021
12. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Move Disord*. (2007) 22:1689–707. doi: 10.1002/mds.21507
13. Goldman JG, Holden S, Ouyang B, Bernard B, Goetz CG, Stebbins GT. Diagnosing PD-MCI by MDS task force criteria: how many and which neuropsychological tests? *Move Disord*. (2015) 30:402–6. doi: 10.1002/mds.26084
14. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. (2007) 6:734–46. doi: 10.1016/S1474-4422(07)70178-3
15. Papp KV, Rentz DM, Mormino EC, Schultz AP, Amariglio RE, Johnson KA. Cued memory decline in biomarker-defined preclinical Alzheimer disease. *Neurology*. (2017) 88:1431–8. doi: 10.1212/WNL.0000000000003812
16. Quenon L, Dricot L, Woodard JL, Hanseeuw B, Gilis N, Lhommel R. Prediction of free and cued selective reminding test performance using volumetric and amyloid-based biomarkers of Alzheimer's disease. *J Int Neuropsychol Soc*. (2016) 22:991–1004. doi: 10.1017/S1355617716000813
17. Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, et al. Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. *Neurology*. (2007) 69:1859–67. doi: 10.1212/01.wnl.0000279336.36610.f7
18. Teichmann M, Epelbaum S, Samri D, Levy Nogueira M, Michon A, Hampel H, et al. Free and Cued Selective Reminding Test—accuracy for the differential diagnosis of Alzheimer's and neurodegenerative diseases: a large-scale biomarker-characterized monocenter cohort study (ClinAD). *Alzheimer's Dementia*. (2017) 13:913–23. doi: 10.1016/j.jalz.2016.12.014
19. Wagner M, Wolf S, Reischies FM, Daerr M, Wolfsgruber S, Jessen F, et al. Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. *Neurology*. (2012) 78:379–86. doi: 10.1212/WNL.0b013e318245f447
20. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology*. (1988) 38:900–3. doi: 10.1212/WNL.38.6.900
21. Lieberman MD, Cunningham WA. Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc Cognitive Affective Neurosci*. (2009) 4:423–8. doi: 10.1093/scan/nsp052
22. Martinez-Horta S, Sampedro F, Pagonabarraga J, Fernandez-Bobadilla R, Marin-Lahoz J, Riba J, et al. Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. *Brain Imaging Behav*. (2017) 11:1334–42. doi: 10.1007/s11682-016-9607-5
23. Vaquero L, Cámara E, Sampedro F, Pérez de los Cobos J, Batlle F, Fabregas JM, et al. Cocaine addiction is associated with abnormal prefrontal function, increased striatal connectivity and sensitivity to monetary incentives, and decreased connectivity outside the human reward circuit. *Addict Biol*. (2017) 22:844–56. doi: 10.1111/adb.12356
24. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*. (2009) 19:2767–96. doi: 10.1093/cercor/bhp055
25. Wu Y, Sun D, Wang Y, Wang Y, Ou S, Hayes DJ. Segmentation of the cingulum bundle in the human brain : a new perspective based on DSI tractography and fiber dissection study. *Front Neuroanat*. (2016) 10:1–16. doi: 10.3389/fnana.2016.00084
26. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: anatomy, function, and dysfunction. *Neurosci Biobehav Rev*. (2018) 92:104–27. doi: 10.1016/j.neubiorev.2018.05.008
27. Fernández-Matarrubia M, Matías-Guiu JA, Cabrera-Martín MN, Moreno-Ramos T, Valles-Salgado M, Carreras JL, et al. Episodic memory dysfunction in behavioral variant frontotemporal dementia: a clinical and FDG-PET study. *J Alzheimer's Dis*. (2017) 57:1251–64. doi: 10.3233/JAD-160874
28. Jones DK, Christiansen KF, Chapman RJ, Aggleton JP. Neuropsychologia Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking : implications for neuropsychological investigations. *Neuropsychologia*. (2013) 51:67–78. doi: 10.1016/j.neuropsychologia.2012.11.018
29. Metzler-Baddeley C, Hunt S, Jones DK, Leemans A, Aggleton JP, O'Sullivan MJ. Temporal association tracts and the breakdown of episodic memory in mild cognitive impairment. *Neurology*. (2012) 79:2233–40. doi: 10.1212/WNL.0b013e31827689e8
30. Metzler-Baddeley C, Jones DK, Steventon J, Westacott L, Aggleton JP, O'Sullivan MJ. Cingulum microstructure predicts cognitive control in older age and mild cognitive impairment. *J Neurosci*. (2012) 32:17612–9. doi: 10.1523/JNEUROSCI.3299-12.2012
31. Sarazin M, Chauviré V, Gerardin E, Colliot O, Kinkingnéhun S, De Souza LC, et al. The amnestic syndrome of hippocampal type in Alzheimer's disease: an MRI study. *J Alzheimer's Dis*. (2010) 22:285–94. doi: 10.3233/JAD-2010-091150
32. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. *Cognit Behav Neurol*. (2004) 17:195–200.
33. Carlesimo GA, Piras F, Assogna F, Pontieri FE, Caltagirone C, Spalletta G. Hippocampal abnormalities and memory deficits in Parkinson disease: a multimodal imaging study. *Neurology*. (2012) 78:1939–45. doi: 10.1212/WNL.0b013e318259e1c5
34. Duffau H. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain*. (2005) 128:797–810. doi: 10.1093/brain/awh423

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 02 June 2020
doi: 10.3389/fneur.2020.00420

The Discriminative Power of Different Olfactory Domains in Parkinson's Disease

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 26 January 2020
Accepted: 22 April 2020
Published: 02 June 2020

Citation:
Zhao Y, He Y, He R, Zhou Y, Pan H, Zhou X, Zhu L, Zhou X, Liu Z, Xu Q, Sun Q, Tan J, Yan X, Tang B and Guo J (2020) The Discriminative Power of Different Olfactory Domains in Parkinson's Disease. Front. Neurol. 11:420. doi: 10.3389/fneur.2020.00420

Background and Purpose: Olfactory dysfunction is one of the most common non-motor symptoms in Parkinson's disease (PD) preceding the motor symptoms for years. This study aimed to evaluate different olfactory domains in PD patients in comparison with healthy controls and to explore the relationships among olfactory deficit and other clinical manifestations in patients with PD.

Methods: Sniffin' Sticks test, which detects olfactory threshold, discrimination, and identification (TDI), were conducted in 500 PD patients and 115 controls. Furthermore, demographic and clinical data including motor and other non-motor symptoms were collected.

Results: In the single olfactory model, the identification test showed the area under the receiver operating characteristic (ROC) curve (AUC = 0.818), followed by threshold test (AUC = 0.731) and discrimination test (AUC = 0.723). Specifically, the identification test has a similar discriminative power as the TDI score (0.818 and 0.828, respectively, $p = 0.481$). In the integrated olfactory model involved with other non-motor manifestations, identification test scores performed as good as the TDI score in differentiating PD patients from controls (0.916 and 0.918, respectively, $p = 0.797$). In PD patients, age and cognition together explained 7.5% of the variance of the threshold score, while age, cognition, and gender accounted for the 15.2% explained variance of the discrimination score, while cognition, age, the ability of daily living, and gender together interpreted 11.1% of the variance of the identification score.

Conclusion: Our results indicated that the identification domain was the most practical olfactory factor in differentiating PD patients, and the combination of several different manifestations was better than a single symptom. Furthermore, the olfactory identification score may be associated with the ability of daily living.

Keywords: Parkinson's disease, Sniffin' sticks, olfactory dysfunction, Chinese population, olfactory domains

INTRODUCTION

The olfactory deficit is one of the most important non-motor symptoms that could appear to precede motor symptoms in Parkinson's disease (PD) (1–4). Olfactory dysfunction has been incorporated both in Movement Disorder Society clinical diagnostic criteria for PD and research criteria for prodromal PD, demonstrating its role in the diagnosis and prediction of PD (5–7). PD-associated smell dysfunction involves several domains of odor perception, i.e., detection threshold, identification, discrimination, and memory (8–10). The structural changes in the olfactory bulb, neurotransmitter system dysfunction, and inflammatory activity in the brain are all possible mechanisms of olfactory impairment in PD (11).

In terms of differentiating PD from control subjects, some studies have shown that the sensitivity and specificity of olfactory testing are better than other biomarkers, including single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) imaging of the dopamine (DA) transporter (12). In PD patients, different odor domains have relatively uniform impairment (13–15); however, data on the magnitude of different odor domains impairment and its ability in distinguishing PD from healthy control remains insufficient. Mahlknecht and colleagues investigated the power of olfactory function in distinguishing PD with a proper sample size, but the olfactory test was limited to the identification domain (16). Krismer and colleagues researched different olfactory domains, but the sample size is relatively small (17). Studies have indicated that combining olfactory tests and other prodromal non-motor features could recognize the risk of PD more efficiently (18); however, similar studies have never been conducted in Chinese PD populations.

In some studies, considered as an independent feature of PD, the olfactory deficit was not found to have significant associations with other symptoms of the disease (19). However, Mahlknecht and colleagues suggested that olfactory dysfunction may facilitate the development of PD from associated with rapid eye movement sleep behavior disorder (RBD) (20). There were still inconsistent conclusions about the relationship between olfactory function and other clinical manifestations in PD (21, 22).

In this study, we comprehensively evaluated the discriminative power of different olfactory domains, as well as in condition of combining other non-motor symptoms for early diagnosis of Chinese PD patients, and explored the potential relationship between olfactory deficit and other motor or non-motor features in Chinese PD patients. The aim was to identify the specific olfactory domain that has the best discriminative power and to ascertain if the olfactory deficits were independent features of PD.

METHODS

Participants

All the PD patients were recruited from the inpatients and outpatients of the Department of Neurology of Xiangya Hospital, Central South University, Hunan, China, between September 2014 and July 2017 at Parkinson's Disease & Movement Disorders Multicenter Database and Collaborative Network in China (PD-MDCNC, http://pd-mdcnc.com:3111/). Patients with idiopathic PD were diagnosed by no less than two experienced neurologists according to the United Kingdom Parkinson's Disease Brain Bank criteria (23). Healthy controls without neurological diseases were recruited from Health Management Centers of Xiangya Hospital. Participants with a history of respiratory system diseases, nasal or sinonasal diseases, and neurological or sinonasal surgery were excluded. The Medical Ethics Committee of Xiangya Hospital approved the study, and the participants gave informed consent for the investigation.

Assessments

Demographic data of all subjects were collected including gender, age, years of education, smoking status, and family history of PD. Seven domains of non-motor symptoms were evaluated by the Non-Motor Symptom Scale (NMSS) (24, 25), including cardiovascular, sleep/fatigue (26), mood, perceptual problems, gastrointestinal, urinary, and sexual issues. Cognitive functions were evaluated by the Mini-Mental State Examination (MMSE) (27, 28). Olfactory function was evaluated by the Sniffin' Sticks test.

In addition, age at onset, course of disease, and anti-PD medication were recorded for patients. Motor functions were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn Yahr Scale (H-Y). In addition, tremor score was measured by adding up scores of tremors at rest and action and postural tremor of hands from the UPDRS score, while bradykinesia score was calculated by score on finger taps, hand movements, rapid alternating movements of hands, and leg agility. Rigidity score was added up by the scores on rigidity of the neck, hands, and feet (29). Disease motor subtype (30) was classified as tremor-dominant (TD) phenotype when the ratio of tremor score and postural instability and gait difficulty (PIGD) score was no <1.5, whereas patients with a ratio of no more than 1.0 were defined to PIGD phenotype, and rest of patients belonged to the indeterminate phenotype. UPDRS is made up of four sections. Of them, UPDRS part II is characterized by questionnaires about self-evaluation of the activities of daily life, including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food. UPDRS part III was used to assess motor ability. A higher UPDRS score means more severe symptoms. A higher MMSE score means better cognitive condition. A higher NMSS score means more severe non-motor symptoms. Dyskinesia was affirmed by experienced neurologists (31).

Sniffin' Sticks

Sniffin' Sticks test consist of three parts, and they were tests for olfactory threshold, discrimination, and identification domain. Threshold and discrimination tests were conducted in the condition of subjects' eyes closed or blindfolded to prevent them from recognizing through the color of pen caps.

Both threshold and discrimination tests comprised 16 triplets' pens (total of 48 pens) numbered from 1 to 16. The color of three pen caps differed from each other, which are red, blue, and green. Identification tests were comprised of 16 common odors,

each of which presented 4 alternative odors to choose from. Odor threshold test could evaluate the ability to perceive the lowest concentration of an odorant by the subject, odor discrimination test measured the ability to differentiate two different odors, and odor identification test measured the ability to perceive and name the presented odor out of four alternative answers (32). The threshold score (*T*-score) equals the mean of the last four of seven scores, while the discrimination score (*D*-score) and identification score (*I*-score) equals the numbers of correct responses, respectively (33). The threshold, discrimination, and identification (TDI) score equals to the total score of three tests. The cutoff of the TDI score was 30.3 for ages from 16 to 35 years, 27.3 for ages from 36 to 55 years, and 19.6 for subjects older than 55 years, according to the standard of Hummel et al. (34). A higher score means better olfactory perception.

Statistics

All data were not normally distributed by the Kolmogorov–Smirnov test. All continuous variables were described as median and interquartile range (IQR), such as age, years of education, disease duration, UPDRS II, UPDRS III, MMSE, NMSS scores, and so on, while the categorical variables were described as a percentage, such as a gender, smoking status, dyskinesia status, and so on.

To establish which of the olfactory test is of service for differentiating PD patients from healthy controls, we calculated the receiver operating characteristic (ROC) curves for each of the olfactory tests separately and for any two or three tests combined. The single binary logistic regression models were developed with diagnosis as the dependent variable: using age, years of education with threshold score; then age, years of education with discrimination score; next age, years of education with identification score; and then age, years of education with any two or three of olfactory domain score added together. Afterward, integrated binary logistic regression models were developed with diagnosis as the dependent variable: using the above variable with each model combining other non-motor features, including MMSE and NMSS (cardiovascular, sleep/fatigue, mood, perceptual problems, gastrointestinal, urinary, and sexual issues). We graphed ROC curves with sensitivity and specificity estimates and corresponding area under the ROC curve (AUC), as well as positive likelihood ratios (LR+), negative likelihood ratios (LR–), positive predictive values (PPV), and negative predictive values (NPV). The ROC cutoffs were chosen when Youden's Index to get the maximum value. We compared AUC between TDI score single model and other single models by MedCalc software, as well as in the integrated models.

To compare demographic information and clinical features between PD with hyposmia and PD with normosmia, we used the analysis of chi-square tests for measurement data and non-parametric tests for continuous data.

To explore the contribution of different variables to the olfactory score, we used four stepwise multiple linear regression analyses (methods = stepwise, F-to-enter = 0.05, F-to-remove = 0.1). In the multiple linear regression analysis, independent variables include demographic factors (age, sex, educational years, smoking status), motor clinical symptoms (disease duration, UPDRS II points, UPDRS III points, dyskinesia), and other clinical symptoms (MMSE, NMSS). We did stepwise multiple linear regression analyses with threshold score, differentiation score, identification score, and TDI score as dependent variables, respectively.

Data were analyzed using SPSS version 18. $p < 0.05$ were considered significant.

TABLE 1 | Basic information and motor features in patients with Parkinson's disease (PD) and controls.

Items	Patients with PD ($n = 500$)	Normal controls ($n = 115$)
Sex (male %)	269 (53.8%)	50 (43.5%)
Age (year)	60 (52–67)	55 (49–64)
Educational years (year)	9 (6–12)	9 (9–12)
Smoking or not	144 (28.8%)	32 (27.8%)
Age of onset (year)	55 (47–62)	–
Duration(year)	3 (2–6)	–
UPDRS II	12 (9–17)	–
UPDRS III	26 (19–38)	–
H-Y stage	2 (1.5–3)	–

Data for continuous variables are presented as medial levels (IQRs).

TABLE 2 | Olfaction function in patients with Parkinson's disease (PD) and controls.

Items	Patients with PD ($n = 500$)	Normal controls ($n = 115$)	*p*-value*
Threshold score (T)	4.75 (2.25–7.00)	7.50 (5.50–9.25)	0.001
Discrimination score (D)	7 (5–9)	10 (8–11)	<0.001
Identification score (I)	7 (5–9)	10 (9–12)	<0.001
TD score	12.50 (8.50–15.75)	16.75 (14.50–19.50)	<0.001
TI score	11.87 (7.75–15.50)	17.75 (15.50–20.75)	<0.001
DI score	14 (11–18)	20 (17–23)	<0.001
TDI score	19.50 (14.25–24.25)	28.25 (24.50–31.00)	<0.00

**p-value was calculated after adjustment of age and educational years.*

RESULTS

Demographic and Clinical Characteristics

In total, we recruited 500 patients (male, 269, 53.8%) with a median age at assessments of 60 years and a median age at onset of 55 years. The 115 healthy controls (male, 50, 43.5%) have a median age of 55 years. Median disease duration of PD was 3 years, whereas the median UPDRS II and UPDRS III scores were 12 and 26, respectively (**Table 1**).

Olfactory Test Alone

Of the 500 included patients, 343 patients had hyposmia, whereas 157 patients had a normal sense of smell, according to the standard of Hummel's (34). The median TDI score of PD patients was 19.50 and that of the control subjects was 28.25. Median threshold, discrimination, and identification scores of

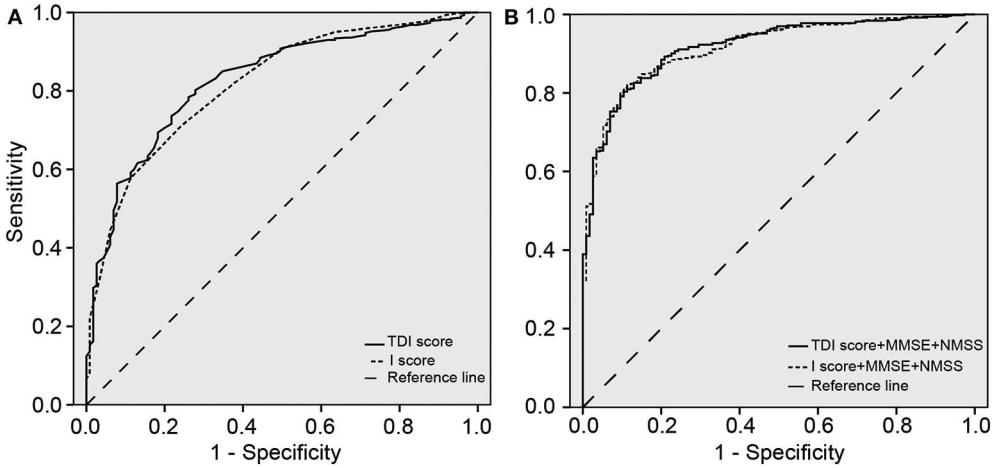

FIGURE 1 | Receiver operating characteristic (ROC) curves. **(A)** Relating sensitivity and specificity for olfactory threshold, discrimination, and identification (TDI) and I scores in differentiating Parkinson's disease (PD) patients from healthy controls. **(B)** Relating sensitivity and specificity for olfactory TDI and I scores combining Mini-Mental State Examination (MMSE) and Non-Motor Symptom Scale (NMSS) in differentiating PD patients from healthy controls.

PD patients were 4.75, 7, and 7, respectively, while control subjects were 7.50, 10, and 10, respectively. After age and years of education correction, every single olfactory score of PD patients were significantly lower than controls subjects (all $p \leq 0.001$), as well as the total TDI score (**Table 2**).

ROC curves of the TDI and I scores were drawn by SPSS (**Figure 1**). Every model had diagnostic value between these two groups (all $p < 0.05$). AUC of different olfactory domains and their sensitivity, specificity, LR+, LR–, PPV, and NPV in single olfactory models and integrated models were reported (**Table 3**).

In single models, the TDI score (AUC = 0.828) and identification score (AUC = 0.818) were better than threshold score (AUC = 0.731) and discrimination score (AUC = 0.723) at differentiating PD patients from controls. By comparing AUC between identification score with TDI score in single models, there was no significant difference of discriminative power between TDI and identification scores (difference between areas = 0.01, z statistic = 0.706, $p = 0.481$).

Olfactory Test Combining Other Non-motor Features

Compared to control subjects, PD patients had poorer performance on other non-motor features, including cognitive, cardiovascular, sleep/fatigue, emotional, perceptual problems, gastrointestinal, and urinary and sexual dysfunction. These integrated models were much better than the corresponding single olfactory models (**Figure 1**; **Table 3**). Similarly, with a combination of other non-motor features mentioned above, the TDI score (AUC = 0.918) and the identification test score (AUC = 0.916) were slightly better than threshold score (AUC = 0.890) and discrimination score (AUC = 0.886) at differentiating PD patients from controls. Identification and TDI scores have no significant difference of discriminative power (difference between areas = 0.002, z statistic = 0.257, $p = 0.797$).

Olfaction in PD Patients

Of the 500 included PD patients, 343 (68.6%) patients had hyposmia. The median TDI scores for the hyposmia and normosmia groups were 16.50 and 24.75 points, respectively. Median threshold, median discrimination, and median identification scores of the normosmia group were 7.25, 9, and 9. By contrast, those of the hyposmia group were 3.50, 6.5, and 6 (**Table S1**).

Compared with the normosmia group, we observed that patients in the hyposmia group were significantly more often men, with fewer educational years, more severe rigidity symptom, and more severe cognitive problems ($p < 0.05$).

Finally, stepwise multiple linear regression analysis removed confounding factors whose $p \geq 0.05$. By multiple regression analysis, the final models interpreted 16.0% of variance in TDI score ($p < 0.001$, $R^2 = 0.160$, **Table S2a**), 7.5% of the variance in threshold score ($p < 0.001$, $R^2 = 0.075$, **Table S2b**), 15.2% of the variance in discrimination score ($p < 0.001$, $R^2 = 0.152$, **Table S2c**), 11.1% of the variance in identification score ($p < 0.001$, $R^2 = 0.111$, **Table S2d**). The variance inflation factor (VIF) showed no evidence of a multicollinearity problem among the independent variables. Older age, lower MMSE scores, and male sex were significantly associated with lower TDI scores. Older age and lower MMSE scores were associated with lower threshold scores. Older age, lower MMSE scores, and male sex were significantly associated with lower discrimination scores. Lower MMSE, older age, higher UPDRS II score, and male sex were associated with lower identification scores.

DISCUSSION

In our study, first of all, we confirmed olfactory deficit in PD, including the impairment of olfactory threshold, discrimination, and identification ability. Meanwhile, the olfactory identification test distinguished best between PD patients and control subjects among three olfactory tests in the single or integrated models.

TABLE 3 | Area under the receiver operating characteristic curve (AUC) of different olfactory domains and their sensitivity, specificity, LR+, LR–, PPV, and NPV in single olfactory models and integrated models.

Models	Olfactory tests	Sensitivity	Specificity	PPV	NPV	LR+	LR–	AUC	*p*1-values	*p*2-values
(A) SINGLE MODELS*										
	TDI score	0.802	0.722	0.891	0.259	2.885	0.274	0.828	<0.05	
	TD score	0.692	0.748	0.884	0.235	2.746	0.412	0.772	<0.05	<0.05
	TI score	0.796	0.730	0.894	0.262	2.948	0.279	0.819	<0.05	0.306
	DI score	0.738	0.748	0.893	0.251	2.929	0.350	0.815	<0.05	0.239
	T score	0.612	0.783	0.888	0.229	2.820	0.496	0.731	<0.05	<0.05
	D score	0.544	0.791	0.875	0.215	2.603	0.576	0.723	<0.05	<0.05
	I score	0.712	0.757	0.894	0.247	2.930	0.380	0.818	<0.05	0.481
(B) INTEGRATED MODELS**										
	TDI score	0.803	0.896	0.971	0.515	7.721	0.220	0.918	<0.05	
	TD score	0.846	0.835	0.956	0.559	5.127	0.184	0.902	<0.05	<0.05
	TI score	0.838	0.870	0.965	0.556	6.446	0.186	0.913	<0.05	0.298
	DI score	0.783	0.913	0.975	0.495	9.000	0.238	0.913	<0.05	0.374
	T score	0.756	0.887	0.966	0.459	6.690	0.275	0.890	<0.05	<0.001
	D score	0.707	0.922	0.975	0.424	9.064	0.318	0.886	<0.05	<0.001
	I score	0.813	0.896	0.971	0.528	7.817	0.209	0.916	<0.05	0.797

p1-values show the significance of differentiating PD patients from controls calculated by SPSS. p2-values were calculated by MedCalc software. p2-values of (A) were calculated by comparing AUC between each score with TDI score in single models, p2-values of (B) were calculated by comparing AUC between each score with TDI score in integrated models. p < 0.05 were considered significant.

**Single models were built upon each corresponding olfactory test, after adjustment of age and educational years.*

***Integrated models were built upon each corresponding olfactory test and MMSE, NMSS, after adjustment of age and educational years.*

PPV, positive predictive values; NPV, negative predictive values; LR+, positive likelihood ratios; LR–, negative likelihood ratios; T, threshold; D, Discrimination; I, Identification.

Previous studies have compared different olfactory domains in discriminating patients with PD and control subjects, as well as other neurodegenerative diseases. For instance, Berendse et al. (35) supported that odor identification was better in differentiating patients with PD from control subjects than the odor discrimination task. Then, the same group (14) supported that a combination of an olfactory threshold test and a 16-item olfactory identification test scored the best in sensitivity and specificity in discriminating between PD patients and controls. A meta-analysis (36) once concluded that the olfactory threshold test should be included in the test for subclinical patients with PD. Hummel et al. (37) reported that PD patients performed relatively well in the olfactory threshold task, while they perform poorly in olfactory discrimination and identification compared to other diseases, such as sinonasal disease, postinfectious and posttraumatic status, and so on.

In the background of these published studies, our current study had resembled but more detailed implications. In our study, a combination of olfactory identification and discrimination tests could not improve the diagnostic accuracy of a single olfactory identification test, which was partly in accordance with other studies (14, 35). However, combining three olfactory tests did slightly improve the diagnostic value, which still supported that olfactory deficit was based on the dysfunction of multiple olfactory domains (38).

However, besides PD, the olfactory deficit was also the feature of other causes (39). Therefore, we usually combine other non-motor manifestations to distinguish between PD patients and controls. In our integrated model of differentiation, no matter which single or combined odor tests were chosen to represent for olfactory function, olfactory dysfunction was always included in the model. In summary, we may believe that the olfactory test was an essential part of the PD clinical studies, especially in a large scale of screening of PD or in PD modeling establishment. It was consistent with the study of Antje et al. (40) that the combination of olfactory tests and other tests may constitute a screening tool for PD.

When the entire three olfactory tasks represented olfactory function, its corresponding integrated model had the highest AUC based on the corresponding ROC curve, whereas the AUC of an integrated model constructed by odor identification was not significantly lower. Therefore, in large scales of studies containing an olfactory evaluation of patients with PD, we may believe that the olfactory identification test was sufficient enough to represent olfactory function in an integrated model to differentiated PD patients from controls subjects. After all, the entire olfactory test was more time and energy consuming. In large-scale studies, it can save researchers' and patients' time and energy to accomplish other necessary non-motor manifestations in the integrated model.

According to the standard of olfactory dysfunction (34), patients with olfactory deficit were more often men, had fewer educational years, and presented more severe cognitive problems. Liu et al. (41) also supported that male patients had significantly more deficits in olfaction than female patients. It may also suggest that not only the age of subjects but also gender and educational years should be considered into the future standard of olfactory deficits.

Moreover, in the olfactory threshold and discrimination domains, other clinical manifestations did not remain in their corresponding regression models. It indicated that olfactory threshold and discrimination domains were independent features of PD, just like tremors (42), which were not clearly related to other PD manifestations. We found a lack of relationship between dyskinesia and olfactory function in PD, which was consistent with the conclusion of Stephenson et al. (43) that there was no significant effect of olfactory performance on the risk of motor complications, such as falls and dyskinesia. This result indicated that olfactory threshold and discrimination deficit developed and progressed before the development of motor symptoms and maintained throughout the process of the disease (44). However, in the olfactory identification domain, the UPDRS II score was included in its regression model except for age, gender, and MMSE score, which partly resembled the observations in other studies that disease stage explained part of the variance in olfactory discrimination score of PD patients (13, 35). The lesser UPDRS II scores were associated with higher identification scores, which indicated that the odor identification task is associated with the activities of daily living. As previous studies pointed out, the performance of daily activities can be limited and conditioned by non-motor symptoms (45). An alternative explanation for the association between the odor identification and daily activities, but not UPDRS III, is methodological, since the former section is mainly based on a patient/caregiver self-completed questionnaire, whereas UPDRS III is based on professional rating (46). Therefore, it deserves further replication in larger cohorts in the future.

In conclusion, our study showed that the odor identification domain can basically represent olfactory functions in discriminating PD patients from controls, suggesting a specific aspect of one symptom may be an adequate representation of this certain symptom, which was energy and time saving especially in data collection of a large cohort study. Our data also indicated that the combination of different kinds of symptoms would be better in discriminating PD than a single symptom. Furthermore, the olfactory threshold and discrimination domains were independent features of PD, while worse daily living ability was associated with lower olfactory identification scores.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Xiangya Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YZha, YH, JG, BT, and QS designed the experiments. YZha, YH, RH, YZho, XiZ, XuZ, LZ, ZL, QX, JT, and XY collected clinical data and performed phenotype analyses. YZha, YH, and HP analyzed the data and reference management. YZha, YH, and JG wrote and revised the manuscript. All authors contributed to read and approved the submitted version.

FUNDING

This study was supported by the National Key Research and Development Program of China (Grant No. 2017YFC0909100; No. 2016YFC1306000) to JG and BT, the Central Public-Interest Scientific Institution Basal Research Fund of Chinese Academy of Medical Sciences (Grant No. 2018-12M-HL-025) to JG, the National Natural Science Foundation of China (Grant No. 81873785) to JG, Science and Technology Major Project of Hunan Provincial Science and Technology Department (2018SK1030) to JG, the innovative team program from Department of Science & Technology of Hunan Province (No. 2019RS1010) to JG, and the Innovation-Driven Team Project (No. 2020CX016) from Central South University.

ACKNOWLEDGMENTS

The authors thank all the PD patients and healthy controls for participating in the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00420/full#supplementary-material

REFERENCES

1. Masala C, Solla P, Liscia A, Defazio G, Saba L, Cannas A, et al. Correlation among olfactory function, motors' symptoms, cognitive impairment, apathy, and fatigue in patients with Parkinson's disease. *J Neurol.* (2018) 265:1764–71. doi: 10.1007/s00415-018-8913-9
2. Cecchini MP, Federico A, Zanini A, Mantovani E, Masala C, Tinazzi M, et al. Olfaction and taste in Parkinson's disease: the association with mild cognitive impairment and the single cognitive domain dysfunction. *J Neural Transm.* (2019) 126:585–95. doi: 10.1007/s00702-019-01996-z
3. Haehner A, Masala C, Walter S, Reichmann H, Hummel T. Incidence of Parkinson's disease in a large patient cohort with idiopathic smell and taste loss. *J Neurol.* (2019) 266:339–45. doi: 10.1007/s00415-018-9135-x
4. Solla P, Masala C, Liscia A, Piras R, Ercoli T, Fadda L, et al. Sex-related differences in olfactory function and evaluation of possible confounding factors among patients with Parkinson's disease. *J Neurol.* (2020) 267:57–63. doi: 10.1007/s00415-019-09551-2

5. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord.* (2015) 30:1600–11. doi: 10.1002/mds.26431
6. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* (2015) 30:1591–601. doi: 10.1002/mds.26424
7. He R, Yan X, Guo J, Xu Q, Tang B, Sun Q. Recent advances in biomarkers for Parkinson's disease. *Front Aging Neurosci.* (2018) 10:305. doi: 10.3389/fnagi.2018.00305
8. Chen H, Shrestha S, Huang X, Jain S, Guo X, Tranah GJ, et al. Olfaction and incident Parkinson disease in US white and black older adults. *Neurology.* (2017) 89:1441–7. doi: 10.1212/WNL.0000000000004382
9. Dall'Antonia I, Sonka K, Dusek Olfaction P, Colour Vision. What can they tell us about Parkinson's disease? *Prague Med Rep.* (2018) 119:85–96. doi: 10.14712/23362936.2018.8
10. Nielsen T, Jensen MB, Stenager E, Andersen AD. The use of olfactory testing when diagnosing Parkinson's disease - a systematic review. *Dan Med J.* (2018) 65:A5481.
11. Doty RL. Olfaction in Parkinson's disease and related disorders. *Neurobiol Dis.* (2012) 46:527–52. doi: 10.1016/j.nbd.2011.10.026
12. Deeb J, Shah M, Muhammed N, Gunasekera R, Gannon K, Findley LJ, et al. A basic smell test is as sensitive as a dopamine transporter scan: comparison of olfaction, taste DaTSCAN in the diagnosis of Parkinson's disease. *QJM.* (2010) 103:941–52. doi: 10.1093/qjmed/hcq142
13. Tissingh G, Berendse HW, Bergmans P, DeWaard R, Drukarch B, Stoof JC, et al. Loss of olfaction in *de novo* and treated Parkinson's disease: possible implications for early diagnosis. *Mov Disord.* (2001) 16:41–6. doi: 10.1002/1531-8257(200101)16:1<41::aid-mds1017>3.0.co;2-m
14. Boesveldt S, de Muinck Keizer RJ, Knol DL, Wolters E, Berendse HW. Extended testing across, not within, tasks raises diagnostic accuracy of smell testing in Parkinson's disease. *Mov Disord.* (2009) 24:85–90. doi: 10.1002/mds.22325
15. Fullard ME, Morley JF, Duda JE. Olfactory dysfunction as an early biomarker in Parkinson's disease. *Neurosci Bull.* (2017) 33:515–25. doi: 10.1007/s12264-017-0170-x
16. Mahlknecht P, Pechlaner R, Boesveldt S, Volc D, Pinter B, Reiter E, et al. Optimizing odor identification testing as quick and accurate diagnostic tool for Parkinson's disease. *Mov Disord.* (2016) 31:1408–13. doi: 10.1002/mds.26637
17. Krismer F, Pinter B, Mueller C, Mahlknecht P, Nocker M, Reiter E, et al. Sniffing the diagnosis: olfactory testing in neurodegenerative parkinsonism. *Parkinsonism Relat Disord.* (2017) 35:36–41. doi: 10.1016/j.parkreldis.2016.11.010
18. Siderowf A, Jennings D, Eberly S, Oakes D, Hawkins KA, Ascherio A, et al. Impaired olfaction and other prodromal features in the Parkinson at-risk syndrome study. *Mov Disord.* (2012) 27:406–12. doi: 10.1002/mds.24892
19. Verbaan D, Boesveldt S, van Rooden SM, Visser M, Marinus J, Macedo MG, et al. Is olfactory impairment in Parkinson disease related to phenotypic or genotypic characteristics? *Neurology.* (2008) 71:1877–82. doi: 10.1212/01.wnl.0000336651.48596.c7
20. Mahlknecht P, Iranzo A, Hogl B, Frauscher B, Muller C, Santamaria J, et al. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. *Neurology.* (2015) 84:654–8. doi: 10.1212/WNL.0000000000001265
21. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology.* (1988) 38:1237–44. doi: 10.1212/WNL.38.8.1237
22. Haehner A, Boesveldt S, Berendse HW, Mackay-Sim A, Fleischmann J, Silburn PA, et al. Prevalence of smell loss in Parkinson's disease–a multicenter study. *Parkinsonism Relat Disord.* (2009) 15:490–4. doi: 10.1016/j.parkreldis.2008.12.005
23. Gibb WR, Lees AJ. The relevance of the lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (1988) 51:745–52. doi: 10.1136/jnnp.51.6.745
24. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord.* (2007) 22:1901–11. doi: 10.1002/mds.21596
25. Wang G, Hong Z, Cheng Q, Xiao Q, Wang Y, Zhang J, et al. Validation of the Chinese non-motor symptoms scale for Parkinson's disease: results from a Chinese pilot study. *Clin Neurol Neurosurg.* (2009) 111:523–6. doi: 10.1016/j.clineuro.2009.02.005
26. Xiang YQ, Xu Q, Sun QY, Wang ZQ, Tian Y, Fang LJ, et al. Clinical features and correlates of excessive daytime sleepiness in Parkinson's disease. *Front Neurol.* (2019) 10:121. doi: 10.3389/fneur.2019.00121
27. Wang YQ, Tang BS, Yan XX, Chen ZH, Xu Q, Liu ZH, et al. A neurophysiological profile in Parkinson's disease with mild cognitive impairment and dementia in China. *J Clin Neurosci.* (2015) 22:981–5. doi: 10.1016/j.jocn.2014.11.030
28. Yang Y, Tang BS, Guo JF. Parkinson's disease and cognitive impairment. *Parkinsons Dis.* (2016) 2016:6734678. doi: 10.31193/ssap.01.978750979 1011
29. Janvin C, Aarsland D, Larsen JP, Hugdahl K. Neuropsychological profile of patients with Parkinson's disease without dementia. *Dement Geriatr Cogn Disord.* (2003) 15:126–31. doi: 10.1159/000068483
30. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Mov Disord.* (2006) 21:1123–30. doi: 10.1002/mds.20897
31. Zhou X, Guo J, Sun Q, Xu Q, Pan H, Yu R, et al. Factors associated with dyskinesia in Parkinson's disease in mainland China. *Front Neurol.* (2019) 10:477. doi: 10.3389/fneur.2019.00477
32. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses.* (1997) 22:39–52. doi: 10.1093/chemse/22.1.39
33. Rumeau C, Nguyen DT, Jankowski R. How to assess olfactory performance with the Sniffin' Sticks test[(R)]. *Eur Ann Otorhinolaryngol Head Neck Dis.* (2016) 133:203–6. doi: 10.1016/j.anorl.2015.08.004
34. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol.* (2007) 264:237–43. doi: 10.1007/s00405-006-0173-0
35. Boesveldt S, Verbaan D, Knol DL, Visser M, van Rooden SM, van Hilten JJ, et al. A comparative study of odor identification and odor discrimination deficits in Parkinson's disease. *Mov Disord.* (2008) 23:1984–90. doi: 10.1002/mds.22155
36. Mesholam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. *Arch Neurol.* (1998) 55:84–90. doi: 10.1001/archneur.55.1.84
37. Whitcroft KL, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. *Laryngoscope.* (2016) 127:291–5. doi: 10.1002/lary.26229
38. Martzke JS, Kopala LC, Good KP. Olfactory dysfunction in neuropsychiatric disorders: review and methodological considerations. *Biol Psychiatry.* (1997) 42:721–32. doi: 10.1016/S0006-3223(96) 00442-8
39. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol.* (2008) 63:159–66. doi: 10.1002/ana.21293
40. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. Olfactory loss may be a first sign of idiopathic Parkinson's disease. *Mov Disord.* (2007) 22:839–42. doi: 10.1002/mds.21413
41. Liu R, Umbach DM, Peddada SD, Xu Z, Troster AI, Huang X, et al. Potential sex differences in nonmotor symptoms in early drug-naive Parkinson disease. *Neurology.* (2015) 84:2107–15. doi: 10.1212/WNL.00000000000 01609
42. Louis ED, Tang MX, Cote L, Alfaro B, Mejia H, Marder K. Progression of parkinsonian signs in Parkinson disease. *Arch Neurol.* (1999) 56:334–7. doi: 10.1001/archneur.56.3.334
43. Stephenson R, Houghton D, Sundararajan S, Doty RL, Stern M, Xie SX, et al. Odor identification deficits are associated with increased risk of neuropsychiatric complications in patients with Parkinson's disease. *Mov Disord.* (2010) 25:2099–104. doi: 10.1002/mds. 23234

44. Kim JY, Lee WY, Chung EJ, Dhong HJ. Analysis of olfactory function and the depth of olfactory sulcus in patients with Parkinson's disease. *Mov Disord.* (2007) 22:1563–6. doi: 10.1002/mds.21490
45. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, Group NV. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord.* (2011) 26:399–406. doi: 10.1002/mds.23462
46. Song J, Fisher BE, Petzinger G, Wu A, Gordon J, Salem GJ. The relationships between the unified Parkinson's disease rating scale and lower extremity functional performance in persons with early-stage Parkinson's disease. *Neurorehabil Neural Repair.* (2009) 23:657–61. doi: 10.1177/1545968309332878

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 02 July 2020
doi: 10.3389/fneur.2020.00532

Modeling of Electric Fields in Individual Imaging Atlas for Capsular Threshold Prediction of Deep Brain Stimulation in Parkinson's Disease: A Pilot Study

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Background: Modeling of deep brain stimulation electric fields and anatomy-based software might improve post-operative management of patients with Parkinson's disease (PD) who have benefitted from subthalamic nucleus deep brain stimulation (STN-DBS).

Objective: We compared clinical and software-guided determination of the thresholds for current diffusion to the pyramidal tract, the most frequent limiting side effect in post-operative management of STN-DBS PD patients.

Methods: We assessed monopolar reviews in 16 consecutive STN-DBS PD patients and retrospectively compared clinical capsular thresholds, which had been assessed according to standard clinical practice, to those predicted by volume of tissue activated (VTA) model software. All the modeling steps were performed blinded from patients' clinical evaluations.

Results: At the group level, we found a significant correlation ($p = 0.0001$) when performing statistical analysis on the z-scored capsular thresholds, but with a low regression coefficient ($r = 0.2445$). When considering intra-patient analysis, we found significant correlations ($p < 0.05$) between capsular threshold as modeled with the software and capsular threshold as determined clinically in five patients (31.2%).

Conclusions: In this pilot study, the VTA model software was of limited assistance in identifying capsular thresholds for the whole cohort due to a large inter-patient variability. Clinical testing remains the gold standard in selecting stimulation parameters for STN-DBS in PD.

Keywords: Parkinson's disease, deep brain stimulation, subthalamic nucleus, capsular prediction, volume of tissue activated

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico

Reviewed by:
Chengyuan Wu, Thomas Jefferson University, United States
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *16 February 2020*
Accepted: *13 May 2020*
Published: *02 July 2020*

Citation:
Béreau M, Kibleur A, Bouthour W, Tomkova Chaoui E, Maling N, Nguyen TAK, Momjian S, Vargas Gomez MI, Zacharia A, Bally JF, Fleury V, Tatu L, Burkhard PR and Krack P (2020) Modeling of Electric Fields in Individual Imaging Atlas for Capsular Threshold Prediction of Deep Brain Stimulation in Parkinson's Disease: A Pilot Study. Front. Neurol. 11:532. doi: 10.3389/fneur.2020.00532

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for advanced Parkinson's disease (PD) (1). Numerous prospective and open-label studies have demonstrated benefits of DBS for motor and non-motor signs, as well as improved quality of life in PD (2–6). Initial DBS programming is based on establishing and ranking contacts that exhibit the larger therapeutic window, calculated as the difference between stimulation amplitudes at persistent side effects and meaningful improvement of rigidity (7). Side effects are either related to stimulation of the sensorimotor part of the STN on its own, or to current diffusion to neighboring structures including limbic or cognitive parts of the STN, internal capsule (IC), pallidothalamic tract, as well as the cerebellothalamic tract (8–10). Thus, outcome greatly depends on the electrode position and precise knowledge of the surrounding anatomy (11, 12). The most prominent side effect is linked to current diffusion to the corticospinal and corticonuclear tracts (CSNT) within the IC [see **Figure 1**, adapted from Hamani et al. (13)]. Current diffusion to the CSNT induces tonic muscle contractions, mainly in the face area and fine muscles of the hand, and less frequently in the lower limbs (14), likely reflecting somatotopic arrangement of CSNT fibers in the vicinity of the STN. Dysarthria is related to current diffusion to corticonuclear fibers that innervate muscles involved in speech, i.e., lips, tongue, pharynx, and larynx muscles (8, 14, 15). Although basic algorithms for programming and troubleshooting sessions have been continuously refined, computational modeling of DBS electric fields may potentially provide new information that could be of further aid in DBS programming sessions (16). These models allow calculation of the volume of tissue activated (VTA), for instance, using a diffusion tensor-based finite element neurostimulation model (17). Recently, new directional electrodes have been developed according to multiple independent current source control technology (18, 19). As opposed to conventional electrodes, directional electrodes are characterized by the ability to steer current toward three distinct directions, not only along the *Z*-axis (*Z*), but also in the horizontal plane (*X*, *Y*) (18, 19). While conventional electrodes generate a spherical electrical field that encompasses all adjacent structures equally, directional contacts produce a limited and adaptable electrical field biased toward the active contact (18, 19). Few studies have outlined the potential interest of directional electrodes for patient management (7, 20, 21). Importantly, the number of individual stimulation parameter combinations increases substantially with the use of directional electrodes, making post-operative management more challenging and time-consuming. Thus, clinical tools including VTA models could be helpful in identifying effective parameter settings for each patient more easily. The goal of this pilot study was to evaluate the usefulness of a new software designed for clinical practice in the refinement of DBS parameters.

Abbreviations: STN, subthalamic nucleus; DBS, deep brain stimulation; VTA, volume of tissue activated; CTA, capsular threshold amplitude; VTA-CTA, VTA modeled capsular threshold amplitude; IC, internal capsule; CSNT, corticospinal and corticonuclear tracts.

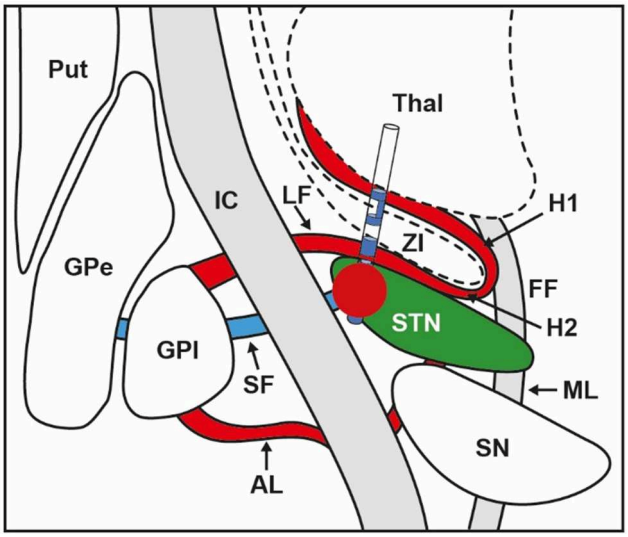

FIGURE 1 | Anatomical relations between electrode position within the STN, volume of tissue activated (VTA) illustrated by the red bubble, and surrounding structures. STN, subthalamic nucleus; VTA, volume of tissue activated; GPi, globus pallidus internus; GPe, globus pallidus externus; Put, putamen; SN, substantia nigra; Thal, thalamus; IC, internal capsule; SF, subthalamic fasciculus; AL, ansa lenticularis; LF, lenticularis fasciculus; ZI, zona incerta; ML, medial lemniscus; FF, fields of Forel; H1, H1 field of Forel; H2, H2 field of Forel. Adapted from Hamani et al. (13).

MATERIALS AND METHODS

Population

We enrolled 16 STN-DBS PD patients. All patients were implanted with Cartesia directional devices (Boston Scientific, Valencia, CA) (20, 22) that each contained one ventral and one dorsal non-segmented ring (rings 1, 8 and 9, 16 for left and right STN, respectively), and two segmented rings in between (one ventral and one dorsal segmented ring), each containing three contacts (contacts 2, 3, 4 and 5, 6, 7 for left STN ventral and dorsal segmented rings, and contacts 10, 11, 12 and 13, 14, 15 for right STN ventral and dorsal segmented rings, respectively).

Clinical Evaluation

We assessed monopolar reviews according to standard clinical practice during one session after a 12-h overnight withdrawal from dopaminergic medication as described previously (23). We tested each electrode separately and kept the contralateral STN-DBS ON for the patient's comfort. We predefined a frequency of 130 Hz and pulse width of 60 μs for all sessions. We determined the capsular threshold amplitude (CTA) by testing for each side the two non-segmented rings, the two segmented rings in between on omnidirectional stimulation (vertical steering), as well as the six directional contacts from the two segmented rings (horizontal steering), which added up to a total of 10 measures per electrode. We gradually increased current amplitude by steps of 0.5 mA until the appearance of a visible facial or limb contraction. Then, we decreased the current amplitude in steps of 0.1 mA until the exact contraction threshold was reached (23).

Capsular Threshold Modeling

We used the Guide™ XT software for all steps detailed in this section. MB performed manual refinement of the IC volume and AK performed capsular threshold determination on the images using the VTA. We carried out all the modeling procedures blinded from patients' clinical evaluations, with anonymization of the patient's name on the MRI images. We first performed coregistration of the preoperative 3D T1, specific STN visualization T2 MRI sequences (3D T2 SPACE in sagittal orientation, FOV 450 mm, TR/TE 2400/225 ms, flip angle 120°), and the post-operative CT scan. Then, an automatic anatomical segmentation of the STN and the IC was computed. For each patient, we manually refined the IC using both the T2 image and the Schaltenbrand atlas (24), in order to extend IC boundaries to the cerebral peduncles in the midbrain, a process that enables visualization of the CSNT in the vicinity of the STN. Manual refinement of the IC was the longest step of the process, and took 10–15 min per patient. Lead trajectories were automatically reconstructed from the CT scans. We subsequently adjusted the lead orientations determined from the post-operative sagittal and coronal topograms using the radiopaque marker embedded in each lead. Finally, we sequentially built VTAs by increasing the current amplitude virtually for each contact tested until the VTA border touched the capsule border. We labeled the corresponding amplitude as the CTA of the VTA model (VTA-CTA).

Statistics

For each patient, we computed statistical analysis on the data to test the correlation between the clinical thresholds and the modeled capsular threshold. We used the corrcoef function of the Matlab (Mathworks, Natick, MA) statistical toolbox. We also performed a correlation analysis on the whole group and normalized the data to compare patients by using the z-scores. We then reported the resulting p and correlation coefficients r for each patient. Lastly, we refined the analysis for the patients who did not show any significant effect by separating the analysis for the left and right hemispheres to see if the effect had been hidden by one side where the modeling predicted the capsular threshold poorly.

RESULTS

Population

We tested 29/32 STNs from 16 consecutive patients (6 women and 10 men). Three STNs were ruled out given that no capsular side effects were observed between 0 and 6 mA, and CTA was not determined. Mean patient age was 60.1 ± 2.0 years, and mean PD duration was 10.5 ± 1.2 years. Mean presurgical MDS-UPDRS part III scores in off and on drug conditions were 47.1 ± 4.0 and 14.3 ± 2.0, respectively, corresponding to a mean improvement of 70.2 ± 3.5%. Monopolar reviews took place between 2.5 and 6 months after surgery (mean, 3.7 ± 0.2), and mean levodopa equivalent daily dose (LEDD) before and after DBS were 1182.8 ± 115.8 mg and 452.6 ± 88.4 mg, respectively, corresponding to a mean reduction of dopaminergic therapy dosage of 60.9 ± 7.5% (25).

Clinical Threshold vs. Capsular Threshold

At the group level, when performing statistical analysis on the z-scored capsular thresholds, we found a significant correlation ($p = 0.0001$), with a relatively low regression coefficient ($r = 0.2445$). When considering intra-patient analysis, we found significant ($p < 0.05$) correlations between capsular threshold as modeled with the software and capsular threshold as determined clinically in five patients (see **Figure 2**). In these five patients, the resulting mean correlation coefficient was 0.70 (±0.16). Furthermore, in one additional patient, there was a tendency toward significant correlation ($p = 0.0746$).

Vertical and Horizontal Virtual Current Steering

We analyzed virtual current steering in patients for whom CTA was correctly predicted by the VTA-CTA model. We arbitrarily chose the constant parameter settings as follows: 3 mA, 60 μs, and 130 Hz. Then, we built a VTA according to the software and successively considered the vertical and horizontal virtual current steering (see **Figure 3**). Vertical virtual current steering consisted of representing the lead position and overlap between the VTA and STN automatically segmented by the software. Horizontal virtual current steering consisted of representing the lead position and overlap between VTA, STN, and IC in the best ring previously identified, in order to rank its contacts from lowest to highest capsular threshold.

DISCUSSION

In this pilot study, we tested the hypothesis that VTA model software could help clinicians with capsular threshold determination in STN-DBS PD patients during post-operative management. To do this, we retrospectively compared predicted capsular thresholds modeled using the software with clinical capsular thresholds clinically assessed during the monopolar review in 16 STN-DBS PD patients.

At the group level, we found a significant correlation ($p = 0.0001$), between image-defined and clinically defined capsular thresholds, but the regression coefficient was relatively low ($r = 0.2445$ points). Intra-patient analyses showed significant ($p < 0.05$) correlations in only 5/16 patients (31.2%), meaning that for each of these patients, contacts were accurately ranked by the software from the lowest to the highest capsular threshold. The low regression coefficient in analysis at the group level can therefore be explained by some variability of the tool as confirmed in intra-patient analyses, with an excellent matching in some, but not all, of the patients.

Although the small size of this pilot study, a lack of statistical power, and a learning curve effect for both clinical and VTA-modeled capsular threshold measurements must be mentioned first, factors related to the different steps needed for capsular threshold modeling may be considered one by one to explain the discrepancy observed between global and intra-patient analyses.

Coregistration between preoperative 3D T1, specific STN visualization T2 MRI sequences, and the post-operative CT scan was performed automatically by the software. Visual inspection

Patient	*nb of thresholds*	*R*	*P*
P1	12	0.9061	0.0001
P2	20	0.6164	0.0038
P3	19	0.4985	0.0298
P4	20	0.6686	0.0013
P5	7	0.8257	0.0221
P6	20	0.4074	0.0746
P7	18	-0.1751	0.4871
P8	10	-0.3423	0.3330
P9	15	-0.1507	0.5919
P10	18	0.0631	0.8035
P11	18	0.3688	0.1320
P12	13	0.3591	0.2282
P13	20	0.2461	0.2955
P14	7	0.2513	0.5867
P15	19	0.2783	0.2487
P16	10	0.1457	0.5640
mean	**15.4**	**0.31**	**0.28**
std	**4.8**	**0.35**	**0.26**

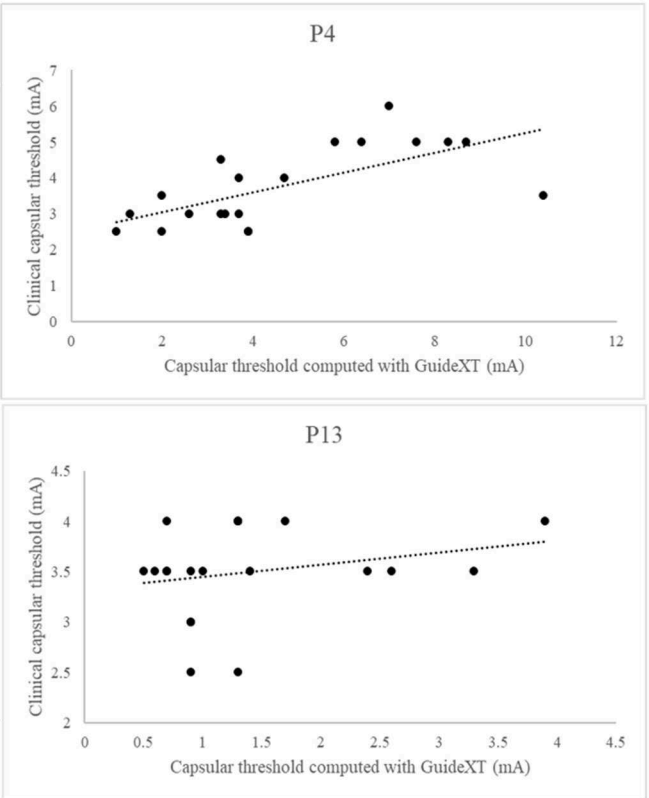

FIGURE 2 | Table of correlation coefficients and associated *p*-values between Guide™ XT predicted capsular threshold and clinically measured threshold. Examples of scatterplots from one good correlation (P4) and one bad correlation result (P13). The number of calculated capsular thresholds per patients is indicated in the first column.

of coregistration quality was systematically performed before anatomical segmentation. Coregistration was correctly done in all cases and does not appear to be a critical factor contributing to the variability observed between patients.

Anatomical segmentation in the software does not include the CSNT *per se* but the IC, which does not integrate the diencephalic–mesencephalic junction. Thus, in order to determine the VTA-modeled capsular threshold, we manually drew the CSNT in the vicinity of the STN, by extending the automatically segmented IC from the diencephalon to the mesencephalon. Nevertheless, this step, the longest of the capsular threshold modeling, was not highly reproducible, which might broadly explain the variability observed from one patient to another. One would expect that capsular threshold as modeled with the software depends on the distance between the internal border of the CSNT drawn manually and the lead where the VTA is built. In the near future, tractography could be a great help to reduce this bias (24–27).

Determination of the electrode position from the post-operative CT scan and coregistration of the CT with the T1 pre-operative MRI is also associated with some intrinsic limitations of the software, namely, electrode position reconstruction from the CT artifact, brainshift pre- and post-implantation, and T1 image artifacts.

Lead orientations that have been performed manually from the topograms (sagittal and coronal views) may also constitute a source of error in the modeling as they can change the determination of the capsular threshold between the three contacts at each depth of directional contact. Methods such as 3D rotational fluoroscopy and CT scan-based algorithms have been developed to determine orientation automatically with higher precision and less variability, but had not been included in the software at the time of the study (28, 29).

The VTA model used by the software for capsular threshold modeling is a critical point to discuss. The model makes several assumptions that influence its threshold estimates. The first is a simplified electrical medium that represents the brain as a homogenous and isotropic volume conductor. This means that every point in the model has the same electrical conductivity value (homogeneous) and that those conductivity values are the same in every direction (isotropic). Heterogenous and anisotropic estimates of tissue conductivity are an area of ongoing research (30). Furthermore, we do not know the amplitude range for which the model is valid (power dispersion in biological anisotropic tissue). Additionally, all axons in the model are assumed to be equal in diameter, perfectly straight, and running perpendicular to the trajectory of the lead. The diameter of an axon is known to strongly influence its excitability

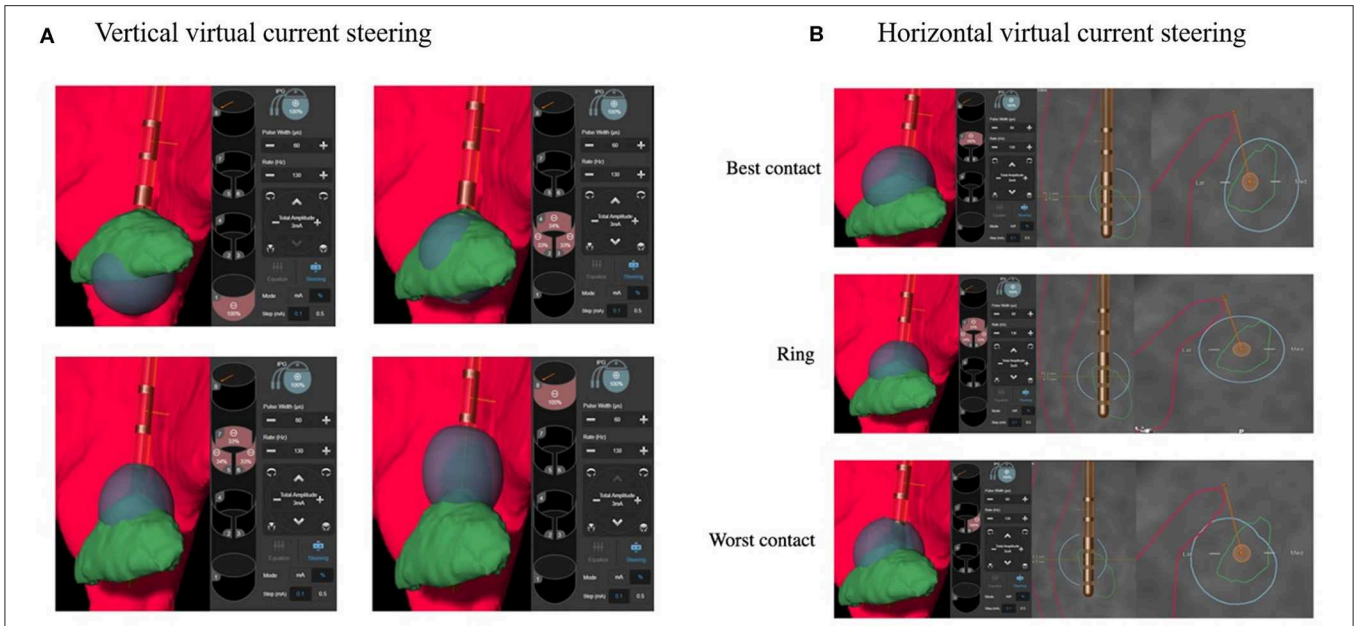

FIGURE 3 | Example of vertical **(A)** and horizontal **(B)** virtual current steering with Guide™ XT. Vertical virtual current steering **(A)** shows that contact 1 is within the ventral part of the STN, and contact 8 is outside the STN. Ventral (2–4) and dorsal (5–7) rings are within the ventromedial and dorsolateral parts of the STN, respectively. According to horizontal virtual current steering **(B)**, modeled VTA of contact 7, "the best contact," does not touch the CSNT, whereas modeled VTA of either the ring or contact 6, "the worst contact," shows current diffusion touching the CSNT. VTA (in blue): volume of tissue activated modeled by Guide™ XT, STN (in green): subthalamic nucleus automatically segmented by Guide™ XT, internal capsule (in red) including CSNT manually refined: corticospinal and corticonuclear tracts.

(31), and the IC exhibits axons with a range of diameters (32). Furthermore, the trajectory and orientation of the axons also influence the excitability of the model. These model assumptions were instituted both to simplify the model and to tend toward the side of excitability.

Despite the multiple sources of error and current limitations discussed above, the software could offer the opportunity to obtain a more comprehensive anatomy-based approach for directional DBS and potentially less time-consuming bedside management for a given patient. Although clinical capsular threshold determination remains the gold standard, VTA model software could be a useful tool for the refinement of parameter settings in patients for whom the clinical threshold and VTA modeled threshold are congruent (see **Figure 3**). Vertical virtual current steering, which consists of arbitrarily choosing constant parameter settings, for instance: 3 mA, 60 μs, 130 Hz, and drawing the VTA for the four electrode levels may help clinicians to visualize the lead position within the STN and the overlap between the VTA and the sensorimotor part of the STN. This virtual approach may help to more rapidly determine the best anatomical match out of four levels for stimulation from ventral to dorsal, targeting the sensorimotor STN for optimal improvement in parkinsonism. Horizontal virtual current steering, which consists of arbitrarily choosing constant parameter settings, for instance: 3 mA, 60 μs, 130 Hz, and drawing the VTA for the three contacts contained in one segmented ring, could illustrate overlap between the VTA, STN, and IC in order to rank contacts from the lowest to the highest capsular threshold. Such information could be valuable in determining visually guided and anatomically based horizontal steering strategies, when stimulation is limited by side effects related to current diffusion to surrounding fiber systems such as the CSNT. This approach could also be extended to other DBS side effects such as paresthesia, which is related to current diffusion to the medial lemniscus.

CONCLUSION

In this pilot study, software that superimposes VTA and anatomy was of limited assistance in the identification of capsular thresholds for the whole cohort due to large inter-patient variability. So far, this new tool allows visualization of the IC, but it has not been designed to identify corticonuclear and corticobulbar tracts inside this very large structure. Integration of fiber tracking tools that can visualize these fiber systems might lead to a better match between visual modeling and clinical testing, which would be an important first step to a more automatized post-operative management of DBS. Currently, clinical testing remains the gold standard in selecting stimulation parameters for STN-DBS in PD. Further studies with larger sample sizes remain mandatory to assess the usefulness of VTA model software for practical management of STN-DBS PD patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical approval was not required as per local legislation and national guidelines. The patients/participants [legal guardian/next of kin] provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB, AK, WB, PK, and PB: conception and organization of the research project. MB, AK, WB, ET, and AZ: execution of the research project. MB, AK, and WB: writing of the first draft of the manuscript. ET, NM, TN, SM, MV, AZ, JB, LT, PB, and PK: review and critique of the manuscript. All authors: contributed to the article and approved the submitted version.

FUNDING

This work was supported by an unrestricted fund from Boston Scientific.

ACKNOWLEDGMENTS

We thank all participants for taking part in this study. We thank Emmanuel Laurent for his assistance in creating **Figure 1**. We thank Jennifer Dobson for proofreading this manuscript.

REFERENCES

1. Krack P, Martinez-Fernandez R, Del Alamo M, Obeso JA. Current applications and limitations of surgical treatments for movement disorders. *Mov Disord.* (2017) 32:36–52. doi: 10.1002/mds.26890
2. Krack P, Batir A, Van Blercom N, Chabardès S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med.* (2003) 349:1925–34. doi: 10.1056/NEJMoa035275
3. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med.* (2006) 355:896–908. doi: 10.1056/NEJMoa060281
4. Schuepbach WMM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med.* (2013) 368:610–22. doi: 10.1056/NEJMoa1205158
5. Lhommée E, Klinger H, Thobois S, Schmitt E, Ardouin C, Bichon A, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. *Brain.* (2012) 135:1463–77. doi: 10.1093/brain/aws078
6. Lhommée E, Wojtecki L, Czernecki V, Witt K, Maier F, Tonder L, et al. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *Lancet Neurol.* (2018) 17:223–31. doi: 10.1016/S1474-4422(18)30035-8
7. Dembek TA, Reker P, Visser-Vandewalle V, Wirths J, Treuer H, Klehr M, et al. Directional DBS increases side-effect thresholds-A prospective, double-blind trial. *Mov Disord.* (2017) 32:1380–8. doi: 10.1002/mds.27093
8. Krack P, Fraix V, Mendes A, Benabid A-L, Pollak P. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. *Mov Disord.* (2002) 17 Suppl 3:S188–97. doi: 10.1002/mds.10163
9. Pollak P, Krack P, Fraix V, Mendes A, Moro E, Chabardes S, et al. Intraoperative micro- and macrostimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord.* (2002) 17(Suppl 3):S155–61. doi: 10.1002/mds.10158
10. Castrioto A, Volkmann J, Krack P. Postoperative management of deep brain stimulation in Parkinson's disease. *Handb Clin Neurol.* (2013) 116:129–46. doi: 10.1016/B978-0-444-53497-2.00011-5
11. Petersen M V, Lund TE, Sunde N, Frandsen J, Rosendal F, Juul N, et al. Probabilistic versus deterministic tractography for delineation of the cortico-subthalamic hyperdirect pathway in patients with Parkinson disease selected for deep brain stimulation. *J Neurosurg.* (2017) 126:1657–68. doi: 10.3171/2016.4.JNS1624
12. Wodarg F, Herzog J, Reese R, Falk D, Pinsker MO, Steigerwald F, et al. Stimulation site within the MRI-defined STN predicts postoperative motor outcome. *Mov Disord.* (2012) 27:874–9. doi: 10.1002/mds.25006
13. Hamani C, Florence G, Heinsen H, Plantinga BR, Temel Y, Uludag K, et al. Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. *eNeuro.* (2017) 4:e0140-17.2017. doi: 10.1523/ENEURO.0140-17.2017
14. Tommasi G, Krack P, Fraix V, Le Bas J-F, Chabardes S, Benabid A-L, et al. Pyramidal tract side effects induced by deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry.* (2008) 79:813–9. doi: 10.1136/jnnp.2007.117507
15. Mahlknecht P, Akram H, Georgiev D, Tripoliti E, Candelario J, Zacharia A, et al. Pyramidal tract activation due to subthalamic deep brain stimulation in Parkinson's disease. *Mov Disord.* (2017) 32:1174–82. doi: 10.1002/mds.27042
16. McIntyre CC, Foutz TJ. Computational modeling of deep brain stimulation. *Handb Clin Neurol.* (2013) 116:55–61. doi: 10.1016/B978-0-444-53497-2.00005-X
17. Butson CR, McIntyre CC. Current steering to control the volume of tissue activated during deep brain stimulation. *Brain Stimul.* (2008) 1:7–15. doi: 10.1016/j.brs.2007.08.004
18. Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain.* (2014) 137:2015–26. doi: 10.1093/brain/awu102
19. Contarino MF, Bour LJ, Verhagen R, Lourens MAJ, de Bie RMA, van den Munckhof P, et al. Directional steering: a novel approach to deep brain stimulation. *Neurology.* (2014) 83:1163–9. doi: 10.1212/WNL.0000000000000823
20. Timmermann L, Jain R, Chen L, Maarouf M, Barbe MT, Allert N, et al. Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson's disease (the VANTAGE study): a non-randomised, prospective, multicentre, open-label study. *Lancet Neurol.* (2015) 14:693–701. doi: 10.1016/S1474-4422(15)00087-3
21. Steigerwald F, Müller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neurostimulation device. *Mov Disord.* (2016) 31:1240–3. doi: 10.1002/mds.26669
22. Bronstein JM, Tagliati M, McIntyre C, Chen R, Cheung T, Hargreaves EL, et al. The rationale driving the evolution of deep brain stimulation to constant-current devices. *Neuromodulation.* (2015) 18:85–8; discussion 88–9. doi: 10.1111/ner.12227
23. Bouthour W, Wegrzyk J, Momjian S, Péron J, Fleury V, Tomkova Chaoui E, et al. Short pulse width in subthalamic stimulation in Parkinson's disease: a randomized, double-blind study. *Mov Disord.* (2018) 33:169–73. doi: 10.1002/mds.27265
24. Schaltenbrand W. *Atlas for Stereotaxy of the Human Brain*. Stuttgart: Thieme (1977).
25. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord.* (2010) 25:2649–53. doi: 10.1002/mds.23429
26. Calabrese E. Diffusion tractography in deep brain stimulation surgery: a review. *Front Neuroanat.* (2016) 10:45. doi: 10.3389/fnana.2016.00045
27. Rodrigues NB, Mithani K, Meng Y, Lipsman N, Hamani C. The emerging role of tractography in deep brain stimulation: basic principles and current applications. *Brain Sci.* (2018) 8:23. doi: 10.3390/brainsci8020023

28. Reinacher PC, Krüger MT, Coenen VA, Shah M, Roelz R, Jenkner C, et al. Determining the orientation of directional deep brain stimulation electrodes Using 3D rotational fluoroscopy. *AJNR Am J Neuroradiol.* (2017) 38:1111–6. doi: 10.3174/ajnr.A5153
29. Hellerbach A, Dembek TA, Hoevels M, Holz JA, Gierich A, Luyken K, et al. DiODe: directional orientation detection of segmented deep brain stimulation leads: a sequential algorithm based on CT imaging. *Stereotact Funct Neurosurg.* (2018) 96:335–41. doi: 10.1159/000494738
30. Howell B, McIntyre CC. Role of soft-tissue heterogeneity in computational models of deep brain stimulation. *Brain Stimul.* (2017) 10:46–50. doi: 10.1016/j.brs.2016.09.001
31. McIntyre CC, Grill WM. Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. *J Neurophysiol.* (2002) 88:1592–604. doi: 10.1152/jn.2002.88.4.1592
32. Innocenti GM, Vercelli A, Caminiti R. The diameter of cortical axons depends both on the area of origin and target. *Cereb Cortex.* (2014) 24:2178–88. doi: 10.1093/cercor/bht070

Conflict of Interest: MB, WB, and SM received travel and accommodation funding from Boston Scientific unrelated to the research covered in this article. PK reports grants and fees for lecturing from Boston Scientific (paid to employer) and grants from Swiss National Science Foundation, ROGER DE SPOELBERCH Foundation, Bertarelli Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, and the Michael J. Fox Foundation, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 31 July 2020
doi: 10.3389/fneur.2020.00779

Embarrassment and Shame in People With Parkinson's Disease: A New Tool for Self-Assessment

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Edited by:
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Reviewed by:
Simon J. G. Lewis, Brain and Mind Research Institute, Australia
Chien Tai Hong, Taipei Medical University, Taiwan

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *22 April 2020*
Accepted: *24 June 2020*
Published: *31 July 2020*

Citation:
Fleury V, Catalano Chiuvé S, Forjaz MJ, Di Marco M, Messe M, Debove I, Angulo J, Hariz G-M, Burkhard PR, Martinez-Martin P, Rodriguez-Blazquez C and Krack P (2020) Embarrassment and Shame in People With Parkinson's Disease: A New Tool for Self-Assessment. Front. Neurol. 11:779. doi: 10.3389/fneur.2020.00779

Shame and embarrassment related to Parkinson's disease (PD) are rarely addressed in clinical practice nor studied in neuroscience research, partly because no specific tool exists to detect them in PD.

Objective: To develop a self-applied assessment tool of shame and embarrassment specifically related to PD or its treatment, to promptly identify the presence and severity of these two emotions in PD.

Methods: Identification and selection of relevant items were obtained from the collection of PD patients' opinions during support groups and interviews. Several further items were added following a literature review. Subsequently, a two-phase pilot study was performed for identification of ambiguous items and omissions, and to obtain preliminary data on acceptability, reliability, validity and relevance of the new scale (SPARK).

Results: A total of 105 PD patients were enrolled in the study. Embarrassment was reported in 85% of patients, while shame was present in 26%. Fifteen percent of patients did not describe any shame or embarrassment. On average, the intensity of these two emotions was low with a marked floor effect in SPARK items and subscales. However, SPARK total score inter-individual variability was important (range 1–84 out of 99). Acceptability and quality of data were satisfactory with no floor or ceiling effects (2.9% each) or missing data. Internal consistency (Cronbach's alpha) was 0.94 for total score and 0.73–0.87 for subscales. The scale correlated $\geq$0.60 with instruments measuring related constructs. Content validity was satisfactory. SPARK total score strongly correlated with impaired health-related quality of life ($r_S = 0.81$), the propensity to feel embarrassed or ashamed ($r_S = 0.68$ and 0.66, respectively), and anxiety ($r_S = 0.72$) and depression ($r_S = 0.63$) levels. Moderate to high correlations were observed between SPARK total score and apathy ($r_S = 0.46$) and a more pronounced personality trait directed toward harm avoidance ($r_S = 0.46$). No significant differences in SPARK

scores were found by sex, education level, PD duration, Hoehn and Yahr stages or PD phenotype.

Conclusion: Preliminary analysis of psychometric properties suggests that SPARK could be an acceptable and reliable instrument for assessing shame and embarrassment in PD. SPARK could help healthcare professionals to identify and characterize PD-induced shame and embarrassment.

Keywords: parkinson's disease, shame, embarrassment, questionnaire, non-motor symptoms

INTRODUCTION

Patients affected with Parkinson's disease (PD) perceive non-motor symptoms as serious challenges and barriers to a satisfying quality of life (1). PD-related shame and embarrassment are rarely addressed in clinical practice nor studied in neuroscience research (2). The prevalence of shame and embarrassment in PD is unknown and no specific tool exists to detect and measure them in PD.

Shame and embarrassment are two negative self-conscious emotions associated with painful states, where the self (i.e., the affective representation of one's identity) is focal in attention. The individual believes that she/he has failed to meet appropriate standards of conduct, and thinks that she/he has done so in the eyes of others. No consensus has been reached on how shame and embarrassment differ (3). Intuitively, for English speakers at least, shame and embarrassment are members of the same family and the differences between the two are subtle. The establishment of explicit differential criteria to distinguish shame from embarrassment has proven difficult in the literature. Shame is psychologically more challenging than embarrassment, marked by intensely painful negative self-evaluation commonly exhibited by an individual upon realizing that she/he has committed an offense or violated an important (usually social) norm. Shame is more long-lasting and produces more damage to self-esteem. Shame is also associated with a more serious breach of fundamental norms or rules. Upon contemplating the transgression, the individual concludes that she/he is incapable, worthless, fundamentally flawed, reprehensible, and worthy of contempt. Whereas, embarrassment is about minor transgressions or failures in role enactments or failure in one's ability to present her/himself to others in an ideal manner. Embarrassment is associated with a motivational response directed toward the preservation of one's social reputation, rather than a concern for others' well-being and a need to make amends, as in guilt, or with a concern for oneself with a need to hide as in shame (4).

Abbreviations: BDI-II, Beck Depression Inventory II; LEDD, levodopa equivalent daily dose; MDS-UPDRS motor score, motor scale of Movement Disorder Society Unified Parkinson's Disease Rating Scale; MOCA, MOntreal Cognitive Assessment; PD, Parkinson's disease; PD, phenotype: TR, tremor dominant, AR, akinetorigid form; PDQ-8, Parkinson's Disease Questionnaire 8 items (Health-related quality of life); PFQ-2, Personal Feelings Questionnaire (shame and embarrassment scale); SD, standard deviation; STAI, State-Trait Anxiety Inventory; SPARK, Shame and embarrassment in PARKinson's disease questionnaire; TPQ, Tridimensional Personality Questionnaire.

Shame and embarrassment in PD may emerge from different sources: (1) PD symptoms, especially visible motor symptoms but also non-motor symptoms; (2) increasing physical dependence and need for help induced by PD; and (3) deteriorated body image (2). Consequences of PD-related shame on health-related quality of life are probably important but have not been studied in detail. Consequently, shame and embarrassment should be actively explored and addressed in patients affected with PD.

To do so, a specific tool to detect and measure these emotions in PD is needed. We therefore created a self-applied questionnaire rating shame and embarrassment specifically induced by PD or its treatment, to promptly identify the presence and severity of these emotions in PD patients as well as to better understand what clinically promotes these emotions. The objective of this pilot study is to describe the development process of this rating scale, including its conception and the analysis of its relevance and adequateness to the target population as well as its psychometric properties.

MATERIALS AND METHODS

The study was approved by the Geneva Ethics Committee. All participants gave their informed written consent.

Identification and Selection of Items of Interest (Phase 1)

Identification of relevant items was based on a set of opinions and perspectives expressed by 44 PD patients during support groups and informal interview. The inclusion criteria for participants was a diagnosis of PD. The only exclusion criteria was the presence of dementia. The content of the expressed views was subsequently analyzed and reduced to a set of qualitative themes or meaning units. This preliminary phase of the study was from our point of view an essential component, as it allowed us to better understand shame and embarrassment related to the disease in PD patients. In addition, a comprehensive review of the literature on shame and stigmatization in PD was carried out. It revealed that the utterances expressed by patients were, generally, on the mark. Following further understanding obtained from this review process, new items were added to the emerging scale. Extra items were implemented from two scales: 2 items from the PDQ-39 (5) and 6 items from the Stigma Scale for Chronic Illness 8-item version (6). Data obtained during phase 1 provided the construction of a preliminary scale including 26 items. Responses reflected a scale of intensity (from 0 to 3: 0 = not at all, 1 = a little,

2 = moderately, 3 = very much). The scale was called Shame and embarrassment in Parkinson's disease (SPARK).

Construction of the First Draft of the Scale and Pre-testing (Phase 2)

The preliminary SPARK scale was applied to 26 patients with a diagnosis of PD based on the United Kingdom Parkinson's Disease Society Brain Bank criteria (7). Patients were recruited from the Neurology Department of the Geneva University Hospital. PD patients with any kind of dementia (including mild and moderate) defined by a Montreal cognitive assessment (MOCA) score (8) <26/30 were excluded. A cognitive debriefing questionnaire was administered after completion of the SPARK scale, asking patients about their opinions on the relevance of the subject for their medical follow-up, length of the questionnaire, simplicity to respond, embarrassment with any item, omissions and global view. This was done to identify ambiguities, redundancies and omissions as well as to obtain preliminary data of acceptability and relevance of the subject. This questionnaire consists of 8 items with two possible answers (yes or no). A space for text where subjects could express their opinion was also available for each question.

Reformulation and Construction of the Second Version of the Scale

The preliminary scale was adapted after the analysis of the cognitive debriefing questionnaire. The new scale was reviewed by five experts in PD and four experts in questionnaire validation. A second version of the SPARK questionnaire was created, with 33 items grouped into 6 subscales: (1) Shame and embarrassment arising from PD symptoms (items 1–5, 8, 11–16, 20); (2) Shame and embarrassment arising from the increasing physical dependence and need for help induced by PD (items 7, 10, 18); (3) Shame and embarrassment arising from the deteriorated body image (items 6, 9, 17, 19, 21); (4) Consequence of related shame and embarrassment on patient's self-esteem (items 22, 25, 26); (5) Stigmatization (items 23, 24, 27–31); (6) Type of emotion (item 32 for embarrassment, item 33 for shame). A summary score was calculated by adding up all individual item scores, for a maximum of 99 points. The self-assessment SPARK questionnaire takes ∼5 min to perform.

Testing of the Second Version of the Scale (Phase 3)

Thirty-five PD patients with no dementia were enrolled. A neurological assessment was performed including a brief medical history aimed to determine PD duration, stage of the disease established by Hoehn and Yahr scale (9), levodopa equivalent daily dose (LEDD) (10) and educational level, as well as a motor assessment including a MDS-UPDRS part 3 (11), the determination of the type of PD phenotype (12) and the level of dyskinesia using the Marconi Dyskinesia Rating Scale (13). The previously described SPARK debriefing questionnaire used during the pretesting phase was applied. Other questionnaires were also administered to assess psychobehavioral symptoms such as depression using the Beck Depression Inventory II (BDI-II) (14), anxiety with the State-Trait Anxiety Inventory for Adults (STAI) (15) and apathy with the Apathy scale (16). Personality dimensions were assessed with the Tridimensional Personality questionnaire (TPQ) (17). The impact on health-related quality of life was studied with a shorter version of the Parkinson's Disease Questionnaire (PDQ)-39, called the PDQ-8 (18, 19). To compare our results with two previously validated scales exploring the propensity to feel embarrassed or ashamed, we used the Personal Feelings Questionnaire (PFQ-2) (20–22) and the Embarrassment scale (21, 23).

Construction of the Final Version of the Scale

Patients' comments provided during the debriefing questionnaire were discussed between the authors. Comments judged relevant were used to create the final version of the SPARK scale (**Figure 1** and **Supplementary Data 1**) that will be used in a future validation study.

Data Analysis

Descriptive statistics of the sample characteristics and the applied rating scales were carried out. SPARK psychometric properties were studied only in the 35 PD patients who took part in phase 3 of the study. The following psychometric properties were analyzed, following the Classical Test Theory (CTT) (24):

- Data quality and acceptability (25, 26): missing data (standard criterion: <10%), fully computable data (criterion: >90%); distribution of scores, floor and ceiling effects (criterion: <15%) and skewness (criterion: between −1 and +1).
- Reliability in terms of internal consistency (27, 28): Cronbach's alpha (standard criterion: >0.70), inter-item correlation (criterion: 0.20–0.75), item homogeneity coefficient (criterion: >0.15) and corrected item-total correlation (criterion: ≥0.30).
- Validity. Three aspects of validity were assessed: convergent and known-groups validity (29), internal validity and content validity. For convergent validity, Spearman rank correlation (r_S) was calculated between SPARK (total and subscale scores) and scores obtained with the two previously validated scales measuring shame and embarrassment as well as scores obtained with scales measuring depression, anxiety, apathy, type of personality and quality of life impact, constructs that theoretically should be related with the shame and embarrassment. A high correlation was established if the coefficient value r_S was ≥0.60 (30). A moderate to high correlation was considered if r_S was between 0.30 and 0.59. A moderate or weak was defined if r_S was <0.30. Known-group validity was tested by determining the differences in SPARK total and subscales scores with subgroups based on sex, level of education according to the International Standard Classification of Education, PD duration (by the median), Hoehn and Yahr (9) severity stage, and type of PD phenotype (using MDS-UPDRS scores and applying the formula as explained in **Supplementary Table**) (12). The Mann-Whitney test was utilized to determine the significance of the differences. Internal validity was assessed by

This questionnaire aims the severity of embarrassment and shame which can be experienced in people with Parkinson's disease.

For each statement, please circle the response that best to identify the presence and describes the way you have been feeling recently. Please take into account the beginning of the sentence marked in bold for each of the following questions.

I feel embarrassed or ashamed due to Parkinson's disease…				
… because of my visible symptoms such as:				
1. Tremor	No	A little	Moderately	A lot
2. Slowness, small writing, lack of dexterity, stiffness	No	A little	Moderately	A lot
3. Dry mouth or excess saliva	No	A little	Moderately	A lot
4. Walking, balance or postural difficulties	No	A little	Moderately	A lot
5. Jerking or involuntary movements	No	A little	Moderately	A lot
6. … because others have an image of me that doesn't correspond to who I really am.	No	A little	Moderately	A lot
7. … because I need to ask for help from my family or people around me.	No	A little	Moderately	A lot
8. … because my speech difficulties (e.g., articulation, voice, rhythm, understandability) affect my ability to communicate with others.	No	A little	Moderately	A lot
9. … because this disease is perceived to be a disease of older people.	No	A little	Moderately	A lot
10. … because I am no longer able to do what I once did in the past.	No	A little	Moderately	A lot
11. … because my lack of facial expression is misinterpreted as being unfriendly, odd or ill-tempered.	No	A little	Moderately	A lot
I feel embarrassed or ashamed due to Parkinson's disease…				
… because of my non motor symptoms such as:				
12. Modification of emotions (over sensitivity, blunting)	No	A little	Moderately	A lot
13. Problems with memory or concentration difficulties, or slow thinking	No	A little	Moderately	A lot
14. Hallucinations	No	A little	Moderately	A lot
15. Behavioral changes (e.g., gambling addiction, hypersexuality, compulsive buying, boulimia)	No	A little	Moderately	A lot
16. Reduced motivation	No	A little	Moderately	A lot
I feel embarrassed or ashamed due to Parkinson's disease…				
17. … because people think that I am more fragile than I really am.	No	A little	Moderately	A lot
18. … because I am progressively losing my independence.	No	A little	Moderately	A lot
19. … because my body no longer represents who I really am.	No	A little	Moderately	A lot
20. … because of my urinary problems (urgent need to go to the toilet), stomach problems (e.g., constipation) or my sexual difficulties.	No	A little	Moderately	A lot
21. … because I am losing control of my body.	No	A little	Moderately	A lot
Due to Parkinson's disease, ….				
22. … I feel useless.	No	A little	Moderately	A lot
23. … some people seem uncomfortable around me.	No	A little	Moderately	A lot
24. … people avoid looking at me.	No	A little	Moderately	A lot
25. … I feel worthless.	No	A little	Moderately	A lot
26. … I feel incompetent.	No	A little	Moderately	A lot
27. … I avoid going out, talking in public or social encounters.	No	A little	Moderately	A lot
28. … I feel left out of things.	No	A little	Moderately	A lot
29. … I am not being taken seriously.	No	A little	Moderately	A lot
30. … I feel that I have to hide my disease.	No	A little	Moderately	A lot
31. … I feel worried by others' reaction to me.	No	A little	Moderately	A lot
32. … I feel embarrassed.	No	A little	Moderately	A lot
33. … I feel ashamed.	No	A little	Moderately	A lot

FIGURE 1 | The SPARK questionnaire.

means of the inter-correlation of domains, using Spearman's rank correlation coefficients (criterion, $r_S = 0.30–0.70$). For content validity, in addition to the input from experts opinion and literature review during the construction process, the qualitative evidence from the pre-testing debriefing questionnaire with patients was analyzed, to ensure that items in the scale were representative of the construct being measured (28). For the debriefing questionnaire, the frequency of yes/no responses was reported. The comments of the patients were analyzed descriptively to assess their opinions. All calculations were made using IBM SPSS version 25.0.

RESULTS

A total of 105 patients were enrolled in our study: 44 patients for phase 1, 26 for phase 2 and 35 for phase 3 of the pilot study. Demographic and clinical characteristics are reported in **Table 1**. Among the 61 patients who participated in phases 2 and 3 of the study, most patients (85%) were experiencing embarrassment, whereas shame concerned fewer patients (26%). When shame was present, embarrassment was always associated with it. Fifteen percent of patients did not describe any shame or embarrassment.

The phase 3 of our study analyzed SPARK's psychometric properties. The SPARK total mean score was 23.97 (standard deviation SD: 18.53; range: 1–84) (**Table 2**). SPARK total score presented a skewness of 1.50, with no floor or ceiling effects (2.9% each) or missing data. Responses to items covered the full range of scale scores (0–3) except for 3 items. Most subscales and items showed a marked floor effect (**Table 2**).

Regarding internal consistency (**Table 3**), Cronbach's alpha ranged from 0.73 (Physical dependence subscale) to 0.87 (subscale Self-esteem), with a value of 0.94 for the total score. Item homogeneity coefficient ranged from 0.29 (PD symptoms subscale) to 0.70 (Self-esteem subscale). Most items (except items 1, 3 and 24) showed an item-total corrected correlation >0.40.

SPARK total score strongly correlated with PDQ-8 ($r_S = 0.81$), PFQ-2 total and Shame subscale ($r_S = 0.66$ and 0.69, respectively), Embarrassment scale ($r_S = 0.68$), STAI State and Trait ($r_S = 0.62$ and 0.72, respectively) and BDI-II ($r_S = 0.63$) (**Table 4**). Moderate to high correlations were observed between SPARK total score and Apathy scale ($r_S = 0.46$) and TPQ Harm

TABLE 1 | Patients demographic and clinical characteristics for the three phases of the study.

	Numbers	Median	Range (min-max)
		Pilot study 1	
Number of participants (men)	44 (15)		
Age (years)		65	60–75
Disease duration in years		5.0	2–10
		Pilot study 2	
Number (men)	26 (16)		
Age (years)		64.6	39–82
Hoehn and Yahr (/4)		2	1.5–4
Motor score MDS-UPDRS III (/132)		18	5–40
MOCA (/30)		28	26–30
		Pilot study 3	
Number (men)	35 (15)		
Age (years)		67	43–77
Education level (I, II, ≥III)	4 I, 12 II, 19≥III		
Disease duration in years		8.7	1.9–19.1
Motor score MDS-UPDRS III (/132)		17	6–54
Dyskinesia score (/28)		2	0–10
Levodopa-equivalent daily dose (mg/day)		785	100–2,100
PD phenotype	10 TR, 24 AR, 1 Mixed		
MOCA (/30)		29	26–30
Hoehn and Yahr (/4)		2	1.5–4
PDQ-8 (/32)		9	0–27
Apathy scale (Starkstein) (/42)		9	3–23
Anxiety state score (STAI) (/80)		25	20–58
Anxiety trait score (STAI) (/80)		34	23–58
Depression score (BDI-II) (/63)		9	1–28

BDI-II, Beck Depression Inventory II; Dyskinesia, Marconi Dyskinesia Rating scale; MDS-UPDRS motor score, motor scale of Movement Disorder Society Unified Parkinson's Disease Rating Scale; MOCA, MOntreal Cognitive Assessment; PD, Parkinson's disease; PD, phenotype: TR, tremor-dominant; AR, akinetic-rigid dominant; PDQ-8, Parkinson's Disease Questionnaire; Education level, Level I is defined as subjects who received a primary education, Level II a lower secondary education, and level 3 and above at least an upper secondary education.

avoidance ($r_S = 0.46$). A negative weak to moderate correlation was observed between SPARK total score and age ($r_S = -0.37$). PD duration, LEDD, motor score and type of PD phenotype showed weak to moderate correlations with SPARK. All SPARK subscales significantly correlated with PDQ-8 ($r_S \geq 0.60$). SPARK subscales PD Symptoms and Body image strongly correlated ($r_S = 0.68$ and 0.73, respectively) with PFQ-2 Shame subscale; and PD Symptoms and Stigma strongly correlated ($r_S = 0.63$ and 0.68, respectively) with the Embarrassment scale. PD duration, LEDD and MDS-UPDRS part 3 showed weak correlations with SPARK.

Regarding known-groups validity (**Supplementary Data 2**), SPARK total and subscales scores did not present significant differences by sex, education level, PD duration, Hoehn and Yahr severity stages or PD phenotype.

Regarding internal validity, SPARK subscales correlated from 0.31 to 0.74 between them (**Table 5**). In terms of content validity, patients' responses to the debriefing questionnaire (**Table 6**) demonstrated that >85% of the group found the scale to be relevant to their current situation, helpful for their healthcare professionals to understand their current state, understandable and with adequate length. Questions were described as embarrassing or difficult to answer only by 8.6 and 11.4% of the sample, respectively. Thirty-two percent of patients made comments. See **Supplementary Data 3** for a summary of patients' comments. Some items were consequently modified and some subitems were added in order to capture the topic as comprehensively as possible. Comments on embarrassment and shame induced by sleep disturbances such as daytime sleepiness and acting out dreams were not included in the final version of the scale because this comment was made by a single patient.

DISCUSSION

SPARK is a new self-administered questionnaire assessing shame and embarrassment induced by PD. The aim of our study was to show how SPARK was conceived and designed. In addition, some psychometric properties have been tested to orient the developers toward potential problems with the current structure. Preliminary analyses of the psychometric properties suggest that SPARK could be an acceptable and reliable instrument for assessing shame and embarrassment in PD. Higher scores of shame and embarrassment were related to impaired health-related quality of life and higher levels of depression and anxiety. Consequently, PD-related embarrassment and shame probably deserve our attention. SPARK could be a useful tool for healthcare professionals and researchers to identify and rate these two negative emotions, as well as to better understand what clinically promotes these two painful and disruptive emotions.

Regarding the psychometric analysis, SPARK had a satisfactory acceptability and data quality with no missing data, due to good procedures during data collection. Internal consistency and internal validity were acceptable, suggesting that the scores of our instrument were an adequate reflection of the dimensionality of the construct (embarrassment and shame) that we thought to measure. Content validity was very satisfactory, with the vast majority of patients thinking that the questionnaire was relevant to their current situation and could be helpful for their healthcare professional for their follow-up. SPARK was judged by patients as easily understandable and of adequate length, taking about 5 min to complete. The content validity was excellent, probably due to the SPARK construction and testing process which involved a collaborative effort with multiple exchanges between PD patients and healthcare professionals specialized in PD.

In terms of the frequency of shame and embarrassment induced by PD, most of our patients (85%) were experiencing embarrassment whereas shame concerned far fewer patients (26%). When shame was present, it was associated with embarrassment in 100% of cases. Our results argue for the fact that embarrassment and shame are two closely related

TABLE 2 | Data quality and acceptability of SPARK.

	N	Mean	Median	SD	Skewness	Min	Max	Floor effect %	Ceiling effect %
Item SPARK1	35	0.89	1.00	0.90	0.49	0	3	42.90	2.90
Item SPARK2	35	1.26	1.00	0.98	0.44	0	3	22.90	14.30
Item SPARK3	35	0.46	0.00	0.74	1.76	0	3	65.70	2.90
Item SPARK4	35	1.09	1.00	1.07	0.59	0	3	37.10	14.30
Item SPARK5	35	0.86	0.00	1.11	0.97	0	3	54.30	14.30
Item SPARK 6	35	0.94	1.00	0.97	0.74	0	3	40.00	8.60
Item SPARK 7	35	0.60	0.00	0.81	1.23	0	3	57.10	2.90
Item SPARK 8	35	0.69	0.00	0.90	1.20	0	3	54.30	5.70
Item SPARK 9	35	0.74	0.00	1.12	1.21	0	3	62.90	14.30
Item SPARK 10	35	1.34	1.00	1.16	0.23	0	3	31.40	22.90
Item SPARK 11	35	0.86	0.00	1.11	0.97	0	3	54.30	14.30
Item SPARK 12	35	0.89	1.00	0.99	1.00	0	3	42.90	11.40
Item SPARK 13	35	0.77	1.00	0.91	1.23	0	3	45.70	8.60
Item SPARK 14	35	0.06	0.00	0.24	3.99	0	1	94.30	5.70
Item SPARK 15	35	0.46	0.00	0.92	1.82	0	3	77.10	5.70
Item SPARK 16	35	0.69	0.00	1.02	1.39	0	3	60.00	11.40
Item SPARK 17	35	0.60	0.00	0.91	1.65	0	3	60.00	8.60
Item SPARK 18	35	0.94	1.00	1.11	0.80	0	3	48.60	14.30
Item SPARK 19	35	0.86	1.00	0.97	1.11	0	3	42.90	11.40
Item SPARK 20	35	1.06	1.00	1.16	0.60	0	3	45.70	17.10
Item SPARK 21	35	0.77	0.00	0.97	0.90	0	3	54.30	5.70
Item SPARK 22	35	0.51	0.00	0.89	1.97	0	3	65.70	8.60
Item SPARK 23	35	0.40	0.00	0.60	1.26	0	2	65.70	5.70
Item SPARK 24	35	0.09	0.00	0.28	3.09	0	1	91.40	8.60
Item SPARK 25	35	0.34	0.00	0.84	2.44	0	3	82.90	5.70
Item SPARK 26	35	0.63	0.00	0.97	1.65	0	3	60.00	11.40
Item SPARK 27	35	1.00	1.00	1.16	0.71	0	3	48.60	17.10
Item SPARK 28	35	0.54	0.00	0.85	1.37	0	3	65.70	2.90
Item SPARK 29	35	0.29	0.00	0.67	2.75	0	3	80.00	2.90
Item SPARK 30	35	0.77	0.00	1.06	1.12	0	3	57.10	11.40
Item SPARK 31	35	0.71	0.00	1.07	1.22	0	3	62.90	11.40
Item SPARK 32 Embarrassment	35	1.34	1.00	0.87	0.37	0	3	14.30	11.40
Item SPARK 33 Shame	35	0.54	0.00	0.95	1.72	0	3	68.60	8.60
Subscale SPARK PD symptoms	35	10.00	9.00	7.21	1.34	1	30	5.70	2.90
Subscale SPARK Physical dependence	35	3.91	3.00	3.84	0.66	0	9	25.70	2.90
Subscale SPARK Body image deterioration	35	2.89	3.00	2.52	1.32	0	15	17.10	2.90
Subscale SPARK Self-esteem	35	1.49	1.00	2.42	2.17	0	9	48.60	5.70
Subscale SPARK Stigmatization	35	3.80	3.00	3.94	0.96	0	15	28.60	2.90
SPARK **Total (/99)**	**35**	**23.97**	**19.00**	**18.53**	**1.50**	**1**	**84**	**2.90**	**2.90**

N, number of items in the questionnaire; SD, standard deviation.

self-conscious emotions belonging to the same continuum of emotion, varying on a range of factors such as intensity, public exposure and physical reaction (31). To the best of our knowledge, the exact prevalence of the shame and embarrassment in PD is unknown and our percentages would have to be checked in a larger sample. Parkinson's UK, a patients' association, found that 41% of PD patients reported experiencing discrimination because of PD, including some

experiences of misinterpretation of symptoms or verbal abuse in public (32).

In terms of the intensity of shame and embarrassment, SPARK total score had a mean of 24 out of 99 with a wide range of scores (1–84) showing that the severity of the shame and embarrassment varied greatly among patients. Floor effect in SPARK items and subscales indicated that most patients showed low levels of shame and embarrassment. However, SPARK scores were associated with a lower level of health-related quality of life, as well as with higher levels of depression and anxiety. Shame and embarrassment may contribute to psychological difficulties such as personal distress, self-identity alteration, social isolation, depression, and social anxiety (33–36). The impact of shame and embarrassment on patients' quality of life might be exacerbated by the fact that patients do not talk about this feeling because it is a taboo subject (37). Many PD patients do not spontaneously discuss these experiences with their relatives or their neurologist because, ironically, they think that it is considered embarrassing or shameful to talk about one's embarrassment or the sources of one's shame (2).

The wide range of SPARK scores among patients probably reflects the inter-individual variability of the experience of shame and embarrassment. These two emotions vary depending on self-awareness, personality traits, level of self-esteem and self-blame, and culture (38–41). Our results are in accordance with this assumption, whereby higher SPARK scores were related to the personality propensity to feel embarrassed or ashamed and with a personality trait directed toward harm avoidance.

The role of PD neuropathology itself in the experience of shame and embarrassment is unknown. According to our study, an indirect and a direct role of PD are probable. An indirect role is probable through symptoms caused by PD as well as the increasing physical dependence and the deteriorated body image. However, a direct role of PD on the emotional experience might also be associated, but remains to be demonstrated. PD is secondary to neurodegeneration involving predominantly dopaminergic neurons (42). Higher

TABLE 3 | Internal consistency of SPARK.

Subscales	Item-total corrected correlation	Cronbach's Alpha	Inter-item correlation	Item homogeneity
PD symptoms	0.01–0.71	0.84	−0.36–0.73	0.29
Physical dependence	0.44–0.71	0.73	0.30–0.63	0.47
Body image	0.58–0.71	0.83	0.41–0.80	0.50
Self-esteem	0.71–0.85	0.87	0.59–0.77	0.70
Stigmatization	0.05–0.62	0.77	−0.13–0.70	0.32

TABLE 4 | Convergent validity of SPARK scale and subscales.

