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Parkinson's disease: Technological trends for diagnosis and treatment improvement

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Parkinson's disease: Technological trends for diagnosis and treatment improvement

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Editorial: Parkinson's disease: Technological trends for diagnosis and treatment improvement

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Editorial on the Research Topic
Parkinson's disease: Technological trends for diagnosis and treatment improvement

Parkinson's Disease (PD) is a very complex condition, presenting a wide range of motor and non-motor symptoms. It is considered the second neurodegenerative condition, after Alzheimer's Disease, in terms of prevalence, and some recent studies announce a drastic rising in the number of affected persons in the coming years. PD has no cure and its progression is always ineluctable. According to normal medical praxis, after the initial diagnosis, a pharmacological treatment is commonly started to improve the Quality of Life (QoL) of the affected person.

Nowadays, neurologists and related professionals can obtain benefits from the use of correctly addressed technologies. These possible benefits can help them in three different axes: (a) early detection of the disease for early initiation of the possible treatment, (b) obtaining additional objective information for a better adjustment of the treatment and (c) identification of candidates for advanced device-aided therapies (Second-line therapies—SLT) like Deep Brain Stimulation (DBS) or infusion pumps.

The present Research Topic entitled "*Parkinson's Disease: Technological Trends for Diagnosis and Treatment Improvement*" explores the contribution of technology, considered in a wide sense, to the improvement of healthcare services in the domain of PD. The 10 manuscripts included in this Research Topic deal with very different aspects and approaches, but all of them concern the improvement of the current treatments, the consideration of a new therapy or other considerations that can contribute to improving the QoL of the patients or their awareness about the disease.

A commonly reported and accepted difficulty that neurologists note, during the diagnosis and follow-up patients' visits, is the difficulty that many of them have to correctly identify and report their symptoms and the main states and temporal evolution of their condition. Timpka et al. present the conclusions about the observed discrepancies in the Home-diary annotations done by the patients participating in the study and those done by the qualified observers. The paper formulates a question about when the community will have the availability of an automatic or objective Home-diary, based on the technology. In this regard, the papers by Rodríguez-Martin et al., Zhang et al., and Geritz et al. contribute to this aspect. The first one presents a complete review of an already available CE-marked medical device that is commercialized to become a real Holter for the monitorization of the PD-related motor symptoms in real-life conditions. This solution is based on IMU and Machine Learning algorithms. In the other papers, the authors use IMU and MEMS-based

technology for the identification of gait parameters permitting to distinguish and identify people affected by PD or to predict spatio-temporal walking parameters in hospitalized PD patients.

Apart from the above-mentioned technologies, many others can be applied and contribute to the early detection of PD and better diagnosis. For example, Suppa et al. address Machine Learning methods applied to voice disorders recognition for early assessment of PD and its monitoring along the treatment. An additional contribution is the proposal of a new score (the LR value) as a new measure of voice impairment. Another paper by Xu et al. applies phonation tests to persons affected by PD and makes a comparison with those done by healthy people. Comparison is done on the observation of the facial muscles' movement using a concrete commercial image treatment software platform. In another context, a better understanding of PD can be obtained when using signal processing analysis of the different bands in the EEG data of different PD patients. The paper contributed by Conti et al. extracts interesting conclusions on this topic, permitting the advance in the monitoring activity of recently diagnosed patients.

The rest of the papers contained in the Research Topic deals with complementary, but very promising usage of the technology to progress and improve the QoL of patients. For example, the Bianchini et al. paper explores the feasibility, safety and effectiveness of telerehabilitation in mild-to-moderate PD patients, demonstrating that remote physiotherapy programs could be viable and very useful to overcome situations with limited access to healthcare service (as a pandemic situation, for example).

Among SLT, DBS can be applied to selected advanced PD patients, but exhibits some problems in the process of programming and adjusting the stimulation parameters. Mei et al., apply image analysis techniques for the improvement of the DBS programming, concluding that using imaging-guided programming of directional DBS led to reducing programming time and the collection of side effects for the patients.

The last paper in the Research Topic, corresponds to Baek et al. on the possible future use of Focused Ultrasound (FUS) stimulation for the treatment of various brain diseases, including PD. The paper discusses future possible applications and the related challenges of this promising technology.

In conclusion, the contents of the present Research Topic allow us to be very confident with the existing and coming technologies. The main existing challenge is to completely overpass the still-existing adoption barriers. The benefits of the use of the technology will be evident when its adoption by all healthcare actors, including the patients, will be a reality.

Author contributions

JC: conception, design, drafting, and critical revision of the editorial. AS: conception, design, and critical revision of the editorial. GÓ: critical revision of the editorial. All authors contributed to the article and approved the submitted version.

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.

Publisher's note

Abbreviations: PD, Parkinson's Disease; IMU, inertial measurement unit; DBS, deep brain stimulation; QoL, quality of life; SLT, second-line therapy; MEMS, microelectromechanical system; FUS, focused ultrasound.

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Voice in Parkinson's Disease: A Machine Learning Study

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Introduction: Parkinson's disease (PD) is characterized by specific voice disorders collectively termed hypokinetic dysarthria. We here investigated voice changes by using machine learning algorithms, in a large cohort of patients with PD in different stages of the disease, OFF and ON therapy.

Methods: We investigated 115 patients affected by PD (mean age: 68.2 ± 9.2 years) and 108 age-matched healthy subjects (mean age: 60.2 ± 11.0 years). The PD cohort included 57 *early-stage* patients (Hoehn &Yahr ≤2) who never took L-Dopa for their disease at the time of the study, and 58 *mid-advanced-stage* patients (Hoehn &Yahr >2) who were *chronically-treated* with L-Dopa. We clinically evaluated voices using specific subitems of the Unified Parkinson's Disease Rating Scale and the Voice Handicap Index. Voice samples recorded through a high-definition audio recorder underwent machine learning analysis based on the support vector machine classifier. We also calculated the receiver operating characteristic curves to examine the diagnostic accuracy of the analysis and assessed possible clinical-instrumental correlations.

Results: Voice is abnormal in *early-stage* PD and as the disease progresses, voice increasingly degradres as demonstrated by high accuracy in the discrimination between healthy subjects and PD patients in the *early-stage* and *mid-advanced-stage*. Also, L-dopa therapy improves but not restore voice in PD as shown by high accuracy in the comparison between patients OFF and ON therapy. Finally, for the first time we achieved significant clinical-instrumental correlations by using a new score (LR value) calculated by machine learning.

Conclusion: Voice is abnormal in *early-stage* PD, progressively degrades in *mid-advanced-stage* and can be improved but not restored by L-Dopa. Lastly, machine learning allows tracking disease severity and quantifying the symptomatic effect of L-Dopa on voice parameters with previously unreported high accuracy, thus representing a potential new biomarker of PD.