	PD Symptoms	Physical dependence	Body image	Self- esteem	Stigma	Item 32 Embarr.	Item 33 Shame	SPARK TOTAL
Age	−0.33	−0.27	−0.19	−0.23	−0.36*	−0.34*	−0.45**	−0.37*
Duration of PD	0.20	−0.09	0.22	−0.03	0.03	−0.13	−0.33	0.10
LEDD	0.27	−0.03	0.18	0.00	0.08	−0.12	0.04	0.11
MOCA	−0.23	−0.20	−0.22	−0.03	0.15	−0.00	0.31	−0.14
MDS-UPDRS 3	0.03	0.05	0.13	0.10	0.16	0.09	−0.02	0.10
Tremor score	−0.31	0.12	−0.14	−0.09	−0.32	−0.02	−0.05	−0.21
Akinetic-rigid score	0.19	0.06	0.22	0.20	0.31	0.08	0.02	0.23
PIGD score	−0.12	−0.01	0.06	−0.17	−0.20	−0.15	−0.28	−0.09
Apathy scale	0.39*	0.29	0.26	0.59**	0.45**	0.22	0.25	0.46**
PDQ-8 total	0.75**	0.64**	0.68**	0.60**	0.69**	0.47**	0.41*	0.81**
PFQ-2 total	0.62**	0.50**	0.63**	0.42*	0.53**	0.41*	0.40*	0.66**
PFQ-2 shame	0.68**	0.54**	0.73**	0.43*	0.52**	0.41*	0.26	0.69**
PFQ-2 guilt	0.40*	0.37*	0.36*	0.32	0.43*	0.34*	0.51**	0.47**
Embarrassment scale	0.63**	0.46**	0.59**	0.54**	0.68**	0.38*	0.22	0.68**
TPQ novelty seeking	0.32	0.15	0.32	0.11	0.21	−0.10	0.06	0.29
TPQ Harm avoidance	0.37*	0.44**	0.38*	0.60**	0.36*	0.20	0.24	0.46**
TPQ reward dependence	0.22	0.36*	0.28	0.14	−0.10	0.09	0.06	0.25
STAI state	0.55**	0.53**	0.43*	0.62**	0.46**	0.28	0.39*	0.62**
STAI trait	0.57**	0.64**	0.59**	0.61**	0.64**	0.48**	0.36*	0.72**
BDI-II total	0.56**	0.53**	0.43**	0.48**	0.52**	0.35*	0.47**	0.63**

Scores are expressed using Spearman rank correlation coefficient value (r_S). A score $r_S \geq 0.60$ is considered to have a high correlation level. A score between 0.30 and 0.59 is considered to have a moderate to high correlation level. A score < 0.30 is considered to have a moderate to weak correlation level.

**p < 0.05; **p < 0.01. p refers to the significance level of the correlation coefficients.*

BDI-II, Beck Depression Inventory II; Embarr, embarrassment; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MOCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PDQ-8, Parkinson's Disease Questionnaire (Health-related quality of life), 8 items; PQF-2, Personal Feelings Questionnaire (shame and embarrassment scale); TPQ, Tridimensional Personality Questionnaire; STAI, State-Trait Anxiety Inventory.

TABLE 5 | Internal validity.

	PD symptoms	Physical dependence	Body image	Self Esteem	Stigma	Item 32 embarrassment
Physical dependence	0.59**					
Body image	0.71**	0.74**				
Self Esteem	0.60**	0.56**	0.49**			
STIGMA	0.61**	0.47**	0.59**	0.70**		
Item 32 Embarrassment	0.38*	0.58**	0.47**	0.45**	0.57**	
Item 33 Shame	0.48**	0.34*	0.31	0.43**	0.53**	0.48**

*Standard: $r_S > 0.50$; * $p < 0.05$; ** $p < 0.01$.*

TABLE 6 | Responses to the debriefing questionnaire about SPARK.

	Answer	*N*	%
Relevance for the patient's current situation	No	5	14.3
	Yes	30	85.7
Helpfulness for their healthcare professionals to understand the patient's current situation	No	1	2.9
	Yes	34	97.1
Good understandability	No	0	0.0
	Yes	35	100.0
Missing aspects	No	24	68.6
	Yes	11	31.4
Lenght	No	34	97.1
	Yes	1	2.9
Embarrassing questions	No	32	91.4
	Yes	3	8.6
Difficulty to answer questions	No	31	88.6
	Yes	4	11.4
Comments	No	22	62.9
	Yes	13	37.1

N, number of patients.

SPARK scores were related to a more pronounced personality variant toward harm avoidance, whereas SPARK scores were not linked with the two other personality dimensions defined by Cloninger's biosocial model of personality (novelty seeking and reward dependence) (43). The harm avoidance dimension is characterized by a tendency to respond intensely to signals of aversive stimuli, thereby learning to inhibit behavior to avoid punishment, novelty and frustrative non rewarding situations. Individuals with higher levels of harm avoidance show anticipatory worry, fear of uncertainty, shyness with strangers as well as fatigability and asthenia. Yet harm avoidance has been linked with hypodopaminergic behaviors such as apathy, depression, anxiety, irritability, and hyperemotionality (44–46) as well as with PD (47). In addition, SPARK scores were strongly related with higher levels of depression and anxiety, and moderately associated with the level of apathy. We hypothesized a dopaminergic modulation to embarrassment and shame in PD. We expect that shame and embarrassment would decrease in the case of hyperdopaminergia (euphoria, hyperactivity, hypomania, and impulse control disorders) when also depression, anxiety, apathy and harm avoidance largely disappear. This assumption remains to be elucidated.

No relationship was found between the intensity of PD-induced shame and embarrassment and PD duration and the severity of motor symptoms. These results might suggest that other factors might be involved in the intensity of the shame and embarrassment. A longitudinal study investigating the evolution of SPARK scores depending on the phase of PD would be interesting. Our hypothesis is that the intensity of shame and embarrassment might be higher before the dopaminergic replacement therapy is introduced and during the early post-diagnosis phase when the patient is learning to adapt to her/his disease. Another hypothesis would be that shame and embarrassment are little related with motor symptoms as compared with neuropsychiatric symptoms.

Nevertheless, our scale contains several limitations. Three items presented low item-total corrected correlations with their respective subscales. Two pairs of items showed high inter-item correlation which might suggest redundancy. This aspect will be checked during the validation study in a larger sample. As pointed out by the debriefing questionnaire, some aspects contributing to shame and embarrassment were missing. Some new items were consequently added (stiffness, dysarthria, dry mouth, posture difficulties) in order to capture the topic as comprehensively as possible. The final version of SPARK will be utilized during the future validation study. As mentioned by several patients and because of the type of rating scale that we chose, SPARK measures the intensity of shame and embarrassment but not the frequency of the occurrence of these two emotions. SPARK also does not differentiate clearly if shame and embarrassment are internal or external. Internal shame or embarrassment describes the negative evaluation a person applied to her/himself whereas external shame or embarrassment relates to the evaluation of what the person believes others think about her/him i.e. the distressing awareness that "I think others view me negatively" (48). The amount of psychosocial support received by patients was not able to be measured. It is however data that may well influence PD-induced shame and embarrassment and in this sense, should be taken into account

in future studies. Finally, SPARK could encounter difficulties at a linguistic level in non-English or non-French speaking countries. Indeed, the distinction between shame and embarrassment may not be obvious depending on the language. In Spanish for example, the distinction between shame and embarrassment does not exist in the common (everyday life) language. For this reason, we chose to combine embarrassment and shame as a single combined score. Future studies should also address the role of culture on shame and embarrassment in PD. How emotions are understood and expressed varies across cultures (40, 41). Some social groups view the self in individualistic psychological terms as a self that is bounded, separate from others. Shame and embarrassment are then perceived as a psychological event occurring inside an individual. Meanwhile, other cultures favor a collectivist conception wherein shame and embarrassment are emotions that happen interpersonally, outside, between people (39). The appraisal of how shame and embarrassment are felt and expressed, as well as the responsibility for resolving them, also varies (38). International studies are needed, with a more diverse sample of PD patients in order to explore cultural differences regarding the embarrassment and shame by a formal study. Finally, our sample size was relatively small.

In conclusion, the SPARK scale could be a reliable questionnaire which promptly measures the severity of shame and embarrassment specifically induced in patients in the context of PD. A validation study would be useful to confirm this assumption. The availability of this rating scale could raise awareness on these two emotions in PD. The SPARK scale could help healthcare professionals to identify the problem of shame and embarrassment affecting PD patients and to better understand what clinically promotes these two emotions. Our study demonstrated that PD-associated embarrassment is extremely frequent. Shame and embarrassment were associated with a lower level of health-related quality of life, as well as with higher levels of depression and anxiety. As such, PD-related shame and embarrassment deserve our attention. Further studies are needed to deepen the understanding of the subject, such as studies exploring clinical, cultural or socioeconomic factors influencing these two painful emotions. The clinical implication of this score system could be important especially in patients who score high on SPARK total score and shame sub-item as shame probably contributes to psychological difficulties such as personal distress, depression, suicidal ideation, and social encounter avoidance. A high SPARK score should alert healthcare professionals to the potential presence of psychological difficulties. The SPARK questionnaire could therefore help healthcare professionals to implement psychological support to patients' management in a timely fashion in order to help patients cope with their disease. Cognitive-behavioral intervention strategies such as systematic desensitization, role playing, thought stopping, disputing the inner critic, identification of irrational thinking and dysfunctional cognitive schemas could be clinically beneficial for these 2 emotions (49, 50). The SPARK scale could also help indirectly researchers to better understand the biological role of monoaminergic neurotransmitter depletion in these negative emotions. Understanding the biology behind shame and embarrassment could allow more targeted pharmacological management in addition to enhancing coping strategies.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Geneva Ethics Committee (SwissEthics). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VF, SC, MF, MM, ID, G-MH, PM-M, CR-B, and PK: conception and design of the study. VF, SC, MF, MM, JA, PB, and CR-B: acquisition and analysis of data. VF, SC, MF, MD, MM, ID, G-MH, JA, PB, PM-M, CR-B, and PK: writing and review of the text and preparing tables and figures. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank Dr. Daniel Weintraub and Thierry Lecerf for their input during the construction of SPARK. We thank Dr. Michael Nissen for his assistance with the proofreading.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00779/full#supplementary-material

REFERENCES

1. Muller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early parkinson's disease parkinsonism. *Relat Disord*. (2013) 19:1027–32. doi: 10.1016/j.parkreldis.2013.07.010

2. Angulo J, Fleury V, Péron JA, Penzenstadlerf L, Zullino D, Krack P. Shame in Parkinson's disease: a review. *J Parkinson's Dis*. (2019) 9:489–99. doi: 10.3233/JPD-181462

3. Crozier WR. Differentiating shame from embarrassment. *Emotion Rev*. (2014) 6:269–76. doi: 10.1177/1754073914523800

4. Tangney JP, Miller RS, Flicker L, Barlow DH. Are shame, guilt, and embarrassment distinct emotions? *J Pers Soc Psychol*. (1996) 70:1256–69. doi: 10.1037/0022-3514.70.6.1256
5. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res*. (1995) 4:241–8. doi: 10.1007/BF02260863
6. Molina Y, Choi SW, Cella D, Rao D. The stigma scale for chronic illnesses 8-item version. (SSCI-8): development, validation and use across neurological conditions. *Int J Behav Med*. (2013) 20:450–60. doi: 10.1007/s12529-012-9243-4
7. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. (1992) 55:181–4. doi: 10.1136/jnnp.55.3.181
8. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
9. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology*. (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
10. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord*. (2010) 25:2649–53. doi: 10.1002/mds.23429
11. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, 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*. (2008) 23:2129–70. doi: 10.1002/mds.22340
12. Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. *Neurology*. (2016) 86:1400–7. doi: 10.1212/WNL.0000000000002461
13. Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Mov Disord*. (1994) 9:2–12. doi: 10.1002/mds.870090103
14. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. (1996) 67:588–97. doi: 10.1207/s15327752jpa6703_13
15. Spielberger CD. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press (1983).
16. Starkstein SE, Merello M, Jorge R, Brockman S, Bruce D, Power B. The syndromal validity and nosological position of apathy in Parkinson's disease. *Mov Disord*. (2009) 24:1211–6. doi: 10.1002/mds.22577
17. Cloninger CR, Przybeck TR, Svrakic DM. The tridimensional personality questionnaire: U.S. normative data. *Psychol Rep*. (1991) 69(3 Pt 1):1047–57. doi: 10.2466/pr0.1991.69.3.1047
18. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: development and validation of a short-form Parkinson's disease questionnaire. *Psychology and Health*. (1997) 12:805–14. doi: 10.1080/08870449708406741
19. Jenkinson C, Fitzpatrick R. Cross-cultural evaluation of the short form 8-item parkinson's disease questionnaire (PDQ-8): results from America, Canada, Japan, Italy and Spain. *Parkinsonism Relat Disord*. (2007) 13:22–8. doi: 10.1016/j.parkreldis.2006.06.006
20. Harder DH, Zalma A. Two promising shame and guilt scales: a construct validity comparison. *J Pers Assess*. (1990) 55:729–45. doi: 10.1207/s15327752jpa5503andamp;4_30
21. Kelly KM, Jones WH. Assessment of dispositional embarrassability. *Anxiety Stress Coping*. (1997) 10:307–33. doi: 10.1080/10615809708249306
22. Nugier A, Gil S, Chekroun P. Validation of the French version of the Test of self-conscious affect-3. (TOSCA-3): a measure for the tendencies to feel ashamed and guilty. *Eur Rev Appl Psychol*. (2012) 62:19–27. doi: 10.1016/j.erap.2011.09.004
23. Maltby J, Day L. The reliability and validity of a susceptibility to embarrassment scale among adults. *Personal Individual Diff*. (2000) 29:749–56. doi: 10.1016/S0191-8869(99)00229-9
24. Nunnally JC, Bernstein IH. *Psychometric Theory*. New York, NY: McGraw-Hill (1994).
25. Hays RD, Anderson R, Revicki D. Psychometric considerations in evaluating health-related quality of life measures. *Qual Life Res*. (1993) 2:441–9. doi: 10.1007/BF00422218
26. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? *Qual Life Res*. (1995) 4:293–307. doi: 10.1007/BF01593882
27. Clark LA, Watson D. Constructing validity: basic issues in objective scale development. *Psychol Assessment*. (1995) 7:309–19. doi: 10.1037/1040-3590.7.3.309
28. Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument. (DEMQOL) and an evaluation of current methodology. *Health Technol Assess.* (2005) 9:1–93. doi: 10.3310/hta9100
29. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol*. (2010) 63:737–45. doi: 10.1016/j.jclinepi.2010.02.006
30. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ. A comparison of health utility measures for the evaluation of multiple sclerosis treatments. *J Neurol Neurosurg Psychiatry*. (2005) 76:58–63. doi: 10.1136/jnnp.2003.017897
31. Kaufman G. *The Psychology of Shame: Theory and Treatment of Shame-Based Syndromes*. 2nd ed. Springer Publishing Co. (1996).
32. UK PS. *People with Parkinson's Subject to "intolerable" Discrimination and Prejudice*. Available online at: http://forum.parkinsons.org.uk/aboutus/mediacentre/pressreleasepaw2013.aspx (2013).
33. Harder DW, Cutler L, Rockart L. Assessment of shame and guilt and their relationships to psychopathology. *J Pers Assess*. (1992) 59:584–604. doi: 10.1207/s15327752jpa5903_12
34. Cheung MSP, Gilbert P, Irons C. An exploration of shame, social rank and rumination in relation to depression. *Personal Individ Diff*. (2004) 36:1143–53. doi: 10.1016/S0191-8869(03)00206-X
35. Simpson J, McMillan H, Reeve D. Reformulating psychological difficulties in people with Parkinson's disease: the potential of a social relational approach to disablism. *Parkinsons Dis*. (2013) 2013:608562. doi: 10.1155/2013/608562
36. Lewis DS, Anderson KH, Feuchtinger J. Suicide prevention in neurology patients: evidence to guide practice. *J Neurosci Nurs*. (2014) 46:241–8. doi: 10.1097/JNN.0000000000000062
37. Brown B. *I Thought It Was Just Me (But It isn't): Telling the Truth about Perfectionism, Inadequacy and Power*. New York, NY: Gotham Books; Penguin (2007).
38. Kitayama S, Markus HR, Kurokawa M. Culture, emotion, and well-being: good feelings in Japan and the United States. *Cogn Emotion*. (2000) 14:93–124. doi: 10.1080/026999300379003
39. Mesquita B. Emotions in collectivist and individualist contexts. *J Pers Soc Psychol*. (2001) 80:68–74. doi: 10.1037/0022-3514.80.1.68
40. Boiger M, Mesquita B, Tsai AY, Markus H. Influencing and adjusting in daily emotional situations: a comparison of European and Asian American action styles. *Cogn Emot*. (2012) 26:332–40. doi: 10.1080/02699931.2011.572422
41. Boiger M, Gungor D, Karasawa M, Mesquita B. Defending honour, keeping face: Interpersonal affordances of anger and shame in Turkey and Japan. *Cogn Emot*. (2014) 28:1255–69. doi: 10.1080/02699931.2014.881324
42. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Primers*. (2017) 3:17013. doi: 10.1038/nrdp.2017.13
43. Cloninger R. A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry*. (1987) 44:573–88. doi: 10.1001/archpsyc.1987.01800180093014
44. Ardouin C, Chereau I, Llorca PM, Lhommee E, Durif F, Pollak P, et al. [Assessment of hyper- and hypodopaminergic behaviors in Parkinson's

disease]. *Rev Neurol.* (2009) 165:845–56. doi: 10.1016/j.neurol.2009.06.003
45. Kim JH, Son YD, Kim HK, Lee SY, Cho SE, Kim YB, et al. Association of harm avoidance with dopamine D2/3 receptor availability in striatal subdivisions: a high resolution PET study. *Biol Psychol.* (2011) 87:164–7. doi: 10.1016/j.biopsycho.2011.02.011
46. Lhommee E, Boyer F, Wack M, Pelissier P, Klinger H, Schmitt E, et al. Personality, dopamine, and parkinson's disease: insights from subthalamic stimulation. *Mov Disord.* (2017) 32:1191–200. doi: 10.1002/mds.27065
47. Santangelo G, Garramone F, Baiano C, D'Iorio A, Piscopo F, Raimo S, et al. Personality and Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord.* (2018) 49:67–74. doi: 10.1016/j.parkreldis.2018.01.013
48. Gilbert P, Procter S. Compassionate mind training for people with high shame and self-criticism: Overview and pilot study of a group therapy approach. *Clin Psychol Psychother.* (2006) 13:353–79. doi: 10.1002/cpp.507
49. Brown B. *Connections: A 12-Session Psychoeducational Shame-Resilience Curriculum.* Center City, MN : Hazelden (2009).
50. Gilbert P. Introducing compassion-focused therapy. *Adv Psychiatr Treat.* (2009) 15:199–208. doi: 10.1192/apt.bp.107.005264

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 August 2020
doi: 10.3389/fneur.2020.00731

Clinical Characterization of Parkinson's Disease Patients With Cognitive Impairment

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Background: Cognitive impairment is one of the most frequent and disabling non-motor symptoms in Parkinson disease (PD) and encompasses a continuum from mild cognitive impairment (PD-MCI) to dementia (PDD). The risk factors associated with them are not completely elucidated.

Objective: To characterize the presence and clinical presentation of PD-MCI and PDD in patients with idiopathic PD, examining motor and non-motor features and determining factors associated with cognitive impairment.

Methods: Multicenter, cross-sectional study in 298 PD patients who underwent clinical [Hoehn and Yahr (HY) staging and Clinical Impression of Severity Index for Parkinson Disease], neurological [Scales for Outcomes in Parkinson's Disease (SCOPA)-Motor], neuropsychological (Mini Mental State Examination, SCOPA-Cognition, Frontal Assessment Battery and Clinical Dementia Rating Scale), neuropsychiatric [SCOPA-Psychiatric complications, SCOPA-Psychosocial (SCOPA-PS), and Hospital Anxiety and Depression Scale (HADS)], and health-related quality of life [Parkinson Disease Questionnaire for quality of life (PDQ-8)] assessment. Movement Disorders Society criteria were applied to classify patients as normal cognition (NC), PD-MCI, and PDD. The association between variables was explored using multivariate binary and multinomial logistic regression models.

Results: Seventy-two patients (24.2%) were classified as NC, 82 (27.5%) as PD-MCI, and 144 (48.3%) as PDD. These last two groups reported more psychosocial problems related with the disease (mean SCOPA-PS, 16.27 and 10.39, respectively), compared with NC (7.28) and lower quality-of-life outcomes (PDQ-8 48.98 and 28.42, respectively) compared to NC (19.05). The logistic regression analysis showed that both cognitive impaired groups had a more severe stage of PD measured by HY [odds ratio (OR) for MCI-PD, 2.45; 95% confidence interval (CI), 1.22–4.90; OR for PDD 2.64; 95% CI, 1.17–5.98]. Specifically, age (OR, 1.30; 95% CI, 1.16–1.47), years of education (OR, 0.91; 95% CI, 0.83–0.99), disease duration (OR, 1.19; 95% CI, 1.07–1.32), HADS-D (OR, 1.20; 95% CI, 1.06–1.35), and hallucinations (OR, 2.98; 95% CI, 1.16–7.69) were related to PDD.

OPEN ACCESS

Edited by:
Emilia Mabel Gatto, Sanatorio de la Trinidad Mitre, Argentina

Reviewed by:
Pedro Chana-Cuevas, University of Santiago, Chile
Dennis Qing Wang, Southern Medical University, China

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *11 April 2020*
Accepted: *15 June 2020*
Published: *04 August 2020*

Citation:
Simon-Gozalbo A, Rodriguez-Blazquez C, Forjaz MJ and Martinez-Martin P (2020) Clinical Characterization of Parkinson's Disease Patients With Cognitive Impairment. Front. Neurol. 11:731. doi: 10.3389/fneur.2020.00731

Conclusions: Cognitive impairment in PD is associated with more severe disease stage, resulting in a global, neuropsychiatric, psychosocial, and quality-of-life deterioration. This study provides a better understanding of the great impact that cognitive impairment has within the natural history of PD and its relationship with the rest of motor and non-motor symptoms in the disease.

Keywords: cognitive dysfunction, Parkinson's disease, motor and non-motor symptoms, dementia, mild cognitive impairment, clinical characteristics

BACKGROUND

Idiopathic Parkinson disease (PD) is a common, chronic, and neurodegenerative disorder characterized by the presence of motor manifestations such as tremor, rigidity, bradykinesia, or instability. However, there are also non-motor features including cognitive dysfunction, sleep disorders, neuropsychiatric symptoms, autonomic dysfunction, pain, fatigue, and olfactory disorders that may be present since the earliest stages of PD or even prior to its diagnosis, generating a great impact on patients and caregivers (1, 2). In conjunction with this fact, the latest evidence from clinical, genetic, neuropathological, and imaging studies suggests the initiation of PD-specific pathology prior to the initial presentation of the classical motor clinical features by years (preclinical and prodromal stages of PD). The existence of these "premotor biomarkers" opens up the possibility to new therapies that would help prevent the onset of the disease or retard the progression (3). One of the most recent neuroprotective substances would be the cystatin C, which seems to play a significant role in neural and vascular cell function in neurodegenerative diseases (4, 5). Another new biomarker related to PD progression could be the decreased serum levels of mitochondrial creatine kinase. However, no significant relationship was found between this levels and the Hoehn and Yahr (HY) stage or non-motor symptoms scales (6).

With regard to cognition, the heterogeneous presentations encompass a continuum from cognitively intact patients to subjective cognitive decline, mild cognitive impairment (PD-MCI), and, finally, PD dementia (PDD), with a progressive severity gradient (7). Cognitive decline is one of the most frequent clinical manifestations of PD, being a prognostic variable of institutionalization and mortality (8). Prevalence of PD-MCI is estimated between 15 and 40% of PD patients according to recent studies and ∼40% of patients with PD-MCI decline to PDD over 3 years (9). In 2007 and 2012, the Movement Disorder Society (MDS) published the diagnostic criteria PDD and PD-MCI, respectively. For both disorders, MDS established two levels of diagnostic certainty: level I, using a brief neuropsychological evaluation; and level II, which includes a much more extensive battery of tests (10, 11).

Several sociodemographic and disease-related features have been identified as potential risk factors that increase the progression of cognitive decline in PD, such as old age, low educational level, severity of disease, high age at onset, disease duration, high doses of levodopa, or use of anticholinergic medication (12, 13). Other clinical manifestations, such as neuropsychiatric symptoms, hallucinations, or rapid eye movement–sleep behavior disorder (RBD), have also been investigated and even considered as prodromal markers of PD (3, 14). The pathophysiological mechanisms underlying RBD and its relation with PDD include a major cholinergic denervation, a higher burden of cerebrovascular disease, and a more advanced deposition of synaptic nucleoprotein in brain areas (15). With regard to the link between depression symptoms and different types of dementia, some animal models have been developed, showing that exposure to several exogenous factors (economic status, education, family support, and social environment) and endogenous factors (such as aging, cerebral small vessel disease, brain circuits, neuroendocrine activity, neurochemistry, neurotransmitters, and inflammatory cytokines) could contribute to the pathogenesis of depression. Overall, non-motor symptoms in PD patients have been associated with dysfunction of the microbiota–gut–brain axis (16). Specifically, PDD has been associated to certain biomarkers such as low cerebrospinal fluid levels of β-amyloid 42, low serum uric acid levels, low serum Trefoil factor 3 levels, low serum cholinesterase activity, and high serum levels of homocysteine (17). In addition, some proinflammatory substances such as lipoprotein-associated phospholipase A_2, superoxide dismutase, and high-sensitivity C-reactive protein are linked to neuroinflammation and therefore to progression of disease and cognitive impairment (18–20).

Concerning PD-MCI status, there are only a few studies on associated risk factors, and they suggest that older age, late age at onset, male gender, depression, and more advanced motor impairment have been associated with PD-MCI (9, 21). However, when reviewing the existing literature, the results are still conflicting regarding some of these factors. For example, contradictory findings have been reported for gender, education, age at onset, disease duration, HY stage, depression, and levodopa dose (12, 13, 22, 23). It is suggested that the reason for this is due to differences in populations, differences in methodology, outcome measures, and lack of robust studies with large sample size (24). In neuroimaging studies, PD-MCI patients showed more severe atrophy in the right entorhinal cortex, compared to PD patients without cognitive impairment, suggesting this brain area as a neuroanatomical biomarker in PD-MCI (25).

In the last decades, studies have tried to achieve a better understanding of the clinical heterogeneity in PD by defining different subtypes within the disease via cluster analysis, which could predict disease course, underlie neuropathological mechanisms, and lead to more efficient, personalized, therapeutic

strategies (26, 27). The traditional subtyping systems were based on motor symptoms and motor complications, such as tremor-dominant PD (TD) vs. postural instability and gait difficulty (PIGD) with an akinetic-rigid predominance (28, 29). The TD motor phenotype was considered to have a more favorable prognosis than the PIGD phenotype, whereas the latter is associated to a more rapid and greater progression of the disease, including cognitive impairment (30, 31). Several studies have defined subtypes in relation to demographic and disease-related factors, such as the age at onset, claiming that patients with young-onset PD had a slower progression of disease than those with late-onset PD, concluding that age at onset was a major determinant of the course of disease (32). In recent years, the increasing importance of non-motor symptoms in PD has led to non-motor symptoms based subtypes, such as cognitive PD phenotypes (33, 34). However, the clinical, neuropsychological, and neuropathological boundaries between PDD and dementia with Lewy bodies (DLBs) have challenged the concept of different clinical entities. Conventionally, the diagnosis of PDD is usually made when dementia develops within the context of an established PD, whereas DLBs might be more appropriate when dementia precedes or coincides within 1 year of Parkinsonism onset (35). The so-called "Park cognitive" subtype is characterized by developing cognitive impairment even at an early stage, progressing rapidly to dementia (36). In other cognitive models graded by severity of cognitive impairment, cognitively intact patients were significantly younger and had received more years of formal education, whereas patients in the more cognitive impaired clusters had more severe motor symptoms, longer disease duration, and more axial signs (7).

Finally, the latest cluster analysis includes clinical, neuropsychological, neuroimaging, biospecimen, and genetic information to develop criteria to assign patients to a PD subtype (30, 37). The so-called "diffuse malignant" phenotype, in which three critical non-motor features (MCI, RBD, and orthostatic hypotension) at baseline identified the most rapidly progressive subtype, showed more severe motor and non-motor symptoms, more atrophy in substantia nigra–connected areas, more dopaminergic deficit on SPECT, reduced β-amyloid in cerebrospinal fluid, and shorter survival rates (38). Moreover, this subtype had greater decline in cognition and in dopamine functional neuroimaging after an average of 2.7 years (30).

However, subtyping PD has been challenging, because of inconsistent reliability and possibility of confusion between subtypes and different stages of disease progression (27). Therefore, there is currently no clear way to define and divide subtypes in PD.

The aim of the present study is to examine and compare the sociodemographic, disease-related, and clinical characteristics in a sample of PD patients with different degrees of cognitive impairment determined using the MDS diagnostic criteria. Additionally, a detailed analysis of the relationship between cognitive decline in PD and other manifestations of the disease will be carried out. The aforementioned aspects are not fully understood and are key to the management and well-being promotion of these patients. Moreover, these clinical markers have still potential to be used alongside with other biological and neuroimaging biomarkers as indicators of cognitive impairment (39).

METHODS

This study used data from a previous international, multicenter, cross-sectional study (40). Patients 30 years or older and diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Criteria were included (41). To obtain an adequate sample size of at least 100 patients with PDD, patients with cognitive impairment were specifically overrecruited. Exclusion criteria were as follows: (1) parkinsonism other than idiopathic PD; (2) acute or chronic concomitant disease that could interfere in the evaluation of PD; and (3) any type of disability that could interfere with answering the questionnaires, with the exception of cognitive impairment. In cognitive impaired patients, information pertaining to self-administered and patient-reported outcome (PRO) scales was obtained from clinical interview to the caregiver.

Patients were recruited from movement disorder clinics in Brazil ($n = 76$), Ecuador ($n = 95$), and Romania ($n = 127$). A neurologist with expertise in movement disorders collected sociodemographic and disease-related data. In addition, a neurological, neuropsychological, neuropsychiatric, functional, and quality-of-life assessment was carried out, applying different rating scales: the global severity of PD was defined according to the HY staging (42) and the Clinical Impression of Severity Index (CISI-PD) (43); functional status was assessed through the Barthel Index (44); the motor manifestations were evaluated by the Scales for Outcomes in Parkinson's Disease-Motor (SCOPA-Motor) (45); the assessment of cognitive status included the Mini-Mental State Examination (MMSE) (46), the SCOPA-Cognition (SCOPA-Cog) (47), the Frontal Assessment Battery (FAB) (48, 49), and the Clinical Dementia Rating Scale (CDR) (50); the neuropsychiatric symptoms were collected through the SCOPA-Psychiatric (SCOPA-PC) (51). Finally, each patient completed the following self-administered questionnaires: the Hospital Anxiety and Depression Scale (HADS), with two subscales, HADS-A and HADS-D, respectively (52); the 8-item Parkinson Disease Questionnaire for quality of life (PDQ-8) (53); and the SCOPA-Psychosocial (SCOPA-PS) for psychosocial consequences of PD (54). For all instruments except cognitive tests (MMSE, SCOPA-Cog, and FAB) and the Barthel Index, higher scores reflect poorer functioning. A cutoff of ≥ 11 in the HADS-A and HADS-D was used as indicative of presence of anxiety and depression (52). All evaluations were performed during "on" state. The culturally adapted and validated versions were used in each country.

Neurologists evaluated the severity of cognitive impairment using the neuropsychological examination and the clinical interview with patient and caregiver, CDR scale scores, the presence or absence of dementia according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, and item 3 of the CISI-PD scale, which refers to the patient's cognitive status. Cognitive symptoms started at least 1 year after the onset of PD in all participants.

TABLE 1 | Classification criteria based on MDS criteria and literature review.

	Main criteria	Secondary criteria (for doubtful cases)*
PDD	1 Clinical criteria: - CDR ≥1 - DSM IV compatible with dementia - CISI-PD cognitive status ≥3 + Objective criteria: - MMSE <26 + ≥2 cognitive domains affected	≥2 Clinical criteria: - CDR ≥1 - DSM IV compatible with dementia - CISI-PD cognitive status ≥3
PD-MCI	1 Clinical criteria: - CDR = 0.5 - CISI-PD cognitive status = 1–2 + Objective criteria: - SCOPA Cog 17–23	2 Clinical criteria: - CDR = 0.5 - CISI-PD cognitive status = 1–2
NC	1 Clinical criteria: - CDR = 0 - CISI-PD cognitive status = 0 + Objective criteria: - SCOPA Cog ≥24	≥2 Clinical criteria: - CDR=0 - CISI-PD cognitive status = 0

*PDD, Parkinson's disease dementia; PD-MCI, Parkinson's disease-Mild cognitive impairment; NC, normal cognition; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; CISI-PD, Clinical Impression of Severity Index-Parkinson's disease; MMSE, Mini Mental State Examination; SCOPA-Cog, Scales for Outcomes in Parkinson's disease-Cognition. *Cases that did not fulfill all the criteria.*

Subsequently and independently, patients were classified by the research team into three groups, namely, normal cognition (NC), PD-MCI, and PDD, using criteria based on those proposed by the MDS (level I) and literature review [**Table 1**; (10, 11, 40, 55)].

The study was formally approved by the local institutional review boards. Written informed consent was obtained from all patients prior to participating in the study. In those with severe dementia, informed consent was signed by the main caregiver.

Statistical Analysis

In addition to descriptive statistics, tests for determining the differences between the 3 groups of patients were used. For data not fitting the normal distribution, non-parametric tests were applied. Chi-square χ^2-tests were used for comparing categorical variables, whereas the Kruskal–Wallis test was applied in continuous variables that were not normally distributed.

Two multivariate binary logistic regression models were subsequently performed: one with the presence of any degree of cognitive impairment (NC vs. MCI-PD/PDD) and the other one with the presence of dementia (NC/MCI-PD vs. PDD), as dependent variables. The independent variables were motor and non-motor symptoms variables and time since diagnosis in years. Moreover, a multinomial logistic regression model was undertaken, with the same independent variables and using the three diagnostic groups as the outcome variable. Variables with $p < 0.10$ from the univariate analysis and those that were considered clinically relevant were selected for inclusion in the multivariate analyses. Age, sex, and education were controlled. Odds ratio (OR) with 95% confidence intervals (CIs) was used to assess the significance of associations. The binary logistic regression models were carried out to help clarifying the interpretation of data in the two stages of cognitive decline (MCI-PD and PDD) and, at the same time, adding more information to the topic, contrasting and completing the data provided by the multinomial logistic regression model.

In the logistic regression models, the cognitive assessment tests were not included because they had been used for the classification of the diagnostic groups and therefore could interfere in the results of the analysis. To analyze the relationship between the different variables, Spearman correlation coefficients were determined. Coefficients of ≥0.60 were considered as collinearity. According to this test, the CISI-PD was not included, because of collinearity with the SCOPA-Motor scale and the HY. Likewise, the SCOPA-PC was not introduced in the models, as it may have interactions with hallucinations (an item from the scale) and HADS. Finally, because the age at onset is dependent on the patient's baseline age and the disease duration, it was also excluded.

Statistical calculations were performed with the Statistical Package for the Social Sciences version 22.0 IBM (Armonk, New York).

RESULTS

Sociodemographic and Disease-Related Characteristics

The sample was composed of 298 patients (186 men and 112 women). Applying the MDS criteria, 72 participants (24.2%) were classified as NC, 82 (27.5%) as PD-MCI, and 144 (48.3%) as PDD (**Table 2**).

The mean age of the total sample was 68.06 [standard deviation (*SD*) = 9.62] years with 8.7 (*SD* = 4.41) years of education. Parkinson disease MCI and PDD patients were significantly older and presented a lower education level than NC patients. No differences by sex were found between the three cognition groups. Overall, age at onset was 58.49 (*SD* = 10.12) years, with a statistically significantly higher age at onset in the PDD group than the other groups. The average duration of the disease at the time of data collection was 9.57 (*SD* = 6.47) years, being significantly higher in the cognitive impaired groups (12.36 for PDD vs. 6.28 years for NC). Dopamine agonists were more frequently taken in NC patients (33.3% in the intact vs. 6.3% in the PDD group, $p < 0.05$), and there were no significant differences regarding L-dopa treatment between the groups.

Motor and Non-motor Symptoms

Parkinson disease MCI and PDD patients presented a more severe stage of disease (according to HY), as well as a worse clinical, motor, and functional status (measured by the CISI-PD, SCOPA-Motor, and Barthel index, respectively) than NC patients. Regarding the cognitive sphere, as expected, all cognitive test scores were worse in the cognitively impaired groups, with the lowest scores for PDD patients. The latter also obtained the highest average score on the neuropsychiatric symptom scale (SCOPA-PC). Specifically, 43.8% of PDD patients

TABLE 2 | Sociodemographic and disease-related features of study groups.

	Total (298)	95% CI	NC (72)	PD-MCI (82)	PDD (144)	*p**
Age, year	68.06 (9.62)	66.96–69.16	63.26 (10.17)	63.90 (9.46)	72.83 (6.78)	<0.001[a]
Sex, % men	62.40		65.30	52.40	66.70	0.089[b]
Education, year	8.70 (4.41)	8.20–9.21	11.19 (4.08)	9.23 (4.35)	7.16 (3.98)	<0.001[a]
Age at onset, year	58.49 (10.12)	57.34–59.65	56.99 (10.98)	56.35 (11.77)	60.47 (8.17)	0.026[a]
Disease duration, year	9.57 (6.47)	8.83–10.31	6.28 (4.26)	7.55 (4.62)	12.36 (7.09)	<0.001[a]
Treatment, %						
L-dopa	62.80		59.70	64.60	63.20	0.811[b]
Agonists	18.10		33.30	25.60	6.30	<0.001[b]
Marital status, % married	68.80		73.60	72.00	64.60	0.309[b]
Employment, % employees	17.10		47.20	15.90	2.80	<0.001[b]

*Continuous variables are expressed as means (standard deviations). Categorical variables are expressed as percentages. *Differences are calculated with [a]Kruskal-Wallis test and [b]Chi-square test. CI, confidence interval; NC, normal cognition; PD-MCI, Parkinson's disease-Mild cognitive impairment; PDD, Parkinson's disease dementia.*

TABLE 3 | Motor and non-motor symptoms in study groups.

	NC (*n* = 72)	PD-MCI (*n* = 82)	PDD (*n* = 144)	*p*
Hoehn and Yahr stage	2 (1–2)	3 (2–3)	3 (3–4)	<0.001
CISI-PD	7.00 (4.29)	10.06 (3.62)	16.36 (3.39)	<0.001
Barthel Index	97.22 (10.51)	87.65 (17.74)	63.23 (28.44)	<0.001
SCOPA-Motor, total score	15.96 (10.05)	22.29 (10.96)	36.42 (13.50)	<0.001
Motor examination	8.57 (5.26)	12.13 (6.09)	19.35 (7.93)	<0.001
Activities of daily living	5.31 (3.28)	6.91 (3.51)	11.73 (4.40)	<0.001
Motor complications	2.08 (3.13)	3.24 (2.90)	5.34 (3.42)	<0.001
MMSE, total score	29.06 (1.26)	27.22 (2.31)	16.24 (6.85)	<0.001
SCOPA-Cog, total score	30.14 (5.87)	22.80 (5.17)	9.69 (5.67)	<0.001
Memory	12.86 (4.29)	8.68 (3.41)	3.88 (2.60)	<0.001
Attention	3.83 (0.47)	3.41 (1.03)	1.23 (1.45)	<0.001
Executive functions	9.42 (1.79)	7.48 (1.93)	3.27 (2.18)	<0.001
Visuospatial functions	4.03 (0.85)	3.23 (1.03)	1.32 (1.36)	<0.001
FAB, total score	15.56 (2.59)	13.09 (2.83)	6.63 (3.99)	<0.001
SCOPA-PC, total score	4.11 (3.36)	3.27 (3.63)	5.84 (5.25)	<0.001
Hallucinations, %	5.60	8.50	34.00	<0.001
HADS, Anxiety	6.42 (4.19)	8.51 (3.85)	9.77 (4.46)	<0.001
Patients with anxiety, %	20.80	29.30	43.80	0.002
HADS, Depression	6.08 (4.18)	7.63 (3.82)	10.36 (4.22)	<0.001
Patients with depression, %	16.70	15.90	55.60	<0.001
PDQ-8	19.05 (16.74)	28.42 (22.44)	48.98 (22.22)	<0.001
SCOPA-PS, total score	7.28 (5.45)	10.39 (6.40)	16.27 (7.03)	<0.001

Continuous variables are expressed as means (standard deviations). Hoehn and Yahr stage is expressed as median (interquartile range). Categorical variables are expressed as percentages. Differences were calculated with Kruskal-Wallis test in continuous variables and Chi-square test in categorical variables. NC, normal cognition; PD-MCI, Parkinson's disease-Mild cognitive impairment; PDD, Parkinson's disease dementia; CISI-PD, Clinical Impression of severity Index for Parkinson's Disease; SCOPA-Motor, Scales for Outcomes in Parkinson's Disease-Motor; MMSE, Mini Mental State Examination; SCOPA-Cog, SCOPA-Cognition; FAB, Frontal Assessment Battery; SCOPA-PC, SCOPA-Psychiatric Complications; HADS, Hospital Anxiety and Depression Scale; PDQ-8, 8-item Parkinson's Disease Questionnaire; SCOPA-PS, SCOPA-Psychosocial.

exceeded the cutoff point for anxiety, and 55.6% surpassed it for depression. One-third of PDD patients (34%) had hallucinations, compared to only 8 and 5% in PD-MCI and NC, respectively. There were lower quality-of-life and more psychosocial consequences in the cognitively impaired groups. All tests showed significant differences ($p < 0.05$) between the three study groups (**Table 3**).

Association Between Cognitive Impairment and Motor and Non-motor Symptoms

In the first regression model (**Table 4**), with cognitive impairment (PD-MCI or PDD) as dependent variable, two variables were found to be significant. Hoehn and Yahr stage (OR, 2.06; 95% CI, 1.10–3.85) and the motor exploration subscale in SCOPA-Motor scale (OR, 1.11; 95% CI, 1.01–1.21) showed a positive association

TABLE 4 | Binary logistic regression model for normal cognition vs. cognitive impairment (PD-MCI/PDD).

	Univariate analysis			Multivariate analysis		
	Crude OR	**95% CI**	***p***	**Adjusted OR**	**95% CI**	***p***
Sex (women)	1.17	0.67–2.04	0.56	1.51	0.74–3.09	0.255
Age	1.07	1.04–1.10	**<0.001**	1.01	0.97–1.05	0.411
Age at onset	1.02	0.99–1.05	0.148	–	–	–
Years of education	0.84	0.79–0.90	**<0.001**	0.9	0.83–0.98	**0.013**
Disease duration	1.18	1.10–1.27	**<0.001**	1.07	0.96–1.18	0.204
Hoehn and Yahr	4.28	2.94–6.23	**<0.001**	2.06	1.10–3.85	**0.022**
Barthel Index	0.9	0.87–0.94	**<0.001**	0.94	0.90–0.97	**0.002**
SMS-Motor examination	1.19	1.13–1.25	**<0.001**	1.11	1.01–1.21	**0.019**
SMS-ADL	1.31	1.21–1.42	**<0.001**	0.86	0.72–1.03	0.101
SMS-Motor complications	1.29	1.16–1.42	**<0.001**	0.87	0.72–1.04	0.137
SCOPA-PC	1.04	0.98–1.10	0.199	–	–	–
Hallucinations*	5.6	1.95–16.04	0.001	1.57	0.41–5.99	0.504
HADS, Anxiety	1.17	1.09–1.25	**<0.001**	1,00	0.89–1.13	0.904
HADS, Depression	1.21	1.12–1.30	**<0.001**	1.07	0.95–1.21	0.213

*OR, odds ratio; CI, confidence interval; SMS, Scales for Outcomes in Parkinson's disease-Motor Scale; ADL, activities of daily living; SCOPA-PC, Scales for Outcomes in Parkinson's disease-Psychiatric Complications; HADS, Hospital Anxiety and Depression Scale. *Hallucinations: item from SCOPA-PC. Bold indicates the significant values.*

TABLE 5 | Binary logistic regression model for dementia vs. no dementia (NC/PD-MCI).

	Univariate analysis			Multivariate analysis		
	Crude OR	**95% CI**	***p***	**Adjusted OR**	**95% CI**	***p***
Sex (women)	0.70	0.44–1.12	0.144	0.76	0.37–1.54	0.455
Age	1.15	1.11–1.20	**<0.001**	1.30	1.16–1.47	**<0.001**
Age at onset	1.04	1.01–1.07	**<0.001**	–	–	–
Years of education	0.84	0.79–0.89	**<0.001**	0.91	0.83–0.99	**0.044**
Disease duration	1.18	1.12–1.25	**<0.001**	1.19	1.07–1.32	**0.001**
Hoehn and Yahr	5.56	3.67–8.43	**<0.001**	1.45	0.75–2.80	0.26
Barthel Index	0.94	0.92–0.95	**<0.001**	0.97	0.95–0.99	**0.038**
SMS-Motor examination	1.18	1.14–1.23	**<0.001**	1.05	0.98–1.14	0.134
SMS-ADL	1.41	1.30–1.53	**<0.001**	0.99	0.84–1.18	0.967
SMS-Motor complications	1.27	1.17–1.37	**<0.001**	0.82	0.69–0.98	**0.029**
SCOPA-PC	1.11	1.05–1.18	**<0.001**	–	–	–
Hallucinations*	6.70	3.31–13.55	**<0.001**	2.98	1.16–7.69	**0.023**
HADS, Anxiety	1.12	1.06–1.19	**<0.001**	0.9	0.81–1.01	0.09
HADS, Depression	1.21	1.14–1.29	**<0.001**	1.2	1.06–1.35	**0.002**

*OR, odds ratio; CI, confidence interval; SMS, Scales for Outcomes in Parkinson's disease-Motor Scale; ADL, activities of daily living; SCOPA-PC, Scales for Outcomes in Parkinson's disease-Psychiatric complications; HADS, Hospital Anxiety and Depression Scale. *Hallucinations: item from SCOPA-PC. Bold indicates the significant values.*

with cognitive dysfunction. This model explained 49.0% of the variance.

The second regression model (**Table 5**), with dementia as dependent variable, showed that dementia was positively associated with higher age (OR, 1.30; 95% CI, 1.16–1.47) and disease duration (OR, 1.19; 95% CI, 1.07–1.32), an increased score in HADS-D (OR, 1.20; 95% CI, 1.06–1.35), and more hallucination symptoms (OR, 2.98; 95% CI, 1.16–7.69). The motor complications SCOPA-Motor subscale (OR, 0.82; 95% CI, 0.69–0.98) was negatively associated with the presence of dementia. This model explained 63.5% of the variance.

Finally, in the multinomial model (**Table 6**), there was a positive association between the presence of PD-MCI and HY stage (OR, 2.45; 95% CI, 1.22–4.90). On the other hand, age (OR, 1.24; 95% CI, 1.07–1.44), HY stage (OR, 2.64; 95% CI, 1.17–5.98), and the depression HADS subscale (OR, 1.19; 95% CI, 1.02–1.37) were positively associated with the PDD group, whereas years of education (OR, 0.87; 95% CI, 0.78–0.97) was negatively associated. This model explained 61.6% of the variance.

TABLE 6 | Multinomial logistic regression model (NC vs. PD-MCI vs. PDD).

	PD-MCI				PDD			
	Crude OR	***P***	**Adjusted OR (95% CI)**	***P***	**Crude OR**	***p***	**Adjusted OR (95% CI)**	***p***
Sex (women)	1.7	0.108	1.77 (0.83–3.80)	0.142	0.94	0.84	1.19 (0.49–2.88)	0.71
Age	1.01	0.682	0.99 (0.95–1.03)	0.705	1.15	**<0.001**	1.09 (1.04–1.16)	**0.001**
Years of education	0.9	**0.007**	0.93 (0.85–1.01)	0.097	0.79	**<0.001**	0.87 (0.78–0.97)	**0.014**
Disease duration	1.08	0.053	0.94 (0.82–1.07)	0.353	1.25	**<0.001**	1.13 (0.99–1.30)	0.065
Hoehn and Yahr	2.38	**<0.001**	2.45 (1.22–4.90)	**0.011**	9.65	**<0.001**	2.64 (1.17–5.98)	**0.02**
Barthel Index	0.92	**<0.001**	0.94 (0.91–0.98)	**0.008**	0.88	**<0.001**	0.93 (0.89–0.97)	**0.001**
SMS-Motor examination	1.1	**0.001**	1.07 (0.96–1.18)	0.191	1.26	**<0.001**	1.10 (0.99–1.22)	0.058
SMS-ADL	1.14	**0.007**	0.83 (0.69–1.00)	0.058	1.53	**<0.001**	0.88 (0.71–1.09)	0.244
SMS-Motor complic	1.15	**0.015**	0.99 (0.80–1.22)	0.938	1.38	**<0.001**	0.82 (0.65–1.03)	0.102
SCOPA-PC	0.94	0.192	–	–	1.08	**0.012**	–	–
Hallucinations*	1.58	0.477	0.87 (0.19–3.85)	0.858	8.76	**<0.001**	2.65 (0.63–11.08)	0.183
HADS, Anxiety	1.12	**0.003**	1.08 (0.95–1.23)	0.222	1.2	**<0.001**	0.96 (0.83–1.12)	0.664
HADS, Depression	1.1	**0.016**	1.00 (0.88–1.13)	0. 970	1.29	**<0.001**	1.19 (1.02–1.37)	**0.021**

*OR, odds ratio; CI, confidence interval; SMS, Scales for Outcomes in Parkinson's disease-Motor Scale; ADL, activities of daily living; Motor complic, motor complications; SCOPA-PC, Scales for Outcomes in Parkinson's disease-Psychiatric Complications; HADS, Hospital Anxiety and Depression Scale. *Hallucinations: item from SCOPA-PC. Bold indicates the significant values.*

DISCUSSION

This study applied the level I diagnostic criteria proposed by the MDS to analyze the differences between groups of PD patients according to their cognitive status. We found significant differences in sociodemographic, disease-related, and clinical variables depending on the severity of cognitive impairment, suggesting the usefulness of these criteria to classify PD-MCI and PDD patients according to their cognitive status. Recent studies reveal that levels I and II MCIs in PD classification have similar discriminative ability to predict the hazard of PDD (56). Nevertheless, previous studies suggest that level I criteria could be too broad and have a poor sensibility to classify PD patients; therefore, results should be interpreted carefully (57–59).

Participants with cognitive impairment (PD-MCI or PDD) were older and less educated than cognitively intact patients. In addition, they presented longer duration of PD, worse clinical and functional situation, higher levels of anxiety, depression, and greater presence of hallucinations than patients cognitively intact. Participants with cognitive impairment also had a worse quality of life and a more severe psychosocial impact of their disease, even in the early stages of cognitive decline (PD-MCI). Our findings are in line with other cross-sectional (24, 60, 61) and follow-up (24, 62) studies and highlight the importance of assessing these risk factors in the clinical setting. Moreover, non-motor symptoms have also been reported to affect the quality of life of PD patients to a greater extent than motor features, and this negative impact would appear from the very beginning of the disease (63).

Parkinson disease MCI and PDD patients were found to be more globally impaired than NC PD patients, with higher deterioration of both motor and non-motor symptoms, especially axial motor symptoms, depression, hallucinations, and cognitive performance measured by neuropsychological tests (64–66). All these features, considered even more disabling than the classic motor symptoms of PD, lead to a significant reduction in the quality of life of cognitive impaired patients.

A significant, although inverse, relationship between the degree of functionality (measured by the Barthel Index) and the presence of cognitive impairment was also found. This association, meaning that the less level of disability (corresponding to higher scores in Barthel index) is negatively associated with PD-MCI and PDD, compared to NC, is the only that consistently appeared in the binary and multinomial regression models. Multiple studies have already pointed out that dementia in PD results in a functional decline, and it

has even been seen that the instrumental activities of daily life are also affected from the stage of MCI-PD (67). This relationship could be considered valid in both directions, because not only does cognitive impairment lead to greater disability, but also greater disability and physical frailty can eventually lead to "cognitive frailty," meaning more decline in cognitive functions. As a matter of fact, these two conditions could share similar pathophysiological mechanisms, such as chronic inflammation, impaired hypothalamic–pituitary axis stress response, imbalanced energy metabolism, mitochondrial dysfunction, oxidative stress, and neuroendocrine dysfunction (68). A previous study has highlighted the important role of preserving cognitive functions to prevent disability and functional impairment (69).

The global severity of PD, measured by HY stage, and motor symptoms in PD were strongly associated with the presence of any type of cognitive impairment. Previous studies and reviews have shown that motor impairment is related to the overall presence of cognitive impairment (70, 71) and specifically to PD-MCI (72) and PDD (73, 74). In line with these previous studies, we found that the presence of cognitive impairment was associated with a more severe HY stage of PD. Conversely, the inverse association between motor complications and the presence of dementia that was found in one of our logistic regression models is not consistent with the reviewing literature that report motor complications as a risk factor for the development of PDD (24, 75). However, there is limited evidence on this topic, and the short length of the subscale that we have used (only four items, two for dyskinesias, and two for motor fluctuations) in combination with the lack of information on patient's treatment could explain a negative association between dementia and motor complications. Moreover, one study found that dyskinesias, but not motor fluctuations, were significantly related to dementia (24).

Our findings suggest that PD-MCI and PDD patients showed more neuropsychiatric symptoms than the NC patients. In the vast majority of studies, with different rating scales, neuropsychiatric symptoms seem to be related to cognitive impairment (74). Moreover, these disruptions could independently affect to disease progression by means of damaging frontal–subcortical pathways (76). Our study has found that behavior disorders are highly common in PD, and as suggested in previous studies, there may be a certain overlap between this symptomatology and cognitive symptoms (77).

We found a high prevalence of anxiety, depression, and hallucinations in PDD patients. Studies have shown that these features occur in ∼30% of PD patients, often in the early stage of the disease (3). In binary logistic regression models, a statistical association between the last two and the presence of PDD was also found, in agreement with previous studies (12, 66). Visual hallucinations have been proposed as predictors of future development of dementia in patients with PD (12, 22). With the presence of cognitive dysfunction emerges the possibility of a higher frequency of hallucinations and depressive symptomatology. Studies indicate that both dementia and visual hallucinations share the same limbic system networks (24). Moreover, depression in PD has been associated to decreased white matter in the fornix, as well as cognitive impairment and apathy (78), and differences in brain circuitry appear since mild stages of depression (79).

Higher age and low educational level are well-known risk factors in the general population for developing cognitive impairment and dementia (24, 71), and the same is true for PDD (30, 36, 41, 49), as shown in our study. According to some authors, advanced age in PD is associated with a much higher risk of dementia than the effect of age alone (24), suggesting some kind of interaction effect between age and severity of PD in the risk of dementia (60). On the other hand, the relationship between age, educational level, and PD-MCI is not completely clear (72) but higher educational level seems to be a protective factor in recent studies, in line with our trends (80, 81).

Our results did not find association between gender and cognitive impairment, in agreement with previous studies (66, 72). As women are older than men when they start with the symptoms, they have a shorter disease duration, compared with men of the same age. Therefore, men with PD would have a more advanced disease stage than women of the same age, increasing their risk of PDD (71). However, there are also studies that have found an association between male sex and PDD/MCI-PD after controlling for age and disease duration (21, 65, 82), so the significance of this risk factor remains unclear.

Regarding the disease-related risk factors, a positive relationship between PD duration and PDD was found. However, age is also related to the duration of the disease, and for that reason, it is difficult to unravel the effects of each one on the risk of dementia. Furthermore, a very recent cross-sectional study assessing dementia in long-term PD patients did not find any significant differences between age, age at onset, or disease duration between PD patients with and without dementia (83).

Several limitations of this study should be acknowledged. Although we carried out the assessment during "on" state, cognitive fluctuations are always possible in PD. Because we performed a single evaluation over time, and PRO scales (HADS, SCOPA-PS and PDQ-8) in cognitive impairment patients were completed by caregivers (proxy evaluations), the results have to be taken with caution and should not be interpreted as causal. In addition, we do not know the premorbid performance or cognitive reserve of the participating patients, and the results of cognitive scales could have been affected by these factors.

Our study, designed for a broader goal, did not allow applying a completely exhaustive neuropsychological evaluation. Therefore, only the "possible" PD-MCI and PDD status could be achieved. However, all the applied tests have been widely validated in the literature, and in particular, the screening test used, SCOPA-Cog, was proposed by the MDS as a scale of global cognitive abilities validated for use in PD, whose clinimetric characteristics are satisfactory (84). This fact increases the reliability of the finding results.

At last, we would like to remark that we did not carry out a cluster analysis in this study, as there is no widely accepted consensus of how best to group patients (85). Yet, the criteria to identify subtypes and predict individual prognosis remain unclear and therefore lack clinical applicability and

reproducibility (30). Moreover, differences in inclusion criteria from datasets, variable selection, and methodology between studies using cluster analysis have made it difficult to compare the subtypes, and the features describing them can be confusing and overlapping (86). Most of studies are cross-sectional, with a short follow-up, so they are often considered of limited utility (87). Finally, the division of PD into major subtypes has been criticized because it could be a simplification of the heterogeneous reality in the disease (36).

In this study, cognitive decline was associated with a worse disease stage at a global, psychiatric, and psychosocial level and therefore with an impairment of quality of life. We also observed that the patients with greater physical disability had worse cognitive functioning, so it seems important to identify the progression of disease to prevent cognitive impairment.

Some patient characteristics, such as age and lower educational level, were independently associated with dementia, as reported in previous studies. These data could help to understand the deeply impact that cognitive decline has on PD prognosis and highlight the importance of design and deliver integrated care for PD patients and their families. The greater knowledge on non-motor features would undoubtedly lead to a more accurate PD diagnosis and better treatments. As a result, the quality of life of these patients and the living conditions of their caregivers and family members would also improve. We strongly recommend assessing cognitive status at the time of PD diagnosis; exploring premorbid cognitive status, appearance, and type of deficits; and monitoring changes in disease severity over time. It is also relevant to pay special attention to neuropsychiatric symptoms, mainly depression and presence of hallucinations, as they seem to be strongly associated with cognitive impairment. Nevertheless, further research is required to understand the underlying pathophysiological mechanisms that link cognitive impairment with the remaining non-motor symptoms in PD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements, as all datasets were fully anonymized prior to transfer and processing. Our paper is a retrospective (secondary) study, not requiring review and approval.

AUTHOR CONTRIBUTIONS

PM-M initiated and designed the study, and collected the data within the Cog-PD study. AS-G, CR-B, and MF conducted the data analysis and wrote the main manuscript text. All authors reviewed the manuscript.

FUNDING

This study was partially funded by the QASP research project (Institute of Health Carlos III, Intramural Strategical Action in Health AESI 2018, Ref: PI18CIII/00046).

ACKNOWLEDGMENTS

To all patients and caregivers that made this study possible. To the researchers that conducted the Cog-PD study, from which the data were collected:

- C. Falup-Pecurariu, from Department of Neurology, University Hospital, Faculty of Medicine, Transilvania University, Braşov, Romania.
- M. Serrano-Dueñas, from Movement Disorder and Biostatistic Units and Neurological Service, in Carlos Andrade Marín Hospital and Medicine Faculty, Pontifical Catholic University of Ecuador, Quito, Ecuador.
- F. J. Carod Artal, from Department of Neurology, Virgen de la Luz Hospital, Cuenca, Spain.
- J. M. Rojo, Department of Statistics, Centre of Human and Social Sciences, Spanish Council for Scientific Research, Madrid, Spain.
- D. Aarsland, Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, England.

This manuscript was partly presented as conference paper at the 2019 International Congress of Parkinson's Disease and Movement Disorders organized by International Parkinson and Movement Disorder Society (MDS), September 2019, Nice, France.

REFERENCES

1. Xu Y, Yang J, Shang H. Meta-analysis of risk factors for Parkinson's disease dementia. *Transl Neurodegener.* (2016) 5:11. doi: 10.1186/s40035-016-0058-0
2. Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov Disord.* (2015) 30:229–37. doi: 10.1002/mds.26077
3. Xie F, Gao X, Yang W, Chang Z, Yang X, Wei X, et al. Advances in the research of risk factors and prodromal biomarkers of Parkinson's disease. *ACS Chem Neurosci.* (2019) 10:973–90. doi: 10.1021/acschemneuro.8b00520
4. Zou J, Chen Z, Wei X, Chen Z, Fu Y, Yang X, et al. Cystatin C as a potential therapeutic mediator against Parkinson's disease via VEGF-induced angiogenesis and enhanced neuronal autophagy in neurovascular units. *Cell Death Dis.* (2017) 8:e2854. doi: 10.1038/cddis.2017.240
5. Weng R, Wei X, Yu B, Zhu S, Yang X, Xie F, et al. Combined measurement of plasma cystatin C and low-density lipoprotein cholesterol: a valuable tool for evaluating progressive supranuclear palsy. *Parkinsonism Relat Disord.* (2018) 52:37–42. doi: 10.1016/j.parkreldis.2018.03.014
6. Xu J, Fu X, Pan M, Zhou X, Chen Z, Wang D, et al. Mitochondrial creatine kinase is decreased in the serum of idiopathic Parkinson's

disease patients. *Aging Dis.* (2019) 10:601-10. doi: 10.14336/AD.2018.0615
7. Dujardin K, Leentjens AFG, Langlois C, Moonen AJH, Duits AA, Carette A-S, et al. The spectrum of cognitive disorders in Parkinson's disease: a data-driven approach. *Mov Disord.* (2013) 28:183–9. doi: 10.1002/mds.25311
8. de Lau LML, Verbaan D, Marinus J, van Hilten JJ. Survival in Parkinson's disease. Relation with motor and non-motor features. *Parkinsonism Relat Disord.* (2014) 20:613–6. doi: 10.1016/j.parkreldis.2014.02.030
9. Weintraub D, Tröster AI, Marras C, Stebbins G. Initial cognitive changes in Parkinson's disease. *Mov Disord.* (2018) 33:511–9. doi: 10.1002/mds.27330
10. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. *Mov Disord.* (2012) 27:349–56. doi: 10.1002/mds.24893
11. Dubois B, Burn D, Goetz C, Aarsland D, Brown RG, Broe GA, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov Disord.* (2007) 22:2314–24. doi: 10.1002/mds.21844
12. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol.* (2003) 60:387–92. doi: 10.1001/archneur.60.3.387
13. Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RH, et al. A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology.* (2000) 54:1596–602. doi: 10.1212/WNL.54.8.1596
14. Postuma RB, Bertrand J-A, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov Disord.* (2012) 27:720–6. doi: 10.1002/mds.24939
15. Zhang F, Niu L, Liu X, Liu Y, Li S, Yu H, et al. Rapid eye movement sleep behavior disorder and neurodegenerative diseases: an update. *Aging Dis.* (2020) 11:315–26. doi: 10.14336/AD.2019.0324
16. Zheng W, He R, Yan Z, Huang Y, Huang W, Cai Z, et al. Regulation of immune-driven pathogenesis in Parkinson's disease by gut microbiota. *Brain Behav Immun.* (2020) 87:890–7. doi: 10.1016/j.bbi.2020.01.009
17. Zou J, Chen Z, Liang C, Fu Y, Wei X, Lu J, et al. Trefoil factor 3, cholinesterase and homocysteine: potential predictors for Parkinson's disease dementia and vascular Parkinsonism dementia in advanced stage. *Aging Dis.* (2018) 9:51–65. doi: 10.14336/AD.2017.0416
18. Tao X, Yang W, Zhu S, Que R, Liu C, Fan T, et al. Models of poststroke depression and assessments of core depressive symptoms in rodents: How to choose? *Exp Neurol.* (2019) 322:113060. doi: 10.1016/j.expneurol.2019.113060
19. Zhu S, Wei X, Yang X, Huang Z, Chang Z, Xie F, et al. Plasma lipoprotein-associated phospholipase A2 and superoxide dismutase are independent predicators of cognitive impairment in cerebral small vessel disease patients: diagnosis and assessment. *Aging Dis.* (2019) 10:834–46. doi: 10.14336/AD.2019.0304
20. Yang W, Chang Z, Que R, Weng G, Deng B, Wang T, et al. Contra-directional expression of plasma superoxide dismutase with lipoprotein cholesterol and high-sensitivity c-reactive protein as important markers of parkinson's disease severity. *Front Aging Neurosci.* (2020) 12:53. doi: 10.3389/fnagi.2020.00053
21. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology.* (2010) 75:1062–9. doi: 10.1212/WNL.0b013e3181f39d0e
22. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sørensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology.* (2001) 56:730–6. doi: 10.1212/WNL.56.6.730
23. Mahieux F, Fénelon G, Flahault A, Manifacier MJ, Michelet D, Boller F. Neuropsychological prediction of dementia in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (1998) 64:178–83. doi: 10.1136/jnnp.64.2.178
24. Zhu K, van Hilten JJ, Marinus J. Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG. *Parkinsonism Relat Disord.* (2014) 20:980–5. doi: 10.1016/j.parkreldis.2014.06.006
25. Jia X, Wang Z, Yang T, Li Y, Gao S, Wu G, et al. Entorhinal cortex atrophy in early, drug-naive Parkinson's disease with mild cognitive impairment. *Aging Dis.* (2019) 10:1221–32. doi: 10.14336/AD.2018.1116
26. Fereshtehnejad S-M, Romenets SR, Anang JBM, Latreille V, Gagnon J-F, Postuma RB. New clinical subtypes of Parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes. *JAMA Neurol.* (2015) 72:863–73. doi: 10.1001/jamaneurol.2015.0703
27. Qian E, Huang Y. Subtyping of Parkinson's disease - where are we up to? *Aging Dis.* (2019) 10:1130–9. doi: 10.14336/AD.2019.0112
28. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. *Neurology.* (1990) 40:1529–34. doi: 10.1212/WNL.40.10.1529
29. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord.* (2013) 28:668–70. doi: 10.1002/mds.25383
30. Fereshtehnejad S-M, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain J Neurol.* (2017) 140:1959–76. doi: 10.1093/brain/awx118
31. Marras C, Chaudhuri KR. Nonmotor features of Parkinson's disease subtypes. *Mov Disord.* (2016) 31:1095–102. doi: 10.1002/mds.26510
32. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neurol.* (2014) 71:499–504. doi: 10.1001/jamaneurol.2013.6233
33. Lawton M, Ben-Shlomo Y, May MT, Baig F, Barber TR, Klein JC, et al. Developing and validating Parkinson's disease subtypes and their motor and cognitive progression. *J Neurol Neurosurg Psychiatry.* (2018) 89:1279–87. doi: 10.1136/jnnp-2018-318337
34. van Rooden SM, Colas F, Martínez-Martín P, Visser M, Verbaan D, Marinus J, et al. Clinical subtypes of Parkinson's disease. *Mov Disord.* (2011) 26:51–8. doi: 10.1002/mds.23346
35. Sauerbier A, Rosa-Grilo M, Qamar MA, Chaudhuri KR. Nonmotor Subtyping in Parkinson's Disease. *Int Rev Neurobiol.* (2017) 133:447–78. doi: 10.1016/bs.irn.2017.05.011
36. Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. *Parkinsonism Relat Disord.* (2016) 22(Suppl. 1):S41–6. doi: 10.1016/j.parkreldis.2015.09.027
37. Uribe C, Segura B, Baggio HC, Abos A, Garcia-Diaz AI, Campabadal A, et al. Progression of Parkinson's disease patients' subtypes based on cortical thinning: 4-year follow-up. *Parkinsonism Relat Disord.* (2019) 64:286–92. doi: 10.1016/j.parkreldis.2019.05.012
38. de Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of Parkinson disease. *JAMA Neurol.* (2019) 76:470–9. doi: 10.1001/jamaneurol.2018.4377
39. Martin GP, McDonald KR, Allsop D, Diggle PJ, Leroi I. Apathy as a behavioural marker of cognitive impairment in Parkinson's disease: a longitudinal analysis. *J Neurol.* (2020) 267:214–27. doi: 10.1007/s00415-019-09538-z
40. Martinez-Martin P, Falup-Pecurariu C, Rodriguez-Blazquez C, Serrano-Dueñas M, Carod Artal FJ, Rojo Abuin JM, et al. Dementia associated with Parkinson's disease: applying the movement disorder society task force criteria. *Parkinsonism Relat Disord.* (2011) 17:621–4. doi: 10.1016/j.parkreldis.2011.05.017
41. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (1988) 51:745–52. doi: 10.1136/jnnp.51.6.745
42. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology.* (2001) 57(10 Suppl. 3):S11–26. doi: 10.1212/wnl.17.5.427
43. Martínez-Martín P, Rodríguez-Blázquez C, Forjaz MJ, de Pedro J, Spanish-American Longitudinal PD Patient Study Group. The clinical impression of severity index for Parkinson's disease: international validation study. *Mov Disord.* (2009) 24:211–7. doi: 10.1002/mds.22320
44. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J.* (1965) 14:61–5. doi: 10.1037/t02366-000
45. Marinus J, Visser M, Stiggelbout A, Rabey J, Martinez-Martin P, Bonuccelli U, et al. A short scale for the assessment of motor impairments disabilities in Parkinson's disease: the SPES/SCOPA. *J Neurol Neurosurg Psychiatry.* (2004) 75:388–95. doi: 10.1136/jnnp.2003.017509
46. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the

clinician. *J Psychiatr Res.* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
47. Marinus J, Visser M, Verwey NA, Verhey FRJ, Middelkoop HAM, Stiggelbout AM, et al. Assessment of cognition in Parkinson's disease. *Neurology.* (2003) 61:1222–8. doi: 10.1212/01.WNL.0000091864.39702.1C
48. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology.* (2000) 55:1621–6. doi: 10.1212/WNL.55.11.1621
49. Hurtado-Pomares M, Terol-Cantero MC, Sánchez-Pérez A, Leiva-Santana C, Peral-Gómez P, Valera-Gran D, et al. Measuring executive dysfunction in Parkinson's disease: reliability and validity of the Spanish version of Frontal Assessment Battery (FAB-E). *PLoS ONE.* (2018) 13:e0207698. doi: 10.1371/journal.pone.0207698
50. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry J Ment Sci.* (1982) 140:566–72. doi: 10.1192/bjp.140.6.566
51. Visser M, Verbaan D, van Rooden SM, Stiggelbout AM, Marinus J, van Hilten JJ. Assessment of psychiatric complications in Parkinson's disease: The SCOPA-PC. *Mov Disord.* (2007) 22:2221–8. doi: 10.1002/mds.21696
52. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x
53. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol.* (1998) 245(Suppl. 1):S10–4. doi: 10.1007/PL00007730
54. Marinus J, Visser M, Martínez-Martín P, van Hilten JJ, Stiggelbout AM. A short psychosocial questionnaire for patients with Parkinson's disease: the SCOPA-PS. *J Clin Epidemiol.* (2003) 56:61–7. doi: 10.1016/S0895-4356(02)00569-3
55. Isella V, Mapelli C, Morielli N, Siri C, de Gaspari D, Pezzoli G, et al. Diagnosis of possible mild cognitive impairment in Parkinson's disease: validity of the SCOPA-Cog. *Parkinsonism Relat Disord.* (2013) 19:1160–3. doi: 10.1016/j.parkreldis.2013.08.008
56. Hoogland J, Boel JA, de Bie RMA, Schmand BA, Geskus RB, Dalrymple-Alford JC, et al. Risk of Parkinson's disease dementia related to level I MDS PD-MCI. *Mov Disord.* (2019) 34:430–5. doi: 10.1002/mds.27617
57. Szeto JYY, Mowszowski L, Gilat M, Walton CC, Naismith SL, Lewis SJG. Assessing the utility of the movement disorder society task force level 1 diagnostic criteria for mild cognitive impairment in Parkinson's disease. *Parkinsonism Relat Disord.* (2015) 21:31–5. doi: 10.1016/j.parkreldis.2014.10.020
58. Barton B, Grabli D, Bernard B, Czernecki V, Goldman JG, Stebbins G, et al. Clinical validation of movement disorder society-recommended diagnostic criteria for Parkinson's disease with dementia. *Mov Disord.* (2012) 27:248–53. doi: 10.1002/mds.24059
59. Uysal-Cantürk P, Hanagasi HA, Bilgiç B, Gürvit H, Emre M. An assessment of movement disorder society task force diagnostic criteria for mild cognitive impairment in Parkinson's disease. *Eur J Neurol.* (2018) 25:148–53. doi: 10.1111/ene.13467
60. Cholerton BA, Zabetian CP, Quinn JF, Chung KA, Peterson A, Espay AJ, et al. Pacific Northwest Udall Center of excellence clinical consortium: study design and baseline cohort characteristics. *J Park Dis.* (2013) 3:205–14. doi: 10.3233/JPD-130189
61. Campos LS, Guimarães RP, Piovesana LG, de Azevedo PC, Santos LMB, D'Abreu A. Clinical predictors of cognitive impairment and psychiatric complications in Parkinson's disease. *Arq Neuropsiquiatr.* (2015) 73:390–5. doi: 10.1590/0004-282X20150016
62. Broeders M, de Bie RMA, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. *Neurology.* (2013) 81:346–52. doi: 10.1212/WNL.0b013e31829c5c86
63. Müller B, Assmus J, Herlofson K, Larsen JP, Tysnes O-B. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat Disord.* (2013) 19:1027–32. doi: 10.1016/j.parkreldis.2013.07.010
64. Aarsland D, Andersen K, Larsen JP, Perry R, Wentzel-Larsen T, Lolk A, et al. The rate of cognitive decline in Parkinson disease. *Arch Neurol.* (2004) 61:1906–11. doi: 10.1001/archneur.61.12.1906
65. Pigott K, Rick J, Xie SX, Hurtig H, Chen-Plotkin A, Duda JE, et al. Longitudinal study of normal cognition in Parkinson disease. *Neurology.* (2015) 85:1276–82. doi: 10.1212/WNL.0000000000002001
66. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. *Lancet Neurol.* (2017) 16:66–75. doi: 10.1016/S1474-4422(16)30328-3
67. Pirogovsky E, Schiehser DM, Obtera KM, Burke MM, Lessig SL, Song DD, et al. Instrumental activities of daily living are impaired in Parkinson's disease patients with mild cognitive impairment. *Neuropsychology.* (2014) 28:229–37. doi: 10.1037/neu0000045
68. Ma L, Chan P. Understanding the physiological links between physical frailty and cognitive decline. *Aging Dis.* (2020) 11:405–18. doi: 10.14336/AD.2019.0521
69. Wang CY, Chan L, Wu D, Chi W-C, Yen C-F, Liao H-F, et al. Effect of cognitive disability and ambulation status on functioning in moderate-to-advanced Parkinson disease. *Front Neurol.* (2019) 10:1360. doi: 10.3389/fneur.2019.01360
70. Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, et al. Cognitive decline in Parkinson disease. *Nat Rev Neurol.* (2017) 13:217–31. doi: 10.1038/nrneurol.2017.27
71. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *Lancet Neurol.* (2018) 17:559–68. doi: 10.1016/S1474-4422(18)30127-3
72. Monastero R, Cicero CE, Baschi R, Davì M, Luca A, Restivo V, et al. Mild cognitive impairment in Parkinson's disease: the Parkinson's disease cognitive study (PACOS). *J Neurol.* (2018) 265:1050–8. doi: 10.1007/s00415-018-8800-4
73. Hoogland J, Boel JA, de Bie RMA, Geskus RB, Schmand BA, Dalrymple-Alford JC, et al. Mild cognitive impairment as a risk factor for Parkinson's disease dementia. *Mov Disord.* (2017) 32:1056–65. doi: 10.1002/mds.27002
74. Wang Q, Zhang Z, Li L, Wen H, Xu Q. Assessment of cognitive impairment in patients with Parkinson's disease: prevalence and risk factors. *Clin Interv Aging.* (2014) 9:275–81. doi: 10.2147/CIA.S47367
75. Solla P, Cannas A, Floris GL, Orofino G, Costantino E, Boi A, et al. Behavioral, neuropsychiatric and cognitive disorders in Parkinson's disease patients with and without motor complications. *Prog Neuropsychopharmacol Biol Psychiatry.* (2011) 35:1009–13. doi: 10.1016/j.pnpbp.2011.02.002
76. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, García-Sánchez C, Gironell A, Trapecio Group Study. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Mov Disord.* (2008) 23:1889–96. doi: 10.1002/mds.22246
77. McDermott KL, Fisher N, Bradford S, Camicioli R. Parkinson's disease mild cognitive impairment classifications and neurobehavioral symptoms. *Int Psychogeriatr.* (2018) 30:253–60. doi: 10.1017/S1041610217002265
78. Hollocks MJ, Lawrence AJ, Brookes RL, Barrick TR, Morris RG, Husain M, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain J Neurol.* (2015) 138(Pt 12):3803–15. doi: 10.1093/brain/awv304
79. Dobkin RD, Interian A. Improved understanding, detection, and management of neuropsychiatric complications: essential components to the optimal treatment of Parkinson's disease. *Int Psychogeriatr.* (2019) 31:1–4. doi: 10.1017/S1041610219000048
80. Nie K, Gao Y, Mei M, Guo M, Huang Z, Wang L, et al. The clinical characteristics and cognitive features of mild cognitive impairment in Parkinson's disease and the analysis of relevant factors. *J Clin Neurosci.* (2019) 63:142–8. doi: 10.1016/j.jocn.2019.01.021
81. Nicoletti A, Luca A, Baschi R, Cicero CE, Mostile G, Davì M, et al. Incidence of mild cognitive impairment and dementia in Parkinson's disease: the Parkinson's disease cognitive impairment study. *Front Aging Neurosci.* (2019) 11:21. doi: 10.3389/fnagi.2019.00021
82. Levy G, Tang MX, Cote LJ, Louis ED, Alfaro B, Mejia H, et al. Motor impairment in PD: relationship to incident dementia and age. *Neurology.* (2000) 55:539–44. doi: 10.1212/WNL.55.4.539
83. Szeto JYY, Walton CC, Rizos A, Martinez-Martin P, Halliday GM, Naismith SL, et al. Dementia in long-term Parkinson's disease patients: a multicentre retrospective study. *NPJ Park Dis.* (2020) 6:2. doi: 10.1038/s41531-019-0106-4

84. Martínez-Martín P, Frades-Payo B, Rodríguez-Blázquez C, Forjaz MJ, de Pedro-Cuesta J, Grupo Estudio Longitudinal de Pacientes con Enfermedad de Parkinson. Psychometric attributes of scales for outcomes in Parkinson's disease-cognition (SCOPA-Cog), Castilian language. *Rev Neurol.* (2008) 47:337–43. doi: 10.33588/rn.4707.2008430
85. Lawton M, Baig F, Rolinski M, Ruffman C, Nithi K, May MT, et al. Parkinson's disease subtypes in the Oxford Parkinson Disease Centre (OPDC) discovery cohort. *J Park Dis.* (2015) 5:269–79. doi: 10.3233/JPD-140523
86. Fereshtehnejad S-M, Postuma RB. Subtypes of Parkinson's disease: what do they tell us about disease progression? *Curr Neurol Neurosci Rep.* (2017) 17:34. doi: 10.1007/s11910-017-0738-x
87. Mestre TA, Eberly S, Tanner C, Grimes D, Lang AE, Oakes D, et al. Reproducibility of data-driven Parkinson's disease subtypes for clinical research. *Parkinsonism Relat Disord.* (2018). 56:102–6. doi: 10.1016/j.parkreldis.2018.07.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 August 2020
doi: 10.3389/fneur.2020.00821

Echogenicity Changes in Brainstem Raphe Detected by Transcranial Parenchymal Sonography and Clinical Characteristics in Parkinson's Disease

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OPEN ACCESS

Edited by:
Carmen Rodriguez-Blazquez, Instituto de Salud Carlos III (ISCIII), Spain

Reviewed by:
Christos Krogias, Ruhr University Bochum, Germany
Kezhong Zhang, Nanjing Medical University, China

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *12 April 2020*
Accepted: *30 June 2020*
Published: *07 August 2020*

Citation:
Bei H-Z, Chen J-P, Mao C-J, Zhang Y-C, Chen J, Du Q-Q, Xue F, He P-C, Jin H, Wang F-Y and Liu C-F (2020) Echogenicity Changes in Brainstem Raphe Detected by Transcranial Parenchymal Sonography and Clinical Characteristics in Parkinson's Disease. Front. Neurol. 11:821. doi: 10.3389/fneur.2020.00821

Background: Decreased brainstem raphe (BR) echogenicity detected by transcranial parenchymal sonography (TCS) is associated with depression in psychiatric and neurologic diseases. However, previous studies focusing on the relationship between motor and non-motor symptoms and echogenicity changes in BR in patients with PD yielded controversial results.

Objectives: To investigate the relationship between echogenicity changes in BR detected by TCS and motor and a series of non-motor symptoms in patients with PD.

Methods: Consecutive PD patients were recruited from the Second Affiliated Hospital of Soochow University. Demographic information and Motor and non-motor symptoms for all subjects were collected. TCS was used to detect the echogenicity changes in BR in PD patients.

Results: One hundred and thirty-five consecutive patients with PD were enrolled in the study. The BR abnormal rate was significantly higher in PD patients with anxiety ($p = 0.003$) or depression ($p = 0.022$) than patients without. Spearman correlation analyses showed that Hamilton Rating Scale for Depression(HRSD) ($r = 0.274$, $p = 0.002$) and Parkinson's Disease Questionnaire 39-item(PDQ-39) ($r = 0.208$, $p = 0.034$) scores were positively correlated with abnormal BR echogenicity. Multivariate logistic regression analyses showed that HRSD and HAMA scores were associated with BR hypoechogenicity, the corresponding odds ratios (confidence intervals) were 1.07 (95% CI, 1.01–1.13) and 1.10(1.01–1.18), respectively. However, the PDQ-39 score was not associated with BR hypoechogenicity.

Conclusion: The abnormal reduction in BR echogenicity detected by TCS is associated with depression and anxiety, but not motor symptoms in PD patients.

Keywords: Parkinson's disease, depression, anxiety, transcranial parenchymal sonography, brainstem raphe

INTRODUCTION

Parkinson's disease (PD) is pathologically characterized by degeneration and loss of dopamine neurons in the substantia nigra (SN) and decreased dopamine content in the striatum, which result in motor symptoms such as tremor, rigidity and bradykinesia, and non-motor symptoms such as psychiatric symptoms, cognitive dysfunction, autonomic dysfunction, sleep disorder, and abnormal sensation. Transcranial parenchymal sonography (TCS), a type of non-invasive neuroimaging technology can detect brain parenchymal lesions directly *in vivo* and was first used in PD patients by Becker in 1995 (1). Abnormal hyperechogenicity of the SN is also considered to be a prodromal marker of PD. The sensitivity and specificity of SN hyperechogenicity for predicting PD are 82.4 and 82.5%, respectively (2). Recent studies have shown that patients with depression have abnormal brainstem raphe (BR) echogenicity (3–5). Combining SN hyperechogenicity with BR hypoechogenicity may be useful to detect individuals at risk for developing PD (6). The incidence of BR hypoechogenicity was much higher in PD patients with depression than patients without depression and controls (7, 8). Besides depression, reduced echogenicity of BR also indicated an increased risk of other non-motor symptoms in PD patients, such as urinary incontinence (9). However, previous studies focusing on the relationship between motor and non-motor symptoms and echogenicity changes in BR in patients with PD yielded controversial results. For example, Bouwmans et al. found no association between depression and hyperechogenic SN or hypoechogenic BR in PD patients (10).

In this study, TCS was used to detect the changes in BR echogenicity in PD patients whose motor and non-motor symptoms were comprehensively evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) and several non-motor symptom scales. We aimed to investigate the relationship between the changes in BR echogenicity and motor and a series of non-motor symptoms in PD patients.

MATERIALS AND METHODS

Subjects

All PD subjects come from outpatient and hospitalized patients in the Second Affiliated Hospital of Soochow University from January 2011 to December 2015 and satisfied the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (11). All subjects underwent TCS. Subjects were excluded if they had a secondary parkinsonism syndrome, deep brain stimulation,

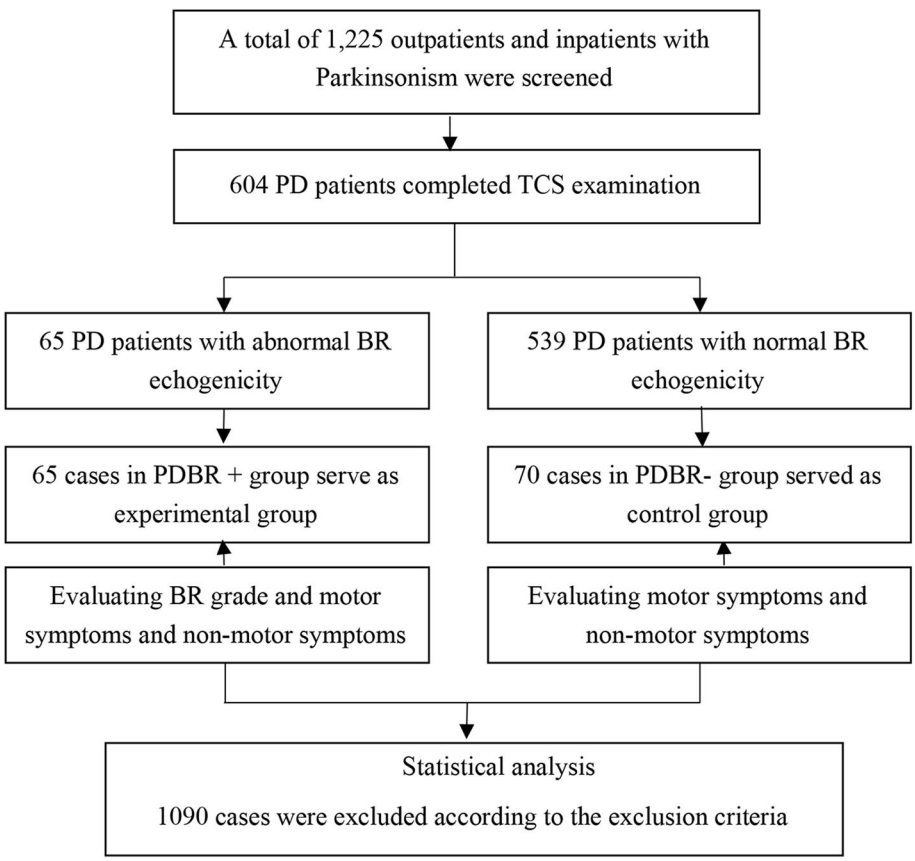

FIGURE 1 | Flowchart of patient enrollment. This figure shows how the subjects enrolled in the study.

parkinson-plus syndrome, atypical parkinsonian syndrome, malignant neoplasm, epilepsy, or severe cardiopulmonary disease. Subjects who could not complete the motor or non-motor symptoms evaluation were also excluded. The flow chart shows the procedure for subject enrollment (**Figure 1**).

Demographic data, including age, gender, age at onset, disease duration, and detailed medical history were collected. All subjects were carefully evaluated by a movement disorder specialist. The UPDRS (12) and Hoehn & Yahr (H&Y) (13) scale were applied in all PD subjects during the "ON" medication state to evaluate motor symptoms. A Chinese version of the Montreal Cognitive Assessment (MoCA) (14) questionnaire (Beijing version) were used to evaluate the cognitive function of these patients. Neuropsychiatric symptoms were evaluated by the Hamilton Rating Scale for Depression (HRSD-24) (15)and the Hamilton Anxiety Scale (HAMA-14) (16). For HRSD-24, each item can range from 0 to 4 points. Patients with PD with HRSD-24 score $\geq$8 were defined as PD with depression. Parkinson's Disease Questionnaire 39-item (PDQ-39) (17) were also used in PD patients (**Figure 1**).

Calculation of a daily levodopa equivalent dose (LED) for each patient was based on theoretical equivalence to levodopa as

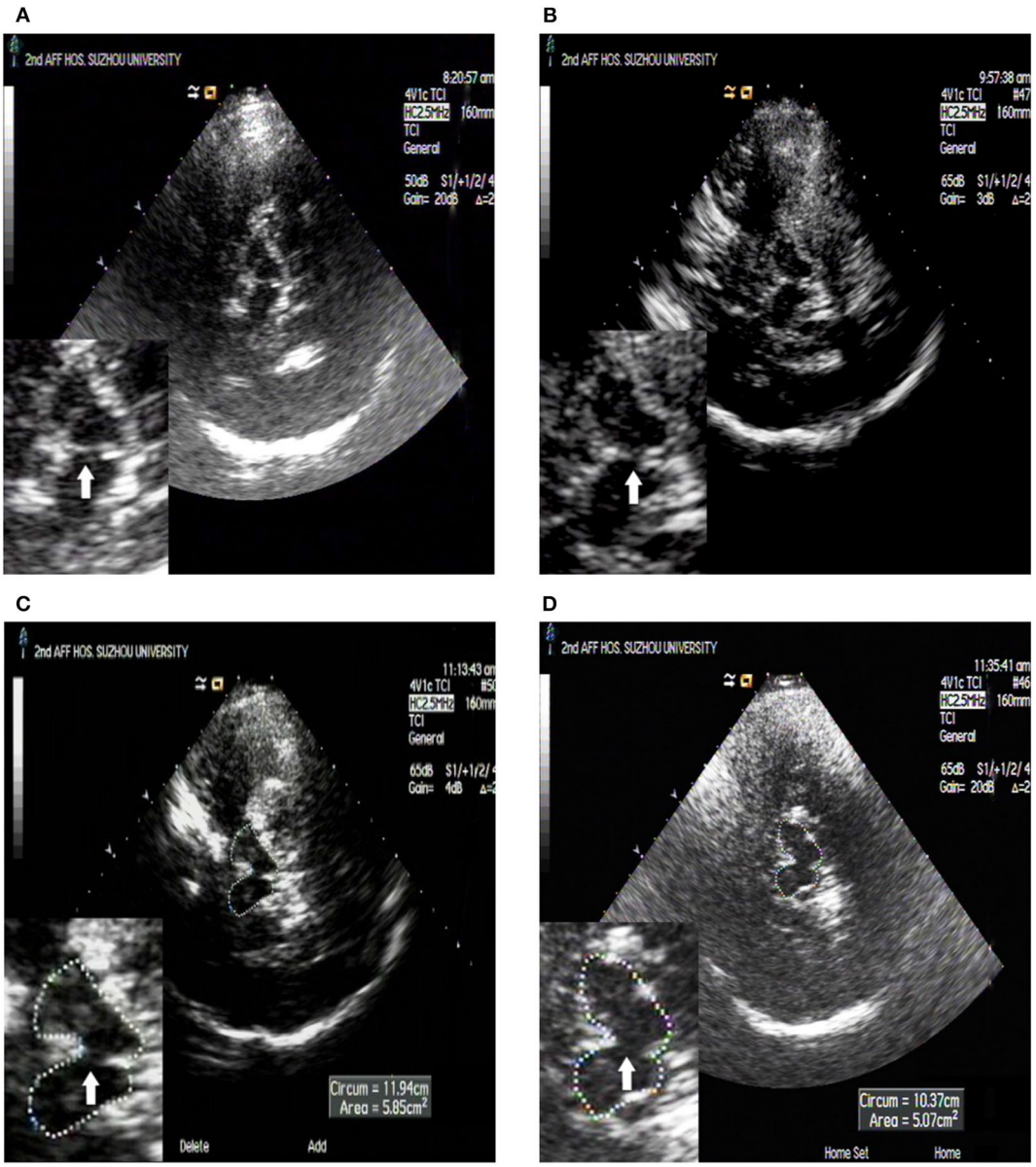

FIGURE 2 | TCS images of BR echogenicity. BR semiquantitatively rated grade scale: the white arrow shows the BR. **(A)** Normal raphe, with the same echogenicity as the red nucleus according to previous recommendations; **(B)** Decreased raphe, echogenic raphe was decreased compared with the red nucleus but it was continuous; **(C)** Interrupted raphe, echogenic raphe was interrupted compared with the red nucleus; **(D)** Invisible raphe, echogenic raphe was not visible.

TABLE 1 | Demographic data of PD patients in the abnormal and normal BR echogenicity group.

Characteristics*	Total (n = 135)	BR abnormal group (n = 65)	BR normal group (n = 70)	p-value
Male	83 (61.48)	35 (53.85)	48 (68.57)	0.079
Age, years	63.62 ± 8.90	64.15 ± 8.42	63.13 ± 9.36	0.506
Age at onset, years	59.88 ± 9.11	60.13 ± 8.63	59.66 ± 9.60	0.768
Disease duration, months	36.0 (22.0–60.0)	46.5 (22.5–63.0)	33.0 (22.0–60.0)	0.145
Education				
Illiteracy	25 (18.52)	14 (21.54)	11 (15.71)	0.709
Primary school	26 (19.26)	13 (20.00)	13 (18.57)	
Middle school	40 (29.63)	16 (24.62)	24 (34.29)	
High school	20 (14.81)	11 (16.92)	9 (12.86)	
University	24 (17.78)	11 (16.92)	13 (18.57)	
Daily levodopa-equivalent dose(mg)	262.5 (0–400.0)	300.0 (37.5–400.0)	250.0 (0–381.0)	0.314
Areas of SN hyperechogenicity	0.58 (0.39–0.99)	0.62 (0.49–1.06)	0.56 (0.39–0.93)	0.332
Number of SN hyperechogenicity (n,%)	(58, 43.0%)	(22, 33.8%)	(36, 51.4%)	0.039

**Continuous variables are expressed as mean ± standard deviation or as median (interquartile range). Categorical variables are expressed as frequency (percent). SN, substantia nigra.*

follows: levodopa dose + levodopa dose × 1/3 if on entacapone + piribedil (mg) + pramipexole (mg) 100 + selegiline (mg) × 10 +amantadine (mg) + controlled release levodopa (mg) × 0.75.

Only one patient was on the treatment with antidepressants.

Transcranial Parenchymal Sonography

A color-coded phased-array ultrasound system, equipped with a 2.5 MHz transducer (Sequoia 512, Siemens Medical Solutions USA, Inc. 4V1C transducer) was used to detect signals through the right and left temporal bone windows in the axial plane (18–21).

The midbrain was identified as a butterfly-shaped low-echogenic area, surrounded by the hyperechogenic basal cistern. SN is a hyperechogenic area with respect to surrounding structures. SN echogenic size measurements were performed on axial TCS scans automatically after manually encircling the outer circumference of the SN's echogenic area. Areas with SN echogenicity $\geq$0.20 cm^2 on either side were classified as hyperechogenic (22).

The BR was detected as a hyperechogenic continuous line in the middle of the midbrain with the same echogenicity as the red nucleus. The best images were selected for the study (20, 21). BR echogenicity was categorized according to current guideline recommendations on 2 grades of BR echogenicity (normal vs. reduced echogenicity) (20). Patients with BR echogenicity same as red nucleus were determined as BR echogenicity normal group, while patients with BR echogenicity as reduced, interrupt or not visible were determined as BR echogenicity abnormal group in this study (**Figure 2**).

All TCS assessments were performed by two experienced examiners who were blinded to the clinical data. Patients with different BR grades as rated by the two sonologists were excluded.

This study was approved by the ethics committee of our hospital and an informed consent was obtained from each patient.

Statistical Analysis

Normally distributed continuous variables are presented as means ± standard deviations (SD), skewed distributed continuous variables are presented as median (interquartile range), and comparisons between two groups were performed by the Student's t-test or non-parametric test, respectively. Categorical variables are described as frequencies (percentages) and compared between groups using the Chi-square test. Bonferroni correction has been applied for multiple comparisons. Spearman rank correlation and multivariate logistic regression analysis were used to assess the correlation between BR echogenicity score and the motor and non-motor symptoms. All p-values were 2 tailed, and a significance level of 0.05 was used. Statistical analysis was conducted using SPSS version 21 (IBM SPSS, Chicago, IL, USA).

RESULTS

There were 652 PD patients undergoing the TCS examination. Forty-eight (7.36%, 48/652) PD patients were excluded due to insufficient transtemporal bone window. Six hundred four patients with PD completed the TCS examination. One hundred and thirty-five consecutive patients with PD were enrolled in this study, eventually.

Demographic Data and Changes in BR Measured by TCS

Sixty-five (35 males and 30 females) patients had abnormal BR echogenicity and were aged 64.15 ± 8.42 years, age at onset was 60.13 ± 8.63 years, and disease duration was 46.5 (42.25) months. Seventy (48 males and 22 females) patients had normal BR echogenicity. The average age of the patients was 63.13 ± 9.36 years, age at onset was 59.66 ± 9.60 years, and disease duration was 33–39 months. No statistically significant differences were observed for gender, age, age at onset, disease duration, and education between the BR echogenicity normal group and abnormal group (**Table 1**).

Changes in BR Echogenicity and Motor and Non-motor Symptoms in PD Patients

The HRSD (Z = 3.052, p = 0.002), HAMA (t = 2.472, p = 0.017), and PDQ-39 (Z = 2.117, p = 0.034) scores were

TABLE 2 | Comparison of motor and non-motor symptoms between the abnormal and normal BR echogenicity group.

Characteristics*	Total ($n = 135$)	BR abnormal group ($n = 65$)	BR normal group ($n = 70$)	p-value
UPDRS II	10.61 ± 5.70	11.31 ± 6.10	9.97 ± 5.27	0.175
UPDRS III	23.06 ± 12.74	24.29 ± 13.15	21.91 ± 12.33	0.28
H-Y stage	2.0 (1.5–2.5)	2.0 (1.5–3.0)	2.0 (1.5–2.0)	0.106
MoCA	21.28 ± 4.88	21.32 ± 4.76	21.25 ± 4.99	0.945
HRSD	6.0 (2.0–12.0)	9.0 (4.0–15.0)	5.0 (1.0–8.0)	0.002
HRSD≥8	49 (36.3%)	30 (61.2%)	19 (38.8%)	0.022†
HRSD<8	86 (63.7%)	35 (40.7%)	51 (59.3%)	
HAMA	6.52 ± 6.69	9.09 ± 8.88	5.11 ± 4.63	0.017
HAMA≥7	63 (46.7%)	39 (61.9%)	24 (38.1%)	0.003#
HAMA<7	72 (53.3%)	26 (36.1%)	46 (63.9%)	
PDQ-39	15.0 (6.0–39.0)	15.0 (6.0–45.0)	12.0 (9.0–45.0)	0.034

**Continuous variables are expressed as mean ± standard deviation or as median (interquartile range). Categorical variables are expressed as frequency (percent).*
† Comparisons of the abnormal BR echogenicity rate between depression group and non-depression group.
 # Comparisons of the abnormal BR echogenicity rate between anxiety group and non-anxiety group.
UPDRS II, second part of the Unified Parkinson Disease Rating Scale score; UPDRS III, third part of the Unified Parkinson Disease Rating Scale score; H-Y stage, Hoehn-Yahr stage; MoCA, Montreal Cognitive Assessment; HRSD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; PDQ-39, Parkinson's Disease Questionnaire-39.

TABLE 3 | Spearman rank correlation analysis between BR echogenicity and depression, anxiety and PDQ-39.

Variables	r-value	p-value
HRSD	0.274	0.002
HAMA	0.201	0.047
PDQ-39	0.208	0.034

PDQ-39, Parkinson's Disease Questionnaire-39; HRSD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale.

TABLE 4 | Multivariate logistic regression analysis of depression, anxiety, and PDQ-39 with BR hypoechogenicity.

Variables	Odds ratio (95% confidence interval)	p-value
HRSD, per 5 score increase		
Unadjusted model	1.45 (1.13–1.86)	0.004
Adjusted model	1.07 (1.01–1.13)	0.022
HAMA, per 5 score increase		
Unadjusted model	1.59 (1.12–2.26)	0.009
Adjusted model	1.10 (1.01–1.18)	0.021
PDQ-39, per 5 score increase		
Unadjusted model	1.10 (1.00–1.21)	0.05
Adjusted model	1.08 (0.94–1.25)	0.260

Adjusted model included age, gender, age at onset of PD, education, disease duration, daily levodopa-equivalent dose, UPDRS II, UPDRS III, and Hoehn-Yahr stage.

higher in the BR abnormal group than in the BR normal group. The BR abnormal rate was significantly higher in PD patients with anxiety ($p = 0.003$) or depression ($p = 0.022$) than patients without. For multiple comparisons, the threshold for statistical significance after Bonferroni correction was set at $p < 0.007$ (correcting for 7 comparisons: $0.05/7 \approx 0.007$). HRSD was statistically significant after Bonferroni correction ($p < 0.007$) (**Table 2**).

Spearman Rank Correlation and Multivariate Logistic Regression Analysis Between BR Echogenicity and the HRSD, HAMA, and PDQ-39 Score

Spearman rank correlation analysis revealed that abnormal BR echogenicity was positively correlated with the HRSD and PDQ-39 score, with low correlation coefficients ($r = 0.274$, $p = 0.002$ for HRSD; $r = 0.208$, $p = 0.034$ for PDQ-39). Spearman rank correlation analysis suggested a marginally statistical significant association between BR hypoechogenicity and HAMA score ($r = 0.201$, $p = 0.047$). After adjusting age, gender, age at onset of PD, education, disease duration, LED, UPDRS II, UPDRS III, and H-Y stage, only HRSD, and HAMA score were associated with BR hypoechogenicity with ORs 1.07 (95% CI, 1.01–1.13), and 1.10 (1.01–1.18), respectively (**Tables 3**, **4**).

DISCUSSION

It has been proved that TCS is reliable and sensitive in detecting basal ganglia abnormalities, e.g., of SN in PD. Many studies focusing on the echogenicity of the SN and PD diagnosis or clinical characteristics. Hyperechogenicity of SN has high diagnostic accuracy in the diagnosis of PD patients from healthy controls (23). In addition, PD patients with depression had marked SN hyperechogenicity and reduced echogenicity of BR indicating SN hyperechogenicity combined with reduced echogenicity of BR might be useful to detect individuals at risk for developing PD (24). Some studies have demonstrated a correlation between abnormal BR echogenicity and depression (3). BR hypoechogenicity is more common in certain types of PD, such as glucocerebrosidase gene(GBA) mutations related to PD (25). The present study aims to investigate the relationship between changes in BR echogenicity and motor and a series of non-motor symptoms, such as depression, anxiety, and cognition in PD patients.

Spearman rank correlation analysis showed weak correlations between HRSD and PDQ-39 scores and the reduction in BR echogenicity, and multivariate logistic regression revealed that HRSD and HAMA scores were associated with BR hypoechogenicity in the adjusted model. No association was found between PDQ-39 scores and BR hypoechogenicity. Cho et al. found that decreased BR echogenicity was much higher in PD patients with depression (7). PD patients with depression and patients with depression only showed a significantly higher

presence of abnormal BR than those without depression and healthy controls (6). A significant direct relationship was also found between the BDI score and BR hypoechogenicity (8). Our study confirmed the relationship between BR hypoechogenicity and depression. BR alterations in TCS may be a biomarker for depression and apathy in PD patients (26). Decreased BR echogenicity indicates morphological alterations in the midbrain which is involved in the pathogenesis of depression not only in PD patients with depression but also in unipolar depression patients (6, 8, 25). Abnormal BR echogenicity could also be seen in *de novo* PD patients with depression, which could also be found in both control and PD groups without depression (7). These TCS findings support the hypothesis of a pathogenetic link between depression and PD (9). However, conflicting findings have also been reported (6, 10). Bouwmans et al. found no association between depression and hyperechogenic SN or hypoechogenic BR in PD patients (10). The main reason for the difference may be the disease severity. We noticed that the patients included in their study were early PD patients. UPDRS III score of patients was significantly lower than the score of our patients and others (10).

Furthermore, spearman rank correlation analysis suggested a marginal statistical significance association between BR hypoechogenicity and HAMA score. Besides the dopamine system, neurodegeneration of neurons involved several other neurotransmitter systems, such as the norepinephrine system, serotonin system, and acetylcholine system. BR is the main source of serotonin in the prefrontal cortex. Changes in BR echogenicity may reflect a decline in the function of the serotonin system (27). The overlap of widespread dysfunction of the limbic system and complex neurotransmission abnormalities in PD patients with depression and anxiety may explain the correlation between reduced echogenicity of BR and anxiety (28).

In this study, we noticed that only 48 (7.36%, 48/652) PD patients were excluded due to insufficient transtemporal bone window, which is remarkably lower compared to other studies in the Asian population (7, 29), but consistent with our previous studies (30–32). This may be because of the 2.5 MHz transducer we used (Sequoia 512, Siemens Medical Solutions USA, Inc. 4V1C transducer), which was compared with other transducers and showed the best penetration.

There were some limitations of the study. This was a cross-sectional study, and we were unable to draw a conclusion about the relationship between changes in BR echogenicity and the clinical manifestations of PD as the disease progressed. Also, the sample size in this study was relatively small, and studies with a large number of PD patients from multiple centers are needed to confirm the results.

In summary, an abnormal reduction in BR echogenicity detected by TCS is associated with depression and anxiety, but not motor symptoms in PD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Second Affiliated Hospital of Soochow University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-ZB, J-PC, and C-JM designed the study, collected the data, and drafted the manuscript. Y-CZ, JC, FX, P-CH, HJ, and F-YW collected the data. Q-QD analyzed the data. C-FL designed the study. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Key R&D Program of China (grant number 2017YFC0909100); National Natural Science Foundation of China (grant number 81801258); Youth Fund of Jiangsu Province's Natural Science Foundation (grant number BK20170355); Social Development Projects in Jiangsu Province (grant number BE2017653); Joint Project of Science and Technology Million Project of Inner Mongolia Medical University [grant number YKD2017KJBW(LH)051]; Jiangsu Provincial Key R&D Program (grant number BE2018658); Gusu Health Talents Training Project (GSWS2019041); Jiangsu Provincial Medical Key Discipline Project (grant number ZDXKB2016022); Suzhou Clinical Research Center of Neurological Disease (grant number Szzx201503); and Key and Youth Projects of Changshu Health Commission (csws201824, cswsq201801).

ACKNOWLEDGMENTS

We thank the study participants and their relatives, and the clinical staff for their support and contribution to this study.

REFERENCES

1. Becker G, Becker T, Struck M, Lindner A, Burzer K, Retz W, et al. Reduced echogenicity of brainstem raphe specific to unipolar depression: a transcranial color-coded real-time sonography study. *Biol Psychiatry.* (1995) 38:180–4. doi: 10.1016/0006-3223(94)00263-3
2. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal parkinson's disease. *Mov Disord.* (2015) 30:1600–11. doi: 10.1002/mds.26431
3. Walter U, Skoloudik D. Transcranial sonography (TCS) of brain parenchyma in movement disorders: quality standards, diagnostic applications and novel technologies. *Ultraschall Med.* (2014) 35:322–31. doi: 10.1055/s-0033-1356415

4. Walter U, Prudente-Morrissey L, Herpertz SC, Benecke R, Hoeppner J. Relationship of brainstem raphe echogenicity and clinical findings in depressive states. *Psychiatry Res.* (2007) 155:67–73. doi: 10.1016/j.pscychresns.2006.12.001
5. Krogias C, Walter U. Transcranial sonography findings in depression in association with psychiatric and neurologic diseases: a review. *J Neuroimaging.* (2016) 26:257–63. doi: 10.1111/jon.12328
6. Liu XJ, Zhang L, Zhang YF, Xu W, Hu Y, Liu Y, et al. Echogenic alteration in the raphe nuclei measured by transcranial sonography in patients with parkinson disease and depression. *Medicine.* (2018) 97:e13524. doi: 10.1097/MD.0000000000013524
7. Cho JW, Baik JS, Lee MS. Mesencephalic midline change on transcranial sonography in early parkinson's disease patients with depression. *J Neurol Sci.* (2011) 310:50–2. doi: 10.1016/j.jns.2011.07.055
8. Toomsoo T, Randver R, Liepelt-Scarfone I, Kadastik-Eerme L, Asser T, Rubanovits I, et al. Prevalence of depressive symptoms and their association with brainstem raphe echogenicity in patients with parkinson's disease and non-PD controls. *Psychiatry Res Neuroimaging.* (2017) 268:45–49. doi: 10.1016/j.pscychresns.2017.08.005
9. Walter U, Skoloudik D, Berg D. Transcranial sonography findings related to non-motor features of parkinson's disease. *J Neurol Sci.* (2010) 289:123–7. doi: 10.1016/j.jns.2009.08.027
10. Bouwmans AE, Weber WE, Leentjens AF, Mess WH. Transcranial sonography findings related to depression in parkinsonian disorders: cross-sectional study in 126 patients. *PeerJ.* (2016) 4:e2037. doi: 10.7717/peerj.2037
11. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for parkinson disease. *Arch Neurol.* (1999) 56:33–9. doi: 10.1001/archneur.56.1.33
12. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder society URTF movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* (2008) 23:2129–70. doi: 10.1002/mds.22340
13. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
14. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
15. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
16. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x
17. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The parkinson's disease questionnaire (PDQ-39): development and validation of a parkinson's disease summary index score. *Age Ageing.* (1997) 26:353–7. doi: 10.1093/ageing/26.5.353
18. Becker G, Naumann M, Scheubeck M, Hofmann E, Deimling M, Lindner A, et al. Comparison of transcranial sonography, magnetic resonance imaging, and single photon emission computed tomography findings in idiopathic spasmodic torticollis. *Mov Disord.* (1997) 12:79–88. doi: 10.1002/mds.870120114
19. Becker G, Berg D, Kruse N, Schroder U, Warmuth-Metz M, Rieckmann P, et al. Evidence for shoulder girdle dystonia in selected patients with cervical disc prolapse. *Mov Disord.* (2002) 17:710–16. doi: 10.1002/mds.10132
20. Walter U, Behnke S, Eyding J, Niehaus L, Postert T, Seidel G, et al. Transcranial brain parenchyma sonography in movement disorders: state of the art. *Ultrasound Med Biol.* (2007) 33:15–25. doi: 10.1016/j.ultrasmedbio.2006.07.021
21. Berg D, Behnke S, Walter U. Application of transcranial sonography in extrapyramidal disorders: updated recommendations. *Ultraschall Med.* (2006) 27:12–19. doi: 10.1055/s-2005-858962
22. Berg D, Godau J, Walter U. Transcranial sonography in movement disorders. *Lancet Neurol.* (2008) 7:1044–55. doi: 10.1016/S1474-4422(08)70239-4
23. Tao A, Chen G, Deng Y, Xu R. Accuracy of transcranial sonography of the substantia nigra for detection of parkinson's disease: a systematic review and meta-analysis. *Ultrasound Med Biol.* (2019) 45:628–41. doi: 10.1016/j.ultrasmedbio.2018.11.010
24. Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. *Brain.* (2007) 130:1799–807. doi: 10.1093/brain/awm017
25. Bottcher T, Rolfs A, Meyer B, Grossmann A, Berg D, Kropp P, et al. Clinical, genetic, and brain sonographic features related to parkinson's disease in gaucher disease. *J Neurol.* (2013) 260:2523–31. doi: 10.1007/s00415-013-7011-2
26. Richter D, Woitalla D, Muhlack S, Gold R, Tonges L, Krogias C. Brainstem raphe alterations in TCS: a biomarker for depression and apathy in parkinson's disease patients. *Front Neurol.* (2018) 9:645. doi: 10.3389/fneur.2018.00645
27. Becker T, Becker G, Seufert J, Hofmann E, Lange KW, Naumann M, et al. Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. *J Neurol Neurosurg Psychiatry.* (1997) 63:590–6. doi: 10.1136/jnnp.63.5.590
28. Thobois S, Prange S, Sgambato-Faure V, Tremblay L, Broussolle E. Imaging the etiology of apathy, anxiety, and depression in parkinson's disease: implication for treatment. *Curr Neurol Neurosci Rep.* (2017) 17:76. doi: 10.1007/s11910-017-0788-0
29. Komatsu T, Terasawa Y, Arai A, Sakuta K, Mitsumura H, Iguchi Y. Transcranial color-coded sonography of vertebral artery for diagnosis of right-to-left shunts. *J Neurol Sci.* (2017) 376:97–101. doi: 10.1016/j.jns.2017.03.012
30. Zhang Y, Zhang YC, Sheng YJ, Chen XF, Wang CS, Ma Q, et al. Sonographic alteration of basal ganglia in different forms of primary focal dystonia: a cross-sectional study. *Chin Med J.* (2016) 129:942–5. doi: 10.4103/0366-6999.179792
31. Zhang YC, Hu H, Luo WF, Sheng YJ, Chen XF, Mao CJ, et al. Alteration of brainstem raphe measured by transcranial sonography in depression patients with or without parkinson's disease. *Neurol Sci.* (2016) 37:45–50. doi: 10.1007/s10072-015-2350-7
32. Luo WF, Zhang YC, Sheng YJ, Fang JC, Liu CF. Transcranial sonography on parkinson's disease and essential tremor in a Chinese population. *Neurol Sci.* (2012) 33:1005–9. doi: 10.1007/s10072-011-0876-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CLINICAL TRIAL
published: 13 August 2020
doi: 10.3389/fneur.2020.00846

Effects of an Innovative Telerehabilitation Intervention for People With Parkinson's Disease on Quality of Life, Motor, and Non-motor Abilities

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Parkinson's disease (PD) often leads to multifactorial motor and non-motor disabilities with resultant social restrictions. Continuity of care in this pathology, including a tailored home rehabilitation, is crucial to improve or maintain the quality of life for patients. The aim of this multicenter study was to test in a pilot sample of PD patients the efficiency and efficacy of the Human Empowerment Aging and Disability (HEAD) program. The virtual reality HEAD program was administered in two consecutive phases: (1) in clinic (ClinicHEAD, 12 45-minutes sessions, 3 sessions/week); (2) at home (HomeHEAD, 60 45-minutes sessions, 5 sessions/week). Thirty-one PD outpatients were enrolled [mean age (SD) = 66.84 (9.13)]. All patients performed ClinicHEAD, and after allocation (ratio 1:2) were assigned to the HomeHEAD or the Usual Care (UC) group. Motor, cognitive and behavioral outcome measures were assessed at enrollment (T0), at hospital discharge (T1), at 4 (T2) and 7 (T3) months after baseline. After ClinicHEAD (T1 vs. T0 comparison) a significant ($p<0.05$) improvement in functional mobility, balance, upper limb mobility, global cognitive function, memory, quality of life and psychological well-being was observed. After the HomeHEAD intervention there was an additional enhancement for upper limb mobility. At T3 follow-up, the UC group that did not continue the HEAD program at home showed a worsening with respect to the HomeHEAD group in balance and functional mobility. Furthermore, in the HomeHEAD group, a positive association was observed between adherence, mental and physical health (SF-12). A trend was also registered between adherence and positive affect. The digital health patient-tailored rehabilitation program resulted in improving motor and non-motor abilities and quality of life in clinical setting, enhancing the motor function in telerehabilitation at home, and maintaining the non-motor abilities and quality of life at follow-up. In the near future, people with PD can be supported also at home with individualized rehabilitation strategies for a better quality of life and wellbeing along with lower costs for society.

Keywords: rehabilitation, technology, telerehabilitation, nervous system disease, Parkinson's disease, digital health, continuity of care, quality of life

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *31 March 2020*
Accepted: *07 July 2020*
Published: *13 August 2020*

Citation:
Isernia S, Di Tella S, Pagliari C, Jonsdottir J, Castiglioni C, Gindri P, Salza M, Gramigna C, Palumbo G, Molteni F and Baglio F (2020) Effects of an Innovative Telerehabilitation Intervention for People With Parkinson's Disease on Quality of Life, Motor, and Non-motor Abilities. Front. Neurol. 11:846. doi: 10.3389/fneur.2020.00846

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition, causing primarily an impairment in the motor system (1). It is the second most common neurodegenerative disorder after Alzheimer's disease and affects approximately seven million people globally (2). Moderate to severe dopaminergic neuronal loss that affects the *substantia nigra pars compacta* area may be considered the principal cause of the motor clinical manifestations, such as bradykinesia plus rigidity and resting tremor from the early stages of the disease (3). Even though PD is still considered a paradigmatic movement disorder, it is accompanied by remarkable non-motor symptoms, such as cognitive impairment, behavioral disturbances, hyposmia, sleep disorders, and autonomic dysfunction, even from the early stages of the pathology (4–6). Non-motor symptoms may become dominant with the progression of the disease in the clinical manifestation, with significant implications on quality of life and caregiver burden (7).

Among non-motor symptoms, cognitive impairment, which develops in dementia in up to 80 % of patients in the long term (8–10), can be characterized by a dysfunction in different domains, covering executive functions, working memory, attention, visuospatial abilities, and language (11). In particular, executive functions are essential for goal-directed activities (12), and executive dysfunction in PD, principally ascribed to damage of the dorsal striatum and putamen, and resulting in a functional alteration of dorsolateral fronto-subcortical circuits (13), may affect a great variety of goal-directed behaviors. As a result, patients may encounter difficulties with planning, organizational skills, and concentration while undertaking daily activities. Furthermore, the impairment in visuospatial abilities is related to deficits in other cognitive domains (for example, executive functions and verbal memory), postural control and gait, along with functional disability in non-demented patients with mild to moderate PD (14).

Considering the broad spectrum of motor and non-motor symptoms, the management of people with PD needs multidisciplinary interventions in order to provide patients with independent functioning as long as possible. Also, engaging in physical and cognitive exercise for the long term is of utmost importance to mitigate the course of the pathology and to prevent the need for PD medications at the early stages (15). At the same time, long-lasting health care is extremely expensive and often patients are not able to bear the associated costs (16). Recently, a randomized controlled study shed light on the beneficial effect of rehabilitation interventions in a real world setting on clinical deficits in PD (17).

To answer the need of implementing health interventions in the continuity of care together with decreasing health care costs for the chronic management of PD (18, 19), digital health offers several potential advantages. Accordingly, recent contributions described the growing implementation and diffusion of digital health solutions (20), suggesting an imminent integration of this digital revolution into the health care system (21). Especially, three main directions are being adopted: to guarantee a higher accessibility to health care services through telehealth to slow down related costs; to expand the target of intervention mainly focused on acute conditions to also chronic pathologies; to move the setting of rehabilitation from inside the clinic to patient's home (22). This is in line with the recent plan of Sustainable Development Goals that called for an imminent consolidation of the healthcare system with digital technology (23). Moreover, the implication of digital health allows to act and promote lifestyle changes, by reaching patients in their everyday life setting (24). Concerning telerehabilitation interventions, the central role of a digital health platform is recognized, constituting the hub of clinic-home communication and allowing assessment, monitoring and feedback during the rehabilitation period (25, 26).

Recent work regarding the implementation and validation of digital health interventions for PD provide evidence for their beneficial effect on outcome measures and health care costs (17, 27). Furthermore, the perception of patients with PD regarding telemedicine is positive (28) indicating many strengths, such as the cost-related and time-dependence convenience and the possibility of telecommunication with clinicians (29). However, the refinement of digital health solutions with the goal to offer a patient-tailored intervention remains an on-going process (30). Moreover, the study of O'Connor et al. (31) created the digital health engagement model aiming at highlighting the key aspects to be considered to provide digital health products able to be endorsed and accredited by the clinical system.

Recently, a new multidimensional telerehabilitation protocol for chronic neurological disease has been implemented for the continuity of care, named the Human Empowerment Aging and Disability (HEAD) program. This digital health solution proposes a rehabilitation program in a virtual reality (VR) setting to enhance motor and cognitive abilities and quality of life. HEAD has already been shown to promote high adherence coupled with good usability of its technological system (32). However, studies investigating its effectiveness on treating PD-related clinical impairments are still lacking.

The aim of this study was to test the clinical effectiveness of the HEAD telerehabilitation protocol in patients with PD. First, we investigated the efficiency of the HEAD system, in terms of adherence and usability; second, we explored the impact of HEAD program on the outcome measures, such as motor, cognitive functions and quality of life.

METHODS

Intervention Design

The study design was previously described in a recent work (32) and registered (ID: NCT03025126). Briefly, outpatients were involved in 1-month HEAD rehabilitation in the clinic, 45-min-session/3 times per week, for a total of 12 sessions (ClinicHEAD). Then, they were consecutively allocated to the HEAD telerehabilitation (HomeHEAD) or usual care condition (UC) with a ratio of 1:2 (this allocation procedure was due the limited availability of the technological kits). HomeHEAD consisted of a 3-month HEAD telerehabilitation, 45-min-session/5 times per week, in total 60 sessions. In the UC

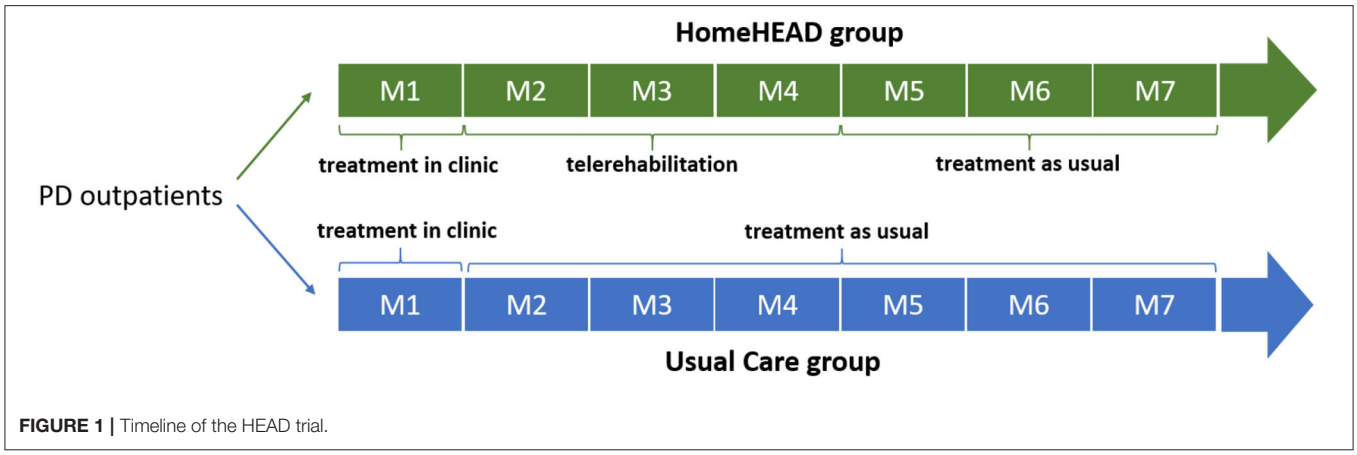

FIGURE 1 | Timeline of the HEAD trial.

condition people performed physical activities they would usually do (**Figure 1**). Participants were assessed for efficiency and effectiveness measures at baseline (T0), after 1-month of ClinicHEAD (T1), after 3-months of HomeHEAD/UC (T2), and after 7 months from the enrollment (T3). The assessors were blind to patients' allocation and were unable to distinguish whether subjects received HomeHEAD treatment or treatment as usual (UC).

The study was approved by the local ethics committees of the three centers in which participants were recruited: the inter-company of the province of Lecco, Como and Sondrio, the Ethics Committee of IRCCS Don Gnocchi Foundation and the inter-company "Città della Salute e della Scienza" of Turin.

The Treatment: HEAD Program vs. Usual Care

The HEAD program is a multidimensional rehabilitation for the enhancement of motor and cognitive functions of people with chronic neurological diseases, such as PD, Multiple Sclerosis and stroke [see for details on the HEAD protocol (32)]. Briefly, each rehabilitative session includes both motor and cognitive tasks, leisure and dual-task activities. These activities are patient-tailored and are conceived to improve balance, endurance, speed, and strength of both upper and lower limbs, executive functions, memory, language, and dual-task capabilities. The activities are embedded in short video clips to motivate the patients to carry out the rehabilitation. The video-clips constitute a reward, a short break or the material of the activity (for example to be memorized). Gaming technological devices are provided to perform activities in a VR scenario using Kinect (Microsoft, WA, USA) and Leap Motion (Leap Motion Inc., CA, USA) devices. Patients access the HEAD portal via Internet in order to perform rehabilitation sessions managed by clinicians in the HEAD digital health platform [for more details see (32)]. During ClinicHEAD, patients familiarized themselves with the HEAD technological kit in clinic and carried out the activities under the supervision of clinical professionals. After 1-month of ClinicHEAD, patients performed rehabilitation activities in the continuity of care at home (HomeHEAD). Technical issues and motivation were managed through periodic phone calls and the availability of the HEAD Help Desk.

Patients who were not allocated to the HomeHEAD were instructed to not take part in motor or cognitive activities related to rehabilitation different from what they usually do (Usual Care condition—UC). They were invited to follow health recommendations of the neurologists for their clinical conditions.

Participants

Thirty-one patients were recruited in three clinics in North Italy: Valduce Hospital Villa Beretta Rehabilitation Center in Lecco, IRCCS Don Carlo Gnocchi Foundation in Milan and District Clinic San Camillo in Turin. In each clinical center, patients were enrolled during their periodical clinical visit by the neurologists. The inclusion criteria for the eligibility for participation in the study were: age < 80 years, diagnosis of PD, stable pharmacological treatment for at least the past 3 months, Hoehn and Yahr (33) score ≤ 2. Exclusion criteria included a Mini-Mental State Examination score < 20 (34), disabling pain, epilepsy, severe visual acuity and auditory perception, communication deficit, severe dysmetry and severe upper limb difficulties in passive range of motion. Before taking part in the study, patients read the information sheet of the study and gave their written informed consent.

In total, 31 people with PD were included in the study. All participants underwent 1 month of ClinicHEAD rehabilitation. Then, 11 patients were allocated to HEAD telerehabilitation while 20 people with PD were included in the UC condition. Three patients in the UC group were not evaluated at T3 (see **Supplementary Material**: CONSORT Flow Diagram for details).

Measurement

The assessment was performed to evaluate output and outcome measures to test *efficiency* and *effectiveness* of HEAD treatment, respectively.

Output Measures

To test *efficiency*, adherence to treatment was registered during ClinicHEAD and HomeHEAD through the number of sessions

performed by participants. This datum was collected in the HEAD platform and allowed clinicians to monitor whether or not patients performed the telerehabilitation activities at home. In fact, information related to each patient's log in the HEAD session and his performance of scheduled rehabilitation activities was saved in the HEAD platform server (32). The 80% of sessions completed has been considered as the cut-off of a high adherence to treatment in the PD sample both for clinic (total sessions > 9) and home (total sessions ≥ 48) program. Also, perceived usability related to the HEAD technological kit was investigated through the System Usability Scale [SUS; (35)]. This scale measures the usability of technology systems and devices by administering 10 items with a 5-point Likert scale, for a total score ranging from 10 to 100. A guideline cut-off of 68 is reported as a good level of usability for the technological system.

Outcome Measures

The *effectiveness* assessment protocol comprised a multi-domain evaluation by measuring cognitive functions, motor abilities and quality of life. Primary outcomes were change in one measure for each domain assessed, as described below. Outcomes on all other scales and tests were secondary.

Motor functions assessment

Motor abilities were evaluated by a physiotherapist blind to the group's allocation of the patients with the following measures:

- Berg Balance Scale [BBS; (36)]. A test for the assessment of patient's static balance and his risk of falling through a 14-item 4-points scale, with a total score ranging from 0 to 56;
- Ten Meter Walk Test [10MWT; (37)]. A test for a quantitative analysis of the walking speed. The speed in meters *per sec* for a walk of 10 meters is measured. It is considered an assessment of functional mobility.
- Two Minute Walk Test [2MWT; (38)]. A test for a quantitative analysis of gait speed and endurance. The distance walked in 2 min is registered, as a functional mobility measure.
- Box and Block Test [BBT; (39)]. A test for the assessment of upper extremity function related to the activities of daily living. Individuals move as many blocks as possible from one compartment to another in 60 s. A score is obtained by counting the number of blocks moved during the 1-min interval.

2MWT score consisted of the primary outcome of the motor domain.

Non-motor functions assessment

The evaluation of cognitive functions was performed by a neuropsychologist blind to the group's allocation of the patients and comprised the following neuropsychological battery:

- Montreal Cognitive Assessment [MoCA; (40)]. It is a sensitive tool for global cognitive level assessment, by screening different domains, such as executive function, memory, language, visual-spatial abilities, attention, calculation, abstraction, spatial and temporal orientation. The total score ranges from 0 to 30. In this study, Conti's (40) correction was adopted to correct scores for age and level of education of individuals;
- Rivermead Behavioral Memory Test-Third Edition [RBMT-3; (41, 42)]. An ecological battery for the assessment of memory abilities. This test evaluates memory through ten tasks: (1) First and Second Names, presentation and delayed memory of names and faces, (2) Belongings, prospective memory consisting of remembering to ask regarding personal belonging at the end of the evaluation session, (3) Appointments, prospective memory task in which subject has to remember to ask two questions when an alarm rings, (4) Picture Recognition, delayed picture recognition against distractors, (5) Story, immediate and delayed recognition of short stories, (6) Face Recognition, delayed recall of faces against distractors, (7) Route, immediate and delayed recall of a short route previously performed with the experimenter, (8) Messages, immediate and delayed remembering to pick up an envelope and a book in the right place of the route, (9) Orientation and Date, questions related to persons, places and timing, (10) Novel Task, immediate and delayed recall of the sequential procedure showed by the examiner to make a star with pieces inside a template. In addition to the sub-test scores, a global memory index score can be obtained.

MoCA score was considered the primary outcome of the cognitive domain.

Quality of life and psychological well-being assessment

The evaluation of quality of life of PD were performed with:

- Short Form Health Survey [SF-12; (43)]. This Scale measures a global assessment of the health-related quality of life from the patients' perspective. Consisting of 12 items, it assesses Mental Health and Physical Health Score.
- Positive Affect and Negative Affect Schedule [PANAS; (44)]. This is a schedule for the positive and negative affective states measure. This scale allows the measuring of the level of positive and negative affect. 20 5-points Likert scale items are administered, and 2 sub-scales are obtained: positive affect and negative affect, ranging 0–50 each.

The scores of the SF-12 Mental and Physical domains represented the primary outcome of the quality of life domain.

Statistical Analyses

All statistical analyses on output and outcome measures were performed using IBM SPSS Statistics software (Version 24). Descriptive statistics were employed to evaluate efficiency and effectiveness data. To evaluate adherence, we computed the percentage of subjects who reached at least the 80% of completed sessions. Multiple imputation by chained equations was performed to replace missing values in order to address potential biases due to incomplete follow-up. The multiple imputation procedure was applied in accordance with guidelines recommended for clinical trial data (45), which suggests that multiple imputation should not be used with a percentage of missing values more than 40%. In the imputation model were

TABLE 1 | Sociodemographic characteristics of the whole PD sample (ClinicHEAD group), and UC and HomeHEAD groups.

	ClinicHEAD	UC	HomeHEAD	UC vs. HomeHEAD *p*
N	31	20	11	
Age [Mean (SD)]	66.84 (9.13)	67.55 (9.33)	65.55 (9.06)	0.563
Education [Mean (SD)]	11.77 (4.33)	12.05 (4.22)	11.27 (4.69)	0.637
Sex (M/F, %)	17/14 (54.8%, 45.2%)	13/7 (65.0%, 35%)	4/7 (36.4%, 63.6%)	0.125
MOTOR FUNCTIONING				
2MWT	131.23(36.72)	131.00 (36.47)	131.64 (38.94)	0.965
BBS [Mean (SD)]	48.67 (6.45)	48.37 (6.80)	49.18 (6.06)	0.733
BBT—dominant [Mean (SD)]	41.48 (13.56)	39.75 (14.88)	44.64 (10.66)	0.338
BBT—non dominant [Mean (SD)]	41.74 (13.59)	41.15 (15.32)	42.82 (10.32)	0.747
10MWT [Mean (SD)]	7.02 (4.90)	6.52 (2.43)	7.86 (7.60)	0.475
NON-MOTOR FUNCTIONING				
MoCA [Mean (SD)]	21.94 (2.82)	22.27 (2.64)	21.35 (3.16)	0.386
RBMT-GMI [Mean (SD)]	83.94 (17.81)	82.25 (16.42)	87.00 (20.58)	0.481

UC, usual care; BBT, Box and Block Test; 2MWT, 2-Meter Walk Test; BBS, Berg Balance Scale; MoCA, Montreal Cognitive Assessment; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; M, Mean; SD, Standard Deviation; p, p-value.

included all primary and secondary outcomes. Fifty datasets after imputation of plausible values to missing data were generated. Each primary/secondary outcome was considered and analyzed separately. We assessed patients' longitudinal performance at four time points: T0, T1, T2, and T3. Due to the multiple imputation procedure available in SPSS, we calculated change scores (Δvalues) from T1-T0, T2-T1, T3-T1, T3-T0 and after that we adopted paired and independent sample *t*-tests. Specifically, paired sample *t*-tests were performed to compare T1 vs. T0 outcome measures in the whole sample of PD patients, and T2 vs. T1 in the HomeHEAD group, while a two-sample *t*-test was performed to compare HomeHEAD and UC groups. Effect sizes were calculated for the primary outcomes. To evaluate the efficacy of HEAD treatment on quality of life and psychological well-being, we computed partial correlations. We explored the relationship between the adherence to the HEAD program and the Physical and Mental Health Scores of the SF-12 Health Survey at T1 in the whole group (ClinicHEAD) and at T2 and T3 separately in the UC and the HomeHEAD groups, controlling for the evaluation at the previous timepoint. An overall alpha-level of 0.05 was fixed for each statistical test. As suggested by Feise (46), regardless of *p*-value adjustments in testing that involves comparing treatments using multiple outcome measures with univariate statistical method to reach a reasonable conclusion, we calculated the magnitude of effects and we included effect sizes in **Tables 2**–**4**. Effects sizes (*Cohen's d*) were interpreted as follows: 0.2 to 0.49 as a small effect; 0.5 to 0.79 as an intermediate effect; 0.8 and higher as a strong effect (47).

RESULTS

Participants

Baseline demographical and clinical characteristic of our sample is reported in **Table 1**. The UC and HomeHEAD groups did not differ for age, years of education and sex (all *p*-values > 0.05).

Output Measures

Adherence

Twenty-six subjects (83.9%) demonstrated a high adherence to ClinicHEAD in terms of a rate of completed sessions above 80%. Moreover, 72.7% of HomeHEAD's participants (8 subjects vs. 11) reached the cut-off score of adherence.

Usability

Data showed a usability score over cut-off after both ClinicHEAD and HomeHEAD treatments. Results from the SUS showed a median value of 70.00 (25–75th percentile 60.00–82.50) at T1, and 85.00 (25–75th percentile 77.50–92.50) at T2.

Outcome Measures

Changes in Motor and Non-motor Outcomes After ClinicHEAD Program (T1 vs. T0)

The T1 vs. T0 comparison showed a significant improvement in functional mobility (2MWT: $t = 2.254$; $df = 30$; $p = 0.024$; *Cohen's d* $= 0.41$); balance (BBS: $t = 2.059$; $df = 30$; $p = 0.043$; *Cohen's d* $= 0.37$); upper limb mobility (BBT – dominant: $t = 4.680$; $df = 30$; $p < 0.001$; *Cohen's d* $= 0.84$; and non-dominant: $t = 2.836$; $df = 30$; $p = 0.005$; *Cohen's d* $= 0.51$); global cognitive function (MoCA: $t = 2.139$; $df = 30$; $p = 0.032$; *Cohen's d* $= 0.38$); memory (RBMT: $t = 3.645$; $df = 30$; $p < 0.001$; *Cohen's d* $= 0.66$). **Table 2** summarizes the results.

Changes in Motor and Non-motor Outcomes After HomeHEAD Program (T2 vs. T1)

In the HomeHEAD group ($N = 11$), the T2 vs. T1 comparison showed an additional enhancement for the upper limb mobility (BBT – non-dominant: $t = 2.861$; $df = 10$; $p = 0.004$; *Cohen's d* $= 0.86$). The positive effects obtained after ClinicHEAD program were also maintained in all other outcome measures in the HomeHEAD group (**Table 3**).

TABLE 2 | Effectiveness of ClinicHEAD program (T0 vs T1).

	T0		T1		*p*	*Cohen's d*
	Mean	**SD**	**Mean**	**SD**		
PRIMARY OUTCOME						
Motor						
2MWT	131.23	36.72	140.30	37.54	**0.024**	0.41
Non-motor						
MoCA	21.94	2.82	22.88	3.51	**0.032**	0.38
SECONDARY OUTCOME						
Motor						
BBS	48.67	6.45	50.43	6.00	**0.040**	0.37
BBT—dominant	41.48	13.56	46.39	13.73	**<0.001**	0.84
BBT—non dominant	41.74	13.59	44.81	13.74	**0.005**	0.51
10MWT	7.02	4.90	5.96	2.12	0.156	0.26
Non-motor						
RBMT-GMI	84.48	18.29	92.10	17.46	**<0.001**	0.66

p-values < 0.05 are reported in bold. BBT, Box and Block Test; 2MWT, 2-Meter Walk Test; BBS, Berg Balance Scale; MoCA, Montreal Cognitive Assessment; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; SD, Standard Deviation; p, p-value.

TABLE 3 | Effectiveness of HomeHEAD program (T1 vs T2).

	T1		T2		*p*	*Cohen's d*
	Mean	**SD**	**Mean**	**SD**		
PRIMARY OUTCOME						
Motor						
2MWT	139.27	29.19	140.91	41.88	0.744	0.10
Non-motor						
MoCA	22.37	4.98	23.47	3.15	0.346	0.28
SECONDARY OUTCOME						
Motor						
BBS	51.64	4.82	50.73	5.78	0.198	0.39
BBT—dominant	48.36	12.11	49.55	9.74	0.472	0.22
BBT—non dominant	44.82	11.29	49.27	10.52	**0.004**	0.86
10MWT	5.46	1.10	5.71	1.83	0.407	0.25
Non-motor						
RBMT-GMI	90.30	19.32	90.10	19.13	0.708	0.11

p-values < 0.05 are reported in bold. UC, usual care; BBT, Box and Block Test; 2MWT, 2-Meter Walk Test; BBS, Berg Balance Scale; MoCA, Montreal Cognitive Assessment; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; SD, Standard Deviation; p, p-value.

Changes in Motor and Non-motor Outcomes: Comparison Between UC and HomeHEAD Group

After ClinicHEAD treatment (ΔT1-T0) the UC group did not differ from the HomeHEAD group (**Table 4**). After home program (ΔT2-T1) differences between the HomeHEAD group and the UC were observed in upper limb mobility (BBT – non-dominant: $t = -3.169$; $df = 29$; $p = 0.002$; Cohen's $d = 1.19$) and functional mobility (2MWT: $t = -2.130$; $df = 29$; $p = 0.033$; *Cohen's* $d = 0.80$). Also, a trend of effect on dominant hand dexterity was observed after HomeHEAD (BBT – dominant: $t = -1.730$; $df = 29$; $p = 0.084$; Cohen's $d = 0.65$).

At the follow-up, the UC showed a worsening compared to the HomeHEAD group in balance (BBS, ΔT3-T1: $t = -2.006$; $df = 29$; $p = 0.045$; *Cohen's* $d = 0.75$; ΔT3-T0: $t = -2.273$; $df = 29$; $p = 0.023$; *Cohen's* $d = 0.85$) and functional mobility (2MWT, ΔT3-T1: $t = -2.007$; $df = 29$; $p = 0.045$; *Cohen's* $d = 0.75$). **Table 4** summarizes the results.

Quality of Life and Psychological Well-Being

The T1 vs. T0 comparison showed a significant improvement in the Mental Health Score of the SF-12 Health Survey ($t = 2.181$, df $= 29$; $p = 0.029$; $df = 30$; $p = 0.019$; *Cohen's* $d = 0.39$) and mood (PANAS positive affect: $t = 2.349$; $df = 30$; $p = 0.019$; *Cohen's* $d = 0.42$).

Investigating the relationship between SF-12 scores and adherence at HEAD treatment we observed:

- ClinicHEAD group: no significant correlation after clinic treatment (T1);
- HomeHEAD group:
  - a positive partial correlation between the percentage of completed sessions at home and the Mental Health Score of the SF-12 Health Survey at T2 including T1 Mental Health Score as covariate ($r = 0.743$; $p = 0.022$);
  - a positive partial correlation between the total completed sessions (Clinic+Home sessions) and the Physical Health Score of the SF-12 Health Survey at T3 including T0 Mental Health Score as covariate ($r = 0.790$; $p = 0.034$).
- UC group: a negative partial correlation between the total completed sessions and the Mental Health Score of the SF-12 Health Survey at T3 including T0 Mental Health Score as covariate ($r = -0.778$; $p < 0.001$).

Moreover, investigating the relationship between PANAS scores and adherence at HEAD treatment we observed:

- ClinicHEAD group: a positive partial correlation was observed between adherence of ClinicHEAD sessions and positive affect at T1, including PANAS score at T0 as covariate ($r = 0.417$; $p = 0.022$).
- HomeHEAD group: a trend was registered between the total number of completed sessions and positive affect at T3, including PANAS score at T0 as covariate ($r = 0.578$; $p = 0.080$)

UC group: no significant correlation at T2 and T3.

DISCUSSION

Digital technology is allowing innovative ways of rehabilitation care for chronic neurological diseases (18, 19), such as PD. Beneficial effects of telerehabilitation have recently been described (17, 27, 29). Given the growing effort spent in implementing increasingly patient-tailored rehabilitation in digital health continuity of care (30, 31), evidence of its effectiveness is needed (48).

TABLE 4 | Comparison between UC and HomeHEAD groups on neuropsychological and motor measures after ClinicHEAD program (ΔT1-T0), after 3-months of HomeHEAD/ UC (ΔT2-T0), after 6-months from ClinicHEAD (ΔT3-T1), and after 7 months from the enrolment (ΔT3-T0) using independent sample *t*-test.

	ΔT1-T0					**ΔT2-T1**					**ΔT3-T1**					**ΔT3-T0**				
	UC		**HomeHEAD**			**UC**		**HomeHEAD**			**UC**		**HomeHEAD**			**UC**		**HomeHEAD**		
	Mean	**SD**	**Mean**	**SD**	***p* (*Cohen's d*)**	**Mean**	**SD**	**Mean**	**SD**	***p* (*Cohen's d*)**	**Mean**	**SD**	**Mean**	**SD**	***p* (*Cohen's d*)**	**Mean**	**SD**	**Mean**	**SD**	***p* (*Cohen's d*)**
PRIMARY OUTCOME																				
Motor																				
2MWT	9.89	23.97	7.64	21.01	0.794 (0.10)	−10.71	14.19	1.64	16.60	**0.033** (0.80)	−20.71	36.99	−0.91	17.09	**0.045** (0.75)	−12.35	49.99	6.73	25.05	0.163 (0.54)
Non-motor																				
MoCA	0.75	1.80	1.27	3.38	0.572 (0.21)	−0.50	2.00	1.10	2.88	0.117 (0.61)	−0.10	3.04	0.09	3.45	0.867 (0.06)	0.90	3.26	1.36	2.34	0.683 (0.15)
SECONDARY OUTCOME																				
Motor																				
BBS	1.37	5.52	2.45	3.56	0.554 (0.22)	−5.00	9.64	−0.91	2.34	0.158 (0.65)	−7.17	14.09	−0.73	2.28	**0.045** (0.75)	−5.72	13.78	1.73	3.80	**0.023** (0.85)
BBT—dominant	5.55	5.94	3.73	5.71	0.408 (0.32)	−2.35	5.17	1.18	5.46	0.084 (0.67)	−1.22	9.08	1.36	4.52	0.307 (0.39)	4.00	9.54	5.09	6.99	0.744 (0.12)
BBT—non dominant	3.65	5.97	2.00	6.24	0.469 (0.28)	−1.65	4.76	4.45	5.16	**0.002** (1.19)	0.33	6.75	2.45	5.66	0.380 (0.33)	3.89	8.24	4.45	8.81	0.863 (0.07)
10MWT	−0.28	1.08	−2.41	6.75	0.173 (0.52)	0.19	0.78	0.25	1.00	0.899 (0.05)	1.31	3.64	0.43	1.40	0.355 (0.35)	1.14	3.96	−1.98	5.49	0.079 (0.68)
Non-motor																				
RBMT-GMI	9.67	13.16	4.27	11.49	0.247 (0.44)	1.33	16.38	−0.20	10.26	0.794 (0.10)	5.25	11.93	1.73	8.60	0.387 (0.33)	10.39	17.94	6.00	11.36	0.459 (0.28)

p-values < 0.05 are reported in bold. UC, usual care; BBT, Box and Block Test; 2MWT, 2-Meter Walk Test; BBS, Berg Balance Scale; MoCA, Montreal Cognitive Assessment; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; SD, Standard Deviation; p, p-value.

Technological usability represents a key prerequisite allowing for the enactment of rehabilitation at home (49). Notably, Palacholla et al. (50) included the lack of technology usability and technical support as a barrier to digital health adoption. Our study supported the technological suitability of the HEAD kit for telerehabilitation by the point of view of patients. Globally, our efficiency findings shed light on the suitability of the HEAD telerehabilitation for PD.

At the same time, high adherence (>80% of all sessions) to HEAD treatment in clinic and at home was reported. Given the active role of the patient in telerehabilitation, adherence is a critical issue, particularly in the home setting where the patient is involved in the management of his/her health care. Without adherence, the patient loses the choices to embrace the full range of benefits related to the continuity of care. In line with this, several studies have focused on factors enhancing positive effects of e-patient activities, named as the non-medical people involved in own healthcare management by technological systems (51, 52). Also, adherence to treatment, mirroring patient's motivation, reflects the patient's empowerment in his/her own health management, in line with the phenomenon of e-patients (53). Interestingly, our data demonstrated a direct relationship between changes in Mental and Physical Health Scores of the SF-12 Health Survey and adherence, in terms of a major amelioration of quality of life in patients who consistently adhered to the HEAD program at home. Whereas, a negative association was observed for the Mental Health Score of the SF-12 Health Survey in the UC group. This finding supports the direct effect of telerehabilitation with VR tools to provide a motivating environment, which promotes greater adherence to an intensive treatment over a long-term period (54).

With respect to the motor and non-motor outcome measures of the trial, our effectiveness results are favorable regarding the HEAD program maintenance and amelioration of PD-related deficits. Especially, the first step of HEAD rehabilitation program (ClinicHEAD) suggests positive influence on motor, non-motor and well-being domains considered. In fact, after 1 month of HEAD rehabilitation in the clinic, PD participants obtained positive results in terms of both upper and lower functional mobility, balance, global cognitive level, memory, positive affect, and mental health. The multidimensional enhancement reflects improvements across the wide spectrum of the PD-related symptoms, which typically start with difficulties involving mainly the motor sphere and subsequently progress to disabling non-motor manifestations (4–7). Thus, our results provide further support in favor of rehabilitation's benefits in PD, even in the initial mild-to-moderate phases of the disease (55).

Considering the second step of HEAD rehabilitation program at home (HomeHEAD), results revealed an additional improvement in motor functioning (functional mobility and the manual gross motor functionality) along with the maintenance of the motor and non-motor performance achieved after 1 month of ClinicHEAD. On the contrary, the UC group worsened in terms of functional mobility. These data confirm the evidence of a recent meta-analysis that found telehealth effects especially with respect to motor functions (55, 56). Notably, our results provide additional evidence that well-structured rehabilitation treatment at home is efficacious (57–59).

Accordingly, our HomeHEAD's participants seemed to maintain the functioning achieved even after 3-months from the end of the telerehabilitation, and especially in terms of equilibrium (Berg Balance Scale). This result fosters the potential of the HomeHEAD program in decreasing incidents of falling, one of the most frequent complications of the disease. Also, the direct association observed between psychological well-being/quality of life and the adherence to telerehabilitation treatment at home provided an additional explanation of the maintenance of the motor capability. Indeed, previous work has underlined a link between subjective well-being and motor impairment (60).

A key and innovative feature of HEAD rehabilitation was the multidimensional treatment approach, also implemented at home, and the inclusion of patient-tailored digital contents. In fact, HEAD program combined motor, cognitive, and occupational activities developed with VR tools and multimedia contents. Previous examples of home-based rehabilitation for PD focused on single target domains such as motor difficulties, while the non-motor domains were less frequently included in rehabilitation protocols (61, 62). On the contrary, recent studies suggested the adoption of an inter-professional approach to provide a successful management of the disease including also the treatment of non-motor symptoms of PD (27, 61, 63). Moreover, all digital contents of HomeHEAD were not designed with a fixed schedule but were tailored based on needs of the single patient. After an initial evaluation, the staff was able to change the composition of exercises (i.e., level, intensity, and multimedia contents) at set time points in response to training task performance. Altogether, these findings underlined and supported the role of the personalized digital medicine in PD population for the delivery of an efficacious multidimensional tele-rehabilitation able to enhance and maintain motor and non-motor functioning and allowing for the continuity of care at home as well as to implement an individually tailored treatment (64).

This study is not without limitations. First, we could not perform a randomized clinical trial given the pilot exploratory nature of the trial and the limited availability of the technological kits. Also, due to this constrain, our sample size is small and our result should be considered with caution. Future trial should expand our results with a wider sample size and performing a randomized controlled trial. Second, the first step of the trial, ClinicHEAD, was performed in all PD sample, preventing us from the possibility to infer efficacy conclusions in comparison to a control group.

In conclusion, our results reflect the positive influence of a multidimensional rehabilitation approach to be performed at home for patients with PD by underlining its effects on motor and non-motor functioning. In the near future, the digital e-health approach will support the introduction of individualized rehabilitation strategies for PD patients, for a better quality of life and well-being, and lower costs for society.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Don Gnocchi Foundation Ethics Committee. The patients/participants provided their written informed consent to participate in this study. This clinical trial has been registered on clinicaltrials.gov, under ID: NCT03025126.

AUTHOR CONTRIBUTIONS

FB, MS, and FM conceived the study. CP, CC, and CG recruited sample and recruited the clinical evaluation. JJ, PG, and GP collected data. SD, SI, and FB performed analysis and interpreted results. FB, SD, and SI wrote the first draft of manuscript. All authors reviewed and approved the final manuscript.

FUNDING

This study had been funded by the Fondazione Cariplo, Italy, and by Italian Ministry of Health (IRCCS Network of Neuroscience and Neurorehabilitation). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

ACKNOWLEDGMENTS

We would like to thank all patients who participated to the study. We would also thank the HEAD study group to make possible to conduct the present study (alphabetic order): Aggujaro S, Barra G, Bellomo M, Bertoni R, Boccini S, Bonanima M, Borgogno P, Bowman T, Canobbio S, Castagna A, Covarrubias M, Del Principe A, Enei L, Ferrari A, Ferrarin M, Fini M, Gencarelli N, Giordano A, Manfredini C, Marino C, Martina L, Mendozzi L, Mocarelli P, Montesano A, Nemni R, Perini G, Peverelli M, Proserpio D, Pugnetti L, Ripamonti E, Rossini M, Ruffin G, Saibene FL, Trombini D, Zanfini A.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00846/full#supplementary-material

REFERENCES

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet.* (2015) 386:896–912. doi: 10.1016/S0140-6736(14)61393-3
2. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol.* (2006) 5:525–35. doi: 10.1016/S1474-4422(06)70471-9
3. Kordower JH, Olanow CW, Dodiya HB, Chu Y, Beach TG, Adler CH, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain.* (2013) 136:2419–31. doi: 10.1093/brain/awt192
4. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Primers.* (2017) 3:17013. doi: 10.1038/nrdp.2017.13
5. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci.* (2017) 18:435–50. doi: 10.1038/nrn.2017.62
6. Trojano L, Papagno C. Cognitive and behavioral disorders in Parkinson's disease: an update. II: behavioral disorders. *Neurol Sci.* (2018) 39:53–61. doi: 10.1007/s10072-017-3155-7
7. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism Relat Disord.* (2006) 12:35–41. doi: 10.1016/j.parkreldis.2005.06.011
8. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol.* (2003) 60:387–92. doi: 10.1001/archneur.60.3.387
9. Aarsland D, Tandberg E, Larsen JP, Cummings JL. Frequency of dementia in Parkinson disease. *Arch Neurol.* (1996) 53:538–42. doi: 10.1001/archneur.1996.00550060082020
10. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord.* (2008) 23:837–44. doi: 10.1002/mds.21956
11. Papagno C, Trojano L. Cognitive and behavioral disorders in Parkinson's disease: an update. I: cognitive impairments. *Neurol Sci.* (2018) 39:215–23. doi: 10.1007/s10072-017-3154-8
12. Lezak MD, Howieson DB, Loring DW, Fischer JS. *Neuropsychological Assessment*. Oxford University Press (2004).
13. Dirnberger G, Jahanshahi M. Executive dysfunction in Parkinson's disease: a review. *J Neuropsychol.* (2013) 7:193–224. doi: 10.1111/jnp.12028
14. Uc EY, Rizzo M, Anderson SW, Qian S, Rodnitzky RL, Dawson JD. Visual dysfunction in Parkinson disease without dementia. *Neurology.* (2005) 65:1907–13. doi: 10.1212/01.wnl.0000191565.11065.11
15. Ellis T, Rochester L. Mobilizing Parkinson's disease: the future of exercise. *J Parkinsons Dis.* (2018) 8(s1):S95–100. doi: 10.3233/JPD-181489
16. Bovolenta TM, de Azevedo Silva SM, Arb Saba R, Borges V, Ferraz HB, Felicio AC. Systematic review and critical analysis of cost studies associated with Parkinson's disease. *Parkinsons Dis.* (2017) 2017:3410946. doi: 10.1155/2017/3410946
17. Ypinga JHL, de Vries NM, Boonen LHHM, Koolman X, Munneke M, Zwinderman AH, et al. Effectiveness and costs of specialised physiotherapy given via Parkinson Net: a retrospective analysis of medical claims data. *Lancet Neurol.* (2018) 17:153–61. doi: 10.1016/S1474-4422(17)30406-4
18. Bohingamu Mudiyanselage S, Watts JJ, Abimanyi-Ochom J, Lane L, Murphy AT, Morris ME, et al. Cost of living with Parkinson's disease over 12 months in Australia: a prospective cohort study. *Parkinsons Dis.* (2017) 2017:5932675. doi: 10.1155/2017/5932675
19. Chen JJ. Parkinson's disease: health-related quality of life, economic cost, and implications of early treatment. *Am J Manag Care.* (2010) 16:S87–93.
20. Waller M, Stotler C. Telemedicine: a primer. *Curr Allergy Asthma Rep.* (2018) 18:54. doi: 10.1007/s11882-018-0808-4
21. Topol EJ. A decade of digital medicine innovation. *Sci Transl Med.* (2019) 11:eaaw7610. doi: 10.1126/scitranslmed.aaw7610
22. Dorsey ER, Topol EJ. State of telehealth. *N Engl J Med.* (2016) 375:154–61. doi: 10.1056/NEJMra1601705
23. Merrell RC, Doarn CR. Sustainable development goals and telemedicine. *Telemed J E Health.* (2016) 22:787–8. doi: 10.1089/tmj.2016.29013.rcm
24. Khan N, Marvel FA, Wang J, Martin SS. Digital health technologies to promote lifestyle change and adherence. *Curr Treat Options Cardiovasc Med.* (2017) 19:60. doi: 10.1007/s11936-017-0560-4

25. Dor-Haim H, Katzburg S, Leibowitz D. A novel digital platform for a monitored home-based cardiac rehabilitation program. *J Vis Exp.* (2019) 146:e59019. doi: 10.3791/59019
26. Di Tella S, Pagliari C, Blasi V, Mendozzi L, Rovaris M, Baglio F. Integrated telerehabilitation approach in multiple sclerosis: a systematic review and meta-analysis. *J Telemed Telecare.* (2019) 27:1357633X19850381. doi: 10.1177/1357633X19850381
27. Bloem BR, Munneke M. Revolutionising management of chronic disease: the parkinsonNet approach. *BMJ.* (2014) 348:g1838. doi: 10.1136/bmj.g1838
28. Lai B, Bond K, Kim Y, Barstow B, Jovanov E, Bickel CS. Exploring the uptake and implementation of tele-monitored home-exercise programmes in adults with Parkinson's disease: a mixed-methods pilot study. *J Telemed Telecare.* (2020) 26:23–63. doi: 10.1177/1357633X18794315
29. Spear KL, Auinger P, Simone R, Dorsey ER, Francis J. Patient views on telemedicine for Parkinson disease. *J Parkinsons Dis.* (2019) 9:401–4. doi: 10.3233/JPD-181557
30. Espay AJ, Bonato, P, Nahab FB, Maetzler, W, Dean JM, Klucken, J, et al. Technology in Parkinson's disease: challenges and opportunities. *Mov Disord.* (2016) 31:1272–82. doi: 10.1002/mds.26642
31. O'Connor S, Hanlon P, O'Donnell CA, Garcia S, Glanville J, Mair FS, et al. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. *BMC Med Inform Decis Mak.* (2016) 16:120. doi: 10.1186/s12911-016-0359-3
32. Isernia S, Pagliari C, Jonsdottir J, Castiglioni C, Gindri P, Gramigna C, et al. Efficiency and patient-reported outcome measures from clinic to home: the human empowerment aging and disability program for digital-health rehabilitation. *Front Neurol.* (2019) 10:1206. doi: 10.3389/fneur.2019.01206
33. Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, Lau PN, et al. Progression of Parkinson's disease as evaluated by hoehn and yahr stage transition times. *Mov Disord.* (2010) 25:710–6. doi: 10.1002/mds.22875
34. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. *Arch Gen Psychiatry.* (1983) 40:812. doi: 10.1001/archpsyc.1983.01790060110016
35. Brooke J. SUS-A quick and dirty usability scale. *Usabil Eval Industry.* (1996) 189:4–7.
36. Berg K, Wood-Dauphinee S, Gayton WD. Measuring balance in the elderly: preliminary development of an instrument. *Physiother Canada.* (1989) 41:304–11. doi: 10.3138/ptc.41.6.304
37. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age Ageing.* (1997) 26:15–9. doi: 10.1093/ageing/26.1.15
38. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J.* (1982) 284:1607–8. doi: 10.1136/bmj.284.6329.1607
39. Desrosiers J, Bravo G, Hébert R, Dutil E, Mercier L. Validation of the box and block test as a measure of dexterity of elderly people: reliability, validity, and norms studies. *Arch Phys Med Rehabil.* (1994) 75:751–5. doi: 10.1016/0003-9993(94)90130-9
40. Conti S, Bonazzi S, Laiacona M, Masina M, Coralli MV. Montreal cognitive assessment (MoCA)-Italian version: regression based norms and equivalent scores. *Neurol Sci.* (2015) 36:209–14. doi: 10.1007/s10072-014-1921-3
41. Wilson BA, Greenfield E, Clare L, Baddeley A, Cockburn J, Watson P, et al. *Rivermead Behavioural Memory Test*. 3rd Ed. Firenze: Giunti O.S. Organizzazioni Speciali (Italian edition in by Beschin, N, Urbano, T and Treccani, B) (2008).
42. Wester AJ, van Herten JC, Egger JI, Kessels RP. Applicability of the rivermead behavioural memory test–third edition (RBMT-3) in Korsakoff's syndrome and chronic alcoholics. *Neuropsychiatr Dis Treat.* (2013) 9:875–81. doi: 10.2147/NDT.S44973
43. Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* (1996) 34:220–33. doi: 10.1097/00005650-199603000-00003
44. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol.* (1988) 54:1063–70. doi: 10.1037/0022-3514.54.6.1063
45. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials–a practical guide with flowcharts. *BMC Med Res Methodol.* (2017) 17:162. doi: 10.1186/s12874-017-0442-1
46. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC Med Res Methodol.* (2002) 2:8. doi: 10.1186/1471-2288-2-8
47. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. London: Academic Press (2013). doi: 10.4324/9780203771587
48. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med.* (2019) 25:44–56. doi: 10.1038/s41591-018-0300-7
49. Batra S, Baker RA, Wang T, Forma F, DiBiasi F, Peters-Strickland T. Digital health technology for use in patients with serious mental illness: a systematic review of the literature. *Med Devices.* (2017) 10:237–51. doi: 10.2147/MDER.S144158
50. Palacholla RS, Fischer N, Coleman A, Agboola S, Kirley K, Felsted J, et al. Provider-and patient-related barriers to and facilitators of digital health technology adoption for hypertension management: scoping review. *JMIR Cardiol.* (2019) 3:e11951. doi: 10.2196/11951
51. Gee PM, Paterniti DA, Ward D, Soederberg Miller LM. e-Patients perceptions of using personal health records for self-management support of chronic illness. *Comput Inform Nurs.* (2015) 33:229–37. doi: 10.1097/CIN.0000000000000151
52. Puspitasari I, Firdauzy A. Characterizing consumer behavior in leveraging social media for e-patient and health-related activities. *Int J Environ Res Public Health.* (2019) 16:E3348. doi: 10.3390/ijerph16183348
53. Gee PM, Greenwood DA, Kim KK, Perez SL, Staggers N, DeVon HA. Exploration of the e-patient phenomenon in nursing informatics. *Nurs Outlook.* (2012) 60: e9–16. doi: 10.1016/j.outlook.2011.11.005
54. Schröder J, van Criekinge T, Embrechts E, Celis X, Van Schuppen J, Truijen S, et al. Combining the benefits of tele-rehabilitation and virtual reality-based balance training: a systematic review on feasibility and effectiveness. *Disabil Rehabil Assist Technol.* (2019) 14:2–11. doi: 10.1080/17483107.2018.1503738
55. van der Kolk NM, de Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol.* (2019) 18:998–1008. doi: 10.1016/S1474-4422(19)30285-6
56. Chen YY, Guan BS, Li ZK, Yang QH, Xu TJ, Li HB, et al. Application of telehealth intervention in Parkinson's disease: a systematic review and meta-analysis. *J Telemed Telecare.* (2020) 26:3–13. doi: 10.1177/1357633X18792805
57. Carey JR, Durfee WK, Bhatt E, Nagpal A, Weinstein SA, Anderson KM, et al. Comparison of finger tracking versus simple movement training via telerehabilitation to alter hand function and cortical reorganization after stroke. *Neurorehabil Neural Repair.* (2007) 21:216–32. doi: 10.1177/1545968306292381
58. Chumbler NR, Quigley P, Li X, Morey M, Rose D, Sanford J, et al. Effects of telerehabilitation on physical function and disability for stroke patients: a randomized, controlled trial. *Stroke.* (2012) 43:2168–74. doi: 10.1161/STROKEAHA.111.646943
59. Tousignant M, Moffet H, Boissy P, Corriveau H, Cabana F, Marquis F. A randomized controlled trial of home telerehabilitation for post-knee arthroplasty. *J Telemed Telecare.* (2011) 17:195–8. doi: 10.1258/jtt.2010.100602
60. Rosqvist K, Hagell P, Odin P, Ekström H, Iwarsson S, Nilsson MH. Factors associated with life satisfaction in Parkinson's disease. *Acta Neurol Scand.* (2017) 136:64–71. doi: 10.1111/ane.12695
61. Vaartio-Rajalin H, Rauhala A, Fagerström L. Person-centered home-based rehabilitation for persons with Parkinson's disease–a scoping review. *Int J Nurs Stud.* (2019) 99:103395. doi: 10.1016/j.ijnurstu.2019.103395

62. Kalbe E, Aarsland D, Folkerts AK. Cognitive interventions in Parkinson's disease: where we want to go within 20 years. *J Parkinsons Dis.* (2018) 8(s1):S107–13. doi: 10.3233/JPD-181473
63. Keus S, Munneke M, Graziano M, Paltamaa J, Pelosin E, Domingos J, et al. *European Physiotherapy Guideline for Parkinson's Disease.* KNGF/ParkinsonNet (2014).
64. Klucken J, Krüger R, Schmidt P, Bloem BR. Management of Parkinson's disease 20 years from now: towards digital health pathways. *J Parkinsons Dis.* (2018) 8(s1):S85–94. doi: 10.3233/JPD-181519

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 13 August 2020
doi: 10.3389/fneur.2020.00808

Efficacy and Characteristics of the Stimuli of Action Observation Therapy in Subjects With Parkinson's Disease: A Systematic Review

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Background: The discovery of the Mirror Neuron System has promoted the development of Action Observation Therapy (AOT) to improve motor and functional abilities in patients with Parkinson's disease (PD). This innovative approach involves observing video-clips showing motor contents, which may vary across the studies influencing AOT efficacy. To date, no studies have systematically summarized the effects of AOT in patients with PD on motor and functional outcomes, underlining the characteristics of visual stimuli in relation to their efficacy.

Objectives: To describe the potential benefits of AOT in patients with PD and discuss the characteristics of visual stimuli used in clinical studies in relation to their efficacy.

Methods: A systematic literature search was carried out using MEDLINE via PubMed, EMBASE, Scopus, and PEDro, from inception until March 2020. Randomized controlled trials that investigated the effects of AOT on motor and functional recovery in patients with PD were included. Two independent reviewers appraised the records for inclusion, assessed the methodological quality, and extracted the following data: number and characteristics of participants, features and posology of the treatments, outcome measures at each follow-up, and main results. Findings were aggregated into a quantitative synthesis (mean difference and 95% confidence interval) for each time point.

Results: Overall, 7 studies (189 participants) with a mean PEDro score of 6.1 (range: 4–8) points were selected. Included studies revealed AOT as effective in improving walking ability and typical motor signs (i.e., freezing of gait and bradykinesia) in patients with PD. Moreover, when this approach incorporated ecological auditory stimuli, changes to functional abilities and quality of life were also induced, which persisted up to 3 months after treatment. However, included studies adopted AOT stimuli with heterogeneous posology (from a single session to 8 weeks) and characteristics of motor contents might be responsible for different motor and functional recovery (person-related and viewing perspectives, transitive or intransitive actions, healthy subjects or patients, and association or not with imitation).

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Silmar Teixeira, Federal University of Piauí, Brazil
Jorik Nonnekes, Radboud University Nijmegen Medical Centre, Netherlands

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *19 April 2020*
Accepted: *29 June 2020*
Published: *13 August 2020*

Citation:
Temporiti F, Adamo P, Cavalli E and Gatti R (2020) Efficacy and Characteristics of the Stimuli of Action Observation Therapy in Subjects With Parkinson's Disease: A Systematic Review. Front. Neurol. 11:808. doi: 10.3389/fneur.2020.00808

Conclusions: AOT leads to improvements in motor and functional abilities in patients with PD and the characteristics of visual stimuli may play a role in determining AOT effects, deserving further investigations.

Keywords: Parkinson's disease, action observation therapy, rehabilitation, functional recovery, motor function

INTRODUCTION

Parkinson's disease (PD) represents a progressive neurodegenerative disorder affecting about 6 million adults worldwide with greater incidence over 60 years of age (1–3). Motor manifestations (i.e., tremor, bradykinesia, muscular rigidity, postural instability, and abnormal gait patterns) and non-motor signs and symptoms (i.e., cognitive and autonomic dysfunctions, sleep disorders, fatigue, and depression) are common deficits causing disability, with consequences on participation and quality of life (4). In addition to pharmacological and surgical interventions, rehabilitation of motor function represents an effective tool to alleviate motor manifestations related to this condition (5–7). Rehabilitation in PD patients consists of approaches addressed to enhance functional abilities in order to reduce disability, improve quality of life, and minimize secondary complications of the disease (8, 9). The most common rehabilitative interventions include physical exercise (i.e., aerobic, resistance, and balance training as well as mobility and coordination exercises), walking training, and other activities such as dance or martial arts, which are often practiced in association with cues (8).

In this scenario, the discovery of the Mirror Neuron System (MNS) has promoted the development of Action Observation Therapy (AOT), which represents an innovative rehabilitative approach involving action observation with or without motor imagery and imitation of observed tasks (10–12). This approach takes advantage of the peculiarity of the Mirror Neurons System, which shows an activity during both execution and observation of actions, playing a key role in understanding actions performed by others (13). These neurons also discharge during the internal rehearsal of motor actions (motor imagery) and are implicated in motor learning through the building of a motor memory (14, 15). In particular, motor memory is a process that enables humans to plan, select, learn, and recall motor behaviors thanks to the interaction between pre-existing and new motor programs (16, 17). Neurophysiological findings have described MNS as an operating cerebral network in PD patients, able to play a potential compensatory role on brain functional alterations responsible for motor deficits (12). Consequently, studies aimed at investigating the effects of AOT on motor and functional abilities have been published over the past years, suggesting that AOT improves autonomy, walking ability, or typical motor signs such as freezing of gait and bradykinesia in patients with PD (17–20); however, a systematic review on this topic is missing. In particular, a single meta-analysis investigating the effectiveness of physiotherapy in these patients have reported positive results of AOT on freezing of gait (21), but the efficacy of this innovative tool on other functional outcome measures adopted in rehabilitation of patients with PD has never been systematically quantified. Moreover, AOT can be delivered alone or in association with usual physiotherapy through video-clips representing motor contents (20, 22). However, characteristics and motor contents of the stimuli delivered to patients vary across the studies (i.e., first-person or/and third-person, transitive or/and intransitive actions, healthy subjects or patients with the same condition as the viewers) (11, 23) and the efficacy of AOT could depend on the characteristics of the visual stimuli delivered to patients in reference to their motor impairment. Additionally, identification of the most appropriate AOT features may enhance the recruitment of the MNS, augmenting motor learning induced by this approach (11). However, to date, no studies have underlined the characteristics of AOT stimuli used in clinical trials in relation to their efficacy.

Against this background, it is relevant to conduct a systematic research aimed at pointing out the efficacy of AOT in patients with PD on motor and functional recovery and discussing the features of visual stimuli used in clinical studies, in order to underline the most effective stimuli.

Abbreviations: AOT, Action Observation Therapy; PD, Parkinson's disease; MNS, Mirror Neuron System; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; H&Y, Hoehn&Yahr; MMSE, Mini-Mental Status Examination; UPDRS, Unified Parkinson's Disease Rating Scale; FoG-diary, Freezing of Gait diary; FoG-Q, Freezing of Gait Questionnaire; PDQ-39, Parkinson's disease Questionnaire -39 items; BBS, Berg Balance Scale; TUG, Timed Up and Go; 10 MWT, 10 Meters Walking Test; FIM, Functional Independence Measure; 6 MWT, 6 Minutes Walking Test; fMRI, functional Magnetic Resonance Imaging.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the guidelines outlined by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (24).

Data Sources and Search Strategy

A literature search was carried out using the academic databases MEDLINE via PubMed, EMBASE, Scopus, and PEDro, from inception until March 2020. The search strategy included terms related to "Parkinson's disease," "action observation," "action observation therapy," "action observation training," and synonymous expressions, which were searched as keywords and free words in titles and abstracts in all databases. The extended version of the PubMed search strategy is provided in Appendix A (**Supplementary Material**). The reference lists of articles of interest were manually checked in order to find additional relevant studies.

Eligibility Criteria

The studies meeting the following inclusion criteria were included in the current review: (1) participants with clinical diagnosis of PD according to UK Parkinson's Disease Society Brain Bank criteria (25); (2) randomized controlled trials on rehabilitative intervention focused on AOT with no restrictions on duration, frequency, and characteristics of the stimuli; (3) comparison with any kind of intervention or placebo or no intervention; (4) outcomes related to motor and/or functional recovery assessed at any time point through clinical or instrumental tools; (5) studies written in English. No restrictions on age, disease duration, and severity of the condition were adopted. Overlapping or duplicated articles, thesis and conference proceedings, and abstracts were excluded.

Study Selection

Two independent reviewers carried out the literature search and all results were imported into EndNote X9 for screening. First, titles, and abstracts were screened to identify relevant studies; subsequently, the full text of the studies retained during the previous step was screened by the two reviewers, independently. In case of disagreement, a third reviewer facilitated the decision process.

Risk of Bias Assessment

Two independent reviewers assessed risk of bias of included studies through the PEDro scale. It represents an effective tool to evaluate methodological quality of clinical trials in rehabilitation; it is composed of 11 items that can contribute 1 point to the total score (10 points), except for item 1 (eligibility criteria), which is dichotomous (yes/no). Articles with a score ≥ 6 were considered as high quality, those with scores of 5 or 4 were considered as fair quality, and those with a score ≤ 3 were defined as low quality (26). In case of disagreement between the two reviewers during the rating process, a third reviewer was consulted to achieve a consensus.

Data Extraction and Synthesis

A reviewer extracted details of included studies (number and characteristics of p articipants, features, and posology of the treatments, outcome measures, and significant main findings). A second reviewer checked the correctness of the data extraction process and any disagreements were resolved through consultation with a third reviewer. Findings of eligible studies were aggregated into a quantitative synthesis and presented as tables. In particular, results of single studies were presented for outcomes measure at baseline and follow-up as mean difference and 95% confidence interval. The analysis was performed through the software RevMan 5.3 from the Cochrane Library.

RESULTS

Table 1 shows the characteristics of the included articles.

Selection of the Studies

In total, 812 records were identified through literature search procedures. Once duplicates (75 records) had been removed, and titles and abstracts were screened, the full text of 13 articles was evaluated for the final inclusion. Finally, 7 articles were selected for the current review. The selection flow chart is shown in **Figure 1**.

Participants

All patients of the studies were able to walk unassisted and had mild to moderate disease severity with a Hoehn&Yahr (H&Y) score of 2 or 3. Studies included participants with a disease duration of at least 5 years and without dementia (Mini-Mental Status Examination > 24). Four studies included patients with freezing of gait, with an incidence of at least one episode in a week and a duration of at least 2 s for each episode (17, 27–29). Finally, in addition to a PD control group, two studies provided a sample of healthy controls matched for age and sex with patients (18, 27).

Characteristics of AOT Interventions

AOT was administered alone (17–19, 27–29) or in association with conventional physiotherapy (20) using video-clips projected on a laptop (17–20, 27, 28) or on a wall located in front of participants (17). During observation, participants were asked to keep their attention on movement details without performing any kind of movement. Only one study, after observation of each video-clip, asked patients to imitate the observed actions while they were still watching the same video (28). Other four studies asked patients to imitate the observed tasks after observation (17, 20, 27, 29), whereas the remaining two studies delivered AOT without imitation (18, 19). Moreover, Agosta et al. (27) asked participants to follow auditory cues during imitation, whereas in the study of Mezzarobba et al. (28) ecological auditory cues were delivered to patients during AOT. Six studies used video-clips showing healthy actors performing actions. Only Jaywant et al. (19) proposed AOT stimuli representing patients with PD performing walking trials in addition to healthy individuals and asked observers to judge if the observed walking task was performed by healthy or PD actors. Motor contents of AOT stimuli represented activities such as walking in different contexts and gait-related tasks (17, 19, 27–29), functional daily tasks (20) or intransitive upper limb tasks as in finger movements (18). All observed actions were delivered using a third-person perspective and from a frontal (17, 27, 29), frontal and lateral (28), and frontal, lateral, and posterior (19) views. The mean duration of each session of training was 56 min (range, 45–60 min). Specifically, 24 min consisted in observing video-clips, whereas the remaining time was dedicated to imitation of observed actions (17, 27–29). The duration of the treatment period was 1 week (19), 4 weeks (17, 27, 29), or 8 weeks (28). A single study explored the effects of a single session of AOT lasting 6 min (18), whereas Buccino et al. (20) gave no information on the treatment duration.

Characteristics of Control Interventions

Control groups received the same posology of AOT intervention in terms of frequency and duration in all studies. In four studies, participants of control groups were asked to watch video-clips showing static landscapes without any motor content (17, 20, 27, 29). After observation, patients had to practice the same motor

TABLE 1 | Characteristics of included studies.

Study	Participants	AOT group intervention	Control group intervention	Posology of interventions	Characteristics of AOT stimuli	Clinical and instrumental outcomes
Agosta et al. (27)	**25 PD**: item 3 FoG-Q ≥ 2; DD ≥ 5 y, H&Y < 4, MMSE > 24. **AOT group**: *n* = 12, 69 ± 8 y, M/F 10/2. **Control group**: *n* = 13, 64 ± 7 y, M/F 8/5.	6 video-clips per week, showing actions with auditory cues associated to movements. After each video-clip, imitation of observed actions at the beat of auditory cues.	Landscape images and execution of the same exercises of AOT group.	**Training**: 12 sessions (3 sessions per week, for 4 weeks). **Each session**: 1 h (24 min of observation and 36 min of execution).	**Motor contents**: body-weight shifting, stepping, walking, turning around a chair, stepping an obstacle, walking through a doorway. • Third-person perspective • Healthy subjects • Frontal viewing perspective	**Clinical**: UPDRS-III (on/off), FoG-Q, UPDRS-II-FoG (on/off), PDQ-39, BBS, 10 MWT. **Time points**: baseline, after 4 weeks of training, at 1 month.
Buccino et al. (20)	**15 PD:** 17–75 y, MMSE > 24. **AOT group**: *n* = 7, 59–80 y, M/F 5/2, DD: 5–19 y. **Control group**: *n* = 8, 67.5–76.5 y, M/F: 5/3, DD: 5.5–13.5 y.	Video-clips showing daily activities plus conventional physiotherapy. Imitation of observed actions.	Video-clips without motor contents plus conventional physiotherapy. Performance of the same actions of the AOT group.	Not specified.	**Motor contents**: functional daily activities.	**Clinical**: UPDRS and FIM. **Time points**: before and after treatment.
Jaywant et al. (19)	**23 PD**, H&Y 1–3, UPDRS gait item ≥ 1. **AOT group**: *n* = 13, 63.7 ± 6.2 y, M/F: 6/7. **Control group**: *n* = 10, 65.8 ± 8.7 y, M/F 4/6.	56 video-clips with PD patients and 56 video-clips with healthy subjects. Participants had to judge whether the observed walking appeared healthy or PD-like gait pattern.	56 video-clips showing water moving roughly and 56 video-clips showing water moving calmly. Participants had to judge whether the water motion was roughly or calmly.	**Training:** 7 days. **Each session**: Not specified.	**Motor contents**: walking in hallway. • Third-person perspective • Healthy and PD subjects • Frontal, lateral, and posterior viewing perspective.	**Clinical**: PDQ-39 mobility. **Instrumental**: Spatial–temporal gait parameters during straight-line walking, walking with turns, and dual-task walking. **Time points**: before and after 8 days of training.
Mezzarobba et al. (28)	**24 PD** with FoG, H&Y: 1–3, BDI ≤ 16, MMSE > 24. **AOT group**: *n* = 12, 74.6 ± 5.9 y M/F: 7/5, DD: 10.7 ± 3.44. **Control group**: *n* = 12, 72 ± 5.87 y, 7/3 M/F, DD: 9.4 ± 4.8.	32 video-clips with 8 gait-related gestures associated to ecological cues. After each video-clip, patients had to practice the same actions for the same amount of time watching the same video-clip.	Execution of the same 8 motor gestures of AOT group through visual or auditory cues. Participants progressively learned to perform gestures without cues.	**Training**: twice a week for 8 weeks **Each session**: 1 h	**Motor contents**: body-weight shifting, taking a step, gait initiation, turn around, stepping over an obstacle, sit-to-walk, normal walking, walking through a doorway. • Third-person perspective • Healthy subjects • Frontal and lateral viewing-perspective	**Clinical**: NFOG-Q, UPDRS-II, UPDRS-III, PDQ-39, TUG, 6 MWT, BBS. **Time points**: baseline, after 8 weeks of training, at 1 and 3 months
Pelosin et al. (29)	**18 PD:** 59–81 y, M/F: 8/12, FOG-Q item 3 ≥ 2 and item 4 ≥ 1), MMSE > 24 **AOT group**: *n* = 9, 68.8 ± 4.1 y, DD: 11.6 ± 4.9 y. **Control group**: *n* = 9, 70.2 ± 6.8 y, DD: 9.5 ± 3.7.	6 video-clips, 6 min each. After observation, patients had to imitate observed actions.	Video-clips showing static landscapes images. After, observation patients had to perform the same movements of AOT group.	**Training** 3 sessions per week, for 4 weeks. **Each session**: 1 h	**Motor contents**: body-weight shifting, stepping, normal walking, turning around a chair, stepping an obstacle, walking through a doorway. • Third-person perspective • Healthy subjects • Frontal viewing perspective	**Clinical**: FOG-Q, FoG-diary, TUG, 10 MWT, Tinetti scale, BBS, and PDQ-39. **Time points**: before training, 2 days, and 4 weeks after training.
Pelosin et al. (18)	**20 PD**: H&Y 1–3, MMSE ≥ 24. **AOT group**: *n* = 10, 68.8 ± 7.4 y, M/F: 3/7, DD: 9.1 ± 3.7. **Control group**: *n* = 10, 66.4 ± 8.9 y; M/F: 4/6, DD: 8.9 ± 3.1 y.	Observation of repetitive finger movements (opposition of thumb to index, medium, ring, and little fingers) paced at 3 Hz.	Listening of acoustic cues paced at 3 Hz.	**Training:** 1 session of 6 min	**Motor contents**: finger opposition with the right hand. • Third-person perspective • Healthy subjects	**Instrumental**: spontaneous movement rate, inter-tapping interval, and touch duration. **Time points**: baseline, immediately after, 45 min, and 2 days after training

(Continued)

TABLE 1 | Continued

Study	Participants	AOT group intervention	Control group intervention	Posology of interventions	Characteristics of AOT stimuli	Clinical and instrumental outcomes
Pelosin et al. (17)	**64 PD**: H&Y 2–3, able to walk unassisted; FOG-Q: item 2 ≥ 1 and item 4 ≥ 2, MMSE > 24. **AOT group**: n = 33, 70.4 ± 4.5 y, M/F: 16/17, DD: 10.7 ± 3.9 y. **Control group**: n = 31, 72.8 ± 3.1 y, M/F: 15/16, DD: 9.5 ± 4.2 y.	6 video-clips, 6 min each. After observation, in the remaining time (36 min) patients had to imitate observed actions.	Video-clips showing static landscapes images. After, observation patients had to perform the same movements of AOT group.	**Training:** 2 times per week for 5 weeks **Each session**: 45 min	**Motor contents**: body-weight shifting, stepping, normal walking, turning around a chair, stepping an obstacle, walking through a doorway. • Third-person perspective • Healthy subjects • Frontal viewing perspective	**Clinical**: FOG-Q, TUG, 10 MWT, and BBS **Time points**: baseline, 1 and 4 weeks after training.

AOT, Action Observation Therapy; PD, Parkinson's disease; M, male; F, female; y, year; DD, disease duration; FOG-Q, Freezing of Gait Questionnaire; H&Y, Hoehn&Yahr; MMSE, Mini-Mental Status Examination; BDI, Beck Depression Inventory; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire−39 items; 10 MWT, 10 Meters Walking Test; BBS, Berg Balance Scale; FIM, Functional Independence Measure; NFOG-Q, New Freezing of Gait Questionnaire; 6 MWT, 6 Minutes Walking Test; FoG-diary, Freezing of Gait diary.

tasks of the AOT group, following the instructions of an operator. In two studies, where AOT was not associated with imitation, control groups observed landscapes with moving water (19) or listened to acoustic cues paced at 3 Hz (18). Finally, in the study of Mezzarobba et al. (28) the control group did not watch any video-clips, but performed motor tasks following auditory or visual cues.

Outcome Measures

Unified Parkinson's Disease Rating Scale (UPDRS) for disease severity was assessed in three studies (20, 27, 28). Four studies focused on improvement in freezing of gait episodes assessed through the Freezing of Gait Diary (FoG-diary) (29), Freezing of Gait Questionnaire (FoG-Q) (17, 27, 29), or the New Freezing of Gait Questionnaire (NFoG-Q) (28). The Parkinson's Disease Questionnaire−39 items (PDQ-39) was used to assess quality of life (19, 27–29), whereas Berg Balance Scale (BBS) (17, 27–29), Tinetti Scale (29), 10 Meters Walking Test (10 MWT) (17, 27, 29), Timed Up and Go test (TUG) (17, 28, 29), and 6 Minutes Walking Test (6 MWT) (28) and Functional Independence Measure (FIM) (20) were adopted as measures of balance, gait speed, functional mobility, endurance, and autonomy. Moreover, Jaywant et al. (19) analyzed spatial–temporal gait parameters during walking in a straight line, with turns, and during a dual task. Finally, Pelosin et al. (18) assessed spontaneous movement rate, inter-tapping intervals, and touch duration during self-paced finger opposition movements in order to understand the effects of AOT on the spontaneous rate of finger movements (18).

Methodological Quality

The risk of bias score of the included studies is shown in Appendix B (**Supplementary Material**). PEDro scores of included studies ranged from 4 to 8 points with an average of 6.1 points. The methodological quality of 4 studies was high (19, 27–29), whereas the other three studies had a moderate quality (17, 18, 20). In particular, all studies did not report blinding of participants and therapists, four studies had no allocation concealment (17, 18, 20, 29) and did not declare intention-to-treat analysis (17, 18, 20, 27), and two studies did not specify the number of missing data at follow-up (18, 20) and blindness of the assessors (17, 19); in another study, there was no reporting of measure of variability (20). Finally, on just one occasion, a PEDro scale item was scored differently by the two reviewers, but after the consultation of the third rater, agreement was reached.

Efficacy of AOT

Results of the current review suggest the efficacy of AOT on motor and functional outcomes in patients with PD, although disagreement among the authors' results was found in some outcomes (**Table 2**). AOT effects were found on walking ability (mean difference −2.2 s for 10 MWT) and typical motor signs of the disease as freezing of gait (mean difference from −1.6 to −5.8 for FoG-diary and from −5.7 to −6.3 for NFoG-Q) and bradykinesia (mean difference: −145 ms for inter-tapping interval). Moreover, additional benefits on disability (mean difference: from −5.6 to −7.0 for UPDRS-II and from −17.8 to 23.2 for UPDRS-III) and quality of life (mean difference:

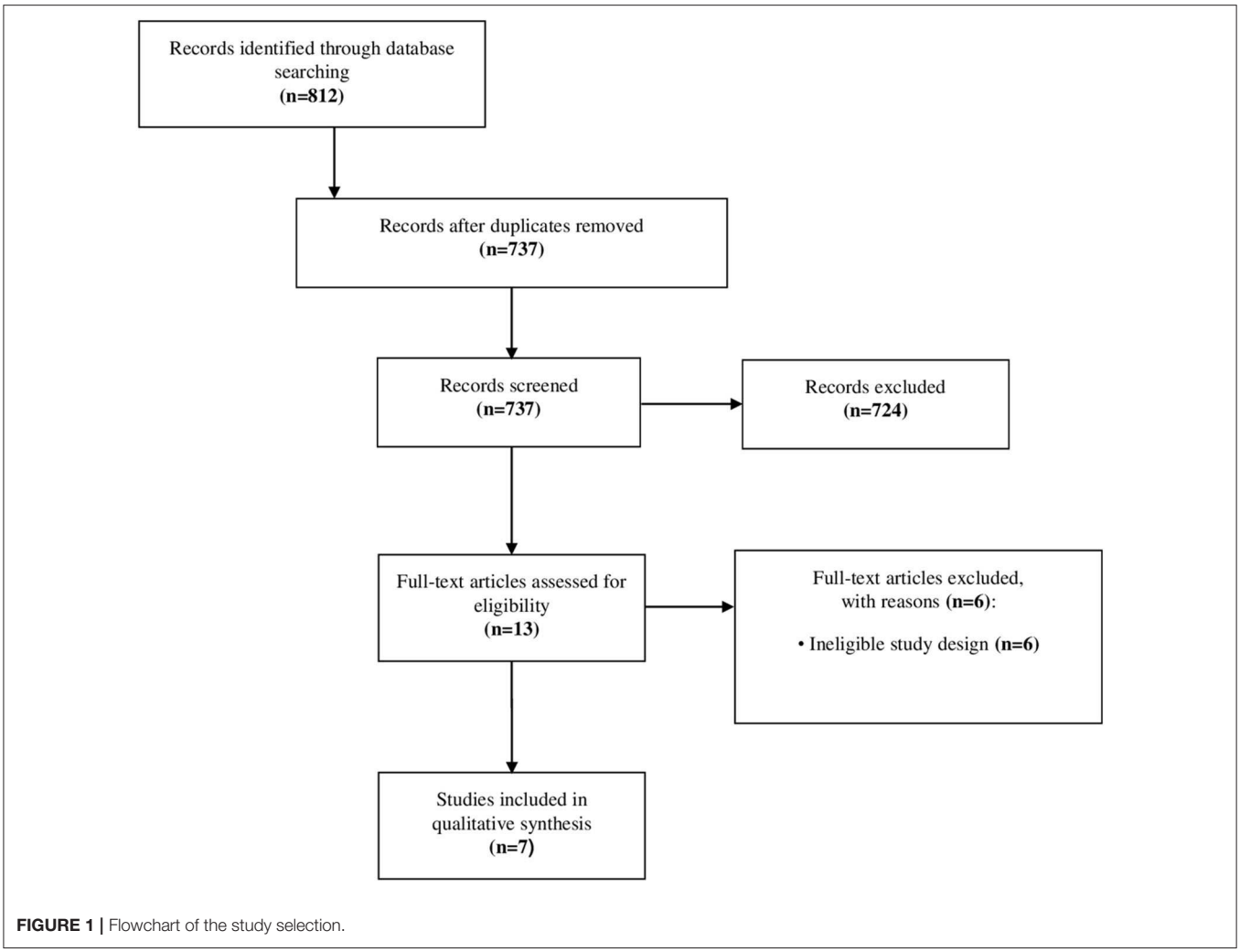

FIGURE 1 | Flowchart of the study selection.

from 28.1 to −31.1 for PDQ-39 related to mobility and −18.7 for PDQ-39 related to bodily discomfort) were found when the intervention was associated with ecological auditory cues (17, 18, 28, 29). In particular, when considering walking ability and related disorders, one study found an effect of AOT on 10 MWT 1 week after the training (17). Moreover, AOT reduced incidence of freezing of gait episodes 2 days, 1, 2, 3, and 4 weeks after the training during walking initiation, and 2, 3, and 4 weeks after the training during turn and in terms of total number of episodes (29). A study reported similar findings, demonstrating that 8 weeks of AOT delivered in association with ecological auditory stimuli produced large improvements for NFoG-Q and UPDRS III directly after the intervention and after 1 and 3 months (28). Moreover, this approach revealed also significant effects for UPDRS II and PDQ-39 related to mobility 1 and 3 months after training, and for PDQ-39 related to bodily discomfort dimension directly after the end of the training (28). In addition, despite the lack of follow-up data, Buccino et al. (20) reported a significant improvement in terms of functional independence (FIM) and disability (UPDRS). Finally, when a single session of AOT was applied to reduce bradykinesia during repetitive finger movements, a reduction of interval duration was found for a finger-tapping task, when compared to acoustic cues intervention. These benefits were found 45 min and 2 days after the intervention (18).

DISCUSSION

The aim of the review was to summarize the effects of AOT in patients with PD and discuss the features of visual stimuli used in clinical studies in relation to their efficacy. Seven RCTs including 189 participants focused on AOT effects on walking ability, typical motor signs, such as freezing of gait and bradykinesia, balance, functional mobility, endurance, disability in daily activities, and quality of life, matched the inclusion criteria. Participants of included studies satisfied the UK Parkinson's Disease Society Brain Bank criteria and were reported as outpatients, except for the study of Buccino et al. where they were inpatients of a hospital rehabilitation department. Patients had mild to moderate disease severity (H&Y 2–3), no dementia, and a disease duration >5 years.

TABLE 2 | Results of included studies with outcomes presented as mean difference and 95% confidence interval (95% CI) comparing Action Observation Therapy (AOT) with control interventions.

Outcome measures		Time point	Mean difference [95% CI]
Agosta et al. (27)			
Action Observation Training (Group 1) vs. Landscape Observation Training (Group 2)			
UPDRS-III off		Post-training	1.20 [−6.89, 9.29]
UPDRS-III on		Post-training	−1.10 [−7.55, 5.35]
		4 wk	1.20 [−6.55, 8.95]
FoG-Q		Post-training	−1.20 [−3.79, 1.39]
		4 wk	−1.10 [−3.31, 1.11]
UPDRS-II-FoG off		Post-training	−0.28 [−0.98, 0.42]
		4 wk	0.13 [−0.73, 0.99]
UPDRS-II-FoG on		Post-training	−0.07 [−0.73, 0.59]
		4 wk	−0.03 [−0.80, 0.74]
PDQ-39		Post-training	−0.07 [−0.73, 0.59]
		4 wk	−0.03 [−0.80, 0.74]
BBS		Post-training	−0.80 [−2.82, 1.22]
		4 wk	−1.00 [−3.06, 1.06]
10 MWT normal speed (s)		Post-training	**1.00 [0.08, 1.92]**
		4 wk	0.52 [−0.75, 1.79]
10 MWT maximum speed (s)		Post-training	0.40 [−0.59, 1.39]
		4 wk	0.00 [−1.51, 1.51]
Buccino et al. (20)			
Action Observation Training (Group 1) vs. Non-motor Observation Training (Group 2)			
UPDRS and FIM		Before training	Not available
		Post-training	Not available
Jaywant et al. (19)			
Action Observation Training (Group 1) vs. Landscape Observation Training (Group 2)			
Walking straight-line	Walking speed (m/s)	1 wk	0.01 [−0.32, 0.34]
	Stride length (m)	1 wk	0.01 [−0.46, 0.48]
	Stride frequency (strides/s)	1 wk	0.00 [−0.17, 0.17]
	Swing time (% of stride)	1 wk	0.80 [−3.78, 5.38]
	Gait asymmetry	1 wk	0.01 [−0.03, 0.05]
Walking with turns	Walking speed (m/s)	1 wk	0.00 [−0.30, 0.30]
	Stride length (m)	1 wk	0.01 [−0.44, 0.46]
	Stride frequency (strides/s)	1 wk	0.01 [−0.17, 0.19]
	Swing time (% of stride)	1 wk	0.60 [−3.44, 4.64]
	Gait asymmetry	1 wk	0.00 [−0.03, 0.03]
Walking with dual task	Walking speed (m/s)	1 wk	0.00 [−0.46, 0.46]
	Stride length (m)	1 wk	0.00 [−0.53, 0.53]
	Stride frequency (strides/s)	1 wk	0.00 [−0.21, 0.21]
	Swing time (% of stride)	1 wk	0.70 [−4.30, 5.70]
	Gait asymmetry	1 wk	0.00 [−0.07, 0.07]
PDQ-39 mobility		1 wk	−3.10 [−8.83, 2.64]
Mezzarobba et al. (28)			
Action Observation plus Sonification Training (Group 1) vs. Motor Gesture with Visual and Auditory Cues (Group 2)			
NFoG-Q		Post-training	**−5.74 [−11.27, −0.22]**
		1 mo	**−6.03 [−11.56, −0.50]**
		3 mo	**−6.28 [−11.81, −0.76]**
UPDRS-II		Post-training	−4.39 [−9.64, 0.86]
		1 mo	**−5.63 [−10.88, −0.38]**
		3 mo	**−7.03 [−12.28, −1.78]**
UPDRS-III		Post-training	**−23.19 [−33.15, −13.22]**
		1 mo	**−14.84 [−24.81, −4.87]**
		3 mo	**−17.79 [−27.76, −7.83]**
PDQ-39 mobility		Post-training	−14.68 [−35.17, 5.81]
		1 mo	**−28.13 [−48.62, −7.64]**
		3 mo	**−31.15 [−51.64, −10.67]**
PDQ-39 bodily discomfort		Post-training	**−18.66 [−35.87, −1.44]**
		1 mo	−10.14 [−27.35, 7.08]
		3 mo	−13.05 [−30.27, 4.16]
PDQ-39 total		Post-training	−7.89 [−31.65, 15.87]
		1 mo	−23.19 [−46.95, 0.56]
		3 mo	−21.21 [−44.97, 2.55]
TUG (s), 6 MWT (s) and BBS		Post-training	Not significant
		1 mo	Not significant
		3 mo	Not significant
Pelosin et al. (29)			
Action Observation Training (Group 1) vs. Landscape Observation Training (Group 2)			
FoG-Q		2 days	−1.60 [−3.40, 0.20]
		4 wk	−2.30 [−4.75, 0.15]
FoG-diary (number of episodes) during start walking		2 days	**−2.10 [−3.70, −0.50]**
		1 wk	**−1.89 [−3.63, −0.14]**
		2 wk	**−2.84 [−4.81, −0.88]**
		3 wk	**−3.77 [−5.39, −2.16]**
		4 wk	**−4.04 [−5.86, −2.22]**
FoG-diary (number of episodes) during turn		2 days	**−2.20 [−3.81, −0.59]**
		1 wk	−1.17 [−2.53, 0.19]
		2 wk	**−3.01 [−4.42, −1.60]**
		3 wk	**−4.73 [−6.16, −3.30]**
		4 wk	**−5.81 [−7.38, −4.23]**
FoG-diary (number of episodes) during obstacle negotiation		2 days	0.36 [−0.64, 1.36]
		1 wk	0.38 [−0.50, 1.25]
		2 wk	−0.32 [−1.63, 0.98]
		3 wk	−0.36 [−1.71, 0.99]
		4 wk	−0.61 [−1.92, 0.69]
FoG-diary (total number of episodes)		2 days	−0.91 [−2.28, 0.47]
		1 wk	−0.58 [−1.83, 0.68]
		2 wk	**−1.63 [−2.99, −0.27]**
		3 wk	**−2.47 [−3.85, −1.08]**
		4 wk	**−3.15 [−4.58, −1.73]**

(Continued)

TABLE 2 | Continued

Outcome measures	Time point	Mean difference [95% CI]
TUG (s), 10 MWT (s), Tinetti Scale, BBS, and PDQ-39	2 days	Not significant
	1 wk	Not significant
	2 wk	Not significant
	3 wk	Not significant
	4 wk	Not significant
Pelosin et al. (18)		
Action Observation Training (Group 1) vs. Acoustic Training (Group 2)		
Self-paced movement rate (Hz)	Immediately post-training	0.04 [−0.40, 0.47]
	45 min	0.31 [−0.21, 0.83]
	2 days	0.36 [−0.03, 0.75]
Inter tapping interval (ms)	Immediately post-training	−59.62 [−130.01, 10.77]
	45 min	**−140.81 [−200.58, −81.04]**
	2 days	**−145.87 [−211.12, −80.62]**
Touch duration (ms)	Immediately post-training	55.39 [−118.84, 229.62]
	45 min	59.61 [−129.00, 248.22]
	2 days	25.85 [−162.70, 214.40]
Pelosin et al. (17)		
Action Observation Training (Group1) vs. Landscape Observation Training (Group2)		
FoG-Q	1 wk	−0.80 [−3.47, 1.87]
	4 wk	−2.60 [−5.46, 0.26]
TUG (s)	1 wk	−1.20 [−3.98, 1.58]
	4 wk	−2.60 [−5.43, 0.23]
BBS	1 wk	−1.10 [−3.67, 1.47]
	4 wk	1.90 [−0.91, 4.71]
10 MWT (s)	1 wk	**−2.20 [−4.26, −0.14]**
	4 wk	−1.60 [−4.05, 0.85]

FOG-Q, Freezing of Gait Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire -39 items; 10 MWT, 10 Meters Walking Test; BBS, Berg Balance Scale; FIM, Functional Independence Measure; NFOG-Q, New Freezing of Gait Questionnaire; 6 MWT, 6 Minutes Walking Test; FoG-diary, Freezing of Gait diary; TUG, Timed Up and Go test; wk, week; mo, month.
Significant results are reported in bold.

AOT Efficacy

Five studies suggested AOT as an effective approach to improve walking ability and typical motor signs (i.e., freezing of gait and bradykinesia) in patients with PD. Moreover, when AOT incorporated ecological auditory stimuli, additional improvements were shown in terms of disability (up to 3 months after the end of the training) and quality of life related to mobility (1 and 3 months after the training) and bodily discomfort (directly after the training) (28). A single study reported improvements in autonomy in hospitalized patients (20). Interestingly, the neural underpinnings of AOT in patients with PD seem to imply the ability of this approach to induce a functional reorganization of the circuits connecting the motor cortex with basal ganglia and the projections from motor cortex to thalamus (30, 31).

Walking represents one of the most compromised daily activities in patients with PD, where the occurrence of typical phenomenon such as freezing of gait increases risk of fall, affecting social participation and quality of life (32, 33). In this review, two studies described the efficacy of AOT on daily frequency of freezing of gait (28, 29). Pelosin et al. (29) demonstrated that a reduction of this frequency took place especially during step initiation and turning phases of gait, circumstances that imply an increase in attentional load. In fact, freezing of gait seems to be triggered by both motor and cognitive factors, which can be improved through the building of a motor memory induced by the observation of actions followed by their imitation (34). Neurophysiological studies have suggested a decrease in supplementary motor area activity, compensated by increased recruitment of basal ganglia during walking in patients with PD (35). When this subcortical hyperactivity collapses in presence of events that require changes in motor planning, the phenomenon of freezing of gait occurs (35). Surprisingly, AOT intervention enhances the recruitment of areas involved in the MNS (premotor cortex, inferior frontal gyrus, and left inferior parietal lobule) as well as fronto-parietal areas (left superior/inferior parietal and right precentral gyri) responsible for attentive processes in response to sudden environmental changes, allowing for reduction in freezing of gait frequency (27, 29). In addition, Mezzarobba et al. (28) demonstrated that when a congruent multisensory stimulation was associated with AOT, effects were amplified, probably thanks to a facilitation in mental representation of observed tasks due to a reduction in cognitive load (36). In this circumstance, benefits were also extended to disability (UPDRS-II and UPDRS-III) and quality of life (PDQ-39) (28). In fact, fMRI studies have demonstrated that observation of actions in association with congruent auditory stimuli increases the activity in superior and medial posterior temporal regions as well as in the insula and the right precentral gyrus, and reinforces the functional connectivity between basal ganglia and frontal and parietal cortical motor areas (36). These regions belong to MNS and cover a key role in sensory integration and cognitive processes (36). Similarly, although Agosta et al. (27) found no differences between experimental and control groups in clinical outcomes, within-group improvements for gait ability and quality of life in AOT group were associated with increased recruitment of fronto-parietal network during observation and execution of a motor task in fMRI. Positive results of AOT have also been documented for the upper limb, where the observation of finger movements seems to increase the finger tapping rate in both healthy subjects and patients with PD. Also in this case, observation of the same task before its performance has been hypothesized to influence the retention of motor information, improving the temporal organization of movements (18).