Keywords: Parkinson's disease, hypokinetic dysarthria, voice analysis, machine learning, L-Dopa

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INTRODUCTION

Patients with Parkinson's disease (PD) often complain of a variable impairment of voice emission including hypophonia, mono-pitch and mono-loudness speech, hypokinetic articulation, collectively called hypokinetic dysarthria (1–4). Parkinsonian patients may manifest voice disorders in the early stage of the disease, with growing evidence showing voice impairment occurring even in the prodromal phase of PD (2, 5–9). Also, voice typically worsens over the course of the disease leading to severe voice impairment in more advanced stages of PD (1, 2). Furthermore, the standardized clinical assessment of voice in PD is currently based only on qualitative evaluation (i.e., a specific subitem of the Unified Parkinson's Disease Rating Scale—UPDRS) (2, 10) thus precluding the objective assessment of the voice impairment in this disorder.

Over recent years, quantitative approaches based on spectral analysis have been developed to examine objectively voice samples (11). Spectral analysis in patients with PD allowed to demonstrate several abnormalities in specific voice features such as reduced fundamental frequency and harmonics-to-noise ratio, and increased jitter and shimmer (3, 12–16). The human voice however, represents a complex phenomenon characterized by high-dimensional data based on an exponential number of features. Accordingly, besides the independent examination through spectral analysis of specific voice features (i.e., fundamental frequency), more advanced techniques able to analyse and dynamically combine and high-dimensional datasets of voice features such as machine-learning algorithms (17–23) would improve significantly the accuracy of the objective classification of voice samples in PD. Indeed, machine learning has allowed to classify voice impairment objectively and automatically in a number of neurologic disorders, with previously unreported high accuracy (19, 21, 22).

To date, concerning the application of machine learning analysis in PD, only a few preliminary studies in rather small and clinically heterogeneous cohorts of patients have been reported (24–26). It is therefore important to examine instrumentally voice impairment in a large and clinically well-characterized cohort of PD. Also, it is relevant to verify whether machine learning can recognize the effect of disease severity by discriminating patients in different stages of the disease. Still, given that the symptomatic effect of L-Dopa on voice is still largely a matter of debate (1, 10, 27–33), it is relevant to compare the instrumental voice analysis with machine learning in patients under and not under L-Dopa treatment.

We here investigated voice in a large and clinically well-characterized cohort of patients with PD. Then, to examine the effect of disease severity on voice, we compared voices collected in patients in *early* and *mid-advanced* stage of PD. Still, to investigate the effect of L-Dopa on voice, we compared patients OFF and ON therapy. To verify the effect of the specific speech tasks, we compared voice recordings during the emission of a vowel and a sentence, according to standardized procedures (19, 21, 22). We assessed the sensitivity, specificity, positive and negative predictive values, and accuracy of all diagnostic tests and calculated the area under the receiver operating characteristic (ROC) curves. Lastly, by providing a machine learning measure of voice impairment severity for each patient, we also assessed possible clinical-instrumental correlations. Our hypothesis is that machine learning analysis of speech samples is able to discriminate PD patients from controls, patients in *early* and *mid-advanced stages,* and finally patients OFF and ON therapy, with previously unreported high accuracy.

METHODS

Subjects

We enrolled a total of 115 patients affected by PD (68.2 ± 9.2 years, range 47–91 years) and 108 age-matched healthy subjects (HS) (60.2 ± 11.0 years). Participants were recruited at the IRCCS Neuromed Institute and at the Department of Systems Medicine, Tor Vergata University of Rome, Italy. All participants (HS and PD patients) were native Italian speakers and non-smokers. None of the participants reported bilateral/unilateral hearing loss, respiratory disorders, other non-neurologic disorders affecting the vocal cords. Participants gave written informed consent, which was approved by the institutional ethics committee (0026508/2019), according to the Declaration of Helsinki.

The clinical diagnosis of PD was made according to current standardized clinical criteria (34). Symptoms and signs associated with PD were scored using Hoehn & Yahr scale (H&Y), UPDRS part III (10). None of the patients manifested atypical parkinsonian symptoms. In all participants (HS and PD patients), we assessed cognitive function and mood using the Mini-Mental State Evaluation (MMSE) (35), the Hamilton Depression Rating Scale (HAM-D) (36) and the Frontal Assessment Battery (FAB). None of the patients were treated with deep brain stimulation or infusional therapies. The clinical evaluation of speech was achieved by two independent raters using two separate clinical scales: (1) the Voice Handicap Index (VHI), Italian version (37), which consists of a patient-based, self-assessed, 30-item scale examining the functional, physical, and emotional aspects of voice disorders; (2) the specific item for speech evaluation included in the UPDRS-III scale (UPDRS-III-v) (10).

The study cohort was designed to include a subgroup of 57 *early stage* patients with PD (H&Y scores ≤2) (38) who never took L-Dopa for their disease at the time of the study *(drug naïve)*(64.2 ± 8.6 years), and a subgroup of 58 *mid-advanced-stage* patients (H&Y scores >2) (38) who were *chronically-treated* with L-Dopa (72.1 ± 8.1 years). We evaluated 31 out of 58 *mid-advanced-stage* patients (71.4 ± 8.7 years) when OFF (after at least 12 h of L-Dopa withdrawal) and ON therapy (1–2 h after the intake of L-Dopa). Participant demographic and clinical features are reported in **Table 1**.

Voice Recordings

Voice recordings were performed by asking participants to produce a specific speech task with their usual voice intensity, pitch, and quality. The speech tasks consisted of the sustained emission of a close-mid front unrounded vowel /e/ for at least 5 s and of the emission of a standardized Italian sentence (19, 22). Voice recordings were collected by using a high-definition audio-recorder H4n Zoom (Zoom Corporation, Tokyo, Japan),

TABLE 1 | Demographic and clinical features of HS and PD.