The number of participants in the included studies was relatively small (from 15 to 25 patients), except for the study of Pelosin et al. (17) (64 patients), and none of the studies estimated sample size a priori. Moreover, not all studies scored well for methodological quality, in particular three studies, which revealed a PEDro score lower than 6 points (moderate quality) (26). In these studies, blinding of participants and assessors were

not applied and the lack of concealed allocation and intention-to-treat analysis might overestimate the effects of the treatment. In addition, no homogeneity in terms of AOT frequency and duration of the treatments was adopted among the included studies, with potential consequences on AOT effects and their persistence over time. In fact, it is reasonable to speculate that the duration of treatment for only 7 days as adopted by Jaywant et al. (19) might not be enough to produce detectable changes on motor abilities. On the other hand, as reported by Mezzarobba et al. (28) 8 weeks of treatment might have contributed to the size of observed benefits. The frequency, ranging from 2 to 3 sessions per week, matched with that suggested by literature in order to maximize the retention of the acquired motor skills (37, 38). The only exceptions were the studies by Jaywant et al. (19) which applied AOT every day, and Pelosin et al. (18), where effects induced by a single session of AOT were investigated (18). Moreover, although walking ability and freezing of gait represented the most assessed variables, a considerable heterogeneity of outcomes was detected, and limitations of some outcome measures must be acknowledged. This is the case of NFoG-Q, where a modest reliability and poor responsiveness with a high Minimal Detectable Change has been described in these patients (39). Finally, only two studies included the assessment of disability and quality of life in addition to patients' motor impairment.

Characteristics of the Stimuli

The characteristics of AOT stimuli vary across the included studies with some research suggesting an association between features of video-clips and AOT efficacy (11). Studies have described additional benefits when AOT is associated with motor imagery in both healthy subjects and patients with neurological disorders (40–43). However, none of the studies administering AOT in subjects with PD took into account the association between AOT and motor imagery. It is worth noting that motor imagery ability in these patients seems to be preserved, especially in early stages, supporting the possible use of this approach as adjuvant to other rehabilitative interventions (12).

AOT is delivered using video-clips representing subjects that execute motor tasks, and its effects on motor recovery may also depend on a person-related perspective from which actions are observed (i.e., first- or third-person perspective and specular or anatomical view in case of first-person perspective) (23, 44, 45). Perspective influences elicited not only brain activity but also the ability to imitate, and higher involvement of a sensorimotor pattern and simplicity in imitation of actions observed in first person was described, when compared to a third-person perspective (44, 46). Moreover, first-person perspective seems to enhance kinesthetic perception, more than third-person perspective, enabling the vividness of mental representation, and improving the imitation of the observed actions (45–48). When investigating AOT applications in neurorehabilitation, this approach is delivered in both perspectives, and studies reporting results after AOT in first-person perspective focused on upper limb rehabilitation (49–51). In the studies considered for the review, given that they were AOT interventions with the focus on improving walking or balance abilities and functional independence in daily activities, the stimuli were delivered from a third-person perspective. Moreover, a third-person perspective was adopted to improve upper limb bradykinesia (18). To date, a single pilot study, which was not included in our review due to the lack of random allocation, explored the feasibility of AOT delivered from a first-person perspective to improve balance and mobility in patients with PD, revealing potential benefits (52).

It is worth underlining that MNS activity during AOT also seems to be influenced by empathy of observers, which is the ability to understand and perceive what another person is experiencing (53, 54). Additionally, studies reported that, not only person-related perspective, but also viewing perspective represent a potential influencing factor on AOT efficacy (55). In particular, observing actions from a perspective that emphasizes motor details seems to improve motor imitation. In the current review, four studies reported viewing perspective of the stimuli, which always consisted of frontal perspective (17, 19, 28, 29) with the addition of sagittal perspective in two studies (19, 28). Video-clips delivered to patients were mainly focused on tasks that emphasized body-weight shifting (i.e., step initiation, stepping an obstacle, etc.) along the frontal plane. Similarly, frontal perspective allowed authors to propose an accurate observation of physiological motor strategies during conditions that elicited typical motor signs in patients with PD (i.e., walking through a doorway) (56). Coherently, lateral perspective was adopted when visual stimuli focused on motor phenomena occurring especially along the sagittal plane (i.e., sit to stand) (19, 28).

Growing evidence describes an activity of the MNS during observation of both transitive (meaningful gestures in presence of an object) and intransitive (meaningful gestures in absence of an object) actions (57, 58). However, neurophysiological studies demonstrated higher brain activity during observation of transitive compared to intransitive tasks (59–61). In addition, congruence of transitive observed actions (i.e., grasping) in context has been reported to influence the MNS activity (62, 63). Included studies used both transitive (i.e., stair climbing, walking through a doorway, stepping an obstacle, etc.) and intransitive (body-weight shifting, stepping in different directions, etc.) actions within the same study, making it impossible to compare their efficacy. Some studies proposed a progression in complexity of observed and imitated tasks, starting from simple intransitive actions, followed by transitive challenging daily tasks (28, 29). Finally, being related to rehabilitation addressed to improve disability through approaches focused on patients' motor impairments, the choice of AOT stimuli might depend on motor deficits, which occurred during both intransitive and object-oriented tasks.

When considering transitive actions, MNS revealed an increased resonance during observation of actions related to daily life, promoting the inclusion of functional activities in video-clips (64, 65), as in the studies included in the current review. Moreover, the brain response to observation of actions has been demonstrated to be influenced by personal motor repertoire, revealing greater MNS activity when the observed actions belong to motor expertise of observers (66, 67). In addition, activity of the MNS seems to be modulated not only by the previous acquisition of motor skills (motor repertoire) but also by the visual familiarity with observed actions (visual practice) (68, 69), where the similarity of the observed kinematics with the

observer's own kinematics seems to enhance the resonance of motor brain areas (70, 71).

In this scenario, it is reasonable to raise the question whether it is better to deliver AOT stimuli representing healthy subjects or patients with the same pathological conditions of observers. In the studies of this review, where AOT was proposed to patients with PD, stimuli showed actions performed by healthy subjects, except for the study of Jaywant et al. (19) which included also patients with PD. Although the use of video-clips representing patients with the same pathological conditions of observers revealed positive results in terms of MNS recruitment in prosthesis users, no studies have investigated the effects of this stimuli characteristics in patients with neurological disorders (55, 72). However, the use of subjects with the same clinical condition as the observers could be limited due to the difficulty in reproducing the features of pathological movements and the need to overcome their motor impairments through AOT stimuli. In fact, whereas the use of a prosthesis is similar in all patients and represents a definitive clinical condition, subjects with neurological diseases have a huge variety of motor manifestations.

Finally, it was hypothesized that observing one's own actions might influence the AOT efficacy (48), but studies are needed to investigate this issue in subjects with PD.

Limitations

Some limitations of the current review need to be underlined. First, our findings were based on a small number of RCTs, where the majority included a small number of participants. Therefore, when considering the incidence of PD in the general population, we cannot exclude the fact that the small number of retrieved studies might be affected by a publication bias. Second, the included studies had a wide variability in terms of posology of the treatments (from 7 days to 2 months), stimuli characteristics, and modalities of AOT administration (i.e., with or without imitation), and included outcome measures affected by psychometric limitations. Therefore, the decision to set no restrictions on these features might have influenced our findings. Third, follow-ups were heterogeneous in timing and only two of the seven studies had a long-term assessment, hindering the possibility to draw conclusions on persistence of AOT effects over time. Finally, reporting was poor in some studies, which only reported that there were no significant between-group differences, without reporting the treatment effects.

Implications for Research and Practice

The review suggests the usefulness of AOT for improving motor function in patients with PD. In particular, treatments lasting at least 4 weeks and incorporating ecological auditory stimuli are reported to induce changes on functional abilities and quality of life. Moreover, imitation of observed actions is suggested to further enhance motor recovery, even though the potential usefulness of AOT alone needs additional investigations. When applied to upper limb, a single session of AOT seems to be enough to reduce bradykinesia, leading us to hypothesize cumulative effects after repeated sessions. In addition, visual stimuli should facilitate patients' empathy through the person-related perspective (third person for locomotor tasks and first person for upper limb activities), the use of transitive actions belonging to patients' motor repertoire, and the similarity of actors with the clinical condition of observers. Meanwhile, the viewing perspective should be taken into account in order to allow patients to focus on movement details.

Future studies with larger number of participants, higher methodological quality, and longer follow-ups are needed to better define the posology of AOT interventions in patients with PD. In addition, the included studies were mainly focused on walking ability or gait-related motor signs whereas additional studies would need to understand AOT effects on other motor and functional domains reported as compromised in these patients. Moreover, AOT alone or in association with other approaches characterized by partial overlap of neural substrates (i.e., motor imagery) deserve further investigations. Finally, future studies should be addressed to study the characteristics of the most effective stimuli.

CONCLUSIONS

In conclusion, AOT leads to improvements in motor and functional performance in patients with PD, especially in terms of walking abilities and gait-related disorders. The characteristics of the training and the visual stimuli delivered to patients play a fundamental role in determining the AOT effects. High-quality randomized controlled trials investigating effects of AOT on less explored motor domains such as postural stability, rate of falls, and functional independence could further expand the applicability of AOT in rehabilitation of patients with PD. Finally, a substantial agreement on the use of AOT stimuli with transitive actions belonging to patients' motor repertoire has been reported. However, original studies aimed at comparing the use of first-person vs. third-person perspective or the observation of video-clips with healthy subjects vs. PD patients as actors could promote additional benefits on recovery induced by AOT.

AUTHOR CONTRIBUTIONS

FT and RG contributed to conception, design of the study. FT, PA, and EC conducted the database search and extracted the data. EC implemented the data analysis. FT and RG wrote the original draft, whereas PA and EC contributed to manuscript revision. All authors reviewed and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors thank Patricia Taylor for the English language revision.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00808/full#supplementary-material

REFERENCES

1. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The incidence of parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology*. (2016) 46:292–300. doi: 10.1159/000445751
2. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. (2015) 386:896–912. doi: 10.1016/S0140-6736(14)61393-3
3. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol*. (2011) 26:S1–58. doi: 10.1007/s10654-011-9581-6
4. Feng YS, Yang SD, Tan ZX, Wang MM, Xing Y, Dong F, et al. The benefits and mechanisms of exercise training for Parkinson's disease. *Life Sci*. (2020) 245:117345. doi: 10.1016/j.lfs.2020.117345
5. Lee DJ, Dallapiazza RF, de Vloo P, Lozano AM. Current surgical treatments for Parkinson's disease and potential therapeutic targets. *Neural Regen Res*. (2018) 13:1342–5. doi: 10.4103/1673-5374.235220
6. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA*. (2014) 311:1670–83. doi: 10.1001/jama.2014.3654
7. Radder DLM, Sturkenboom IH, van Nimwegen M, Keus SH, Bloem BR, de Vries NM. Physical therapy and occupational therapy in Parkinson's disease. *Int J Neurosci*. (2017) 127:930–43. doi: 10.1080/00207454.2016.1275617
8. Tomlinson CL, Herd CP, Clarke CE, Meek C, Patel S, Stowe R, et al. Physiotherapy for Parkinson's disease: a comparison of techniques. *Cochrane Database Syst Rev*. (2014) 2014:CD002815. doi: 10.1002/14651858.CD002815.pub2
9. Bouça-Machado R, Rosário A, Caldeira D, Castro Caldas A, Guerreiro D, Venturelli M, et al. Physical activity, exercise, and physiotherapy in parkinson's disease: defining the concepts. *Mov Disord Clin Pract*. (2019) 7:7–15. doi: 10.1002/mdc3.12849
10. di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: a neurophysiological study. *Exp Brain Res*. (1992) 91:176–80. doi: 10.1007/BF00230027
11. Sarasso E, Gemma M, Agosta F, Filippi M, Gatti R. Action observation training to improve motor function recovery: a systematic review. *Arch Physiother*. (2015) 5:14. doi: 10.1186/s40945-015-0013-x
12. Abbruzzese G, Avanzino L, Marchese R, Pelosin E. Action observation and motor imagery: innovative cognitive tools in the rehabilitation of parkinson's disease. *Parkinsons Dis*. (2015) 2015:124214. doi: 10.1155/2015/124214
13. Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci*. (2004) 27:169–92. doi: 10.1146/annurev.neuro.27.070203.144230
14. Buccino G, Solodkin A, Small SL. Functions of the mirror neuron system: implications for neurorehabilitation. *Cogn Behav Neurol*. (2006) 19:55–63. doi: 10.1097/00146965-200603000-00007
15. Stefan K, Cohen LG, Duque J, Mazzocchio R, Celnik P, Sawaki L, et al. Formation of a motor memory by action observation. *J Neurosci*. (2005) 25:9339–46. doi: 10.1523/JNEUROSCI.2282-05.2005
16. Tallet J, Albaret JM, Rivière J. The role of motor memory in action selection and procedural learning: insights from children with typical and atypical development. *Socioaffect Neurosci Psychol*. (2015) 5:28004. doi: 10.3402/snp.v5.28004
17. Pelosin E, Barella R, Bet C, Magioncalda E, Putzolu M, Di Biasio F, et al. Effect of group-based rehabilitation combining action observation with physiotherapy on freezing of gait in parkinson's disease. *Neural Plast*. (2018) 2018:4897276. doi: 10.1155/2018/4897276
18. Pelosin E, Bove M, Ruggeri P, Avanzino L, Abbruzzese G. Reduction of bradykinesia of finger movements by a single session of action observation in Parkinson disease. *Neurorehabil Neural Repair*. (2013) 27:552–60. doi: 10.1177/1545968312471905
19. Jaywant A, Ellis TD, Roy S, Lin CC, Neargarder S, Cronin-Golomb A. Randomized controlled trial of a home-based action observation intervention to improve walking in parkinson disease. *Arch Phys Med Rehabil*. (2016) 97:665–73. doi: 10.1016/j.apmr.2015.12.029
20. Buccino G, Gatti R, Giusti MC, Negrotti A, Rossi A, Calzetti S, et al. Action observation treatment improves autonomy in daily activities in Parkinson's disease patients: results from a pilot study. *Mov Disord*. (2011) 26:1963–4. doi: 10.1002/mds.23745
21. Cosentino C, Baccini M, Putzolu M, Ristori D, Avanzino L, Pelosin E. Effectiveness of physiotherapy on freezing of gait in parkinson's disease: a systematic review and meta-analyses. *Mov Disord*. (2020) 35:523–36. doi: 10.1002/mds.27936
22. Caligiore D, Mustile M, Spalletta G, Baldassarre G. Action observation and motor imagery for rehabilitation in Parkinson's disease: a systematic review and an integrative hypothesis. *Neurosci Biobehav Rev*. (2017) 72:210–22. doi: 10.1016/j.neubiorev.2016.11.005
23. Ge S, Liu H, Lin P, Gao J, Xiao C, Li Z. Neural basis of action observation and understanding from first- and third-person perspectives: an fMRI study. *Front Behav Neurosci*. (2018) 12:283. doi: 10.3389/fnbeh.2018.00283
24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. (2009) 339:b2700. doi: 10.1136/bmj.b2700
25. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. (1992) 55:181–4. doi: 10.1136/jnnp.55.3.181
26. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*. (2003) 83:713–21. doi: 10.1093/ptj/83.8.713
27. Agosta F, Gatti R, Sarasso E, Volonté MA, Canu E, Meani A, et al. Brain plasticity in Parkinson's disease with freezing of gait induced by action observation training. *J Neurol*. (2017) 264:88–101. doi: 10.1007/s00415-016-8309-7
28. Mezzarobba S, Grassi M, Pellegrini L, Catalan M, Kruger B, Furlanis G, et al. Action observation plus sonification. A novel therapeutic protocol for parkinson's patient with freezing of gait. *Front Neurol*. (2018) 8:723. doi: 10.3389/fneur.2017.00723
29. Pelosin E, Avanzino L, Bove M, Stramesi P, Nieuwboer A, Abbruzzese G. Action observation improves freezing of gait in patients with Parkinson's disease. *Neurorehabil Neural Repair*. (2010) 24:746–52. doi: 10.1177/1545968310368685
30. Buccino G. Action observation treatment: a novel tool in neurorehabilitation. *Philos Trans R Soc Lond B Biol Sci*. (2014) 369:20130185. doi: 10.1098/rstb.2013.0185
31. Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, et al. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. *Mov Disord*. (2008) 23:S548–59. doi: 10.1002/mds.22062
32. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord*. (2004) 19:871–84. doi: 10.1002/mds.20115
33. Tan DM, McGinley JL, Danoudis ME, Iansek R, Morris ME. Freezing of gait and activity limitations in people with Parkinson's disease. *Arch Phys Med Rehabil*. (2011) 92:1159–65. doi: 10.1016/j.apmr.2011.02.003
34. Nieuwboer A, Giladi N. Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon. *Mov Disord*. (2013) 28:1509–19. doi: 10.1002/mds.25683
35. Snijders AH, Takakusaki K, Debu B, Lozano AM, Krishna V, Fasano A, et al. Physiology of freezing of gait. *Ann Neurol*. (2016) 80:644–59. doi: 10.1002/ana.24778
36. Schmitz G, Mohammadi B, Hammer A, Heldmann M, Samii A, Münte TF, et al. Observation of sonified movements engages a basal ganglia frontocortical network. *BMC Neurosci*. (2013) 14:32. doi: 10.1186/1471-2202-14-32
37. Abbruzzese G, Marchese R, Avanzino L, Pelosin E. Rehabilitation for Parkinson's disease: current outlook and future challenges. *Parkinsonism Relat Disord*. (2016) 22:S60–4. doi: 10.1016/j.parkreldis.2015.09.005
38. Pelosin E, Avanzino L, Barella R, Bet C, Magioncalda E, Trompetto C, et al. Treadmill training frequency influences walking improvement in subjects

with Parkinson's disease: a randomized pilot study. *Eur J Phys Rehabil Med.* (2017) 53:201–8. doi: 10.23736/S1973-9087.16.04301-X
39. Hulzinga F, Nieuwboer A, Dijkstra BW, Mancini M, Strouwen C, Bloem BR, et al. The new freezing of gait questionnaire: unsuitable as an outcome in clinical trials? *Mov Disord Clin Pract.* (2020) 7:199–205. doi: 10.1002/mdc3.12893
40. Kawasaki T, Tozawa R, Aramaki H. Effectiveness of using an unskilled model in action observation combined with motor imagery training for early motor learning in elderly people: a preliminary study. *Somatosens Mot Res.* (2018) 35:204–11. doi: 10.1080/08990220.2018.1527760
41. Bek J, Gowen E, Vogt S, Crawford T, Poliakoff E. Action observation produces motor resonance in Parkinson's disease. *J Neuropsychol.* (2018) 12:298–311. doi: 10.1111/jnp.12133
42. Filimon F, Nelson JD, Hagler DJ, Sereno MI. Human cortical representations for reaching: mirror neurons for execution, observation, and imagery. *Neuroimage.* (2007) 37:1315–28. doi: 10.1016/j.neuroimage.2007.06.008
43. Malouin F, Jackson PL, Richards CL. Towards the integration of mental practice in rehabilitation programs. A critical review. *Front Hum Neurosci.* (2013) 7:576. doi: 10.3389/fnhum.2013.00576
44. Watanabe R, Watanabe S, Kuruma H, Murakami Y, Seno A, Matsuda T. Neural activation during imitation of movements presented from four different perspectives: a functional magnetic resonance imaging study. *Neurosci Lett.* (2011) 503:100–4. doi: 10.1016/j.neulet.2011.08.016
45. Jackson PL, Meltzoff AN, Decety J. Neural circuits involved in imitation and perspective-taking. *Neuroimage.* (2006) 31:429–39. doi: 10.1016/j.neuroimage.2005.11.026
46. Angelini M, Fabbri-Destro M, Lopomo NF, Gobbo M, Rizzolatti G, Avanzini P. Perspective-dependent reactivity of sensorimotor mu rhythm in alpha and beta ranges during action observation: an EEG study. *Sci Rep.* (2018) 8:12429. doi: 10.1038/s41598-018-30912-w
47. Villiger M, Estévez N, Hepp-Reymond MC, Kiper D, Kollias SS, Eng K, et al. Enhanced activation of motor execution networks using action observation combined with imagination of lower limb movements. *PLoS ONE.* (2013) 8:e72403. doi: 10.1371/journal.pone.0072403
48. Fuchigami T, Morioka S. Differences between the influence of observing one's own movements and those of others in patients with stroke. *Stroke Res Treat.* (2019) 2019:3083248. doi: 10.1155/2019/3083248
49. Sgandurra G, Ferrari A, Cossu G, Guzzetta A, Fogassi L, Cioni G. Randomized trial of observation and execution of upper extremity actions versus action alone in children with unilateral cerebral palsy. *Neurorehabil Neural Repair.* (2013) 27:808–15. doi: 10.1177/1545968313497101
50. Franceschini M, Ceravolo MG, Agosti M, Cavallini P, Bonassi S, Dall'Armi V, et al. Clinical relevance of action observation in upper-limb stroke rehabilitation: a possible role in recovery of functional dexterity. A randomized clinical trial. *Neurorehabil Neural Repair.* (2012) 26:456–62. doi: 10.1177/1545968311427406
51. Sale P, Ceravolo MG, Franceschini M. Action observation therapy in the subacute phase promotes dexterity recovery in right-hemisphere stroke patients. *Biomed Res Int.* (2014) 2014:457538. doi: 10.1155/2014/457538
52. Giorgi G, Ferrarello F, Merlo F, Fumagalli S, Marchionni N, Di Bari M. First-person perspective action observation training in individuals with parkinson's disease: a consideration-of-concept controlled pilot trial. *J Geriatr Phys Ther.* (2018) 41:134–42. doi: 10.1519/JPT.0000000000000113
53. Woodruff CC, Martin T, Bilyk N. Differences in self- and other-induced Mu suppression are correlated with empathic abilities. *Brain Res.* (2011) 1405:69–76. doi: 10.1016/j.brainres.2011.05.046
54. Bellet PS, Maloney MJ. The importance of empathy as an interviewing skill in medicine. *JAMA.* (1991) 266:1831–2. doi: 10.1001/jama.266.13.1831
55. Lawson DT, Cusack WF, Lawson R, Hardy A, Kistenberg R, Wheaton LA. Influence of perspective of action observation training on residual limb control in naïve prosthesis usage. *J Mot Behav.* (2016) 48:446–54. doi: 10.1080/00222895.2015.1134432
56. Schlenstedt C, Mancini M, Nutt J, Hiller AP, Maetzler W, Deuschl G, et al. Are hypometric anticipatory postural adjustments contributing to freezing of gait in parkinson's disease? *Front Aging Neurosci.* (2018) 10:36. doi: 10.3389/fnagi.2018.00036
57. Enticott PG, Kennedy HA, Bradshaw JL, Rinehart NJ, Fitzgerald PB. Understanding mirror neurons: evidence for enhanced corticospinal excitability during the observation of transitive but not intransitive hand gestures. *Neuropsychologia.* (2010) 48:2675–80. doi: 10.1016/j.neuropsychologia.2010.05.014
58. Papadourakis V, Raos V. Evidence for the representation of movement kinematics in the discharge of F5 mirror neurons during the observation of transitive and intransitive actions. *J Neurophysiol.* (2017) 118:3215–29. doi: 10.1152/jn.00816.2016
59. Balconi M, Vanutelli ME, Bartolo A, Cortesi L. Transitive and intransitive gesture execution and observation compared to resting state: the hemodynamic measures (fNIRS). *Cogn Process.* (2015) 16:125–9. doi: 10.1007/s10339-015-0729-2
60. Coll MP, Press C, Hobson H, Catmur C, Bird G. Crossmodal classification of Mu rhythm activity during action observation and execution suggests specificity to somatosensory features of actions. *J Neurosci.* (2017) 37:5936–47. doi: 10.1523/JNEUROSCI.3393-16.2017
61. Gatti R, Rocca MA, Fumagalli S, Cattrysse E, Kerckhofs E, Falini A, et al. The effect of action observation/execution on mirror neuron system recruitment: an fMRI study in healthy individuals. *Brain Imaging Behav.* (2017) 11:565–76. doi: 10.1007/s11682-016-9536-3
62. Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G. Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol.* (2005) 3:e79. doi: 10.1371/journal.pbio.0030079
63. Kaplan JT, Iacoboni M. Getting a grip on other minds: mirror neurons, intention understanding, and cognitive empathy. *Soc Neurosci.* (2006) 1:175–83. doi: 10.1080/17470910600985605
64. Hétu S, Gagné M, Jackson PL, Mercier C. Variability in the effector-specific pattern of motor facilitation during the observation of everyday actions: implications for the clinical use of action observation. *Neuroscience.* (2010) 170:589–98. doi: 10.1016/j.neuroscience.2010.07.015
65. Oh SJ, Lee JH, Kim DH. The effects of functional action-observation training on gait function in patients with post-stroke hemiparesis: a randomized controlled trial. *Technol Health Care.* (2019) 27:159–65. doi: 10.3233/THC-181388
66. Calvo-Merino B, Glaser DE, Grèzes J, Passingham RE, Haggard P. Action observation and acquired motor skills: an FMRI study with expert dancers. *Cereb Cortex.* (2005) 15:1243–9. doi: 10.1093/cercor/bhi007
67. Calvo-Merino B, Grèzes J, Glaser DE, Passingham RE, Haggard P. Seeing or doing? Influence of visual and motor familiarity in action observation. *Curr Biol.* (2006) 16:1905–10. doi: 10.1016/j.cub.2006.07.065
68. Cross ES, Hamilton AFDC, Grafton ST. Building a motor simulation *de novo*: observation of dance by dancers. *Neuroimage.* (2006) 31:1257–67. doi: 10.1016/j.neuroimage.2006.01.033
69. Cross ES, Hamilton AF, Kraemer DJ, Kelley WM, Grafton ST. Dissociable substrates for body motion and physical experience in the human action observation network. *Eur J Neurosci.* (2009) 30:1383–92. doi: 10.1111/j.1460-9568.2009.06941.x
70. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science.* (2005) 308:662–7. doi: 10.1126/science.1106138
71. De Marco D, Scalona E, Bazzini MC, Avanzini P, Fabbri-Destro M. Observer-agent kinematic similarity facilitates action intention decoding. *Sci Rep.* (2020) 10:2605. doi: 10.1038/s41598-020-59176-z
72. Cusack WF, Cope M, Nathanson S, Pirouz N, Kistenberg R, Wheaton LA. Neural activation differences in amputees

during imitation of intact versus amputee movements. *Front Hum Neurosci.* (2012) 6:182. doi: 10.3389/fnhum.2012.00182

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 September 2020
doi: 10.3389/fneur.2020.00886

Multi-Dimensional, Short-Timescale Quantification of Parkinson's Disease and Essential Tremor Motor Dysfunction

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OPEN ACCESS

Edited by:
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Reviewed by:
Maria Salsone, National Research Council (CNR), Italy
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 21 April 2020
Accepted: 10 July 2020
Published: 18 September 2020

Citation:
Sanderson JB, Yu JH, Liu DD, Amaya D, Lauro PM, D'Abreu A, Akbar U, Lee S and Asaad WF (2020) Multi-Dimensional, Short-Timescale Quantification of Parkinson's Disease and Essential Tremor Motor Dysfunction. Front. Neurol. 11:886. doi: 10.3389/fneur.2020.00886

Introduction: Parkinson's disease (PD) is a progressive movement disorder characterized by heterogenous motor dysfunction with fluctuations in severity. Objective, short-timescale characterization of this dysfunction is necessary as therapies become increasingly adaptive.

Objectives: This study aims to characterize a novel, naturalistic, and goal-directed tablet-based task and complementary analysis protocol designed to characterize the motor features of PD.

Methods: A total of 26 patients with PD and without deep brain stimulation (DBS), 20 control subjects, and eight patients with PD and with DBS completed the task. Eight metrics, each designed to capture an aspect of motor dysfunction in PD, were calculated from 1-second, non-overlapping epochs of the raw positional and pressure data captured during task completion. These metrics were used to generate a classifier using a support vector machine (SVM) model to produce a unifying, scalar "motor error score" (MES). The data generated from these patients with PD were compared to same-day standard clinical assessments. Additionally, these data were compared to analogous data generated from a separate group of 12 patients with essential tremor (ET) to assess the task's specificity for different movement disorders. Finally, an SVM model was generated for each of the eight patients with PD and with DBS to differentiate between their motor dysfunction in the "DBS On" and "DBS Off" stimulation states.

Results: The eight metrics calculated from the raw positional and force data captured during task completion were non-redundant. MES generated by the SVM analysis protocol showed a strong correlation with MDS-UPDRS-III scores assigned by movement disorder specialists. Analysis of the relative contributions of each of the eight metrics showed a significant difference between the motor dysfunction of PD and ET. Much of this difference was attributable to the homogenous, tremor-dominant phenotype

of ET motor dysfunction. Finally, in individual patients with PD with DBS, task performance and subsequent SVM classification effectively differentiated between the "DBS On" and "DBS Off" stimulation states.

Conclusion: This tablet-based task and analysis protocol correlated strongly with expert clinical assessments of PD motor dysfunction. Additionally, the task showed specificity for PD when compared to ET, another common movement disorder. This specificity was driven by the relative heterogeneity of motor dysfunction of PD compared to ET. Finally, the task was able to distinguish between the "DBS On" and "DBS Off" states within single patients with PD. This task provides temporally-precise and specific information about motor dysfunction in at least two movement disorders that could feasibly correlate to neural activity.

Keywords: deep brain stimulation, Parkinson's Disease (PD), essential tremor (ET), machine learning, UPDRS, symptom assessment

INTRODUCTION

Parkinson's disease (PD) is the second-most common neurodegenerative disease worldwide, with an overall prevalence of 0.3 percent (1, 2) and a prevalence of two percent in people above age 70 (3). It is diagnosed clinically based on the presence of bradykinesia and at least one of the following three signs: rest tremor, postural instability, and rigidity. In practice, symptomatology is diverse (4), making comparison of disease severity between patients difficult (5).

Currently, the Movement Disorder Society-Sponsored Revision of the Unified PD Rating Scale (MDS-UPDRS), a rating system developed in 1987 and revised in 2007 (6, 7), remains the standard clinical scale for the evaluation of PD severity (6, 8–12). It consists of five sections, which account for a patient's ability to perform activities of daily living, degree of motor impairment, and alterations in behavior, mood, and cognition. The Motor Examination section (MDS-UPDRS-III) specifically assesses motor impairment, and scoring in this section can alter clinical management (13, 14). The MDS-UPDRS-III consists of 14 subsections, each rated from zero (not present) to four (most severe). Accurate score assignment relies on the experience of the evaluator, and it depends on the patient's medication state and their point in the natural fluctuation of motor dysfunction at the time of evaluation. While it is a useful and validated tool with high inter-rater consistency (8, 9, 11, 15), it cannot provide the immediate, continuous, and temporally precise quantitative data that are required for identifying the neural correlates that dictate increasingly prevalent adaptive and personalized therapies.

The demand for a temporally precise measures of PD motor dysfunction is reflected in the growing body of literature describing technology-based motor assessments. As technology companies, such as Apple Inc., have expanded their health monitoring services, PD has been a focus of early large-scale data gathering studies, such as mPower (16). Many of these approaches, like the one presented in this report, are task-based and require a patient to generate data electively (17–22). Other approaches use background-running software to collect data from a patient's quotidian interactions with their devices (23–26). Still others utilize accelerometers in wearable devices to gather continuous data (27). Some systems evaluate specific domains of motor dysfunction (28, 29), while many, like the one presented in this study, aim for a more comprehensive appraisal. These methods are growing in their acceptance, and researchers are now using improvement as measured by smartphone-based testing as an exploratory endpoint in therapeutic clinical trials (30). While these approaches each have relative advantages and drawbacks, each yields large data sets that will expand our understanding of movement disorders at both a population and an individual level.

Here, we introduce a novel, goal-directed, and naturalistic tablet-based task and a complementary analytic approach to improve upon currently available assessments of PD motor impairment. Specifically, we sought to increase the temporal precision of motor assessment while accounting for the heterogeneity of PD motor dysfunction by using a stylus-mediated "target tracking task" combined with a multidimensional, machine-learning based analysis of multiple movement-derived metrics. We compared patients with PD to non-movement disorder control subjects using this behavioral task and found it to discriminate between these groups with high accuracy at short timescales. This multi-dimensional approach improves upon recently described assessments that rely on fewer metrics (18, 19, 21, 22). Additionally, our approach showed specificity when compared to another movement disorder, essential tremor (ET). Our analysis showed significantly different contributions of each metric to our support vector machine (SVM) classifier in PD and ET. Our SVM-based classification protocol also differentiated between stimulation states in patients with PD with deep brain stimulation (DBS). These results suggest that this objective, multi-dimensional approach to movement disorder assessment can provide information about the motor dysfunction of patients with movement disorders

Abbreviations: ADL, activity of daily living; AUC, area under the curve; DBS, deep brain stimulation; ET, essential tremor; GPi, globus pallidus internus; MES, motor error score; PIGD, postural instability/gait difficulty; PD, Parkinson's disease; ROC, receiver operating characteristic; STN, subthalamic nucleus; SVM, support vector machine; TD, tremor-dominant; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale.

with the temporal precision necessary for correlation to neural activity.

METHODS

Study Participation

Patients undergoing follow-up care or consultation for neuromodulation therapy for either PD or ET at the Rhode Island Hospital movement disorders clinic between 2017 and 2018 were offered the option to participate in this study. No compensation was provided. To avoid possible confounding due to cognitive impairment, a common feature of advanced PD, only patients who were able to demonstrate a clear understanding of the task were asked to participate.

Approximately age-matched controls (often patients' spouses or partners) also participated in this study. Control subjects were required only to be free of any diagnosed or suspected movement disorder and to have no physical limitation preventing them from seeing the display or appropriately manipulating the stylus.

Subjects agreeing to participate in this study signed informed consent documents and the task was administered in accordance with Rhode Island Hospital human research protocol (Lifespan IRB #263157) and the Declaration of Helsinki. All subject data were de-identified. Two-letter subject identifiers that appear in this report were randomly generated and unrelated to subject initials.

Ultimately, 26 patients with PD and without DBS and 12 patients with ET completed the task. Additionally, 20 control subjects volunteered to participate (**Table 1**). Patients with PD who participated in the study were significantly older than control subjects (69.69, SD $\pm$ 8.61, compared to 58.45, SD $\pm$ 10.20, *T*-test, $T = 3.994$, $p = 0.0002$). Patients in the PD group had a mean duration of disease of 7.32 years (SD $\pm$ 5.94), compared to a mean duration of 13.46 years in the ET group (SD $\pm$ 14.52). Because control subjects were frequently the spouses of participating patients, the distribution of self-identified genders in the patient groups differed from that of the control group, although this difference was only significant in the PD group, in which more males than females participated (Chi-square tests *p*-values: PD $= 2.67 \times 10^{-8}$; ET $= 0.0866$).

Patients with PD and without DBS were classified according to their phenotype based on previously described analyses of MDS-UPDRS-III subsection scores (31, 32). Briefly, if the ratio of the average of the "tremor" scores to the average of the "postural instability" and "gait difficulty" scores exceeded 1.5, the patient was considered "tremor-dominant" (TD). If this ratio was between 1 and 1.5, the patient is considered "mixed," and if the ratio was less than 1, the patient was considered "postural instability/gait difficulty" (PIGD).

An additional eight patients with PD with DBS completed the task. Patients with PD with DBS were not significantly different from patients with PD without DBS in age (62.63, SD $\pm$ 7.09, compared to 69.69, SD $\pm$ 8.61, *T*-test, $T = 2.033$, $p = 0.0501$), disease duration (10.75, SD $\pm$ 2.82, compared to 7.32, SD $\pm$ 5.94, *T*-test, $T = 1.606$, $p = 0.118$), or hours since last medication dose (3.44, SD $\pm$ 2.09, compared to 4.50, SD $\pm$ 4.86, *T*-test, $T = 0.569$, $p = 0.574$). However, there were significant differences between the distribution of self-identified gender and handedness between these two groups (Chi-square tests *p*-values: 3.56×10^{-4} and 0.0067, respectively).

Collection of MDS-UPDRS Scores

For patients with PD, MDS-UPDRS-III scores were assessed immediately prior to administration of the tablet tracking task by one of two board-certified neurologists at Rhode Island Hospital with subspecialty training in movement disorders. This uniform sequence ensured that MDS-UPDRS assessments and task completion occurred in approximately the same drug state, and that task performance did not bias the assessment of the clinician. Additionally, the assessing clinician was not present during the administration of the task. MDS-UPDRS-III scores were obtained for all 26 of the patients with PD and without DBS. Same-day MDS-UPDRS-III scores were available for 24 of the 26 patients with PD who completed the task.

Testing of Patients in "On" and "Off" DBS Stimulation States

Patients with DBS implants were alternately assigned to begin in either the "DBS On" or "DBS Off" state. Patients completed several tasks in each stimulation state with a 15-minute, task-free "washout" period after change in DBS setting. In addition to this washout period, unrelated research tasks were also performed. Cumulatively, performance of the task in each stimulation state was typically separated by approximately one hour.

Task Administration and Data Collection

A touchscreen tablet-based motor task was developed for the iOS system (v.11.4, Apple Inc., Cupertino, California, USA) using the Swift programming language (v.4.1, Apple Inc., Cupertino, California, USA) and XCode integrated development environment (v.9.2, Apple Inc., Cupertino, California, USA). The task presented a continuously-moving target designed to capture goal-directed movement. The target path was calculated stochastically using an algorithm derived from the cubic Bezier curve equation:

$$B(t) = (1-t)^3 P_0 + 3(1-t)^2 t P_1 + 3(1-t) t^2 P_2 + t^3 P_3$$

where $0 \leq t \leq 1$, starting point P_0, endpoint P_3, and two semi-random control points P_1 and P_2.

Twenty curves were generated and sequenced into a single continuous path by setting the endpoint of a given curve equal to the starting point of the subsequent curve. Each control point was plotted along the arc of a theoretical circle containing the previous point as the center. The radius of each control point was randomly selected from a range of 2.0–2.4 cm, and the curvature of each control point was selected from a range of 60–75°. The directionality of each curve (clockwise or counterclockwise) was determined randomly unless the target was approaching one of the screen bounds, in which case the path curved away from the edge of the screen. Furthermore, the control points were restricted to collinearity to prevent sharp "kinks" in the path.

The final path was rendered using the Swift UIBezierPath "spline" function, and the target was animated along the

TABLE 1 | Subject characteristics.

	PD (Non-DBS)				ET				Control		
	Documented	**Mean**	**SD**	***p*-value (to control)**	**Documented**	**Mean**	**SD**	***p*-value (to control)**	**Documented**	**Mean**	**SD**
Total	26	-	-	**2.67×10^{-8}**	12	-	-	0.087	20	-	-
Men	20	-	-	-	5	-	-	-	6	-	-
Women	6	-	-	-	7	-	-	-	13	-	-
Age	26	69.69	8.62	**0.0002**	12	65.83	12.99	0.084	20	58.45	10.20
Disease duration	26	7.32	5.94	-	12	13.46	14.52	-	-	-	-
Handedness	26	-	-	0.169	12	-	-	**0.0218**	20	-	-
R-handed	25	-	-	-	9	-	-	-	19	-	-
L-handed	1	-	-	-	1	-	-	-	1	-	-
Ambidextrous	0	-	-	-	2	-	-	-	0	-	-
Last meds	23	4.13	4.86	-	5	17.60	14.50	-	-	-	-
Predominant phenotype	26	-	-	-	-	-	-	-	-	-	-
TD	12	-	-	-	-	-	-	-	-	-	-
PGID	11	-	-	-	-	-	-	-	-	-	-
Mixed	3	-	-	-	-	-	-	-	-	-	-

	PD (DBS)			
	Documented	**Mean**	**SD**	**p-value (to non-DBS PD)**
Total	8	-	-	**3.56×10^{-4}**
Men	5	-	-	-
Women	3	-	-	-
Age	8	60.63	7.09	0.0501
Disease duration	8	10.75	2.81	0.118
Handedness	8	-	-	**0.0067**
R-handed	8	-	-	-
L-handed	0	-	-	-
Ambidextrous	0	-	-	-
Years since implant	8	1.75	1.16	-
Last meds	8	3.44	2.09	0.574

Significant results in bold. Each PD patient was classified as "Tremor-Dominant" (TD), "Postural Instability/Gait Difficulty" (PGID), or "mixed".

path at a constant speed of 4.25 cm per second. Subjects were asked to track the target (a circle with a radius of 4.0 mm) using a pressure-sensing stylus with the dominant hand. The task session was divided into 15 trials, each approximately 25 seconds in duration. The coordinates of both target and subject movements were sampled at a frequency of 100 Hz.

Metric Calculations

Metrics were crafted to capture the heterogeneity of motor dysfunction at each time point *t*. Many of these metrics are based on previous work that employed a similar approach to motor evaluation (33), albeit in intraoperative patients undergoing DBS implantation with a task that used a joystick, rather than a stylus, to capture data. Notably, this work did not assess patients with ET, nor did it test patients in different stimulation states.

Here, data were divided into 1-second, non-overlapping epochs, and metrics were calculated for each epoch. The equations used to calculate each metric are shown in **Table 2**. Seven of the eight metrics were calculated using positional data, while "Pressure" reflects variance in the "force" data captured at the stylus-tablet interface. "Distance" indicates the Euclidean distance from the target trace to the cursor trace. "Tremor" corresponds to the magnitude of the 3–10 Hz tremor in the cursor trace. "VectorError" calculates the magnitude of the difference vector between the cursor and target trace vectors. "TrackingAngle" measures the angle between the cursor and target trace vectors. "Slowness" is an exponentially-transformed measure of velocity such that the maximum curvature occurs at the 80^{th} percentile of velocity. "Speed Difference" is the difference between the speed of the cursor trace and the speed of the target trace. Finally, "Excursion Difference" calculates the Euclidean distance between the cursor trace and the origin (0, 0). The non-tremor metrics were calculated using a 3 Hz low-pass filtered trace of the subject's movements to minimize the possibility of a confounding contribution of tremor.

TABLE 2 | Equations used to calculate metrics used to train the SVM classifiers.

Metric	Definitions	Equation
Distance	–	$D(t) = \sqrt{(x_C(t) - x_T(t))^2 + (y_C(t) - y_T(t))^2}$
Tremor Magnitude	$\tilde{}_C(t)^2$ is the analytic signal of the 3–10 Hz filtered cursor timeseries	$TM(t) = \tilde{x}_C(t)^2 + \tilde{y}_C(t)^2$
Vector Error	–	$VE_i = \lvert C_i - T_i \rvert$
Tracking Angle	–	$TA_i = \cos^{-1}\left(\frac{C_i \cdot T_i}{\lvert C_i \rvert \lvert T_i \rvert}\right)$
Slowness	$b = -0.042$	$S_i^{slow} = \exp\left(\frac{b \cdot \lvert C_i \rvert}{\Delta t_i}\right)$
Speed Difference	–	$S_i^d(t) = \frac{\lvert C_i \rvert}{\Delta t_i} - \frac{\lvert T_i \rvert}{\Delta t_i}$
Excursion Difference	–	$Ex(t) = \lvert C \rvert$
Pressure	Mean variance of the force captured by the iPad over the course of each epoch	–

Supplementary Definitions

Let "target trace" refer to the curve traced out by the target, and let "cursor trace" refer to the curve traced out by the cursor. Given a time $t \in \{t_i\}_{i=0}^{T}$, *define:*

$x_C(t), y_C(t)$: *x and y coordinates of cursor trace.*

$x_T(t), y_T(t)$: *x and y coordinates of target trace.*

Further, given the i^{th} *time (t) bin of* $\Delta t \in \{\Delta t_i\}_{i=1}^{T}$, *define:*

$C_i \triangleq (x_c(i) - x_C(i-1), y_C(i) - y_C(i-1))$: *vector representing the cursor trace for time bin, i.*

$T_i \triangleq (x_T(i) - x_T(i-1), y_T(i) - y_T(i-1))$: *vector representing the target trace for time bin, i.*

Support Vector Machine Analysis

For n metrics, the epochs of a subject trace were transformed into a vector of metrics, $\mathbf{m_i} \in R^n$, where R is the set of real numbers, to the formulas in **Table 2**. To classify the points of a subject's trace as symptomatic or asymptomatic, an SVM was trained for each subject in R^n. The points of the control traces were labeled "non-movement disorder-associated," while the points of a movement disorder patient trace were labeled "movement disorder-associated."

Given the large size of the pooled control subject dataset compared to the single patient dataset to which it was compared, a Monte Carlo method was employed to reduce control bias. For each iteration of this method, control points were randomly subsampled (without replacement) by a factor of $\frac{1}{20}$ to yield a 1:1 ratio of symptomatic to non-symptomatic points (this denominator reflects the total number of control subjects). For each classifier, an SVM with a linear kernel was fit to 80 percent of the data with 10-fold cross-validation as a "training" dataset, to generate a hyperplane in R^n with coefficients $h_n^i \in R^{n+1}$ for iteration *i,* with a constant 0^{th} coordinate, and the 1^{st} through n^{th} coefficients corresponding to the coefficient of each metric. This process was repeated 100 times, and average of the coefficients $\boldsymbol{h}^i$ were used to produce a hyperplane with coefficients $\boldsymbol{h} = \frac{\sum_{i=1}^{100} \boldsymbol{h}^i}{100}$. The SVMs were fit using scikit-learn 0.19.1 (34). The remaining 20 percent of the data were used as a test set for the classifier; validation accuracies are reported from this test dataset. However, "motor error scores" (MES) were calculated from a classifier trained on all of the data to maximize the yield of our dataset. SVM hyperparameters were selected in advance of any of these analysis and were not tuned to individual patients to minimize the possibility of overfitting.

The degree of motor dysfunction at a point was measured by the signed Euclidean distance from that point to the hyperplane; we called these values MES. A positive MES corresponded to increased motor dysfunction. That is, given the coefficients $\boldsymbol{h}$ of a hyperplane and a subject vector $\boldsymbol{m_i}$,

$$SS_i = \frac{\boldsymbol{h_{1:n}} \cdot \mathbf{m_i} + h_0}{|\boldsymbol{h_{1:n}}|} \tag{1}$$

where $\boldsymbol{h_{1:n}}$ is a vector with the 1st to nth coordinates of $\boldsymbol{h}$, and $\boldsymbol{h_0}$ is a constant with the first coordinate of $\boldsymbol{h}$.

The weight of a metric was defined as the square of its corresponding coefficient divided by the sum of the squares of the coefficients. Thus, the weight of the i^{th} metric is given by:

$$w_i = \frac{{h_i}^2}{\sum_{j=1}^{1} {h_j}^2}. \tag{2}$$

Other Analyses and Plot Generation

All other statistical analyses were performed using the "stats" library from SciPy (35), and all graphs were generated using the Matplotlib (36) and seaborn libraries (www.seaborn.pydata.org). All analysis and plotting scripts were executed using Python 3 (www.python.org).

Data and Code Availability

De-identified data and analysis code are available upon request for use in collaboration.

RESULTS

Non-redundant Metrics Were Used to Calculate an Inclusive "Motor Error Score"

Using raw positional and pressure data epochs collected during each trial, eight metrics were calculated (**Table 1**). Across the entire group of either control subjects (**Figure 1A**) or patients with PD (**Figure 1B**), correlations between metrics were calculated to assess for potential redundancy. For each metric pair, Pearson's r^2 was calculated. In both of these groups, "Tracking Angle" and "Tremor" showed r^2 values >0.7;

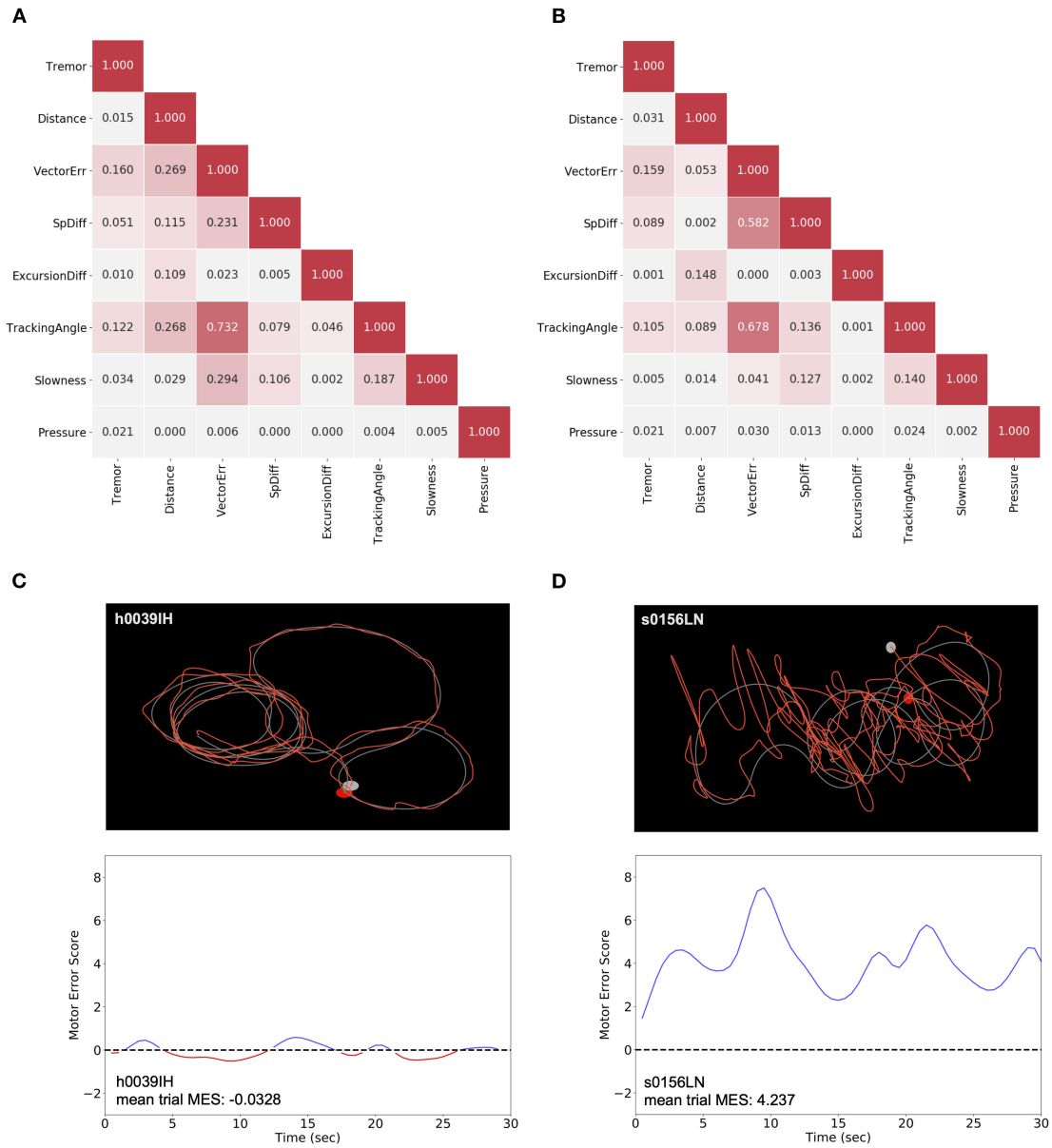

FIGURE 1 | Generation of MES using non-redundant metrics. **(A,B)** For each subject, the distribution for each metric was normalized to the pooled control subject data for that metric. The strength of the association was compared between each pair of normalized metric means across all control subjects **(A)** and patients with PD **(B)**. Pearson's r^2 are shown to indicate the strength of correlation. **(C,D)** The raw trace data from individual trials (top) of control subjects like h0039IH **(C)** and patients with PD, like s0156LN **(D)** were used to calculate the eight metrics. These metrics were then used to generate an SVM classifier model by comparing a single subject to a sampling of pooled control subject data. The distance from each point of patient data to the hyperplane for a given epoch corresponds to the MES, which serves as an aggregate, scalar measure of motor dysfunction across a representative trial (bottom). Here, a Gaussian smoothing function was applied to the MES for visualization purposes.

however, no other metric pairing showed a strong correlation. The overall independence of the metrics suggests that each captures a different component of motor dysfunction, and correlation analysis of the relationships between metrics and MDS-UPDRS sub-scores revealed some evidence, albeit not statistically significant in this sample, in support of this possibility (**Supplementary Figure 1**).

Using these eight metrics, we used SVM, a linear machine learning algorithm, to generate a classifier to differentiate patients with PD and control subjects. Specifically, we produced classifiers to discriminate individual movement disorder subjects from the pooled performance data across control subjects. From these models, we generated a set of "Motor Error Scores" (MES) for each patient, which corresponded to the distance between a given patient's data points and the SVM hyperplane. Thus, these MES are scalar measures of motor dysfunction that capture the constellation of movement abnormalities to reflect the cumulative severity of a patient's

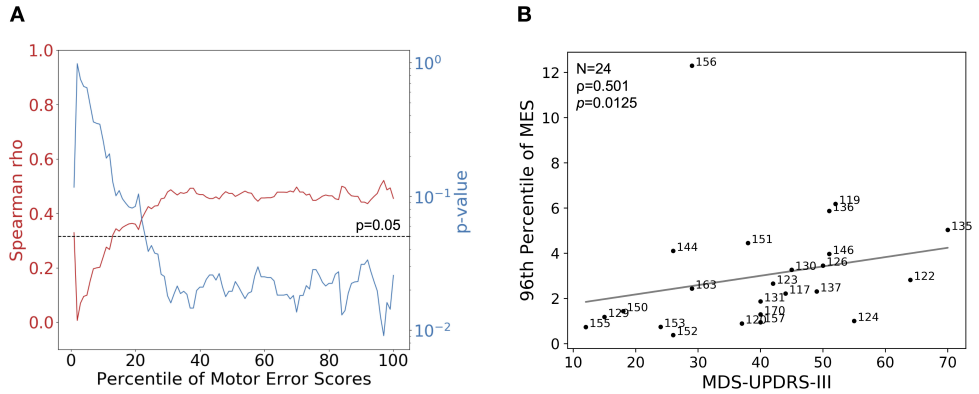

FIGURE 2 | Correlations of MES with MDS-UPDRS-III. **(A)** Using MDS-UPDRS-III, Spearman's correlation coefficient (red line) and corresponding *p*-values (blue line) were calculated using percentiles between 0 and 100 of session-wide MES for each patient. Higher percentiles correspond to progressively smaller fractions of higher-valued MES. The dotted line indicates a *p*-value of 0.05, the selected alpha-level in this analysis. In general, better correlations between MES and MDS-UPDRS were observed when considering patients' epochs of more prominent motor dysfunction; the maximum correlation and lowest *p*-value occurred at the 96th percentile of MES. **(B)** MDS-UPDRS-III (Motor Examination subsection) scores plotted with corresponding 96th percentile session-wide MES for 24 patients with PD for which MDS-UPDRS-III scores were available. Strength of association was determined by calculating Spearman's correlation coefficient ($\rho = 0.501$, $p = 0.0125$).

disease manifestation in short epochs (**Figures 1C,D**). To assess the true effectiveness of the SVM-generated classifier, we re-ran the classification on our cohort of clinic patients with PD or ET after randomly shuffling the labels applied to each subject ("control" or "patient"). This label-shuffling resulted in highly significant decreases in classification accuracy, from 0.839 (SD $\pm$ 0.140) to 0.477 (SD $\pm$ 0.0828) in the PD-control comparison and from 0.892 (SD $\pm$ 0.187) to 0.506 (SD $\pm$ 0.113) in the ET-control comparison. This loss of specificity with label shuffling indicates that our task and analytic approach differentiated specifically between control subjects and patients with motor dysfunction (**Supplementary Figure 2,** Wilcoxon signed-rank tests, $W = 0.0$ and $p = 8.256 \times 10^{-6}$, $W = 0.0$ and $p = 0.00221$ for PD and ET analyses, respectively).

Multi-dimensional Metric-Based Analysis Correlated With Clinician-Assessed MDS-UPDRS-III Scores

Of the 26 patients with PD who performed the behavioral task, same-day clinical MDS-UPDRS-III assessments were available for 24. In all cases, patients underwent the clinical assessment and completed the behavioral task in the same medication state, as described in **Materials and Methods**. We assessed the correlation between MDS-UPDRS-III score and a broad range of percentiles of SVM-generated MES. We calculated the MES for each percentile between 1 and 100 for each patient (a patient's median MES would be represented by the 50th percentile). Then, for a given percentile, the MES for each patient were correlated with their MDS-UPDRS-III scores, and Spearman's rank order correlation analysis was performed. From this analysis, we observed that the *p*-value for this analysis dropped below the pre-selected alpha level of 0.05 near the 20th percentile of MES. The *p*-value of this analysis reached its minimum ($p = 0.0125$) at the 96th percentile of MES. Around this same percentile, we also observed the maximum correlation coefficient ($\rho = 0.501$) (**Figures 2A,B**). This analysis suggests that clinicians were likely generating their clinical assessments based more closely on their perception of a patient's maximum symptom severity. There was no correlation between the MES and the patients' point in their inter-dose interval at the time of task completion (Spearman $\rho = -0.0969$, $p = 0.676$).

A similar analysis was performed using the sum of all components of the MDS-UPDRS-III that assessed symptom severity in the dominant upper extremity (DUE), given that the tracking task collects data related to symptoms only affecting this extremity. In this case, the maximum Spearman's ρ and the minimum *p*-value occured at the 98th percentile of MES, and were 0.351 and 0.0929, respectively (**Supplementary Figure 3B**).

Distributions of MES Were Effective Differentiators Between Subject Types

To assess the ability of MES to classify individual epochs as symptomatic or asymptomatic, we performed pairwise analyses between each individual patient and control. For each pair, a unique classifier was generated using SVM as described above. The MES distributions generated from these SVMs were analyzed using receiver operating characteristic (ROC) curves, and discrimination between the distributions was quantified using the area under these ROC curves (AUC). When comparing patients with PD to control subjects using this method, the mean AUC across all pairs was 0.883 (SD $\pm$ 0.149), indicating good discrimination between these two subject types at the 1-second epoch timescale (**Figure 3A**). Lower AUCs were generally grouped by patient with PD, suggesting that these particular patients had less motor dysfunction at the time of task performance. Importantly, there are no similar groupings by control subject, suggesting lower variability of performance across this group. A similar comparison of patients with ET to

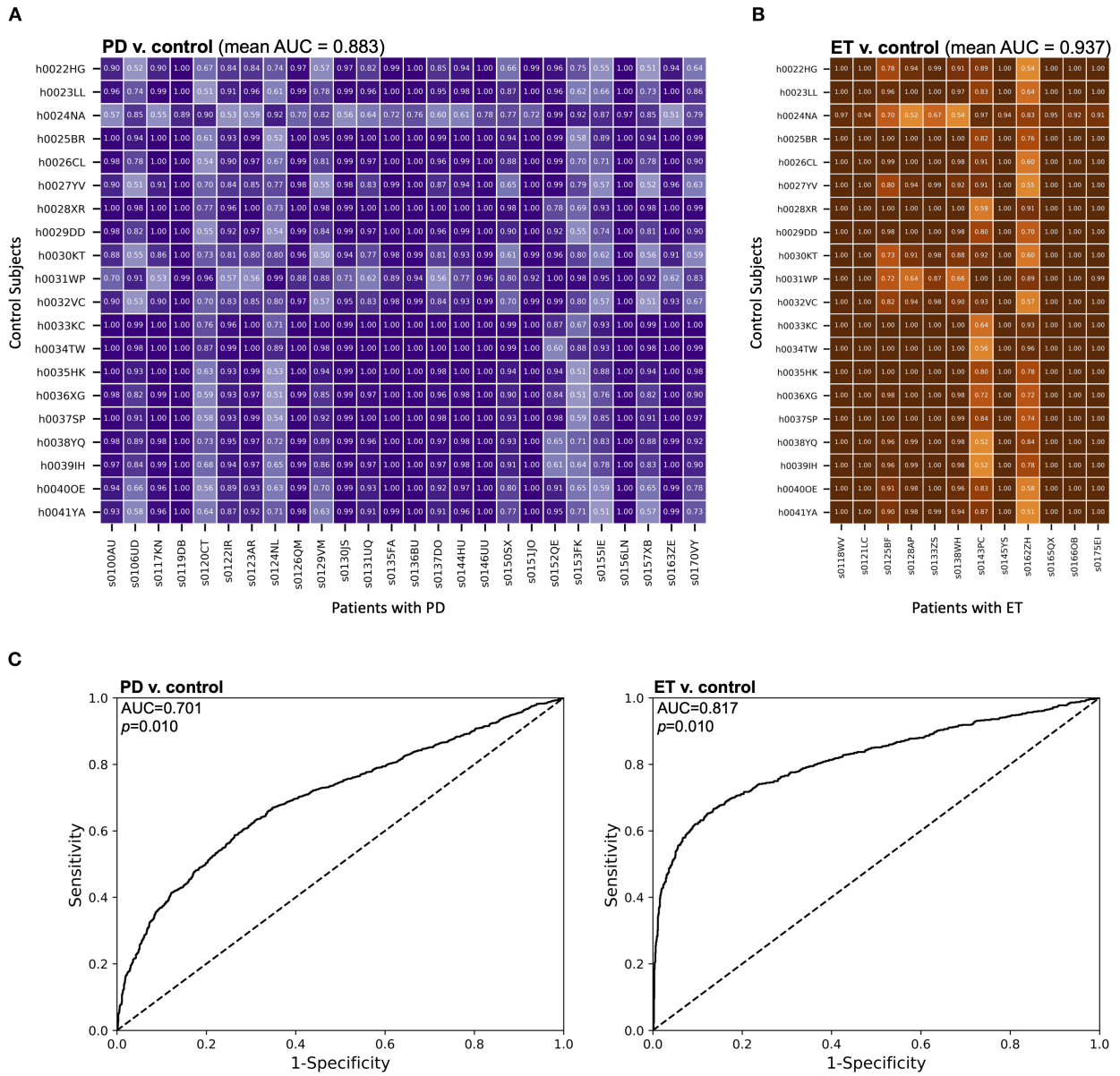

FIGURE 3 | MES effectively discriminated between movement disorder patients and control subjects. **(A,B)** The distributions of MES over a session were compared between individual control subjects and **(A)** patients with PD or **(B)** patients with ET. Here, unique SVM models were generated for each comparison and the resulting MES for each control subject-patient combination were calculated based on these models. These MES distributions were then compared using a ROC analysis. The AUC for each comparison was then calculated. AUCs for each pair-wise comparison are shown. **(C)** ROC curves were generated from compiled MES distributions from each subject group. All MES were derived from an SVM comparison of individual subjects within a group with a random sampling of pooled control data. The AUCs were then calculated to quantify the discriminatory ability of each comparison.

control subjects yielded an even higher mean AUC of 0.937 (SD $\pm$ 0.122) (**Figure 3B**), meaning that, for these cohorts, the task differentiated patients with ET from control subjects significantly better than it did for patients with PD (Mann-Whitney test, $U = 37{,}899$ and $p < 0.0001$). Like the analysis of patients with PD, lower AUCs were generally grouped by patient and not by control subject.

We also compared MES distributions of different groups of subjects at the population level (**Figure 3C**). All MES were derived from SVM classification compared to a random sampling of the pooled control subject data. We then calculated the area under these curves (AUC) to assess the discriminability of experimental groups based upon MES. In our comparison of the MES distributions of patients with PD and control subjects, we found an AUC of 0.701 ($p = 0.010$ by bootstrapping with 100 re-samplings). A similar comparison of patients with ET and control subjects yielded an AUC of 0.817 ($p = 0.010$ by bootstrapping with 100 re-samplings). Therefore, in addition

TABLE 3 | Comparison of metric weights between patients with PD and patients with ET.

Metric	*t* ratio	Adjusted *p*-value
Tremor	**3.947**	**0.00281**
Distance	**3.771**	**0.00467**
VectorErr	2.317	0.211
SpDiff	1.645	0.869
ExDiff	1.561	1.00
TrAngle	1.569	1.00
Slowness	0.414	1.00
Pressure	0.107	1.00

Multiple t-test results with correction using the Bonferroni-Dunn method comparing metric weights between patients with PD or ET, each compared to pooled control subject data. Two-tailed p-values are given. Significant results in bold.

to discriminating between epochs in individual patients, our approach has the ability to discriminate between patients with movement disorders and control subjects on a population level.

Metric-based Analysis Highlighted Motor Differences Between PD and ET Patients

The SVM algorithm returns a "weight" for each metric that reflects its relative contribution to generating the classification hyperplane. Thus, these "metric weights" should approximate the heterogeneity of the motor dysfunction in each movement disorder patient. SVM comparison of individual patients with PD and pooled control subjects showed a high degree of such heterogeneity. This diversity was reflected in the relative variability in metric weights in patients with PD and patients with ET. Mixed effect analysis of these data showed a significant interaction between the metrics and the different movement disorders ($F = 9.39$, $p < 0.0001$). Multiple T-tests comparing metric weights of patients with PD and patients with ET with p-values adjusted using the Bonferroni-Dunn method showed significant differences between "Tremor" and "Distance" at the $p < 0.05$ level (t ratios were 3.947 and 3.771; adjusted p-values were 0.00281 and 0.00467, respectively) (**Table 3**).

On average, patients with ET demonstrated higher MES than those with PD (1.931, SD ± 1.407 compared to 1.027, SD ± 0.945, respectively; Mann-Whitney U test, U = 96.0, $p = 0.0308$) (**Figure 4A**). We hypothesized that the unique constellation of motor abnormalities observed in PD and ET might contribute to the differentiation between these patients in our analysis. Specifically, the differentiation of patients with ET from control subjects relied heavily on the "Tremor" metric (**Figure 4B**), while the metric most important for differentiation between patients with PD and control subjects varied in individual cases. To further interrogate these differences, we compared each patient with PD to a random sampling of pooled data from patients with ET. We chose to use the patient with ET data analogously to the control data in this analysis because the ET-control SVM analysis showed relatively homogenous metric weights relative to patients with PD, suggesting less motor feature variability within this cohort. In this analysis, the SVM distinguished individual patients with PD from the pooled ET subject data with an accuracy of 0.924 (SD ± 0.0764), consistent with the ability of our multi-dimensional approach to motor analysis to differentiate between these movement disorders despite some possible overlap in clinical presentation, specifically with regard to tremor.

To confirm the relative importance of tremor in classifying patients with ET compared to those with PD, we repeated our SVM analyses without including the "Tremor" metric (**Figure 4C**). In the PD-control SVM analysis, excluding "Tremor" reduced the classification accuracy from 0.839 (SD ± 0.140) to 0.772 (SD ± 0.155) (Wilcoxon signed-rank test, $W = 13$ and $p = 3.656 \times 10^{-4}$), while a "Tremor"-excluded ET-control SVM analysis reduced mean classification accuracy from 0.892 (SD ± 0.187) to 0.672 (SD ± 0.190) (Wilcoxon signed-rank test, $W = 0.0$ and $p = 3.346 \times 10^{-3}$). Finally, removing the "Tremor" from the PD-pooled ET SVM comparison reduced classification accuracy from 0.924 (SD ± 0.0764) to 0.760 (SD ± 0.140) (Wilcoxon signed-rank test, $W = 0.0$ and $p = 8.277 \times 10^{-6}$). The mean accuracy difference (with vs. without the "Tremor" metric) in patients with PD was significantly less than the mean accuracy difference in patients with ET (T-test with Welch's correction, $T = 2.872$ and $p = 0.0117$). These analyses indicate that "Tremor" is a more critical metric for differentiation of patients with ET from pooled control subject data compared to classification of patients with PD, consistent with the expected phenotypic dominance of the tremor in patients with ET and the more heterogenous clinical phenotype of patients with PD.

We then analyzed the changes in MES after the removal of "Tremor" from the SVM algorithm (**Figure 4D**). In the PD-control analysis, the mean MES for patients with PD decreased from 1.027 (SD ± 0.945) to 0.760 (SD ± 0.731), a statistically significant change (Wilcoxon signed-rank test, $W = 28.0$ and $p = 2.956 \times 10^{-4}$). In the ET-control analysis, the mean MES for patients with ET decreased from 1.931 (SD ± 1.407) to 0.535 (SD ± 0.684), also a significant change (Wilcoxon signed-rank test, $W = 1.0$ and $p = 2.873 \times 10^{-3}$). The mean MES difference was significantly lower in patients with PD compared to those with ET (T-test with Welch's correction, $T = 3.382$ and $p = 0.0051$), again consistent with the notion that tremor accounts for a larger component of overall motor dysfunction in ET than in PD.

Examination of these data on the level of individual patients further illuminates the relative differences in the diversity of motor manifestations between patients with PD and ET. In both the MES and classification accuracy analyses, all but two of the 12 patients with ET showed a sharp decline in the "Tremor"-excluded analysis, and the two patients that did not show this decline had mild baseline motor impairment according to their tremor-inclusive MES (0.0562, SD ± 0.195). This observation confirms that, in patients with ET who are relatively symptomatic, tremor is the dominant clinical phenotype.

Multi-dimensional SVM Classification Differentiated Between DBS States

We applied our tablet-based task and multi-dimensional SVM analysis to nine patients with PD with implanted DBS systems to determine the task's ability to differentiate between DBS states within individual patients. One of these nine patients was

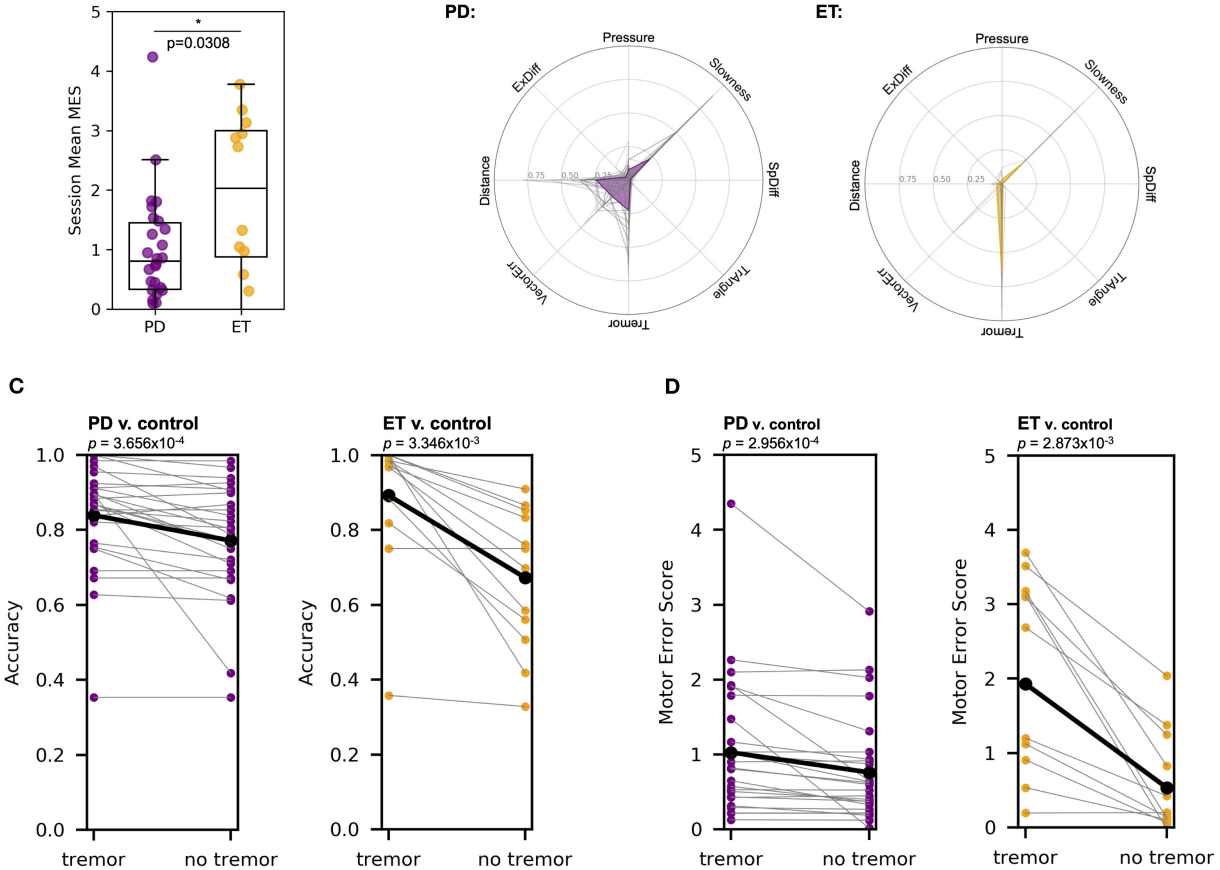

FIGURE 4 | MES metric weights, particularly tremor, differed between patients that have PD compared to ET. **(A)** Mann-Whitney U test showed that patients with ET have a significantly higher mean MES on a session-to-session basis than patients with PD ($U = 96.0$, $p = 0.0308$). Each point represents the mean MES across a single session for a given patient. **(B)** For the SVM classifier developed for each patient compared to pooled control subject data, the relative contribution of each of the seven different metrics varied. The left plot shows the metric weights calculated for each patient with PD (gray lines) and the mean metric weights across all patients with PD (purple line). The right plot shows a similar analysis for patients with ET (orange line). **(C)** Removing the "Tremor" metric from the SVM algorithm reduced the accuracy of the resulting classifier in PD v. pooled control (left, purple) and ET v. pooled control (right, orange) comparisons (Wilcoxon signed-rank tests, test statistics were 13.0 and 0.0, while p-values were 3.656×10^{-4} and 3.346×10^{-3}, respectively). **(D)** Removing the "Tremor" metric from the SVM algorithm reduced the MES generated in PD v. pooled control (left, purple) and ET v. pooled control (right, orange) comparisons (Wilcoxon signed-rank tests, test statistics were 28.0 and 1.0, while p-values were 2.956×10^{-4} and 2.873×10^{-3}, respectively).

excluded due to their inability to complete the task in the "DBS Off" state due to symptom severity. Characteristics of the eight patients who completed the task in both stimulation states are described in **Table 2**.

Patients were alternately assigned to perform the task first either in the "DBS On" or "DBS Off" state to reduce the impact of learning with task repetition affecting results. A single SVM classifier was generated to distinguish between stimulation states within a single patient. The accuracies generated from this analysis were compared to the accuracies produced from an SVM-based analysis for each patient in the DBS state in which labels prior were shuffled prior to generation of the hyperplane. A pair-wise comparison of these analyses showed that shuffling of labels significantly decreased classification accuracy from 0.819 (SD $\pm$ 0.108) to 0.507 (SD $\pm$ 0.0720) (Wilcoxon signed rank test, $W = 0.0$ and one-tailed $p = 0.0117$) (**Figure 5A**), indicating that the SVM effectively distinguished between the two stimulation states.

Separately, we generated classifiers to differentiate between each patient in each stimulation state and pooled control subject data to analyze the differences in metric weights. A two-way ANOVA analysis of these data showed no significant interaction between the metrics and the different movement disorders ($F = 1.966$, $p = 0.0762$) (**Figure 5B**).

DISCUSSION

Using data captured from our naturalistic, goal-directed task and an eight-dimensional, metric-based analysis of these data, we found that, across a cohort of patients with PD, our multi-dimensional "MES" correlated with the cumulative score of the Motor Examination subsection of the MDS-UPDRS. This

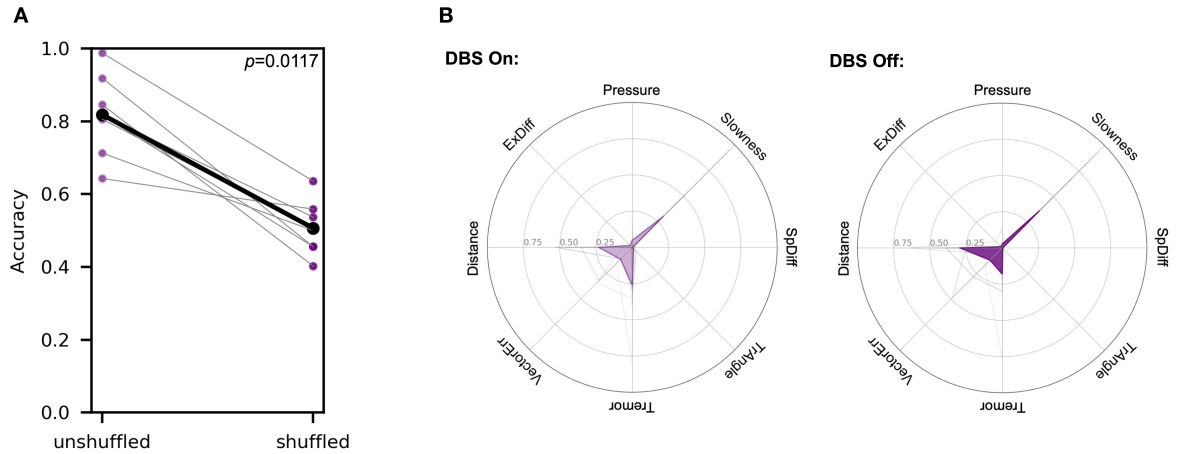

FIGURE 5 | SVM analysis differentiated between DBS states in symptomatic patients. Each patient was tested in both the "DBS On" and "DBS Off" states within the span of 1 h. The order of DBS states tested alternated between patients. **(A)** Accuracies of a single SVM classifier comparing individual patients in two different stimulation states are compared to accuracies produced using an analogous SVM analysis, but with random label shuffling prior to hyperplane generation (Wilcoxon signed rank test, $W = 0.0$ and $p = 0.0117$). **(B)** Metric weights generated by PD patient-pooled control data SVM comparisons were used to examine the relative contributions of each metric in the two different DBS states. The left polar plot depicts the mean metric weights of patients in the "DBS On" state. and the right plot shows the weights of patients in the "DBS Off" state. In each plot, gray lines represent metric weights for individual patients. A two-way ANOVA analysis of these data showed no significant interaction between the metrics and the different movement disorders ($F = 1.966$, $p = 0.0762$).

indicates that our method of motor dysfunction assessment can approximate the severity of a patient's condition when compared to the standardized assessments of trained clinicians. While other tools developed for quantification of motor dysfunction correlate more strongly with MDS-UPDRS-III (37), we did not specifically design our task to optimize this relationship. Rather, our goal was to achieve maximal differentiation between normal and abnormal goal-directed movement. Any correlation with MDS-UPDRS-III, in other words, was incidental. While we did not observe correlations between specific metrics and components of the MDS-UPDRS-III, increased data collection across centers facilitated by the objectivity and usability of our task may reveal a relationship between our metrics and MDS-UPDRS-III subscore "factors" of motor dysfunction (11).

Our task's correlation with MDS-UPDRS-III lends it validity, but it was specifically designed to assess motor dysfunction with high temporal precision and thus provide insight into the short-timescale fluctuations in PD symptomatology (38–40). Importantly, such high-resolution temporal measurement of these fluctuations in motor dysfunction is necessary to correlate behavioral phenotypes with neural activity, a crucial step in the development of adaptive or closed-loop DBS systems (41–44). Additionally, this task can be performed in a non-clinical setting, meaning that the frequency of data collection need not be limited to the interval between office visits. More frequent assessment of symptomatology might allow for more robust projection of trends and more timely implementation of beneficial therapeutic changes (16, 18, 24–26).

Analysis of MES distributions offered strong evidence that the task differentiated between control subjects and movement disorder patients using 1-second epochs of motor performance. However, it is important that such a tool detects motor dysfunction specific to the movement disorder of interest. A direct comparison of patients with PD or ET within a single SVM model showed that differences in metric weight patterns across these groups can be used to generate a high-accuracy classifier. Using linear SVM models allowed us to examine the relative contributions of several different measures of performance to the overall MES. In comparing patients with PD to those with ET, these metric weights reflected broad clinical distinctions between the diseases. Within individual patients and across the entire group, patients with PD showed greater symptom heterogeneity, while MES generated for patients with ET relied predominantly on the "Tremor" metric. Comparison of metric weights across groups confirmed that "Tremor" differs the most among subject groups, although "Distance" also differed significantly (**Table 3**).

Thus, our task and corresponding panel of metrics not only distinguished patients with movement disorders from those without movement disorders, but that it is capable of discriminating between movement disorders directly. Although the textbook clinical pictures of these two movement disorders are distinct, misdiagnosis persists in both directions (45). Some quantitative diagnostic tools designed to distinguish between PD and ET are accelerometer-based and rely on differences in tremor characteristics alone, such as frequency (19, 46, 47). Others require significant training for proper administration, such as those that use electromyography or transcranial sonography (48, 49). Although our task specifically targets PD-associated motor dysfunction without the goal of *de novo* diagnosis, it is an easily-implemented test that can discriminate between ET and PD, even in cases where tremor characteristics may be ambiguous (50, 51).

Importantly, generating classifiers for individual patients proved effective at differentiating between stimulation states within individual patients with PD. Ultimately, the purpose of

a temporally precise, highly quantitative symptom assessment is to correlate behavior with neural activity in order to guide adaptive neuromodulation therapy. This task's ability to detect behavioral changes that correspond to different stimulation states suggests that it has potential to effectively contribute to the understanding of the neural changes related to motor dysfunction in movement disorders.

This study had several limitations. On average, patients with PD were significantly older and more male than control subjects, highlighting two potential confounding factors. Additionally, the task only assesses symptomatology in the dominant upper extremity, which introduces two possible sources of error. Firstly, PD motor dysfunction is generally unilateral, particularly in early stages of the disease, while the tremor of ET is generally bilateral. In our assessment, it is feasible that a patient with PD may have more severe motor dysfunction in their non-dominant hand, while we capture the milder dysfunction in their dominant hand. Secondly, as compared to the MDS-UPDRS-III, our task does not provide a global assessment of the patient's motor dysfunction. We do not assess lower limbs, face, speech, or several other components of this scale. Also, despite screening for significant cognitive impairment, we cannot exclude the possibility that cognitive dysfunction, a well-known sequela of late-stage PD, may affect task performance in a way that our analysis may mistake for pure motor dysfunction. Finally, the tremor phenotypes characteristic of various movement disorders may be unequally assessed by this task. For example, resting tremor is considered a hallmark symptom of PD, although action tremor is still a common finding (52) that correlates with the severity of resting tremor and rigidity, suggesting that it is more likely to be present in advanced disease. Given the small magnitude of movements captured by our task, it likely assesses components of both action and postural tremor. Thus, it may be less effective in patients in earlier stages of PD without components of these two tremor features. Additionally, the action tremor captured through a goal-directed task aligns more closely with the typical clinical phenotype of patients with ET, highlighting the potential problems of a direct comparison of MES of patients with PD and ET. Our study is also limited in terms of its sample sizes, particularly in the assessments of patients with PD and DBS ($N = 8$) and patients with ET ($N = 12$). By performing the task with more patients, we could further elucidate the relationship between our metrics and specific clinical symptoms of different movement disorders.

Overall, despite these limitations, our results suggest that an objective, continuous, naturalistic motor task can capture motor impairment patterns that are specific to PD and ET, can distinguish between DBS states in patients with PD, and can be used to quantify the degree of motor dysfunction with high temporal precision.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Lifespan IRB - Rhode Island Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS, JY, DL, DA, PL, SL, and WA designed the task and analyses. JS, JY, DA, PL, and SL administered the task. AD'A and UA performed MDS-UPDRS-III evaluations. JS and WA wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by a Doris Duke Clinical Scientist Development Award (#2014101) to WA, an NIH COBRE Award: NIGMS P20 GM103645 (PI: Jerome Sanes) supporting WA, a Neurosurgery Research and Education Foundation (NREF) grant to WA, NHLBI T35 grant HL094308 to JS (PI: Elizabeth Harrington, Allan Tunkel), the Lifespan Norman Prince Neurosciences Institute, and the Brown University Carney Institute for Brain Science.

ACKNOWLEDGMENTS

The authors thank the patients and control subjects for their enthusiastic willingness to contribute their time for the benefit of future patients with movement disorders. We also thank Karina Bertsch for administrative support and Ann Duggan-Winkle for clinical support. We finally thank all members of the Asaad Laboratory not named as authors who provided valuable feedback and support throughout this project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00886/full#supplementary-material

Supplementary Figure 1 | MDS-UPDRS-III sub-scores weakly correlated with motor dysfunction metrics. Raw metric data for individual patients with PD were normalized to the aggregated data of this group. Metrics were then compared to each of the shown MDS-UPDRS-III sub-scores, and Pearson's correlation coefficients were calculated. Displayed are Pearson's correlation coefficients (r). * indicates $p < 0.05$.

Supplementary Figure 2 | SVM classifiers specifically differentiated patients with motor dysfunction from control subjects. To confirm that the SVM classification was indicative of the task's ability to broadly distinguish between patients with movement disorders and control subjects instead of simply differentiating between individuals based upon idiosyncratic task performance, PD (left) or ET (right) patient and control subject data labels were randomly shuffled before generation of the hyperplane. This shuffling decreased the mean classification accuracy from 0.839 (SD $\pm$ 0.140) to 0.477 (SD $\pm$ 0.0828) in the PD-control comparison and from 0.892 (SD $\pm$ 0.187) to 0.506 (SD $\pm$ 0.113) in the ET-control comparison (Wilcoxon signed-rank test, $W = 0.0$ and $p = 8.256 \times 10^{-6}$ and $W = 0.0$ and $p = 0.00221$). Each gray line represents a single patient and black lines represent means.

Supplementary Figure 3 | Pooled MDS-UPDRS-III scores for the dominant upper extremity also correlate to calculated MES. **(A)** The sum of all MDS-UPDRS-III score components from each patient's dominant upper extremity (DUE) were plotted with corresponding, session-wide MES means for 24 patients with PD. Spearman's correlation coefficient (red line) and corresponding *p*-values (blue line) and were calculated using percentiles between 0 and 100 of session-wide MES per patient. Dotted line indicates a *p*-value of 0.05, the selected alpha-level in this analysis. The maximum strength of correlation and statistical significance occurred at the 98th percentile of MES. **(B)** Using MDS-UPDRS-III DUE, Spearman's correlation analysis demonstrated significant association between MDS-UPDRS-III DUE and the 98th percentile of session wide MES for each patient ($\rho = 0.351$, $p = 0.0929$).

Supplementary Table 1 | Stimulation parameters of patients with PD with DBS. Electrodes were targeted to stimulate either the subthalamic nucleus (STN) or the globus pallidus internus (GPi).

REFERENCES

1. Lorraine VK, Lang AE. Parkinson's disease. *Lancet*. (2015) 24:92–8. doi: 10.1016/S0140-6736(14)61393-3
2. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Trans*. (2017) 124:901–5. doi: 10.1007/s00702-017-1686-y
3. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. (2014) 29:1583–90. doi: 10.1002/mds.25945
4. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neurol*. (2014) 71:499–504. doi: 10.1001/jamaneurol.2013.6233
5. Martínez-Martín P, Rojo-Abuin JM, Rodríguez-Violante M, Serrano-Dueñas M, Garretto N, Martínez-Castrillo JC, et al. Analysis of four scales for global severity evaluation in Parkinson's disease. *NPJ Parkinson's Dis*. (2016) 2:16007. doi: 10.1038/npjparkd.2016.7
6. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Mov Disord*. (2007) 22:41–7. doi: 10.1002/mds.21198
7. Fahn S, Marsden CD, Calne DB, Goldstein M (eds.). *Recent Developments in Parkinson's Disease*. Vol. 2. Florham Park, NJ. Macmillan Health Care Information (1987). p. 153–63, 293–304.
8. Martínez-Martín P, Gil-Nagel A, Gracia LM, Gómez JB, Martínez-Sarriés J, Bermejo F. Unified Parkinson's disease rating scale characteristics and structure. *Mov Disord*. (1994) 9:76–83. doi: 10.1002/mds.870090112
9. Ramaker C, Marinus J, Stiggelbout AM, van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord*. (2002) 17:867–76. doi: 10.1002/mds.10248
10. Siderowf A, McDermott M, Kieburtz K, Blindauer K, Plumb S, Shoulson I, et al. Test-Retest reliability of the Unified Parkinson's Disease Rating Scale in patients with early Parkinson's disease: results from a multicenter clinical trial. *Mov Disord*. (2002) 17:758–63. doi: 10.1002/mds.10011
11. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, 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*. (2008) 23:2129–70. doi: 10.1002/mds.22340
12. Palmer JL, Coats MA, Roe CM, Hanko SM, Xiong C, Morris JC. Unified Parkinson's Disease Rating Scale-Motor Exam: inter-rater reliability of advanced practice nurse and neurologist assessments. *J Adv Nurs*. (2010) 66:1382–7. doi: 10.1111/j.1365-2648.2010.05313.x
13. Martínez-Martín P, Rodríguez-Blázquez C, Alvarez M, Arakaki T, Arillo VC, Chaná P. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkinsonism Relat Disord*. (2015) 21:50–4. doi: 10.1016/j.parkreldis.2014.10.026
14. Martinez-Martin P, Ray Chaudhuri K. Comprehensive grading of Parkinson's disease using motor and non-motor assessments: addressing a key unmet need. *Exp Rev Neurother*. (2018) 18:41–50. doi: 10.1080/14737175.2018.1400383
15. Greffard S, Verny M, Bonnet A-M, Beinis J-Y, Gallinari C, Meaume S, et al. Motor score of the Unified Parkinson Disease Rating Scale as a good predictor of Lewy body-associated neuronal loss in the substantia nigra. *Arch Neurol*. (2006) 63:584–8. doi: 10.1001/archneur.63.4.584
16. Bot BM, Suver C, Neto EC, Kellen M, Klein A, Bare C, et al. The mPower study, Parkinson disease mobile data collected using ResearchKit. *Sci Data*. (2016) 3:160011. doi: 10.1038/sdata.2016.11
17. Zham P, Kumar DK, Dabnichki P, Arjunan SP, Raghav S. Distinguishing different stages of Parkinson's disease using composite index of speed and pen-pressure of sketching a spiral. *Front Neurol*. (2017) 8:435. doi: 10.3389/fneur.2017.00435
18. Boukhvalova AK, Kowalczyk E, Harris T, Kosa P, Wichman A, Sandford MA, et al. Identifying and quantifying neurological disability via smartphone. *Front Neurol*. (2018) 9:740. doi: 10.3389/fneur.2018.00740
19. Lin P-C, Chen K-H, Yang B-S, Chen Y-J. A digital assessment system for evaluating kinetic tremor in essential tremor and Parkinson's disease. *BMC Neurol*. (2018) 18:25. doi: 10.1186/s12883-018-1027-2
20. Zhan A, Mohan S, Tarolli C, Schneider RB, Adams JL, Sharma S, et al. Using smartphones and machine learning to quantify parkinson disease severity: the mobile Parkinson Disease Score. *JAMA Neurol*. (2018) 75:876–80. doi: 10.1001/jamaneurol.2018.0809
21. Castano-Candamil S, Piroth T, Reinacher P, Sajonz B, Coenen VA, Tangermann M. An easy-to-use and fast assessment of patient-specific DBS-induced changes in hand motor control in Parkinson's Disease. *IEEE Transact Neural Syst Rehabil Eng*. (2019) 27:2155–63. doi: 10.1109/TNSRE.2019.2941453
22. Yang T-L, Kan P-J, Lin C-H, Lin H-Y, Chen W-L, Yau H-T. Using polar expression features and nonlinear machine learning classifier for automated Parkinson's Disease Screening. *IEEE Sensors J*. (2019) 20:501–14. doi: 10.1109/JSEN.2019.2940694
23. Giancardo L, Sánchez-Ferro A, Butterworth I, Mendoza CS, Hooker JM. Psychomotor impairment detection via finger interactions with a computer keyboard during natural typing. *Sci Rep*. (2015) 5:9678. doi: 10.1038/srep09678
24. Arroyo-Gallego T, Ledesma-Carbayo MJ, Sanchez-Ferro A, Butterworth I, Mendoza CS, Matarazzo M, et al. Detection of motor impairment in Parkinson's Disease via mobile touchscreen typing. *IEEE Transact Bio Med Eng*. (2017) 64:1994–2002. doi: 10.1109/TBME.2017.2664802
25. Arroyo-Gallego T, Ledesma-Carbayo MJ, Butterworth I, Matarazzo M, Montero-Escribano P, Puertas-Martín V, et al. Detecting motor impairment in early Parkinson's Disease via natural typing interaction with keyboards: validation of the neuroQWERTY approach in an uncontrolled at-home setting. *J Med Int Res*. (2018) 20:e89. doi: 10.2196/jmir.9462
26. Iakovakis D, Hadjidimitriou S, Charisis V, Bostantzopoulou S, Katsarou Z, Hadjileontiadis LJ. Touchscreen typing-pattern analysis for detecting fine motor skills decline in early-stage Parkinson's disease. *Sci Rep*. (2018) 8:7663. doi: 10.1038/s41598-018-25999-0
27. Cai G, Huang Y, Luo S, Lin Z, Dai H, Ye Q. Continuous quantitative monitoring of physical activity in Parkinson's disease patients by using wearable devices: a case-control study. *Neurol Sci*. (2017) 38:1657–63. doi: 10.1007/s10072-017-3050-2
28. Bank PJM, Marinus J, Meskers CGM, de Groot JH, van Hilten JJ. Optical hand tracking: a novel technique for the assessment of Bradykinesia in Parkinson's Disease. *Mov Disord Clin Pract*. (2017) 4:875–83. doi: 10.1002/mdc3.12536
29. Memar S, Delrobaei M, Pieterman M, McIsaac K, Jog M. Quantification of whole-body bradykinesia in Parkinson's disease participants using multiple inertial sensors. *J Neurol Sci*. (2018) 387:157–65. doi: 10.1016/j.jns.2018.02.001
30. Lipsmeier F, Taylor KI, Kilchenmann T, Wolf D, Scotland A, Schjodt-Eriksen J, et al. Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. *Mov Disord*. (2018) 33:1287–97. doi: 10.1002/mds.27376

31. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DAT ATOP cohort. *Neurology*. (1990) 40:1529. doi: 10.1212/WNL.40.10.1529
32. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord*. (2013) 28:668–70. doi: 10.1002/mds.25383
33. Ahn M, Lee S, Lauro PM, Schaeffer EL, Akbar U, Asaad WF. Rapid motor fluctuations reveal short-timescale neurophysiological biomarkers of Parkinson's Disease. *MedRxiv [Preprint]*. (2020). doi: 10.1088/1741-2552/abaca3. [Epub ahead of print].
34. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O. Scikit-learn: machine learning in Python. *JMLR*. (2011) 12:2825–30. doi: 10.5555/1953048.2078195
35. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods*. (2020) 17:261–72. doi: 10.1038/s41592-019-0686-2
36. Hunter JD. Matplotlib: A 2D graphics environment. *Comp Sci Eng*. (2007) 9:99–104. doi: 10.1109/MCSE.2007.55
37. Huo W, Angeles P, Tai YF, Pavese N, Wilson S, Hu MT, et al. A heterogeneous sensing suite for multisymptom quantification of Parkinson's Disease. *IEEE Transact Neural Syst Rehabil Eng*. (2020). 28:1397–406. doi: 10.1109/TNSRE.2020.2978197
38. Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Move Disord*. (2003) 18, 357–63. doi: 10.1002/mds.10358
39. Daneshzand M, Faezipour M, Barkana BD. Robust desynchronization of Parkinson's disease pathological oscillations by frequency modulation of delayed feedback deep brain stimulation. *PLoS ONE*. (2018) 13:e0207761. doi: 10.1371/journal.pone.0207761
40. Weiner WJ. Motor fluctuations in Parkinson's disease. *Rev Neurol Dis*. (2006) 3:101–8.
41. Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol*. (2013) 74:449–57. doi: 10.1002/ana.23951
42. Popovych OV, Lysyansky B, Tass PA. Closed-loop deep brain stimulation by pulsatile delayed feedback with increased gap between pulse phases. *Sci Rep*. (2017) 7:1033. doi: 10.1038/s41598-017-01067-x
43. Priori A, Foffani G, Rossi L, Marceglia S. Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. *Exp Neurol*. (2013) 245:77–86. doi: 10.1016/j.expneurol.2012.09.013
44. Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, et al. Closed-loop deep brain stimulation is superior in ameliorating Parkinsonism. *Neuron*. (2011) 72:370–84. doi: 10.1016/j.neuron.2011.08.023
45. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? *Arch Neurol*. (2006) 63:1100–4. doi: 10.1001/archneur.63.8.1100
46. Di Biase L, Brittain J-S, Syed A, Shah A, Pedrosa DJ, Cagnan H, et al. Tremor stability index: a new tool for differential diagnosis in tremor syndromes. *Brain*. (2018) 140:1977–86. doi: 10.1093/brain/awx104
47. Molparia B, Schrader BN, Cohen E, Wagner JL, Gupta SR, Gould S, et al. Combined accelerometer and genetic analysis to differentiate essential tremor from Parkinson's disease. *PeerJ*. (2018) 6:e5308. doi: 10.7717/peerj.5308
48. Budisic M, Trkanjec Z, Bosnjak J, Lovrencic-Huzjan A, Vukovic V, Demarin V. Distinguishing Parkinson's disease and essential tremor with transcranial sonography. *Acta Neurol Scand*. (2009) 119:17–21. doi: 10.1111/j.1600-0404.2008.01056.x
49. Zhang J, Xing Y, Ma X, Feng L. Differential diagnosis of parkinson disease, essential tremor, and enhanced physiological tremor with the tremor analysis of EMG. *Parkinson's Dis*. (2017) 2017:1–4. doi: 10.1155/2017/1597907
50. Cohen O, Pullman S, Jurewicz E, Watner D, Louis ED. Rest tremor in patients with essential tremor. *Arch Neurol*. (2003) 60:405. doi: 10.1001/archneur.60.3.405
51. Fekete R, Jankovic J. Revisiting the relationship between essential tremor and Parkinson's disease. *Mov Disord*. (2011) 26:391–8. doi: 10.1002/mds.23512
52. Gigante AF, Bruno G, Iliceto G, Guido M, Liuzzi D, Mancino PV, et al. Action tremor in Parkinson's disease: frequency and relationship to motor and non-motor signs. *Eur J Neurol*. (2015) 22:223–8. doi: 10.1111/ene.12583

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 September 2020
doi: 10.3389/fneur.2020.00940

Responsiveness of Objective vs. Clinical Balance Domain Outcomes for Exercise Intervention in Parkinson's Disease

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OPEN ACCESS

Edited by:
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Reviewed by:
Mark Gregory Carpenter, University of British Columbia, Canada
Veronica Cimolin, Politecnico di Milano, Italy

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *10 March 2020*
Accepted: *20 July 2020*
Published: *25 September 2020*

Citation:
Hasegawa N, Shah VV, Harker G, Carlson-Kuhta P, Nutt JG, Lapidus JA, Jung SH, Barlow N, King LA, Horak FB and Mancini M (2020) Responsiveness of Objective vs. Clinical Balance Domain Outcomes for Exercise Intervention in Parkinson's Disease. Front. Neurol. 11:940. doi: 10.3389/fneur.2020.00940

Background: Balance deficits in people with Parkinson's disease (PD) are often not helped by pharmacological or surgical treatment. Although balance exercise intervention has been shown to improve clinical measures of balance, the efficacy of exercise on different, objective balance domains is still unknown.

Objective: To compare the sensitivity to change in objective and clinical measures of several different domains of balance and gait following an Agility Boot Camp with Cognitive Challenges (ABC-C) intervention.

Methods: In this cross-over, randomized design, 86 individuals with PD participated in 6-week (3×/week) ABC-C exercise classes and 6-week education classes, consisting of 3–6 individuals. Blinded examiners tested people in their practical off state. Objective outcome measures from wearable sensors quantified four domains of balance: sway in standing balance, anticipatory postural adjustments (APAs) during step initiation, postural responses to the push-and-release test, and a 2-min natural speed walk with and without a cognitive task. Clinical outcome measures included the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, the Mini Balance Evaluation Systems Test (Mini-BESTest), the Activities of Balance Confidence (ABC), and the Parkinson's Disease Questionnaire (PDQ-39). The standardized response means (SRM) of the differences between before and after each intervention compared responsiveness of outcomes to intervention. A linear mixed model compared effects of exercise with the active control—education intervention.

Results: The most responsive outcome measures to exercise intervention with an SRM > 0.5 were objective measures of gait and APAs, specifically arm range of motion, gait speed during a dual-task walk, trunk coronal range of motion, foot strike angle, and first-step length at step initiation. The most responsive clinical outcome measure was the patient-reported PDQ-39 activities daily living subscore, but all clinical measures had SRMs <0.5.

Conclusions: The objective measures were more sensitive to change after exercise intervention compared to the clinical measures. Spatiotemporal parameters of gait, including gait speed with a dual task, and APAs were the most sensitive objective measures, and perceived functional independence was the most sensitive clinical measure to change after the ABC-C exercise intervention. Future exercise intervention to improve gait and balance in PD should include objective outcome measures.

Keywords: Parkinson's disease, exercise, gait, anticipatory postural adjustments, automatic postural responses, objective measures, clinical measures, wearable technology

INTRODUCTION

Balance dysfunction is one of the characteristic features of Parkinson's disease (PD) and emerges early, with subtle changes present already at the time of diagnosis (1). Balance dysfunction in people with PD includes impairments in many domains of balance control: (1) postural sway during quiet stance (Sway), (2) automatic postural responses (APRs) to external perturbations, (3) anticipatory postural adjustments prior to gait initiation (APAs), and (4) dynamic balance during walking (Gait) (2).

Balance dysfunction in people with PD are notoriously difficult to treat and are not often helped by pharmacological or surgical treatment, while there is evidence that exercise can improve mobility problems in people with PD. Two recent review papers summarized the effects of exercise intervention in people with PD on balance outcomes (3, 4). Both reviews showed improvements in clinical balance and gait outcomes measures, such as gait speed, the Berg Balance Scale (BBS) (5), disease severity (as measured by the Part III of the Unified Parkinson's disease Rating Scale, UPDRS), and activities of daily living (ADL). However, both reviews showed that exercise outcome measures for PD were limited to a stopwatch measure of gait speed and the BBS as a clinical balance scale but did not investigate the effects of exercise on specific balance domains. Clinical measures of balance or disease severity, such as the BBS or UPDRS, may not be sensitive to change with exercise and do not reflect improvements across specific balance domains (6). Only one recent study investigated the effects of exercise for people with PD using the subscores of the Mini Balance Evaluation Systems Test (Mini-BESTest) (7), a clinical scale that includes four balance domains: anticipatory postural adjustments, automatic postural responses, postural sway in stance in different sensory conditions, and gait (8). The results showed that a muscle strengthening program improved three subscores of the Mini-BESTest, excluding the Gait subscore, in people with PD, but the changes in Mini-BESTest were not achieved at the minimal clinically important difference (MCID) (9).

Objective measures of balance have been shown to be more sensitive to subtle impairments than clinical balance measures in people with PD (10, 11). Recently, wearable sensor systems have been shown to be useful to obtain objective measures across different balance domains in clinical settings due to their portability and quick objective analysis capability (12, 13). Recently, we reported clinimetric properties for objective measures of the four domains of balance (Sway, APRs, APAs, and Gait) from six wearable sensors worn on the feet, wrists, sternum, and lumbar spine (13–16). For example, we have shown that levodopa improves speed of gait and APAs but worsens postural sway instance (17). However, it is still unclear which specific objective measures of balance and gait would be useful as outcome measures for balance exercise intervention in people with PD. Previous studies showed that objective gait measures, but not clinical measures of balance or PD (such as the Mini-BESTest and UPDRS), were improved by dance, treadmill, or multimodal training (18, 19). However, it is unclear whether objective measures across all domains of balance are more sensitive than clinical measures to exercise intervention.

Our group recently showed that an Agility Boot Camp training incorporating cognitive challenges (ABC-C) (20–23) resulted in specific improvements in the APAs domain, measured by the Mini-BESTest, and improvements in clinical measures, such as the Postural Instability and Gait Difficulty (PIGD) score in the MDS-UPDRS, Quality of Life [the Parkinson's Disease Questionnaire-39 (PDQ-39) activities daily living (ADL) subscore] (20), as well as dual-cost of gait speed in people with PD (20, 22). Although we reported changes after the ABC-C intervention only in the APAs domain of the Mini-BESTest, we did not previously evaluate the effects of the ABC-C intervention for any objective measures of balance domains.

Thus, in this exploratory analysis, we compared the effects of the ABC-C intervention on clinical vs. objective outcome measures of balance using the four domains of balance (Sway, APRs, APAs, and Gait) within the Mini-BESTest (13–16). To narrow down the total number of objective measures for the four domains, we used those objective measures that recently were found to better discriminate between people with PD and healthy controls (24).

The purposes of this exploratory analysis are (1) to investigate which specific balance domains improved with the ABC-C intervention by using objective measures and (2) to compare responsiveness to the ABC-C intervention of objective vs. clinical outcome measures. We hypothesized that (1) three of four main balance domains that were part of the intervention (not APRs as postural responses were not practiced) would improve and (2) objective outcome measures of balance would be more sensitive than clinical outcome measures for the ABC-C intervention. We also related the most sensitive objective mobility measures

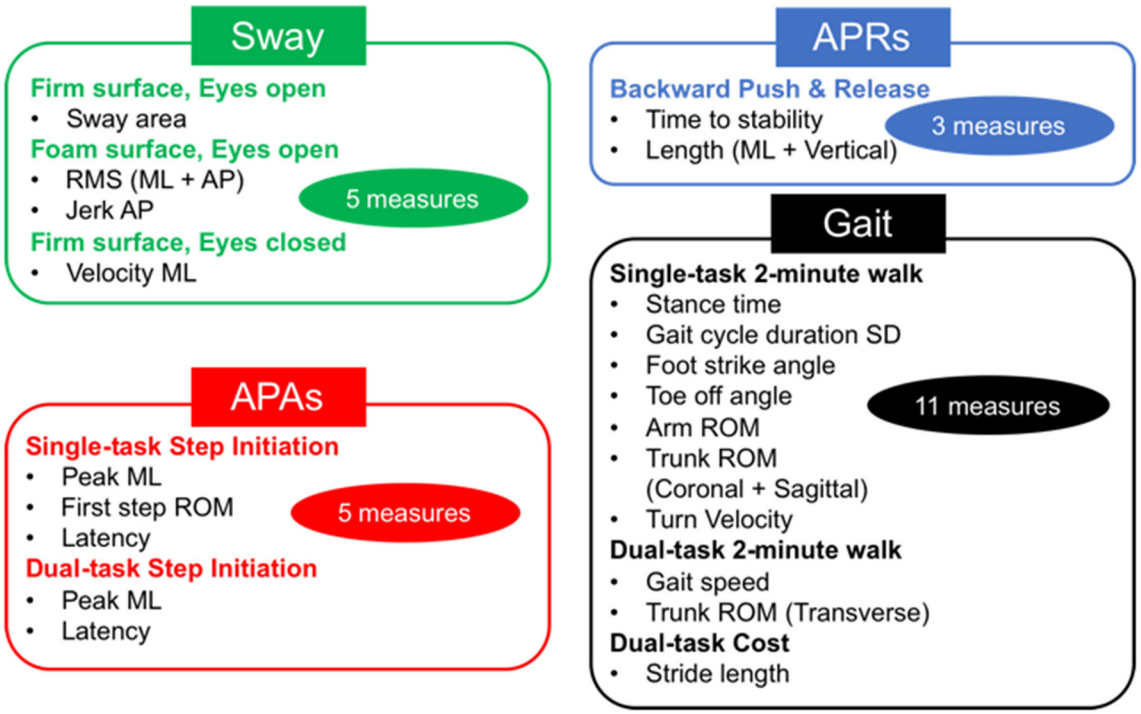

FIGURE 1 | Total objective measures 24. Twenty-four sensitive objective measures have been selected to discriminate between people with Parkinson's disease (PD) and healthy elderly in four postural control domains (20). APAs, anticipatory postural adjustments; APRs, automatic postural responses; ML, mediolateral; AP, anteroposterior; ROM, range of motion; SD, standard deviation.

to perceived change in Mobility and ADL and calculated the MCID.

METHODS

Participants

Details on the participants' characteristics are reported in a previous publication by Jung et al. (20). Briefly, 94 individuals with idiopathic PD were enrolled in this study. Inclusion criteria were the following: (a) age between 50 and 90 years old, (b) no major musculoskeletal or peripheral or central nervous system disorders (other than PD) that could significantly affect their balance and gait, (c) ability to stand and walk unassisted, (d) no recent changes in medication (6 weeks of stable medications), and (e) meet criteria for idiopathic PD according to the Brain Bank Criteria for PD (25). Exclusion criteria were any other neurological disorders or musculoskeletal impairments that interfere with gait or balance and the inability to follow procedures. All participants signed informed consent forms approved by the Oregon Health & Science University institutional review board (approval no. 4131) and the joint OHSU and Veterans Affairs Portland Health Care System (VAPORHCS) institutional review board (approval no. 8979). All work was conducted in accordance with the declaration of Helsinki (1964). This trial was registered on Clinical Trials.gov (NCT02231073 and NCT02236286).

Procedure

A cross-over, randomized, controlled trial design of a 6-week ABC-C intervention for people with PD was conducted from 2014 to 2018 (21). Participants were randomized into one of two intervention groups, Exercise First or Education First, by a computerized block randomization. The researchers who performed and analyzed all baseline, midpoint, and final tests remained blinded to group assignment throughout the duration of the study. Individuals randomized to Exercise First participated in a 6-week ABC-C intervention and crossed over to receive the 6-week education intervention, and individuals in Education First participated in an education class and crossed over to receive ABC-C intervention. Both interventions were designed to have similar frequency and delivered by the same exercise trainers. More details are reported in Jung et al. (20).

The following clinical scales and questionnaires were used as outcome measures for this analysis: (1) Mini-BESTest, (2) MDS-UPDRS (26), (2) the Activities-Specific Balance Confidence scale (ABC-scale) (27), (3) the Montreal Cognitive Assessment (MoCA) (28), (4) the New Freezing of Gait Questionnaire (NFOGQ) (29), and (5) PDQ-39 (30).

Objective measures of balance were obtained via six wearable sensors (Opals, APDM), each including triaxial accelerometers, triaxial gyroscopes, and magnetometers, placed on both feet, wrists, sternum, and the lumbar region, while performing a total of eight different motor tasks, summarized below and in

Figure 1. Participants were tested in their practical Off state after at least 12 h of medication washout. The same battery of clinical and mobility measurements was carried out after 6 weeks of intervention before the participants crossed over into the second intervention and again at the end of the second intervention.

The protocol for both the ABC-C and Education interventions has been detailed in our previous studies (20–23). Briefly, the ABC-C intervention consisted of a 90-min group exercise session, 3 days per week for 6 weeks, led by a certified exercise trainer. The program included the following: (1) gait training, (2) functional skill training (31), (3) agility course, (4) lunges, (5) boxing, and (6) adapted tai chi (32). Each exercise was engaged for 10–20 min with rest periods in between the exercises (21, 23). Each exercise was systematically progressed from beginning to intermediate to advanced levels by challenging (a) divided attention with secondary cognitive tasks, (b) response inhibition, (c) limiting external sensory cues, (d) increasing the length, complexity, and novelty of whole-body movement sequences, and (e) increasing repetitions, speed, amplitude, resistance, or balance requirements.

In the Education intervention, participants were taught how to live better with their chronic conditions. Classes consisted of a group of participants (up to six) meeting with the same trainer for a 90-min session, once a week for 6 weeks. In order to match the dose of the Education intervention with the ABC-C intervention, participants were provided relaxation tapes to be used at home five times per week for 30 min for an overall education dose of 240 min, similar to the exercise dose. Compliance was recorded for both the ABC-C and Education intervention at each session. The trainer coded the progression of exercise difficulty at the end of each week to determine the level of exercise progression for each participant. Additionally, the level of self-reported exertion (0–10) was recorded to determine the level of challenge of the program and to determine if people were progressively challenged during the exercise over time.

Outcome Measures

The full protocol of mobility tasks has been detailed in our previous study (24). The eight motor tasks included Sway, APRs, APAs, and Gait tasks (see **Figure 1**). The Sway task consisted of standing still for 30 s on a firm surface with eyes open or closed (EOFirm and ECFirm), and on a foam surface with eyes open (EOFoam). The APRs task consisted of the push and release test in the backward direction (14). An Instrumented Stand and Walk test (15) and a 2-min walk test were used to extract measures of APAs and Gait, respectively. In addition, both APAs and Gait task were performed with and without a concurrent cognitive task (single and dual task) (24). The dual-task condition consisted of serial subtraction by threes from a three-digit number, during both quiet stance and during the gait initiation (APA task) and in reciting every other letter of the alphabet while walking for the Gait task. As objective outcome measures, we used 24 objective measures that were found to be most sensitive in discriminating between people with PD and healthy controls as determined from our previous study (24) (see details in **Figure 1**). When a Dual task was added, the dual-task cost (DC) was calculated as DC (%) = 100 × (dual-task measure – single-task measure)/single-task measure.

The clinical Mini-BESTest and its four subscores (APAs, APRs, Sway, and Gait) were assessed as a clinical measure of dynamic balance. The total of MDS-UPDRS and the subtotal of Parts II and III were used as measures of disease severity, and the PIGD subscore (sum of items 3.9, 3.10, 3.12, and 3.13 of the MDS-UPDRS) was calculated to assess disease severity focusing on balance. The MoCA score was used as a measure of general cognition. The ABC scale was used to assess balance confidence and balance self-perception. The total PDQ-39 and the Mobility/ADL subscores provided patient-reported quality of life. Lastly, the perceived change in Mobility and ADL after Exercise and Education were determined at the second and third observation according to the following scale: (3) excellent improvement, (2) moderate improvement, (1) mild improvement, (0) no change, (−1) mild worsening, (−2) moderate worsening, and (−3) terrible worsening. For the perceived change in Mobility and ADL, participants were asked the following: "Did you notice a change in the past 6 weeks in your balance and gait?" and "Did you notice a change in the ability to carry out your daily activities in the past 6 weeks?" To determine the MCID of objective measures, the scores after the ABC-C intervention were used for the statistical analysis.

Statistical Analysis

The distribution for each demographic and clinical measure of the two groups (Exercise First/Education First) was examined by the Shapiro–Wilk test at baseline. For data that were nonnormally distributed, the Mann–Whitney *U*-test was used to determine a difference between groups at baseline. Otherwise, independent samples *t*-test and chi-squared tests were used to examine possible group differences at baseline.

To investigate whether outcome measures differed between each intervention, a linear mixed model was fit for each objective measure. Since we had three observations for each participant (baseline, midpoint, and final), we calculated the changes due to the ABC-C intervention as midpoint–baseline for the Exercise first group and final–midpoint for the Education first group. Similarly, the changes due to the Education intervention were calculated as final–midpoint for the Exercise first group and midpoint–baseline for the Education first group. The linear mixed-model design included an indicator of intervention effects (Education vs. Exercise), order effects (Exercise or Education first), and period effects (sequence, Education–Exercise or Exercise–Education, differences) to determine whether the "difference in change" differed between Exercise and Education. The intervention term reflected whether the effects of Exercise differed from the effects of Education. A random effects term was included for participants. In addition, the effect of Exercise and Education were calculated as standardized response mean (SRM) for each clinical and objective measure. The SRM was calculated as the mean change between before and after each intervention period divided by the standard deviation (SD) of the change (33). An SRM value of 0.20

represents a small, 0.50 a moderate, and 0.80 a large effect of the intervention (33).

Last, the MCID of the objective measures with a significant difference between both interventions was determined by using two different types of anchor-based approaches based on the perceived change in Mobility or ADL (9, 34). One of the methods to define the MCID was that the delta of objective measures associated with the perceived change in Mobility or ADL 0 (no change) were compared with the delta of objective measures associated with the perceived change in Mobility or ADL 1 (mild improvement) (34). The other anchor-based method used receiver operating characteristic (ROC) curve technique to find the most suitable MCID values following the method described by Hauser et al. (35). Assuming that false-positive and false-negative identifications are equally unwanted, we determined the cutoff value with the most optimal balance between sensitivity and specificity. The optimal cutoff point to distinguish the delta of objective measures between subjects rated as unchanged (value of 0) from subjects rated as mild improvement (value of 1) was estimated as the point on the ROC curve closest to the point of (0,1). It was calculated as the minimum value of the following formula:

$$The\ value = \sqrt{(1 - Sensitivity)^2 + (1 - Specificity)^2}$$

For the most optimal cutoff values, the positive (LR+) and negative (LR–) likelihood ratios were also determined using the following formulas:

$$LR+ = \frac{True\ positive\ rate}{False\ positive\ rate} = \frac{Sensitivity}{(1 - Specificity)}$$

$$LR- = \frac{False\ negative\ rate}{True\ negative\ rate} = \frac{(1 - Sensitivity)}{Specificity}$$

Furthermore, the area under the curve was calculated to compare the accuracy of the prediction for the perceived change. An area under the curve (AUC) value of 0.56 represents a small, 0.64 a moderate, and 0.71 a high accuracy of the prediction for perceived change (36). Prior to determining the MCID, the association between delta of the objective measures, and the perceived change in Mobility or ADL was calculated using Spearman's rho correlation coefficient. The MCID was detected for the delta of mobility measures that correlated with the perceived change in Mobility or ADL ($r > 0.3$) (34).

The statistical analysis for the demographic data and clinical measures at baseline and association between delta and the perceived change were processed using SPSS Statistics version 25.0 (IBM, Armonk, NY, USA), and a linear mixed model was calculated using MATLAB R2018b (The Mathworks Inc., Natick, MA, USA) with the Statistics and Machine Learning Toolbox. The statistical significance for this exploratory analysis was set to $p < 0.01$.

TABLE 1 | Demographic data.

	All ($N = 86$)		Exercise First ($N = 44$)		Education First ($N = 42$)		
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	***p*-value**
Male/Female	58/28		30/14		28/14		0.881[a]
Age	68.8	7.6	67.7	6.7	70.0	8.2	0.152
Height (cm)	174.0	9.6	174.0	10.3	174.1	8.9	0.997[b]
Weight (kg)	79.4	15.3	81.5	15.6	77.2	14.7	0.195
Disease Duration (years)	6.5	5.0	6.2	4.4	6.7	5.5	0.921[b]
MDS-UPDRS							
Total	68.2	20.4	67.2	20.2	69.3	20.7	0.651
Part III	42.3	12.2	40.7	11.1	43.9	13.1	0.232
PIGD score	5.4	2.8	4.9	2.5	5.9	3.0	0.094[b]
Mini-BESTest	18.1	4.8	18.6	4.3	17.5	5.2	0.438[b]
ABC scale	80.4	16.0	80.3	17.7	80.4	14.0	0.635[b]
PDQ-39	16.5	11.6	16.7	11.5	16.3	11.8	0.788[b]
MoCA	25.6	3.5	26.5	2.9	24.6	3.9	0.016[b]
Hoehn and Yahr stage (I/II/III/IV)	1/69/8/8		1/38/4/1		0/31/4/7		0.104[a]
FoG/without FoG	42/44		23/21		19/23		0.514[a]

Groups compared using independent sample t-test, Mann–Whitney U-test, or chi-squared test and significance level of 0.01.

[a] *Chi-squared test.*

[b] *Mann–Whitney U-test.*

PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait disability; Mini-BESTest, mini Balance Evaluation Systems Test; ABC scale, the Activities-Specific Balance Confidence scale; PDQ-39, Parkinson's Disease Questionnaire-39; MoCA, Montreal Cognitive Assessment; FoG, Freezing of Gait.

RESULTS

Ninety-four participants were randomly assigned into two groups [Exercise First: $n = 46$; Education First: $n = 45$; see cohort diagram in Jung et al. (20)]. Further analysis were performed on the 86 participants who had at least two data points (Exercise First: $n = 44$; Education First: $n = 42$). Age, height, weight, and gender were not different between the Exercise First and Education First groups at baseline (**Table 1**). In addition, there were no significant differences between the Exercise First and Education First group in disease severity (MDS-UPDRS, Hoehn and Yahr stage, and the ratio of freezers), clinical balance function (Mini-BESTest), perceived functional independence (PDQ-39), or general cognitive function (MoCA) before participating this study (details in **Table 1**).

The objective measures showing significant improvements after the ABC-C intervention compared to the Education intervention were in the domains of Gait and APAs (see **Tables 2**, **3** and **Figure 2**). Specifically, arm swing ROM, foot strike angle, and trunk coronal ROM during single-task walking significantly increased after the ABC-C intervention compared to the Education intervention ($p < 0.001$, **Table 2**). In addition, gait speed during dual-task walking was significantly faster after the ABC-C intervention compared to the Education intervention

TABLE 2 | Means and standard deviations (SDs) of each outcome measures at baseline and changes at 6-weeks for Education and ABC-C. Standardized Response Mean with confidence intervals is reported.

Balance domain	Objective measure	Baseline		Change after 6-week education					Change after 6-week ABC-C				
		Mean (SD)		Mean (SD)		SRM	Lower *CI*	Upper *CI*	Mean (SD)		SRM	Lower *CI*	Upper *CI*
Gait	Arm ROM (degree)	26.19	12.09	−0.81	9.37	−0.09	−0.30	0.13	15.02	10.89	0.95	0.68	1.21
	DT Gait speed (m/s)	0.78	0.2	0.01	0.12	0.11	−0.11	0.33	0.12	0.1	0.94	0.67	1.21
	Trunk coronal ROM (degree)	4	1.61	−0.09	0.73	−0.13	−0.35	0.09	0.48	1.07	0.45	0.22	0.68
	Foot strike angle (degree)	11.68	5.46	−0.2	2.29	−0.09	−0.30	0.13	1.44	3.2	0.45	0.22	0.68
	Toe off angle (degree)	30.04	4.66	0.12	1.89	0.07	−0.15	0.28	0.84	1.93	0.43	0.20	0.66
	DC Stride length (%)	−10.6	7.53	0.84	8.6	0.10	−0.12	0.32	2.83	7.14	0.4	0.16	0.63
	Trunk sagittal ROM (degree)	3.78	0.86	0.11	0.68	0.17	−0.05	0.39	0.31	0.85	0.37	0.14	0.59
	Stance time (%)	61.37	1.92	−0.17	0.89	−0.2	−0.41	0.02	−0.47	1.31	−0.36	−0.58	−0.13
	Gait cycle duration SD (s)	0.04	0.02	0	0.01	−0.07	−0.28	0.15	0	0.01	−0.14	−0.36	0.08
	DT Trunk transverse ROM (degree)	6.96	2	0.03	1.73	0.02	−0.20	0.24	0.15	1.73	0.09	−0.14	0.31
	Turn velocity (degree/s)	134.85	35.28	2.26	17.31	0.13	−0.09	0.35	0.75	23.84	0.03	−0.19	0.25
Sway	EOFoam RMS ML (m/s^2)	0.121	0.046	0.005	0.036	0.13	−0.11	0.36	−0.012	0.046	−0.25	−0.50	−0.01
	EOFoam Jerk AP (m/s^5)	8.08	10.26	1.23	13.97	0.09	−0.15	0.33	−3.45	15.9	−0.22	−0.46	0.03
	ECFirm Velocity ML (m/s)	0.125	0.078	0.003	0.092	0.03	−0.19	0.26	−0.019	0.101	−0.19	−0.42	0.04
	EOFoam RMS AP (m/s^2)	0.132	0.047	0.002	0.064	0.03	−0.21	0.26	−0.012	0.073	−0.16	−0.40	0.08
	EOFirm Sway area (m/s^2)	0.095	0.062	0	0.057	0.01	−0.22	0.23	0.007	0.059	0.12	−0.11	0.36
APAs	First step ROM (degree)	30.25	8.63	−1.37	8.09	−0.17	−0.39	0.05	2.55	7.48	0.34	0.11	0.57
	peak ML (m/s^2)	0.032	0.013	−0.003	0.016	−0.21	−0.43	0.02	0.005	0.018	0.28	0.05	0.51
	Latency (s)	0.72	0.28	0.03	0.226	0.13	−0.09	0.36	−0.034	0.25	−0.14	−0.36	0.09
	DT Latency (s)	0.74	0.21	0.052	0.342	0.15	−0.08	0.38	0.031	0.221	0.14	−0.10	0.38
	DT peak ML (m/s^2)	0.031	0.016	−0.001	0.014	−0.05	−0.28	0.18	0	0.016	0	−0.23	0.24
APRs	Length ML (m)	0.153	0.11	0.024	0.128	0.19	−0.05	0.43	−0.018	0.122	−0.14	−0.39	0.11
	Time to stability (s)	1.3	0.63	−0.079	0.662	−0.12	−0.34	0.14	−0.074	0.642	−0.12	−0.37	0.13
	Length vertical (m)	0.044	0.026	0.002	0.022	0.1	−0.16	0.32	−0.002	0.025	−0.09	−0.34	0.16

Lower and upper 95% confidence intervals (CI) for standardized response mean (SRM) are also presented. Objective measures are arranged in descending order of SRM for Exercise intervention. ROM, Range of Motion; DT, Dual-task; DC, Dual-task Cost; EOFirm, Firm surface with Eyes Open; EOFoam, Foam surface with Eyes Open; ECFirm, Firm surface with Eyes Closed; RMS, Root Means Square; ML, Medio-Lateral; APAs, Anticipatory Postural Adjustments; APRs, Automatic Postural Responses.

($p < 0.001$). Lastly, both the peak ML and the first-step ROM during gait initiation were significantly larger after the ABC-C intervention compared to the Education intervention ($p = 0.003$ and $p = 0.001$). None of these measures showed a significant order or period effect ($p > 0.01$). However, two objective measures in the Gait domain, stance time, and toe-off angle showed a significant period effect ($p < 0.01$) in the absence of a significant intervention effect (**Table 2**). In contrast to Gait and APAs, measures of Sway and APRs did not change ($p > 0.01$, **Table 2**).

Out of the Gait measures, arm swing ROM during single-task walking ($SRM_{ABC-C} = 0.95$, $SRM_{Education} = -0.09$), and gait speed during a dual-task walk ($SRM_{ABC-C} = 0.94$, $SRM_{Education} = 0.11$) showed the largest effect sizes after the ABC-C intervention but not after the Education intervention (**Table 2** and **Figure 3A**). Foot strike angle ($SRM_{ABC-C} = 0.45$; $SRM_{Education} = -0.09$) and trunk coronal ROM ($SRM_{ABC-C} = 0.45$; $SRM_{Education} = -0.13$) during a single-task walk showed small effect size after the ABC-C intervention but not after the Education intervention.

The results of a linear mixed model for the clinical measures have been detailed in our previous paper Jung et al. (20). **Figure 3B** summarizes the effect size after the ABC-C and Education interventions on the clinical measures. All of the clinical measures showed small or no effect sizes after the ABC-C intervention compared to the objective measures.

Spearman's correlation coefficient showed that Arm ROM during a single-task walk and Gait speed during a dual-task walk were associated with the perceived change in ADL (rho = 0.36 and 0.46, respectively). In addition, Arm ROM during a single-task walk correlated with the perceived change in Mobility (rho = 0.37). Therefore, we calculated the MCID for these two objective measures. Based on the mean change approach, we found 23.0- and 21.2-degrees improvement as the MCID for Arm ROM during a single-task walk with SRM of 1.19 and 1.25 calculated by perceived change in Mobility and ADL, respectively. We also found a 0.14 m/s improvement as MCID Gait speed during a dual-task walk with SRM of 0.86 calculated by perceived change in ADL (**Table 4**). Based on the ROC approach, the best cut-off value discriminating no change from

TABLE 3 | Results from linear mixed models for the change of each objective measures after intervention.

Balance domain	Measure	Fixed factor	Beta	*t*-value	Lower CI	Upper CI	*p*-value
Gait	**Arm ROM (degree)**	**Intervention**	**−15.883**	**−7.88**	**−19.865**	**−11.902**	**<0.001**
		Order	2.958	1.468	−1.023	6.938	0.144
		Period	−2.057	−1.021	−6.037	1.922	0.309
	DT Gait speed (m/s)	**Intervention**	**−0.102**	**−5.412**	**−0.139**	**−0.065**	**<0.001**
		Order	0.016	0.834	−0.021	0.053	0.406
		Period	−0.043	−2.301	−0.08	−0.006	0.023
	Trunk coronal ROM (degree)	**Intervention**	**−0.58**	**−4.052**	**−0.862**	**−0.297**	**<0.001**
		Order	0.014	0.095	−0.269	0.296	0.925
		Period	−0.005	−0.032	−0.287	0.278	0.974
	Foot strike angle (degree)	**Intervention**	**−1.606**	**−3.75**	**−2.452**	**−0.76**	**<0.001**
		Order	−0.445	−1.04	−1.291	0.4	0.3
		Period	−0.862	−2.012	−1.707	−0.016	0.046
	Toe off angle (degree)	Intervention	−0.706	−2.414	−1.283	−0.128	0.017
		Order	0.176	0.602	−0.401	0.753	0.548
		Period	−0.79	−2.705	−1.368	−0.213	0.008
	DC Stride length (%)	Intervention	−2.021	−1.606	−4.507	0.465	0.11
		Order	1.293	1.028	−1.192	3.777	0.306
		Period	−0.127	−0.101	−2.612	2.358	0.92
	Trunk sagittal ROM (degree)	Intervention	−0.205	−1.714	−0.441	0.031	0.088
		Order	0.209	1.751	−0.027	0.445	0.082
		Period	−0.047	−0.393	−0.283	0.189	0.695
	Stance time (%)	Intervention	0.287	1.684	−0.05	0.623	0.094
		Order	−0.139	−0.815	−0.475	0.198	0.417
		Period	0.469	2.751	0.132	0.805	0.007
	Gait cycle duration SD (s)	Intervention	0.001	0.389	−0.003	0.005	0.698
		Order	−0.001	−0.513	−0.005	0.003	0.609
		Period	0.005	2.45	0.001	0.01	0.015
	DT Trunk transverse ROM (degree)	Intervention	−0.113	−0.41	−0.657	0.431	0.682
		Order	−0.16	−0.581	−0.704	0.384	0.562
		Period	0.031	0.112	−0.513	0.575	0.911
	Turn velocity (degree/s)	Intervention	1.754	0.544	−4.619	8.127	0.587
		Order	−0.575	−0.178	−6.945	5.795	0.859
		Period	−7.29	−2.261	−13.66	−0.92	0.025
Sway	EOFoam RMS ML (m/s^2)	Intervention	0.016	2.233	0.002	0.029	0.027
		Order	0.005	0.719	−0.009	0.019	0.473
		Period	0.007	1.002	−0.007	0.021	0.318
	EOFoam Jerk AP (m^2/s^5)	Intervention	4.871	1.916	−0.159	9.901	0.058
		Order	−0.059	−0.023	−5.086	4.968	0.982
		Period	−3.604	−1.418	−8.632	1.424	0.159
	ECFirm Velocity ML (m/s)	Intervention	0.023	1.443	−0.008	0.054	0.151
		Order	0.01	0.652	−0.021	0.042	0.516
		Period	−0.015	−0.928	−0.046	0.017	0.355
	EOFoam RMS AP (m/s^2)	Intervention	0.013	1.102	−0.01	0.036	0.272
		Order	0.013	1.122	−0.01	0.036	0.264
		Period	0.001	0.044	−0.023	0.024	0.965
	EOFirm Sway area (m/s^2)	Intervention	−0.007	−0.713	−0.025	0.012	0.477
		Order	0.017	1.837	−0.001	0.036	0.068
		Period	0	0.004	−0.019	0.019	0.997
APAs	**First step ROM (degree)**	**Intervention**	**−3.94**	**−3.265**	**−6.323**	**−1.557**	**0.001**
		Order	−1.235	−1.024	−3.617	1.147	0.307

(Continued)

TABLE 3 | Continued

Balance domain	Measure	Fixed factor	Beta	*t*-value	Lower CI	Upper CI	*p*-value
		Period	1.808	1.499	−0.574	4.19	0.136
	Peak ML (m/s^2)	**Intervention**	**−0.008**	**−3.016**	**−0.013**	**−0.003**	**0.003**
		Order	−0.003	−1.305	−0.009	0.002	0.194
		Period	−0.007	−2.613	−0.012	−0.002	0.01
	Latency (s)	Intervention	0.066	1.719	−0.01	0.141	0.088
		Order	0.012	0.324	−0.063	0.088	0.747
		Period	−0.042	−1.087	−0.117	0.034	0.279
	DT Latency (s)	Intervention	0.023	0.47	−0.073	0.118	0.639
		Order	−0.003	−0.072	−0.099	0.092	0.943
		Period	−0.031	−0.641	−0.126	0.064	0.523
	DT peak ML (m/s^2)	Intervention	−0.001	−0.234	−0.005	0.004	0.815
		Order	−0.004	−1.684	−0.009	0.001	0.094
		Period	−0.002	−0.619	−0.006	0.003	0.537
APRs	Length ML (m)	Intervention	0.043	1.969	0	0.086	0.051
		Order	0.007	0.304	−0.037	0.05	0.761
		Period	−0.02	−0.917	−0.063	0.023	0.361
	Time to stability (s)	Intervention	−0.007	−0.06	−0.233	0.219	0.952
		Order	−0.073	−0.638	−0.298	0.153	0.525
		Period	0.047	0.409	−0.179	0.272	0.683
	Length vertical (m)	Intervention	0.005	1.133	−0.003	0.012	0.259
		Order	0.003	0.686	−0.005	0.011	0.494
		Period	−0.005	−1.288	−0.013	0.003	0.2

Values in bold indicate significant intervention effects at p < 0.01. Lower and upper 95% confidence intervals (CIs) for beta are also presented. Italic values indicate standardized response mean (SRM). Objective measures are arranged in descending order of SRM for Exercise intervention.
ROM, range of motion; DT, dual-task; DC, dual-task cost; EOFirm, firm surface with eyes open; EOFoam, foam surface with eyes open; ECFirm, firm surface with eyes closed; RMS, root mean square; ML, medio-lateral; APAs, anticipatory postural adjustments; APRs, automatic postural responses.

mild improvement in the perceived change in Mobility and ADL, respectively, was 17.7 and 17.2 with AUC of 0.64 and 0.67 for Arm ROM during a single-task walk. Furthermore, the best cutoff value to detect a perceived change in ADL was 0.13 m/s improvement for Gait speed during a dual-task walk with AUC of 0.67. **Table 4** summarizes the MCID for Arm ROM during a single-task walk and Gait speed during a dual-task walk determined by two anchor-based approaches.

DISCUSSION

Our findings suggest that objective measures of Gait significantly improved with the ABC-C intervention in a group of 86 individuals with PD. In addition, we found small improvements in objective measures of APAs and Sway, as hypothesized. The effect size of objective measures was larger than the effect sizes of all clinical measures after the ABC-C intervention compared to the Education intervention. To our knowledge, this is the first study to systematically compare the responsiveness of objective measures on four different balance domains (Sway, APRs, APAs, and Gait) vs. clinical balance and gait measures to an exercise intervention.

Consistent with previous studies, including our original Agility Boot Camp training (10, 37), the current ABC-C intervention improved objective measures of gait, as well as of APAs. Gait pace (gait speed and foot strike angle), upper body movement during gait (arm ROM and trunk coronal ROM), and APA (peak ML acceleration and first-step ROM) measures showed significant improvements with the ABC-C intervention but not with the Education (active control) intervention. Interestingly, three of the four most discriminative measures to PD compared to age-matched control subjects in Gait (foot strike angle and arm ROM) and APAs (first-step ROM) improved with the ABC-C intervention (24). Thus, the ABC-C intervention seems to improve the most affected balance and gait signs in a group of people with moderate PD.

Of the four most sensitive objective mobility measures to PD, only turning did not improve with the ABC-C intervention. The lack of change in turning velocity may be related to the fact that the ABC-C intervention did not specifically focus on practicing turning, due to difficulty in maintaining safety with three to six subjects in the group exercise program. In addition, it is not clear if an increased velocity during turning would be a safe strategy in people with PD, as it has been shown that when turning faster, people with PD spend more time with the center of mass outside the base of support, a strategy that could be more prone to falls (38).

As hypothesized, postural responses to a perturbation did not improve after the ABC-C intervention. Previous exercise studies have reported improvements of postural responses (39–41), but these studies specifically trained postural responses to external perturbations. For example, previous studies used repetitive

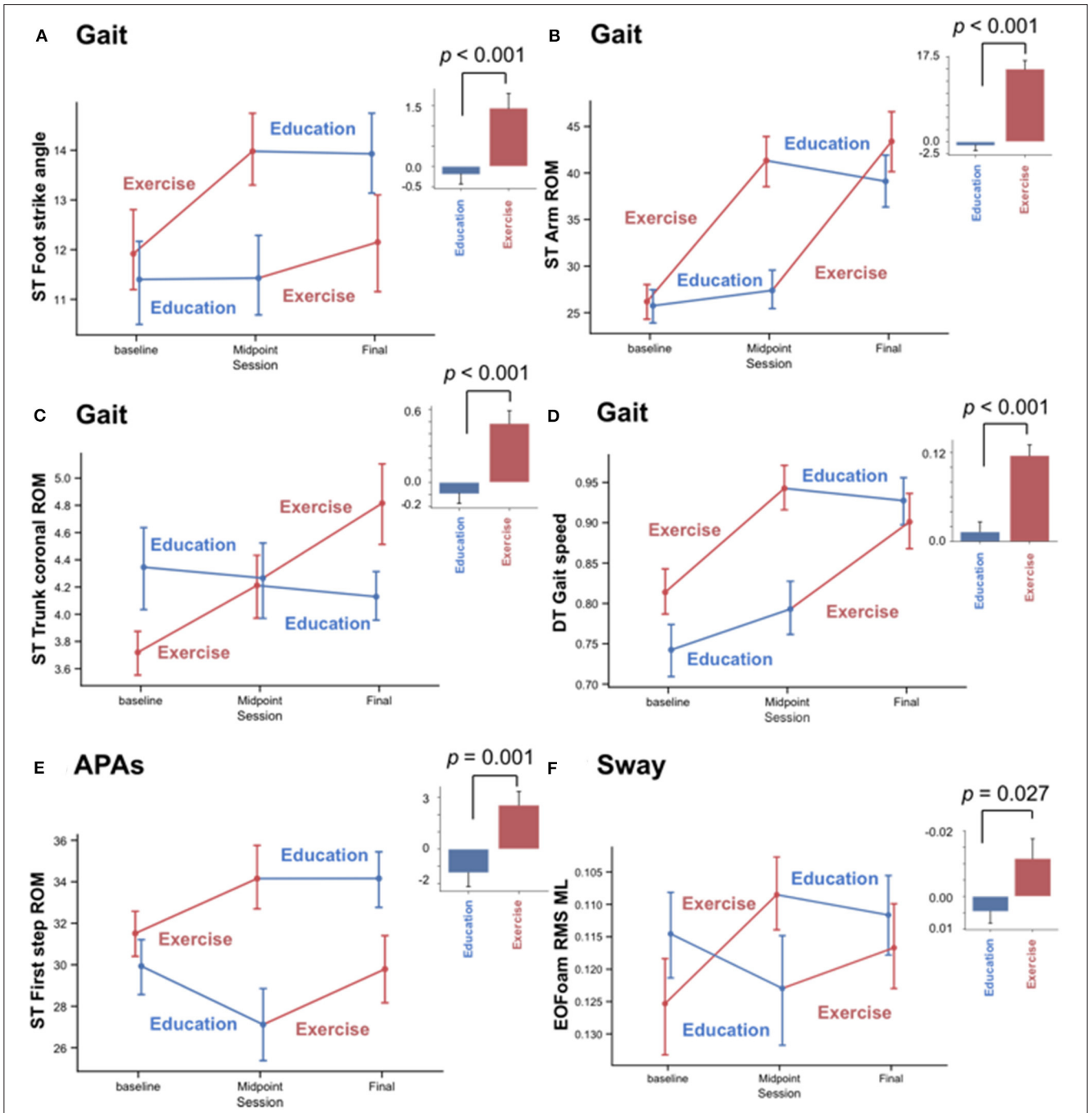

FIGURE 2 | Significant effects of the Exercise but not Education intervention on objective measures of gait and anticipatory postural adjustments (APAs), but not sway. Mean and standard error of mean (SEM) plots of **(A–D)** four gait measures and **(E,F)** two balance measures. **(A)** Foot strike angle, **(B)** Arm range of motion (ROM), and **(C)** trunk coronal ROM, **(D)** gait speed during a dual-task walk (DT), **(E)** anticipatory postural adjustments (APAs) involving first-step ROM at step initiation during a single-task walk (ST), and **(F)** root mean square (RMS) of medio-lateral (ML) sway while standing on a foam surface with eyes open (EOFoam). Plots divide results into the randomized Exercise First and Education First groups with Exercise intervention in red and Education intervention in blue. Histograms summarize the change in each measure before vs. after the Education and Exercise intervention. Error bar shows SEM, and *p*-value was calculated by a linear mixed model.

pulls to the participant's back (39) or repeated perturbation of a platform (40) or treadmill (41). Although the ABC-C intervention may have included postural perturbations induced by boxing with a contact of gloved fist onto a padded hand, these perturbations to both the boxer and the recipient of the punch (on glove) were relatively mild and could be anticipated by the participants. Studies showing improvements in postural stepping responses exposed subjects to many unexpected and

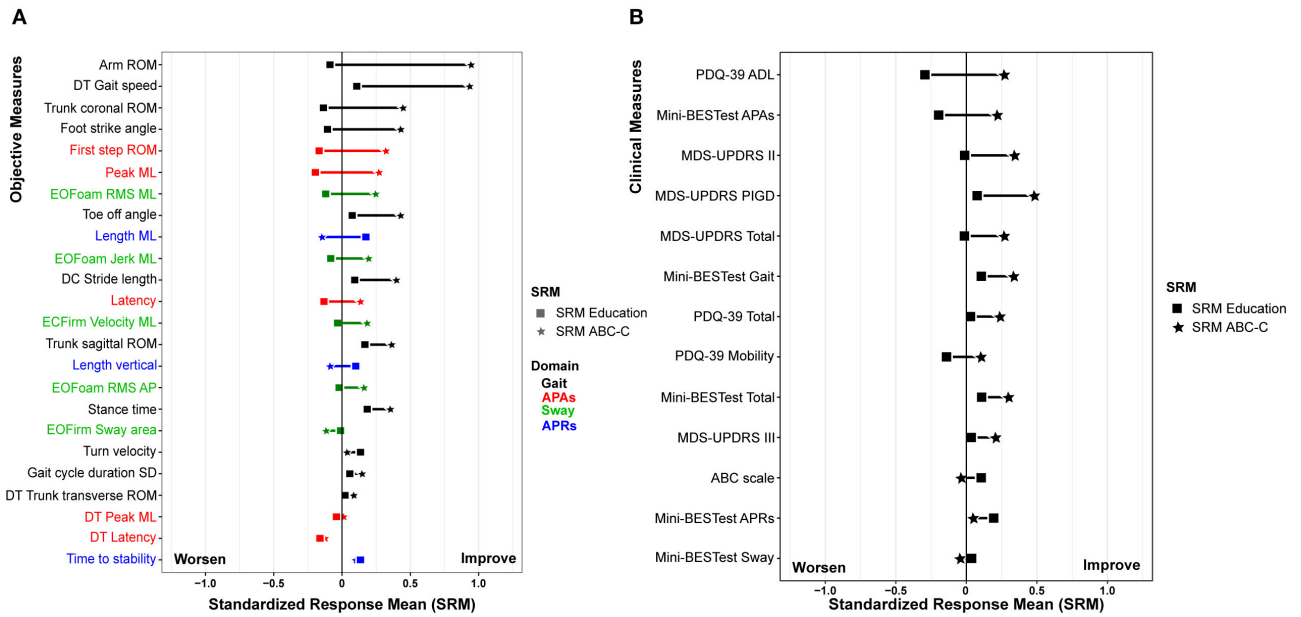

FIGURE 3 | Effect size of the **(A)** objective measure and **(B)** clinical measure after the ABC-C Intervention (square) and Education intervention (star). All of the plots are displayed in descending order of the difference of standardized response means (SRM) between for the education and Agility Boot Camp with Cognitive Challenges (ABC-C) intervention.

TABLE 4 | Mean delta value of objective measures associated with the perceived change score.

			Mean approach					ROC approach					
Objective measure	**Perceived change of Mobility**		***N***	**Mean**	**Lower *CI***	**Upper *CI***	**SRM**	**Cutoff**	**Sensitivity**	**Specificity**	**LR +**	**LR –**	**AUC**
Arm ROM	1	Mild improvement	11	23.00	11.62	34.39	1.19	17.66	0.55	0.70	1.82	0.65	0.64
	0	No change	11	13.53	6.60	20.46	1.15						
	Perceived change of ADL		***N***	**Mean**	**Lower *CI***	**Upper *CI***	**SRM**	**Cutoff**	**Sensitivity**	**Specificity**	**LR +**	**LR –**	**AUC**
Arm ROM	1	Mild improvement	13	21.20	11.22	31.19	1.25	17.16	0.62	0.73	2.26	0.53	0.67
	0	No change	12	11.58	4.53	18.63	0.97						
DT Gait speed	1	Mild improvement	13	0.14	0.08	0.19	1.38	0.13	0.69	0.73	2.54	0.42	0.67
	0	No change	12	0.10	0.03	0.16	0.86						

ROM, range of motion; DT, dual-task; ADL, activities daily living; CI, confidence interval; SRM, standardized response mean; LR+, positive likelihood ratio; LR–, negative likelihood ratio; AUC, area under the curve.

stronger perturbations, and they used the same tests for training and assessing the effects of exercise (39–42).

Lastly, this study also provided MCID values for arm ROM during a single-task walk and gait speed during a dual-task walk, the only two measures significantly associated with perceived changes in Mobility or ADL. The MCID represents the smallest difference in score, which patients perceived as beneficial (9); thus, the value is very useful for assessing effects of a treatment. Both anchor-based approaches gave similar results, and the effect sizes for these two measures were large. Therefore, we considered a 21.2-degree change as the most appropriate MCID for arm ROM during a single-task walk and 0.14 m/s as the MCID for gait speed during a dual-task walk. Furthermore, 28 of 86 participants (32.6%) improved arm swing beyond the MCID of 21.2 degrees with the ABC-C intervention. In addition, the average change in improvement of gait speed in our PD cohort was close to 0.14 m/s MCID, and 44 of 86 participants (51.2%) improved beyond the MCID with the ABC-C intervention.

The clinical outcome measures were less sensitive to change with the ABC-C intervention compared to the objective measures (smaller effect sizes). In fact, we observed a small effect size only for all of the MDS-UPDRS (SRM_{ABC-C}: total score = 0.25, Part II = 0.35, Part III = 0.20, and PIGD = 0.49), total score and APAs and Gait subscore of the Mini-BESTest ($SRM_{ABC-C} = 0.29$, 0.23, and 0.35, respectively), and the PDQ-39 total score and ADL subscore ($SRM_{ABC-C} = -0.24$ and -0.22), see **Figure 3B**. Our results are in keeping with previous studies investigating the effect of exercise in people with PD supporting that the change in objective measures was more sensitive to exercise intervention compared to clinical measures (10, 18, 19). Last, participants averaged 1.73 ± 7.72 points of changed improvement in the PDQ-39 ADL, lower than published MCID from 13.6 to 17.3

points for people with PD (43, 44). The lack of improvement in clinical or patient-reported outcomes may be related to the length of our study. In fact, participants are asked "how often have you had difficulty during the last month?" on the PDQ-39. A 6-week intervention period may be too brief to observe noticeable changes in clinical or perceived measures (8, 18, 45–49). In addition, as the ABC-C intervention was carried out as group exercise, including participants with different disease severity and cognitive abilities in the same group, the program may have been less challenging for people with milder disease severity. Thus, people with more severe symptoms or mildly impaired cognitive abilities may have benefited more from the ABC-C compared to people with PD with mild symptoms and intact cognition (20).

There are several limitations on this study that should be considered when interpreting the results. One limitation is that our larger cohort of people with PD used to identify the most discriminative measures of balance dysfunction included in this analysis is based on the baseline assessment of the participants included here (24). Another limitation was that we did not have a wash-out period; therefore, there could have been a carryover effect of exercise. However, although for few objective measures there was a trend toward a period effect, no objective measures actually showed a significant period effects (at $p < 0.01$). Lastly, only eight participants (9%) were assessed as Hoehn and Yahr stage IV, so results cannot be generalized to more severely affected people with PD. We did not collect fall data in our subjects or have a follow-up period to determine whether the effects of exercise lasted over time.

Further investigations with longer duration interventions, as well as a parallel design and a longer follow-up period, are needed to determine the longer-term effects of the ABC-C on balance and gait dysfunction. In addition, future interventions to improve balance in PD should also include training of multiple domains of balance, including APRs, standing balance on compliant surfaces and turning quality, as well as APAs and gait mobility. This study supports the use of objective measures of gait and balance, such as from wearable technology, by clinicians, as objective measures may be more sensitive to subtle improvements with exercise than clinical measures.

CONCLUSION

This study showed that the ABC-C intervention improved only certain domains of balance control in people with PD even when these changes in objective measures were not reflected in clinical outcome measures. Specifically, gait pace (foot strike angle and gait speed), upper body movements during gait (arm and trunk ROM), and APAs (first-step length) were the most sensitive to change after the ABC-C intervention compared to the active control Education intervention. Among the clinical outcomes, patient-related outcomes, such as QOL, and balance also improved significantly but were not as sensitive to change as the objective measures. These findings suggest that clinicians should add objective measures of gait and balance, such as from wearable technology, before and after therapy interventions, as objective measures may be more sensitive to subtle changes than clinical rating scales.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Oregon Health and Science University (OHSU) and Veterans Affairs Portland Health Care System (VAPORHCS) joint institutional review board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the OHSU (#4131) and the OHSU/VAPORHCS joint IRB (#8979).

AUTHOR CONTRIBUTIONS

NH: data analysis, drafting, and editing of the manuscript. VS: data analysis and editing of the manuscript. SJ: data analysis and editing of the manuscript. JL: statistical design, conceptualization of the study, and editing of the manuscript. PC-K and GH: study coordination, data collection, and editing of the manuscript. JN: conceptualization of the study and editing of the manuscript. NB: execution of the intervention and editing of the manuscript. LK: conceptualization of the study and methodology of the intervention and editing of the manuscript. FH: conceptualization of the study, obtained funding, and editing of the manuscript. MM: conceptualization of the study, supervising of the study, data collection, data analysis, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded by the National Institutes of Health under award number R01AG006457 (PI: Horak), Department of Veterans A airs Merit award number 5I01RX001075 (PI: Horak), and by the Gtant-in-Aid for Early-Career Scientists from Japan Society for the Promotion of Science number 20K19371 (PI: Hasegawa).

ACKNOWLEDGMENTS

The authors thank all participants for generously donating their time to participate; Peter Fino, Carolin Curtze, Mike Fleming, Heather Schlueter, Peter Martin, and Graham Harker for helping with data collection; Daniel Peterson and Katrijn Smulders for data collection and help with study procedures; and Edward King for helping with data collection and management.

REFERENCES

1. Park JH, Kang YJ, Horak FB. What is wrong with balance in Parkinson's disease? *J Mov Disord.* (2015) 8:109–14. doi: 10.14802/jmd.15018
2. Schoneburg B, Mancini M, Horak F, Nutt JG. Framework for understanding balance dysfunction in Parkinson's disease. *Mov Disord.* (2013) 28:1474–82. doi: 10.1002/mds.25613
3. Tomlinson CL, Patel S, Meek C, Herd CP, Clarke CE, Stowe R, et al. Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *BMJ.* (2012) 345:e5004. doi: 10.1136/bmj.e5004
4. Shen X, Wong-Yu IS, Mak MK. Effects of exercise on falls, balance, and gait ability in Parkinson's disease: a meta-analysis. *Neurorehabil Neural Repair.* (2016) 30:512–27. doi: 10.1177/1545968315613447
5. Berg KO, Maki BE, Williams JI, Holliday PJ, Wood-Dauphinee SL. Clinical and laboratory measures of postural balance in an elderly population. *Arch Phys Med Rehabil.* (1992) 73:1073–80.
6. Mancini M, Horak FB. The relevance of clinical balance assessment tools to differentiate balance deficits. *Eur J Phys Rehabil Med.* (2010) 46:239–48.
7. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med.* (2010) 42:323–31. doi: 10.2340/16501977-0537
8. Ortiz-Rubio A, Cabrera-Martos I, Torres-Sánchez I, Casilda-López J, López-López L, Valenza MC. Effects of a resistance training program on balance and fatigue perception in patients with Parkinson's disease: a randomized controlled trial. *Med Clin (Barc).* (2018) 150:460–4. doi: 10.1016/j.medcli.2017.10.022
9. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* (1989) 10:407–15. doi: 10.1016/0197-2456(89)90005-6
10. King LA, Salarian A, Mancini M, Priest KC, Nutt J, Serdar A, et al. Exploring outcome measures for exercise intervention in people with Parkinson's disease. *Parkinsons Dis.* (2013) 2013:572134. doi: 10.1155/2013/572134
11. Zampieri C, Salarian A, Carlson-Kuhta P, Aminian K, Nutt JG, Horak FB. The instrumented timed up and go test: potential outcome measure for disease modifying therapies in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (2010) 81:171–6. doi: 10.1136/jnnp.2009.173740
12. Sprager S, Juric MB. Inertial sensor-based gait recognition: a review. *Sensors (Basel).* (2015) 15:22089–127. doi: 10.3390/s150922089
13. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Mov Disord.* (2013) 28:1544–51. doi: 10.1002/mds.25684
14. El-Gohary M, Peterson D, Gera G, Horak FB, Huisinga JM. Validity of the instrumented push and release test to quantify postural responses in persons with multiple sclerosis. *Arch Phys Med Rehabil.* (2017) 98:1325–31. doi: 10.1016/j.apmr.2017.01.030
15. Mancini M, Salarian A, Carlson-Kuhta P, Zampieri C, King L, Chiari L, et al. ISway: a sensitive, valid and reliable measure of postural control. *J Neuroeng Rehabil.* (2012) 9:59. doi: 10.1186/1743-0003-9-59
16. Mancini M, King L, Salarian A, Holmstrom L, McNames J, Horak FB. Mobility lab to assess balance and gait with synchronized body-worn sensors. *J Bioeng Biomed Sci.* (2011) Suppl 1:7. doi: 10.4172/2155-9538.S1-007
17. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease. *Mov Disord.* (2015) 30:1361–70. doi: 10.1002/mds.26269
18. Rawson KS, McNeely ME, Duncan RP, Pickett KA, Perlmutter JS, Earhart GM. Exercise and Parkinson disease: comparing tango, treadmill, and stretching. *J Neurol Phys Ther.* (2019) 43:26–32. doi: 10.1097/NPT.0000000000000245
19. Capato TTC, de Vries NM, IntHout J, Barbosa ER, Nonnekes J, Bloem BR. Multimodal balance training supported by rhythmical auditory stimuli in Parkinson's disease: a randomized clinical trial. *J Parkinsons Dis.* (2020) 10:333–46. doi: 10.3233/JPD-191752
20. Jung SH, Hasegawa N, King L, Carlson-Kuhta P, Smulders K, Peterson D, et al. Effects of the agility boot camp with cognitive challenge (ABC-C) exercise program for Parkinson's disease. *NPJ Parkinsons Dis.* (2020).
21. King LA, Peterson DS, Mancini M, Carlson-Kuhta P, Fling BW, Smulders K, et al. Do cognitive measures and brain circuitry predict outcomes of exercise in Parkinson Disease: a randomized clinical trial. *BMC Neurol.* (2015) 15:218. doi: 10.1186/s12883-015-0474-2
22. King LA, Mancini M, Smulders K, Harker G, Lapidus JA, Ramsey K, et al. Cognitively challenging agility boot camp program for freezing of gait in Parkinson disease. *Neurorehabil Neural Repair.* (2020) 34:417–7. doi: 10.1177/1545968320909331
23. Peterson DS, King LA, Cohen RG, Horak FB. Cognitive contributions to freezing of gait in parkinson disease: implications for physical rehabilitation. *Phys Ther.* (2016) 96:659–70. doi: 10.2522/ptj.20140603
24. Hasegawa N, Shah VV, Carlson-Kuhta P, Nutt JG, Horak FB, Mancini M. How to select balance measures sensitive to Parkinson's disease from body-worn inertial sensors-separating the trees from the forest. *Sensors (Basel).* (2019) 19:E3320. doi: 10.3390/s19153320
25. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* (1992) 55:181–4. doi: 10.1136/jnnp.55.3.181
26. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, 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.* (2008) 23:2129–70. doi: 10.1002/mds.22340
27. Powell LE, Myers AM. The activities- specific balance confidence (ABC) scale. *J Gerontol A Biol Sci Med Sci.* (1995) 50:M28–M34. doi: 10.1093/gerona/50A.1.M28
28. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
29. Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture.* (2009) 30:459–63. doi: 10.1016/j.gaitpost.2009.07.108
30. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's disease questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing.* (1997) 26:353–7. doi: 10.1093/ageing/26.5.353
31. Farley BG, Koshland GF. Training BIG to move faster: the application of the speed-amplitude relation as a rehabilitation strategy for people with Parkinson's disease. *Exp Brain Res.* (2005) 167:462–7. doi: 10.1007/s00221-005-0179-7
32. Li F, Harmer P, Fitzgerald K. Implementing an evidence-based fall prevention intervention in community senior centers. *Am J Public Health.* (2016) 106:2026–31. doi: 10.2105/AJPH.2016.303386
33. Cohen J. *Statistical Power Analysis for the Behavioural Sciences.* 2nd ed. Hillsdales, NJ: Lawrence Erlbaum (1988).
34. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol.* (2008) 61:102–9. doi: 10.1016/j.jclinepi.2007.03.012
35. Hauser RA, Auinger P; Parkinson Study Group. Determination of minimal clinically important change in early and advanced Parkinson's disease. *Mov Disord.* (2011) 26:813–8. doi: 10.1002/mds.23638
36. Rice ME, Harris GT. Comparing effect sizes in follow-up studies: ROC Area, Cohen's d, and r. *Law Hum Behav.* (2005) 29:615–20. doi: 10.1007/s10979-005-6832-7
37. King LA, Wilhelm J, Chen Y, Blehm R, Nutt J, Chen Z, et al. Effects of group, individual, and home exercise in persons with Parkinson disease: a randomized clinical trial. *J Neurol Phys Ther.* (2015) 39:204–12. doi: 10.1097/NPT.0000000000000101
38. Mellone S, Mancini M, King LA, Horak FB, Chiari L. The quality of turning in Parkinson's disease: a compensatory strategy to prevent postural instability? *J Neuroeng Rehabil.* (2016) 13:39. doi: 10.1186/s12984-016-0147-4
39. Jöbges M, Heuschkel G, Pretzel C, Illhardt C, Renner C, Hummelsheim H. Repetitive training of compensatory steps: a therapeutic approach for postural instability in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (2004) 75:1682–7. doi: 10.1136/jnnp.2003.016550
40. Peterson DS, Horak FB. The effect of levodopa on improvements in protective stepping in People With Parkinson's disease. *Neurorehabil Neural Repair.* (2016) 30:931–40. doi: 10.1177/1545968316648669

41. Gaßner H, Steib S, Klamroth S, Pasluosta CF, Adler W, Eskofier BM, et al. Perturbation treadmill training improves clinical characteristics of gait and balance in Parkinson's disease. *J Parkinsons Dis.* (2019) 9:413–26. doi: 10.3233/JPD-181534
42. Handelzalts S, Kenner-Furman M, Gray G, Soroker N, Shani G, Melzer I. Effects of perturbation-based balance training in subacute persons with stroke: a randomized controlled trial. *Neurorehabil Neural Repair.* (2019) 33:213–24. doi: 10.1177/1545968319829453
43. Fitzpatrick R, Norquist JM, Jenkinson C. Distribution-based criteria for change in health-related quality of life in Parkinson's disease. *J Clin Epidemiol.* (2004) 57:40–4. doi: 10.1016/j.jclinepi.2003.07.003
44. Martínez-Martín P, Serrano-Dueñas M, Vaca-Baquero V. Psychometric characteristics of the Parkinson's disease questionnaire (PDQ-39)-Ecuadorian version. *Parkinsonism Relat Disord.* (2005) 11:297–304. doi: 10.1016/j.parkreldis.2005.02.003
45. Corcos DM, Robichaud JA, David FJ, Leurgans SE, Vaillancourt DE, Poon C, et al. A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. *Mov Disord.* (2013) 28:1230–40. doi: 10.1002/mds.25380
46. Conradsson D, Löfgren N, Nero H, Hagströmer M, Ståhle A, Lökk J, et al. The effects of highly challenging balance training in elderly with Parkinson's disease: a randomized controlled trial. *Neurorehabil Neural Repair.* (2015) 29:827–36. doi: 10.1177/1545968314567150
47. Sparrow D, DeAngelis TR, Hendron K, Thomas CA, Saint-Hilaire M, Ellis T. Highly challenging balance program reduces fall rate in Parkinson disease. *J Neurol Phys Ther.* (2016) 40:24–30. doi: 10.1097/NPT.0000000000000111
48. Wallén MB, Hagströmer M, Conradsson D, Sorjonen K, Franzén E. Long-term effects of highly challenging balance training in Parkinson's disease-a randomized controlled trial. *Clin Rehabil.* (2018) 32:1520–9. doi: 10.1177/0269215518784338
49. Frazzitta G, Maestri R, Bertotti G, Riboldazzi G, Boveri N, Perini M, et al. Intensive rehabilitation treatment in early Parkinson's disease: a randomized pilot study with a 2-year follow-up. *Neurorehabil Neural Repair.* (2015) 29:123–31. doi: 10.1177/1545968314542981

Conflict of Interest: FH has an equity interest in APDM, a company that may have a commercial interest in the results of this study. This potential conflict of interest has been reviewed and managed by the Research and Development Committee at the VA Portland Medical Health Care System and Oregon Health and Science University. They have put in place a plan to help ensure that this research study is not affected by the financial interest.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
published: 29 October 2020
doi: 10.3389/fneur.2020.580285

Neurovestibular Dysfunction and Falls in Parkinson's Disease and Atypical Parkinsonism: A Prospective 1 Year Follow-Up Study

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Our primary aim was to determine whether neurovestibular laboratory tests can predict future falls in patients with either Parkinson's disease (PD) or atypical parkinsonism (AP). We included 25 healthy subjects, 30 PD patients (median Hoehn and Yahr stage 2.5, range 1–4), and 14 AP patients (6 multiple system atrophy, 3 progressive supranuclear palsy, and 5 vascular parkinsonism) in a case-control study design (all matched for age and gender). At baseline, all subjects underwent clinical neurological and neurotological assessments, cervical and ocular vestibular evoked myogenic potentials (VEMP), brainstem auditory evoked potentials (BAEP), subjective visual vertical measurements (SVV), and video nystagmography with caloric and rotary test stimulation. After 1 year follow-up, all subjects were contacted by telephone for an interview about their fall frequency (based upon fall diaries) and about their balance confidence (according to the ABC-16 questionnaire); only one participant was lost to follow-up (attrition bias of 1.4%). Cervical and ocular VEMPs combined with clinical tests for postural imbalance predicted future fall incidents in both PD and AP groups with a sensitivity of 100%. A positive predictive value of 68% was achieved, if only one VEMP test was abnormal, and of 83% when both VEMP tests were abnormal. The fall frequency at baseline and after 1 year was significantly higher and the balance confidence scale (ABC-16) was significantly lower in both the PD and AP groups compared to healthy controls. Therefore, VEMP testing can predict the risk of future fall incidents in PD and AP patients with postural imbalance.

Keywords: falls, Parkinson's disease, atypical Parkinsonism, follow-up, neurovestibular

OPEN ACCESS

Edited by:
Carmen Rodriguez-Blazquez, Instituto de Salud Carlos III (ISCIII), Spain

Reviewed by:
Matteo Bologna, Sapienza University of Rome, Italy
Camila Aquino, McMaster University, Canada

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *05 July 2020*
Accepted: *22 September 2020*
Published: *29 October 2020*

Citation:
Venhovens J, Meulstee J, Bloem BR and Verhagen WIM (2020) Neurovestibular Dysfunction and Falls in Parkinson's Disease and Atypical Parkinsonism: A Prospective 1 Year Follow-Up Study. Front. Neurol. 11:580285. doi: 10.3389/fneur.2020.580285

INTRODUCTION

Falls are highly prevalent in patients with Parkinson's disease (PD) or atypical parkinsonism (AP). Approximately 70% of PD patients have at least one fall episode annually (1). Fall incidents often lead to social isolation which may result in a reduced quality of life, because fall incidents can cause a fear of renewed fall episodes, possibly resulting in a self-imposed restriction of daily activities (2–4).

We previously showed that vestibular dysfunction is an independent risk factor for the occurrence of falls in PD and AP patients (4). The results of vestibular tests mainly reflect central neurological vestibular dysfunction, even though these patients usually do not complain of vertigo or dizziness (4). Patients with PD or AP who had experienced prior falls had more abnormal vestibular test results compared to non-falling patients. After exclusion of the well-established causes of falls (e.g., orthostatic hypotension, freezing of gait, cognitive problems and postural instability) 10–18% of the falling PD and AP patients had vestibular system abnormalities as the only identifiable cause for falling (4). We therefore concluded that vestibular system dysfunction, as established with neurovestibular laboratory tests, is an independent and relevant risk factor for falling in PD and AP.

The primary aim of this prospective study was to determine whether neurovestibular laboratory tests have predictive value for the occurrence of future falls in PD and AP patients and, if so, to determine their sensitivity, specificity, likelihood ratio's, and positive/negative predictive values. The secondary aim was to determine the fall frequency and balance confidence in both PD and AP after 1 year of follow-up, as compared with an age- and gender-matched healthy control group.

METHODOLOGY

Study Participants

Previously we described the methodology and baseline measurements of our study cohort in detail (4). Now we present the data after 1 year follow-up (median 12 months, range 12–14 months). Sixty-eight volunteers completed the follow-up study; 25 healthy controls (mean age 67, range 42–81, 15 men), 30 PD patients [mean age 70, range 59–81, 26 men, all fulfilling the UK Parkinson's Disease Society Brain Bank criteria (5), median Hoehn and Yahr stage 2.5, range 1–4], and 13 atypical parkinsonism (AP) patients (mean age 68, range 52–81, 8 men, 5 multiple system atrophy, 3 progressive supranuclear palsy, and 5 vascular parkinsonism, 1 patient with MSA-P was lost to follow-up). The MSA-P patients all fulfilled the diagnostic criteria for probable MSA-P as proposed in the consensus statement by Gilman (6). Supranuclear palsy patients (PSP) all fulfilled the NINDS-SPSP criteria for possible PSP (7). Vascular parkinsonism patients all fulfilled the criteria of the Winikates and Jankovic vascular rating scale (8).

The study was approved by the regional and local medical ethical committee (CMO Arnhem-Nijmegen, the Netherlands, number 2012/393) and was registered as well in the Dutch trial register (Nederlands Trial Register, NTR-3928). All volunteers signed an informed consent. Healthy controls and patients did not have a relevant medical history (i.e., no relevant neurological, otological, ophthalmological diseases, and/or absence of moderate-to-severe cognitive problems) with the exception of PD or AP (in combination with a related cerebrovascular disorder in the vascular parkinsonism group). Controls were matched for age and gender with the PD and AP patients. Sixty-nine volunteers were included in the baseline case-control study. Only one patient with multiple system atrophy with predominant parkinsonism (MSA-P) was lost to follow-up, resulting in an attrition bias of only 1.4%.

The participants were questioned about their medical history, medication, dizziness, gait and balance problems, prior falls and near falls, motor fluctuations, and freezing of gait. They underwent a detailed neurological and neurotological clinical examination with additional measurements for possible orthostatic hypotension (i.e., blood pressure measurement after lying supine for at least 15 min; followed by blood pressure measurements in a standing position after 1, 3, and 5 min). All PD and AP patients were tested during a regular medication on-state.

All participants completed: (a) the 16 items activities-specific balance confidence scale (ABC-16), (b) the dizziness handicap inventory (DHI), (c) the Edinburgh handedness inventory, (d) all subscales of the standardized unified Parkinson's disease rating scale (UPDRS), (e) the modified Hoehn and Yahr scale, (f) the Schwab and England activities of daily life (ADL) scale, and (g) a standardized falls questionnaire.

All participants received a Berg balance scale examination for quantitative balance assessment with additional pull-testing and functional reach testing for the assessment of the degree of postural imbalance. Partial postural imbalance was defined as a normal functional reach test in combination with an abnormal pull-test (i.e., sudden unexpected forceful backward shoulder pull without any specific prior instructions other than to remain standing upright; the patient was able to recover balance in more than two backward steps). Complete postural imbalance was defined as an abnormal pull-test: the patient would have fallen down if the examiner had not been present behind the patient to catch him/her during the fall. Patients that are informed in more detail about this test tend to shift their center of mass more anterior by leaning forwards in anticipation of the backward shoulder pull, which makes the test less reliable. For this reason patients were not informed in more detail prior to the test.

The neurovestibular laboratory tests conducted at baseline were: (a) cervical and ocular vestibular evoked myogenic potentials (VEMPs), (b) subjective visual vertical (SVV), and (c) video nystagmography (VNG) with additional caloric- and rotatory chair stimulation.

Follow-Up by Telephone Interview

All participants were contacted by telephone for an interview 1 year after the baseline measurements. At baseline, they were instructed to keep record of their falls in the coming year. At the end of the baseline examinations, they were asked to keep track of their fall incidents during the following year by means of a fall diary. During the telephone interview, they were questioned about their fall frequency during the previous year, their fear of falling according to the ABC-16 questionnaire (16-items activities-specific balance confidence scale), acquired injuries related to fall incidents, and whether they had received medical treatment for such injuries.

Statistical Analysis

The statistical database software SPSS version 23.0 (SPSS Inc., USA) was used for statistical analyses. The Shapiro-Wilks test was applied to determine whether parametrical tests were applicable

(the null hypothesis, that the variable was distributed normally, was rejected when $p \leq 0.05$). Because of this test result (Shapiro-Wilks p-values: $0.000 \leq p \leq 0.031$, therefore the variables were not normally distributed) and due to the limited sample size of our study we had to apply non-parametrical tests for further statistical analyses. The Kruskal-Wallis one-way analysis by ranks test was applied for comparison of the continuous non-parametrically distributed data of the three independent groups (controls, PD, and AP), the Mann-Whitney-*U*-test for a group to group comparison, and a significance level of 5%

TABLE 1 | Individual clinical characteristics of patients with Parkinson's disease and atypical Parkinsonism.

		ID	Age	M/F*	Disease duration**	Dominant side	Hoehn-Yahr stage	Ortho***	FOG****	PI*****
Parkinson's disease		1	68	M	4.0	Right	2	–	–	–
		2	60	M	2.0	Left	2.5	+	+	C
		3	73	M	7.0	Symmetrical	3	+	–	C
		4	60	M	2.0	Left	1.5	–	–	P
		5	78	M	2.0	Left	1.5	+	–	P
		6	73	M	2.0	Right	3	–	–	C
		7	64	M	2.0	Right	1	–	–	–
		8	59	F	4.0	Right	2	–	–	–
		9	72	M	5.5	Right	2.5	–	–	P
		10	80	M	1.5	Right	2	–	–	–
		11	58	M	4.0	Left	1	–	–	P
		12	66	M	4.5	Right	3	–	–	C
		13	66	M	2.0	Right	1	–	–	–
		14	70	M	5.0	Left	2.5	–	–	P
		15	59	M	12.0	Left	2	–	–	P
		16	75	F	10.0	Right	3	–	–	C
		17	75	M	3.0	Right	2.5	–	–	P
		18	59	M	2.0	Left	2	–	–	–
		19	76	F	3.5	Right	2.5	–	–	P
		20	76	M	6.0	Left	3	–	+	C
		21	81	F	22.0	Symmetrical	4	–	+	C
		22	75	M	8.0	Left	3	–	+	C
		23	67	M	3.0	Right	2.5	+	–	P
		24	71	M	5.0	Symmetrical	2	–	–	–
		25	76	M	8.0	Left	2.5	–	+	P
		26	65	M	6.0	Right	2	–	–	P
		27	76	M	2.0	Right	1.5	+	–	–
		28	69	M	3.0	Left	2.5	–	–	P
		29	78	M	12.0	Left	2.5	+	+	P
		30	65	M	2.0	Symmetrical	2	–	–	–
Atypical Parkinsonism	MSA	31	73	F	2.5	Symmetrical	4	+	–	C
		32	67	F	6.0	Symmetrical	3	+	–	C
		33	69	M	3.0	Symmetrical	3	+	+	C
		34	71	M	4.0	Symmetrical	4	+	+	C
		35	57	M	9.5	Right	2	+	–	–
		36	61	M	5.0	Symmetrical	4	+	–	C
	PSP	37	71	F	1.5	Right	1	–	–	P
		38	61	M	2.0	Symmetrical	3	–	–	C
		39	74	M	3.0	Symmetrical	3	–	–	P
	Vascular	40	71	F	2.0	Left	2.5	+	–	C
		41	52	F	3.5	Right	2	–	–	–
		42	76	M	6.5	Symmetrical	2.5	–	–	P
		43	65	M	1.0	Left	3	–	–	P
		44	81	M	3.0	Symmetrical	3	–	–	C

*Adapted from Venhovens et al. (4). *Gender (male or female). **Disease duration (calculated from symptom onset in years). ***Orthostatic hypotension (Ortho). ****Freezing of gait (FOG). *****Postural imbalance, PI (C, complete imbalance on pull testing without unaided recovery of balance; P, partial imbalance on pull testing with unaided recovery of balance requiring 2 or more backward steps).*

TABLE 2 | Baseline individual test results of patients with Parkinson's disease and atypical Parkinsonism.

		ID	cVEMP*	oVEMP*	SVV**	VNG + calorisation***						
						C	S	O	P	N	R	F
Parkinson's disease		1	–/–	–/A	+	–	–	–	–	–	–	–
		2	–/–	–/–	+	VP(r)	–	–	–	–	–	–
		3	–/–	A/A	–	VP(l)	–	+	+	–	–	–
		4	–/–	–/–	–	–	–	–	–	–	–	–
		5	–/–	–/–	–	–	–	–	–	–	–	–
		6	–/–	–/A	–	–	+	–	+	–	–	–
		7	–/D	–/–	–	–	–	–	–	–	–	–
		8	A/–	–/D	–	–	–	–	–	–	–	–
		9	–/–	–/–	–	–	–	–	+	–	–	–
		10	D/–	D/–	+	–	–	–	+	–	+	–
		11	D/D	–/A	–	–	–	–	–	–	–	–
		12	–/–	D/A	–	VP(l)	+	+	+	–	+	+
		13	–/–	–/D	–	–	–	–	–	–	–	–
		14	–/–	–/–	–	–	–	–	+	–	+	–
		15	–/–	–/D	–	–	–	–	–	–	–	–
		16	D/–	–/A	+	–	–	–	+	–	–	–
		17	–/–	–/–	+	–	+	+	+	–	–	–
		18	–/–	–/–	–	–	+	–	+	–	+	–
		19	–/–	–/D	+	–	+	–	+	–	+	–
		20	–/–	–/A	+	–	+	–	+	–	–	–
		21	–/–	D/A	–	–	–	–	+	–	–	+
		22	–/D	D/A	–	–	+	–	+	–	–	–
		23	–/–	–/A	–	–	–	–	–	–	–	–
		24	–/D	–/D	+	–	+	–	–	–	–	–
		25	D/–	–/–	+	–	+	+	+	–	–	–
		26	–/D	–/–	–	–	+	–	–	–	–	–
		27	–/–	–/–	+	–	–	–	+	–	–	–
		28	–/–	–/–	+	VP(b)	+	–	+	–	+	–
		29	A/D	–/–	–	–	+	+	–	–	–	–
		30	A/–	–/–	+	–	+	–	+	–	–	–
Atypical Parkinsonism	MSA	31	–/–	A/A	–	–	+	+	+	–	–	+
		32	D/–	–/A	+	–	+	+	+	–	–	+
		33	–/–	–/A	–	–	+	+	+	–	+	–
		34	A/–	–/–	–	DP(l)	+	–	+	–	+	–
		35	–/D	–/A	–	–	+	+	+	+	–	+
		36	D/D	–/–	–	–	+	+	+	–	–	+
	PSP	37	D/–	–/–	+	–	+	–	+	–	–	–
		38	–/–	–/–	–	–	+	–	–	–	–	–
		39	–/–	–/–	–	–	+	–	+	–	+	–
	Vascular	40	D/–	D/–	+	–	–	–	–	–	–	–
		41	–/–	–/A	–	VP(r)	–	+	+	–	+	+
		42	–/–	–/–	+	–	+	–	+	–	–	–
		43	–/–	–/A	–	VP(r)	+	–	+	–	–	–
		44	D/D	D/–	–	–	–	–	–	–	–	–

*Adapted from Venhovens et al. (4). *Cervical (cVEMP) and Ocular (oVEMP) vestibular evoked myogenic potentials: Right/Left responses (A, absent response; D, delayed response; –, normal response). **Subjective Visual Vertical (SVV): +, abnormal; –, normal. ***Videonystagmography (VNG) and calorisation results: C[alorisation; VP, vestibular paresis (left/right/bilateral); DP, directional preponderance (left/right/bilateral)]; S(accade testing); O(ptokinetics); smooth P(ursuit); spontaneous N(ystagmus) in dark and light conditions; R(otary) chair testing; F(ixation) suppression testing; +, abnormal; –, normal.*

TABLE 3 | Individual clinical characteristics concerning the fall frequencies and balance confidence at baseline and during follow-up of patients with Parkinson's disease and atypical Parkinsonism.

		ID	Falls baseline*	Falls follow-up*	ABC-16 baseline**	ABC-16 follow-up**
Parkinson's disease		1	–	–	72	57
		2	–	–	99	100
		3	Y	–	91	90
		4	–	–	95	80
		5	–	–	73	76
		6	–	–	70	64
		7	–	–	78	74
		8	–	–	78	68
		9	–	–	86	90
		10	6M	–	64	59
		11	3M	3M	73	65
		12	–	–	72	65
		13	–	–	98	99
		14	–	–	61	64
		15	–	–	58	71
		16	1M	1M	51	31
		17	–	–	68	63
		18	–	–	71	73
		19	–	6M	38	36
		20	W	W	59	54
		21	W	W	70	66
		22	1M	W	48	46
		23	6M	–	99	95
		24	–	–	76	61
		25	Y	3M	75	68
		26	–	–	74	75
		27	–	–	68	70
		28	–	–	97	93
		29	W	W	58	82
		30	Y	–	68	80
Atypical Parkinsonism	MSA	31	1M	1M	40	20
		32	3M	1M	58	45
		33	W	D	46	0
		34	W	D	39	29
		35	–	–	62	57
		36#	3M	#	43	#
	PSP	37	6M	W	76	58
		38	–	–	75	79
		39	–	–	64	43
	Vascular	40	1M	1M	57	59
		41	6M	–	98	96
		42	Y	–	79	80
		43	6M	3M	92	71
		44	–	–	55	28

*Adapted from Venhovens et al. (4). *Frequency of falling (Y, once a year; 6M, once every 6 months; 3M, once every 3 months; 1M, monthly; W, weekly; D, daily). **ABC-16 questionnaire (16-items specific confidence of balance scale). #Loss to follow-up.*

was used for all analyses. An ordinal logistic regression analysis was applied for comparison of the categorical variables. We did not perform a multivariate regression analysis of the data due to the limited sample size. Also the sensitivity (number of true positives/(number of true positives + number of false negatives), specificity (number of true negatives/(number of true negatives + number of false positives), positive predictive value [PPV = number of true positives/(number of true positives + number of false positives)], negative predictive value [NPV = number of true negatives/(number of true negatives + number of false negatives)], positive likelihood ratio [sensitivity/(1 – specificity)], and the negative likelihood ratio [(1 – sensitivity)/specificity] were calculated for the different neurovestibular tests in relation to the future risk for falling in the different groups (patients with Parkinson's disease and atypical Parkinsonism).

RESULTS

We refer to **Tables 1**, **2** for the PD and AP patients' individual data concerning the clinical and neurovestibular neurophysiological baseline results. The individual 1-year follow-up results in relation to the baseline measurements are shown in **Table 3**, and we refer to **Table 4** for the group characteristics. All four tables were adapted from our baseline study (4). **Tables 5**, **6** show the group characteristics concerning the difference between de falling and non-falling PD and AP patients in the cervical and ocular VEMP tests.

From our data in **Table 4** and additional group-to-group comparisons it may be inferred that the number of falling PD and AP patients was statistically significantly higher in comparison to age- and gender-matched healthy control subjects at baseline. However, at follow-up 1-year later only AP patients fell statistically significantly more often. Moreover, the percentage of falling AP patients was higher than the PD patients, however the difference was only statistically significant at baseline.

The PD patients and the AP patients have a statistically significantly higher fall frequency at baseline in comparison to healthy controls, however during follow-up only the difference between the AP patients and healthy controls remained statistically significant.

The 16-items activities-specific balance confidence scale (ABC-16) differed significantly between the groups in total and the non-falling patients both at baseline and during follow-up 1 year later, which showed a higher fear of falling in the PD patients and especially the AP patients in comparison to the healthy controls. The fear of falling in only the falling patients, however, was the same across the groups. The change in ABC-16 scores between the baseline measurements and after 1 year follow-up was statistically significant in the total group, which showed a larger increase concerning the fear of falling in de PD and AP patients in comparison to the healthy controls. Moreover, the AP patients also had a larger increase concerning the fear of falling in comparison to the PD patients during follow-up 1 year later. The fall related injuries both at baseline or during follow-up and their treatments did not differ significantly.

TABLE 4 | Group characteristics and comparison between the groups concerning the different test results in the Parkinson's disease, atypical Parkinsonism, and healthy control groups.

	Parkinson's disease	Atypical Parkinsonism	Healthy controles	*P*-value*	*P*-value group-to-group comparison*
Number of subjects (*N*)	30	14**	25	0.054	–
Number of falling patients:					
- Baseline (N, percentage)	11 (37)	10 (71)	3 (12)	**<0.001**	**Baseline $P_{PD-controls} = 0.037$**
- Follow-up (N, percentage)	8 (27)	7 (54)	5 (20)	**0.043**	**Baseline $P_{AP-controls}$ <0.001**
					Baseline $P_{PD-PA} = 0.032$
					Follow-up $P_{PD-controls} = 0.571$
					Follow-up $P_{AP-controls} = 0.034$
					Follow-up $P_{PD-PA} = 0.090$
Average falls/year (baseline):					
- All patients in total (average, SD)	6.4 (15.8)	10.2 (18.1)	0.3 (0.9)	**<0.001**	**$P_{PD-controls} = 0.035$**
- Only falling patients (average, SD)	16.0 (22.1)	14.3 (20.3)	2.7 (1.2)		**$P_{AP-controls} = 0.001$**
					$P_{PD-PA} = 0.039$
Average falls/year (follow-up):					
- All patients in total (average. SD)	7.7 (3.3)	63.2 (37.4)	0.9 (0.5)	**0.032**	$P_{PD-controls} = 0.394$
- Only falling patients (average, SD)	28.8 (8.8)	117.4 (64.2)	4.4 (2.0)		**$P_{AP-controls} = 0.032$**
					$P_{PD-PA} = 0.116$
Change in falls/year (absolute, percentage)					
- All patients in total (absolute, percentage)	+1.3 (+21.1)	+53.0 (+518.7)	+0.6 (+175.0)	0.164	–
- Only falling patients (absolute, percentage)	+9.8 (+51.3)	+103.1 (+721.0)	+1.7 (+65.0)		
ABC-16 fear of falling, baseline:					
- All patients in total (average, SD)	72.9 (2.8)	64.7 (5.1)	82.3 (3.6)	**0.006**	**All patients $P_{PD-controls} = 0.028$**
- Only falling patients (average, SD)	59.0 (4.6)	57.9 (6.4)	60.8 (9.4)	0.914	**All patients $P_{AP-controls} = 0.004$**
- Only non-falling patients (average, SD)	78.0 (2.8)	72.2 (6.3)	87.7 (3.0)	**0.010**	All patients $P_{PD-AP} = 0.096$
					Non-falling $P_{PD-controls} = 0.014$
					Non-falling $P_{AP-controls} = 0.009$
					Non-falling $P_{PD-AP} = 0.116$
ABC-16 fear of falling, follow-up:					
- All patients in total (average, SD)	70.5 (3.1)	51.2 (7.5)	80.3 (3.6)	**0.001**	**All patients $P_{PD-controls} = 0.022$**
- Only falling patients (average, SD)	56.0 (6.2)	38.8 (8.4)	53.8 (7.9)	0.190	**All patients $P_{AP-controls} = 0.001$**
- Only non-falling patients (average, SD)	75.8 (2.9)	63.8 (10.5)	87.0 (2.4)	**0.009**	**All patients $P_{PD-AP} = 0.018$**
					Non-falling $P_{PD-controls} = 0.010$
					Non-falling $P_{AP-controls} = 0.004$
					Non-falling $P_{PD-AP} = 0.081$
Change in ABC-16:					
- All patients in total (absolute, percentage)	−2.4 (−3.3)	−13.5 (−20.9)	−2.0 (−2.4)	**0.028**	**All patients $P_{PD-controls} = 0.022$**
- Only falling patients (absolute, percentage)	−3.0 (−5.1)	−19.1 (−33.0)	−7.0 (−11.5)	0.156	**All patients $P_{AP-controls} = 0.001$**
- Only non-falling patients (absolute, percentage)	−2.2 (−2.8)	−8.4 (−11.6)	−0.7 (−0.8)	0.506	**All patients $P_{PD-AP} = 0.018$**
Fall injury, baseline (*N*, percentage):					
- No injury	1 (9)	1 (10)	0 (0)	0.714	–
- Minor (e.g., cuts and bruises)	9 (82)	8 (80)	1 (33)		
- Intermediate (e.g., simple fractures)	1 (9)	0 (0)	0 (0)		
- Severe (e.g., fractures requiring surgery)	0 (0)	1 (10)			
Fall injury, follow-up (*N*, percentage):					
- No injury	0 (0)	0 (0)	1 (20)	0.414	–
- Minor (e.g., cuts and bruises)	7 (88)	6(86)	3(60)		
- Intermediate (e.g., simple fractures)	0 (0)	1 (14)			
- Severe (e.g., fractures requiring surgery)	1 (12)	0 (0)			
Treatment, baseline (*N*, percentage):					
- No treatment necessary	2 (18)	1 (10)	0 (0)	0.714	–
- Self-treatment	6 (55)	7 (70)	2 (67)		
- Outpatient doctor's treatment	2 (18)	1 (10)	1 (33)		
- Hospital admission (no surgery)	1 (9)	0 (0)	0 (0)		
- Hospital admission for surgery	0 (0)	1 (10)	0 (0)		

(Continued)

TABLE 4 | Continued

	Parkinson's disease	Atypical Parkinsonism	Healthy controles	*P*-value*	*P*-value group-to-group comparison*
Treatment, follow-up (*N*, percentage):					
- No treatment necessary	0 (0)	0 (0)	1 (20)	0.427	–
- Self-treatment	7 (88)	5 (72)	2 (40)		
- Outpatient doctor's treatment	0 (0)	1 (14)	1 (20)		
- Hospital admission (no surgery)	0 (0)	1 (14)	0 (0)		
- Hospital admission for surgery	1 (12)	0 (0)	1 (20)		

*Adapted from Venhovens et al. (4). *The P-value is calculated by means of an ordinal regression calculation (in the categorical variables), the Kruskal-Wallis one-way analysis of variance by ranks test (in the continuously distributed, independent, and non-parametrical variables for comparison of the 3 groups), and the Mann-Whitney-U test (in the continuously distributed, independent, and non-parametrical variables for group to group comparison). A significance level of 5 percent (i.e., $P \leq 0.05$) was adopted for each analysis and significant P-value results are printed in bold. **Fourteen patients completed the baseline examinations and one patient was lost to follow-up.*

TABLE 5 | Group characteristics concerning the falling and non-falling Parkinson and atypical Parkinsonism patients in the cervical and ocular vestibular evoked myogenic potentials tests.

	Cervical VEMP		Ocular VEMP		cVEMP and/or oVEMP combined*		cVEMP and oVEMP combined**	
	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal
Falling patients (absolute number)***	9	6	11	4	15	0	5	10
Non-falling patients (absolute number)***	8	20	13	15	16	12	5	23
All patients combined (absolute number)#	17	26	24	19	31	12	10	33

**Abnormal result was defined as having at least one abnormal cVEMP and/or oVEMP test. **Abnormal result was defined as having an abnormal test result in both cVEMP and oVEMP tests combined. ***Absolute number of patients that did fall or did not fall during follow-up. #One patient was lost to follow-up, therefor the total group of patients studied was 43.*

DISCUSSION

Laboratory examinations, and especially the vestibular evoked myogenic measurements, VEMPs (an abnormal VEMP result, defined as having at least one abnormal result at both the cervical and/or ocular VEMP tests combined) have a sensitivity of 100% to predict the occurrence of falls (all 15 falling patients had abnormal test results, see **Table 5**), at the cost of a low PPV of 48.4% (15 of the 31 patients will fall during follow-up). The specificity is 42.9% (12 of 28 the non-falling PD and AP patients have normal cervical and ocular VEMP results, however also 16 of these 28 non-falling patients have abnormal test results). The NPV when both the ocular and cervical VEMP tests are normal is 100% (none of the 12 patients with normal test results will fall during a 1-year follow-up). The positive likelihood ratio for falling when at least one cervical and/or ocular VEMP test is abnormal is 0.9 (15 patients out of the 31 patients with an abnormal result will fall and the other 16 patients with abnormal test results will not fall during a 1-year follow-up), and 1.0 when both VEMP tests are abnormal. The negative likelihood ratio for falling when both the cervical and ocular VEMP tests are normal is 0 (none of the patients that will fall had normal results and 12 of the non-falling patients had normal results), and 0.4 when the cervical and/or ocular VEMP test was abnormal. Therefore, in our pilot study normal cervical and ocular VEMP results in AP and PD patients have a very high negative predictive value for falling in the following year, which means that these patients have a very low risk for falling in the coming year. However, these tests have a very limited diagnostical usefulness to detect those PD and AP patients ad-risk for falling.

The presence of freezing of gait is also a strong predictor for the occurrence of falls (seven out of eight patients will fall, yielding a PPV of 87.5%). However, the sensitivity for detecting patients at risk for future falls is limited as only seven out of 15 patients will be detected (46.6%). The sensitivity for detecting patients at risk for falling is very high concerning the clinical testing for the presence of postural instability (100%; i.e., all 15 falling patients had postural instability), but the PPV is only 46.9% (only 15 of the 32 patients with abnormal test results will fall during 1-year follow-up).

Therefore, there is no single clinical or laboratory test (that is independent of clinical tests) with a high positive predictive value, high likelihood ratio, and a high sensitivity for detecting patients with a high risk for falling. These three test characteristics are needed to make a screening test that is useful in clinical practice in order to detect all patients at risk, however to also prevent a large number of false positive results which would lower the diagnostic value.

However, when both tests are used in combination (i.e., to use VEMP testing for additional screening for future fall incidents in those patients who at least have partial postural imbalance) the sensitivity will still remain 100% (15 out of the 15 falling patients will be detected, see **Table 6**); and the PPV will subsequently be 68.2% when only the ocular and/or the cervical VEMP is

TABLE 6 | Group characteristics concerning a selected group of falling and non-falling Parkinson and atypical Parkinsonism patients, with postural instability on pull-testing, in the cervical and ocular vestibular evoked myogenic potentials tests.

	cVEMP and/or oVEMP combined in patients with postural instability*		cVEMP and oVEMP combined in patients with postural instability**	
	Abnormal	**Normal**	**Abnormal**	**Normal**
Falling patients (absolute number)***	15	0	5	10
Non-falling patients (absolute number)***	7	10	1	16
All patients combined (absolute number)#	22	10	6	26

**Abnormal result was defined as having at least one abnormal cVEMP and/or oVEMP test. **Abnormal result was defined as having an abnormal test result in both cVEMP and oVEMP tests combined. ***Absolute number patients that did fall of did not fall during follow-up. #One patient was lost to follow-up, therefor the total group of patients studied was 43.*

abnormal (15 out of the 22 patients with positive results will fall during the year follow-up), or 83.3% when both VEMP tests are abnormal (5 out of 6 patients with positive results will fall during the follow-up year; with 5 out of 15 falling patients having abnormal results in both VEMP tests). Respectively, this results in positive likelihood ratio's of 2.1 (when only the cervical and/or ocular VEMP tests is abnormal) or 5.0 (when both the cervical and ocular VEMP tests are abnormal). The NPV will subsequently be 61.5% (when only the cervical and/or ocular VEMP tests is normal) and 100% (when both the cervical and ocular VEMP tests are normal), respectively, resulting in negative likelihood ratio's of 0.6 and 0. Therefore, we conclude that (ab)normal cervical and/or ocular VEMP tests in a selected group op PD and AP patients (i.e., with postural instability) is most useful to detect patients ad-risk for falling and to identify patients with a very low risk for falling.

Cervical and ocular VEMP testing combined with the clinical evaluation for postural instability gives additional information concerning the future fall risk of PD and AP patients compared to clinical evaluation of postural instability alone. However, the presence of freezing of gait is such a strong predictor for future falls in both PD and AP patients (PPV 87.5%; all the falling patients with freezing of gait also had abnormal VEMPs and postural instability) that VEMP testing in these patients does not have any additional value. Therefore, cervical and ocular VEMP testing seems to give additional information concerning the future fall risk in selected PD and AP patients (those patients who have postural instability in the absence of freezing of gait). However, one could speculate whether this additional information (possible increase of the PPV from 46.9% to 68.2–83.3%) will aid in guiding future fall prevention therapies (for instance through physical therapy) as PD and AP patients with postural imbalance already have a high risk for falling. A practical consensus-based overview concerning the risk factors and management of falls in PD was published emphasizing the multifaceted origin of the falls and the need for a personalized approach (9).

Decreasing the risk of falling is important, as fall incidents will result in a lowered subjective balance confidence (as can be concluded from the data in **Table 4**), secondarily resulting in self-imposed restrictions in daily life, ultimately leading to social isolation (2, 3). Moreover, patients with parkinsonism are more at risk for fall-related injuries, such as hip fractures secondarily leading to a higher morbidity, mortality, and health care costs in comparison to individuals without Parkinsonism (3, 10).

Our study also has some important limitations, which we also mentioned earlier (4). The first limitation relates to the small sample size; this was explained by the strict inclusion/exclusion criteria and the lengthy nature of the neurovestibular testing, which is especially demanding for elderly and AP patients. Therefore, the results from this study need to be interpreted cautiously and as hypothesis-generating for further research, especially in the heterogeneous AP group. This study, to our knowledge, is the first (prospective) study ever conducted to assess whether neurovestibular tests in both PD and AP can predict future fall incidents. Seen as this pilot study offers the first insights in the prediction of future fall incidents, especially in the heterogeneous AP group, we decided to use the data from both the AP and PD groups for further statistical analysis as discussed above. However, due to the limitations mentioned above, we advocate further research concerning the additional value of VEMP testing for predicting the risk of falling in larger PD and AP (sub)groups to confirm our findings. The second limitation is, that the volunteers may have had a bias concerning the recollection of their falling incidents. We tried to overcome this issue by asking the volunteers to keep track of their fall incidents by keeping personalized fall diaries. However, mal-compliance could bias the results possibly leading to an underestimation of the true fall incidence. Therefore, we questioned the volunteers about their fall frequency instead of the absolute number of falls, to minimize the effects of mal-compliance and recollection bias.

To conclude, we found a high prevalence in the number of falling patients and fall incidents in our follow-up study after 1 year in both PD and AP patients. After 1 year, especially the frequency of the fall incidents in the AP group increased in comparison to the PD and control group, which was not statistically significant (probably as a result of the small group size) as the other groups did also show a less pronounced increase in the number of fall incidents. The risk of future falls in PD and AP patients can be predicted better when patients with postural imbalance on clinical testing are additionally tested by means of cervical and ocular VEMP testing (with the exclusion of patients with freezing of gait). However, it remains unclear if the increase in future fall risk (possible PPV increase from 46.9% to 68.2–83.3%) will aid in the different utilization of fall prevention strategies as PD and AP patients with postural imbalance already have a high risk of falling.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the regional and local medical ethical committee (CMO Arnhem-Nijmegen, the Netherlands, number 2012/393). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JV, WV, JM, and BB: conception or design of the work. JV: data collection. JV, JM, and WV: data analysis and interpretation. JV: drafting the article: first version. JV, WV, JM, and BB: drafting the article: second and third versions. WV, JM, and BB: critical revision of the article. JV, WV, JM, and BB: final approval of the version to be published. All authors have read the final manuscript and have agreed with this submission.

FUNDING

The authors received no financial support with respect to the research, authorship, and/or publication of this article. BB was supported by a centre grant of the National Parkinson Foundation.

ACKNOWLEDGMENTS

The scientific data of this study has already been published as a PhD thesis (11) and can be accessed online (https://hdl.handle.net/2066/183430). The authors also would like to thank the clinical neurophysiological technicians for their technical support and Mrs. Patricia Kap, clinical neurophysiological research assistant, for the administrative support.

REFERENCES

1. Bloem BR, Steijns JAG, Smits-Engelsman BC. An update on falls. *Curr Opin Neurol.* (2003) 16:15–26. doi: 10.1097/00019052-200302000-00003
2. Bloem B, Bhatia K. Gait and balance in basal ganglia disorders. In: Bronstein AM, Brandt T, Nutt JG, Woollacott M, editors. *Clinical Disorders of Balance, Posture and Gait.* London: Arnold (2004). p. 173–206.
3. Grimbergen YAM, Munneke M, Bloem BR. Falls in Parkinson's disease. *Curr Opin Neurol.* (2004) 17:405–15. doi: 10.1097/01.wco.0000137530.68867.93
4. Venhovens J, Meulstee J, Bloem BR, Verhagen WIM. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. *Eur J Neurosci.* (2016) 43:1636–46. doi: 10.1111/ejn.13253
5. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry.* (2007) 79:368–76. doi: 10.1136/jnnp.2007.131045
6. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology.* (2008) 71:670–6. doi: 10.1212/01.wnl.0000324625.00404.15
7. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology.* (1996) 47:1–9. doi: 10.1212/WNL.47.1.1
8. Thanvi B, Lo N, Robinson T. Vascular parkinsonism–an important cause of parkinsonism in older people. *Age Ageing.* (2005) 34:114–9. doi: 10.1093/ageing/afi025
9. van der Marck MA, Klok MPC, Okun MS, Giladi N, Munneke M, Bloem BR, et al. Consensus-based clinical practice recommendations for the examination and management of falls in patients with Parkinson's disease. *Park Relat Disord.* (2014) 20:360–9. doi: 10.1016/j.parkreldis.2013.10.030
10. Pressley JC, Louis ED, Tang M-X, Cote L, Cohen PD, Glied S, et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. *Neurology.* (2003) 60:87–93. doi: 10.1212/WNL.60.1.87
11. Venhovens J. *Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism* (dissertation). Radboud University, Nijmegen, Netherlands (2018). Available online at: https://hdl.handle.net/2066/183430

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 29 October 2020
doi: 10.3389/fneur.2020.582471

Clinical Characteristics and Electrophysiological Biomarkers of Parkinson's Disease Developed From Essential Tremor

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Background and Objective: Parkinson's disease developed from essential tremor (ET-PD) is a distinct clinical syndrome that is different from essential tremor (ET) and Parkinson's disease (PD). There is currently a lack of research on ET-PD. Tremor characteristics (amplitude and frequency) are primary quantitative indexes for diagnosing and monitoring of tremors. In this study, we aimed to explore specific clinical and electrophysiological biomarkers for the identification of ET-PD.

Methods: The study included patients with ET-PD (n = 22), ET (n = 42), and tremor-dominant PD (t-PD, n = 47). We collected demographic data, clinical characteristics (including motor and non-motor symptoms), and tremor analysis. The frequency, amplitude, contracting patterns of resting tremor and postural tremor were collected. The analysis of ET-PD and ET/t-PD was compared. The receiver operating characteristic (ROC) curve was used to analyze the electrophysiological features in distinguishing ET-PD from ET or t-PD.

Results: Compared with ET, hyposmia, bradykinesia, rigidity, postural abnormality, and resting tremor were more common in the ET-PD group (P = 0.01, 0.003, 0.001, 0.001, 0.019, respectively). The postural tremor frequencies of the head, upper limbs, and lower limbs were significantly lower in the ET-PD than in the ET (P = 0.007, 0.003, 0.035, respectively), which were the most appropriate variables for distinguishing ET-PD from ET (AUC: 0.775, 0.727, and 0.701, respectively). Compared with t-PD, bradykinesia, rigidity, postural abnormality (both $P < 0.001$), and resting tremor (P = 0.024) were less common in the ET-PD. The postural tremor amplitudes of the head and upper limbs were significantly higher in the ET-PD than in the t-PD (P = 0.022, 0.001, respectively), which were the most appropriate variables for distinguishing ET-PD from t-PD (AUC: 0.793 and 0.716).

Conclusions: Hyposmia and electrophysiological biomarkers (postural tremor frequencies and amplitudes) help early recognition of ET-PD.

Keywords: Parkinson's disease, essential tremor, tremor, clinical, electrophysiological

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Fabiana Novellino, National Research Council (CNR), Italy
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *12 July 2020*
Accepted: *22 September 2020*
Published: *29 October 2020*

Citation:
Wang X, Cao Z, Liu G, Liu Z, Jiang Y, Ma H, Wang Z, Yang Y, Chen H and Feng T (2020) Clinical Characteristics and Electrophysiological Biomarkers of Parkinson's Disease Developed From Essential Tremor. Front. Neurol. 11:582471. doi: 10.3389/fneur.2020.582471

INTRODUCTION

Essential tremor (ET) and idiopathic Parkinson's disease (PD) are two of the most common movement disorders. PD's motor and non-motor features may overlap with ET, making it difficult to distinguish them based on clinical characteristics (1). For example, besides the typical resting tremor, patients with PD also often exhibit postural tremor, which is more often observed in patients with ET (2). In turn, in a population-based setting, resting tremor is a common clinical feature in patients with ET, and the prevalence can reach nearly 50% (3). ET patients have significant movement slowness compared to healthy controls, and a considerable number of ET patients have movement abnormalities similar to those observed in PD patients (4). Depression, anxiety, cognitive disorders, and family history of tremors/PD were similar in both patient groups (5, 6). Thus, clinical and experimental evidence indicates that there are similarities between ET and PD.