	Age (years)	Weight (kg)	Height (cm)	DD (years)	MMSE	HAM-D	FAB	H&Y	UPDRS-III OFF	UPDRS-III ON	UPDRS-III-v OFF	UPDRS-III-v ON	VHI OFF	VHI ON
PD (whole group)	68.2 ± 9.2	71.8 ± 11.6	172.1 ± 9.4	5.6 ± 4.7	28.4 ± 2.1	3.5 ± 1.8	16.5 ± 1.4	2.2 ± 0.8	22.3 ± 14.2	–	1.8 ± 1.1	–	16.7 ± 16.9	–
Early-stage PD	64.2 ± 8.6	71.8 ± 10.6	172.9 ± 9.8	2.1 ± 0.9	28.9 ± 1.1	3.2 ± 2.0	16.6 ± 1.0	1.5 ± 0.4	12.1 ± 4.1	–	0.9 ± 0.7	–	7.3 ± 4.9	–
Mid-advanced-stage PD	72.1 ± 8.1	71.9 ± 12.6	171.2 ± 9.0	9.0 ± 4.4	28.0 ± 2.6	3.9 ± 1.6	16.4 ± 1.6	2.8 ± 0.4	32.3 ± 13.5	28.3 ± 13.8	2.7 ± 0.6	2.4 ± 0.5	25.9 ± 19.2	20.0 ± 17.7
HS	70.3 ± 10.3	68.5 ± 10.6	169.0 ± 10.1	–	29.0 ± 0.8	3.3 ± 1.7	16.6 ± 1.1	–	–	–	–	–	–	–

DD, disease duration; MMSE, Mini-Mental State Evaluation; HAM-D, Hamilton Depression Rating Scale; FAB, Frontal Assessment Battery; H&Y, Hoehn and Yahr Scale for assessment stage of PD; HS, healthy subjects; PD, patients with Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; UPDRS-III-v, Unified Parkinson's Disease Rating Scale part III, voice impairment subitem; VHI, Voice Handicap Index; OFF, not-under the effect of L-Dopa; ON, under the effect of L-Dopa. Results are expressed as average ± standard deviation.

connected with a Shure WH20 Dynamic Headset Microphone (Shure Incorporated, USA), which was placed at a distance of 5 cm from the mouth. Voice samples were recorded in linear PCM format (.wav) at a sampling rate of 44.1 kHz, with 16-bit sample size.

Machine Learning Analysis

Each voice sample underwent feature extraction pre-process by using OpenSMILE (audEERING GmbH, Germany) (39). For each voice sample, we extracted 6,139 voice features included in the INTERSPEECH2016 Computational Paralinguistics Challenge (IS ComParE 2016) feature dataset (39). To identify a subset of the most relevant features, the extracted voice features underwent feature selection pre-process using the Correlation Features Selection algorithm (CSF) (40). CFS was applied in order to select (uncorrelated) voice features highly correlated with the class. As a result, redundant and/or irrelevant features were removed from the original dataset. All the selected features were then ranked in order of relevance, by measuring the information gain concerning the class, through the Information Gain Attribute Evaluation (IGAE) algorithm, which is based on the Pearson's correlation method. To further increase the accuracy of results, we used the discretization pre-process, which is an optimization procedure consisting in calculating the best splitting point from the two classes and assigning a binary value to the features. Discretization was achieved using the Fayyad & Irani's discretization method, according to standardized procedures.

Given the relatively small dataset analyzed in the study, the Support Vector Machine (SVM) classifier based on linear kernel was used to achieve a binary classification, reducing the likelihood for "overfitting." We used only the first 30 most relevant features ranked by the IGAE (22). This approach was applied to reduce the number of selected features needed to perform the machine learning analysis, in according to standardized procedures (18, 19, 21, 22). A list of the first 30 features which represent functionals applied to audio low-level descriptors (LLDs)—extracted from the vowel and the sentence for the comparison between HS and PD is reported in **Table 2**. The SVM was trained using the sequential minimal optimization method. Both the procedures of feature selection and classification were performed through MATLAB (MathWorks, USA). The training was performed using an optimization procedure aimed to find the best hyperparameter values for binary classification (i.e., box constraint "C" value, for linear kernel). Different combinations of hyperparameter values were tested by using an optimization scheme that seeks to minimize the model classification error (41, 42).

We performed a further machine learning analysis for clinical-instrumental correlation purposes, after achieving feature extraction and selection, in parallel to the SVM classification procedures. We used a feed-forward artificial neural network (ANN), consisting of a 30-neurons input layer, a 10-neurons hidden layer and a one-neuron output layer. Input for ANN consisted of the first 30 most relevant selected features, which thus matched the 30-neurons input layer. Then, the ANN was trained to calculate a continuous numerical value (the likelihood

TABLE 2 | List of the first 30 selected features for the comparison between HS and PD.

	Vowel			Sentence		
Ranking position	**Families of LLDs**	**LLDs**	**Functionals**	**Families of LLDs**	**LLDs**	**Functionals**
1	RASTA coefficients	Coefficient of band 22	Standard deviation of falling slope	Spectral LLD	Spectral Roll Off point 0.90	Absolute peak range
2	Voicing Related LLD	Fundamental Frequency (fo)	Minimum segment length	Spectral LLD	Spectral Roll Off point 0.50	Inter-quartile 1–3
3	Energy Related LLD	Sum of auditory spectrum	Flatness	Spectral LLD	Spectral Roll Off point 0.50	Quartile 3
4	Spectral LLD	Spectral Flux	Quadratic regression coefficient 1	Energy Related LLD	Zero Crossing Rate	99% percentile
5	RASTA coefficients	Coefficient of band 2	Linear prediction coefficient 4	Spectral LLD	Spectral Variance	Range
6	RASTA coefficients	Coefficient of band 21 (de)	Standard deviation of rising slope	Spectral LLD	Spectral Roll Off point 0.25	Quartile 3
7	Spectral LLD	Spectral Slope (de)	Position of max	Spectral LLD	Spectral Roll Off point 0.25	Linear prediction coefficient 0
8	RASTA coefficients	Coefficient of band 25	Flatness	Spectral LLD	Psychoacoustic Sharpness	1% percentile
9	Spectral LLD	Spectral energy 250–650 Hz	Relative min range	RASTA coefficients	Coefficient of band 8 (de)	Flatness
10	Energy Related LLD	RMS Energy (de)	Linear prediction coefficient 0	Spectral LLD	Spectral Centroid	99% percentile
11	Spectral LLD	Spectral Flux	Standard deviation of falling slope	Spectral LLD	Spectral Roll Off point 0.75	Absolute peak range
12	Voicing Related LLD	Fundamental Frequency (fo)	1% percentile	RASTA coefficients	Coefficient of band 1	Mean of rising slope
13	MFCC	8th Mel Coefficient	Inter-quartile 1–2	Spectral LLD	Spectral Roll Off point 0.25	Quadratic regression coefficient 2
14	RASTA coefficients	Coefficient of band 25 (de)	Gain of linear prediction	MFCC	2nd Mel Coefficient	Quadratic regression quadratic
15	Spectral LLD	Spectral Flux	Range	Spectral LLD	Spectral Roll Off point 0.25	Inter-quartile 2–3
16	Spectral LLD	Spectral Flux	Quadratic regression coefficient 2	Spectral LLD	Spectral Entropy	Range
17	Spectral LLD	Spectral Slope	Gain of linear prediction	Energy Related LLD	Zero Crossing Rate	Standard deviation of rising slope
18	Spectral LLD	Spectral Slope	Standard deviation of rising slope	Spectral LLD	Spectral Roll Off point 0.50	Quadratic regression coefficient 3
19	Spectral LLD	Spectral Variance (de)	Relative peak mean	Voicing Related LLD	Fundamental frequency	Inter-quartile 2–3
20	MFCC	5th Mel Coefficient (de)	Skewness	Spectral LLD	Spectral Entropy	Absolute peak mean
21	RASTA coefficients	Coefficient of band 4 (de)	Skewness	MFCC	3rd Mel Coefficient	1% percentile
22	Energy Related LLD	RMS Energy	Mean of falling slope	Spectral LLD	Spectral Variance	Inter-quartile 2–3
23	Spectral LLD	Spectral Roll Off point 0.75	Linear prediction coefficient 3	RASTA coefficients	Coefficient of band 18	Position of min
24	RASTA coefficients	Coefficient of band 5	Linear prediction coefficient 4	MFCC	3rd Mel Coefficient	Relative peak mean
25	Energy Related LLD	Zero Crossing Rate	Linear prediction coefficient 0	Spectral LLD	Spectral Kurtosis	Absolute peak range
26	MFCC	4th Mel Coefficient (de)	Relative peak range	RASTA coefficients	Coefficient of band 9 (de)	Flatness
27	Voicing Related LLD	Shimmer (Local)	Position of max	RASTA coefficients	Coefficient of band 4	Position of min
28	RASTA coefficients	Coefficient of band 2	Linear prediction coefficient 3	Spectral LLD	Spectral Centroid	1% percentile
29	RASTA coefficients	Coefficient of band 1 (de)	Standard deviation	Spectral LLD	Spectral Skewness	Mean segment length
30	Voicing Related LLD	Shimmer (Local) (de)	Quadratic regression coefficient 2	RASTA coefficients	Coefficient of band 22	Position of min