It has been reported that patients with ET seem to be about four to five times more likely to develop PD than the general population (7). ET that eventually develops into PD is called essential tremor–Parkinson's disease (ET-PD) (8). Clinically, patients with ET-PD can exhibit different types of tremor, including PD-associated resting tremor and ET-associated postural tremor. Whether ET-PD is a co-occurrence of two relatively common pathologies or if ET is a prodromal stage of PD in some patients is yet to be elucidated. Electromyographic (EMG) examination is a useful tool for tremor analysis and can characterize different tremor types according to tremor amplitude, frequency, and pattern (9). Interestingly, a recent study demonstrated that patients with ET-PD, unlike patients with tremor-dominant PD (t-PD), exhibited the synchronous pattern of resting tremor (10). However, the exact phenomenology and etiology of this finding remain unclear. Besides, due to the scarce clinical data for ET-PD, it remains unknown which clinical and tremor features can differ it from ET or t-PD. This also means that the objective factors to predict the progression of ET to PD are limited. Thus, it is difficult to obtain an accurate diagnosis of ET-PD in the early stages. Considering that electrophysiological methods can effectively characterize tremor, we systematically analyzed differences in clinical and neurophysiological features between patients with ET-PD and ET/t-PD to determine clinical and electrophysiological markers of ET-PD in order to obtain useful and targeted treatment in the early stage of ET-PD.

MATERIALS AND METHODS

Patients

From March 2018 to October 2019, patients with ET-PD ($n = 22$), ET ($n = 42$), and t-PD ($n = 47$) were recruited from Beijing Tiantan Hospital. A diagnosis of PD was made according to the Movement Disorders Society Clinical Diagnostic Criteria for Parkinson's disease in 2015 (11). The t-PD group's inclusion criteria were as follows: patients had at least one-limb resting or postural tremor, and the age of onset was >50 years old. Exclusion criteria for the t-PD group were as follows: (1) secondary parkinsonism; (2) atypical PD; and (3) severe heart disease, liver or kidney disease, or any other chronic disease meaning that the patient could not complete the examinations. A diagnosis of ET was made using criteria from the Movement Disorder Society Tremor Investigation Group (12). A diagnosis of ET was not assigned if bradykinesia, rigidity, or resting tremor appeared within 5 years of the onset of tremor attributed to ET.

Inclusion criteria of the ET-PD (13) group were as follows: (1) ET had been diagnosed at least 5 years before the PD diagnosis and (2) when they had received a previous diagnosis of ET, patients exhibited significant characteristics of postural tremor without any symptoms or signs of PD. Exclusion criteria for ET-PD were as follows: (1) age at PD diagnosis <40 years old; (2) atypical PD or secondary parkinsonism; and (3) patients with a history of postural or action tremor <5 years.

For all patients, we collected demographic data (sex and age), clinical data including motor symptoms, non-motor symptoms, age of onset of PD, disease duration, tremor location, tremor pattern, past medical history, family history, medication history, and anti-tremor drug responsiveness. The Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn & Yahr (H&Y) scale in an "off" phase (>12 h after the last dose of dopaminergic medication; >24 h after anticholinergics or β-blockers) were evaluated for the t-PD and ET-PD groups (14).

This study was approved by the Ethics Committee of Beijing Tiantan Hospital and was performed in accordance with the Declaration of Helsinki. All patients provided informed consent.

Definition of Non-motor Features

Constipation was defined according to the Rome III diagnostic criteria (15).

Olfactory function was evaluated with the 12-item Sniffin' Sticks test (Burghart Messtechnik GmbH, Wedel, Germany). Patients were considered to have rapid eye movement sleep behavior disorder (RBD) when they fulfilled the criteria determined by the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) (16).

Depression was assessed using the Hamilton Depression Rating Scale (HAMD) (17), and anxiety was assessed using the Hamilton Anxiety Rating Scale (HAMA) (18).

Cognitive status was assessed using the Mini-Mental State Examination (MMSE) scale (19) and the Montreal Cognitive Assessment (MoCA) scale (20).

Tremor Analysis

Tremor was recorded using an electromyography evoked potential meter (Nicolet EDX, USA), which has four pairs of surface electrodes and two piezoresistive accelerators. The recording electrodes were placed on the muscle bellies of the flexor carpi and extensor carpi of both forearms and lower limbs. The reference electrode was placed on the corresponding tendon, and the accelerator was fixed at the proximal end of the third metacarpal of the ipsilateral hand. For head tremor examination, the recording electrode was placed at the midpoint of the sternocleidomastoid muscle, and the reference electrode was placed in the supraclavicular fossa. The EMG parameters were as follows: amplifier sensitivity at 100 μV/div, sweep speed at 100

ms/div, and a filter width of 10.0 Hz−10.0 kHz; piezoresistive accelerometer sensitivity at 2.2 mV/g and a filter width in the range 0.5–30.0 Hz.

Tremor was assessed under the following six conditions: (1) resting tremor of the head was assessed while patients sat in an armchair, leaning their head and back against the chair back, and relaxing their head; (2) resting tremor in the upper limbs was assessed while patients sat in an armchair with the forearms and hands completely rested on the armrests; (3) resting tremor in the lower limbs was assessed while patients sat in an armchair, with their feet placed flatly on the ground, and while they were utterly relaxed; (4) postural tremor in the head was assessed while patients sat in an armchair, keeping their head upright; (5) postural tremor in the upper limbs was assessed while patients sat in an armchair with wrists/fingers outstretched on a horizontal plane; and (6) postural tremor in the lower limbs was assessed while patients sat in an armchair with both sides of their toes touching the ground and with their heels hanging. Each measurement session lasted for 30 s. The EMG data were analyzed using the TRAS system (21). All tests were performed during the patients' "off" state (22). Resting and postural tremor frequency, tremor amplitude, and systolic patterns were recorded.

Statistical Analysis

Analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL, USA). Graphs were delineated by using Prism 7.0 (GraphPad software, La Jolla, CA, USA). The normality of distribution of continuous variables was tested by one-sample Kolmogorov–Smirnov test. Continuous variables with normal distribution were presented as mean ± standard deviation (SD). The differences in continuous variables between the ET-PD and ET/t-PD groups were assessed using independent samples Student's test when the data were normally distributed and using Mann–Whitney *U* test if the data were not normally distributed. A chi-square test was used to compare categorical variables between the groups. Sensitivity and specificity for differentiating ET-PD from ET or t-PD were calculated using the optimal cutoff value determined by receiver operating characteristic (ROC) curve analysis. The optimum cutoff value for the ROC curve was determined using the Youden Index. Differences with a $P < 0.05$ were considered to be statistically significant.

RESULTS

Comparison of Demographic, Clinical, and Electrophysiological Features Between Patients With Essential Tremor–Parkinson's Disease and Essential Tremor

Differences in Demographic Variables

The demographic data are shown in **Table 1**. Compared with the ET group, there was no difference in the ET-PD group regardless of sex or age.

TABLE 1 | Comparison of demographic, clinical, and electrophysiological features between patients with ET-PD and ET.

Variables	ET-PD (*n* = 22)	ET (*n* = 42)	*P*-value
Demographic characteristics			
Age, years (mean ± SD)	64.14 ± 9.26	59.10 ± 10.47	0.56
Sex: No. men/women	10/12	23/19	0.48
Clinical characteristics			
Family history (Postural/kinetic tremor), *n* (%)	13 (59)	27 (63)	0.683
Age at onset of ET, years (mean ± SD)	50.86 ± 12.11	41.83 ± 16.62	0.025*
Disease duration of ET, years (mean ± SD)	13.27 ± 9.99	17.40 ± 11.47	0.054
Disease duration from ET to PD onset, years (mean ± SD)	12.30 ± 2.18	-	-
Constipation, *n* (%)	7 (32)	9 (21)	0.362
Hyposmia, *n* (%)	6 (27)	2 (5)	0.01*
RBD, *n* (%)	8 (36)	7 (17)	0.077
HAMD (mean ± SD)	12.88 ± 6.90	9.50 ± 7.43	0.122
HAMA (mean ± SD)	13.88 ± 4.39	9.40 ± 8.03	0.114
MMSE (mean ± SD)	23.38 ± 7.96	22.80 ± 8.77	0.572
MoCA (mean ± SD)	17.50 ± 7.71	18.70 ± 8.06	0.909
Bradykinesia, *n* (%)	10 (45.50)	5 (12)	0.003*
Rigidity, *n* (%)	7 (32)	1 (2)	0.001*
Postural abnormality, *n* (%)	7 (32)	1 (2)	0.001*
Drinking responsiveness, *n* (%)	5 (23)	18 (43)	0.111
Arotinolol responsiveness, *n* (%)	6 (37.50)	25 (60)	0.014*
Unilateral disease onset, *n* (%)	13 (59)	13 (31)	0.029*
Bilateral disease onset, *n* (%)	9 (41)	29 (69)	0.029*
Upper limb tremor, *n* (%)	22 (100)	42 (100)	-
Lower limb tremor, *n* (%)	15 (68)	9 (21)	<0.001*
Head tremor, *n* (%)	10 (45.50)	18 (43)	0.842
Mandibular tremor, *n* (%)	5 (23)	2 (5)	0.029*
Resting tremor, *n* (%)	16 (73)	20 (48)	0.019*
Postural tremor, *n* (%)	22 (100)	41 (98)	0.466
Electrophysiological description			
Resting tremor			
Frequency (Hz)			
Head	4.78 ± 0.25	5.92 ± 0.98	0.058
Upper limbs	4.56 ± 0.87	5.33 ± 1.20	0.064
Lower limbs	4.72 ± 0.88	-	-
Amplitude (μV)			
Head	352.00 ± 98.57	309.10 ± 105.55	0.525
Upper limbs	1104.27 ± 435.39	689.11 ± 313.05	0.132
Lower limbs	469.23 ± 313.38	-	-
Synchronous patterns, *n* (%)			
Head	4/5 (80)	5/5 (100)	0.292
Upper limbs	5/16 (31)	9/18 (50)	0.332
Lower limbs	5/10 (50)	0	-

(Continued)

TABLE 1 | Continued

Variables	ET-PD ($n = 22$)	ET ($n = 42$)	*P*-value
Alternating patterns, *n* (%)			
Head	0/5 (0)	0/5 (0)	-
Upper limbs	8/16 (50)	8/18 (44)	0.877
Lower limbs	3/10 (30)	0	-
Synchronous and alternating patterns, *n* (%)			
Head	1/5 (20)	0/5 (0)	0.292
Upper limbs	3/16 (19)	1/18 (6)	0.212
Lower limbs	2/10 (20)	0	-
Postural tremor			
Frequency (Hz)			
Head	4.50 ± 0.45	5.41 ± 1.01	0.007*
Upper limbs	5.15 ± 1.04	6.13 ± 1.49	0.003*
Lower limbs	5.10 ± 1.37	6.35 ± 0.91	0.035*
Amplitude(μV)			
Head	474.07 ± 166.99	661.97 ± 242.99	0.738
Upper limbs	1,419.70 ± 426.17	922.91 ± 135.29	0.364
Lower limbs	1,039.23 ± 221.46	504.96 ± 263.43	0.132
Synchronous patterns, *n* (%)			
Head	5/7 (71)	14/16 (87.50)	0.499
Upper limbs	4/22 (18)	22/40 (55)	0.005*
Lower limbs	8/11 (73)	3/3 (100)	0.308
Alternating patterns, *n* (%)			
Head	0/7 (0)	1/16 (6.25)	0.349
Upper limbs	10/22 (46)	9/40 (22.50)	0.061
Lower limbs	1/11 (9)	0/3 (0)	0.588
Synchronous and alternating patterns, *n* (%)			
Head	2/7 (29)	1/16 (6.25)	0.144
Upper limbs	8/22 (36)	9/40 (22.50)	0.242
Lower limbs	2/11 (18)	0/3 (0)	0.425

ET-PD, Parkinson's disease developed from essential tremor; ET, essential tremor; RBD, rapid eye movement sleep behavioral disorder; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; UPDRS, Unified Parkinson's Disease Rating Scale.
**This P-value indicates a statistically significant difference.*

Differences in Clinical Characteristics

All clinical data are shown in **Table 1**. The ET-PD group had an older mean age at onset of ET than the ET group ($P = 0.025$). The average latency of ET to PD diagnosis in the ET-PD group was 12.30 ± 2.18 years. Hyposmia was significantly more common in the ET-PD group than the ET group ($P = 0.01$), but no other significant differences in non-motor features were found between these two groups. Concerning motor features, the proportion of patients with ET-PD with asymmetric motor symptoms (59%) was higher than that in the ET group ($P = 0.029$). Bradykinesia, rigidity, and postural abnormalities were more common in the ET-PD group than the ET group ($P = 0.003$, 0.001, 0.001, respectively). Resting tremor was found in 73% of the ET-PD group, which was a significantly higher proportion than that in the ET group ($P = 0.019$). Lower limb tremor was significantly more common in the ET-PD group than that in the ET group ($P < 0.001$), as was mandibular tremor ($P = 0.029$).

Difference in Electrophysiological Results

Postural tremor was observed in almost all patients in the ET-PD and ET groups. However, the postural tremor frequency differed between the ET-PD and ET groups. The postural tremor frequencies of the head, upper limbs, and lower limbs were significantly lower in the ET-PD group than those in the ET group ($P = 0.007$, 0.003, 0.035, respectively; **Table 1**). The cutoff value of head postural tremor frequency to distinguish patients with ET-PD from ET was 5.20 Hz, with a sensitivity of 67% and specificity of 100%. The cutoff value of postural tremor frequency to distinguish patients with ET-PD from ET was 5.45 Hz for the upper limbs and 5.98 Hz for the lower limbs, with a sensitivity of 100% and specificity of 83%, respectively (**Table 3**, **Figure 1A**). Furthermore, upper limb postural tremor patterns were less synchronous in the ET-PD group than those in the ET group (**Table 1**).

Comparison of Demographic, Clinical, and Electrophysiological Features Between Patients With Essential Tremor–Parkinson's Disease and Tremor-Dominant Parkinson's Disease

Differences in Demographic Variables

The demographic data are shown in **Table 2**. Compared with the t-PD group, there was no difference in the ET-PD group regardless of sex or age.

Differences in Clinical Characteristics

All clinical data are shown in **Table 2**. The ET-PD group had an older mean age at onset of PD than the t-PD group ($P = 0.004$). Some non-motor features were significantly less common in the ET-PD group than the t-PD group, including constipation ($P < 0.001$), hyposmia ($P = 0.044$), and RBD ($P = 0.033$). The HAMD, HAMA, MMSE, and MoCA scores did not differ between the two groups. Concerning motor features, the proportion of patients with ET-PD with asymmetric motor symptoms was lower than that in the t-PD group ($P < 0.001$). Bradykinesia, rigidity, and postural abnormalities were less common in the ET-PD group than the t-PD group (both $P < 0.001$). Resting tremor was found in 73% of the ET-PD group, which was lower than that in the t-PD group ($P = 0.024$). Head tremor was more common in the ET-PD group than the t-PD group ($P < 0.001$). Mandibular tremor was less common in the ET-PD group than the t-PD group ($P = 0.038$).

Difference in Electrophysiological Results

The head and upper limbs' postural tremor amplitudes were significantly higher in the ET-PD group than those in the t-PD group ($P = 0.022$, 0.001, respectively; **Table 2**). To distinguish patients with ET-PD from t-PD, the cutoff value of head postural tremor amplitude was 477.50 μV, with a sensitivity of 57% and specificity of 90%. For the upper limbs, the postural tremor amplitude cutoff value was 393.00 μV, with a sensitivity of 86% and specificity of 60% (**Table 3**, **Figure 1B**).

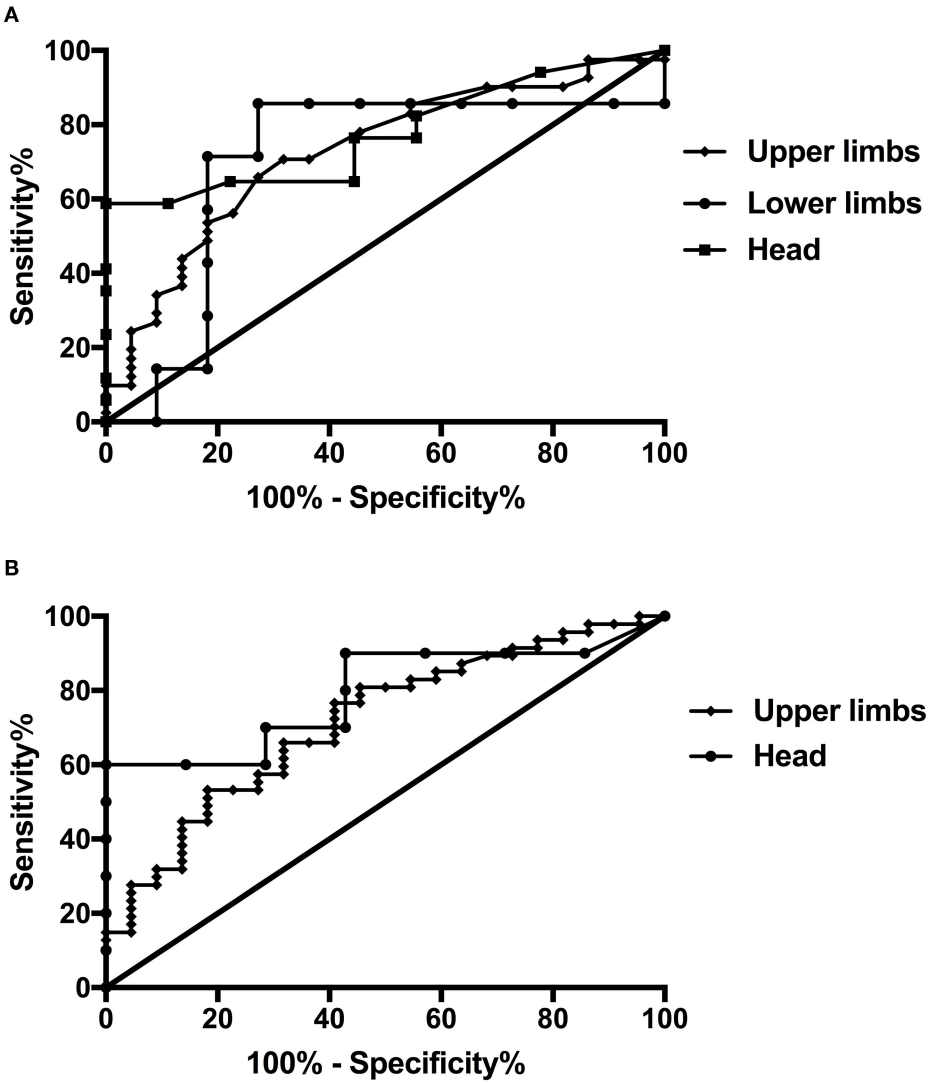

FIGURE 1 | Receiver operating characteristic (ROC) curve differentiating essential tremor–Parkinson's disease (ET-PD) from essential tremor (ET) or tremor-dominant Parkinson's disease (t-PD). **(A)** ROC curve of postural tremor frequency to differentiate ET-PD from ET. **(B)** ROC curve of postural tremor amplitude to differentiate ET-PD from t-PD.

DISCUSSION

ET-PD and ET/t-PD can be clinically difficult to differentiate because of overlapping motor and non-motor symptoms. This study showed that hyposmia and electrophysiological biomarkers (postural tremor frequencies and amplitudes) could distinguish patients with ET-PD from those with ET or t-PD.

Epidemiological and clinical evidence has supported the view that the lifetime risk of developing PD was higher in patients with ET than those without ET (23). A long latency could be up to 50 years (24). Like previous studies (6, 25), we found that the average latency for ET patients to develop PD was 12.30 ± 2.18 years. Furthermore, in the ET-PD group, the age of onset of ET tended to be older than that in the ET group, while the age of onset of PD was older than that in the t-PD group. There was no significant difference between the ET-PD and ET groups concerning sex, which is in accordance with a previous study (25) but conflicts with another study that reported a male predominance of ET-PD (26). It may need a further prospective study to explore the epidemiological characteristics of ET-PD.

In our cohort, the HAMD, HAMA, MMSE, and MoCA scores did not differ between ET-PD and ET/t-PD. However, constipation, hyposmia, and RBD were more common in the t-PD group than the ET-PD group, while hyposmia, rather than constipation or RBD, was more common in the ET-PD group than the ET group, which was consistent with previous studies (5, 25). Another study found no significant differences between patients with ET-PD and ET with regard to non-motor features (10). These conflicting results may be due to different mean durations of ET development into PD and/or the different

TABLE 2 | Comparison of demographic, clinical, and electrophysiological features between patients with ET-PD and t-PD.

Variables	ET-PD ($n = 22$)	t-PD ($n = 47$)	*P*-value
Demographic characteristics			
Age, years (mean ± SD)	64.14 ± 9.26	63.28 ± 7.01	0.07
Sex: No. men/women	10/12	24/23	0.67
Clinical characteristics			
Family history (Postural/kinetic tremor), *n* (%)	13 (59)	9 (19)	0.001*
Age at onset of PD, years (mean ± SD)	63.16 ± 9.62	56.51 ± 8.05	0.004*
Disease duration, years (mean ± SD)	13.27 ± 9.99	6.83 ± 4.53	0.008*
Constipation, *n* (%)	7 (32)	39 (83)	<0.001*
Hyposmia, *n* (%)	6 (27)	25 (53)	0.044*
RBD, *n* (%)	8 (36)	30 (64)	0.033*
HAMD (mean ± SD)	12.88 ± 6.90	11.13 ± 9.02	0.774
HAMA (mean ± SD)	13.88 ± 4.39	12.84 ± 7.34	0.920
MMSE (mean ± SD)	23.38 ± 7.96	26.00 ± 3.09	0.777
MoCA (mean ± SD)	17.50 ± 7.71	22.19 ± 4.71	0.168
Bradykinesia, *n* (%)	10 (45.50)	47 (100)	<0.001*
Rigidity, *n* (%)	7 (32)	43 (91.5)	<0.001*
Postural abnormality, *n* (%)	7 (32)	45 (96)	<0.001*
UPDRS part 3 (mean ± SD)	31.00 ± 1.41	38.39 ± 17.71	0.661
Hoehn–Yahr (mean ± SD)	2.41 ± 0.42	2.75 ± 0.85	0.054
Dopaminergic responsiveness, *n* (%)	7 (32)	30 (64)	0.013*
Unilateral disease onset, *n* (%)	13 (59)	47 (100)	<0.001*
Bilateral disease onset, *n* (%)	9 (41)	0 (0)	<0.001*
Upper limb tremor, *n* (%)	22 (100)	44 (94)	0.226
Lower limb tremor, *n* (%)	15 (68)	27 (57)	0.593
Head tremor, *n* (%)	10 (45.50)	3 (6)	<0.001*
Mandibular tremor, *n* (%)	5 (23)	22 (47)	0.038*
Resting tremor, *n* (%)	16 (73)	42 (89)	0.024*
Postural tremor, *n* (%)	22 (100)	47 (100)	-
Electrophysiological description			
Resting tremor			
Frequency (Hz)			
Head	4.78 ± 0.25	4.63 ± 0.56	0.887
Upper limbs	4.56 ± 0.87	4.47 ± 0.60	0.947
Lower limbs	4.72 ± 0.88	4.21 ± 0.55	0.336
Amplitude (μV)			
Head	352.00 ± 98.57	318.56 ± 184.14	0.646
Upper limbs	1,104.27 ± 435.39	703.53 ± 112.51	0.464
Lower limbs	469.23 ± 313.38	426.22 ± 74.97	0.776
Synchronous patterns, *n* (%)			
Head	4/5 (80)	5/9 (56)	0.360
Upper limbs	5/16 (31)	6/37 (16)	0.215
Lower limbs	5/10 (50)	10 (48)	0.595
Alternating patterns, *n* (%)			
Head	0/5 (0)	1/9 (11)	0.439
Upper limbs	8/16 (50)	23/37 (62)	0.409
Lower limbs	3/10 (30)	7 (33)	0.560
Synchronous and alternating patterns, *n* (%)			
Head	1/5 (20)	3/9 (33)	0.597
Upper limbs	3/16 (19)	8/37 (22)	0.813
Lower limbs	2/10 (20)	4 (19)	0.950
Postural tremor			
Frequency (Hz)			
Head	4.50 ± 0.45	4.40 ± 0.79	0.850
Upper limbs	5.15 ± 1.04	4.96 ± 0.70	0.948
Lower limbs	5.10 ± 1.37	4.84 ± 0.79	0.924
Amplitude(μV)			
Head	474.07 ± 166.99	293.35 ± 174.01	0.022*
Upper limbs	1,419.70 ± 426.17	787.48 ± 197.85	0.001*
Lower limbs	1,039.23 ± 221.46	740.85 ± 126.07	0.157
Synchronous patterns, *n* (%)			
Head	5/7 (71)	10/11 (91)	0.280
Upper limbs	4/22 (18)	16/42 (38)	0.103
Lower limbs	8/11 (73)	18/31 (58)	0.390
Alternating patterns, *n* (%)			
Head	0/7 (0)	0/11 (0)	-
Upper limbs	10/22 (46)	12/42 (29)	0.177
Lower limbs	1/11 (9)	5/31 (16)	0.567
Synchronous and alternating patterns, *n* (%)			
Head	2/7 (29)	1/11 (9)	0.280
Upper limbs	8/22 (36)	14/42 (33)	0.808
Lower limbs	2/11 (18)	8/31 (26)	0.610

ET-PD, Parkinson's disease developed from essential tremor; t-PD, tremor-dominant Parkinson's disease; RBD, rapid eye movement sleep behavioral disorder; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; UPDRS, Unified Parkinson's Disease Rating Scale.

**This P-value indicates a statistically significant difference.*

methodologies used in each study. In our study, early non-motor features, especially the appearance of hyposmia, may indicate that ET is beginning to develop into ET-PD. Hyposmia may be an early symptom of ET-PD/PD and is associated with cellular damage in the olfactory bulb (27).

Among the motor features, we found that bradykinesia, rigidity, and postural abnormality were more common in patients with ET-PD than ET. Bradykinesia is the cardinal motor symptom in PD, which has also been reported in ET (4, 28). Several studies have shown that cerebellar dysfunction is involved in the pathophysiology of movement slowness in ET (4, 29). As in ET, the cerebellum is thought to be involved in the pathophysiology of bradykinesia in ET-PD, which is now considered a network disorder (30). Together with basal ganglia–cortical loops, the cerebellum may be involved in the execution of repetitive movements, which play a role in movement feedback and compensate for impaired basal ganglia function (30). Moreover, bradykinesia, rigidity, and postural abnormalities are all related to the parkinsonism, resulting from

TABLE 3 | Sensitivity, specificity, and AUC of electrophysiological features in distinguishing ET-PD patients from ET and t-PD patients.

Groups	Cutoff	Sensitivity	Specificity	AUC	*P*-value
ET-PD vs. ET					
Postural tremor frequency					
Head	5.20	67%	100%	0.775	0.023
Upper limbs	5.45	100%	83%	0.727	0.003
Lower limbs	5.98	100%	83%	0.701	0.160
ET-PD vs. t-PD					
Postural tremor amplitude					
Head	477.50	57%	90%	0.793	0.040
Upper limbs	393.00	86%	60%	0.716	0.004

ET-PD, Parkinson's disease developed from essential tremor; t-PD, tremor-dominant Parkinson's disease; ET, essential tremor.

decreased dopaminergic transmission in the motor region of the striatum, involving connectivity of the globus pallidus to the cortico-basal ganglia-cerebello motor circuit (31). Several recent clinicopathological studies suggested that the dramatic loss of these dopaminergic neurons starts before the onset of motor symptoms (32). Maybe the appearance of motor features in patients with ET-PD is also related to the change in their dopamine levels and could be an early symptom of the conversion from ET to ET-PD.

EMG examination is a convenient and inexpensive tool to discriminate patients with ET-PD from ET/t-PD (33) compared with the magnetic resonance support vector machine (34). In accordance with previous studies (8, 26), resting tremor was significantly more common in the ET-PD group than the ET group in our study. Recent studies observed higher connectivity of the globus pallidus pars interna (GPi) and putamen to the cerebello–thalamic circuit (35) and an impairment of the basal ganglia–thalamocortical loop (36, 37). Another study showed that the globus pallidus, caudate nucleus, and supplementary motor area were specifically damaged in ET patients with resting tremor (38). These works suggested that dopaminergic loss in the pallidum might induce hyperactivity in the cerebello–thalamic circuit, leading to resting tremor. Since it was found that a subset of patients with ET eventually developed PD (5), we hypothesized that resting tremor may be a prominent feature of early-stage ET-PD, which may involve similar pathological loops as those in t-PD patients (10).

Besides resting tremor, we also observed that postural tremor frequencies of the head, upper limbs, and lower limbs were significantly lower in patients with ET-PD than those with ET. Furthermore, the head and upper limbs' postural tremor amplitudes were significantly higher in patients with ET-PD than those with t-PD. The cutoff values to distinguish patients with ET-PD from those with ET/t-PD have high sensitivity and specificity. Indeed, the exact central oscillators in the genesis of postural tremor in ET-PD are not fully understood. Some studies have concluded that postural tremor is triggered by the basal ganglia (39, 40) and mediated by the cerebello–thalamic–cortical network (41, 42). Tremor amplitude and frequency are primary quantitative indexes for diagnosing and monitoring of tremors. There is evidence that the tremor frequency decreases with time, which could be an essential factor leading to a deterioration of ET (43). Another study showed that patient's conditions directly affect neural oscillations related to tremor frequencies (44). Central oscillators control tremor frequency while peripheral nerves and muscles exert a modulatory influence on tremor amplitude. The reduction of tremor amplitude is accompanied by increased variability of tremor frequency due to the desynchronization of central oscillators (39). We observed that the postural tremor amplitudes were higher in the ET-PD group than those in the t-PD group, and that the postural tremor frequencies were lower in the ET-PD group than those in the ET group. We try to explain this phenomenon as a consequence of increasing the number of active central oscillators and an increased synchronization of central oscillators in the ET-PD group.

To our knowledge, very few studies were conducted to explore the quantitative electrophysiological biomarkers for ET-PD at present. Furthermore, this is also the highlight of our research. This study may be the first research about the clinical and electrophysiological characteristics of ET-PD and ET/t-PD in Chinese populations. However, our research also has some limitations. For example, the sample size of this study is small, and the definite diagnosis of these patients was not confirmed by the pathological results. Nonetheless, all patients were carefully evaluated by professional movement specialists during hospitalization.

CONCLUSION

In the current study, we present the clinical characteristics to distinguish patients with ET-PD from those with ET, including the early appearance of hyposmia and motor symptoms. Our findings indicate that quantitative electrophysiological biomarkers, including a distinct frequency and amplitude of postural tremor, could be useful for the earlier recognition of ET-PD and beneficial to further patient treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by the National Key R&D Program of China (Nos. 2016YFC1306501 and 2018YFC1312001), National Natural Science Foundation of China (No. 81771367), and Beijing Municipal Science & Technology Commission (Z151100003915150 and Z171100001017041).

REFERENCES

1. Thenganatt MA, Jankovic J. The relationship between essential tremor and Parkinson's disease. *Parkinsonism Relat Disord*. (2016) 22(Suppl. 1):S162–5. doi: 10.1016/j.parkreldis.2015.09.032
2. Gigante AF, Bruno G, Iliceto G, Guido M, Liuzzi D, Mancino PV, et al. Action tremor in Parkinson's disease: frequency and relationship to motor and non-motor signs. *Eur J Neurol*. (2015) 22:223–8. doi: 10.1111/ene.12583
3. Louis ED, Hernandez N, Michalec M. Prevalence and correlates of rest tremor in essential tremor: cross-sectional survey of 831 patients across four distinct cohorts. *Eur J Neurol*. (2015) 22:927–32. doi: 10.1111/ene.12683
4. Bologna M, Paparella G, Colella D, Cannavacciuolo A, Angelini L, Alunni-Fegatelli D, et al. Is there evidence of bradykinesia in essential tremor? *Eur J Neurol*. (2020) 27:1501–9. doi: 10.1111/ene.14312
5. Lau HL, Marmol SE, Margolesky J. Features in essential tremor and the development of Parkinson's disease vs. parkinsonism. *Neurol Sci*. (2020). doi: 10.1007/s10072-020-04439-w. [Epub ahead of print].
6. Tarakad A, Jankovic J. Essential tremor and Parkinson's disease: exploring the relationship. *Tremor Other Hyperkinet Mov (N Y)*. (2018) 8:589. doi: 10.7916/d8md0gvr
7. Benito-Leon J, Louis ED, Bermejo-Pareja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. *J Neurol Neurosurg Psychiatry*. (2009) 80:423–5. doi: 10.1136/jnnp.2008.147223
8. Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. *Parkinsonism Relat Disord*. (2007) 13:67–76. doi: 10.1016/j.parkreldis.2006.05.033
9. Cohen O, Pullman S, Jurewicz E, Watner D, Louis ED. Rest tremor in patients with essential tremor: prevalence, clinical correlates, and electrophysiologic characteristics. *Arch Neurol*. (2003) 60:405–10. doi: 10.1001/archneur.60.3.405
10. Arabia G, Lupo A, Manfredini LI, Vescio B, Nistico R, Barbagallo G, et al. Clinical, electrophysiological, and imaging study in essential tremor-Parkinson's disease syndrome. *Parkinsonism Relat Disord*. (2018) 56:20–6. doi: 10.1016/j.parkreldis.2018.06.005
11. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424
12. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. *Ad Hoc* Scientific Committee. *Mov Disord*. (1998) 13(Suppl. 3):2–23. doi: 10.1002/mds.870131303
13. Louis ED, Wise A, Alcalay RN, Rao AK, Factor-Litvak P. Essential tremor-Parkinson's disease: a double whammy. *J Neurol Sci*. (2016) 366:47–51. doi: 10.1016/j.jns.2016.04.040
14. Noffs G, de Campos Duprat A, Zarzur AP, Cury RG, Cataldo BO, Fonoff E. Effect of Levodopa + carbidopa on the laryngeal electromyographic pattern in Parkinson disease. *J Voice*. (2017) 31:383.e319–83.e323. doi: 10.1016/j.jvoice.2016.09.001
15. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. (2006) 130:1480–91. doi: 10.1053/j.gastro.2005.11.061
16. Marelli S, Rancoita PM, Giarrusso F, Galbiati A, Zucconi M, Oldani A, et al. National validation and proposed revision of REM sleep behavior disorder screening questionnaire (RBDSQ). *J Neurol*. (2016) 263:2470–5. doi: 10.1007/s00415-016-8285-y
17. Williams JB. Standardizing the Hamilton Depression Rating Scale: past, present, and future. *Eur Arch Psychiatry Clin Neurosci*. (2001) 251(Suppl. 2):II6–12. doi: 10.1007/BF03035120
18. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6
20. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
21. Lauk M, Timmer J, Lucking CH, Honerkamp J, Deuschl G. A software for recording and analysis of human tremor. *Comput Methods Programs Biomed*. (1999) 60:65–77. doi: 10.1016/s0169-2607(99)00012-7
22. Chou KL, Stacy M, Simuni T, Miyasaki J, Oertel WH, Sethi K, et al. The spectrum of "off" in Parkinson's disease: what have we learned over 40 years? *Parkinsonism Relat Disord*. (2018) 51:9–16. doi: 10.1016/j.parkreldis.2018.02.001
23. LaRoia H, Louis ED. Association between essential tremor and other neurodegenerative diseases: what is the epidemiological evidence? *Neuroepidemiology*. (2011) 37:1–10. doi: 10.1159/000328866
24. Chaudhuri KR, Buxton-Thomas M, Dhawan V, Peng R, Meilak C, Brooks DJ. Long duration asymmetrical postural tremor is likely to predict development of Parkinson's disease and not essential tremor: clinical follow up study of 13 cases. *J Neurol Neurosurg Psychiatry*. (2005) 76:115–7. doi: 10.1136/jnnp.2004.046292
25. Ghika A, Kyrozis A, Potagas C, Louis ED. Motor and non-motor features: differences between patients with isolated essential tremor and patients with both essential tremor and Parkinson's disease. *Tremor Other Hyperkinet Mov (N Y)*. (2015) 5:335. doi: 10.7916/d83777wk
26. Minen MT, Louis ED. Emergence of Parkinson's disease in essential tremor: a study of the clinical correlates in 53 patients. *Mov Disord*. (2008) 23:1602–5. doi: 10.1002/mds.22161
27. Hawkes CH, Shephard BC, Daniel SE. Is Parkinson's disease a primary olfactory disorder? *QJM*. (1999) 92:473–80. doi: 10.1093/qjmed/92.8.473
28. Goubault E, Nguyen HP, Ayachi FS, Bogard S, Duval C. Do bradykinesia and tremor interfere in voluntary movement of essential tremor patients? Preliminary findings. *Tremor Other Hyperkinet Mov (N Y)*. (2017) 7:459. doi: 10.7916/d822319x
29. Haubenberger D, Hallett M. Essential tremor. *N Engl J Med*. (2018) 379:596–7. doi: 10.1056/NEJMc1807690
30. Bologna M, Paparella G, Fasano A, Hallett M, Berardelli A. Evolving concepts on bradykinesia. *Brain*. (2020) 143:727–50. doi: 10.1093/brain/awz344
31. Barbagallo G, Caligiuri ME, Arabia G, Cherubini A, Lupo A, Nistico R, et al. Structural connectivity differences in motor network between tremor-dominant and nontremor Parkinson's disease. *Hum Brain Mapp*. (2017) 38:4716–29. doi: 10.1002/hbm.23697
32. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Primers*. (2017) 3:17013. doi: 10.1038/nrdp.2017.13
33. Nisticò R, Pirritano D, Novellino F, Salsone M, Morelli M, Valentino P, et al. Blink reflex recovery cycle in patients with essential tremor associated with resting tremor. *Neurology*. (2012) 79:1490–5. doi: 10.1212/WNL.0b013e31826d5f83
34. Cherubini A, Nisticó R, Novellino F, Salsone M, Nigro S, Donzuso G, et al. Magnetic resonance support vector machine discriminates essential tremor with rest tremor from tremor-dominant Parkinson disease. *Mov Disord*. (2014) 29:1216–9. doi: 10.1002/mds.25869
35. Helmich RC, Janssen MJ, Oyen WJ, Bloem BR, Toni I. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Ann Neurol*. (2011) 69:269–81. doi: 10.1002/ana.22361
36. Pan PL, Song W, Shang HF. Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease. *Eur J Neurol*. (2012) 19:199–206. doi: 10.1111/j.1468-1331.2011.03474.x

37. Stoessl AJ, Martin WW, McKeown MJ, Sossi V. Advances in imaging in Parkinson's disease. *Lancet Neurol*. (2011) 10:987–1001. doi: 10.1016/s1474-4422(11)70214-9
38. Caligiuri ME, Arabia G, Barbagallo G, Lupo A, Morelli M, Nistico R, et al. Structural connectivity differences in essential tremor with and without resting tremor. *J Neurol*. (2017) 264:1865–74. doi: 10.1007/s00415-017-8553-5
39. Bartolic A, Pirtosek Z, Rozman J, Ribaric S. Tremor amplitude and tremor frequency variability in Parkinson's disease is dependent on activity and synchronisation of central oscillators in basal ganglia. *Med Hypotheses*. (2010) 74:362–5. doi: 10.1016/j.mehy.2009.06.057
40. Du G, Zhuang P, Hallett M, Zhang YQ, Li JY, Li YJ. Properties of oscillatory neuronal activity in the basal ganglia and thalamus in patients with Parkinson's disease. *Transl Neurodegener*. (2018) 7:17. doi: 10.1186/s40035-018-0123-y
41. Pinto AD, Lang AE, Chen R. The cerebellothalamocortical pathway in essential tremor. *Neurology*. (2003) 60:1985–7. doi: 10.1212/01.wnl.0000065890.75790.29
42. Cerasa A, Novellino F, Quattrone A. Connectivity changes in Parkinson's disease. *Curr Neurol Neurosci Rep*. (2016) 16:91. doi: 10.1007/s11910-016-0687-9
43. Hellwig B, Mund P, Schelter B, Guschlbauer B, Timmer J, Lücking CH. A longitudinal study of tremor frequencies in Parkinson's disease and essential tremor. *Clin Neurophysiol*. (2009) 120:431–5. doi: 10.1016/j.clinph.2008.11.002
44. Lee HJ, Lee WW, Kim SK, Park H, Jeon HS, Kim HB, et al. Tremor frequency characteristics in Parkinson's disease under resting-state and stress-state conditions. *J Neurol Sci*. (2016) 362:272–7. doi: 10.1016/j.jns.2016.01.058

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 30 October 2020
doi: 10.3389/fneur.2020.575975

Technology-Enabled Care: Integrating Multidisciplinary Care in Parkinson's Disease Through Digital Technology

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Parkinson's disease (PD) management requires the involvement of movement disorders experts, other medical specialists, and allied health professionals. Traditionally, multispecialty care has been implemented in the form of a multidisciplinary center, with an inconsistent clinical benefit and health economic impact. With the current capabilities of digital technologies, multispecialty care can be reshaped to reach a broader community of people with PD in their home and community. Digital technologies have the potential to connect patients with the care team beyond the traditional sparse clinical visit, fostering care continuity and accessibility. For example, video conferencing systems can enable the remote delivery of multispecialty care. With big data analyses, wearable and non-wearable technologies using artificial intelligence can enable the remote assessment of patients' conditions in their natural home environment, promoting a more comprehensive clinical evaluation and empowering patients to monitor their disease. These advances have been defined as technology-enabled care (TEC). We present examples of TEC under development and describe the potential challenges to achieve a full integration of technology to address complex care needs in PD.

Keywords: Parkinson's disease, technology, multidisciplinary care model, home care (HC), rehabilitation

OPEN ACCESS

Edited by:
Maria João Forjaz, Instituto de Salud Carlos III (ISCIII), Spain

Reviewed by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *24 June 2020*
Accepted: *24 August 2020*
Published: *30 October 2020*

Citation:
Luis-Martínez R, Monje MHG, Antonini A, Sánchez-Ferro Á and Mestre TA (2020) Technology-Enabled Care: Integrating Multidisciplinary Care in Parkinson's Disease Through Digital Technology. Front. Neurol. 11:575975. doi: 10.3389/fneur.2020.575975

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder with motor and non-motor clinical manifestations (NMS) that dictate the accrual of loss of autonomy and increasing complexity of care. The increase in life expectancy and expected doubling of PD prevalence in coming years (1) further support the development of PD management strategies with high dissemination and greater usability potential.

The organization of healthcare teams dedicated to care delivery for people living with PD (PwP) is an active research field. The vast majority of system-based approaches consist of care delivery models centered in a PD tertiary center either in the form of an all-in-one multidisciplinary clinic or as a hub of a care network articulated with regional healthcare centers.

The use of technology in PD has gathered great interest. The potential to generate a more continuous and remote health monitoring and the enhancement of patient care communication are bound to deliver a revolution in PD care.

In this review, we first introduce concepts and state-of-the-art knowledge about the use of technology in PD evaluation, the approaches to multidisciplinary care, and the concept of technology-enabled care (TEC). We provide real-world scenarios on how these three concepts can be implemented jointly in a digital revolution for care today and in the future.

TECHNOLOGY IN PD: OVERVIEW AND CORE CONCEPTS

In the last decades, there has been a growing interest in improving health-related outcomes using technology. In PD, technology-based solutions have been developed mainly with the aim of generating an accurate, objective, and reproducible measurement of motor function. Novel sensor-based and wearable technologies enable a shift of the evaluation of PD from the traditional clinical examination and clinical scales to one based on more objective health monitoring of daily function in an everyday-life naturalistic environment. For example, the detailed analyses of movement patterns in the home are expected to provide greater insight on patients' clinical status and their response to treatment.

The most relevant new technologies supporting this paradigm change are inertial measurement units (IMUs). Most IMUs have a triaxial accelerometer and gyroscope, although a magnetometer is frequently included. IMU-based devices are based on the same general principles: (a) preprocessing of the signal generated by the IMU, (b) extraction of the essential characteristics of the movement signal, and (c) creation of a summary variable of the pattern of movement (2). Other examples of technologies being used include virtual reality (VR)-based systems, optoelectronic systems, or a combination of these (3).

IMUs have been embedded in devices worn by the patient (i.e., wearable sensors and systems) in the clinic and, for remote monitoring, in the home setting. As such, wearable technology may more realistically portray motor function for clinical and research purposes. Currently, technologies developed for the management and treatment of PwP have enabled measurement of variations in movement parameters, such as frequency and amplitude that have moderate to high agreement with traditional motor standards such as the Movement Disorders Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) (3, 4). These data could potentially allow clinicians to assess the full spectrum of PD's clinical manifestation including the presence and severity of the cardinal features and treatment-related motor complications of PD (4). Less frequently, technology may be used to monitor NMS such as cognition, sleep, dysautonomia, and neuropsychiatric features (3). The main challenges to the mature development of these technologies include the ability to capture the full spectrum of the disease, standardize validation protocols, use naturalistic environments to determine ecological validity, and enhance the maturation processes of assessment systems with a particular focus on the definition of the context of clinical use from early stages of development (5).

Ultimately, the development of sensor-based and wearable technologies and the growing internet-enabled access to information and mass data storage would facilitate the integration of these technologies in a multisensor/multidomain healthcare framework that we describe below (see the Technology-Enabled Care section).

MODELS OF MULTISPECIALTY CARE

Currently, allied health interventions are carried out most commonly in isolation, with insufficient collaboration and communication with other disciplines involved in PD care (6, 7). The actions of a broad group of physicians and other healthcare professionals in PD care warrant a dedicated organization to optimize care delivery to PwP. The different approaches to multispecialty care can be broadly divided into three categories. (i) In multidisciplinary care, each care provider is responsible for a specific patient care need in the absence of standardized coordination. Commonly, the care providers in this care model are colocated in a single location, raising issues of feasibility and wide dissemination for providing a holistic care for PwP. (ii) In interdisciplinary care, there is active collaboration of healthcare team members to make group decisions. (iii) In integrated care, a care plan is delivered by a coordinated team of healthcare providers (2) guided by consensus building and engagement of patients as team members (3, 4). Integrated care involves the support to the navigation of care resources available in the hospital and community and, more commonly, includes patient education and self-management combined with a structured clinical follow-up and case management. Initial evaluations of integrated care delivered as a PD-dedicated care network in the community with a specialized PD nurse playing the role of a care integrator documented an improvement in quality of life (QoL) and patient and caregiver satisfaction over 6 months (6, 7).

TECHNOLOGY-ENABLED CARE

Technology can play a significant role in care delivery in PD as it is designed to increase the engagement of people in their healthcare and foster self-management in a highly personalized way. The term TEC has been adopted to express the transformative potential of different technological solutions such as telemedicine, online coaching, and self-care apps for care. TEC aims to cover the following goals in the PD care paradigm: (i) assess and measure a wide range of symptoms to capture subtle changes at the prodromal stage and document clinical progression, (ii) support therapeutic choices especially in the presence of multimorbidity, (iii) facilitate rehabilitation and physical activity, and (iv) facilitate remote care.

There are two critical gaps in the care of PwP that technology can help overcome. First, most commonly, each specialty provides care in a silo. Second, with few exceptions, the patient's current assessment is restricted to the hospital or clinic setting. Three main technological breakthroughs can enable care integration supported by technology. One is the digitalization of medicine, which permits patients' connectivity with the hospital from the home environment and the connection between specialists (8); second is the availability of wearable devices that can objectively monitor the patient outside of the

hospital/outpatient environment as described before. Finally, technologies for neurorehabilitation are also enabling some models of care in the home setting.

An important aspect to highlight is that not all systems bear the same degree of development. Like drug trials, where the different phases reflect how close a new drug is from being approved for medical use, in technology, the maturity or "readiness level" reflects how close a system is to being validated for use in routine care. The Technology Readiness Level (TRL) scale developed by NASA in the 1970s is a scale commonly used for this purpose (9) (**Figure 1**). We will review the status of the different technological breakthroughs introduced here.

Digital Health and the Connectivity of Patients and Specialists

Digital health technologies, namely, telemedicine, telehealth, and health information technologies, have the potential to reduce the burden of care by connecting patients with the specialist and deliver personalized health services directly to the home (10), supporting multidisciplinary care to manage the complex care needs of PwP (7). Multiple online digital health platforms are available and have a TRL9 (**Figure 1**) for connectivity between patients and clinicians (10). Web-based video conferencing solutions may offer similar clinical benefits to in-person care, while saving patients and caregivers an average of 100 miles of travel and 3 h compared with regular in-person visits (11). In addition, digital heath initiatives suggest that comprehensive PD home-based care models are feasible and have the potential to integrate multispecialty data and care (e.g., physiotherapy, speech therapy, and telerehabilitation). The most advanced initiative is the ParkinsonNet, a multidisciplinary care model in the Netherlands. In this network, remotely supervised home-based aerobic exercise was feasible and had a positive impact on the motor aspects of PD (12). Despite their proven added value, current online platforms do not provide integration and real-time communication among different care providers and have a low technological maturity (TRL2) for this specific use.

Digitalization is also characterized by the progressive use of electronic health records (EHRs), which in the last decade has been an essential advance for the efficient transformation of medical care institutions. EHRs have proven essential for preventing medical errors, improving efficiency and quality, increasing costumers' trust, improving medical care, and cutting down on healthcare costs (13). Electronic repositories can overcome the ineffectiveness of traditional paper-based records, usually used to store and organize an ever-increasing number of diverse data. EHRs enable the complete integration of PwP health status across providers, generating an interactive and flexible platform to communicate. For instance, Epic Systems Corporation (EPIC), iPatientCare EHR, ReLi Med Solutions (ReLiMedEMR), or 75Health proposes a software solution to support patient care, namely, patient registration, visit scheduling, and medical staff access.

The SARS-CoV2 pandemic has amplified the need to adopt digital healthcare (14). Both health professionals and patients demand technologies that enable integrated multispecialty care beyond the hospital and facilitate knowledge exchange among professionals, a concept called "liquid hospitals" by some (15). Despite this need, its implementation is challenging (16). Other barriers worth mentioning are internet access, preservation of privacy, and data protection. In summary, the digitalization of medicine positions itself as the main driver of TEC, once the integration between different specialists can be widely used securely and privately.

Sensor Technology

Another key element of TEC is the sensing of different health-related phenomena at "home," more specifically, the natural environment of the patient. Wearable devices enable the remote assessment of patients' conditions in their natural settings (17) and measure relevant outcomes (e.g., physical activity, sleep, and falls), which are hard to assess in a regular outpatient clinical visit using clinical interview, patient recall, and clinical exam time-locked to a given visit.

As mentioned earlier, IMUs represent the most widely used technology used in PD and may well-serve the goal of providing data meaningful for healthcare. Over time, IMU-based sensors have become more refined and portable, allowing for unobtrusive monitoring of PD in the home environment. Currently, the main applications of these sensors include (i) the accurate evaluation of cardinal motor features (mainly for bradykinesia and tremor) (18, 19) and (ii) the detection of complications that appear throughout the disease (e.g., the exact quantification of on vs. off states and motor fluctuations or the freezing of gait and falls in a home environment) (20, 21) (**Figure 2**). For example, the Kinesia™ system uses an IMU placed on the patient's index finger or the heel and can differentiate between a healthy subject and a patient with bradykinesia and measure the presence of tremor (18, 26). Other systems like the PDMonitor® (multisensors), the PKG® (clock-shaped IMU), or Mobility Lab System-APDM® can continually record several motor signals and differentiate between motor patterns, on–off states, and dyskinesia (19, 22, 23). On the other hand, other devices can detect movement transition changes (e.g., falls and posture transitions). Significantly, the STAT-ON® device, a waist position device, can detect motor fluctuations (on–off periods) for PD advanced stages or even freezing of gait, which is potentially groundbreaking progress for PD management (24). Currently, the above-mentioned devices created for the evaluation of PwP have reached the maximum level of development (i.e., TRL9) (**Table 1**) and have been approved by regulatory agencies in the EU and USA for routine clinical practice (e.g., for the remote monitoring of axial motor symptoms, bradykinesia, and tremor) (18, 20, 22, 27). Other systems using other types of sensors or tailored to detect other manifestations have a lower TRL (3).

The collection of wearable sensor data at home requires increased computing power, mass data storage capacities, and widespread internet access, which imply that the digitalization of medicine is enabled. The integration of multiple devices within the home environment may have a two-fold impact, allowing for a more comprehensive clinical assessment and

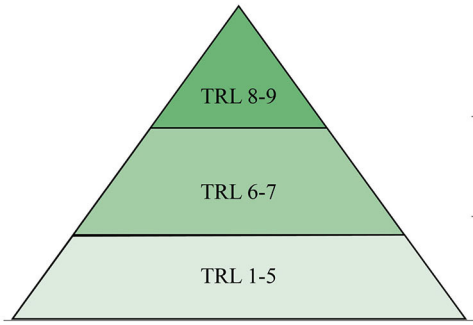

FIGURE 1 | Technology readiness levels (TRLs) and systems mentioned in the review. IMUs, Inertial Measurement Units; EHS, Electronic Health Records; LSVT, Lee Silverman Voice Treatment Device; LOPES, Lokomat, ReoAmbulator, Lower Extremity Powered ExoSkeleton. [1]Based on two authors' (MHGM, ASF) consenus opinion after reviewing available literature as of June 23, 2020. [2]https://www.movementdisorders.org/MDS/About/Committess--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide/Step-1-Obtain-Necessary-Equipement-and-Software-Equipement.htm.

TABLE 1 | Currently available systems with advance regulatory status for the objective quantification of movement in Parkinson's disease patients.

System	Application	Use	Performance	Sensor	Outcome	Regulatory status*
Kinesia-ONE™ Kinesia-360 (18)	Tremor Bradykinesia Dyskinesia	Clinical practice Home Research	MDS-UPDRS III tasks	- Distal index finger - Heel	MDS-UPDRS-based score (0 to 4)	CE mark FDA approved
Personal KinetiGraph® (PKG) (19)	Bradykinesia Dyskinesia Gait (continuous monitoring)	Clinical practice Home Research	Free activity	-Wrist	Time in ON–OFF, time with dyskinesia	CE mark FDA approved
PDMonitor® (22)	Bradykinesia Dyskinesia (continuous monitoring)	Clinical practice Home Research	Free activity	-Both wrists -Both feet	Time in ON–OFF, time with dyskinesia, freezing of gait, falls	CE mark
Mobility lab system-APDM® (23)	Gait (continuous monitoring)	Clinical practice Research	TUG Free activity	-Both wrists -Both feet -Waist	Gait parameters (speed, cadence, swing)	CE mark FDA approved
STAT-ON (24)	Gait (continuous monitoring)	Clinical practice Home Research	Free activity	-Waist	Duration of ON and OFF, freezing of gait, falls	CE mark
MoveMonitor-McRoberts (25)	Gait (continuous monitoring)	Clinical practice Home Research	TUG Free activity	-Waist	Type of activity and time in each activity	CE mark FDA approved

**As listed in the respective companies' website or grey literature. The indication of use for each device as per CE Mark/FDA approval is linked to a specific clinical indication. Off-label use is not recommended. CE, Conformité Européenne; FDA, Food and Drug Administration; MDS-UPDRS-III, Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; TUG, Time Up and Go.*

empowering patients to monitor their disease in a delivery of highly personalized care (5). In the near future, we may witness the use of different sensors for a more comprehensive remote evaluation. Current technology-based gaps and challenges have been described elsewhere. The main barriers for TEC include the lack of integration among different wearable systems, the lack of consensus on patient-centered digital outcomes, and easiness to adopt technology (5). It is vital that standards of validation for these devices are widely used to overcome these barriers. Together with digitalization and connectivity, the expanding capabilities of sensors will allow movement of care from the hospital to the home in an integrated manner.

Technologies for Neurorehabilitation

The field of neurorehabilitation is an ideal example of how technology could be implemented to support medical care. VR and augmented reality (AR) have become more popular recently in this field to enable remote care. A virtual environment established by a computer is used in VR, while in AR, the

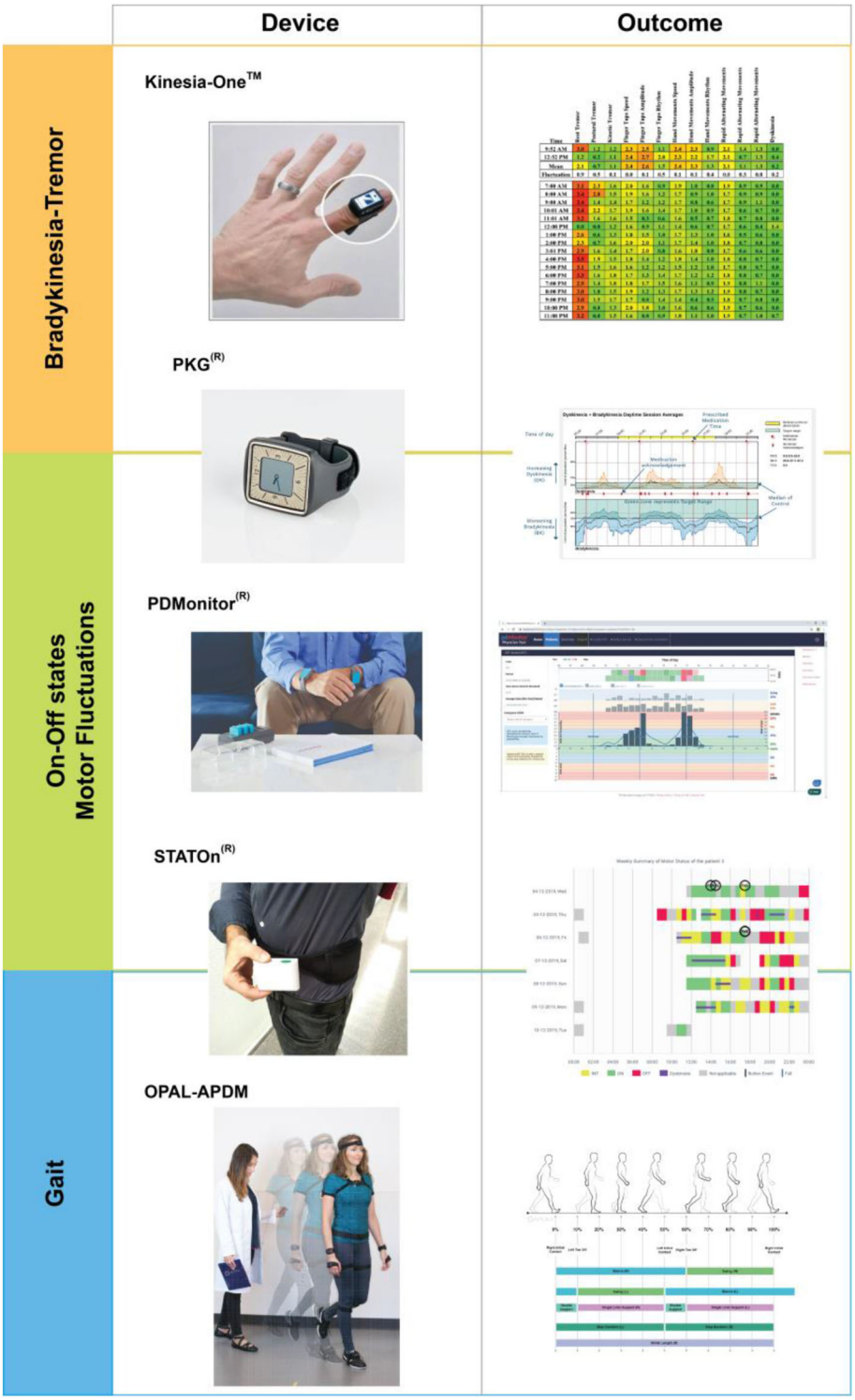

FIGURE 2 | Inertial measurement unit devices approved for used in movement disorders. Relevant examples of different devices and the generated information are presented according to their main application (i.e., the Kinesia system can also be used for dyskinesia and gait, see **Table 1**). The different results obtained with the use of each of the devices are presented. Images provided by Kinesia™, Great Lakes NeuroTechnologies; PKG®, Global Kinetics Corporation; PDMonitor®, PD Neurotechnology® Medical Solutions; STAT-ON, Sense4Care; Opal, APDM Wearable Technologies. Adapted from *Monje MHG and Sánchez-Ferro A. Sistemas inerciales y análisis del movimiento. In: Manual de Nuevas Tecnologías en Trastornos de Movimiento, 2020 (in press)*.

experience of a real environment is enhanced by computer-generated perceptual information. Since 2008, VR research in PD has been conducted with the first studies of gait evaluation using VR (28) Another more recent example is the use of smart glasses in PwP (29). Other studies have suggested that training in fully immersive VR can improve motor function, balance and coordination, cognitive function and mental health, QoL, and activities of daily living (30). Furthermore, VR offers the possibility of replicating real-life scenarios and may improve the effect of conventional rehabilitation therapy with a better performance in some PD manifestations, especially in balance and gait parameters (31, 32). However, more rigorously designed studies are necessary to provide stronger evidence.

In addition, commercial video games (VGs) like video games, exergames, serious gaming, PlayStation, Nintendo, Wii, Wii Fit, Xbox, or Kinect have shown positive results in combination with traditional physical therapy. VGs seem to be effective for treating gait, balance, and strength PD symptoms (33). Neurorehabilitation by exergaming has been confirmed as safe and flexible, has high adherence rates, and may enhance cognitive performance (34). However, due to the large variability in the protocols used (e.g., intervention of duration and number of sessions), studies linking game parameters with conventional assessments methods, such as MDS-UPDRS scores, are required. Likewise, insights into task-oriented exercises for transferring VG rehabilitation goals to real-life functionality are needed (33, 34).

VGs let patients interact in a two-dimensional environment real time and may represent a strategy to engage both mental and motor functions at the same time, possibly enhancing several PD cognitive domains (35). Exergames could be considered either as a supplemental treatment to conventional rehabilitation or as a strategy to extend the benefits of conventional programs at home (36).

Apart from that of cognitive functions, technological implementation for rehabilitation of other clinical manifestations such as speech and language is unfortunately limited. However, communication and swallowing problems, together with hypomimia, are highly prevalent in PD (37). A limited number of studies with the Lee Silverman Voice Treatment showed benefits on swallowing and reduced parkinsonian hypomimia (38). Maintenance of functional communication and swallowing over time is a considerable challenge for PwP, and more technological solutions are urgently required.

Exoskeletons and robotic devices are one of the technological advances in the field of neurorehabilitation. To date, several systems have been developed like the Lokomat, ReoAmbulator, Lower Extremity Powered ExoSkeleton (LOPES), and Anklebot (39). Although more data are required, some benefits have been found. Robotic-assisted gait seems to play a significant role in improving gait function and reducing freezing-of-gait episodes in PD (39–41), but the complexity and high costs of this multimodal integration must be carefully considered. In addition, the quality of evidence of current literature remains low. The studies are chiefly case reports (41).

INTEGRATION OF TECHNOLOGY IN PD CARE: POTENTIAL, CHALLENGES, AND FUTURE OUTLOOK

All the technologies described in the previous section and others not described here have the potential to reformulate PD management routines. Current standards for PD clinical care rely on assessment using clinical scales such as the MDS-UPDRS, Hoehn and Yahr staging, the Schwab and England rating of activities of daily living, and self-reported patient diaries (42). Although these are the most widely used scales in research and clinical routine, there are significant limitations. First, PwP often do not easily recognize motor features like dyskinesia, tremor, or motor fluctuations to fill in their diaries (43). Second, NMS like cognitive dysfunction, dysautonomia, fatigue, and pain contribute significantly to frailty and worsen QoL but are frequently underdiagnosed. To date, only a few comprehensive global scales are available, such as the Scales for Outcomes in Parkinson's disease and the Movement Disorder Society Non-motor Rating Scale (44). Moreover, the clinimetric limitations of clinical scales may lead to suboptimal measurement of motor symptoms and NMS, which in turn can negatively impact the provision of care (45). In the last decade, there has been growing interest in measuring health-related outcomes using technological devices and in the validation of digital endpoints. Therefore, many studies have investigated the characteristic manifestations of PD using technology-based devices, addressing a gap in the ability to monitor PD features over a long period. Technology objective measures in PD have been considered the cutting edge of unbiased measurements but remain yet to fully prove their clinical utility.

Traditional models of care focused on the management of a single chronic condition do not fit the paradigm of care required for PwP characterized by multimorbidity and frailty. In most healthcare systems, the "interface" between inpatient and outpatient management remains unsatisfactory and fragmented, which often leads to PwP receiving suboptimal care. Although elderly PwP will have other chronic diseases, most clinical guidelines focus almost exclusively on motor manifestations and neglect clinical heterogeneity (46, 47). Only recently have clinicians started to consider stratifying PwP based on progression of their functional disability, a process that may benefit from more profound integration of technology in routine care (48).

Wearable sensors, accelerometers, gyroscopes, and non-wearable devices have been tested as ambulatory devices to assess motor parameters such as gait, kinematic features, sway, physical activity, tremor, and bradykinesia (49, 50). These technologies can result in safe, objective, real-time behavioral assessments in clinical routine and facilitate the identification of care problems with more time dedicated to developing management plans and provide patient education during a clinical encounter. NMS have been less amenable to gyroscopic or accelerometer analysis in spite of their

prevalence and significance for PwP. Albeit many aspects of cognition may be effectively monitored through neurocognitive tests applications, mood disorders are still complex to tackle. Simple technological approaches have failed in successful remote monitoring of anxiety or depression. In case of monitoring of sleep quality, biometric and sleep actigraphy monitors are already commercially available. In connection, sleep studies employed polysomnography and actigraphy to evaluate the quality of sleep in PD (51, 52) or even to diagnose PD-associated sleep conditions. For assessing large body movement during sleep, accelerometers have also been employed in several studies; however, the results have not been tied to any sleep quality. On the other hand, autonomic dysfunction remains underrecognized in PD (53), in part because its confirmation relies on cardiovascular autonomic testing available only in a few specialized laboratories (54). Overall, NMS technological development is imperative.

There are significant challenges in the implementation of technology objective measures in day-to-day clinical practice. PD is a progressive disorder, with a significant compromise of functional independence, self-care, and QoL. Moreover, it is frequently associated with multimorbidity, requiring a considerable number of clinical visits and hospital care, resulting in high medical and economic burden (55–57). The integration of technology in PD care needs to be safe, effective, patient-centered, timely, efficient, equitable, and secure. Several barriers exist for the appropriate clinical validation of available devices. Robust accuracy and validity in metrics are necessary with a high degree of confidence. The definition of compliance and feasibility for users is of particular relevance. In the absence of a proper definition and validation of TEC utility, the lack of accuracy, sensitivity, and reproducibility standards may lead to heterogeneous implementation and usage. Therefore, a future key development of healthcare technology is the need to create standard definitions using a multidisciplinary approach. Moreover, financial issues and universal technology access are also delaying the migration of care to the home. Thus, it is time to take this technological chance and face this challenge (5, 58–60).

The current technological development offers the opportunity to achieve an eHealth environment, where gaps of current care models are overcome and a more effective model of care is established. The foundational steps include implementing patient-operated digital platforms integrated with sensors and clinical and non-clinical applications, information sharing (e.g., health monitoring data, visit scheduling and timeline, and educational material) among patients and caregivers and healthcare providers, to complement face-to-face visits and enhance standard care pathways. The design of this technology needs to ensure engagement and effective use in real life. Suitable systems will be defined and used to support sensible and appropriate healthcare usage going beyond the traditional "telehealth" approach. The objective is to develop a system where multidisciplinary care managers and empowered patients operate and enable timely and coordinated access to healthcare providers.

INTEGRATION OF TECHNOLOGY IN PD CARE: REAL-LIFE EXAMPLES

Thanks to the advances described above, new models of care delivery in PD begin to emerge, profiting from the advances in telecommunications (and technology at large), that enable the emerging generation of digitalization of medicine at "home." Yet few of these models are integrated widely into PD management. Emerging care modalities require the unification of multispecialty teams and the migration of patient necessities into their home or community. In this context, PD-Pal, a multicenter European medical project, proposes an innovative approach to the care and management of PwP in the most advanced stages. At this stage, symptoms are complex, and treatment is challenging, with a severe compromise of QoL of patients and family members. Moreover, in this advanced PD stage, patient care necessities change frequently, which makes management difficult and leads to a high number of clinical visits. By integrating electronic tools to monitor movement and cognitive functions at home, for example, and defining the standards for an integrated multidisciplinary path, it will be possible to validate this approach. To achieve this goal, the project will incorporate the integration of a new wearable technology system, PDMonitor®, for remote patient monitoring in their natural environments. This device will inform the management of advanced PD patients overcoming architectural barriers and social isolation. The PD-Pal project could successfully shape multidisciplinary palliative care in PD, integrating technology at home and defining new European standards for care pathways in the advanced stages of PD (61).

The multinational consortium iCARE-PD is another example of technology integration for care delivery. iCARE-PD aims to develop an innovative, pragmatic healthcare model that shifts the hub of care from outpatient care to home-based community across a wider spectrum of disease stages in PD. This model consists of an integrated care network supported by a digital platform shaped as a virtual PD coach that incorporates principles of integrated care, self-management support, and TEC and integrates various eHealth solutions for PwP using co-design (62, 63). Co-design incorporates the input of stakeholders, namely, patients, care partners, and healthcare providers, in the development of technological solutions. The co-design in iCARE-PD is expected to enhance a patient-centered care delivery and, ultimately, to increase usability. Another aspect that characterizes the development of the virtual PD coach is the use of an agnostic platform. This feature will help to address the challenges of a hyperdynamic development of new technological solutions as it allows by design for any TOM to be incorporated at any time as a module of the virtual PD coach.

Another example is the vCare European project. vCare stands for virtual coaching activities for rehabilitation in the elderly and aims at improving rehabilitation for people as they age. vCare will develop and validate new information and communications technology based on a virtual coaching approach for empowering and motivating people with chronic diseases like PD. vCare proposes to support the recovery to an

active and independent life at home, providing rehabilitation guidance and guaranteeing the continuity of care in the home environment. This project has the following aims: (i) coaching activities based on the underlying care pathway system; (ii) integration of a semantic layer enabling technologies such as reasoning, machine learning, behavioral models, and predictive analytics; and (iii) a continuous personalization regarding the cognitive, physical, and social conditions with seamless context integration and non-obtrusiveness in a home environment using open platforms like FIWARE (64). Therefore, this system would allow integration of clinical pathways, allowing a patient-specific adjustment of the rehabilitation program. The coaching environment will provide configurable services to personalize the intensity, content, and requests for optimal engagement of the patient to the individual rehabilitation program. Adequate health promotion can lead to a long-term behavioral change of habits, which decreases the economic effects and the probability of a relapse. This is especially so in the case of chronic diseases. Thereby, it becomes also an essential supplement for direct contact with the clinical specialists (65).

A final example of integrative PD management is a stand-alone technological integrated solution, the PD-manager. The PD-manager uses a set of mobile and wearable devices such as a smartwatch, smartphone, and sensor insoles for monitoring and collection of adherence data. The core of the system is a cloud system that provides all the necessary functionality for users and services communication, along with computing power for data processing and storage. This mHealth platform is accessible through the patients' mobile application and can be shared to clinicians to perform a clinical evaluation using a dedicated medical mobile application. Among the functionalities of the PD-manager, there is a pillbox to optimize medication intake, a dedicated nutritional study, game-based physiotherapy at home, and personalized management suggestions through education.

CONCLUDING REMARKS

The current landscape of technology applied to PD evaluation and care is full of potential. The integration of technology in PD care is not a matter of possibility but how to fulfill the promise. For a successful implementation of TEC, it is urgent to create standards of validation for the intended clinical use of each technological modality and for their integration in a manner that is usable by patients. Ongoing and future collaborative projects will inform how the future eHealth environment will emerge to reduce care inequities and provide a more comprehensive care for empowered patients.

AUTHOR CONTRIBUTIONS

TM, AA, and Á-SF developed the structure and topic of revision. TM provided critique and review to the initial draft. All authors contributed to the initial draft.

FUNDING

MM and ÁS-F were sponsored by the Joint Program for Neurodegenerative Diseases via the Instituto de Salud Carlos III (Grant Number: AC18/00042).

REFERENCES

1. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. (2007) 68:384–6. doi: 10.1212/01.wnl.0000247740.47667.03
2. Bloem BR, Munneke M. Revolutionising management of chronic disease: the ParkinsonNet approach. *BMJ*. (2014) 348:g1838. doi: 10.1136/bmj.g1838
3. Sánchez-Ferro Á, Elshehabi M, Godinho C, Salkovic D, Hobert MA, Domingos J, et al. New methods for the assessment of Parkinson's disease (2005 to 2015): a systematic review. *Mov Disord*. (2016) 31:1283–92. doi: 10.1002/mds.26723
4. Monje MHG, Foffani G, Obeso J, Sánchez-Ferro Á. New sensor and wearable technologies to aid in the diagnosis and treatment monitoring of parkinson's disease. *Annu Rev Biomed Eng*. (2019) 21:111–43. doi: 10.1146/annurev-bioeng-062117-121036
5. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Tůůúúechnology in parkinson's disease: challenges and opportunities. *Mov Disord*. (2016) 31:1272–82. doi: 10.1002/mds.26642
6. Mestre T, Kessler D, Shen J, Basndwah A, Shinawi H, Nussey C, et al. Pilot testing of the Integrated Parkinson's Disease Care Network: úúúú, efficacy outcomes and cost description analysis [abstract]. *Mov Disord*. (2019) 34(suppl 2). Available online at: https://www.mdsabstracts.org/abstract/pilot-testing-of-the-integrated-parkinsons-disease-care-network-feasibility-efficacy-outcomes-and-cost-description-analysis/
7. Eggers C, Dano R, Schill J, Fink GR, Hellmich M, Timmermann L, et al. Patient-centered integrated healthcare improves quality of life in Parkinson's disease patients: a randomized controlled trial. *J Neurol*. (2018) 265:764–73. doi: 10.1007/s00415-018-8761-7
8. Hersh W. Health care information technology: progress and barriers. *JAMA*. (2004) 292:2273–4. doi: 10.1001/jama.292.18.2273
9. European Comission. Technology readiness levels (TRL). HORIZON (2020). – *WORK PROGRAMME 2014-2015 General Annexes*. Available online at: https://ec.europa.eu/research/participants/portal/desktop/en/support/faqs/faq-2890.html (accessed June 20, 2020).
10. Dorsey ER, Glidden AM, Holloway MR, Birbeck GL, Schwamm LH. Teleneurology and mobile technologies: the future of neurological care. *Nat Rev Neurol*. (2018) 14:285–97. doi: 10.1038/nrneurol.2018.31
11. Dorsey ER, Venkataraman V, Grana MJ, Bull MT, George BP, Boyd CM, et al. Randomized controlled clinical trial of ≪ virtual house calls ≫ for Parkinson disease. *JAMA Neurol*. (2013) 70:565–70. doi: 10.1001/jamaneurol.2013.123
12. van der Kolk NM, de Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol*. (2019) 18:998–1008. doi: 10.1016/S1474-4422(19)30285-6
13. Robinson KE, Kersey JA. Novel electronic health record (EHR) education intervention in large healthcare organization improves quality, efficiency, time, and impact on burnout. *Medicine (Baltimore)*. (2018) 97:e12319. doi: 10.1097/MD.0000000000012319
14. Pérez Sust P, Solans O, Fajardo JC, Medina Peralta M, Rodenas P, Gabaldà J, et al. Turning the crisis into an opportunity: digital health strategies deployed during the COVID-19 outbreak. *JMIR Public Health Surveill*. (2020) 6:e19106. doi: 10.2196/19106
15. Sant Joan de Déu presents its Liquid Hospital | *Biocat* [Internet]. Available online at: https://www.biocat.cat/en/news/sant-joan-deu-presents-its-liquid-hospital (accessed June 22, 2020).
16. Hassan A, Dorsey ER, Goetz CG, Bloem BR, Guttman M, Tanner CM, et al. Telemedicine use for movement disorders: a global

survey. *Telemed J E-Health*. (2018) 24:979–92. doi: 10.1089/tmj.2017.0295
17. Del Din S, Godfrey A, Mazzà C, Lord S, Rochester L. Free-living monitoring of Parkinson's disease: lessons from the field. *Mov Disord*. (2016) 31:1293–313. doi: 10.1002/mds.26718
18. Giuffrida JP, Riley DE, Maddux BN, Heldman DA. Clinically deployable kinesia technology for automated tremor assessment. *Mov Disord*. (2009) 24:723–30. doi: 10.1002/mds.22445
19. Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *J Park Dis*. (2012) 2:47–55. doi: 10.3233/JPD-2012-11071
20. Mera TO, Heldman DA, Espay AJ, Payne M, Giuffrida JP. Feasibility of home-based automated Parkinson's disease motor assessment. *J Neurosci Methods*. (2012) 203:152–6. doi: 10.1016/j.jneumeth.2011.09.019
21. Rodríguez-Martín D, Samà A, Pérez-López C, Català A, Moreno Arostegui JM, Cabestany J, et al. Home detection of freezing of gait using support vector machines through a single waist-worn triaxial accelerometer. *PLoS ONE*. (2017) 12:e0171764. doi: 10.1371/journal.pone.0171764
22. Tzallas AT, Tsipouras MG, Rigas G, Tsalikakis DG, Karvounis EC, Chondrogiorgi M, et al. PERFORM: a system for monitoring, assessment and management of patients with Parkinson's disease. *Sensors*. (2014) 14:21329–57. doi: 10.3390/s141121329
23. Mancini M, Horak FB. Potential of APDM mobility lab for the monitoring of the progression of Parkinson's disease. *Expert Rev Med Devices*. (2016) 13:455–62. doi: 10.1586/17434440.2016.1153421
24. Rodríguez-Martín D, Pérez-López C, Samà A, Català A, Moreno Arostegui JM, Cabestany J, et al. A waist-worn inertial measurement unit for long-term monitoring of parkinson's disease patients. *Sensors*. (2017) 17:827. doi: 10.3390/s17040827
25. Coelln R von, Dawe RJ, Leurgans SE, Curran TA, Truty T, Yu L, et al. Quantitative mobility metrics from a wearable sensor predict incident parkinsonism in older adults. *Parkinsonism Relat Disord*. (2019) 65:190–6. doi: 10.1016/j.parkreldis.2019.06.012
26. Heldman DA, Giuffrida JP, Cubo E. Wearable sensors for advanced therapy referral in parkinson's disease. *J Park Dis*. (2016) 6:631–8. doi: 10.3233/JPD-160830
27. Pahwa R, Isaacson SH, Torres-Russotto D, Nahab FB, Lynch PM, Kotschet KE. Role of the personal KinetiGraph in the routine clinical assessment of Parkinson's disease: recommendations from an expert panel. *Expert Rev Neurother*. (2018) 18:669–80. doi: 10.1080/14737175.2018.1503948
28. Davidsdottir S, Wagenaar R, Young D, Cronin-Golomb A. Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease. *Brain J Neurol*. (2008) 131(Pt 11):2882–93. doi: 10.1093/brain/awn237
29. Mcnaney R, Vines J, Roggen D, Balaam M, Zhang P, Poliakov I, et al. "Exploring the acceptability of google glass as an everyday assistive device for people with Parkinsons," in *Proceedings of the 32nd Annual ACM Conference on Human Factors in Computing Systems - CHI 14*. (2014).
30. Triegaardt J, Han TS, Sada C, Sharma S, Sharma P. The role of virtual reality on outcomes in rehabilitation of Parkinson's disease: meta-analysis and systematic review in 1031 participants. *Neurol Sci*. (2020) 41:529–36. doi: 10.1007/s10072-019-04144-3
31. Cano Porras D, Siemonsma P, Inzelberg R, Zeilig G, Plotnik M. Advantages of virtual reality in the rehabilitation of balance and gait: systematic review. *Neurology*. (2018) 90:1017–25. doi: 10.1212/WNL.0000000000005603
32. Lei C, Sunzi K, Dai F, Liu X, Wang Y, Zhang B, et al. Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: a systematic review. *PLoS ONE*. (2019) 14:e0224819. doi: 10.1371/journal.pone.0224819
33. Bonnechère B, Jansen B, Omelina L, Van Sint Jan S. The use of commercial video games in rehabilitation: a systematic review. *Int J Rehabil Res*. (2016) 39:277–90. doi: 10.1097/MRR.0000000000000190
34. Garcia-Agundez A, Folkerts A-K, Konrad R, Caserman P, Tregel T, Goosses M, et al. Recent advances in rehabilitation for parkinson's disease with exergames: a systematic review. *J Neuroeng Rehabil*. (2019) 16:17. doi: 10.1186/s12984-019-0492-1
35. Galeote L, Montiel-Company J, Bavoso D, Francisca J, Cecato J. Working memory and executive functions in Parkinson's disease after intervention with non-immersive virtual reality. *Front Integr Neurosci*. (2013) 7:75. doi: 10.3389/fnint.2013.00075
36. Mura G, Carta MG, Sancassiani F, Machado S, Prosperini L. Active exergames to improve cognitive functioning in neurological disabilities: a systematic review and meta-analysis. *Eur J Phys Rehabil Med*. (2018) 54:450–62. doi: 10.23736/S1973-9087.17.04680-9
37. Theodoros D, Aldridge D, Hill AJ, Russell T. Technology-enabled management of communication and swallowing disorders in Parkinson's disease: a systematic scoping review. *Int J Lang Commun Disord*. (2019) 54:170–88. doi: 10.1111/1460-6984.12400
38. Miles A, Jardine M, Johnston F, de Lisle M, Friary P, Allen J. Effect of lee silverman voice treatment (LSVT LOUD®) on swallowing and cough in Parkinson's disease: a pilot study. *J Neurol Sci*. (2017) 383:180–7. doi: 10.1016/j.jns.2017.11.015
39. Calabrò RS, Cacciola A, Bertè F, Manuli A, Leo A, Bramanti A, et al. Robotic gait rehabilitation and substitution devices in neurological disorders: where are we now? *Neurol Sci*. (2016) 37:503–14. doi: 10.1007/s10072-016-2474-4
40. Alwardat M, Etoom M, Alwardat M, Etoom M. Effectiveness of robot-assisted gait training on freezing of gait in people with Parkinson disease: evidence from a literature review. *J Exerc Rehabil*. (2019) 15:187–92. doi: 10.12965/jer.1836618.309
41. Ustinova K, Lyudmila C, Bilimenko A, Telenkov A, Epstein N. Effect of robotic locomotor training in an individual with Parkinson's disease: a case report. *Disabil Rehabil Assist Technol*. (2011) 6:77–85. doi: 10.3109/17483107.2010.507856
42. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord*. (2002) 17:867–76. doi: 10.1002/mds.10248
43. Papapetropoulos SS. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Ther*. (2012) 18:380–7. doi: 10.1111/j.1755-5949.2011.00253.x
44. Chaudhuri KR, Schrag A, Weintraub D, Rizos A, Rodriguez-Blazquez C, Mamikonyan E, et al. The movement disorder society nonmotor rating scale: initial validation study. *Mov Disord*. (2020) 35:116–33. doi: 10.1002/mds.27862
45. Regnault A, Boroojerdi B, Meunier J, Bani M, Morel T, Cano S. Does the MDS-UPDRS provide the precision to assess progression in early Parkinson's disease? Learnings from the Parkinson's progression marker initiative cohort. *J Neurol*. (2019) 266:1927–36. doi: 10.1007/s00415-019-09348-3
46. Schrag A, Dodel R, Spottke A, Bornschein B, Siebert U, Quinn NP. Rate of clinical progression in Parkinson's disease. A prospective study. *Mov Disord*. (2007) 22:938–45. doi: 10.1002/mds.21429
47. Poewe W, Mahlknecht P. The clinical progression of Parkinson's disease. *Parkinsonism Relat Disord*. (2009) 15(Suppl. 4):S28–32. doi: 10.1016/S1353-8020(09)70831-4
48. Antonini A, Bravi D, Sandre M, Bubacco L. Immunization therapies for Parkinson's disease: state of the art and considerations for future clinical trials. *Expert Opin Investig Drugs*. (2020) 29:685–95. doi: 10.1080/13543784.2020.1771693
49. Channa A, Popescu N, Ciobanu V. Wearable solutions for patients with parkinson's disease and neurocognitive disorder: a systematic review. *Sensors*. (2020) 20:2713. doi: 10.3390/s20092713
50. Ramdhani RA, Khojandi A, Shylo O, Kopell BH. Optimizing clinical assessments in parkinson's disease through the use of wearable sensors and data driven modeling. *Front Comput Neurosci*. (2018) 12:72. doi: 10.3389/fncom.2018.00072
51. Perez-Lloret S, Rossi M, Nouzeilles MI, Trenkwalder C, Cardinali DP, Merello M. Parkinson's disease sleep scale, sleep logs, and actigraphy in the evaluation of sleep in parkinsonian patients. *J Neurol*. (2009) 256:1480–4. doi: 10.1007/s00415-009-5141-3
52. Alatriste-Booth V, Rodríguez-Violante M, Camacho-Ordoñez A, Cervantes-Arriaga A. Prevalence and correlates of sleep disorders in Parkinson's disease: a polysomnographic study. *Arq Neuropsiquiatr*. (2015) 73:241–5. doi: 10.1590/0004-282X20140228
53. Merola A, Romagnolo A, Rosso M, Lopez-Castellanos JR, Wissel BD, Larkin S, et al. Orthostatic hypotension in parkinson's disease: does

it matter if asymptomatic? *Parkinsonism Relat Disord*. (2016) 33:65–71. doi: 10.1016/j.parkreldis.2016.09.013
54. Stamford JA, Schmidt PN, Friedl KE. What engineering technology could do for quality of life in parkinson's disease: a review of current needs and opportunities. *IEEE J Biomed Health Inform*. (2015) 19:1862–72. doi: 10.1109/JBHI.2015.2464354
55. Lindgren P. Economic evidence in parkinson's disease: a review. *Eur J Health Econ.* (2004) 5(Suppl. 1):S63–66. doi: 10.1007/s10198-005-0290-5
56. Findley LJ. The economic impact of Parkinson's disease. *Parkinsonism Relat Disord*. (2007) 13:S8–12. doi: 10.1016/j.parkreldis.2007.06.003
57. McCrone P, Allcock LM, Burn DJ. Predicting the cost of parkinson's disease. *Mov Disord*. (2007) 22:804–12. doi: 10.1002/mds.21360
58. Achey M, Aldred JL, Aljehani N, Bloem BR, Biglan KM, Chan P, et al. The past, present, and future of telemedicine for Parkinson's disease. *Mov Disord.* (2014) 29:871–83. doi: 10.1002/mds.25903
59. Goecks J, Jalili V, Heiser LM, Gray JW. How machine learning will transform biomedicine. *Cell.* (2020) 181:92–101. doi: 10.1016/j.cell.2020.03.022
60. Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov Disord*. (2019) 34:657–63. doi: 10.1002/mds.27671
61. Antonini A, Gentile G, Giglio M, Marcante A, Gage H, Touray MML, et al. Acceptability to patients, carers and clinicians of an mHealth platform for the management of Parkinson's disease (PD_Manager): study protocol for a pilot randomised controlled trial. *Trials*. (2018) 19:492. doi: 10.1186/s13063-018-2767-4
62. Kessler D, Hauteclocque J, Grimes D, Mestre T, Côtéd D, Liddy C. Development of the integrated parkinson's care network (IPCN): using co-design to plan collaborative care for people with Parkinson's disease. *Qual Life Res.* (2019) 28:1355–64. doi: 10.1007/s11136-018-2092-0
63. Vizcarra JA, Sánchez-Ferro Á, Maetzler W, Marsili L, Zavala L, Lang AE, et al. The parkinson's disease e-diary: developing a clinical and research tool for the digital age. *Mov Disord*. (2019) 34:676–81. doi: 10.1002/mds.27673
64. Smart Cities - FIWARE Open Source Platform for Smart Cities. Available online at: https://www.fiware.org/community/smart-cities/ (accessed June 20, 2020).
65. Tropea P, Schlieter H, Sterpi I, Judica E, Gand K, Caprino M, et al. Rehabilitation, the great absentee of virtual coaching in medical care: scoping review. *J Med Internet Res*. (2019) 21:e12805. doi: 10.2196/12805

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 05 November 2020
doi: 10.3389/fneur.2020.570833

Comparing Objective and Subjective Measures of Parkinson's Disease Using the Parkinson's KinetiGraph

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Background: Parkinson's disease (PD) is a neurodegenerative disease that can lead to impaired motor function and execution of activities of daily living (ADL). Since clinicians typically can only observe patients' symptoms during visits, prescribed medication schedules may not reflect the full range of symptoms experienced throughout the day. Therefore, objective tools are needed to provide comprehensive symptom data to optimize treatment. One such tool is the Parkinson's KinetiGraph® (PKG), a wearable sensor that measures motor symptoms of Parkinson's disease.

Objective: To build a mathematical model to determine if PKG data measuring Parkinson's patients' motor symptoms can predict patients' ADL impairment.

Methods: Thirty-four patients with PD wore the PKG device for 6 days while performing their ADL. Patients' PKG scores for bradykinesia and dyskinesia, as well as their responses to a questionnaire asking if their ADL-level had been impacted by various motor symptoms, were used to build a multiple regression model predicting the patients' Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II scores.

Results: Calculation of bradykinesia score response to medication showed that using a dosage response time of 30 min yielded a greater bradykinesia response than when the response time was set to 40, 50, 60, 70, 80, or 90 min. The overall multiple regression model predicting MDS-UPDRS part II score was significant ($R^2 = 0.546$, $p < 0.001$).

Conclusion: The PKG's ability to provide motor symptom data that correlates with clinical measures of ADL impairment suggests that it has strong potential as a tool for the assessment and management of Parkinson's disease motor symptoms.

Keywords: Parkinson's disease, PKG, subjective and objective data, motor symptoms, wearable device, activities of daily life (ADL), UPDRS, mathematical model

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Jong-Min Kim, Seoul National University Bundang Hospital, South Korea
Stuart Isaacson, Boca Raton Regional Hospital, United States

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *09 June 2020*
Accepted: *01 October 2020*
Published: *05 November 2020*

Citation:
Knudson M, Thomsen TH and Kjaer TW (2020) Comparing Objective and Subjective Measures of Parkinson's Disease Using the Parkinson's KinetiGraph. Front. Neurol. 11:570833. doi: 10.3389/fneur.2020.570833

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that affects more than 10 million people worldwide. The disease is characterized by motor symptoms such as tremor, rigidity, bradykinesia, motor complications such as dyskinesia, and non-motor symptoms such as cognitive difficulties (1).

In recent years, wearable sensors that detect motor symptoms have been used to monitor and manage the treatment of PD. These sensors can be worn on the body and use algorithms to

determine the presence and severity of these symptoms. Currently, wearable sensors are capable of measuring several various Parkinsonian motor symptoms and complications, such as bradykinesia (slow movements and a decreased ability to move the body), dyskinesia (involuntary muscle movements), and tremors (2).

Parkinsonian patients may experience difficulty in recognizing and reporting their symptoms, and subjective recordings, such as surveys and diaries, can be prone to bias and inaccuracies (3). Thus, wearable sensors can provide objective symptom data that can help clinicians modify medications to more effectively manage symptoms of Parkinson's disease (4, 5). While studies involving these sensors often compare device results to clinical assessments, to our knowledge, no study so far has analyzed device results in conjunction with patients' subjective experiences regarding their motor symptoms (6–8).

This article aims to evaluate the potential of the Global Kinetics Corporation's Parkinson's KinetiGraph® (PKG) wearable device in accurately monitoring motor symptoms of Parkinson's disease. Using a multiple regression model, PKG measurements of patients' motor symptoms were compared to patients' subjective experiences of their motor symptoms and to their score from the Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II, a validated scale for measuring motor aspects of experiences of daily living (9).

MATERIALS AND METHODS

Patients

We examined 34 patients with mild to moderate Parkinson's disease (Hoehn and Yahr scale 2–3 in ON state) aged 50–75 years who had had symptoms of Parkinson's disease for 3–7 years and had no dementia. All patients met the United Kingdom Brain Bank diagnostic criteria for PD (10). The patients were recruited from the Movement Disorder Clinic of Zealand University Hospital in Roskilde, Denmark as well as from a recruitment notice in a magazine for members of the Danish Parkinson's Association. The patients were clinically assessed for the presence and nature of their motor symptoms before joining the study, and patients' motor symptoms and motor complications were clinically assessed after inclusion using the MDS-UPDRS part III and part IV (data not reported). Age, gender, disease duration, number of Parkinson's drugs taken, number of doses per day, and illness severity (Hoehn and Yahr scale) data were recorded.

A control group was not used as part of this study, but a previous study by Griffiths et al. (11) has shown that the PKG reports different bradykinesia and dyskinesia score distributions between control subjects and patients with Parkinson's disease.

PKG Monitoring

The necessary permissions to use the PKG hardware were obtained from the copyright holders of the product (Global Kinetics Corporation).

Patients were asked to wear the accelerometer at home over a period of seven days, during which they performed their normal daily activities. Each patient wore the PKG device on his or her most affected side. The PKG device contains a rechargeable battery, a triaxial accelerometer, flash memory, and sensors that detect when the device is being worn (11). The PKG was programmed to vibrate to alert the patient that a dose of medication was due, and the patient confirmed the actual time of the dose by placing his or her thumb on the screen of the PKG.

The PKG accelerometer measured bradykinesia and dyskinesia levels during 2-min epochs from 5:00 a.m. to 11:00 a.m. This time period was chosen to specifically study the response to dopaminergic treatment in the morning, as many patients who experience bradykinesia have poor motor function before the first medication dosage has been administered, known as Early Morning OFF episodes (EMOs) (12).

The PKG's algorithms recognized bradykinesia as movements that have low acceleration and amplitude, with long intervals between movements. Dyskinesia was recognized as movements with normal acceleration and amplitude, but with shorter intervals that contained no movements (11). Using the algorithm, the PKG produced a bradykinesia score and dyskinesia score for each 2-min epoch, for a total of 180 data points per symptom per patient per day over the course of the 6-h period of monitoring (ibid.).

MDS-UPDRS Part II

The MDS-UPDRS part II provides a clinical measure of ADL-impairment and has been shown to highly correlate with other disability rating scales (13). The rating system quantifies motor experiences of daily living using 13 self-assessed items (speech, saliva and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting, doing hobbies and other activities, turning in bed, tremor, getting out of a bed, car, or deep chair, walking and balance, freezing). A score was determined for each patient using the scale 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe to assess each item, yielding an overall possible score range of 0 to 52. Results are summarized in **Table 1**.

TABLE 1 | Demographic characteristics of the patients.

	Mean	**Standard deviation**
Age	66.44	6.05
Disease duration (years)	5.03	1.40
Hoehn & Yahr score	2.24	0.43
	N	**%**
Women	18	53
Men	16	47
Number of PD drugs = 1	2	5.9
Number of PD drugs = 2	20	58.8
Number of PD drugs = 3	12	35.5
Number of doses = 1, 2	10	29.4
Number of doses = 3, 4	24	70.6
	Mean	**Range**
UPDRS part II score	12.92	5–27

Questionnaire

The questionnaire section was comprised of eight yes/no questions regarding four specific motor symptoms and complications: bradykinesia, dyskinesia, fluctuations, and early morning off-periods. Four of these eight questions asked the patient if they felt their ADLs were significantly impacted by the respective symptoms; these questions constituted the subjective component of the questionnaire. The remaining four questions asked if the patient had demonstrated the respective symptoms according to the PKG measurements; these questions were completed by the clinician, and constituted the objective component of the questionnaire. For each question, a response of "no" corresponded to a score of 0, and a response of "yes" corresponded to a score of 1. Thus, the overall score could take values from 0 to 8, where a low score would correspond to a low level of motor symptom impact on ADLs, and a high score would correspond to a high level of motor symptom impact on ADLs.

Data Analysis

Data analysis was performed using Microsoft Excel's Data Analysis ToolPak and MATLAB R2019a.

Since most patients did not put on the PKG device until partway through the first day, only the data from the second through seventh day were used for data analysis. All PKG data collected within this timeframe were used; percent of time with immobility (PTI) was tested using an analysis of variance (ANOVA) test and was not shown to be significantly different among patients.

An essential measure of drug effect is the bradykinesia response to medication. To determine the time until the drug took effect, bradykinesia score changes were calculated using seven different "response times," representing the time until the medication took effect. Clinical experiences and statements from the patients regarding medication effects suggested that most patients experienced the ON state 30- to 60-min after medication was administered; as a result, response times of 30, 40, 50, 60, 70, 80, and 90 minutes post-dosage were chosen to examine the time until maximum bradykinesia reduction.

To calculate the response to medication for the 30-min analysis, the average bradykinesia score from the "pre-medication" and the "post-medication" period were calculated for each patient. The "pre-medication" score was defined as the average bradykinesia score from the beginning of the measurement period (5:00 a.m.) until 30 min after the first dosage, and the "post-medication" score was defined as the average bradykinesia score from 30 min after the first dosage until the end of the measurement period (11:00 a.m.). If a patient took more than one dose of levodopa within the 5:00 a.m. to 11:00 a.m. time window, the analysis was only conducted over the period before the second dose was taken. Then, the difference between the pre-medication and post-medication averages was calculated to obtain a "BK change" score for each patient. The process was repeated for the 40-, 50-, 60-, 70-, 80-, and 90-min response time analyses.

For the questionnaire results, two-sample *t*-tests were conducted to determine if there was a significant difference in the overall average bradykinesia and dyskinesia scores of those who responded "yes" to a question vs. those who responded "no" to a question. These *t*-tests were conducted on the results of both the subjective questions, which asked patients about their experiences with Parkinson's symptoms, and the objective questions, which used PKG data to place patients in the "yes" group or the "no" group.

Multiple linear regression models were made to determine the impact of bradykinesia response, dyskinesia score, and questionnaire score (dependent variables) on the UPDRS part II score (independent variable), which measures the impact of motor symptoms on ADLs.

RESULTS

Patient Data

Thirty-four patients fulfilled the required criteria and completed the data collection period. All patients received typical drug combinations of levodopa, dopamine agonists, MAO-B, and/or COMT inhibitors, with 32 out of 34 (94%) patients receiving levodopa. The clinical and sociodemographic characteristics of the sample are shown in **Table 1**.

Dosage Response Time

Onset of bradykinesia improvement after levodopa intake is strongly correlated with plasma dopamine levels, so dosage response time was calculated by determining bradykinesia score change (14). Using seven time values representing time until medication response occurs (30, 40, 50, 60, 70, 80, 90 min), bradykinesia change was calculated in the manner described in the Data Analysis section. To account for the variability in medication response time that can occur on daily basis, the analysis was conducted on the averaged bradykinesia scores of all 34 patients over 6 days. Calculations showed that the largest change in bradykinesia score occurred when the medication response time was set as 30 min, with a decrease of 31.11 points in bradykinesia score (**Table 2**).

Questionnaire Responses

Sixteen *t*-tests were conducted to determine if there was a significant difference in the overall average bradykinesia and dyskinesia scores of those who responded "yes" to a question vs. those who responded "no" to a question.

TABLE 2 | Bradykinesia (BK) score change for seven dosage response times.

Minutes	Pre-medication effect BK average	Post-medication effect BK average	BK change
30	67.28	36.17	31.11
40	65.61	35.83	29.78
50	64.33	35.36	28.97
60	63.16	34.94	28.23
70	61.96	34.48	27.48
80	60.80	33.96	26.84
90	59.64	33.50	26.14

Four of the *t*-tests of average bradykinesia scores of responders were significant. Patients who experienced bradykinesia symptoms during more than 50% of waking time had significantly higher average bradykinesia scores than those who did not, and patients who reported that severe bradykinesia impacted their ADL also had significantly higher average bradykinesia scores than those who reported no impact. With regards to dyskinesia impact on ADL, patients who experienced dyskinesia symptoms during more than 50% of waking time had significantly lower bradykinesia scores than those who did not, and patients who reported that severe dyskinesia impacted their ADL also had significantly lower bradykinesia scores than those who reported no impact (**Table 3**).

Three of the *t*-tests of average dyskinesia scores of responders were significant. Patients who experienced bradykinesia symptoms during more than 50% of waking time had significantly lower dyskinesia scores than those who did not, and patients who reported that severe bradykinesia impacted their ADL also had significantly lower dyskinesia scores than those who did not report an impact. Patients who experienced dyskinesia during more than 50% of waking time had significantly higher dyskinesia scores than those who did not (**Table 4**).

Regression Modeling

Multiple regression analysis was performed with UPDRS part II score as the output variable, modeled by three input variables. The first input variable, called BK change, represents the change in the before-medication average bradykinesia score and the after-medication average bradykinesia score using a medication response time of 30 min. The second variable, called DK average, is the patient's overall average dyskinesia score over 6 days. The third variable, called subjective, is the sum of the responses to the eight questions in the questionnaire where, for each question, a response of "yes" equals 1, and a response of "no" equals 0. The results of the regression indicated that the model explained 54.6% of the variance and that the model was a significant predictor of UPDRS part II score [$F_{(3,30)} = 12.033$, $p < 0.001$].

The multiple regression equation predicting UPDRS score is:

$$\text{UPDRS} = -0.112(\text{BK change}) - 0.297(\text{DK average}) + 1.376(\text{subjective}) + 13.496$$

Therefore, patients' predicted UPDRS part II score was inversely correlated with their bradykinesia change score (**Figure 1**) and their dyskinesia score (**Figure 2**), and positively correlated with their subjective score (**Figure 3**). Specifically, UPDRS part II score decreased 0.112 points for each one-point increase in bradykinesia change, decreased by 0.297 points for each one-point increase in dyskinesia score, and increased by 1.376 points for each one-point increase in subjective score. All three coefficients had $p < 0.05$; the BK change coefficient had $p = 0.006$, the DK average coefficient had $p = 0.007$, and the subjective score coefficient had $p = 0.0009$. Therefore, each variable had a statistically significant effect on UPDRS part II score.

DISCUSSION

The main findings of this paper are as follows. First, the maximum reduction of bradykinesia symptoms occurred 30 min after intake of medication. Second, PKG data averages for 30-min bradykinesia change and overall dyskinesia, combined with patients' score on the eight-question subjective questionnaire, were used to create a significant multiple regression model predicting UPDRS part II score. The statistical significance of the model ($R^2 = 0.546$) in predicting UPDRS part II score, a

TABLE 3 | Mean overall bradykinesia scores of "yes" responders and "no" responders.

	No		Yes		
Question	**BKS**	**SD**	**BKS**	**SD**	***p*-value**
BK measured during more than 50% of waking time?	41.07	10.19	52.91	7.40	<0.001***
Does severe BK impact patient's ADL?	44.38	11.33	51.43	8.49	0.047*
DK measured during more than 50% of waking time?	53.36	6.19	40.26	10.63	<0.001***
Does severe DK impact patient's ADL?	49.16	9.58	36.40	10.81	0.019*
EMO (early morning off) measured?	48.99	6.17	48.10	11.14	0.832
Did the patient experience EMO?	50.31	9.39	46.32	10.69	0.257
Fluctuation time measured during waking time?	46.67	11.30	49.72	9.62	0.419
Do fluctuations impact patient's ADL?	48.06	10.16	49.50	10.35	0.685

*$p < 0.05$, ***$p < 0.001$.

TABLE 4 | Mean overall dyskinesia scores of "yes" responders and "no" responders.

	No		Yes		
Question	**DKS**	**SD**	**DKS**	**SD**	***p*-value**
BK measured during more than 50% of waking time?	12.60	8.11	3.94	3.05	<0.001***
Does severe BK impact patient's ADL?	10.46	8.27	4.85	4.62	0.016*
DK measured during more than 50% of waking time?	3.92	2.92	12.63	8.16	<0.001***
Does severe DK impact patient's ADL?	6.59	6.69	10.03	7.37	0.346
EMO (early morning off) measured?	3.23	2.03	8.04	7.31	0.077
Did the patient experience EMO?	5.52	5.50	8.47	7.68	0.206
Fluctuation time measured during waking time?	7.78	7.49	6.62	6.51	0.645
Do fluctuations impact patient's ADL?	8.59	7.87	5.20	4.84	0.147

*$p < 0.05$, ***$p < 0.001$.

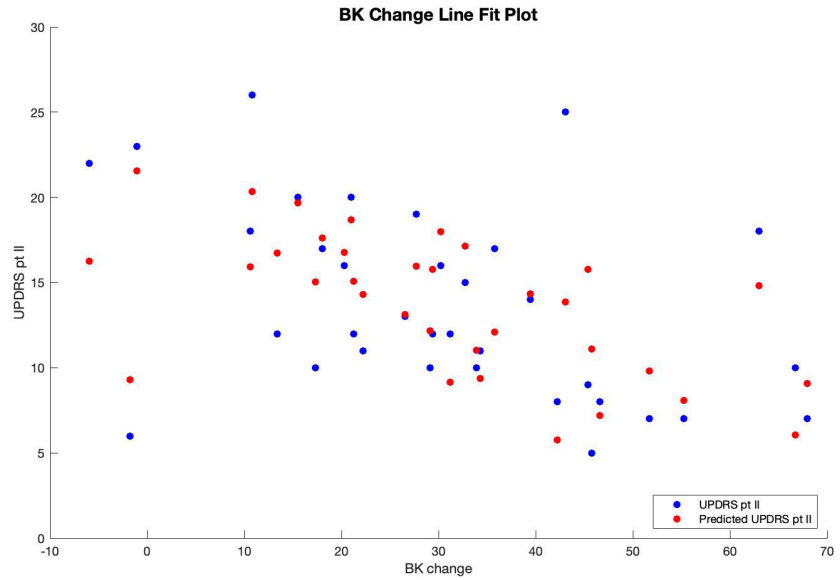

FIGURE 1 | Line fit plot of bradykinesia response vs. UPDRS part II score.

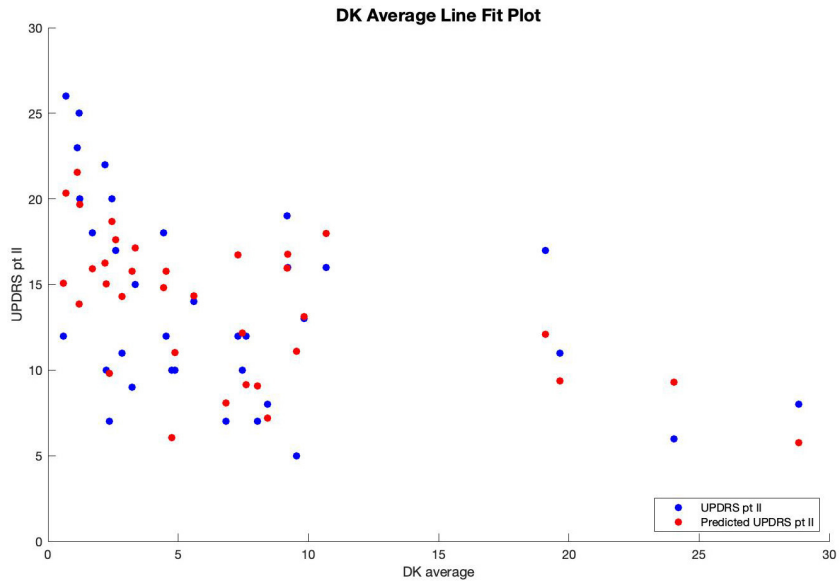

FIGURE 2 | Line fit plot of average dyskinesia score vs. UPDRS part II score.

validated scale in predicting motor aspects of daily living (9), suggests that PKG measurements correlate with motor symptoms of Parkinson's disease.

Dosage Response Time

Analysis of bradykinesia response to medication showed that there is a greater reduction of bradykinesia symptoms when a dosage response time of 30 min is used than when a dosage response time of 40–90 min is used. This result is a generalization based on the averaged responses of 34 patients taking different combinations of medications, and potential variations in patient responses as well as differences in patients' plasma drug concentration levels must also be considered. However, this metric could prove to be a useful baseline in determining the medication response time of individual patients. Several recent studies have shown that motor symptom data from wearable devices can help clinicians to better assess motor symptoms as well as to potentially alter medication schedule for better

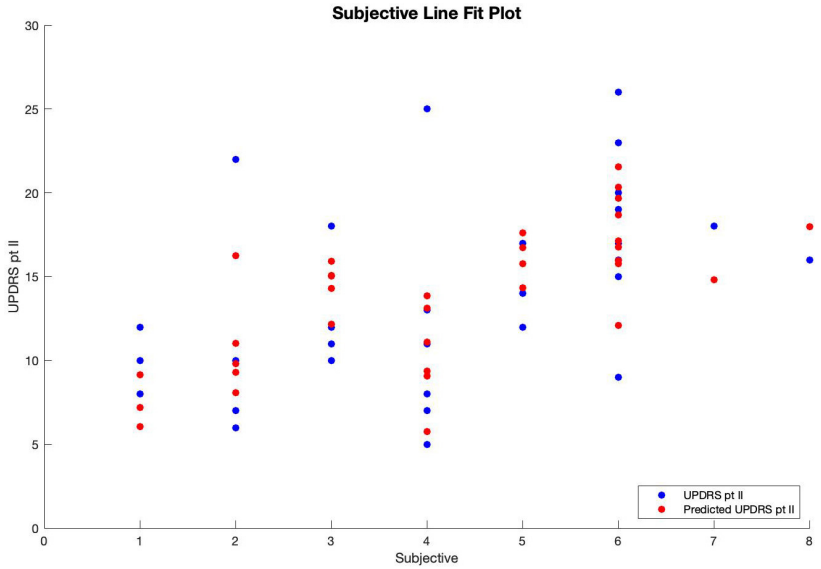

FIGURE 3 | Line fit plot of subjective score vs. UPDRS part II score.

treatment and management of the disease (4, 15–17). Patients wearing a PKG or other similar wearable sensor could provide their motor symptom data to clinicians, who would be able to use sensor data in conjunction with this response time finding to determine the magnitude of the response to medication as well as the individual's expected response time.

Two-Sample *t*-Tests

Two-sample *t*-tests yielded several significant results. The *t*-tests suggested that there is an inverse relationship between bradykinesia and dyskinesia; the average bradykinesia scores of those experiencing dyskinesia more than 50% of the time were significantly lower than those who did not, with $p < 0.001$, and the average dyskinesia scores of those experiencing bradykinesia more than 50% of the time were significantly lower than those who did not, with $p < 0.001$.

The inverse relationship between bradykinesia and dyskinesia can be attributed to the way in which levodopa dosages affect these symptoms. While levodopa treatment reduces bradykinesia symptoms by increasing dopamine levels, levodopa treatment can also increase dyskinesia symptoms in patients, especially when levodopa has been administered for a long period of time (18). Therefore, low average bradykinesia scores indicate that motor symptoms are well-treated with levodopa, but this is associated with the side effect of high average dyskinesia scores.

Multiple Regression Analysis

The multiple regression analysis produced a model that had negative coefficients for the bradykinesia response and average dyskinesia variables, and a positive coefficient for the subjective score variable. This implies that a smaller (worse) bradykinesia response to medication, a lower average dyskinesia score, and a higher subjective score (high impact of motor symptoms on ADL) are each associated with a higher UPDRS part II score.

The bradykinesia response relationship to UPDRS part II score and the subjective score relationship to UPDRS part II score are not unexpected; patients who see less bradykinesia symptom improvement after taking medication would be expected to have higher levels of ADL impairment as measured by the UPDRS part II, and patients who report that they have a greater number of motor symptoms that impact their ADL would similarly be expected to have a higher UPDRS part II score. This result is in agreement with previous results that associate bradykinesia with lower quality of life (19). The inverse relationship between overall dyskinesia score and UPDRS part II score is also not unexpected, as previous studies have shown correlation between dyskinesia levels and quality of life (20, 21).

The overall regression model was significant, showing that data obtained from the PKG, combined with patients' subjective experiences of the impact of motor symptoms on their ADL, can provide an estimation of ADL impairment that is close to the actual UPDRS part II score. Significantly, this model incorporates both the patients' subjective experiences and their UPDRS part II score.

This study is, to the best of the authors' knowledge, the first PKG study to use a subjective questionnaire about motor symptoms as an evaluation tool. The significant result of the model suggests that the symptom data from the PKG can provide an accurate assessment of patients' overall level of impairment, and that the PKG has potential for use in evaluating and managing motor symptoms of Parkinson's disease. When used at home for extended periods of time, the data obtained from the PKG can give clinicians a more complete and realistic picture of a patient's experiences with motor symptoms, and aid in clinical decision-making (5, 22, 23).

Limitations

One limitation in this study was the high amount of variability observed in the PKG data; for some patients, bradykinesia and dyskinesia averages would vary considerably between days. The presence of potentially outlying data points was attempted to be reduced by using more robust methods, such as averaging data over several days to produce a single score, but nonetheless may have negatively impacted the overall accuracy of the multiple regression model. This could be remedied by using a larger group of patients in order to minimize the influence of outliers. While the focus of this study was on response to dopaminergic treatment in the morning, results could also possibly be improved by recording PKG data throughout the day rather than just in the morning.

The high variability in PKG data also limited the dosage response time analysis. In particular, when calculating BK change for response times of fewer than 30 min, patients' average BK score for the pre-medication period would vary significantly on a day-to-day basis due to the small number of data points used to calculate the average pre-medication score. Due to the high degree of variance observed when calculating BK change for these short response times and clinical experiences with time until medication effect, only the response times of 30–90 min were reported. However, in order to verify our finding that a 30-min response time provided the greatest reduction in bradykinesia, it would be necessary to test additional response times.

Another potential limitation of this study is that two of the 34 patients did not receive levodopa, and only received agonist treatment. Exclusion of the two patients who only received agonist treatment may impact medication response time and model predictions, although previous statistical analysis on the same patient cohort showed that there was no significant difference between the number of PD drugs taken and the patients' MDS UPDRS part II score ($p < 0.076$) (24).

Future Directions

In the future, similar studies could be done with a larger number of patients for a longer period of time so that data patterns would not be as strongly impacted by outliers. Experiments could also be done with patients who had more severe Parkinson's disease to see if the same results apply. In addition, PKG data could be used to predict different measures of disease severity and act as a "red flag" indicating the transition into the advanced phase of Parkinson's disease, thus enabling physicians to begin the appropriate treatment within a narrower timeframe. Hopefully, future studies will be able to supplement this study's findings about how wearable technologies can be used to both improve the quality of life of Parkinson's patients and clarify the relationship between management of ADL and response to medication.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of GDPR regulations. Requests to access the datasets should be directed to trint@regionsjaelland.dk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Danish Protection Agency (IBR: REG-110-2017) Regional Scientific Committee (IBR 58638). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK was responsible for the authorship of the manuscript, creation of figures and tables, and statistical analysis. THT was responsible for conducting the patient study, contributed literature references, and edited the article. TWK supervised the patient study, supervised the writing of the manuscript, and helped to edit the article. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Carleton College, DIS Copenhagen, and the Department of Clinical Neurophysiology and Neurology at Zealand University Hospital, Roskilde.

ACKNOWLEDGMENTS

We would like to thank the DIS Copenhagen research program and the Department of Clinical Neurophysiology and Neurology at Zealand University Hospital for offering this research opportunity, and for their generous support of the publication of this paper.

REFERENCES

1. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry.* (2008) 79:368–76. doi: 10.1136/jnnp.2007.131045
2. Maetzler W, Domingos J, Srulijes K, Ferreira JJ, Bloem BR. Quantitative wearable sensors for objective assessment of Parkinson's disease. *Mov Disord.* (2013) 28:1628–37. doi: 10.1002/mds.25628
3. Papapetropoulos S. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Therap.* (2012) 18:380–7. doi: 10.1111/j.1755-5949.2011.00253.x
4. Nahab FB, Abu-Hussain H, Moreno L. Evaluation of clinical utility of the Personal KinetiGraph in the management of Parkinson's disease. *Adv Parkinson's Dis.* (2019) 8:42. doi: 10.4236/apd.2019.83005
5. Isaacson SH, Boroojerdi B, Waln O, McGraw M, Kreitzman DL, Klos K, et al. Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting with transdermal rotigotine patch: a pilot study. *Parkins Related Disord.* (2019) 64:132–7. doi: 10.1016/j.parkreldis.2019.01.025
6. Dai H, Lin H, Lueth TC. Quantitative assessment of parkinsonian bradykinesia based on an inertial measurement unit. *Biomed Eng Online.* (2015) 14:68. doi: 10.1186/s12938-015-0067-8

7. Pastorino M, Cancela J, Arredondo MT, Pansera M, Pastor-Sanz L, Villagra F, et al. Assessment of bradykinesia in Parkinson's disease patients through a multi-parametric system. In: *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. (2011). p. 1810–1813. doi: 10.1109/IEMBS.2011.6090516
8. Teshuva I, Hillel I, Gazit E, Giladi N, Mirelman A, Hausdorff JM. Using wearables to assess bradykinesia and rigidity in patients with Parkinson's disease: a focused, narrative review of the literature. *J Neural Transm.* (2019) 126:699–710. doi: 10.1007/s00702-019-02017-9
9. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A. Expanded and independent validation of the Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS). *J Neurol.* (2013) 260:228–36. doi: 10.1007/s00415-012-6624-1
10. Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. *Ann Neurol.* (1992) 32:S125–S127. doi: 10.1002/ana.410320721
11. Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *J Parkinson's Dis.* (2012) 2:47–55. doi: 10.3233/JPD-2012-11071
12. Han C, Mao W, An J, et al. Early morning off in patients with Parkinson's disease: a Chinese nationwide study and a 7-question screening scale. *Transl Neurodegener.* (2020) 9:29. doi: 10.1186/s40035-020-00208-z
13. Rodriguez-Blazquez C, Rojo-Abuin JM, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A, et al. The MDS-UPDRS part II (motor experiences of daily living) resulted useful for assessment of disability in Parkinson's disease. *Parkins Related Disord.* (2013) 19:889–93. doi: 10.1016/j.parkreldis.2013.05.017
14. Vingerhoets FJG, Schulzer M, Calne DB, Snow BJ. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? *Ann Neurol.* (2004) 41:58–64. doi: 10.1002/ana.410410111
15. Farzanehfar P, Woodrow H, Braybrook M, McGregor S, Evans A, Nicklason F, et al. Objective measurement in routine care of people with Parkinson's disease improves outcomes. *NPJ Parkinson's Dis.* (2018) 4:10. doi: 10.1038/s41531-018-0046-4
16. Joshi R, Bronstein JM, Keener A, Alcazar J, Yang DD, Joshi M, et al. PKG movement recording system use shows promise in routine clinical care of patients with Parkinson's disease. *Front Neurol.* (2019) 10:1027. doi: 10.3389/fneur.2019.01027
17. Santiago A, Langston JW, Gandhy R, Dhall R, Brillman S, Rees L, et al. Qualitative evaluation of the Personal KinetiGraph movement recording system in a Parkinson's clinic. *J Parkinson's Dis.* (2019) 9:207–19. doi: 10.3233/JPD-181373
18. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. *Mov Disord.* (2005 20(S11):S11–S16. doi: 10.1002/mds.20458
19. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Q Life Res.* (1995) 4:241–8. doi: 10.1007/BF02260863
20. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord.* (2005) 20:224–30. doi: 10.1002/mds.20279
21. Carod-Artal FJ, Vargas AP, Martinez-Martin P. Determinants of quality of life in Brazilian patients with Parkinson's disease. *Mov Disord.* (2007) 22:1408–15. doi: 10.1002/mds.21408
22. Thorp JE, Adamczyk PG, Ploeg HL, Pickett KA. Monitoring motor symptoms during activities of daily living in individuals with Parkinson's disease. *Front Neurol.* (2018) 9:1036. doi: 10.3389/fneur.2018.01036
23. Pahwa R, Isaacson SH, Torres-Russotto D, Nahab FB, Lynch PM, Kotschet KE. Role of the Personal KinetiGraph in the routine clinical assessment of Parkinson's disease: recommendations from an expert panel. *Expert Rev Neurother.* (2018) 18:669–80. doi: 10.1080/14737175.2018.1503948
24. Thomsen TH, Kjær TW, Jørgensen LB, Haahr A, Winge K. "Does the response to morning medication predict the ADL-level of the day in Parkinson's Disease?" *Parkinson's Dis.* (2020) 2020:7140984. doi: 10.1155/2020/7140984

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 22 December 2020
doi: 10.3389/fneur.2020.580127

Quantification of Blood Caffeine Levels in Patients With Parkinson's Disease and Multiple System Atrophy by Caffeine ELISA

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Edited by:
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Reviewed by:
Francisco José Pan-Montojo, Ludwig Maximilian University of Munich, Germany
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 04 July 2020
Accepted: 01 December 2020
Published: 22 December 2020

Citation:
Ohmichi T, Kasai T, Shinomoto M, Matsuura J, Koizumi T, Kitani-Morii F, Tatebe H, Sasaki H, Mizuno T and Tokuda T (2020) Quantification of Blood Caffeine Levels in Patients With Parkinson's Disease and Multiple System Atrophy by Caffeine ELISA. Front. Neurol. 11:580127. doi: 10.3389/fneur.2020.580127

Caffeine is considered to be a neuroprotective agent against Parkinson's disease (PD) and is expected to offer a blood-based biomarker for the disease. We herein investigated the ability of this biomarker to discriminate between PD and neurodegenerative diseases. To quantify caffeine concentrations in serum and plasma, we developed a specific competitive enzyme-linked immunosorbent assay (ELISA). To validate the diagnostic performance of the assay, we conducted a case control-study of two independent cohorts among controls and patients with PD and multiple system atrophy (MSA). Parallelism, recovery rate, and intra- and inter-assay precision of our assay were within the standard of acceptance. In the first cohort of 31 PD patients, 18 MSA patients and 33 age-matched controls, serum caffeine levels were significantly lower in PD patients than in Controls ($p = 0.018$). A similar trend was also observed in the MSA group, but did not reach the level of significance. In the second cohort of 50 PD patients, 50 MSA patients and 45 age-matched controls, plasma caffeine levels were significantly decreased in both PD and MSA groups compared to Controls ($p < 0.001$). This originally developed ELISA offered sufficient sensitivity to detect caffeine in human serum and plasma. We reproducibly confirmed decreased blood concentrations of caffeine in PD compared to controls using this ELISA. A similar trend was observed in the MSA group, despite a lack of consistent significant differences across cohorts.

Keywords: caffeine, biomarkers, Parkinson's disease, multiple system atrophy, ELISA

INTRODUCTION

Many reports have examined the relationship between Parkinson's disease (PD) and caffeine in epidemiology, animal experiments, and clinical pharmacology. Epidemiologically, caffeine intake has been established to exert neuroprotective effects against onset and progression of PD (1–4). In a PD animal model treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, caffeine attenuates the degeneration of dopaminergic neurons by inhibiting the adenosine A2A receptor (5). Based on clinical trial results, a selective adenosine A2A receptor antagonist of istradefylline improved motor

symptoms of patients with PD (6). Recent metabolome analyses have shown that blood levels of caffeine metabolites were significantly lower in PD patients than in healthy subjects, and could be used as a candidate biomarker for predicting progression of PD (7–9).

In those reports, however, plasma caffeine concentration was quantified using mass spectrometry, which is ill-suited to application in clinical practice due to the high running costs. For clinical usage, cost-effective measurements of molecule concentration using an apparatus capable of easy maintenance, such as enzyme-linked immunosorbent assay (ELISA), still need to be developed. Moreover, the utility of quantifying caffeine concentration has not been confirmed as useful for discriminating PD from other neurodegenerative diseases, such as multiple system atrophy (MSA).

This study aimed to develop a novel caffeine ELISA applicable to human plasma/serum and to validate the method. We then conducted case-control studies of two independent cohorts to compare plasma and serum caffeine concentrations among control participants and individuals with PD and MSA.

METHODS

Participants and Study Design

All study subjects provided written informed consent before participation in this study. The study protocols were approved by the medical ethics committees at Kyoto Prefectural University of Medicine (approval number: RBMR-C-559-5 and ERB-C-1702) and Hokkaido University Graduate School of Medicine (approval number: 14-004). Informed consent was obtained from each subject when possible, or from the appropriate legal guardian when not possible. All study procedures were designed and performed in accordance with the Declaration of Helsinki. According to a priori power analysis (with 80% power and 5% type I error rate) of the results of previous studies (9, 10), the minimum number for the sample was found to be 24 patients for the comparative study of the blood caffeine level in PD and control groups.

In the first cohort (discovery cohort), caffeine levels in serum were measured. Serum samples were collected from the registrations for dementia and related disorders in Kyoto Prefectural University of Medicine (KPUM) from September 2009 to March 2014. Clinical data, including Hoehn & Yahr (H&Y) stages, Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) scores, heart/mediastinum (H/M) ratio in the early phases of myocardial imaging with 123I-metaiodobenzylguanidine (MIBG), and levodopa equivalent daily dose (LEDD) were evaluated within 1 month of sample collection. Plasma samples of the second cohort were collected at Hokkaido University from July 2008 to July 2018.

Patients were eligible for inclusion if they had been diagnosed according to the internationally standardized criteria of PD (11) and MSA (12). We enrolled age-matched participants with PD and controls in the first cohort as well as with PD, MSA, and controls in the second cohort. On the other hand, the age-matching between PD and MSA in the first cohort was incomplete because of an insufficient number of MSA patients. Subjects were excluded if they had a history of cancer, aspiration pneumonia, or collagen vascular diseases. Serum and plasma samples were obtained via venous puncture under resting conditions in the hospital. Subjects were asked not to eat anything or to drink caffeinated beverages for at least 3 h before sampling. After collection, serum and plasma were separated by centrifugation for 15 min at 2,000 g, then stored at −80°C until analysis.

Caffeine ELISA

ELISA plates (96-well RIA/EIA Clear Flat Bottom Polystyrene High Bind Microplate; Corning Inc., Corning, NY) were coated by overnight incubation at 4°C with 2 μg/ml of anti-caffeine monoclonal antibody (CalBioReagents, San Mateo, CA) at 100 μl/well diluted in phosphate-buffered saline (PBS). Each plate was washed five times with PBS containing 0.05% Tween 20 (PBST) and incubated with blocking buffer (2% bovine serum albumin) for 30 min at 37°C. After washing five times with PBST, 50 μl of standard solutions (Caffeine OQ/PV sample; Agilent Technologies, Santa Clara, CA) or samples, and 50 μl of horseradish peroxidase-conjugated caffeine (CalBioReagents) was added to each well. After 30 min of incubation at 37°C, plates were washed, and 100 μl per well of substrate solution (1 step ultra TMB ELISA; Thermo Fisher Scientific, Rockford, IL) was added. After incubation for 15 min at room temperature in a dark room, color development was stopped with 100 μl/well of 1 mol/L sulfuric acid and absorbance was measured at 450 nm using a microplate spectrophotometer (SpectraMax Plus 384; Molecular Devices Corporation, Tokyo, Japan). For quantitation, standards were fitted to a logistic model curve. Both standards and samples were determined in triplicate on each plate.

Validation of ELISA Methods

The procedure of method validation was conducted according to the guiding principles of the previous report (13). All experiments were performed using serum samples as well as plasma samples.

Precision

We collected two samples with known high and low concentrations of caffeine and made 20 aliquots of each sample. On days 1–4, we measured five replicates on each sample and calculated the mean, SD, and coefficient of variation (%CV) for both repeatability and intermediate precision.

Limits of Quantification and Detection

We prepared 16 aliquots of a blank sample (PBS solution), measured "background" signals by caffeine ELISA, and calculated the mean and SD of the signal. The lower limit of quantification (LOQ) and lower limit of detection (LOD) of the assay were determined as an interpolated caffeine concentration derived from signals of mean minus 10 SD and 2.5 SD of the value of signals for blank samples, respectively.

Dilution Linearity and Parallelism

Serial dilutions of three samples, which were diluted with PBS in small vials until the theoretical concentration was below the lower LOQ, were analyzed in duplicate, on the same plate and

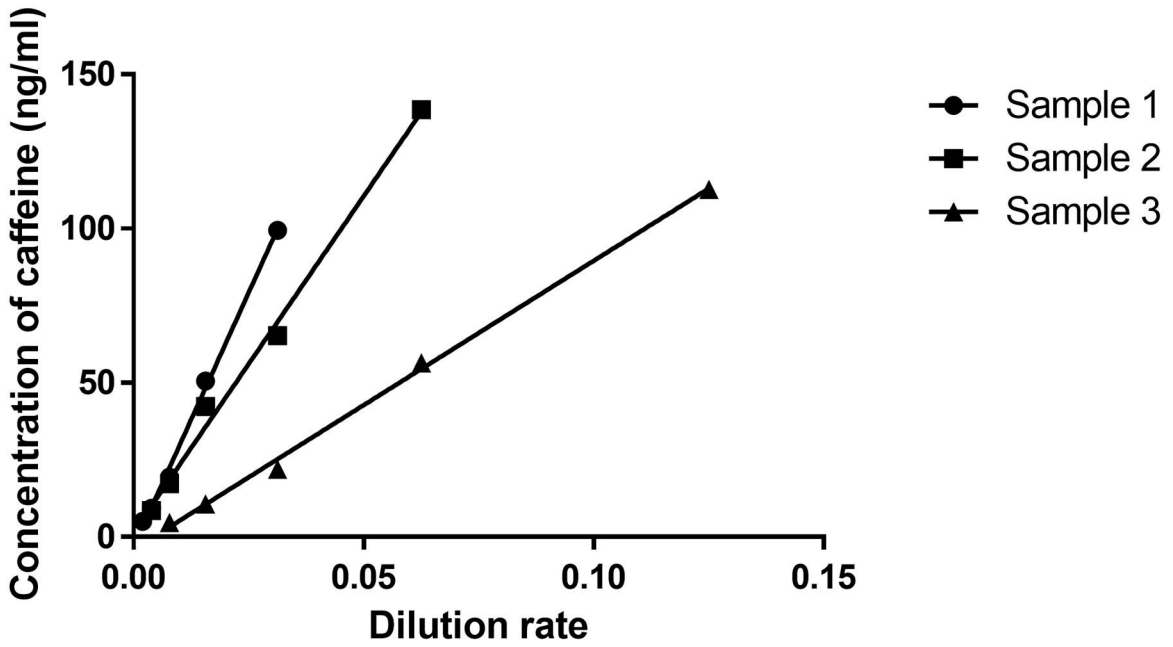

FIGURE 1 | Dilutional linearity. After screening various control plasma samples, we chose three serum samples representing low (Sample 1), middle (Sample 2), and high (Sample 3) levels of caffeine. A serum dilution study was then undertaken to analyze linearity and slope in those three samples. X and Y axes indicate dilution rates and concentrations of caffeine (ng/ml).

compensated for the dilution factor. For each sample, %CV was calculated using results from the dilutions.

Recovery

Three samples with determined concentrations of caffeine were collected. Three aliquots of the same sample were prepared and spiked with 0 and 100 μg or 200 μg of caffeine for spike recovery experiments. Recovery rates were calculated using the following formula:

$$Recovery\ rate\ (\%) = \frac{Measured\ Concentration\ spiked\ sample - Measured\ Concentration\ neat\ sample}{Theoritical\ Concentration} \times 100$$

Concentration After Caffeine Intake

We measured caffeine levels for three healthy volunteers in their thirties before and 2 h after drinking commercially available coffee. They did not eat anything or drink caffeinated beverages for at least 3 h before first sampling. Two of the volunteers drank 2 mg/kg of caffeine and the other drank 4 mg/kg of caffeine.

Statistical Analysis

Mean differences in caffeine between PD, MSA, and Control groups were analyzed by one-way ANOVA and Bonferroni's multiple comparison test. Regression lines between caffeine levels and clinical parameters were assessed using the Spearman rank correlation test. We also derived receiver operating characteristic (ROC) curves for the diagnosis of PD and MSA using caffeine levels as the predictor and estimated area under the curve (AUC; AUC = 0.5 indicates no discrimination, AUC = 1 indicates a perfect diagnostic test) to evaluate the diagnostic utility of caffeine. Significance was accepted for values of $p < 0.05$. Statistical analyses were performed using GraphPad Prism software (GraphPad, La Jolla, CA).

RESULTS

Quality Performance of Caffeine ELISA

Intra-assay %CV, as a predictor of the precision of repeatability, was 13.4% in the sample with a low concentration of caffeine (621 ng/ml), and 15.1% in the sample with a high concentration of caffeine (7,914 ng/ml). Inter-assay %CV, as a predictor of immediate precision, was 12.1% in the former group and 15.1% in the latter group. Lower LOQ and LOD from caffeine ELISA were 3.66 and 0.35 ng/ml, respectively.

Figure 1 shows dilution curves between the lower and upper LOQ of the assay based on the results of dilutional linearity and parallelism. Upper LOQ was estimated as 150 ng/ml. Goodness of fit was 0.99 on Sample 1, 0.98 on Sample 2, and 0.99 on Sample 3. The recovery rate of each sample was 87–113% (**Supplementary Table 1**).

Similar results were obtained in the experiments with plasma samples (**Supplementary Table 2**).

Changes in Serum Caffeine Concentration With Coffee Intake

Caffeine concentration in serum increased with coffee intake in proportion to the volume of intake (**Table 1**). Consuming

TABLE 1 | Caffeine concentrations in serum samples before and after coffee intake.

	Caffeine concentration in serum (ng/ml)	
	Before coffee intake	**After coffee intake**
Sample 1	348	2,761
Sample 2	589	2,275
Sample 3	612	7,914

caffeine led to an 8- to 12-time elevation in serum caffeine signals on ELISA.

Serum Concentrations of Caffeine in the First Cohort

We enrolled 82 subjects, comprising 31 patients with PD [mean (± SD) age, 65.2 ± 12.9 years; range, 41–84 years; 23 men, eight women] and 18 patients with MSA (mean age, 60.9 ± 8.3 years; range, 44–75 years; eight men, 11 women), and 33 age-matched disease controls (mean age, 61.5 ± 17.7 years; range, 16–84 years; 24 men, nine women). Disease controls included patients with cranial and peripheral neuropathy ($n = 11$), cervical spondylosis ($n = 11$), myopathy ($n = 3$), disuse syndrome ($n = 2$), benign positional vertigo ($n = 1$), idiopathic intracranial hypertension ($n = 1$), hyponatremia ($n = 1$), Asperger syndrome ($n = 1$), head drop syndrome ($n = 1$), and dysarthria ($n = 1$). The demographic data are shown in **Supplementary Table 3**. Caffeine concentrations in serum samples from the first cohort are summarized in **Figure 2A** significant overall difference among the three groups was observed from one-way ANOVA. *Post-hoc* analysis showed that serum concentrations were significantly lower in patients with PD compared to Controls, but only tended to be lower in the MSA group compared to Controls, with no significant difference (PD vs. Control: $p = 0.022$; MSA vs. Control: $p > 0.999$; PD 1,608 ± 1,966 ng/mL, MSA 3,212 ± 3,172 ng/mL, Control 4,650 ± 5,308 ng/mL; **Figure 2A**). The difference between PD and MSA groups was not significant (PD vs. MSA, $p = 0.079$). The AUC of ROC curves for the classification of patients with PD and disease controls was 0.687 (**Figure 2B**).

Plasma Concentrations of Caffeine in the Second Cohort

The second cohort comprised 50 patients with PD (mean age, 71.5 ± 6.9 years; range, 53–84 years; 25 men, 25 women), 50 patients with MSA (mean age, 68.6 ± 7.0 years; range, 53–81 years; 25 men, 25 women) and 45 age-matched healthy controls (mean age, 70.4 ± 7.0 years; range, 56–80 years; 25 men, 25 women). As with the first cohort, a significant overall difference was seen between groups. Plasma caffeine concentrations were significantly lower in patients with PD than in Controls (PD vs. Control, $p < 0.001$; MSA vs. Control, $p < 0.001$; PD 1,459 ± 1,616 ng/mL, MSA 1,484 ± 1,805 ng/mL, Ctrl 4,186 ± 2,740 ng/mL; **Figure 3A**) in *post-hoc* tests. Moreover, plasma concentrations of caffeine in patients with MSA were significantly decreased compared to Controls, and did not differ significantly from those in PD (MSA vs. PD: $p > 0.999$). AUCs of ROC curves for patients with PD and MSA compared with disease controls were 0.821 and 0.810, respectively (**Figures 3B,C**).

Correlation Between Caffeine Level and Clinical Characteristics of Patients With PD and MSA

Serum caffeine levels in the PD group did not correlate with H&Y stage, UPDRS-III score, or H/M ratio of MIBG uptake (**Supplementary Figures 1A–D**). Serum caffeine levels in the PD group did not correlate with duration from onset (**Supplementary Figure 1E**). No significant correlation was identified between serum caffeine levels and age in the PD, MSA, and Control groups (**Supplementary Figures 1F–H**).

DISCUSSION

The originally developed ELISA examined in this study offered sufficiently high sensitivity to detect caffeine in human serum and plasma. Both intra- and inter-assay precision (%CV) of our assay were below 20%, which is the recommended acceptance criterion for single-laboratory accuracy of a biomarker (14). Consuming caffeine led to an 8- to 12-time elevation in serum caffeine signals on ELISA. This rate of increase supports the findings of a previous observation (15), suggesting that this caffeine ELISA system reasonably worked even *in vivo*.

The assays in the first cohort showed a significant decrease in serum caffeine concentration for PD patients as compared to Controls. This result was reproducibly observed in plasma levels of caffeine in the second cohort. Those findings were consistent with previous metabolomic analyses (8, 9) and also matched with a report stating that serum concentrations of the caffeine metabolite, theophylline, were significantly decreased in the PD group compared to controls (10). In the second cohort, plasma caffeine concentration of MSA was significantly decreased compared to that of the control group. A similar trend was observed in the first cohort despite the lack of significance. This result implied that plasma and serum caffeine levels in MSA might be lower than those in controls, similar to the case of PD. Fujimaki et al. speculated that impaired gastrointestinal dysfunction and dysmotility in PD were responsible for reduced caffeine levels, based on the lack of correlation between caffeine intake and blood caffeine levels in their PD cohort. The decreased plasma caffeine levels in MSA, which also cause serious autonomic failure including intestinal dysfunction, could support this speculation.

Serum caffeine levels in the PD group of the first cohort did not correlate with age, duration from onset, severity of disease, or H/M ratio of MIBG uptake. These results are consistent with those of previous reports (8, 9).

We acknowledge that the small sample size represents a major limitation to this study. As other limitations, no information was available regarding the daily caffeine intakes or genetic backgrounds of participants. In the future, case-control studies involving sufficient numbers of participants with information on

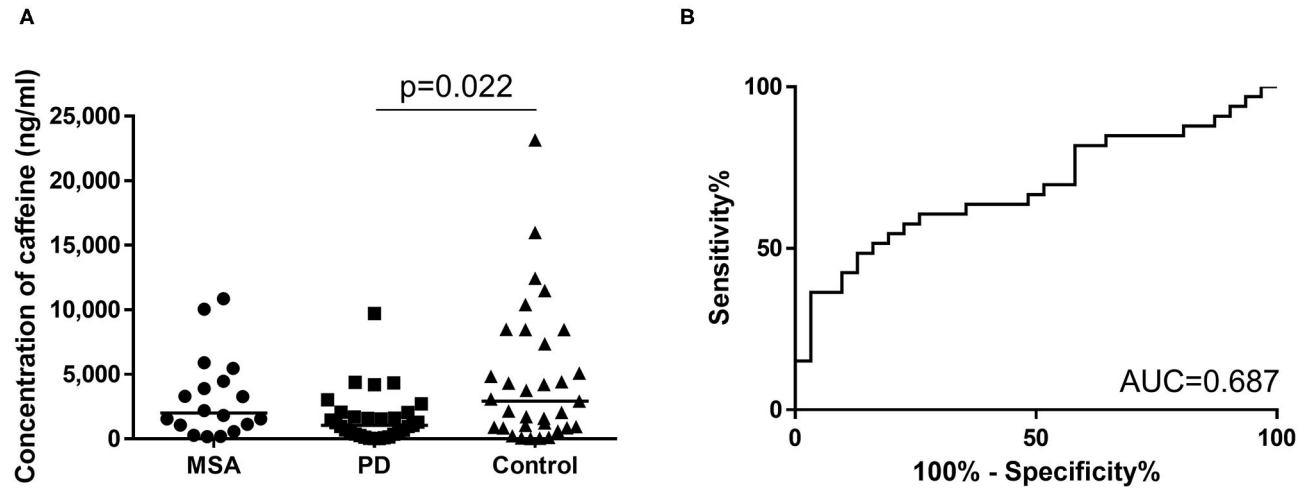

FIGURE 2 | (A) Scatter plots of caffeine levels in the first cohort showing serum levels of caffeine in the MSA ($n = 18$), PD ($n = 31$), and control ($n = 33$) groups. Bars indicate median values. Levels of caffeine were significantly lower in the PD group than in the Control group. No significant difference in plasma caffeine levels was seen between PD and MSA groups (PD vs. MSA: $p = 0.079$). **(B)** Receiver operating characteristic (ROC) curves of caffeine for differential diagnosis of PD and Controls in the first cohort. Area under the curve (AUC) is 0.687.

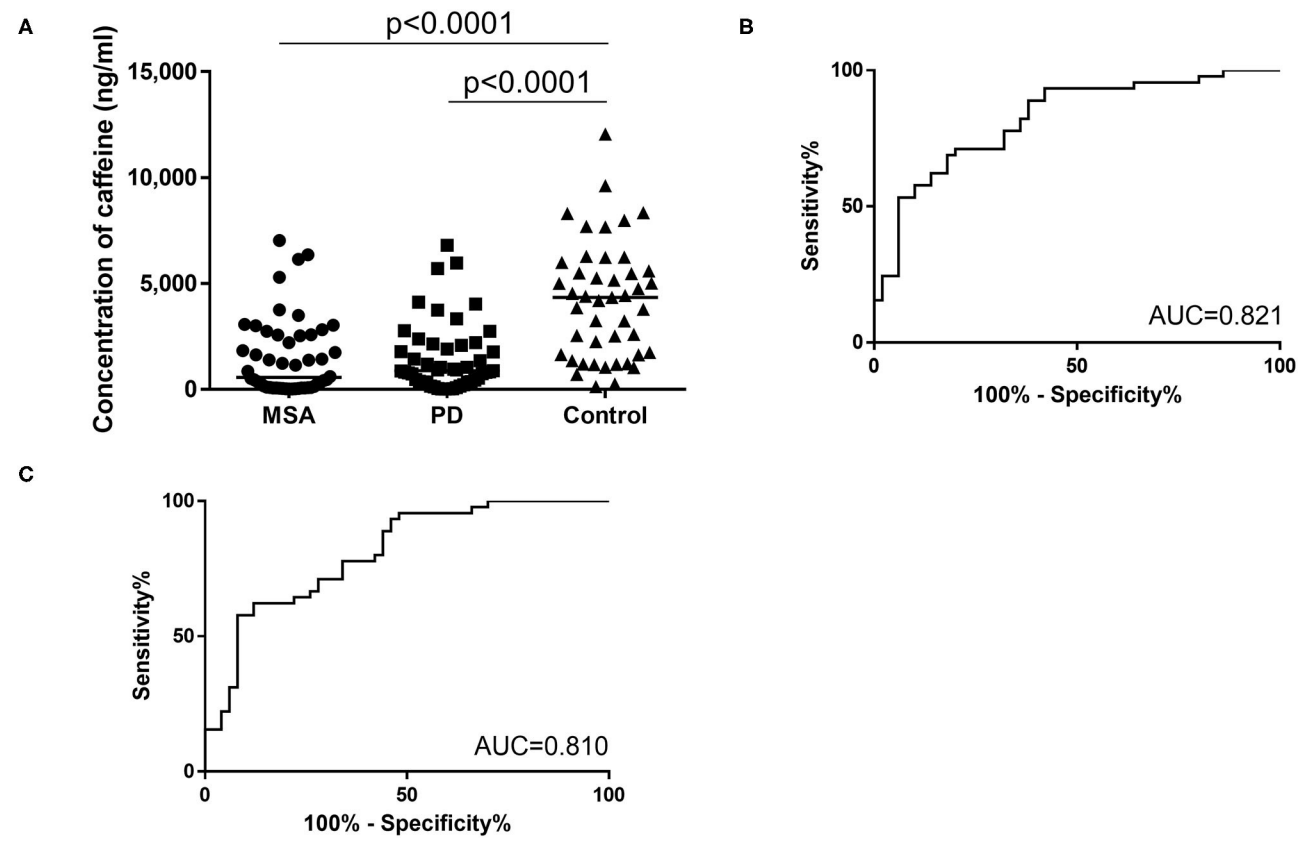

FIGURE 3 | (A) Scatter plots of caffeine levels in the second cohort showing levels of plasma caffeine in the MSA ($n = 50$), PD ($n = 50$), and control ($n = 45$) groups. Bars indicate median values. Levels of caffeine were significantly lower in the PD and MSA groups than in the Control group. Plasma caffeine levels did not differ significantly between PD and MSA groups (MSA vs. PD: $p > 0.999$). **(B,C)** Receiver operating characteristic (ROC) curves of caffeine for differential diagnosis of PD and Controls **(B)** and for differential diagnosis of MSA and controls **(C)** in the second cohort. Area under the curve (AUC) is 0.821 for PD and controls and 0.810 for MSA and controls.

caffeine consumption as well as genetic information affecting caffeine pharmacokinetics (e.g., ADORA2A and CYP1A2 gene polymorphisms) are needed to confirm our findings (16). Moreover, it remains unclear in the current study why PD (and MSA) patients have lower blood caffeine levels. It might be because of less consumption, less absorption in the gastrointestinal tract, or quicker metabolism of caffeine. To test these hypothetical ideas, comparison of time-dependent changes of blood caffeine levels after caffeine ingestion between PD/MSA patients and controls would be also important in future studies.

CONCLUSION

We have developed a specific ELISA system for detecting caffeine in blood and performed method validation. This originally developed ELISA offered sufficiently high sensitivity to detect caffeine in human serum and plasma. We reproducibly confirmed decreased blood caffeine concentrations in PD compared to controls by ELISA. These findings confirm previous observations from retrospective case-control studies, and provide evidence that this ELISA can work as a diagnostic biomarker for PD. A similar decreasing trend was also observed in the MSA group. This result implies potential clinical utility of blood caffeine levels as a biomarker for MSA. Future validation studies are still needed for this issue, because of a lack of consistent significant differences across cohorts.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committees at Kyoto Prefectural University of Medicine and Hokkaido University Graduate School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TKa and TT: conception and study design. TO, HT, FK-M, MS, JM, TKo, and HS: data acquisition. TO and TKa: drafting first version of the manuscript and figure and tables. TO, TKa, MS, JM, TKo, FK-M, HT, HS, TM, and TT: final version of the manuscript. TM: study supervision. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported mainly by a grant from the Japan Agency for Medical Research and Development [AMED-CREST, program for Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS)] (to TT), in part by Grants-in-Aid (Nos. 15K09319 and 18K07506 to TKa; No 20K16605 to TO) from the Ministry of Education, Culture, Sports, Science and Technology of Japan to TK, and research grants from Dainippon Sumitomo Pharma in 2018 (to TO) and 2017 (to TKa).

ACKNOWLEDGMENTS

We would like to thank Mrs. Dr. Yuka Hama (Department of Neurology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University) for the provision of samples.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.580127/full#supplementary-material

REFERENCES

1. Schwarzschild MA, Xu K, Oztas E, Petzer JP, Castagnoli K, Castagnoli N, et al., et al. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. *Neurology.* (2003) 61(11 Suppl. 6):S55–61. doi: 10.1212/01.WNL.0000095214.53646.72
2. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol.* (2012) 72:893–901. doi: 10.1002/ana.23687
3. Ascherio A, Chen H. Caffeinated clues from epidemiology of Parkinson's disease. *Neurology.* (2003) 61(11 Suppl. 6):S51–4. doi: 10.1212/01.WNL.0000095213.86899.21
4. Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr Gerontol Int.* (2014) 14:430–9. doi: 10.1111/ggi.12123
5. Chen JF, Xu K, Petzer JP, Staal R, Xu YH, Beilstein M, et al. Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease. *J Neurosci.* (2001) 21:Rc143. doi: 10.1523/JNEUROSCI.21-10-j0001.2001
6. Mizuno Y, Kondo T. Adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. *Mov Disord.* (2013) 28:1138–41. doi: 10.1002/mds.25418
7. LeWitt PA, Li J, Lu M, Guo L, Auinger P. Metabolomic biomarkers as strong correlates of Parkinson disease progression. *Neurology.* (2017) 88:862–9. doi: 10.1212/WNL.0000000000003663
8. Hatano T, Saiki S, Okuzumi A, Mohney RP, Hattori N. Identification of novel biomarkers for Parkinson's disease by metabolomic technologies. *J Neurol Neurosurg Psychiatry.* (2016) 87:295–301. doi: 10.1136/jnnp-2014-309676
9. Fujimaki M, Saiki S, Li Y, Kaga N, Taka H, Hatano T, et al. Serum caffeine and metabolites are reliable biomarkers of early Parkinson disease. *Neurology.* (2018) 90:e404–11. doi: 10.1212/WNL.0000000000004888
10. Ohmichi T, Kasai T, Kosaka T, Shikata K, Tatebe H, Ishii R, et al. Biomarker repurposing: therapeutic drug monitoring of serum theophylline offers a potential diagnostic biomarker of Parkinson's disease. *PLoS ONE.* (2018) 13:e0201260. doi: 10.1371/journal.pone.0201260
11. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases.

J Neurol Neurosurg Psychiatry. (1992) 55:181–4. doi: 10.1136/jnnp.55.3.181

12. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. (2008) 71:670–6. doi: 10.1212/01.wnl.0000324625.00404.15
13. Andreasson U, Perret-Liaudet A, van Waalwijk van Doorn LJ, Blennow K, Chiasserini D, Engelborghs S, et al. A practical guide to immunoassay method validation. *Front Neurol*. (2015) 6:179. doi: 10.3389/fneur.2015.00179
14. DeSilva B, Smith W, Weiner R, Kelley M, Smolec J, Lee B, et al. Recommendations for the bioanalytical method validation of ligand-binding assays to support pharmacokinetic assessments of macromolecules. *Pharm Res*. (2003) 20:1885–900. doi: 10.1023/B:PHAM.0000003390.51761.3d
15. Chen F, Hu ZY, Parker RB, Laizure SC. Measurement of caffeine and its three primary metabolites in human plasma by HPLC-ESI-MS/MS and clinical application. *Biomed Chromatogr*. (2017) 31:e3900. doi: 10.1002/bmc.3900
16. Popat RA, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, et al. Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. *Eur J Neurol*. (2011) 18:756–65. doi: 10.1111/j.1468-1331.2011.03353.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 14 January 2021
doi: 10.3389/fneur.2020.587992

Association Between BDNF Val66Met Polymorphism and Mild Behavioral Impairment in Patients With Parkinson's Disease

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OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Vikram Venkappayya Holla, National Institute of Mental Health and Neurosciences, India
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 27 July 2020
Accepted: 02 December 2020
Published: 14 January 2021

Citation:
Ramezani M, Ruskey JA, Martens K, Kibreab M, Javer Z, Kathol I, Hammer T, Cheetham J, Leveille E, Martino D, Sarna JR, Gan-Or Z, Pfeffer G, Ismail Z and Monchi O (2021) Association Between BDNF Val66Met Polymorphism and Mild Behavioral Impairment in Patients With Parkinson's Disease. Front. Neurol. 11:587992. doi: 10.3389/fneur.2020.587992

Neuropsychiatric symptoms (NPS) are common in Parkinson's disease (PD) and have demonstrated an association with the p. Val66Met, a polymorphism in the *BDNF* gene. Mild behavioral impairment (MBI) is a validated syndrome describing emergent and persistent NPS in older adults as a marker of potential cognitive decline and dementia. This study investigated if PD patients with the Met allele were more likely to have MBI and whether they had impairments in specific domains of MBI using the Mild Behavioral Impairment Checklist (MBI-C) as the MBI ascertainment tool. One hundred forty-six PD patients were screened for neuropsychiatric and cognitive impairments with the MBI-C and the Montreal Cognitive Assessment (MoCA). All participants were genotyped for the *BDNF* p.Val66Met single-nucleotide polymorphism (SNP) using TaqMan Genotyping Assay. Statistical analysis was performed using multiple linear and logistic regression models. Met carriers had a 2 times higher likelihood of being MBI positive (MBI-C total score $\geq$8) than Val carriers. Met carriers had significantly higher MBI-C total scores and significantly greater impairments in the mood/anxiety and the psychotic domains of MBI-C compared to Val carriers. These findings indicate that the *BDNF* Met allele is associated with a higher neuropsychiatric burden in PD.

Keywords: BDNF, Parkinson's disease, mild behavioral impairment, neuropsychiatric symptoms, depression

INTRODUCTION

Neuropsychiatric symptoms (NPS) are common in Parkinson's disease (PD) patients. These NPS include depression, anxiety, psychosis, etc., which occur more frequently in PD patients than in the general population (1, 2). NPS can be present at early stages of PD and even precede the emergence of cardinal motor symptoms of PD (1). They have a severe social and emotional impact on the quality of life in PD patients and their families/caregivers (3). Mild behavioral impairment (MBI) is a validated syndrome characterized by the emergence of persistent NPS in older adults as an at-risk state for incident cognitive decline, and for some, MBI is the index manifestation of dementia, emerging in advance of cognitive symptoms (4). Early evidence in PD has linked MBI to altered

corticostriatal connectivity, middle temporal lobe atrophy, and cognitive impairment which suggest a higher risk of developing dementia (5, 6).

Brain-derived neurotrophic factor (BDNF) is a crucial protein in the central nervous system (CNS) with a substantial role in differentiation, survival, and protection of CNS neurons (7). Studies have investigated a potential role for p.Val66Met (G758A, rs6265), a single-nucleotide polymorphism (SNP) in exon 11 of the *BDNF* gene, and PD (8–10). The p.Val66Met SNP substitutes a valine (Val) residue at position 66 with a methionine (Met) residue in the pro-domain of the BDNF protein (7).The Met allele has been found to be associated with cognitive impairments in PD patients and late-life psychiatric symptoms in the general population (8, 9, 11). This substitution is not transferred to the final form of BDNF; however, this structural change in the BDNF protein precursor can significantly decrease the secretion of BDNF extracellularly and subsequently reduce its availability to the CNS neurons (7). Recent evidence suggests a role of the Met allele in the induction of long-term depression (LTD) in the brain, likely via altered interaction of BDNF pro-domain with sortilin receptors (12, 13). The altered interaction might explain the connection of this polymorphism with NPS in the general population and in neurodegenerative diseases (14, 15). Recent longitudinal data in Alzheimer disease (AD) patients revealed strong evidence of Met association with depression (15). Moreover, recent meta-analysis reported higher likelihood of mild cognitive impairment in PD patients with the Met allele (9). These evidences suggest a link between the p.Val66Met polymorphism and NPS in PD patients and therefore encourage an investigation of this relationship.

In this study, we tested whether the p.Val66Met SNP in PD patients is associated with MBI burden using the Mild Behavioral Impairment Checklist (MBI-C). Specifically, we hypothesized that PD patients with at least one Met allele (Met carriers) would have greater likelihood of having MBI and higher total MBI-C score than those who are Val homozygotes (Val group). Additionally, we hypothesized that Met carriers would have higher MBI-C domain scores compared to Val group.

METHODS

Participants

One hundred forty-six PD patients at Hoehn and Yahr stages II–III were recruited. Patients had a confirmed diagnosis of idiopathic PD by a Movement Disorder Clinic neurologist, meeting the UK Brain Bank criteria for idiopathic PD. All patients were on prescribed dopaminergic medication and were responsive to it. Exclusion criteria were the following: (1) any neurological disorder other than PD; (2) alcohol dependency; (3) history or presence of a severe psychiatric disorder; and (4) cerebrovascular disorders. The severity of motor symptoms was assessed using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III). All participants provided written informed consent according to the declaration of Helsinki, and the study was approved by the Conjoint Health Research Ethics Board (REB14-2463) at the University of Calgary.

Genotyping

A blood sample was collected from each participant, and DNA was extracted using the MagMax DNA Multi-Sample Ultra 2.0 kit and the King Fisher Duo Prime Robot (Thermo Fisher Scientific). DNA samples were screened for the *BDNF* p.Val66Met SNP (rs6265) using TaqMan SNP Genotyping Assay C-11592758-10 on C-1000 Touch Thermal cycler (Bio-Rad). TaqMan assay reading was done on Applied Biosystems QuantStudio 7 Flex Real-Time PCR system (Fisher Scientific) according to the manufacturer's instructions. The TaqMan assay results were analyzed using the Bio-Rad CFX Maestro software.

Neuropsychiatric and Cognitive Assessment

NPS in all participants was evaluated using the MBI-C (16, 17). The MBI-C contains 34 questions to cover the five domains of MBI including the following: (1) impaired drive/motivation (apathy); (2) emotional dysregulation (mood and anxiety symptoms); (3) impulse dyscontrol (agitation, aggression, abnormal reinforcement, and reward salience); (4) social inappropriateness (impaired social cognition); and (5) abnormal thoughts/perception (psychotic symptoms). This checklist is completed by each patient's caregiver/close family member. Consistent with the MBI criteria, symptoms should have lasted for at least 6 months and present a meaningful change of behavior from longstanding patterns. An MBI-C total score cut point of $\geq$8 was used to classify a patient as MBI case positive (5, 18, 19). All participants completed the Montreal Cognitive Assessment (MoCA) for a brief cognitive assessment and completed a questionnaire on their demographics and daily activity level.

Statistical Analysis

Statistical analyses of continuous variables were performed using either the student *T* test or Mann-Whitney (M-W) *U* test based on the data normality. The Fisher exact and chi-square tests were used to test the categorical variables. Logistic regression was used to test the relationship between the MBI positive condition (the categorical dependent variable) and the two BDNF genotype groups, including any independent variables that were significantly different between the two conditions.

MBI-C total score (the continuous dependent variable) was compared between the two groups using a multiple linear regression model after checking for the multiple linear regression model assumptions. The independent variables that were correlated with MBI-C total score were included in the regression model. Values of $p < 0.05$ were considered significant for single tests, and significance of 0.01 was used to test MBI-C domains using Bonferroni correction. The same analysis was used to study association of p.Val66Met and MBI-C domain scores. All statistical tests were performed using IBM SPSS Statistics for Mac v. 26 (IBM Corp., Armonk, N.Y., USA). Power analysis was performed using G-Power software 3.1.9.6 (20).

RESULTS

Demographics of Participants

The demographic and clinical characteristics of the participants are summarized in **Table 1**. Ten patients were identified as outliers based on values that were more than three standard deviation away from the mean of each allelic group for the following variables: age, education, UPDRS, Levodopa equivalent daily dosage (LEDD), disease duration, MoCA, and MBI-C total score.

Among the 136 remaining PD participants, Val homozygous patients (GG) represented the majority of the cohort ($n = 90$). Because of the low number of homozygous Met/Met patients ($n = 4$), all Met carriers were pooled as one group. Forty-six patients were heterozygous or homozygous for the Met allele (GA, AA) with a frequency of 0.18, which was in accordance with Hardy-Weinberg equilibrium. The two groups had no significant differences in any of their demographic or clinical characteristics, ethnicity, and weekly exercise level (**Table 1**).

Association of Val66Met and MBI-C Score

Met carriers were twice as likely to be MBI positive than the Val carriers; 39% of Met carriers were MBI positive, whereas in the Val group only 20% of patients were MBI positive. The Met group had a significantly greater mean value for MBI-C total score than Val carriers (7.39 vs. 4.06, respectively). Two factors were included in the multiple logistic regression as independent variables in addition to the *BDNF* groups based on significant differences between the two groups in the Mann-Whitney *U* test; MoCA and UPDRS-III ($M\text{-}W\ U = 1230.5$, $p = 0.005$, and $M\text{-}W\ U = 2441.5$, $p = 0.002$, respectively). The logistic regression analysis revealed a significant contribution of the Met allele for the likelihood of being MBI positive ($OR = 2.88$, CI 95% = 1.22–6.78, $p = 0.02$) (**Table 2**).

Most Val Carriers had Either Zero or Very Low MBI-C Total Score (**Figure 1**).

MBI-C total and MoCA scores were negatively correlated [Pearson's $r = (134)\ 0.17$, $p = 0.04$]. Also, UPDRS-III and MBI-C total scores had a positive correlation [Pearson's $r = (134)\ 0.23$, $p = 0.007$]. These factors were included in the multiple linear regression model. The difference between the MBI-C total score between the two allelic groups was statistically significant when controlling for MoCA and UPDRS-III scores in the regression model [$r^2 = 0.13$, $Beta = 0.25$, $F\ (3, 135) = 6.36$, $p = 0.013$, Cohen's $f^2 = 0.15$]. A power analysis was conducted, which revealed that our samples size of 136 would yield a power of 0.99 assuming type-I error rate of 0.05.

Association results of *BDNF* alleles with MBI-C domain scores are shown in **Table 3**. Patients with the Met allele had significantly higher MBI-C scores for the mood/anxiety ($r^2 = 0.10$, $Beta = 0.24$, $p = 0.004$) and the psychosis domains ($r^2 = 0.12$, $Beta = 0.23$, $p = 0.006$) when controlling for MoCA and UPDRS-III scores (**Table 3**).

We performed an extra analysis in order to confirm that MBI classification results were derived from *BDNF* alleles and not driven by a few participants with marginally higher or lower MBI-C total score than the cutoff value (≥ 8). All participants with an MBI-C total score of 7 and 8 were excluded from the sample, and analysis was repeated. In total, 10 patients were removed; only one Met-carrier had the score of 7. In the Val group, three patients had the score of 7, and six patients had the score of 8 for MBI-C. Similar to the main analysis, two factors were included

TABLE 1 | Demographic and clinical characteristics of PD participants.

Characteristics mean, SD (Min–Max)	Val carriers (GG) $n = 90$	Met carriers (GA, AA) $n = 46$ (TT = 4)	*p*-value
Age	69.2, ±8.1 (47–86)	66.7, ±7.8 (48–79)	0.09[a]
Sex (female percentage)	36%	48%	0.20[b]
Education (year)	14.8, ±2.8 (8–21)	14.87, ±2.5 (9–19)	0.89[a]
LEDD	809.7, ±401.6 (200–1925)	822.3, ±373.3 (225–1675)	0.86[a]
Disease duration (year)	5.71, ±4.4 (0.2–16.1)	5.57, ±3.9 (0.2–18.2)	0.86[a]
UPDRS-III	18.2, ±10.0 (0–50)	20.3, ±11.2 (0–49)	0.27[a]
MoCA	25.3, ±4.0 (13–30)	25.9, ±3.2 (18–30)	0.42[a]
Handedness			
Right-handed	84%	87%	0.49 [c]
Left-handed	12%	6%	
Ambidextrous	2%	2%	
NA	1%	4%	
Ethnicity %			
Caucasian	86.7%	91.3%	
Other	7.8%	4.0%	
NA	5.5%	4.0%	0.7 [c]
Exercise (hours per week)	5.8 ± 4.8 (0–28) [d]	6.2 ± 4.5 (0–20)	0.8[c]

Outliers were identified based on three standard deviations away from the mean values of demographic and clinical characteristics; 10 participants were removed as outliers. Val, valine; Met, methionine; SD, standard deviation; Min, minimum; Max, maximum; LEDD, Levodopa equivalent daily dosage; UPDRS-III, unified Parkinson's disease rating scale part III; MoCA, montreal cognitive assessment.

[a] *Student t test.*

[b] *Fisher exact test (two-sided).*

[c] *Chi-square test (two-sided).*

[d] *Data were not available for two of the participants in the Val group.*

TABLE 2 | Multiple logistic regression analysis of *BDNF* p.Val66Met and MBI positive likelihood.

Covariate	Estimate	SE	Wald's chi square	*p*-value*	OR	95% CI
BDNF Met allele	1.06	0.44	5.82	0.02[a*]	2.88	1.22–6.78
MoCA	−0.14	0.06	5.96	0.02[a*]	0.87	0.78–0.97
UPDRS-III	0.05	0.02	4.68	0.03[a*]	1.05	1.00–1.09
Constant	0.10	1.60	0.004	0.95[a]	NA	NA

Val, valine; Met, methionine; MBI-C, mild behavioral impairment checklist; SE, standard error; OR, odds ratio; CI, confidence interval; NA, not applicable.

[a] *Multiple logistic regression model, N = 136, Nagelkerke pseudo $R^2 = 0.22$, Hosmer and Lemeshow goodness-of-fit test $p = 0.85$ ($df = 8$), correct cases overall percentage = 74.3%. *$p < 0.05$.*

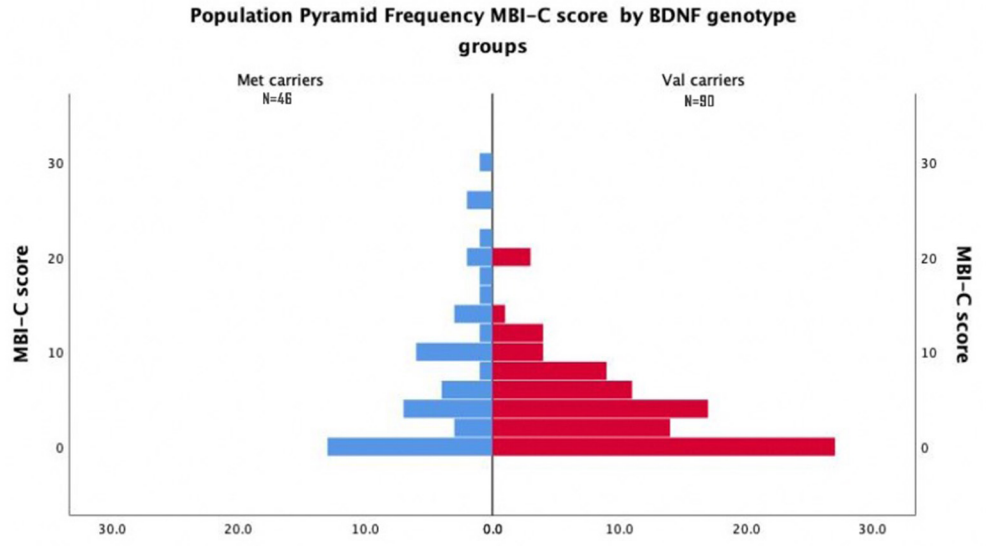

FIGURE 1 | Population pyramid frequency MBI-C score by BDNF genotype groups.

in the multiple logistic regression as independent variables in addition to the *BDNF* groups, based on their significant differences between the two groups in the Mann-Whitney *U* test; MoCA and UPDRS-III (*M-W U* = 1024.5, $p = 0.02$, and *M-W U* = 1914.5, $p = 0.007$, respectively). Results revealed a significant contribution of the Met allele for the likelihood of being MBI positive (*OR* = 4.38, CI 95% = 1.72–11.14, $p = 0.002$) (**Table 4**).

Each MBI-C domain score was compared between the two groups using Mann-Whitney *U* test (**Table 5**). The results were similar to the whole cohort analysis. Met carriers had significantly higher MBI-C total score than the Val group. Also, Met carriers had significantly higher score for the mood/anxiety domain when compared to the Val group and a trend for higher psychosis score (**Table 5**).

DISCUSSION

To our knowledge, the present study is the first to explore the association of the *BDNF* p.Val66Met SNP and MBI in patients with PD. Patients with at least one Met allele had significantly higher MBI-C total score and significantly higher scores in the emotional dysregulation and the abnormal thoughts/perception domains. Furthermore, PD patients with at least one Met allele had a significantly higher prevalence of MBI than patients in the Val group using MBI-C as the case ascertainment instrument. Our findings implicate the *BDNF* p.Val66Met SNP in the pathogenesis of MBI in PD patients and suggest this variant as a genetic risk factor for MBI in PD with a medium effect size (Cohen's $f^2 = 0.15$). These findings are consistent with the evidence in the AD, which imply that the Met allele can be a risk factor for incident cognitive decline and dementia in PD (4, 15, 21).

An increasing body of evidence suggests a link between the development of NPS and cognitive decline in different types of dementia (5, 22–24). Studies demonstrating that *BDNF* p.Val66Met SNP is found to be associated with both NPS and cognitive impairments in AD are consistent with a biological understanding of NPS (25–29), and previous evidence linking *BDNF* and NPS (8, 15). The presence of amyloid-β pathology in PD patients together with Lewy body pathology might be a possible explanation of similar NPS profile in AD and PD patients. However, it should be mentioned that different studies have teased apart how the psychiatric profile of PD and AD patients are different (30, 31).

Patients who experience NPS in the early stages of PD show an increased risk of cognitive decline (1, 5), which is consistent with the findings in non-PD dementia (24, 32–36). A recent study reported that PD patients with a variety of NPS, for example, depression, apathy, and hallucinations, displayed impairments in at least one of the main cognitive domains (executive function, language, memory, attention, and visuospatial) and in global cognition (5). These findings hint at the importance of early diagnosis of sustained NPS as markers of cognitive decline in PD patients, in order to identify patients at risk of incident cognitive decline and dementia.

A recent meta-analysis reported an association between the *BDNF* Met allele and cognitive impairments in PD for 532 patients and 802 controls ($p = 0.003$). However, the cognitive impairments were found to be more specific to the Caucasian populations (9). Several studies suggested that p.Val66Met SNP might have an association with depression, particularly geriatric depression (14, 37, 38). Nonetheless, this association might differ based on a variety of factors, e.g., the origin of the study population, sex, and the fundamental issue of whether depression is chronic, recurrent, or of later life onset as most depression rating scales do not differentiate (8, 33). The association of *BDNF*

TABLE 3 | MBI-C total and domain scores.

MBI-C scores Mean, SD (Min–Max)	Val carriers (GG) $N = 90$	Met carriers (GA, AA) $N = 46$	r^2, Beta (CI 95%)	p-value*
MBI-C total	4.06, ±4.50 (0–20)	7.39, ±8.05 (0–29)	0.13, 0.25 (1.17–5.35)	0.003**
Drive/motivation	1.10, ±1.72 (0–8)	1.43, ±2.02 (0–8)	0.06, 0.07 (−0.38 to 0.92)	0.41
Mood/anxiety	1.48, ±2.21 (0–13)	2.87, ±3.36 (0–12)	0.10, 0.24 (0.46–2.35)	0.004**
Impulse dyscontrol	0.79, ±1.43 (0–8)	1.15, ±2.80 (0–13)	0.03, 0.10 (−0.28 to 1.16)	0.23
Social inappropriateness	0.16, ±0.62 (0–4)	0.43, ±1.41 (0–7)	0.04, 0.14 (−0.07 to 0.63)	0.11
Abnormal thoughts/perception	0.53, ±1.09 (0–4)	1.50, ±2.54 (0–11)	0.12, 0.23 (0.26–1.48)	0.006**

MoCA and UPDRS scores were used in a multiple linear regression model. In total, 10 PD participants were identified as outliers and removed from the analysis.
Val, valine; Met, methionine; MBI-C, mild behavioral impairment checklist; SD, standard deviation; Min, minimum; Max, maximum; MoCA, montreal cognitive assessment; CI 95%, 95% confidence interval.
**Analysis was performed using multiple linear regression model including MoCA and UPDRS scores in the model. MoCA and MBI-C total scores were negatively correlated ($r_p = 0.17$, $p = 0.043$), while UPDRS and MBI-C total scores were positively correlated ($r_p = 0.23$, $p = 0.007$).*
***p-value was set to <0.01 to correct for multiple tests, Bonferroni correction.*

TABLE 4 | Multiple logistic regression analysis of *BDNF* p.Val66Met and MBI positive likelihood after removing participants with total MBI-C score of 7 and 8.

Covariate	Estimate	SE	Wald's chi square	p-value*	OR	95% CI
BDNF Met allele	1.48	0.48	9.54	0.002[a*]	4.37	1.71–11.14
MoCA	−0.14	0.06	4.84	0.03[a]	0.87	0.77–0.98
UPDRS-III	0.04	0.02	3.76	0.053[a]	1.04	1.00–1.09
Constant	−0.71	1.71	0.19	0.67[a]	NA	NA

Ten participants were removed, including only one Met carrier with the score of 7 (n = 126).
Val, valine; Met, methionine; MBI-C, mild behavioral impairment checklist; SE, standard error; OR, odds ratio; CI, confidence interval; NA, not applicable.
[a]Multiple logistic regression model, N = 126, Nagelkerke pseudo $R^2 = 0.24$, Hosmer and Lemeshow goodness-of-fit test $p = 0.31$ ($df = 8$), correct cases overall percentage = 77.8%.
**p-value was set to <0.01 corrected for multiple tests, Bonferroni correction.*

TABLE 5 | MBI-C total and domain scores after removing participants with total MBI-C score of 7 and 8.

MBI-C scores Mean, SD (Min–Max)	Val carriers (GG) $N = 81$	Met carriers (GA, AA) $N = 45$	p-value*
MBI-C total	3.65, ±4.56 (0–20)	7.40, ±8.14 (0–29)	0.03**
Drive/motivation	1.00, ±1.72 (0–8)	1.40, ±2.03 (0–8)	0.26
Mood/anxiety	1.35, ±2.21 (0–13)	2.84, ±3.40 (0–12)	0.008**
Impulse dyscontrol	0.64, ±1.34 (0–8)	1.18, ±2.83 (0–13)	0.87
Social inappropriateness	0.10, ±0.46 (0–3)	0.44, ±1.42 (0–7)	0.09
Abnormal thoughts/perception	0.57, ±1.13 (0–4)	1.53, ±2.56 (0–11)	0.02

Ten participants were removed, including only one Met carrier with the score of 7 (n = 126).
Val, valine; Met, methionine; MBI-C, mild behavioral impairment checklist; MoCA, montreal cognitive assessment; SD, standard deviation; Min, minimum; Max, maximum.
**All the analysis was done by Mann–Whitney U test because of the data normality.*
***p-value was set to <0.01 to correct for multiple tests, Bonferroni correction.*

Met allele and geriatric depression was investigated in a meta-analysis including 523 cases and 1,220 controls (age ≥ 60 years) (14). An association between the Met allele and an increased risk for late-life depression was reported ($p = 0.004$) (8). However, one study reported that the Val allele is associated with anxiety and depression using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) in 104 PD patients. Nevertheless, their population structure was greatly different than the one in our study. Seventeen percent of their participants had early onset PD with a positive family history (39), while in our sample there were only two participants (1.4%) with early onset PD and all of the participants had a confirmed diagnosis of idiopathic PD. Other reasons explaining the different results between the Cagni et al., (39) study and ours are linked to measurement differences of NPS. The BDI and BAI are self-report measures assessing the presence of mood and anxiety symptoms over the last 2 and 4 weeks, respectively. In contrast, the MBI-C measures later life emergent and persistent (for at least 6 months) NPS, identified by a reliable informant. These are quite different approaches to measurement of symptoms, with the MBI-C developed explicitly to capture later life emergent symptoms that either serve as risk factors for cognitive decline and dementia or more likely represent early manifestations of dementia.

Furthermore, BDNF involvement in depression/anxiety disorders has been confirmed through measuring peripheral BDNF levels as well (40, 41). A meta-analysis reported a strong evidence of an association between depression and a decrease in BDNF levels ($p < 6.8 \times 10^{-8}$) (40). These meta-analyses highlight the crucial role of BDNF in depressive disorders and specifically the impact of p.Val66Met SNP on geriatric depression. The Met allele exhibits LTD properties, reduces the neural plasticity, and can also substantially affect the docking of BDNF secretory vesicles into the cellular membrane and decrease its release into the synaptic cleft (7). The BDNF pro-domain with a Met residue is shown to have an independent function by induction of LTD, reducing spine density and neuronal plasticity. These molecular changes are linked to depression and anxiety disorders in both animal models and clinical studies (7, 42, 43). These findings are in agreement with our results that PD patients with at least one Met allele are more susceptible to impairments in the affective/mood dysregulation and abnormal thoughts/perception domains of MBI-C.

We found a strong association between abnormal thoughts/perception in PD patients and Met allele in our

cohort. Abnormal thoughts/perception represent psychotic symptoms, specifically hallucinations and delusions, which are associated with impairments in global cognition (1, 44). An abrupt visual memory function is suggested as a potential cause of visual hallucinations. Since BDNF plays a prominent role in the molecular mechanisms of memory in hippocampus, this indicates a possible role for BDNF in the development of such NPS (1, 7). Meta-analytical results of p.Val66Met SNP and psychotic disorders, for example, schizophrenia, are inconclusive at the moment (8, 45). However, the Met allele was found to be linked to higher susceptibility to hippocampal volume loss and deteriorated memory abilities in bipolar patients (46). These findings are in agreement with our results that PD patients with at least one Met allele are more susceptible to symptoms in the affective/mood dysregulation and abnormal thoughts/perception domains.

This study has some limitations that need to be considered. Although the findings of this study showed a fair level of robustness, the sample size is relatively small. The results of this study need to be replicated in a larger sample with an age-matched control group. Nevertheless, the *post hoc* power analysis indicates sufficient power in our cohort to detect the true effect of *BDNF* p.Val66Met. A full cognitive assessment of participants would benefit the exploration of p.Val66Met SNP impact on the aging brain, specifically in PD. Antidepressant medications was not considered. It has been shown that antidepressant medications can elevate peripheral BDNF and improve reversible NPS (40).

In conclusion, we observed an association between the *BDNF* p.Val66Met SNP and susceptibility for the development of late-life behavioral changes in PD patients. PD patients with at least one Met allele had a higher likelihood of MBI compared to non-carriers. Moreover, PD patients with one Met allele had a greater tendency to exhibit mood and anxiety symptoms as well as psychotic symptoms compared to the Val carriers. These findings indicate a potential role for the *BDNF* p.Val66Met SNP in late-life psychiatric impairment, subsequent cognitive decline, and dementia in PD patients.

DATA AVAILABILITY STATEMENT

The data that support the finding of this article are available from the corresponding author, upon request. Requests to access the datasets should be directed to Oury Monchi, Monchioury.monchi@ucalgary.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Conjoint Health Research Ethics Board (REB14-2463) at the University of Calgary. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MR: study design, data analysis, interpretation, manuscript writing, and revision. JR, KM, MK, ZJ, IK, TH, JC, EL, DM, JS, ZG-O, and GP: data collection. ZI: study design, analysis, and manuscript revision. OM: study design, data analysis, supervision, and manuscript revision. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by a project grant from the Canadian Institutes of Health Research (CIHR) (PJT-166123), the Tourmaline Oil Chair in Parkinson's Disease, and the Canada Research Chair in non-motor symptoms of Parkinson's disease to OM. MR received a scholarship from the Parkinson Association of Alberta.

ACKNOWLEDGMENTS

The authors would like to thank all the PD patients and their families who were willing to participate and provide information for this study.

REFERENCES

1. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. *Neurobiol Dis.* (2012) 46:581–9. doi: 10.1016/j.nbd.2011.12.041
2. Weintraub D, Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Siderowf A, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. *Mov Disord.* (2015) 30:919–27. doi: 10.1002/mds.26170
3. Martinez-Martin P, Rodriguez-Blazqueza C, JoãoForjaz M, Frades-Payo B, Agüera-Ortizc L, Weintraub D, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. *Parkinsonims Relat Disord.* (2015) 21:629–34. doi: 10.1016/j.parkreldis.2015.03.024
4. Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement.* (2016) 12:195–202. doi: 10.1016/j.jalz.2015.05.017
5. Yoon E, Ismail Z, Hanganu A, Kibreab M, Hammer T, Cheetham J, et al. Mild behavioral impairment is linked to worse cognition and brain atrophy in Parkinson's disease. *Neurology.* (2019) 93:e766–77. doi: 10.1212/WNL.0000000000007968
6. Lang S, Yoon EJ, Kibreab M, Kathol I, Cheetham J, Hammer T, et al. Mild behavioral impairment in Parkinson's disease is associated with altered corticostriatal connectivity. *NeuroImage Clin.* (2020) 26:102252. doi: 10.1016/j.nicl.2020.102252
7. Hempstead BL. Brain-derived neurotrophic factro: three ligands, many actions. *Trans Am Clin Climatol Assoc.* (2015) 126:9–19.
8. Tsai SJ. Critical issues in BDNF Val66Met genetic studies of neuropsychiatric disorders. *Front Mol Neurosci.* (2018) 11:156. doi: 10.3389/fnmol.2018.00156
9. Wang Q, Liu J, Guo Y, Dong G, Zou W, Chen Z. Association between BDNF G196A (Val66Met) polymorphism and cognitive impairment in patients with

Parkinson's disease: a meta-analysis. *Braz J Med Biol Res.* (2019) 52:e8443. doi: 10.1590/1414-431x20198443
10. Mogi M, Togaria A, Kondo T, Mizuno Y, Komure O, Kuno S, et al. Brain-derived growth factor and nerve growth factor concentrations are decreased in the substantia nigra in Parkinson's disease. *Neurosci Lett.* (1999) 270:45–8.doi: 10.1016/S0304-3940(99)00463-2
11. Altmann V, Schumacher-Schuh AF, Rieck M, Callegari-Jacques SM, Rieder CR, Hutz MH. Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. *Neurosci Lett.* (2016) 615:88–91. doi: 10.1016/j.neulet.2016.01.030
12. Kowianski P, Lietzau G, Czuba E, Waskow M, Steliga A, Morys J. BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity. *Cell Mol Neurobiol.* (2018) 38:579–93. doi: 10.1007/s10571-017-0510-4
13. Hempstead BL. Brain-derived neurotrophic factro: three ligands, many actions. Transactions of the American Clinical and Climatological Association. (2015) 126:9–19.
14. Pei Y, Smith AK, Wang Y, Pan Y, Yang J, Chen Q, et al. The brain-derived neurotrophic-factor (BDNF) val66met polymorphism is associated with geriatric depression: a meta-analysis. *Am J Med Genet B Neuropsychiatr Genet.* (2012) 159B:560–6. doi: 10.1002/ajmg.b.32062
15. Bessi V, Mazzeo S, Bagnoli S, Padiglioni S, Carraro M, Piaceri I, et al. The implication of BDNF Val66Met polymorphism in progression from subjective cognitive decline to mild cognitive impairment and Alzheimer's disease: a 9-year follow-up study. *Eur Arch Psychiatry Clin Neurosci.* (2019) 270:471–482. doi: 10.1007/s00406-019-01069-y
16. Ismail Z, Aguera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, et al. The mild behavioral impairment checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. *J Alzheimers Dis.* (2017) 56:929–38. doi: 10.3233/JAD-160979
17. Creese B, Griffiths A, Brooker H, Corbett A, Aarsland D, Ballard C, et al. Profile of mild behavioral impairment and factor structure of the mild behavioral impairment checklist in cognitively normal older adults. *Int Psychogeriatr.* (2020) 32:705–17. doi: 10.1017/S1041610219001200
18. Mallo SC, Ismail Z, Pereiro AX, Facal D, Lojo-Seoane C, al. e. Assessing mild behavioral impairment with the mild behavioral impairment checklist in people with subjective cognitive decline. *Int Psychogeriatr.* (2019) 31:231–9. doi: 10.1017/S1041610218000698
19. Mallo SC, Ismail Z, Pereiro AX, Facal D, Lojo-Seoane C, Campos-Magdaleno M, et al. Assessing mild behavioral impairment in people with subjective cognitive complaints (SCCS) with the mild behavioral impairment checklist (MBI-C): a pilot study. *J Alzheimer Assoc.* (2017) 13:364–5. doi: 10.1016/j.jalz.2017.06.312
20. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res.* (2007) 39:175–91. doi: 10.3758/BF03193146
21. VanDam D, Vermeiren Y, Dekker AD, Naudé PJW, DeDeyn PP. Neuropsychiatric disturbances in alzheimer's disease-what have we learned from neuropathological studies? *Curr Alzheimer Res.* (2016) 13:1145–64. doi: 10.2174/1567205013666160502123607
22. Chiu PY, Tsai CT, Chen PK, Chen WJ, Lai TJ. Neuropsychiatric symptoms in parkinson's disease dementia are more similar to alzheimer's disease than dementia with lewy bodies: a case-control study. *PLoS ONE.* (2016) 11:e0153989. doi: 10.1371/journal.pone.0153989
23. López-Pousa S, Vilalta-Franch J, Garre-Olmo J, Pons S, Cucurella MG. Characterisation and prevalence of the psychological and behavioural symptoms in patients with dementia. *Europe PMC.* (2007) 45:683–8. doi: 10.33588/rn.4511.2007535
24. Taragano FE, Allegri RF, Heisecke SL, Martelli MI, Feldman ML, Sánchez V, et al. Risk of conversion to dementia in a mild behavioral impairment group compared to a psychiatric group and to a mild cognitive impairment group. *J Alzheimer's Dis.* (2018) 62:227–38. doi: 10.3233/JAD-170632
25. Naude J, Gill S, Hu S, McGirr A, Forkert N, Monchi O, et al. Plasma neurofilament light: a marker of cognitive decline in mild behavioural impairment. *J Alzheimes Dis.* (2020) 76:1017–27. doi: 10.3233/JAD-200011
26. Andrews SJ, Ismail Z, Anstey KJ, Mortby ME. Association of Alzheimer's genetic loci with mild behavioral impairment. *Am J Med Genet B Neuropsychiatr Genet.* (2018) 177:727–35. doi: 10.1002/ajmg.b.32684
27. Gill S, Mouches P, Hu S, Rajashekar D, MacMaster FP, Smith EE, et al. Using machine learning to predict dementia from neuropsychiatric symptom and neuroimaging data. *J Alzheimes Dis.* (2020) 75:277–88. doi: 10.3233/JAD-191169
28. Creese B, Brooker H, Aarsland D, Corbett A, Ballard C, Ismail Z. Genetic risk for Alzheimer disease, cognition and Mild Behavioral Impairment in healthy older adults. *medRxiv. [Preprint].* doi: 10.1101/2020.05.13.20100800
29. Lussier FZ, Pascoal TA, Chamoun M, Therriault J, Tissot C, Savard M, et al. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimers Dement.* (2020) 16:192–9. doi: 10.1002/alz.12007
30. Aarsland D, Cummings JL, Larsen JP. Neuropsychiatric difference between Parkinson's disease with dementia and Alzheimer's disease. *Int J Geriatr Psychiatry.* (2001) 16:184–91. doi: 10.1002/1099-1166(200102)16:2<184::aid-gps304>3.0.co;2-k
31. Noe E, Marder K, Bell KL, D.M. J, Manly JJ, Yaakov Stern Y. Comparison of dementia with lewy bodies to alzheimer's disease and parkinson's disease with dementia. *Mov Disord.* (2004) 19:60–7. doi: 10.1002/mds.10633
32. Matsuoka T, Ismail Z, Narumoto J. Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. journal of alzheimer's disease. (2019) 70:505–13. doi: 10.3233/JAD-190278
33. Ismail Z, Gatchel J, Bateman DR, Barcelos-Ferreira R, Chantillon M, Jaeger J, et al. Affective and emotional dysregulation as pre-dementia risk markers: exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria. *Int Psychogeriatr.* (2018) 30:185–96. doi: 10.1017/S1041610217001880
34. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild behavioral impairment and subjective cognitive decline predict mild cognitive impairment. *medRxiv. [Preprint].* (2020). doi: 10.1101/2020.05.24.20112284
35. Creese B, Brooker H, Ismail Z, Wesnes KA, Hampshire A, Khan Z, et al. Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults. *Am J Geriatr Psychiatry.* (2019) 27:823–34. doi: 10.1016/j.jagp.2019.01.215
36. Mortby ME, Black SE, Gauthier S, Miller DS, Porsteinsson A, Smith EE, et al. Dementia clinical trial implications of mild behavioral impairment. *Int Psychogeriatr.* (2018) 30:171–5. doi: 10.1017/S1041610218000042
37. Taylor WD, Züchner S, McQuoid DR, Steffens DC, Speer MC, Krishnan KRR. Allelic differences in the brain-derived neurotrophic factor Val66Met polymorphism in late-life depression. *Am J Geriatr Psychiatry.* (2007) 15:850–7. doi: 10.1097/JGP.0b013e318050c9d5
38. Hwang JP, Tsai SJ, Hong CJ, Yang CH, Lirng JF, Yang YM. The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. *Neurobiol Aging.* (2006) 27):1834–7. doi: 10.1016/j.neurobiolaging.2005.10.013
39. Cagni FC, Campelo C, Coimbra DG, Barbosa MR, Junior LGO, Neto ABS, et al. Association of BDNF Val66MET polymorphism with Parkinson's disease and depression and anxiety symptoms. *J Neuropsychiatry Clin Neurosci.* (2017) 29:142–7. doi: 10.1176/appi.neuropsych.16040062
40. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry.* (2008) 64:527–32. doi: 10.1016/j.biopsych.2008.05.005
41. Suliman S, Hemmings, S. M., Seedat, S. Brain-derived neurotrophic factor (BDNF) protein levels in anxiety disorders: systematic review and meta-regression analysis. *Front Integr Neurosci.* (2013) 7:55. doi: 10.3389/fnint.2013.00055
42. De Vincenti AP, Rios AS, Paratcha G, Ledda F. Mechanisms That modulate and diversify BDNF functions: implications for hippocampal synaptic plasticity. *Front Cell Neurosci.* (2019) 13:135. doi: 10.3389/fncel.2019.00135

43. Rex CS, Lauterborn JC, Lin CY, Kramar EA, Rogers GA, Gall CM, et al. Restoration of long-term potentiation in middle-aged hippocampus after induction of brain-derived neurotrophic factor. *J Neurophysiol.* (2006) 96:677–85. doi: 10.1152/jn.00336.2006
44. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. *Mov Disord.* (2009) 24:2175–86. doi: 10.1002/mds.22589
45. Goren JL. Brain-derived neurotrophic factor and schizophrenia. *Ment Health Clin.* (2016) 6:285–8. doi: 10.9740/mhc.2016.11.285
46. Cao B, Bauer IE, Sharma AN, Mwangi B, Frazier T, Lavagnino L, et al. Reduced hippocampus volume and memory performance in bipolar disorder patients carrying the BDNF val66met met allele. *J Affect Disord.* (2016) 198:198–205. doi: 10.1016/j.jad.2016.03.044

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 25 January 2021
doi: 10.3389/fneur.2020.603582

Hypomimia in Parkinson's Disease: What Is It Telling Us?

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Introduction: Amimia is one of the most typical features of Parkinson's disease (PD). However, its significance and correlation with motor and nonmotor symptoms is unknown. The aim of this study is to evaluate the association between amimia and motor and nonmotor symptoms, including cognitive status, depression, and quality of life in PD patients. We also tested the blink rate as a potential tool for objectively measuring upper facial bradykinesia.

Methods: We prospectively studied amimia in PD patients. Clinical evaluation was performed using the Unified Parkinson's Disease Rating Scale (UPDRS) and timed tests. Cognitive status, depression, and quality of life were assessed using the Parkinson's Disease Cognitive Rating Scale (PD-CRS), the 16-Item Quick Inventory of Depressive Symptomatology (QIDS-SR16), and the PDQ-39, respectively. Amimia was clinically evaluated according to item 19 of UPDRS III. Finally, we studied upper facial amimia by measuring resting blink frequency and blink rate during spontaneous conversation.

Results: We included 75 patients. Amimia (item 19 UPDRS III) correlated with motor and total UPDRS (r: 0.529 and 0.551 Spearman), and its rigidity, distal bradykinesia, and motor axial subscores (r: 0.472; r: 0.252, and r: 0.508, respectively); Hoehn and Yahr scale (r: 0.392), timed tests, gait freezing, cognitive status (r: 0.29), and quality of life (r: 0.268) correlated with amimia. Blinking frequency correlated with amimia (measured with item 19 UPDRS), motor and total UPDRS.

Conclusion: Amimia correlates with motor (especially axial symptoms) and cognitive situations in PD. Amimia could be a useful global marker of overall disease severity, including cognitive decline.

Keywords: facial bradykinesia, Parkinson's disease (PD), hypomimia, amimia, motor symptom, non-motor symptom

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
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Jaime Kulisevsky, Hospital de la Santa Creu i Sant Pau, Spain

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *07 September 2020*
Accepted: *01 December 2020*
Published: *25 January 2021*

Citation:
Maycas-Cepeda T, López-Ruiz P, Feliz-Feliz C, Gómez-Vicente L, García-Cobos R, Arroyo R and García-Ruiz PJ (2021) Hypomimia in Parkinson's Disease: What Is It Telling Us? Front. Neurol. 11:603582. doi: 10.3389/fneur.2020.603582

INTRODUCTION

Hypomimia, amimia, facial bradykinesia, or reduced facial expression (amimia for short) is present in several conditions, including dementia and depression (1–4). Amimia is one of the most classical features of Parkinson's disease (PD) (1, 2, 4–8). It has been well recognized since classic texts (9, 10). In 1860, Charcot described the characteristics of "masked face" in PD (11), and some years later, Wilson gave a vivid description of the parkinsonian facial expression: "The parkinsonian face is

a mask," "the patient has a reptilian stare," and "little or no play of expression animates his/her countenance." Wilson used the term *amimia* to include this typical facial signature of PD (10).

Cattaneo et al. summarized some interesting aspects of human facial expression (12). Facial movements differ from limb movements in critical characteristics, including the lack of joints, visual feedback, the conventional proprioceptive feedback system (13), and the absence of the characteristic triphasic EMG pattern seen in limb movements (14, 15). In addition, there is a dissociation between voluntary and emotional facial movements, critically influenced by the amygdala and the limbic system (12).

More recently, Bologna and Marsili summarized the main characteristics and distinctive physiological features of facial bradykinesia in PD (7, 8). Amimia is a peculiar parkinsonian sign: in contrast to limb bradykinesia, amimia is rarely asymmetric (16–18), and it may be present in very early stages of the disease, being evident often years before the clinical diagnosis of PD (19, 20).

Nevertheless, despite being a well-known clinical sign of PD, the relationship between amimia and other motor and nonmotor symptoms of PD is largely unknown.

The main objective of this study is to evaluate the association between amimia and motor and nonmotor symptoms, including cognitive status, depression, and quality of life in PD patients. We also study whether amimia correlates with motor complications, such as freezing of gait and dyskinesias. In addition, we tested the blink rate as a potential tool for objectively measuring upper facial bradykinesia.

METHOD

Patients were recruited between December 2016 and June 2018 from the outpatient Movement Disorders Units of Hospital Universitario Quironsalud Madrid and Hospital Fundación Jiménez Díaz (Madrid).

The diagnosis of PD was made according to the UK Brain Bank criteria definition (21). Patients with features consistent with atypical parkinsonism were excluded from the study (such as early and severe loss of postural reflexes, supranuclear gaze abnormalities, dementia during the first 2 years, or significant autonomic symptoms). Patients were also excluded if they suffered from any clinical condition that could potentially affect gait, mobility, or facial movements (including facial paralysis or hemifacial spasm, among others). The clinical evaluation of amimia was based on item 19 of UPDRS III. We also studied upper facial bradykinesia by measuring blinking frequency (the blinking rate was defined as the number of blinks per minute) both resting and during spontaneous conversation. Facial evaluations were recorded on video in order to calculate the blinking rate.

The PD clinical assessment was performed using the Schwab and England Activities of Daily Living Scale, the Hoehn and Yahr Scale, the Unified Parkinson's Disease Rating Scale (UPDRS) (22), and the four timed tests of the CAPIT protocol (23, 24) [including pronation–supination (PS), finger dexterity (FD), movement between 2 points (MTP), and the walking test (WT)]. Tremor score was calculated as the sum of items 20 (tremor at rest) and 21 (action or postural tremor) of UPDRS III; rigidity score was the sum of item 22 of UPDRS III (rigidity of neck and upper and lower extremities); distal bradykinesia score was the sum of items 23 (finger tapping), 24 (hand movements), 25 (rapid alternating movements), and 26 (leg agility); and axial motor score was calculated as the sum of items 18 (speech), 27 (arising from chair), 28 (posture), 29 (gait), and 30 (postural stability) of UPDRS III (25).

Patients were classified according to their main symptom into akinetic-rigid PD, tremor-dominant PD, or mixed PD.

Cognitive and psychiatric aspects of PD were assessed using the Disease-Cognitive Rating Scale (PD-CRS), the 16-Item Quick Inventory of Depressive Symptomatology (QIDS-SR16), and the Parkinson's Disease Questionnaire (PDQ-39).

All patients were evaluated in the mid-morning, after taking their regular medication, in a stable ON condition in order to

TABLE 1 | Demographic and descriptive results.

	Total ($n = 75$)
Age, mean ± SD	70.7 ± 9.6
Sex	
Female, *n* (%)	29 (38.7)
Male, *n* (%)	46 (61.3)
Motor subtype	
Akinetic-dominant, *n* (%)	35 (46.7)
Tremor-dominant, *n* (%)	31 (41.3)
Mixed, *n* (%)	9 (12.0)
LED, median [IQR]	375.0 [520.0]
H and Y, median [IQR]	2.0 [1.5]
SE, median [IQR]	90.0 [20.0]
MDS-UPDRS ON: UPDRS Total, median [IQR]	28.0 [28.0]
MDS-UPDRS ON: UPDRS I, median [IQR]	2.0 [3.0]
MDS-UPDRS ON: UPDRS II, median [IQR]	6.0 [10.0]
MDS-UPDRS ON: UPDRS III, median [IQR]	20.0 [13.0]
UPDRS-19, median [IQR]	2.0 [1.0]
Timed test: PS, median [IQR]	18.6 [28.1]
Timed test: FD, median [IQR]	19.2 [60.9]
Timed test: MTP, median [IQR]	15.7 [28.3]
Blink rate: Resting, median [IQR]	11.5 [17.0]
Blink rate: Conversation, median [IQR]	16.0 [19.0]
PD-CRS: Total, mean ± SD	76.4 ± 24.2
PD-CRS: Cortical, median [IQR]	28.0 [4.0]
PD-CRS: Subcortical, mean ± SD	50.2 ± 21.0
QUIDS-16, median [IQR]	6.0 [7.3]
PD duration, median [IQR]	5 [7]
PDQ-39, median [IQR]	19.2 [27.6]

PD, Parkinson's Disease; LED:L-dopa equivalent dose; H and Y, Hoehn and Yahr scale; SE, Schwad and England Activities of Daily Living Scale; UPDRS, the Unified Parkinson's Disease Rating Scale; PS, pronation–supination; FD, finger dexterity; MPT, movement between 2 points; WT, walking test; UPDRS 19, Item 19 of the UPDRS III; PD-CRS, Disease Cognitive Rating Scale; QUIDS-16, the 16-Item Quick Inventory of Depressive Symptomatology; PDQ-39, the Parkinson's Disease Questionnaire.

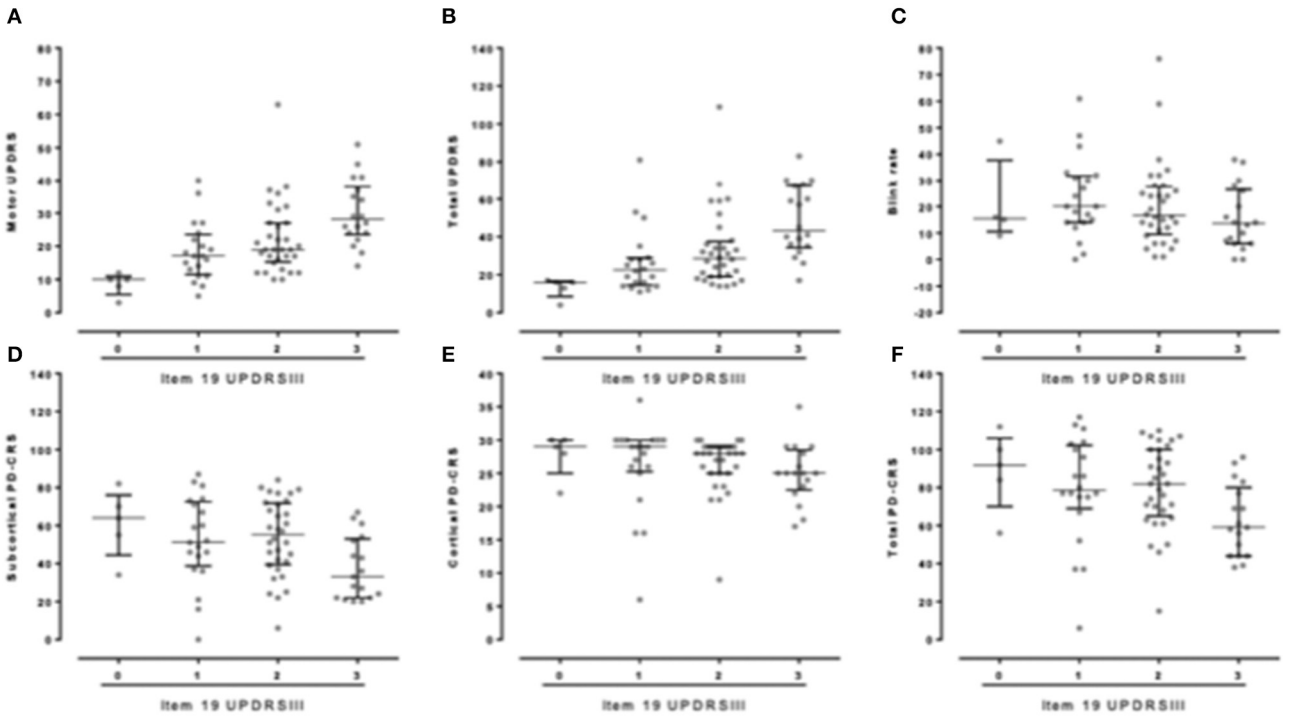

FIGURE 1 | (A,B) Correlation between facial bradykinesia (item 19UPDRS III) and UPDRS (**A**. motor-UPDRS; **B**. Total UPDRS). **(C)** Correlation between facial bradykinesia (item 19UPDRS III) and blink rate at rest. **(D–F)** Correlation between facial bradykinesia (item 19UDPRS III) and cognitive test. **(D)** PD-CRS subcortical score; **(E)** PD-CRS cortical score; **(F)** Total PD-CRS.

assess the clinical condition of our patients as similarly as possible to everyday clinical practice.