The table refers to selected voice features for the comparison between healthy subjects and patients with Parkinson's disease. Ranking of the first 30 features (functionals applied to low-level descriptors—LLDs) extracted using a dedicated software (OpenSMILE) and selected using Information Gain Attribute Evaluation (IGAE) algorithm for the comparison between healthy subjects and the whole group of patients with PD, during the sustained emission of the vowel and sentence. MFCC, mel-frequency cepstral coefficient; de, first derivative of the LLD.

ratio—LR), ranging from 0 to 1 and reflecting the degree of voice impairment in each patient with PD (i.e., the closer the LRs to 1, the higher the degree of voice impairment). ANN was trained by using the same selected features used to train the SVM. The experimental paradigm is also summarized in **Figure 1** (39–42).

Statistical Analysis

The normality of all parameters was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney *U* test was used to compare demographic and anthropometric parameters in HS and PD patients. The Mann-Whitney U test was also used to compare demographic parameters and clinical scores in *early-stage* and *mid-advanced-stage* patients. The Wilcoxon signed-rank test was used to compare UPDRS-III, UPDRS-III-v, and VHI scores in *mid-advanced-stage* patients when OFF and ON therapy. The Wilcoxon signed-rank test was also used to compare the possible L-Dopa-induced improvement of voice (UPDRS-III-v-ON/OFF*100) and motor symptoms (UPDRS-III-ON/OFF*100) in *mid-advanced-stage* patients.

ROC analyses were calculated to identify the optimal diagnostic cut-off values to discriminate between HS and PD, *early-stage* and *mid-advanced-stage* patients, and finally *mid-advanced-stage* patients OFF and ON therapy. We reported in detail the Sensibility (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Accuracy (Acc.). Also, we showed the output of the ROC analysis by calculating the Youden Index (YI) and its optimal criterion value, the associated criterion (Ass. Crit.). We also compared the independent ROC curves referring to the emission of the vowel and the sentence.

Spearman's rank correlation coefficient was used to assess correlations between clinical scores and LR values.

A p-value <0.05 was considered statistically significant.

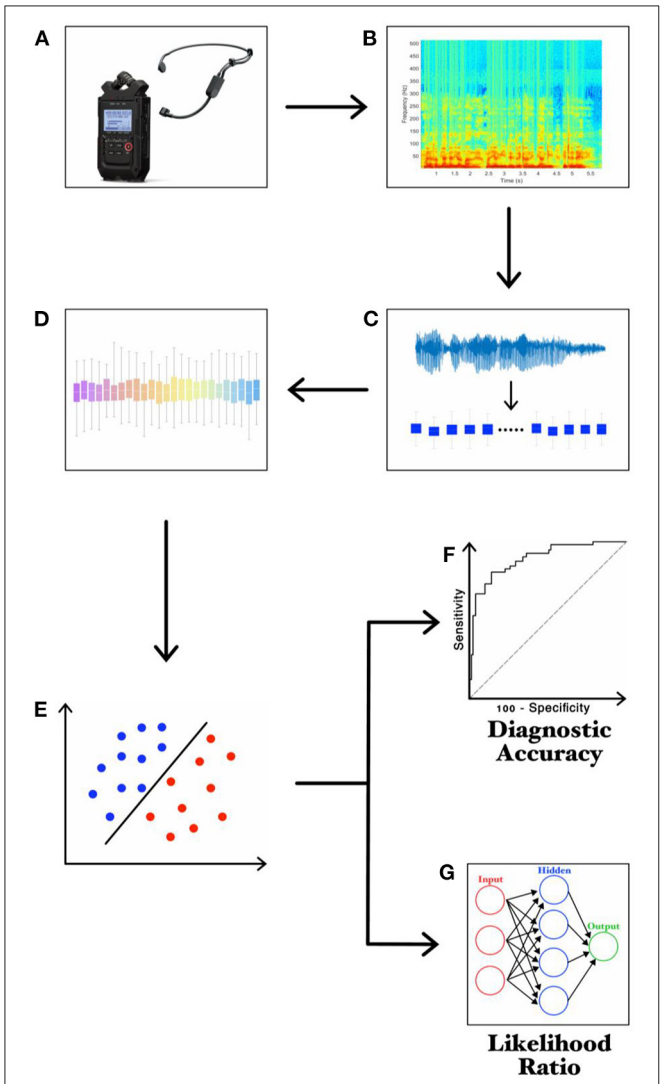

FIGURE 1 | Experimental design. **(A)** recording of voice samples through a high-definition audio recorder; **(B)** narrow-band spectrogram of the acoustic voice signal; **(C)** feature extraction; **(D)** feature selection; **(E)** feature classification; **(F)** ROC curve analysis; **(G)** LR values calculated through ANN.

RESULTS

Demographic and anthropometric parameters were normally distributed in HS, in PD as well as in *early-stage* and *mid-advanced-stage* patients ($p > 0.05$). Weight, height, and BMI were comparable among groups ($p > 0.05$). Mean age was comparable between HS and *mid-advanced-stage* patients ($p > 0.05$), whereas it was higher in HS and *mid-advanced-stage* patients than in *early-stage* patients ($p < 0.05$). MMSE, HAM-D and FAB were comparable among groups ($p > 0.05$ for all comparisons). *Mid-advanced-stage* patients showed higher scores on the H&Y, UPDRS-III, UPDRS-III-v and VHI scales than *early-stage* patients ($p < 0.05$ for all comparisons). The L-Dopa-induced improvement of voice was lower than that in the remaining motor symptoms ($p < 0.05$) (**Table 1**).

Voice Impairment in PD

We found that 84% of the patients included in our cohort (97 out of 115 patients) manifested a variable degree of clinically overt voice impairment (UPDRS-III-v $\geq$1). Also, we found a clinically overt voice impairment in 68% of *early-stage* patients and 100% of *mid-advanced-stage* patients.

Voice samples collected in 7 patients with PD (3 patients from the *early-stage* subgroup and 4 patients from the *mid-advanced-stage* subgroup including voice recordings collected in 2 patients ON and OFF therapy) were excluded from the instrumental analysis owing to file corruption. We first compared voice samples recorded during the emission of vowel and sentence in HS and the whole group of patients. This analysis showed a significant and comparable diagnostic performance between speech tasks (delta-AUC = 0.002, $z = 0.605$, SE = 0.036, $p = 0.54$) (**Figure 2A**, **Table 3**).

When discriminating HS and *early-stage* patients, ROC analyses identified high accuracy with comparable results between speech tasks (delta-AUC = 0.024, $z = 0.520$, SE = 0.046, $p = 0.60$) (**Figure 2B**, **Table 3**).

When comparing HS and *mid-advanced-stage* patients OFF therapy, ROC analyses again showed high classification accuracy

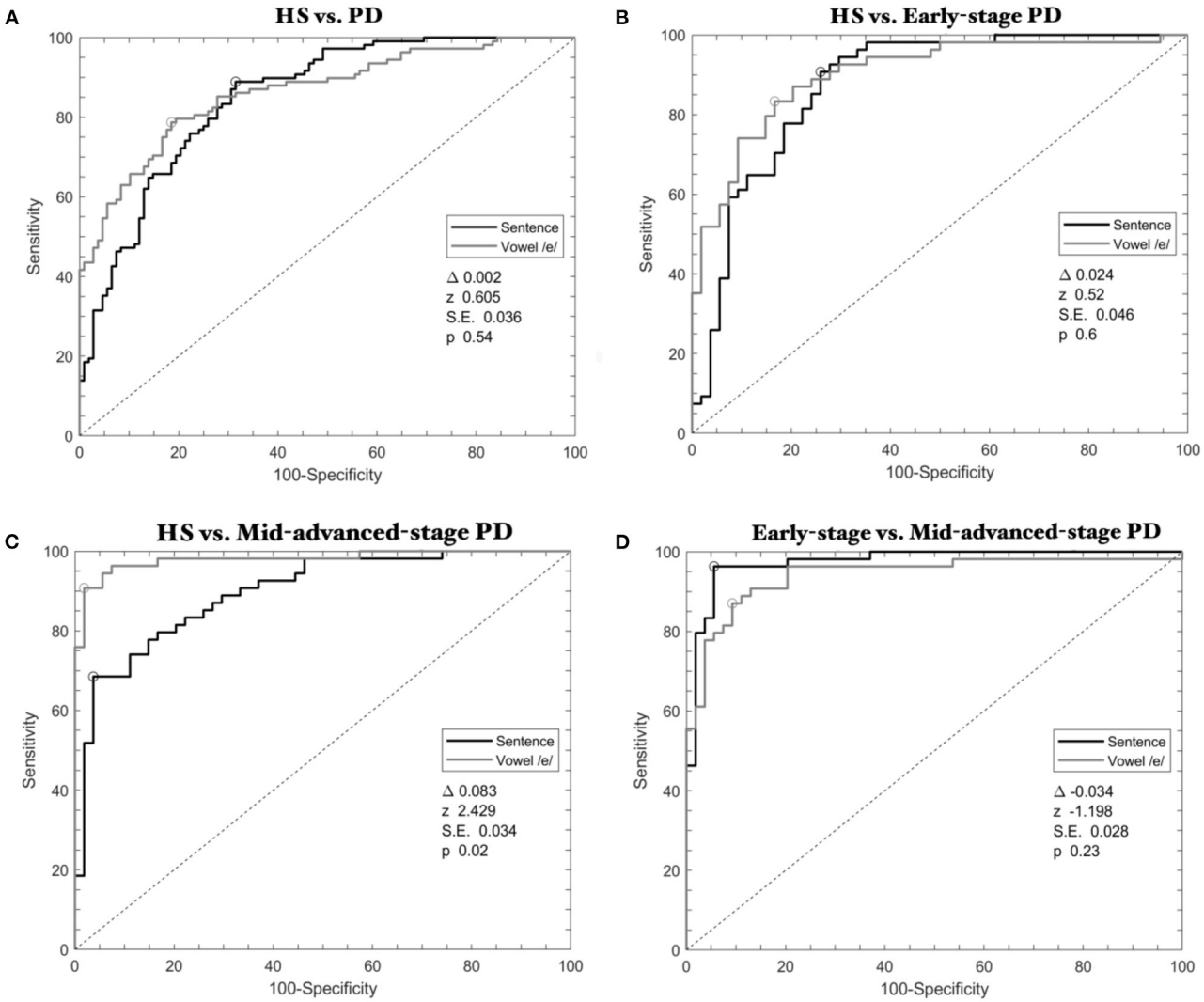

FIGURE 2 | ROC curves calculated through SVM classifier in Parkinson's disease. **(A)** HS vs. the whole group of PD patients; **(B)** HS vs. *early-stage* patients; **(C)** HS vs. *mid-advanced-stage* patients OFF therapy; **(D)** *Early-stage* vs. *mid-advanced-stage* patients OFF therapy. Gray lines refer to the emission of the vowel, whereas black lines refer to the sentence.

but the analysis showed higher results for the vowel than the sentence (delta-AUC = 0.083, $z = 2.429$, SE = 0.034, $p = 0.02$) (**Figure 2C**, **Table 3**).

Also, when discriminating *early-stage* and *mid-advanced-stage* patients, ROC curves showed high and comparable results between speech tasks (delta-AUCs = −0.034, $z = -1.198$, SE = 0.028, $p = 0.23$) (**Figure 2D**, **Table 3**).