The present study was performed in accordance with the ethical standards of the WMA Declaration of Helsinki and was approved by the Local Ethics Committee. Written informed consent was obtained from all participants.

Statistical Analyses

Qualitative variables were expressed as absolute (n) and relative (%) frequencies. The Shapiro-Wilk test was used to evaluate the normality of the quantitative variables. Mean values ± standard deviation (SD) are given for normal distributions; for non-normal distributions, the data are reported as medians with interquartile range (IQR).

The correlation between amimia (item 19 UPDRS III) and the continuous variables was performed using the Spearman correlation. For quantitative variables, Student's t or Mann-Whitney U tests (depending on the normality distribution) were applied to analyze differences between dementia and nondementia group values; chi-square or Fisher's exact test were used for qualitative variables. Finally, univariable linear regression analyses were performed between amimia and age, disease duration, UPDRS and its subscores, rigidity, distal bradykinesia, motor axial, freezing, PD-CRS, PDQ39, and blink rate. Multivariable analyses were performed with the variables that resulted in significant association.

Data analysis was performed with the IBM-SPSS statistical software program, version 21.0 (IBM Inc., Chicago, IL, USA). The significance level was set as $p < 0.05$.

RESULTS

We included 75 PD patients. Demographic and descriptive results are shown in **Table 1**.

1) Amimia (measured by item 19 UPDRS III) correlated with clinical scales including total ($p < 0.01$, r: 0.551) and motor UPDRS ($p < 0.01$, r: 0.529) (**Figures 1A,B**). Amimia correlated with rigidity score ($p < 0.001$, r: 0.472), distal bradykinesia score (p: 0.029, r: 0.252), and axial motor score ($p < 0.001$, r: 0.508). In contrast, amimia did not correlate with tremor score.

2) Amimia scores also correlated with bradykinesia measured by timed tests: PS ($p < 0.05$, r: 0.257), FD ($p < 0.01$, r: 0.395), and MTP ($p < 0.01$, r: 0.437) (**Table 2**).

3) Concerning nonmotor symptoms, amimia correlated with cognitive performance, including PD-CRS total, cortical, and subcortical ($p = 0.010$, r:−0.29; $p = 0.019$, r:−0.27; and $p = 0.011$, r:−0.29) (**Figures 1D–F**). Cognitive decline (defined as PD-CRS $\leq$ 64) (26) also correlated with amimia ($p < 0.05$; $r = -0.282$). The distribution score for amimia was clearly different between those patients with dementia compared with those without dementia ($p < 0.05$) (**Table 3**). In contrast, no correlation was found between amimia and depression scores.

4) Regarding motor complications, amimia correlated with the frequency of gait freezing episodes ($p < 0.05$, r: 0.282) and with the presence of dyskinesias ($p < 0.01$, r:−0.391) (**Table 2**).

5) We also found correlation between amimia and PDQ-39 scores ($p < 0.05$, r: 0.268) and disease duration ($p < 0.01$, r: 0.378) (**Table 2**).

6) Upper facial bradykinesia measured by resting blink frequency correlated with total UPDRS ($p < 0.01$, r:−0.30), motor UPDRS ($p < 0.05$, r:−0.246), and cortical PD-CRS ($p < 0.05$; r:−0.262) but not with the rest of the studied variables. Amimia measured by item 19 UPDRS III correlated with resting blink rate ($p < 0.01$; r:−0.36) (**Figure 1C**), but not with blink frequency while participating in spontaneous conversation ($p > 0.05$, r: −0.198).

7) Finally, we carried out a multivariable regression analyses taking into account age, UPDRS III, rigidity, axial and distal bradykinesia subscores, freezing of gait, and cognition. Amimia was the dependent variable. Only distal bradykinesia (ß−0.500; 95% CI−0.178-0.08, $p < 0.05$) and UPDRS III scores (ß 1.155; 95% CI−0.019-0.155, $p < 0.05$) were significant.

TABLE 2 | Main correlation results using Spearman test.

	Mimic (Item 19 UPDRS III)
Total UPDRS	$r = 0.551$; $p < 0.01$
UPDRS III	$r = 0.529$; $p < 0.01$
Rigidity score	$r = 0.472$; $p < 0.01$
Distal bradykinesia score	$r = 0.252$; p = 0.029
Motor axial score	$r = 0.448$; $p < 0.01$
Timed test	
PS	$r = 0,257$; $p < 0.05$
MTP	$r = 0.437$; $p < 0.01$
FD	$r = 0.395$; $p < 0.01$
Freezing episodes	$r = 0.282$; $p = 0.016$
PD- CRS	
Total	$r = -0.290$; $p = 0.010$
Cortical	$r = -0.270$; $p = 0.019$
Subcortical	$r = -0.290$; $p = 0.011$
PDQ-39	$r = 0.268$; $p = 0.020$
Dyskinesia	$r = -0.391$; $p < 0.01$

UPDRS, the Unified Parkinson's Disease Rating Scale. PS, pronation–supination; FD, finger dexterity; MPT, movement between 2 points; PD-CRS, Disease Cognitive Rating Scale; PDQ-39, the Parkinson's Disease Questionnaire.

TABLE 3 | Comparison between patients with and without dementia.

Item19 UPDRS III	Dementia group ($n = 23$)	Nondementia group ($n = 51$)	*P*-value
Value, mean ± SD	2.2 ± 0.9	1.7 ± 0.8	0.016
Categorical value:			0.044
0	1 (4.3)	4 (7.8)	
1	4 (17.4)	16 (31.4)	
2	8 (34.8)	24 (47.1)	
3	10 (43.5)	7 (13.7)	

In the first line are results of the Mann-Whitney U test (p: 0.016). The rest of the lines show the values for the chi-squared study for all the values of the UPDRS III item 19 ($p < 0.05$).

DISCUSSION

The current study was designed to explore the relationship between amimia and other motor and nonmotor symptoms of PD and to evaluate the clinical impression that patients with higher amimia scores have a more severe illness, not only regarding motor symptoms, but also in terms of cognitive status.

Although loss of facial expression is a recognized parkinsonian sign that is well described by classic authors (9–11), its significance and correlation with other PD symptoms is poorly understood. Amimia is one of the most distinctive clinical features in PD and may be one of the earliest symptoms (19). However, in many cases, early amimia might be misinterpreted as lack of interest or depression by attending physicians and families (27). Bologna et al. summarizes several distinctive characteristics of facial expression in PD (7). It is worth recalling that rigidity and tremors scarcely affect the face in PD (15), amimia is rarely asymmetric (7, 16–18), and its response to levodopa and DBS is highly variable (14). For all these reasons, amimia is a peculiar PD symptom, much more laborious to assess than the rest of the PD signs. Furthermore, at this moment, the lack of objective tools to measure amimia makes its evaluation even more difficult.

Our sample shows the usual characteristics of a typical PD population sample (28). In our series, amimia correlated with most motor and nonmotor symptoms. It correlated with motor and total UPDRS scores, and in addition, amimia correlated with timed tests, an objective measure of bradykinesia. Globally, amimia is an indicator of motor impairment as a whole, including axial symptoms and freezing of gait. These results are in line with those from a very recent article published by Ricciardi et al. in which patients with hypomimia had a more severe burden of motor symptoms and higher axial scores (29).

A remarkable result of our study is the possible relationship between amimia and other axial symptoms, such as gait freezing. The results of Riccardi et al. support our findings, describing that patients with amimia have more severe axial symptoms (29). Previous reports also show that patients with freezing of gait often present a nontremor phenotype and have a worse cognitive status (30–32), but to the best of our knowledge, this is the first time that the relationship between amimia and gait freezing has been directly studied.

In our study, amimia also correlated with cognitive status measured by standard scales. Indeed, patients with dementia had greater amimia scores compared with the nondementia PD group. Previous studies report contradictory results about the relationship between amimia and dementia. Recently, Ricciardi et al. find that facial expression is not related to cognitive impairment (29) although Gasca-Salas suggests that *de novo* PD patients with mild cognitive impairment have more severe hypomimia than patients with normal performance in cognition

tests (33). The cohort of Riccardi is younger than ours, which could explain, at least in part, the discrepancies in our results (70.7 ± 9.6 in our series vs. 60.3 ± 6.75) (29). According to our findings, the relationship between amimia and cognitive impairment is supported by previous reports in which patients with Lewy Body Disease exhibited more facial bradykinesia compared with PD patients (2, 34–36).

Amimia can be misdiagnosed as depression, a nonmotor symptom of PD (4); however, the relationship between amimia and depression is unclear. Although some studies associate amimia with poor facial emotion recognition and impaired simulated facial expressions (7, 36–38), we find no correlation between depression and facial bradykinesia as previously described (4, 29).

Finally, we aimed to develop an objective method for assessing amimia. In contrast to limb bradykinesia, facial bradykinesia is difficult to estimate based on clinical assessment (14). In order to find a complementary and more objective score than item 19 of UPDRS III, we studied upper facial bradykinesia by measuring both spontaneous resting blink rate and that during conversation. Unfortunately, blink rate correlated poorly with other symptoms of PD. However, resting blink frequency correlated with some motor scores (UPDRS III) as reported by Agostini and Korosec (39, 40), but it had a poor correlation with nonmotor symptoms. Additionally, spontaneous speaking blink frequency was a poor predictor of facial bradykinesia. Although most patients with PD hypomimia have a decrease in blinking frequency, it is suggested that some patients with advanced PD may have an increased spontaneous blink frequency as a form of dystonia (41). Our results suggest that the assessment of amimia should evaluate facial motility as a whole and not upper face motility alone.

Limitations of the present study include the difficulty in making an objective evaluation of amimia as item 19 UPDRS is the only clinically validated tool. At the same time, we did not evaluate the effect of dopa therapy because we assessed patients in the ON situation in order to have a sample as representative as possible of everyday patients. In addition, patients with different levels of severity were included, and for some of them, it would have been difficult to come to our outpatient clinic in an OFF condition.

On the other hand, this study was conducted prospectively on a wide spectrum of idiopathic PD patients with different cognitive and functional situations. We used a comprehensive clinical and cognitive study, including objective timed-test assessment of bradykinesia.

In conclusion, our results suggest that amimia is a potential predictor of global PD severity, including axial symptoms and cognitive decline. Nevertheless, an objective measurement of amimia that is more accurate than UPDRD19 is needed.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at (42).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comite De Ética De La Investigacion De La Fundacion Jimenez Diaz. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TM-C and PG-R were involved in the study concept and design, the acquisition, analysis, and interpretation of study data, and in the critical revision of the manuscript for important intellectual content. PL-R collaborated in the acquisition of study data and in the critical revision of the manuscript for important intellectual content. CF-F, LG-V, and RG-C worked in the acquisition of data. RA participated in the study design and in the critical revision of the manuscript for important intellectual content. All authors have approved the final version for submission.

ACKNOWLEDGMENTS

The authors thank Donna Leick for the English revision and Israel John Thuissard Vasallo for the statistical analyses.

REFERENCES

1. Ellis RJ, Caligiuri M, Galasko D, Thal LJ. Extrapyramidal motor signs in clinically diagnosed Alzheimer disease. *Alzheimer Dis Assoc Disord.* (1996) 10:103–14. doi: 10.1097/00002093-199601020-00008
2. Aarsland D, Ballard C, McKeith I, Perry RH, Larsen JP. Comparison of extrapyramidal signs in dementia with lewy bodies and Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* (2001) 13:374–9. doi: 10.1176/jnp.13.3.374
3. Mergl R, Mavrogiorgou P, Hegerl U, Juckel G. Kinematical analysis of emotionally induced facial expressions: a novel tool to investigate hypomimia in patients suffering from depression. *J Neurol Neurosurg Psychiatry.* (2005) 76:138–40. doi: 10.1136/jnnp.2004.037127
4. Katsikitis M, Pilowsky I. A controlled quantitative study of facial expression in Parkinson's disease and depression. *J Nerv Ment Dis.* (1991) 179:683–8. doi: 10.1097/00005053-199111000-00006
5. Hunker CJ, Abbs JH, Barlow SM. The relationship between parkinsonian rigidity and hypokinesia in the orofacial system: a quantitative analysis. *Neurology.* (1982) 32:749–54. doi: 10.1212/wnl.32.7.749
6. Katsikitis M, Pilowsky I. A study of facial expression in Parkinson's disease using a novel microcomputer-based method. *J Neurol Neurosurg Psychiatry.* (1988) 51:362–6. doi: 10.1136/jnnp.51.3.362
7. Bologna M, Fabbrini G, Marsili L, Defazio G, Thompson PD, Berardelli A. Facial bradykinesia. *J Neurol Neurosurg Psychiatry.* (2013) 84:681–5. doi: 10.1136/jnnp-2012-303993
8. Marsili L, Agostino R, Bologna M, Belvisi D, Palma A, Fabbrini G, et al. Bradykinesia of posed smiling and voluntary movement of the lower

face in Parkinson's disease. *Parkinsonism Relat Disord.* (2014) 20:370–5. doi: 10.1016/j.parkreldis.2014.01.013
9. Gowers WR. *A Manual of Diseases of the Nervous System*. London: Churchill. (1886).
10. Neurology (volumes I&II) by Kinnier Wilson, S.A. *[Samuel alexander] (edited by a. Ninian Bruce]: Very good Original Grey Cloth Hardback*. Third Impression. Edinburgh Books. (1944). Available online at: https://www.abebooks.com/first-edition/Neurology-volumes-III-Kinnier-Wilson-S.A/22828917676/bd [Accessed November 7, 2020]
11. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. *Cold Spring Harb Perspect Med.* (2011) 1:8862. doi: 10.1101/cshperspect.a008862
12. Cattaneo L, Pavesi G. The facial motor system. *Neurosci Biobehav Rev.* (2014) 38:135–59. doi: 10.1016/j.neubiorev.2013.11.002
13. Lako IM, Wigman JTW, Klaassen RMC, Slooff CJ, Taxis K, Bartels-Velthuis AA. Psychometric properties of the self-report version of the quick inventory of depressive symptoms (QIDS-SR16) questionnaire in patients with schizophrenia. *BMC Psychiatry*. (2014) 14:247. doi: 10.1186/s12888-014-0247-2
14. Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. *Brain J Neurol.* (2001) 124:2131–46. doi: 10.1093/brain/124.11.2131
15. Bologna M, Fasano A, Modugno N, Fabbrini G, Berardelli A. Effects of subthalamic nucleus deep brain stimulation and l-DOPA on blinking in Parkinson's disease. *Exp Neurol.* (2012) 235:265–72. doi: 10.1016/j.expneurol.2012.02.004
16. Zingler VC, Strupp M, Jahn K, Brandt T. Hemihypomimia in Parkinson's disease. *Eur Neurol.* (2005) 53:92–3. doi: 10.1159/000085505
17. Crosiers D, Maréchal E, van Ael Y, Cras P. Left-sided hemihypomimia in Parkinson's disease. *Acta Neurol Belg.* (2011) 111:225–7.
18. Ozekmekçi S, Benbir G, Ozdogan FY, Ertan S, Kiziltan ME. Hemihypomimia, a rare persistent sign in Parkinson's disease: follow up of 11 patients. *J Neurol.* (2007) 254:347–50. doi: 10.1007/s00415-006-0372-z
19. Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. *Brain J Neurol.* (2012) 135:1860–70. doi: 10.1093/brain/aws093
20. Fereshtehnejad S-M, Yao C, Pelletier A, Montplaisir JY, Gagnon J-F, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with lewy bodies: a prospective study. *Brain J Neurol.* (2019) 142:2051–67. doi: 10.1093/brain/awz111
21. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* (1992) 55:181–4. doi: 10.1136/jnnp.55.3.181
22. Munsat TL. *Assessment of Parkinson's disease. Quantification of Neurological Deficit. Edición: 1*. Boston: Butterworth-Heinemann (1989).
23. Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, et al. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord Off J Mov Disord Soc.* (1992) 7:2–13. doi: 10.1002/mds.870070103
24. Garcia Ruiz PJ, Muñiz de Igneson J, Ayerbe J, Frech F, Sánchez Bernardos V, Lopez Ferro O, et al. Evaluation of timed tests in advanced Parkinsonian patients who were candidates for subthalamic stimulation. *Clin Neuropharmacol.* (2005) 28:15–7. doi: 10.1097/01.wnf.0000150869.44630.71
25. Lau B, Meier N, Serra G, Czernecki V, Schuepbach M, Navarro S, et al. Axial symptoms predict mortality in patients with Parkinson disease and subthalamic stimulation. *Neurology.* (2019) 92:e2559–e70. doi: 10.1212/WNL.0000000000007562
26. Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Mov Disord Off J Mov Disord Soc.* (2008) 23:998–1005. doi: 10.1002/mds.22007
27. Scott NJ, Kramer RSS, Jones AL, Ward R. Facial cues to depressive symptoms and their associated personality attributions. *Psychiatry Res.* (2013) 208:47–53. doi: 10.1016/j.psychres.2013.02.027
28. García-Ruiz PJ, Del Val J, Fernández IM, Herranz A. What factors influence motor complications in Parkinson disease?: a 10-year prospective study. *Clin Neuropharmacol.* (2012) 35:1–5. doi: 10.1097/WNF.0b013e31823dec73
29. Ricciardi L, De Angelis A, Marsili L, Faiman I, Pradhan P, Pereira EA, et al. Hypomimia in Parkinson's disease: an axial sign responsive to levodopa. *Eur J Neurol.* (2020) 27:2422–29. doi: 10.1111/ene.14452
30. Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology.* (2001) 56:1712–21. doi: 10.1212/WNL.56.12.1712
31. Zhang H, Yin X, Ouyang Z, Chen J, Zhou S, Zhang C, et al. A prospective study of freezing of gait with early Parkinson disease in Chinese patients. *Medicine.* (2016) 95:e4056. doi: 10.1097/MD.0000000000004056
32. Ehgoetz Martens KA, Lukasik EL, Georgiades MJ, Gilat M, Hall JM, Walton CC, et al. Predicting the onset of freezing of gait: a longitudinal study: anxiety is a predictor of fog onset. *Mov Disord.* (2018) 33:128–35. doi: 10.1002/mds.27208
33. Gasca-Salas C, Urso D. Association between hypomimia and mild cognitive impairment in *de novo* Parkinson's disease patients. *Can J Neurol Sci J Can Sci Neurol.* (2020) 2020:1–3. doi: 10.1017/cjn.2020.93
34. Stern Y, Marder K, Tang MX, Mayeux R. Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology.* (1993) 43:1690–2. doi: 10.1212/wnl.43.9.1690
35. Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study: cognition in Parkinson. *Eur J Neurol.* (2009) 16:1278–84. doi: 10.1111/j.1468-1331.2009.02707.x
36. Herrera E, Cuetos F, Rodríguez-Ferreiro J. Emotion recognition impairment in Parkinson's disease patients without dementia. *J Neurol Sci.* (2011) 310:237–40. doi: 10.1016/j.jns.2011.06.034
37. Argaud S, Vérin M, Sauleau P, Grandjean D. Facial emotion recognition in Parkinson's disease: a review and new hypotheses. *Mov Disord.* (2018) 33:554–67. doi: 10.1002/mds.27305
38. Ricciardi L, Visco-Comandini F, Erro R, Morgante F, Bologna M, Fasano A, et al. Facial emotion recognition and expression in Parkinson's disease: an emotional mirror mechanism? *PLoS ONE.* (2017) 12:e169110. doi: 10.1371/journal.pone.0169110
39. Korošec M, Zidar I, Reits D, Evinger C, VanderWerf F. Eyelid movements during blinking in patients with Parkinson's disease. *Mov Disord.* (2006) 21:1248–51. doi: 10.1002/mds.20930
40. Agostino R, Bologna M, Dinapoli L, Gregori B, Fabbrini G, Accornero N, et al. Voluntary, spontaneous, and reflex blinking in Parkinson's disease. *Mov Disord Off J Mov Disord Soc.* (2008) 23:669–75. doi: 10.1002/mds.21887
41. Kimber TE, Thompson PD. Increased blink rate in advanced Parkinson's disease: a form of 'off'-period dystonia? *Mov Disord Off J Mov Disord Soc.* (2000) 15:982–5. doi: 10.1002/1531-8257(200009)15:5<982::aid-mds1033>3.0.co;2-p
42. Maycas T. *Parkinson's Disease and Facial Bradykinesia. Mendeley Data*. (2020). Available online at: https://data.mendeley.com/datasets/4tjd8jrhp8/1

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 08 March 2021
doi: 10.3389/fneur.2021.568841

Prevalence and Clinical Features of FOG in Chinese PD Patients, a Multicenter and Cross-Sectional Clinical Study

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *02 June 2020*
Accepted: *01 February 2021*
Published: *08 March 2021*

Citation:
Gan J, Liu W, Cao X, Xie A, Li W, Yuan C, Jin L, Liu S, Jin L, Guo D, Shen Y, Wu Y and Liu Z (2021) Prevalence and Clinical Features of FOG in Chinese PD Patients, a Multicenter and Cross-Sectional Clinical Study. Front. Neurol. 12:568841. doi: 10.3389/fneur.2021.568841

Objectives: Freezing of gait (FOG) is generally considered as an independent symptom of Parkinson's disease (PD) with a complex pathophysiology. There is a wide range of associated clinical features of FOG reported from different studies without consistent conclusion. Thus, a multicenter, cross-sectional study was designed to investigate the prevalence and clinical features of FOG together with its unique contribution quality of life in Chinese PD patients.

Methods: Eight hundred and thirty eight PD patients were consecutively recruited into this study from 12 hospital centers in six provinces in China. Clinical information, including motor and neuropsychological features as well as pharmacological details, was collected.

Results: Of 827 PD patients, 245 (29.63%) reported FOG. The prevalence of FOG was strongly correlated with modified H-Y stages and symptomatic duration ($p < 0.01$). 84.90% freezers experienced FOG during turning and 88.98% experienced when initiating the first step. Compared with non-freezers, freezers reported longer disease duration (7.73 ± 5.44 vs. 4.69 ± 3.94, $p < 0.000$), higher frequent PIGD phenotype (61.22 vs. 35.91%, $p < 0.000$), higher scores of UPDRS III (32.85 ± 15.47 vs. 22.38 ± 12.89, $p < 0.000$), HAMA (10.99 ± 7.41 vs. 7.59 ± 6.47, $p < 0.000$), HAMD (15.29 ± 10.29 vs. 10.58 ± 8.97, $p < 0.000$) and lower MMSE score (25.12 ± 5.27 vs. 26.63 ± 3.97, $p < 0.000$), and higher daily levodopa dosage (432.65 ± 264.31 vs. 319.19 ± 229.15, $p < 0.000$) with less frequent initial use of dopaminergic agonist (8.57 vs. 14.78%, $p < 0.05$). Using binary logistic regression, the associated factors of FOG might be non-tremor dominant onset (OR = 3.817, $p < 0.000$), the presence of anxiety

(OR = 2.048, $p < 0.000$) and imbalance (OR = 4.320, $p = 0.012$). Freezers had poorer quality of life than non-freezers and FOG impacted PDQ-8 independently.

Conclusion: Nearly one third of the PD patients experienced FOG. Its frequency increased with PD progression and FOG reduced independently the quality of life. Non-tremor dominant, disease progression, and anxiety were risk factors of FOG.

Keywords: parkinson's disease (PD), freezing of gait (FOG), anxiety, quality of life, prevalence, epidemiological investigation

INTRODUCTION

Freezing of gait (FOG) was one of the most disabling symptoms in Parkinson's disease (PD). FOG was defined as "a brief episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (1). Its sudden and unpredictable nature contributed to PD patients' fallings, which lead to the immobility and loss of independence (1, 2). Currently, the pathogenesis of FOG is still unclear. Studies demonstrated that FOG was poorly associated with parkinsonian cardinal motor features and had selective response to levodopa (1, 3). It suggested that non-dopaminergic pathophysiologic mechanisms might be involved in FOG development. As a poor indicator of PD patients' quality of life (QoL), FOG still lacks effective treatments. Therefore, it would be more meaningful to clarify the risk factors of FOG to help clinicians make proper treatment therapies to delay the occurrence of FOG.

The prevalence and clinical factors related to FOG have been reported in several studies (4–16). However, the data varied depending on diverse detection methods or genetic backgrounds or populations (1, 4–13). It reached no consistent conclusion on the FOG associated factors of gender, motor fluctuation, some non-motor symptoms like hallucination, depression, anxiety as well as the usage of antimuscarinic drugs (6–12, 14–16). Notably, the relationship between dopamine replacement therapy and FOG was debated (5, 6, 12, 14), and little information was acquired about FOG's association with the initial antiparkinsonian medications which was an interventive factor. Additionally, PD patients always experienced various motor and non-motor symptoms, it was unclear about FOG' contribution value to the decline of PD-QoL among all these symptoms.

At this background, we conducted this large sample, multi-center, cross-sectional study in Chinese PD patients to clarify the FOG's prevalence and associated factors, together with its unique contribution to the QoL.

PATIENTS AND METHODS

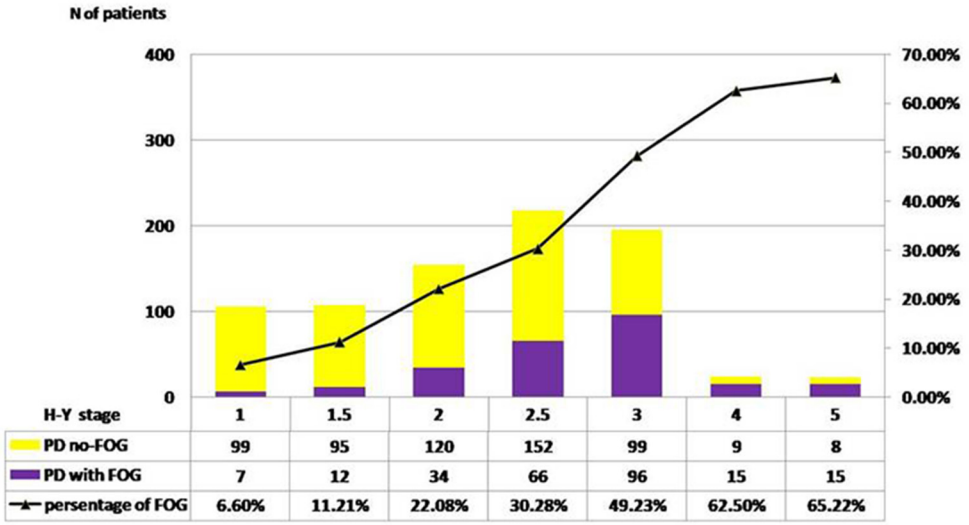
Participants

PD patients' data were obtained from a multicenter, cross-sectional, observational study (clinical registration No: NCT03026595). The recruitment, which lasted for 1 year from October 2017 to November 2018, was conducted in outpatient clinics and hospitalization in 12 hospital centers from six different regions of China. All participants were diagnosed with PD according to the UK Brain Bank Diagnostic Criteria for PD, with the age above 18 years old. The exclusion criteria were as follows: (1) who had atypical or secondary parkinsonism, (2) who were pregnant or lactating, (3) who were unable to cooperate with the assessment, (4) who had participated other clinical research within the recent 30 days. All patients involved in this study gave their signed informed consent form. The study was approved by the Research Ethics Committee of each center of each study center.

Data Collection

Before the recruitment, all neurologists were trained for clinical assessments for this study together to reduce the bias. Standard demographic details, including age, gender, disease duration, onset age, and onset site, were collected. Patients were evaluated at their "ON" status. The clinical assessments included the Unified Parkinson's Disease Rating Scale (UPDRS), modified Hoehn and Yahr scale, Berg Balance Scales (BBS), the Mini-Mental Scale Examination (MMSE), Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD) (24 items), and the 8-item Parkinson's Disease Questionnaire (PDQ-8). PD motor subtype was classified as tremor dominant (TD), posture instability and gait difficulties (PIGD), or intermediate (IND), based on the UPDRS scores (7). According to BBS, cumulative points above 40 are considered as "normal," a range of 21–40 points considered as "decreased balance ability" implying that patients could walk with assistance, points below 20 (inclusive) considered as "poor balance" implying that patients need to use wheelchairs (17). Patients would be considered as having anxiety or depression if they had eight points or more of HAMA or HAMD scales, respectively (18). Cognitive dysfunction was defined as MMSE <24 points for alphabets or <17 points for analphabets (19, 20). Information of pharmacological treatment was collected in detail, and levodopa daily dose (LDD) and levodopa equivalent daily dose (LEDD) were finally accounted (21).

FOG was assessed via a self-report structured questionnaire named the new FOG questionnaire (NFOG-Q) which was developed by Nieuwboer et al. (22). It included three parts. Part I was used to detect FOG (patients and/or their caregivers recall if patients feel/present feet get glued to the floor while walking, making a turn, or start walking during the past month). Part II was used to assess the severity of FOG. Part III was used to assess the impact of FOG on daily life.



H-Y stage	1	1.5	2	2.5	3	4	5
PD no-FOG	99	95	120	152	99	9	8
PD with FOG	7	12	34	66	96	15	15
persentage of FOG	6.60%	11.21%	22.08%	30.28%	49.23%	62.50%	65.22%

FIGURE 1 | Pareto chart of FOG frequency across H-Y stages. H-Y 1.0, the prevalence of FOG was 6.60%;H-Y 1.5, the prevalence was 11.21%; H-Y 2.0, 22.08%; H-Y 2.5, 30.28%; H-Y 3.0, 49.23%; H-Y 4.0, 62.50%; H-Y 5.0, 65.22%. A significant linear trend across H-Y stages was disclosed by result χ^2 test ($p < 0.01$).

Statistical Analysis

All data were presented as the percentage or mean ± standard deviations (SD). Descriptive statistics received normality test. Bivariate analysis was performed with Student's *t*-test or $\chi 2$ test as appropriate between PD patients with and without FOG. Analysis of variance was used to evaluate the relation between levodopa dosage and freezing span. A binary logistic regression analysis based on forward stepwise method was conducted to determine the significant variables which were correlated with FOG. The presence of FOG or not was used as a dependent variable. The variables with significant differences in univariate analysis were used as covariables, including disease duration, onset age, PD subtypes, onset lower limbs or not, H-Y stages, motor fluctuation or not, dyskinesia or not, balance stages, DA agonist as initial treatment or not, anxiety or not, depressive or not, cognitive impairment or not, LDD, and LEDD. The results were shown with odds ratio (OR) and 95% confidence intervals (CIs). Spearman correlation analysis was used to determine the major influencing factors of PDQ-8. Hierarchical regression analysis was used to determine the FOG's impact contributing value to the quality of life. Quality of life (PDQ-8) was used as a dependent variable. The major influencing factors of PDQ-8 were used as covariables. These variables were divided into three groups: group I was the scores of mood and cognition (HAMD, HAMA, and MMSE scores); group II, the scores of motor function (UPDRS III and IV scores); and group III was the score of FOG. Then, we put the variables of group I into the first level and variables of group II into the second level during the hierarchical regression analysis based on a stepwise method. Controlling the influencing factors (mood disorder, cognitive impairment, and motor dysfunction) which were also associated with PDQ-8, the independent impact value of FOG on quality of life was analyzed. The multicollinearity was absent for the model. Statistical Package for the Social Science (SPSS) version 25 was used in the analysis. A significance level of 0.05 was set for all statistical tests.

RESULTS

FOG Point Prevalence and Distribution in Chinese PD Study Population

Eight hundred and thirty eight PD patients were screened in this study, of them, 3 patients were excluded for incooperation, 1 patient was excluded because of participating other clinical research, 6 patients were excluded from the analysis due to the missing data on NFOG-Q score. Finally, 827 PD patients were included into analysis. According to the NFOG-Q part I, 245 patients reported FOG, and the point prevalence of FOG was 29.63%. The mean score of NFOG-Q part II was 11.36 ± 4.64 (0–19) and that of NFOG-Q part III was 4.96±2.11 (0–9).

The distribution of FOG in different H-Y stages was shown in **Figure 1**. The prevalence of FOG at the stage of H-Y 1.0 was 6.60% and gradually increased to the highest value of 65.22% at H-Y 5.0. The prevalence of FOG was statistically different among different H-Y stages ($p < 0.01$). Moreover, the frequency of FOG increased with the progression of the disease duration. FOG was identified in 20.0% of PD patients with disease duration <5 years, 38.42% in disease duration between 5 and 10 years, 60.27% in disease duration between 10 and 15 years, and 54.0% in disease duration over 15 years (**Table 1** and **Figure 2**).

Ninety three PD patients with FOG (93/245, 37.96%) experienced very frequent freezing events (frequency > once a day), 65 patients (26.53%) experienced freezing once a day, 60 (24.49%) had freezing once a week, and 27 (11.02%) had occasional freezing (< once a week). Mostly, FOG occurred at the episodes of turning (208/245, 84.90%) or initiating the first step (218 cases, 88.98%). The time span of freezing usually lasted

TABLE 1 | Demographic details of PD patients with or without FOG in this study.

	PD patients with FOG ($n = 245$)	PD patients without FOG ($n = 582$)	t /χ2 value	p
Age (mean ± SD)[a]	65.76 ± 9.30	65.27 ± 8.91	−0.709	0.478
Gender, male(%)[b]	57.55%	52.23%	1.961	> 0.05
H-Y stage (mean ± SD)[a]	2.78 ± 0.83	2.11 ± 0.79	0.215	0.000
Disease duration (mean ± SD)[a]	7.73 ± 5.44	4.69 ± 3.94	−7.896	0.000
< 5 years (%)[b]	42.21%	70.74%	73.363	< 0.01
5–10 years (%)	31.97%	21.51%		
10–15 years (%)	18.03%	4.99%		
> 15 years (%)	7.79%	2.75%		
Onset age (mean ± SD)[a]	58.10 ± 10.50	60.58 ± 9.24	3.194	0.002
< 50 years (%)[b]	23.67%	14.60%	9.638	< 0.01
≥ 50 years (%)	76.33%	85.40%		
PD subtypes[b]				
TD (%)	22.45%	56.36%	80.649	< 0.01
PIGD (%)	61.22%	35.91%		
IND (%)	16.33%	7.73%		
Onset symptoms[b]				
Onset side (left, %)	47.45%	48.85%	0.111	> 0.05
Onset site (lower limbs, %)	44.81%	32.46%	9.063	< 0.01
UPDRS Total scores (mean ± SD)[a]	57.26 ± 22.34	36.74 ± 19.20	−12.548	0.000
UPDRS I	4.11 ± 2.50	2.77 ± 2.27	−7.521	0.000
UPDRS II	16.64 ± 6.88	9.89 ± 5.38	−13.690	0.000
UPDRS III	32.85 ± 15.47	22.38 ± 12.89	−9.315	0.000
UPDRS IV	3.26 ± 3.04	1.71 ± 2.82	−6.862	0.000
PD motor fluctuations (%)[b]	44.49%	17.70%	65.569	< 0.01
Dyskinesia (%)[b]	23.67%	4.81%	65.838	< 0.01
Berg balance scores (mean ± SD)[a]	42.11 ± 12.66	49.94 ± 7.79	8.988	0.000
Antiparkinsonian medication[b]				
LD+DA (%)	56.33%	48.97%	3.735	> 0.05
Levodopa monotherapy (%)	15.51%	22.85%	5.667	< 0.05
DA agonist monotherapy (%)	2.04%	8.59%	10.884	< 0.01
MAOIs (%)	23.27%	14.60%	9.093	< 0.01
Levodopa as initial treatment (%)	57.60%	56.70%	0.186	> 0.05
DA agonist as initial treatment (%)	8.57%	14.78%	6.094	< 0.05
LDD/day (mean ± SD)	432.65 ± 264.31	319.19 ± 229.15	−5.834	0.000
LEDD/day (mean ± SD)	514.90 ± 303.70	382.92 ± 242.11	−6.020	0.000
HAMA (mean ± SD)[a]	10.99 ± 7.41	7.59 ± 6.47	−6.230	0.000
HAMD (mean ± SD)[a]	15.29 ± 10.29	10.58 ± 8.97	−6.219	0.000
MMSE (mean ± SD)[a]	25.12 ± 5.27	26.63 ± 3.97	3.840	0.000
PDQ-8 (mean ± SD)[a]	8.56 ± 5.33	5.29 ± 5.18	−8.088	0.000

[a]*Data were performed for group differences with Student's t-test.*
[b]*Data were performed for group differences with Chi-square test.*

for 5–30 s in nearly half of the patients with turning FOG, more than 30 s in 29% of patients with turning FOG. In the contrast, for the FOG that occurred in patients initiating the first step, the freezing span lasted for 2–5 s in 50.67% of patients with FOG and 5–30 s in 23.11% in patients with FOG.

Clinical Features of FOG in Chinese PD Patients

Demographic, clinical characteristics, and medical information of the study populations were detailed in **Table 1**.

Clinical Characteristics Difference Between FOG and Non-FOG Patients

Compared with the non-FOG patients, FOG patients had a higher percentage of lower limb onset as the initial motor symptoms (44.81 vs. 32.46%, $p < 0.01$), PIGD motor types (61.22 vs. 35.91%, $p < 0.01$), early-onset PD (onset age <50 yrs) (23.67 vs. 14.60%, $p < 0.01$), and a younger onset age (58.10 ± 10.50 vs. 60.58 ± 9.24, $p = 0.002$).

In terms of motor symptoms, FOG patients had higher UPDRS III (32.85 ± 15.47 vs. 22.38 ± 12.89, $p < 0.000$) and

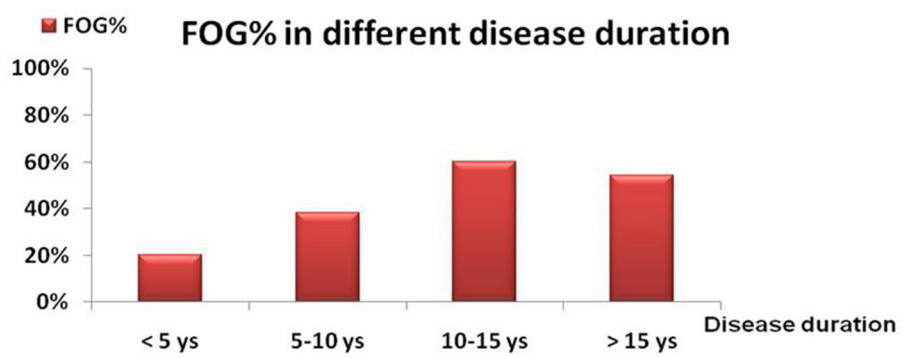


FIGURE 2 | The frequency of FOG (%) in different symptomatic durations. The frequency of FOG was 20% in PD patients with clinical course of <5 years; 38.42% in PD patients with a course with 5–10 years; 60.27% in PD patients with a course with 10–15 years and 54.0% in PD patient with a course with >15years.

UPDRS IV scores (3.26 ± 3.04 vs. 1.71 ± 2.82, $p < 0.000$), higher H-Y stage (2.78 ± 0.83 vs. 2.11 ± 0.79, $p < 0.000$), and higher percentage of motor complications than non-FOG patients. Freezers had lower balance score than that of non-freezers (42.11 ± 12.66 vs. 49.94 ± 7.79, $p < 0.000$). With respect to neuropsychological symptoms, FOG patients had higher scores of UPDRS I (4.11 ± 2.50 vs. 2.77 ± 2.27, $p < 0.000$), HAMA (10.99 ± 7.41 vs. 7.59 ± 6.47, $p < 0.000$), and HAMD (15.29 ± 10.29 vs. 10.58 ± 8.97, $p < 0.000$) whereas a lower MMSE score (25.12 ± 5.27 vs. 26.63 ± 3.97, $p < 0.000$), compared with non-FOG patients.

In addition, FOG patients received higher dosage of LDD and LEDD than non-FOG patients. In terms of the medication types, we found FOG patients were less frequently administrated with dopamine receptor agonist (DA) as the initial anti-PD medication treatment (8.57% vs. 14.78%, $p < 0.05$), however, there was no significant difference in initial levedopa use between two groups. Moreover, FOG patients were treated more frequently with combination medications, compared to non-FOG patients. The use frequency of monoamine oxidase B inhibitors (MAOIs) was much higher in FOG patients than in non-FOG patients (23.27 vs. 14.60%, $p < 0.01$). The One-way ANOVA indicated that "the freezing episode span in turning" was related neither to LDD nor to LEDD ($F = 1.541$, $p = 0.191$ and $F = 1.085$, $p = 0.364$, respectively). Similarly, no correlation was found between "the freezing episode span in initiating the first step" and LDD or LEDD ($F = 1.034$, $p = 0.391$ and $F = 1.069$, $p = 0.372$, respectively).

FOG patients experienced worse quality of life than non-freezers according to PDQ-8 (8.56 ± 5.33 vs. 5.29 ± 5.18, $p < 0.000$) and UPDRS II (16.64 ± 6.88 vs. 9.89 ± 5.38, $p < 0.000$).

Clinical Influencing Factors of FOG

Variables with significantly statistical difference between FOG and non-FOG groups were further included into the binary logistic regression analysis, including disease durations, onset age, PD subtypes (tremor or non-tremor), onset lower limbs or not, H-Y stages, motor fluctuation or not, dyskinesia or not, balance stages, DA agonist as initial treatment or not, anxiety or not, depression or not, cognitive impairment or not, LDD, and LEDD. Finally, freezing was associated with younger onset age (OR = 0.973, 95% CI = 0.953–0.995, $p = 0.015$), longer disease duration (OR = 1.058, 95% CI = 1.011–1.108, $p = 0.015$), non-tremor phenotype onset (OR = 3.817, 95% CI = 2.550–5.714, $p < 0.000$), advanced H-Y stage (OR = 1.621, 95% CI = 1.238–2.124, $p < 0.000$), worse balance (OR = 4.320, 95% CI = 1.381–13.517, $p = 0.012$), the presence of motor complications and anxiety (OR = 2.048, 95% CI = 1.407–2.983, $p < 0.000$). (shown in **Table 2**).

TABLE 2 | Clinical factors related to FOG in this study.

Variables		OR (95% CI)	*p*
Disease duration		1.058 (1.011–1.108)	0.015
Onset age		0.973 (0.953–0.995)	0.015
Phenotype	Tremor	1.00	0.000
	No-tremor	3.817 (2.550–5.714)	
H-Y stage		1.621 (1.238–2.124)	0.000
Presence of dyskinesia		2.339 (1.280–4.274)	0.006
Presence of motor fluctuation		2.035 (1.335–3.102)	0.001
Balance stage	Normal	1.00	
	Decreased balance ability	4.320 (1.381–13.517)	0.012
	Poor balance	1.964 (1.138–3.391)	0.015
HAMA scores ≥ 8		2.048 (1.407–2.983)	0.000

A logistic regression analysis based on forward stepwise method was conducted to determine the most significant variables which were correlated with FOG in PD.

Relationship Between FOG and the Quality of Life

The relationship between FOG and the quality of life was analyzed in PD patients with FOG. PDQ-8 score was positively correlated with the scores of UPDRS III ($r = 0.346$, $p < 0.000$), NFOG ($r = 0.324$, $p < 0.000$), UPDRS IV ($r = 0.298$, $p < 0.000$), HAMD ($r = 0.657$, $p < 0.000$), HAMA ($r = 0.616$, $p < 0.000$), and negatively correlated with the scores of MMSE ($r = -0.237$, $p < 0.000$) and BBS ($r = -0.423$, $p < 0.000$).

TABLE 3 | A hierarchical regression model of the PDQ-8 scale.

	Adjusted R^2	R^2 change	Standardized beta	*t*	*p*
Step 1	0.462	-	-	-	0.000
Step 2	0.520	0.062	-	-	0.000
Step 3	0.541	0.023	-	-	0.001
HAMD score	-	-	0.544	10.812	0.000
UPDRS III score	-	-	0.193	3.805	0.000
FOG impact score	-	-	0.169	3.300	0.001

The hierarchical regression was used to determine the impact of FOG on quality of life of PD patients. The significant variables were divided into three groups: group I: the HAMD, HAMA scores and the MMSE score, group II: the UPDRS III score, UPDRS IV score, group III: FOG score. Then, the variables of group I were put into the first level and variables of group II into the second level during the hierarchical regression analysis based on stepwise method. Controlling the factors of group I and II, the independent contributing value of FOG on quality of life was 2.3%. The multicollinearity was absent for the final model. The Tolerance of HAMD, MMSE, HAMA, UPDRS III, UPDRS IV and FOG was 0.832, 0.840, 0.282, 0.817, 0.898 and 0.803, respectively. The VIF was 1.201, 1.191, 3.548, 1.224, 1.113, and 1.248, respectively.

PDQ-8 score was not associated with the onset age ($r = -0.012$, $p = 0.852$) or sex distribution ($r = -0.012$, $p = 0.846$). This indicated that parkinsonians' quality of life was associated with motor symptoms (including FOG), motor complications, mood, and cognitive impairment.

Then, a hierarchical regression analysis was used to determine the FOG's contributing value to the quality of life. Controlling the influencing factors (mood disorder, cognitive impairment, and motor dysfunction), we analyzed the impact of FOG on quality of life independently. Finally, the analysis indicated that the scores of HAMD, UPDRS III, and FOG had the strongest impact on the PDQ-8 scores, with the contributing value of 54.1% among all included variables. The FOG score was an independent influencing factor of PDQ-8, with the contributing value of 2.3% (shown in **Table 3**).

DISCUSSION

In this study, we found that FOG increasingly occurred during the progression of PD and played an independent negative impact on patients' quality of life. Moreover, PD patients with non-tremor phenotype or anxiety were more likely to develop FOG. The patients with non-tremor phenotype would be 3.5 times more likely to occur FOG than tremor phenotype.

The prevalence of FOG ranged from 7% of *de novo* PD patients (4) to 81% of PD patients with disease duration over 20-years (8–11, 23) from the literatures. In our study, the FOG point prevalence was nearly one third (29.63%) in mixed patients with early and advanced phase who were still ambulatory. Our prevalence was quite lower than the other results (7, 11). It might be attributed to a higher percentage (71.6%) of PD patients at a lower H-Y stage (1–2.5). In addition, the difference in the inclusion criteria and genetic backgrounds may contribute to the discrepancy of the prevalence among studies. Our data confirmed that FOG patients had a longer disease duration and were at a more advanced disease stage, experienced a higher incidence of motor complications and poorer balance, a greater amount of dopaminergic therapy as well as worse quality of life, which was consistent with previous reports (1, 6, 7, 9–11, 14, 24). These results strongly supported that FOG was associated with PD progression (25).

Our data showed that the percentage of PIGD motor phenotype was almost double as high as non-FOG patients. The binary regression analysis showed that non-tremor motor phenotype was a powerful potential influencing factor of FOG. Previous studies also found that (11, 24, 26) PD-FOG patients tended to be dominated by PIGD motor phenotype. This suggested different pathologic progression underlaid the two motor phenotypes of PD. The postmortem findings indicated that patients initially presenting with a tremor-dominant motor phenotype had a more serious limbic Lewy bodies burden whereas patients with a non-tremor-dominant motor phenotypes had a more serious neocortical Lewy bodies burden (24, 27). In our study, the frequency of lower limbs onset was much higher in the FOG group than that in the non-FOG group, but it was not associated with FOG in the final logistic analysis. Currently, the association between the lower limbs of onset symptom and FOG controversial (8, 12, 26, 28), which still required further long-term follow-up to confirm.

There was little information about the association between initial antiparkinsonian medications and FOG. We wanted to know whether different medication types in the initiation of anti-parkinsonian treatment would have a different impact on the occurrence of FOG. Of all the medication types, we found that the non-FOG group used more DA as initial medical treatment than the FOG group, however, the regression analysis failed to show that a close relation between the first drug type choice and FOG. Our initial anti-PD drugs were collected retrospectively, there might be recall bias. Initial antiparkinsonian treatments were first analyzed in two groups of freezers and non-freezers. Previous follow-up studies were rare and did not focus on the correlation between initial antiparkinsonian medications and FOG occurrence (25, 27). Although longer levodopa treatment duration was found to be associated with FOG (1), the mechanism was still unknown. It was not clear what role levodopa play in the development of FOG (29, 30). Alternatively, given that dopaminergic dysfunction might impact the degree to which network loops cross over, dopamine agonists may play a crucial role in the development of FOG (26). Thus, the relation between dopaminergic medicaments and FOG may be worth exploring in future research.

Our results confirmed that FOG patients have a more frequent and serious neuropsychological symptoms, which was consistent with previous studies (1, 24–26, 31). It has been suggested that neuropsychological symptoms were not only related to FOG but also involved in the pathophysiology of this phenomenon (1, 15, 29, 31, 32). In our study, of these neuropsychological symptoms, only anxiety was found as a risk factor for FOG onset in the logistic regression model. Our patients with anxiety were twice as likely to present FOG as those without anxiety. Many evidences supported that anxiety closely correlated with FOG. Studies indicated that there were high levels of anxiety in PD patients with FOG and anxiety could predict the onset of FOG at 1-year follow up (15, 25–31). A recent longitudinal study indicated that anxiety was a strong predictor of FOG

with the accuracy of 82.1% that predicting FOG development in the next 15 months (26). Anxiety contributed not only to the frequent occurrence of FOG but also to a longer duration of FOG episodes (33). The cerebral network hypothesis that involved in the interaction between gait and emotion was confirmed by functional imaging studies, which found an increased striato-limbic connectivity as well as a lack of top-down control by frontal-parietal network over amygdale in FOG PD patients. Dysfunctional limbic circuitry was involved in the pathogenesis of FOG (15, 30, 31). These theories implied the relation between anxiety and FOG. Depression and cognitive impairment failed to become clinical predictors of FOG statistically in our study, although there were different results and opinions (1, 8, 24, 28). Thus, the long-term follow-up studies were necessary for us to conduct the relationship between neuropsychological symptoms and FOG.

Finally, we confirmed that FOG was an independent negative influencing factor of quality of life (34). The contribution of FOG impact score to the model was 2.3% uniquely while controlling for other factors which were also associated with PDQ. The impact of FOG was the third largest of all factors, only next to depression and motor severity.

These results gave us some clinical implications. Although the progress of PD cannot be stopped presently, we can carry out disease modification treatment in early stage or optimize the pharmacological treatment to delay PD progression. For no-tremor PD patients, gait and balance should be regularly assessed and early gait rehabilitation training. Early detection of anxiety and early intervention may play a role in delaying the occurrence FOG. Our study has several limitations. First, we did not differentiate the "ON" or "OFF" status of FOG. This information might be useful to explore the association between dopamine therapy and FOG (24). Secondly, we did not evaluate frontal function, which was reported to be closely related to FOG occurrence (6). Future research on FOG should include all frontal lobe-related symptoms. Thirdly, this was a cross-sectional study and the relation between FOG and the clinical variables still required a longitudinal evaluation to be testified.

CONCLUSION

Our epidemiology study showed that the prevalence of FOG in China was nearly one third in our ambulatory PD patients and was strongly associated with disease progression. Freezers experienced poor quality of life independently influenced by FOG. No-tremor phenotype, disease progression, and presence of anxiety were significant FOG risk factors. Future prospective study should be done to determine accurate clinical predictors and further exploring the mechanism of FOG.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical approval for the original study was obtained from the Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG and ZL were involved in the manuscript preparation, writing of the first draft, and statistical analysis with design and execution. WLiu, XC, AX, WLi, CY, LirJ, SL, LinJ, DG, YS, and YW were involved in the initiation of the project, organization, and execution of the project. All authors read and approved the final manuscript.

FUNDING

This study was supported by the National Key R&D Program of China (2017YFC1310300), Projects of National Science Foundation of China (81974173, 81771211, 81703852), Projects of the Shanghai Committee of Science and Technology (17401901000), Innovation research team of high-level local universities in Shanghai, Shanghai Municipal Commission of Health (2019SY024). Shanghai health and family planning commission foundation special plan for clinical research in health industry (201940021).

ACKNOWLEDGMENTS

We thank all neurologists participated in the patients' selection and data collection. Jiahao Zhao, Yuzhen Chen (Department of Neurology, Xinhua Hospital Affiliated to Shanghai Jiaotong University, School of Medicine, Shanghai); Cuiyu Yu (Department of Neurology, Nanjing Brain Hospital Affiliated Nanjing Medical University, Nanjing); Huimin Wang (Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao); Ling Liu (Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan); Weiwei Wang (Department of Neurology, Shanghai municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai); Qing Ye (Department of Neurology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai); Zhen Huang (Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai); Tingling Wang (Department of Neurology, The Affiliated Taizhou Hospital, Wenzhou Medical University, Taizhou); Tianyu Zhang (Department of Neurology, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai); Xiaoying Zhu (Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai).

REFERENCES

1. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* (2011) 10:734–44. doi: 10.1016/S1474-4422(11)70143-0
2. Okuma Y, Silva de Lima AL, Fukae J, Bloem BR, Snijders AH. A prospective study of falls in relation to freezing of gait and response fluctuations in Parkinson's disease. *Parkinsonism Relat Disord.* (2018) 46:30–5. doi: 10.1016/j.parkreldis.2017.10.013
3. Bartels AL, Balash Y, Gurevich T, Schaafsma JD, Hausdorff JM, Giladi N. Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia. *J Clin Neurosci.* (2003) 10:584–8. doi: 10.1016/S0967-5868(03)00192-9
4. Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology*. (2001) 56:1712–21. doi: 10.1212/WNL.56.12.1712
5. Ge HL, Chen XY, Lin YX, Ge TJ, Yu LH, Lin ZY, et al. The prevalence of freezing of gait in Parkinson's disease and in patients with different disease durations and severities. *Chin Neurosurg J*. (2020) 6:17. doi: 10.1186/s41016-020-00197-y
6. Perez-Lloret S, Negre-Pages L, Damier P, Delval A, Derkinderen P, Destée A, et al. Prevalence, determinants, and effect on quality of life of freezing of gait in Parkinson disease. *JAMA Neurol.* (2014) 71:884–90. doi: 10.1001/jamaneurol.2014.753
7. Amboni M, Stocchi F, Abbruzzese G, Morgante L, Onofrj M, Ruggieri S, et al. Prevalence and associated features of self-reported freezing of gait in Parkinson disease: The DEEP FOG study. *Parkinsonism Relat Disord.* (2015) 21:644–9. doi: 10.1016/j.parkreldis.2015.03.028
8. Ou R, Guo X, Song W, Cao B, Yang J, Wei Q, et al. Freezing of gait in Chinese patients with Parkinson disease. *J Neurol Sci.* (2014) 345:56–60. doi: 10.1016/j.jns.2014.07.002
9. Sawada M, Wada-Isoe K, Hanajima R, Nakashima K. Clinical features of freezing of gait in Parkinson's disease patients. *Brain Behav*. (2019) 9:e01244. doi: 10.1002/brb3.1244
10. Hall JM, Shine JM, O'Callaghan C, Walton CC, Gilat M, Naismith SL, et al. Freezing of Gait and its associations in the early and advanced clinical motor stages of parkinson's disease: a cross-sectional study. *J Parkinsons Dis.* (2015) 5:881–91. doi: 10.3233/JPD-150581
11. Macht M, Kaussner Y, Möller JC, Stiasny-Kolster K, Eggert KM, Krüger HP, et al. Predictors of freezing in Parkinson's disease: a survey of 6,620 patients. *Mov Disord.* (2007) 22:953–56. doi: 10.1002/mds.21458
12. Ou R, Wei Q, Cao B, Song W, Hou Y, Liu H, et al. Predictors of freezing of gait in Chinese patients with Parkinson's disease. *Brain Behav*. (2018) 8:e00931. doi: 10.1002/brb3.931
13. Tang X, Yu L, Yang J, Guo W, Liu Y, Xu Y, et al. Association of sleep disturbance and freezing of gait in Parkinson disease: prevention/delay implications. *J Clin Sleep Med.* (2020). doi: 10.5664/jcsm.9022. [Epub ahead of print].
14. Zhang H, Yin X, Ouyang Z, Chen J, Zhou S, Zhang C, et al. A prospective study of freezing of gait with early Parkinson disease in Chinese patients. *Medicine*. (2016) 95:e4056. doi: 10.1097/MD.0000000000004056
15. Avanzino L, Lagravinese G, Abbruzzese G, Pelosin E. Relationships between gait and emotion in Parkinson's disease: a narrative review. *Gait Posture.* (2018) 65:57–64. doi: 10.1016/j.gaitpost.2018.06.171
16. Banks SJ, Bayram E, Shan G, LaBelle DR, Bluett B. Non-motor predictors of freezing of gait in Parkinson's disease. *Gait Posture.* (2019) 68:311–6. doi: 10.1016/j.gaitpost.2018.12.009
17. Downs S, Marquez J, Chiarelli P. The Berg Balance Scale has high intra- and inter-rater reliability but absolute reliability varies across the scale: a systematic review. *J Physiother.* (2013) 59:93–9. doi: 10.1016/S1836-9553(13)70161-9
18. Tang YH. Hamilton Depression Rating Scale. *Shanghai Arch Psychiatr.* (1984) 2:61–4.
19. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc.* (1992) 40:922–35. doi: 10.1111/j.1532-5415.1992.tb01992.x
20. Li H, Jia J, Yang Z. Mini-mental state examination in elderly chinese: a population-based normative study. *J Alzheimers Dis.* (2016) 53:487–96. doi: 10.3233/JAD-160119
21. Gan J, Wan Y, Shi J, Zhou M, Lou Z, Liu Z. A survey of subjective constipation in Parkinson's disease patients in shanghai and literature review. *BMC Neurol.* (2018) 18:29. doi: 10.1186/s12883-018-1034-3
22. Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture.* (2009) 30:459–63. doi: 10.1016/j.gaitpost.2009.07.108
23. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord.* (2008) 23:837–44. doi: 10.1002/mds.21956
24. Virmani T, Moskowitz CB, Vonsattel JP, Fahn S. Clinicopathological characteristics of freezing of gait in autopsy-confirmed Parkinson's disease. *Mov Disord*. (2015) 30:1874–84. doi: 10.1002/mds.26346
25. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. (2015) 386:896–912. doi: 10.1016/S0140-6736(14)61393-3
26. Ehgoetz Martens KA, Lukasik EL, Georgiades MJ, Gilat M, Hall JM, Walton CC, et al. Predicting the onset of freezing of gait: a longitudinal study. *Mov Disord.* (2018) 33:128–35. doi: 10.1002/mds.27208
27. Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. A clinico-pathological study of subtypes in Parkinson's disease. *Brain*. (2009) 132(Pt 11):2947–57. doi: 10.1093/brain/awp234
28. Herman T, Shema-Shiratzky S, Arie L, Giladi N, Hausdorff JM. Depressive symptoms may increase the risk of the future development of freezing of gait in patients with Parkinson's disease: findings from a 5-year prospective study. *Parkinsonism Relat Disord*. (2019) 60:98–104. doi: 10.1016/j.parkreldis.2018.09.013
29. Nieuwboer A, Giladi N. Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon. *Mov Disord.* (2013) 28:1509–19. doi: 10.1002/mds.25683
30. Weiss D, Schoellmann A, Fox MD, Bohnen NI, Factor SA, Nieuwboer A, et al. Freezing of gait: understanding the complexity of an enigmatic phenomenon. *Brain*. (2020) 143:14–30. doi: 10.1093/brain/awz314
31. Martens KAE, Hall JM, Gilat M, Georgiades MJ, Walton CC, Lewis SJG. Anxiety is associated with freezing of gait and attentional set-shifting in Parkinson's disease: a new perspective for early intervention. *Gait Posture.* (2016) 49:431–6. doi: 10.1016/j.gaitpost.2016.07.182
32. Ehgoetz Martens KA, Hall JM, Georgiades MJ, Gilat M, Walton CC, Matar E, et al. The functional network signature of heterogeneity in freezing of gait. *Brain*. (2018) 141:1145–60. doi: 10.1093/brain/awy019
33. Pimenta M, Moreira D, Nogueira T, Silva C, Pinto EB, Valenca GT, et al. Anxiety independently contributes to severity of freezing of gait in people with parkinson's disease. *J Neuropsychiatry Clin Neurosci.* (2019) 31:80–5. doi: 10.1176/appi.neuropsych.17090177
34. Walton CC, Shine JM, Hall JM, O'Callaghan C, Mowszowski L, Gilat M, et al. The major impact of freezing of gait on quality of life in Parkinson's disease. *J Neurol.* (2015) 262:108–15. doi: 10.1007/s00415-014-7524-3

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 March 2021
doi: 10.3389/fneur.2021.637620

Kinematic and Clinical Outcomes to Evaluate the Efficacy of a Multidisciplinary Intervention on Functional Mobility in Parkinson's Disease

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OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Giovanni Mostile, University of Catania, Italy
Matteo Bologna, Sapienza University of Rome, Italy

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 03 December 2020
Accepted: 15 February 2021
Published: 23 March 2021

Citation:
Bouça-Machado R, Branco D, Fonseca G, Fernandes R, Abreu D, Guerreiro T, Ferreira JJ and The CNS Physiotherapy Study Group (2021) Kinematic and Clinical Outcomes to Evaluate the Efficacy of a Multidisciplinary Intervention on Functional Mobility in Parkinson's Disease. Front. Neurol. 12:637620. doi: 10.3389/fneur.2021.637620

Introduction: Functional mobility (FM) is a concept that incorporates the capacity of a person to move independently and safely to accomplish tasks. It has been proposed as a Parkinson's disease (PD) functional and global health outcome. In this study, we aimed to identify which kinematic and clinical outcomes changes better predict FM changes when PD patients are submitted to a specialized multidisciplinary program.

Methods: PD patients engaged in a pre-defined specialized multidisciplinary program were assessed at admission and discharge. Change from baseline was calculated for all kinematic and clinical outcomes, and Timed Up and Go (TUG) was defined as the primary outcome for FM. A stepwise multivariate linear regression was performed to identify which outcome measures better predict TUG changes.

Results: Twenty-four patients were included in the study. The changes in TUG Cognitive test, supervised step length, and free-living (FL) step time asymmetry were identified as the best predictors of TUG changes. The supervised step length and FL step time asymmetry were able to detect a small to moderate effect of the intervention (*d* values ranging from −0.26 to 0.42).

Conclusions: Our results support the use of kinematic outcome measures to evaluate the efficacy of multidisciplinary interventions on PD FM. The TUG Cognitive, step length, and FL step time asymmetry were identified as having the ability to predict TUG changes. More studies are needed to identify the minimal clinically important difference for step length and FL step time asymmetry in response to a multidisciplinary intervention for PD FM.

Keywords: Parkinson's disease, functional mobility, outcome measures, gait, sensors, digital health, wearable, technology

INTRODUCTION

Functional mobility (FM) in Parkinson's disease (PD) has been recently described as a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living at home, at work, and in the community (1, 2). From the early disease stage, PD patients experience limitations in their FM. With disease progression, these limitations are usually a major cause of disability and loss of independence (1).

FM has been reported as a useful outcome measure to understand patients' overall health status, to address their daily needs related to mobility and social participation, and for monitoring, in a closer and more realistic fashion, the impact of disease progression and the effect of therapeutic interventions (2–4). The Timed Up and Go (TUG) test is a quick and easy-to-use test, specifically designed to measure FM that includes the three anchors of the concept, i.e., gait, balance, and postural transitions (2, 4, 5). Although it is the recommended tool for assessing FM in PD, other clinical tests are also used (2, 4, 5).

The development of technology-based objective measures (TOMs) and the possibility of using accurate and reliable quantitative information to evaluate PD patients' gait enable a more objective and ecological (i.e., closer to patients' real-life environment performance) perspective of patients' FM (6, 7). A recent systematic review on outcome measures for assessing FM in PD included nine studies using kinematic gait parameters (2). The authors emphasize the important role of TOMs in monitoring FM throughout disease progression. They also highlight that despite the capacity of current devices to capture large amounts of data and a great diversity of parameters, the best kinematic parameters for assessing FM in PD remain to be defined (2).

In this study, we aimed to identify which kinematic and clinical outcome measures better predict FM changes when PD patients are submitted to a specialized multidisciplinary intervention.

METHODS

Study Design

A pragmatic prospective clinical study was conducted.

Objective

The objective of this study is to identify the kinematic and clinical outcome measures that better predict FM changes when PD patients are submitted to a specialized multidisciplinary intervention.

Participants

Study participants were recruited from CNS—Campus Neurológico, a tertiary specialized movement disorders center in Portugal. Patients were eligible if they had a diagnosis of probable or clinically established PD (according to the International Parkinson and Movement Disorder Society criteria), had engaged in the specialized multidisciplinary program for parkinsonian patients at the CNS between January and September 2019, and if they agreed to participate. Exclusion criteria were the inability to adopt a standing position and/or to walk 3 m, postural instability compromising patient safety during the assessment, and the presence of cognitive deficits preventing understanding of the test instructions (according to a physiotherapist's best judgment). The study was undertaken with the understanding and written consent of each participant, with the approval from the CNS Ethics Committee (ref. 10/19), and in compliance with national legislation and the Declaration of Helsinki. Participants were required to agree to all aspects of the study and were able to leave the study at any time.

Therapeutic Intervention

The specialized multidisciplinary program combined pharmacological and non-pharmacological therapies, including up to 20 h per week of individually tailored neurorehabilitation sessions of physiotherapy, occupational therapy, speech therapy, and cognitive training, according to the patient's needs and rehabilitation goals. All rehabilitation sessions had a duration of 50 min.

The physiotherapy sessions aim to optimize independence, safety, and well-being, through movement rehabilitation, maximization of functionality, and minimization of secondary complications. The sessions focused on physical capacity training, gait, mobility, balance, sensorimotor coordination, and development, as well as teaching the patient and the usual caregivers adaptive strategies to enhance functionality.

Clinical Assessment Protocol

Patients were assessed in ON-state medication, by a trained health professional from each area, 48 h following admission and before discharge. The following parameters were collected:

- Demographic and clinical data;
- Disease severity: Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score and score from each sub-section (8), Hoehn and Yahr scale (8, 9), and Clinical and Patient Global Impression (CGI and PGI, respectively) of Severity and Change; (10)
- Motor function: The Timed Up and Go (TUG) test with and without a cognitive and manual dual-task (5, 11, 12), Mini-BESTest (5, 13, 14), Five times Sit-to-Stand test (5 STS) (15, 16), and Schwab and England scale (17).

Analysis of Kinematic Data

Kinematic gait parameters were collected during the supervised motor assessments and for 3 days at the end of each assessment, in a free-living (FL) context. Each participant wore a single tri-axial accelerometer-based body-worn monitor (Axivity AX3) on their lower back (L5), programmed to capture raw data at 100 Hz with a dynamic range of ± 8 g. Each subject performed two trials of each assessment, on each visit, and wore the AX3 for 3 days after each assessment.

In the supervised motor assessment, the physiotherapist used a mobile application to mark the start and end of each trial, which was synced with the AX3 internal clock. Departing from the segmentation of test trials provided by the application, we

manually adjusted the start and end of each test to match with the exact start and end of the movement and removed reported periods of pause. To extract meaningful data from the raw accelerometer signal, we started by resampling data to 100 Hz using linear interpolation, to mitigate known fluctuations of the sample rate (18). Afterward, offset was removed as well as machine noise using a second-order Butterworth low pass filter of 17 Hz (19). We focused the kinematic gait analysis in the study of spatiotemporal gait parameters. To extract gait parameters, the process was divided into two steps. First, we identified the walking bouts as the 2-s moving windows where summed standard deviations of tri-axial accelerations were above 0.1 (20). Then, an algorithm to detect initial contact (IC)/final contact (FC) points was applied, from which we calculated the gait parameters (21). A concurrent validity analysis of the reported number of steps (by the physiotherapist observing the trial) and the automatic detection revealed an intra-class correlation above 0.85.

In the FL context, where walking bouts are not previously annotated, a conservative approach was followed, meaning that high precision was sought (seeking that all detected bouts are indeed bouts), even if at the cost of lower recall (i.e., not all bouts are detected). Pre-processing of FL raw data followed a similar approach as the controlled assessment (resample and filtering). To improve walking bout detection in FL, we estimated an optimized scale of the Gaussian continuous wavelet transform (22) ("gaus2") and considered only the segments with a duration above 5 s and at least five detected ICs. Additionally, the first and last detected steps of each bout were trimmed off, given their specific transition characteristics. All remaining bouts (and steps) were subjected to extraction of parameters. An average per subject of 285.3 (SD = 175.2, min = 17, max = 622) walking bouts were extracted at the period of admission, and an average of 270.4 (SD = 129.0, min = 32, max = 647) were detected at the period of discharge, in the 3-day period. Gait parameters were calculated from the detected bouts as in the supervised motor assessment (21). Following previously published evidence in FL assessment, gait parameters were categorized in bouts from 5 to 15 s, 15 to 30 s, 30 to 60 s, and longer than 60 s (21). Our implementation of the extraction of gait parameters from walking bouts is available and open-sourced (https://github.com/Gustavo-SF/gait_extractor).

Statistical Analysis

Descriptive statistics were used for demographic, clinical, and therapeutic data. Continuous outcomes were defined as change from baseline for all the previously mentioned outcome measures and presented as a mean ± standard deviation (SD).

Our main goal was to explore the best predictors of changes in TUG (the gold standard for evaluating FM in PD). To do this, stepwise multiple linear regression analyses were performed using different independent variables (clinical measures, gait parameter assessment during the 10-m walk test, and FL gait parameters analyzed in bouts longer than 60 s). To validate the analysis, the normal distribution of residuals and the absence of multicollinearity were ascertained.

Only the outcome measures able to detect an effect of the intervention were used in the main analysis. This required an assessment, before our main analysis, of the existence of an intervention effect and the ability of the included outcome measures to detect it. We started by studying normality, using the Kolmogorov–Smirnov and the Shapiro–Wilk tests, and applying the paired sample *T*-test and the Wilcoxon S-R test to each parameter to analyze the effects of the program (statistical significance was set at $p < 0.05$). Cohen's *d* was employed as a measure of effect size to assess small (0.20–0.49), medium (0.50–0.80), and large (>0.80) effects (23).

We also performed some exploratory analysis to better understand how the outcome measures, selected as best predictors of FM changes, behave if used as the primary outcome in a future study. Power analysis and sample size calculations were performed using G*Power software, to understand how many participants would be needed to enable statistically significant results (80% power) if the TUG test or one of the outcome measures able to detect at least a small effect size were used as the primary outcome in a clinical study. A significance level of $\alpha = 0.05$ and a power $= 1 - \beta = 0.80$ were assumed. To explore the variability of the different gait parameters, a power analysis assuming 10, 20, and 30% of change from baseline and using the mean SD of change from baseline was calculated for each parameter. The choice of the 30% magnitude of effect was based on the minimal clinically important difference (MCID) reported for the TUG test, the recommended measurement tool for assessing FM in PD. It also used a 20% magnitude of effect, based on MCID reported for spatial asymmetry in a previous study evaluating the effect of rehabilitation training on PD patients' gait parameters (25.76%) (24).

Additionally, and also as an exploratory analysis, we applied paired sample *t*-test and the Wilcoxon S-R test to the different bout lengths of FL assessment to investigate how the length of the bout contributes to the existence of a statistically significant difference between admission and the end of the program (significance was achieved with a *p*-value < 0.05).

RESULTS

Cohort Demographic and Clinical Data

Of the 54 PD patients who engaged in a CNS specialized multidisciplinary program between January and September 2019, a total of 24 participants were included in this study. The reasons for exclusion were lack of collaboration/missing data (27.8%, $n = 15$), motor inability to perform the assessments (18.5%, $n = 10$), and the presence of cognitive impairment and behavioral disturbances (9.3%, $n = 5$). Eight patients did not perform the FL assessment due to behavioral disturbances and refusal of the belt that supports the trunk sensor. Some of the included patients did not fulfill all the clinical assessment battery due to fatigue and lack of collaboration. The mean age of the participants was 73.0 ± 8.0 years, and 66.7% ($n = 16$) were men. At admission, the average disease duration was 8.0 ± 5.1 years, with a mean Hoehn and Yahr stage of 2.3 ± 0.9 and a mean MDS-UPDRS motor score of 39.4 ± 12.8. All patients were under antiparkinsonian treatment, and 50% ($n = 12$) had motor fluctuations.

TABLE 1 | Demographical and clinical characteristics of the sample.

Demographic features ($n = 24$)				
Age (Mean, SD)	73.04 ± 8.00			
Male sex [% (*n*)]	66.67% (16)			
Body mass index (BMI) (Mean, SD)	25.79 ± 3.90			
Time since diagnosis (Mean, SD)	8.04 ± 5.10			
Presence of motor fluctuations [% (*n*)]	50% (12)			
Clinical data [Mean (SD), (Range)]				
	Admission	**Discharge**	**Change**	***p*-value**
MDS-UPDRS I (range 0–52; $n = 19$; ↓)	13.95 ± 7.09	8.25 ± 4.90	−5.53 ± 6.81 (39.6%)	**0.002**
MDS-UPDRS II (range 0–52; $n = 19$; ↓)	17.18 ± 9.24	12.65 ± 7.04	−4.95 ± 10.02 (28.8%)	**0.045**
MDS-UPDRS III (range, 0–132; $n = 19$; ↓)	39.36 ± 12.77	32.20 ± 12.22	−8.52 ± 9.92 (21.7%)	**0.001**
MDS-UPDRS IV (range 0–24; $n = 19$; ↓)	1.95 ± 2.82	1.35 ± 2.16	−0.21 ± 2.53 (10.8%)	0.721
MDS-UPDRS Total (range 0–260; n = 19; ↓)	72.45 ± 25.75	54.45 ± 20.50	−19.26 ± 22.18 (26.6%)	**0.001**
Hoehn and Yahr stage (range 1–5; $n = 24$; ↓)	2.30 ± 0.93	2.35 ± 0.71	0.09 ± 0.68 (3.9%)	0.540
Schwab and England (range 0–100; $n = 24$; ↑)	73.75 ± 16.37	75.83 ± 15.86	2.08 ± 8.33 (2.8%)	0.225
TUG Normal ($n = 24$; ↓)	13.36 ± 7.27	11.68 ± 4.75	−1.69 ± 6.90 (12.7%)	0.243
TUG DT Cognitive ($n = 23$; ↓)	17.22 ± 10.42	14.10 ± 7.29	−2.80 ± 8.91 (16.3%)	0.146
TUG DT Manual ($n = 19$; ↓)	12.80±5.21	11.37±4.35	−0.92 ± 8.69 (7.2%)	0.417
Mini-best (range 0–28; $n = 19$; ↑)	20.19±3.97	20.70±4.59	0.63 ± 3.25 (3.1%)	0.408
5 Sit-to-Stand Normal ($n = 22$; ↓)	19.36 ± 6.99	14.29 ± 5.24	−4.31 ± 2.94 (22.3%)	**0.000**
5 Sit-to-Stand Fast ($n = 22$; ↓)	17.56 ± 4.91	13.25 ± 5.19	−5.07 ± 3.48 (28.9%)	**0.000**
	Severity (Baseline)		**Change (Discharge)**	
Clinical Global Impression ($n = 24$; ↓)	4.0 ± 0.83		2.83 ± 0.82	
Patient Global Impression ($n = 24$; ↓)	3.91 ± 1.02		2.50 ± 0.86	

↑ - a higher score means an improvement, ↓ - a lower score means an improvement. The paired-samples T-test and the Wilcoxon S-R tests were applied to investigate the existence of a statistically significant difference between admission and the end of the program. Significance was achieved with a p-value < 0.05. Bold values is to highlight the outcomes that reached statistical significance.

Patients' demographic and clinical characteristics at admission and discharge are summarized in **Table 1**. **Table 2** summarizes the changes in gait parameter values in both assessment conditions.

All the clinical and gait parameters from the supervised assessment showed an improvement, having reached statistical significance ($p \leq 0.05$) in the MDS-UPDRS parts I, II, III, and total score; in the 5 STS test; and the following gait parameters: gait velocity, stride and step velocity, step length, and swing time asymmetry (**Tables 1**, **2**). The improvement in the TUG test did not reach statistical significance, contrary to gait velocity, stride and step velocity, step length, and swing time asymmetry measured during the test. In FL conditions, an improvement was detected when the analysis was made using bouts of at least 30 s. Specifically, the following gait parameters have reached statistical significance ($p \leq 0.05$): cadence, step time, stance time, swing time, and double support time when data was analyzed in bouts of 30–60 s and stance, swing, and double support phases when bouts of more than 60 s were used in the analysis (**Table 2** and **Appendix 1**).

Prediction of FM Changes

The stepwise multivariate linear regression analysis, between TUG (dependent variable) and the clinical outcome measures able to detect an effect, indicated the TUG Cognitive as the best variable to predict TUG changes (adjusted $R^2 = 0.72$). The same analysis using supervised and FL kinematic gait parameters as independent variables identified step length (adjusted $R^2 = 0.53$) and step time asymmetry (adjusted $R^2 = 0.51$) as the best predictors of TUG changes for each assessment condition (**Table 3**).

Responsiveness to Intervention

The TUG test was able to detect a small effect size ($d = -0.24$) of the intervention (**Appendix 2**).

From the supervised assessment, the outcome measures able to detect a large effect size were the STS Normal ($d = -1.46$) and Fast ($d = -1.47$) and the MDS-UPDRS total score ($d = -0.87$).

From the FL assessment, the outcome parameters with higher sensitivity to the intervention were stance time asymmetry ($d = -0.38$), stride length ($d = 0.37$), double support time variability ($d = -0.37$), and step length ($d = 0.36$).

Sample Size Calculation

A power analysis was performed to understand how many participants would be needed to enable statistically significant results (80% power), if the TUG test or one of the outcome measures able to detect at least a small effect size was used as

TABLE 2 | Admission (i.e., baseline) and change from baseline values (i.e., mean post-pre assessment difference and respective percentage value) of gait parameters in the supervised and free-living assessments.

Gait parameters supervised assessment	Supervised assessment						Free-living assessment		
	TUG normal			10-meter walk test			Bouts longer than 60 s		
	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value
Gait velocity (m/s)	0.71 ± 0.19	0.06 ± 0.13 (8.5%)	**0.037**	0.82 ± 0.21	0.05 ± 0.18 (6.1%)	0.188	0.59 ± 0.14	0.04 ± 0.13 (6.8%)	0.209
Cadence (steps/min)	118.77 ± 12.00	1.94 ± 13.02 (1.6%)	0.472	119.92 ± 13.72	3.66 ± 12.95 (3.1%)	0.180	104.93 ± 10.33	−0.92 ± 9.17 (0.9%)	0.695
Stride length (m)	0.78 ± 0.18	0.06 ± 0.14 (7.7%)	0.057	0.89 ± 0.20	0.04 ± 0.17 (4.5%)	0.204	0.69 ± 0.16	0.05 ± 0.13 (7.2%)	0.160
Stride velocity (m/s)	0.71 ± 0.19	0.06 ± 0.13 (8.5%)	**0.033**	0.82 ± 0.21	0.05 ± 0.18 (6.1%)	0.225	0.59 ± 0.14	0.04 ± 0.13 (6.8%)	0.202
Step length (m)	0.39 ± 0.09	0.03 ± 0.07 (7.7%)	**0.049**	0.45 ± 0.10	0.02 ± 0.08 (4.4%)	0.230	0.34 ± 0.08	0.02 ± 0.06 (5.9%)	0.171
Step velocity (m/s)	0.72 ± 0.19	0.06 ± 0.13 (8.3%)	**0.037**	0.82 ± 0.21	0.05 ± 0.18 (6.1%)	0.182	0.60 ± 0.14	0.04 ± 0.13 (6.7%)	0.220
Stance phase (% of gait cycle)	75.26±1.36	−0.11 ± 1.35 (0.2%)	0.708	75.35 ± 0.49	−0.18 ± 1.32 (0.2%)	0.514	75.11 ± 0.55	0.20 ± 0.36 (0.3%)	**0.047**
Swing phase (% of gait cycle)	24.74 ± 1.36	0.11 ± 1.35 (0.5%)	0.708	24.65 ± 0.49	0.18 ± 1.32 (0.7%)	0.514	24.89 ± 0.55	−0.20 ± 0.36 (0.8%)	**0.047**
Double support phase (% of gait cycle)	25.33 ± 1.33	−0.13 ± 1.36 (0.5%)	0.643	25.34 ± 0.51	−0.19 ± 1.27 (0.8%)	0.476	25.11 ± 0.54	0.19 ± 0.36 (0.8%)	**0.050**
Step time (seconds)	0.56 ± 0.06	−0.02 ± 0.06 (3.6%)	0.893	0.55 ± 0.07	−0.01 ± 0.06 (1.8%)	0.525	0.60 ± 0.06	0.002 ± 0.06 (0.3%)	0.896
Stance time (seconds)	0.84 ± 0.09	−0.01 ± 0.09 (1.2%)	0.800	0.83 ± 0.10	−0.01 ± 0.09 (1.2%)	0.589	0.90 ± 0.09	0.004 ± 0.09 (0.4%)	0.845
Swing time (seconds)	0.28 ± 0.04	0.002 ± 0.04 (0.7%)	0.828	0.27 ± 0.03	−0.001 ± 0.03 (3.7%)	0.902	0.30 ± 0.03	−0.001 ± 0.03 (0.3%)	0.930
Double support time (seconds)	0.28 ± 0.03	−0.004 ± 0.03 (1.4%)	0.561	0.28 ± 0.03	−0.004 ± 0.03 (1.4%)	0.916	0.30 ± 0.03	0.004 ± 0.03 (1.3%)	0.583
Stride time variability (% CV)	0.07 ± 0.04	−0.004 ± 0.04 (5.7%)	0.636	0.04 ± 0.02	−0.001 ± 0.03 (2.5%)	0.880	0.12 ± 0.03	−0.01 ± 0.04 (8.3%)	0.393
Step length variability (% CV)	0.05 ± 0.02	−0.003 ± 0.03 (6%)	0.516	0.03 ± 0.01	0.004 ± 0.02 (13.3%)	0.260	0.06 ± 0.01	0.003 ± 0.02 (5%)	0.446
Step time variability (% CV)	0.05 ± 0.03	−0.002 ± 0.03 (4%)	0.730	0.03 ± 0.02	−0.0004 ± 0.02 (1.3%)	0.930	0.09 ± 0.02	−0.01 ± 0.03 (11.1%)	0.210
Step velocity variability (% CV)	0.11 ± 0.04	−0.008 ± 0.04 (7.3%)	0.352	0.06 ± 0.02	0.01 ± 0.04 (16.7%)	0.163	0.13 ± 0.03	0.004 ± 0.03 (3.1%)	0.657
Stance time variability (% CV)	0.06 ± 0.03	−0.005 ± 0.03 (8.3%)	0.384	0.03 ± 0.02	−0.002 ± 0.02 (6.7%)	0.665	0.10 ± 0.03	−0.01 ± 0.03 (10%)	0.340

(Continued)

TABLE 2 | Continued

Gait parameters supervised assessment	Supervised assessment						Free-living assessment		
	TUG normal			10-meter walk test			Bouts longer than 60 s		
	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value
Swing time variability (% CV)	0.03 ± 0.02	−0.006 ± 0.02 (20%)	0.884	0.02 ± 0.01	0.001 ± 0.02 (20%)	0.862	0.05 ± 0.02	−0.01 ± 0.02 (20%)	0.216
Double support variability (% CV)	0.03 ± 0.02	−0.003 ± 0.02 (10%)	0.455	0.02 ± 0.01	0.00002 ± 0.01 (0.1%)	0.994	0.05 ± 0.02	−0.01 ± 0.02 (20%)	0.163
Stride time asymmetry (% CV)	0.01 ± 0.01	0.002 ± 0.02 (20%)	0.959	0.01 ± 0.01	−0.001 ± 0.01 (10%)	0.584	0.01 ± 0.004	−0.001 ± 0.01 (1%)	0.300
Step time asymmetry (% CV)	0.02 ± 0.02	0.005 ± 0.02 (25%)	0.262	0.03 ± 0.02	0.003 ± 0.02 (10%)	0.496	0.03 ± 0.02	−0.01 ± 0.02 (33.3%)	0.318
Stance time asymmetry (% CV)	0.02 ± 0.02	−0.003 ± 0.02 (15%)	0.622	0.02 ± 0.02	−0.003 ± 0.02 (15%)	0.420	0.02 ± 0.01	−0.01 ± 0.02 (50%)	0.153
Swing time asymmetry (% CV)	0.02 ± 0.01	0.008 ± 0.02 (40%)	**0.036**	0.02 ± 0.01	−0.003 ± 0.02 (15%)	0.423	0.02 ± 0.01	−0.01 ± 0.02 (50%)	0.195
Step length asymmetry (% CV)	0.03 ± 0.02	−0.002 ± 0.02 (6.7%)	0.605	0.02 ± 0.02	0.0002 ± 0.02 (1%)	0.959	0.02 ± 0.01	−0.002 ± 0.01 (10%)	0.504

The paired-samples T-test and the Wilcoxon S-R tests were applied for each parameter to investigate the existence of a statistically significant difference between admission and the end of the program (statistical significance was achieved with p-value < 0.05). Bold values is to highlight the outcomes that reached statistical significance.

TABLE 3 | Stepwise multiple linear regression analysis with TUG as a dependent variable and (1) the clinical outcome measures, (2) gait parameters assessed during the 10-meter walk test, in supervised conditions, (3) gait parameters assessed in free-living conditions and analyzed in bouts longer than 60 s, as independent variables.

Dependent variable: TUG change from baseline	Predictors	R^2	Adjusted R^2	R^2 change	F	p-value	Unstandardized B	Standardized coefficients ß	Collinearity VIF
Independent variables: Clinical outcome measures	TUG cognitive	0.75	0.72	0.75	23.59	0.001	0.42	0.86	1.000
Independent variables: Kinematic outcome measures – Supervised assessment	Step length	0.55	0.53	0.55	27.11	0.000	−61.96	−0.74	1.000
Independent variables: Kinematic outcome measures – Free-living assessment	Step time asymmetry	0.55	0.51	0.55	16.79	0.001	104.88	0.74	1.000

a primary outcome in a clinical study. **Appendix 2** summarizes the sample size calculations assuming 10, 20, and 30% change from baseline.

DISCUSSION

Although this study was not designed to conclude on efficacy, the results obtained suggest an overall improvement (**Tables 1**, **2**). This enables us to identify the best predictors of FM changes when PD patients are submitted to a specialized multidisciplinary program. It also enables performing other exploratory analyses to better understand how the outcome measures behave if used as primary outcomes in future studies.

From the pool of outcome measures able to detect at least a small effect size of the intervention, those identified as the best predictors of TUG changes were the TUG Cognitive, step length, and step time asymmetry.

Clinical Assessment

The TUG Cognitive test was the clinical parameter with the best ability to predict TUG changes. This can be explained because the TUG Cognitive is a modified version of the TUG (i.e., it adds a cognitive task to the motor task) (25, 26). Since daily activities frequently require motor and cognitive tasks to be carried out simultaneously, this version of the test may give a more realistic perspective of the patients' FM. However, as it is only a modified version of the same test, some major limitations remain (e.g., it is limited to patients without significant postural instability and is subject to learning effects).

The Mini-BESTest test was not sensitive to the intervention, and the observed differences were not statistically significant. However, this is a very complete clinical test that includes the assessment of static and dynamic balance (i.e., biomechanical constraints, verticality/stability limits, anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait) and the TUG Cognitive test itself (5, 13, 14). Although not formally validated to measure FM, this instrument provides a more complete approach to the three anchors of the concept, i.e., gait, balance, and postural transitions (5, 13, 14). We believe that future studies should clarify the Mini-BESTest's suitability to assess FM changes.

Clinical vs. Kinematic Assessment

Our results identified step length and step time asymmetry as the gait parameters with the best ability to predict TUG (and FM) changes, in supervised and FL conditions, respectively. Compared with the TUG, both showed higher responsiveness to change.

FM is a major source of disability for PD patients and requires an individualized and complex management approach that strongly depends on the information about the actual state of the patients in their daily lives (1). Although the TUG remains the gold standard for assessing PD FM, as is the case for all traditional clinical scales, it presents some limitations that can be overcome by the use of TOMs (27).

To optimize the accuracy of clinical evaluation, evidence suggests that patients should focus on the goal of the task asked and not on the movement required to achieve it. This is hampered when a reassessment using the TUG test takes place after a multidisciplinary program. During the physiotherapy sessions of the program, patients usually learn safety strategies to apply during walking and postural transitions that require being focused on the movement while doing it. Many of these strategies are applied during the TUG test, thereby hindering its ability to detect an improvement in patients' FM (27).

There is increasing evidence that TOMs may improve the sensitivity, accuracy, reproducibility, and feasibility of data capture, detecting improvements that the clinical tests are not able to find (6). Previous studies reported a greater sensitivity of TOMs, over the traditional clinical scales, in differentiating the gait and turning of PD patients from healthy controls (27).

The use of outcome measures of higher sensitivity and accuracy, which can predict TUG changes (step length and step time asymmetry), may help obtain a more complete and objective evaluation of patients' FM limitations and thereby favoring more personalized clinical decision making (6, 28). In the research field, the use of standardized outcome measures, with high responsiveness to change and low variability, not only enables better interpretation and discussion of research findings but also avoids unnecessary increases in complexity, duration, and financial expenses of studies (6).

Despite the benefits associated with the use of TOMs for assessing FM, from our experience, they also have some

limitations. The currently available sensors, although smaller and lighter, remain too intrusive, leading patients to reject their use. Also, in PD patients with behavioral changes, the use of sensors may not be possible. One of the patients was excluded from the FL analysis, after having thrown away the sensors during an episode of delirium.

Supervised vs. Free-Living Assessment

According to our results, the responsiveness of the outcomes and their ability to predict TUG changes differ depending on the type of assessment.

There is a growing awareness that, depending on the assessment conditions, the results related to gait and postural transitions can differ substantially, with a weak association between the results in both scenarios having been reported (28, 29). Many factors can contribute to these differences: (1) the clear and standardized environment in supervised assessment, in the absence of distractions, emphasizes a measure of someone's best, rather than their usual performance; (2) FL conditions, with narrow corridors, variable lighting, obstacles, etc., forces continuous gait adaptations, inducing large variability and asymmetry in walking patterns; (3) movements in a supervised assessment are triggered by instruction, while FL movements are usually self-initiated, goal-directed, and embedded in a rich behavioral environment; and (4) patients frequently improve their performance when they know that they are being evaluated (21, 28, 29).

In the FL context, gait parameters, and therefore FM, may be influenced not only by physical characteristics but also by ongoing environmental and cognitive challenges (29). Variability and asymmetry-related parameters are especially sensitive to behavioral and environmental factors, better reflecting patients' interaction with the context and their ability to adapt gait patterns (28, 29). We hypothesize that this may be one of the causes of step time asymmetry identified as the FL kinematic gait parameter, which better predicts TUG changes. Although it has only captured a small effect size of the intervention, having a high ecological validity, FL step time asymmetry seems to provide a more realistic picture of the impact of the disease in PD FM, whereby even small changes should be valued (27).

Length of Walking Bouts

We performed an exploratory analysis to understand how FL gait parameters behave when different bout lengths were used in the analysis. According to our results, there appears to be a link between the ability to capture an improvement and the length of the bout. The longer the walking bouts, the higher the velocity and length of stride/step and the lower the cadence, variability, and asymmetry.

A previous study exploring the impact of environment and bout length in PD patients' gait reached similar conclusions, i.e., the longer the bouts, the higher the increase in step velocity, step length and swing time variability and the lower the variability and asymmetry of gait. The authors also reported that the parameters analyzed in longer bouts were more similar to those measured in a supervised environment (21).

Walking bout length is influenced by the type of environment and activity patients are engaged in (21). Currently, the most suitable length of walking bouts used in FL analysis is not established (21). The majority of studies investigating gait characteristics in FL conditions use bouts longer than 60 s. However, it has been reported that PD patients in FL conditions more often perform a large number of very short bouts ($\leq$10 s) than prolonged bouts (21). According to the literature, bouts of 30–60 s usually represent indoor activities, while bouts $>$ 120 s correspond to walking outdoors. Only bouts with at least 30–60 s were able to discriminate PD patients from healthy controls (21).

Limitations

This study presents two major limitations: a small sample size ($n = 24$) and high heterogeneity in the included population. We believe that these aspects may overestimate the variability of the measurement tools, influencing the power calculations. We expect that future studies with a large and less heterogeneous population will need a smaller sample size. As an open non-controlled study, we hypothesize that in future larger, controlled trials, the detected effect size will be smaller. However, since this was not an efficacy study (due to the absence of a control group) and an improvement was observed, despite these limitations, we believe that our results are informative and important for the PD field. Also, we believe that the use of broad inclusion criteria in this study not only did not interfere with its aims but also better mimics the real scenario of the intervention and assessments, increasing its external validity. To minimize the impact, the study was conducted in a single tertiary care center.

According to our results, the TUG test did not achieve a statistically significant improvement. However, some of the gait parameters (including step length) not only reached a statistically significant result but also showed a higher sensitivity to change. Since all other results point to an improvement at the end of the program, we believe that this difference may be explained by the greater accuracy and sensitivity to change of TOMs when compared to the traditional clinical scales. A previous study has already highlighted this potential problem, highlighting that the validation of TOMs is often based on their correlation with validated clinical measures and that results may be undesirable, due to the superior capacity of TOMs for capturing the phenomena of interest (30).

CONCLUSION

Although we cannot attribute the observed improvements to the specialized multidisciplinary program, our results suggest a methodological approach for identifying outcome measures to assess FM changes, in response to a therapeutic intervention.

From all the outcome measures included in the study, only the TUG Cognitive, step length, and FL step time asymmetry were identified as having the ability to predict TUG changes. The kinematic parameters seem to present higher responsiveness to change when compared with the traditional clinical tests. According to our results, supported by published evidence, the longer the bouts, the higher the sensitivity of detecting an improvement.

Our results support the use of kinematic assessments in evaluating the effect of multidisciplinary interventions in PD FM. The FL step time asymmetry seems a very promising outcome measure to assess FM in PD. Nevertheless, there are some aspects of FL assessments that need to be improved, such as establishing the best data collection protocol and developing less intrusive sensors.

To improve the interpretation of results of responsiveness to change in a complex and fluctuating disease such as PD, it is necessary to clarify the variation of gait parameters in the absence of pharmacological and non-pharmacological therapeutic interventions. This requires repeating the assessment protocol in ON- and OFF-state medication and several times during a short period, thereby clarifying the effect of pharmacological interventions, permitting an understanding of the impact of motor fluctuations and minimizing the interference of disease progression. More studies are also needed to explore the cut-off points from which FM is considered to be affected and the smallest amount of change, in the identified parameters, considered important by the patient or clinician (i.e., the minimal clinically important difference).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CNS Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

RB-M and JF contributed to the conception and design of the study. The CNS physiotherapy study group contributed to the participants' recruitment and assessments. RB-M performed the assessments and performed the statistical analysis. DB, GF, and TG analyzed kinematic data. RB-M and JF drafted the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

FUNDING

The authors would like to acknowledge the support of Fundação para a Ciência e a Tecnologia (FCT) (SFRH/BD/120773/2016 to RB-M; SFRH/BD/144242/2019 to DB, UIDB/00408/2020 and UIDP/00408/2020 to LASIGE).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.637620/full#supplementary-material

REFERENCES

1. Bouça-Machado R, Maetzler W, Ferreira JJ. What is functional mobility applied to Parkinson's disease? *J Parkinsons Dis.* (2018) 8:121–30. doi: 10.3233/JPD-171233
2. Bouça-Machado R, Duarte GS, Patriarca M, Castro Caldas A, Alarcão J, Fernandes RM, et al. measurement instruments to assess functional mobility in Parkinson's disease: a systematic review. *Movement Disord Clin Pract.* (2020) 7:129–39. doi: 10.1002/mdc3.12874
3. Bhidayasiri R, Martinez-Martin P. Clinical assessments in Parkinson's disease. *Int Rev Neurobiol.* (2017) 132:129–82. doi: 10.1016/bs.irn.2017.01.001
4. Verheyden G, Kampshoff CS, Burnett ME, Cashell J, Martinelli L, Nicholas A, et al. Psychometric properties of 3 functional mobility tests for people with Parkinson disease. *Phys Ther.* (2014) 94:230–9. doi: 10.2522/ptj.20130141
5. Bloem BR, Marinus J, Almeida Q, Dibble L, Nieuwboer A, Post B, et al. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: critique and recommendations. *Mov Disord.* (2016) 31:1342–55. doi: 10.1002/mds.26572
6. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson disease: challenges and opportunities. *Mov Disord.* (2016) 31:1272–82. doi: 10.1002/mds.26642
7. Muro-de-la-Herran A, García-Zapirain B, Méndez-Zorrilla A. Gait analysis methods: an overview of wearable and non-wearable systems, highlighting clinical applications. *Sensors.* (2014) 14:3362–94. doi: 10.3390/s140203362
8. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, 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.* (2008) 23:2129–70. doi: 10.1002/mds.22340
9. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
10. Martínez-Martín P, Rojo-Abuin JM, Rodríguez-Violante M, Serrano-Dueñas M, Garretto N, Martínez-Castrillo JC, et al. Analysis of four scales for global severity evaluation in Parkinson's disease. *NPJ Park Dis.* (2016) 2:16007. doi: 10.1038/npjparkd.2016.7
11. Podsiadlo D, Richardson S. The timed "up & go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* (1991) 39:142–8. doi: 10.1111/j.1532-5415.1991.tb01616.x
12. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the timed 'up, & go' test in people with Parkinson disease. *Phys Ther.* (2001) 81:810–8. doi: 10.1093/ptj/81.2.810
13. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the balance evaluation systems test: the mini-BESTest. *J Rehabil Med.* (2013) 42:323–31. doi: 10.2340/16501977-0537
14. Leddy AL, Crowner BE, Earhart GM. Utility of the mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J Neurol Phys Ther.* (2011) 35:90–7. doi: 10.1097/NPT.0b013e31821a620c

15. Mayhew T, Rothstein J. Measurement of muscle performance with instruments. *Percept Mot Skills.* (1995) 80:163–6. doi: 10.2466/pms.1995.80.1.163
16. Duncan RP, Leddy AL, Earhart GM. Five times sit-to-stand test performance in Parkinson's disease. *Arch Phys Med Rehabil.* (2011) 92:1431–6. doi: 10.1016/j.apmr.2011.04.008
17. Bjornestad A, Tysnes OB, Larsen JP, Alves G. Reliability of three disability scales for detection of independence loss in Parkinson's disease. *Parkinsons Dis.* (2016) 2016:1941034. doi: 10.1155/2016/1941034
18. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK biobank study. *PLoS ONE.* (2017) 12:e0169649. doi: 10.1371/journal.pone.0169649
19. Hickey A, Del Din S, Rochester L, Godfrey A. Detecting free-living steps and walking bouts: validating an algorithm for macro gait analysis. *Physiol Meas.* (2017) 38:N1–N15. doi: 10.1088/1361-6579/38/1/N1
20. Lyons GM, Culhane KM, Hilton D, Grace PA, Lyons D. A description of an accelerometer-based mobility monitoring technique. *Med Eng Phys.* (2005) 27:497–504. doi: 10.1016/j.medengphy.2004.11.006
21. Del Din S, Godfrey A, Galna B, Lord S, Rochester L. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. *J Neuroeng Rehabil.* (2016) 13:46. doi: 10.1186/s12984-016-0154-5
22. Pham MH, Elshehabi M, Haertner L, Del Din S, Srulijes K, Heger T, et al. Validation of a step detection algorithm during straight walking and turning in patients with Parkinson's disease and older adults using an inertial measurement unit at the lower back. *Front Neurol.* (2017) 8:1–9. doi: 10.3389/fneur.2017.00457
23. Aron, A. *Statistics for Psychology* (2003).
24. Serrao M, Chini G, Caramanico G, Bartolo M, Castiglia SF, Ranavolo A, et al. Prediction of responsiveness of gait variables to rehabilitation training in Parkinson's disease. *Front Neurol.* (2019) 10:826. doi: 10.3389/fneur.2019.00826
25. Campbell CM, Rowse JL, Ciol MA, Shumway-cook A. The effect of cognitive demand on timed up and go performance in older adults with and without Parkinson disease. *Neurol Rep.* (2003) 27:2–7. doi: 10.1097/01253086-200327010-00002
26. Hofheinz M, Schusterschitz C. Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin Rehabil.* (2010) 24:831–42. doi: 10.1177/0269215510367993
27. Del Din S, Godfrey A, Mazzà C, Lord S, Rochester L. Free-living monitoring of Parkinson's disease: lessons from the field. *Mov Disord.* (2016) 31:1293–313. doi: 10.1002/mds.26718
28. Warmerdam E, Hausdorff JM, Atrsaei A, Zhou Y, Mirelman A, Aminian K, et al. Long-term unsupervised mobility assessment in movement disorders. *Lancet Neurol.* (2020) 19:462–70. doi: 10.1016/S1474-4422(19)30397-7
29. Rispens SM, Van Dieën JH, Van Schooten KS, Lizama LE, Daffertshofer A, Beek PJ, et al. Fall-related gait characteristics on the treadmill and in daily life. *J Neuroeng Rehabil.* (2016) 13:12. doi: 10.1186/s12984-016-0118-9
30. Artusi CA, Mishra M, Latimer P, Vizcarra JA, Lopiano L, Maetzler W, et al. Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases. *Park Relat Disord.* (2018) 46:S53–6. doi: 10.1016/j.parkreldis.2017.07.022

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