The Effect of L-Dopa on Voice

We found that pharmacological treatment with L-Dopa induced a significant clinical improvement of both motor and voice impairment, as demonstrated by reduced UPDRS-III (PD-ON: 28.3 ± 13.8; PD-OFF: 32.3 ± 13.5; $z = -4.9$; W = 0; $p < 0.01$), UPDRS-III-v (PD-ON: 2.4 ± 0.5; PD-OFF: 2.7 ± 0.6; $z = -2.9$; W = 0; $p < 0.05$) and VHI scores (PD-ON: 20.0 ± 17.7; PD-OFF: 25.9 ± 21.4; $z = -4.9$; W = 0; $p < 0.01$).

When comparing *mid-advanced-stage* patients OFF and ON, ROC analysis showed comparable results between speech tasks with high accuracy (delta-AUC = −0.032, $z = -0.364$, SE = 0.088, $p = 0.72$) (**Figure 3A**, **Table 3**).

When discriminating HS and *mid-advanced-stage* patients ON therapy, ROC analysis showed high classification performance (delta-AUC = −0.072, $z = -1.678$, SE = 0.043, $p = 0.09$) (**Figure 3B**, **Table 3**).

Finally, concerning the comparison between *early-stage* and *mid-advanced-stage* patients when ON therapy, ROC analysis showed high statistical results for both the speech tasks (delta-AUC = −0.007, $z = -0.537$, SE = 0.013, $p = 0.59$) (**Figure 3C**, **Table 3**).

TABLE 3 | Performance of the machine learning algorithm.

Comparisons	Speech-task	Instances	Cross validation	Associated criterion	Youden index	Se (%)	Sp (%)	PPV (%)	NPV (%)	Acc (%)	AUC
HS vs. PD	Vowel	98	10 folds	−0.03	0.60	82.7	77.1	75.0	84.3	79.6	0.870
	Sentence	94	10 folds	0.02	0.57	72.5	84.7	88.0	66.7	77.3	0.848
HS vs. *early-stage* PD	Vowel	67	10 folds	−0.36	0.64	87.0	77.4	74.1	88.9	81.5	0.900
	Sentence	93	10 folds	0.16	0.66	75.8	90.5	92.6	70.4	81.5	0.876
HS vs. mid-*advanced-stage* PD	Vowel	100	10 folds	0.16	0.87	92.7	94.3	94.4	92.6	93.5	0.980
	Sentence	82	10 folds	0.18	0.63	82.7	80.4	79.6	83.3	81.5	0.897
Early-stage vs. *mid-advanced-stage* PD	Vowel	119	10 folds	0.16	0.76	87.2	88.7	88.9	87.0	88.0	0.934
	Sentence	102	10 folds	0.10	0.85	91.1	94.1	94.4	90.7	92.6	0.981
Mid-advanced-stage PD OFF vs. ON	Vowel	22	10 folds	0.02	0.46	69.7	76.0	79.3	65.5	72.4	0.754
	Sentence	6	10 folds	0.03	0.49	71.9	76.9	79.3	69.0	74.1	0.786
HS vs. *mid-advanced-stage* PD ON	Vowel	82	10 folds	0.97	0.66	85.2	80.6	79.3	86.2	82.8	0.913
	Sentence	69	10 folds	−0.01	0.93	96.6	96.6	96.6	96.6	96.6	0.985
Early-stage PD vs. *mid-advanced-stage* PD ON	Vowel	71	10 folds	−0.18	0.94	100	93.5	93.1	100	96.6	0.992
	Sentence	78	10 folds	0.62	0.97	100	96.7	96.6	100	98.3	0.999

Performance of SVM linear classifier elaborating the 30 most relevant selected features during the sustained emission of the vowel and the sentence for seven independent conditions: (1) HS vs. the whole group of PD patients; (2) HS vs. early-stage patients; (3) HS vs. mid-advanced-stage patients; (4) Early-stage vs. mid-advanced-stage patients; (5) Mid-advanced-stage patients OFF vs. ON therapy; (6) HS vs. mid-advanced-stage patients ON therapy; (7) Early-stage patients vs. mid-advanced-stage patients ON therapy. Selected features refer to the number of features able to obtain the best results; instances refer to the number of subjects considered in each comparison; cross validation refers to standardized validation procedures (see methods for details). Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy; AUC, area under the curve.

Correlation Analysis

In the whole group of PD patients, the Spearman test disclosed a positive correlation between disease duration and VHI ($r = 0.64$, $p < 0.01$) (**Figure 4A**), H&Y and UPDRS-III-v scores ($r = 0.76$, $p < 0.01$), and between H&Y and VHI ($r = 0.64$, $p < 0.01$), i.e., the greater disease duration and disability, the higher impairment of voice. We also found a positive correlation between UPDRS-III and UPDRS-III-v scores ($r = 0.81$, $p < 0.01$), and between UPDRS-III and VHI ($r = 0.64$, $p < 0.01$) (**Figure 4B**), i.e., the greater disease severity, the higher impairment of voice. Furthermore, there was a positive correlation also between LEDDs and VHI scores ($r = 0.34$, $p < 0.01$), and UPDRS-III-v scores ($r = 0.44$, $p < 0.01$), i.e., the higher LEDDs, the higher impairment of voice. Lastly, MMSE and FAB negatively correlated with VHI scores ($r = -0.37$, $p < 0.01$ and $r = -0.28$, $p < 0.01$, respectively), i.e., the greater cognitive impairment, the higher impairment of voice.

Concerning the clinical-instrumental correlations, we found a positive correlation between LRs collected in the overall group of PD patients and disease duration ($r = 0.35$, $p < 0.01$) (**Figure 4C**), H&Y ($r = 0.34$, $p < 0.01$), UPDRS-III ($r = 0.41$, $p < 0.01$) (**Figure 4D**), UPDRS-III-v ($r = 0.33$, $p < 0.01$), and VHI ($r = 0.33$, $p < 0.01$) (**Figure 4E**). When considering *mid-advanced-stage* PD patients ON therapy, we found a positive correlation between LRs and UPDRS-III scores ($r = 0.47$, $p < 0.05$) (**Figure 4F**). Accordingly, the higher LR values attributed by machine learning, the higher disease duration, disability, and severity of motor as well as voice symptoms.

DISCUSSION

We here report the objective and automatic recognition, by means of machine learning, of voice abnormalities in a large and clinically well-characterized cohort of patients with PD. We demonstrated the effect of disease severity on voice changes in PD by discriminating *early-stage* and *mid-advanced-stage* patients. Also, we clarified the effect of L-Dopa on voice in PD by recognizing voice changes in patients OFF and ON therapy. The significant clinical-instrumental correlations further support the high diagnostic accuracy of our voice analysis.

All the subjects here enrolled were non-smokers and native Italian speakers. HS and PD had comparable demographic, anthropometric and cognitive characteristics including MMSE scores corrected for years of education. We recruited a balanced number of patients in the two patients' subgroups (*early-stage* and *mid-advanced stage*) (38). Moreover, since all *early-stage* patients were also *drug-naïve,* we excluded possible confounding on voice recordings from chronic treatment with L-Dopa thus allowing the objective and automatic recognition of PD-related voice disorders *per se*. Concerning the specific speech tasks, we compared the sustained emission of a vowel and a sentence by using standardized procedures (11, 17–19, 22,

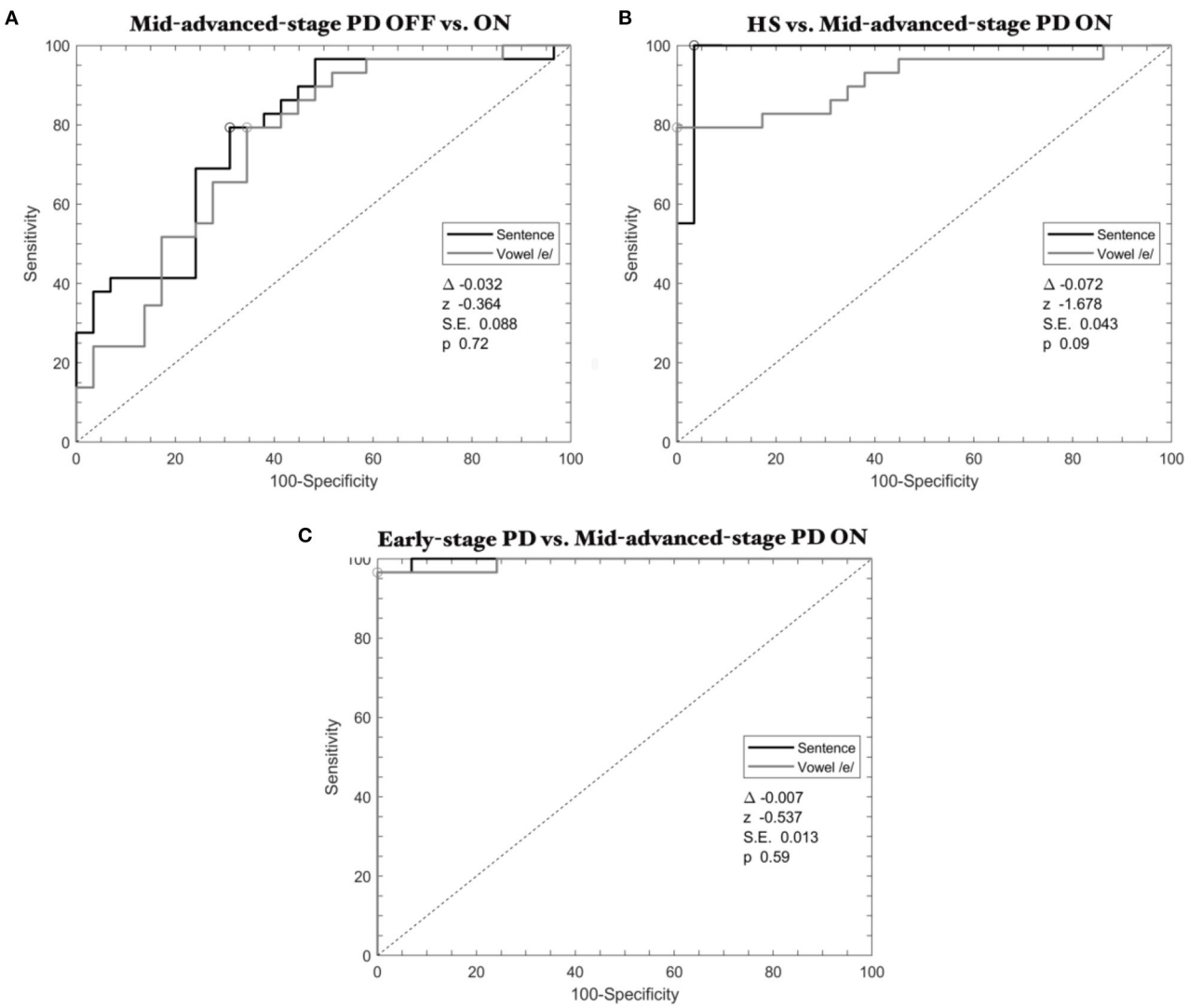

FIGURE 3 | ROC curves calculated through SVM classifier in Parkinson's disease: the effect of L-Dopa. **(A)** *Mid-advanced-stage* patients OFF vs. ON therapy; **(B)** HS vs. *mid-advanced-stage* patients ON therapy; **(C)** *Early-stage* patients vs. *mid-advanced-stage* patients ON therapy. Gray lines refer to the emission of the vowel, whereas black lines refer to the sentence.

43) thus also verifying the effect of PD on voice samples of different complexity.

The clinical observation that 84% of the PD patients (68% of *early-stage* and 100% of *mid-advanced-stage* patients) manifested voice impairment (UPDRS-III-v $\geq$1), agrees with the estimated prevalence of hypokinetic dysarthria in PD, which ranges from 70 to 90% (1–4, 44). Furthermore, the severity of voice impairment correlated with disease duration and the overall motor disability and severity, and finally, with the degree of cognitive impairment in PD. Hence, our findings demonstrate that PD patients manifest voice disorders in the *early-stage* of the disease (2, 5), with significant worsening of speech over the course of the disease (1, 2).

The application of machine learning analysis showed that voice is abnormal in PD as demonstrated by high diagnostic accuracy in the discrimination of voices between PD patients and HS. Our findings confirm and expand preliminary machine learning studies only focused on specific methodological aspects of voice analysis, achieved in pre-existing datasets or in rather heterogeneus cohorts of patients with PD (24–26). Our study is therefore the first one to provide a thorought classification of voice in PD patients, according to the stage (i.e., *de novo*) and severity of the disease as well as the effect of chronic L-Dopa treatment. Also, supporting the biological plausibility of our results, the most relevant voice features selected by our machine learning algorithms (among the large dataset of features examined), include those previously identified by spectral analysis such as the fundamental frequency (3, 12–16, 26, 45). Moreover, our study showed for the first time significant clinico-instrumental correlations: the higher LR values attributed

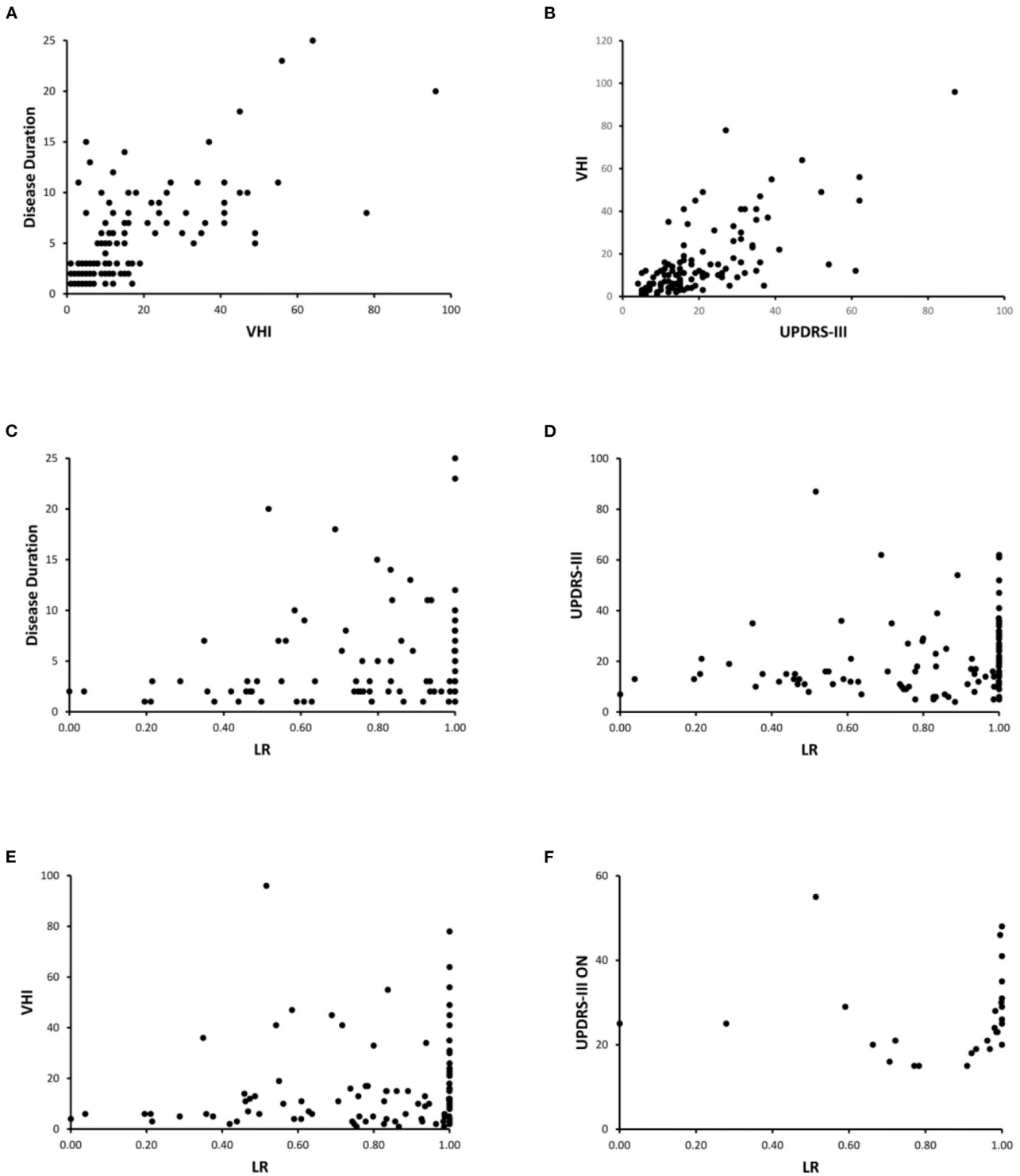

FIGURE 4 | Clinical-instrumental correlations. **(A)** Disease Duration and VHI; **(B)** UPDRS-III and VHI; **(C)** Disease Duration and LRs; **(D)** UPDRS-III and LRs; **(E)** VHI and LRs; **(F)** UPDRS-III ON and LRs. Note that the correlation analysis only refers to the emission of the vowel. Similar results have been achieved when analyzing the emission of a sentence (data not shown). In addition, correlation analysis shown in **(A–E)** refers to the whole group of PD patients, whereas **(F)** shows the correlation assessed in the subgroup of *mid-advanced stage* patients ON therapy.

by machine learning, the longer the disease duration, the higher severity of motor symptoms, and finally the greater voice impairment in patients with PD. Hence, we demonstrated for the first time that the degree of voice changes in PD correlates with disease duration and severity and finally, LR values can be considered reliable scores to express the complexity of voice impairment in PD.

A further relevant finding of the study concerns the subclinical impairment of voice in *early-stage* PD as demonstrated by high statistical accuracy achieved by machine learning in discriminating *early-stage* patients from HS (2). Given that 32% of *early-stage* patients did not manifest a clinically overt voice impairment, we speculate that the high accuracy in discriminating *early-stage* patients and HS would reflect the ability of machine learning to recognize subclinical voice impairment in PD.

As the disease progresses, voice increasingly degrades in PD as demonstrated by our ROC analysis achieving high statistical accuracy in discriminating *mid-advanced-stage* patients OFF therapy from HS. Again, for the first time we demonstrate significant clinico-instrumental correlations: the higher LR values, the greater severity of voice symptoms in *mid-advanced-stage* patients.

Another important finding in this study concerns the effect of L-Dopa on voice abnormalities in PD which is still a matter of debate given previous reports on beneficial (28, 29, 31–33) or null effect (27, 30). We here demonstrated that L-Dopa exerts significant improvement of voice in *mid-advanced-stage* patients. Furthermore, our clinical evaluation allowed us to demonstrate that L-Dopa improved voice less than other motor symptoms, a finding pointing to the weaker clinical effect of L-Dopa on axial signs in PD, as also shown by the correlations between LEDDs and VHI as well as UPDRS-III-**v** (1, 27, 30). By using an objective and automatic voice analysis, we demonstrated the significant effect of L-Dopa on voice in PD as suggested by high diagnostic accuracy in the comparison of patients OFF and ON therapy. Still, we found for the first time significant clinico-instrumental correlations also in patients ON therapy: the greater LR values, the higher severity of motor symptoms. However, although L-Dopa improved voice in PD, it failed to restore it as demonstrated by high diagnostic accuracy in the discrimination between HS and patients ON therapy.

The diagnosis of PD is currently based on clinical examination with the aid of several standardized clinical scales (34). Hence, the development of innovative disease biomarkers in PD would gain tremendous advances in the field. According to the FDA, an ideal disease biomarker would imply the identification of a certain biological variable specific for PD and able to allow early and objective diagnosis and track the severity of the disease. Also, an ideal disease biomarker in PD would require a safe, easy, and cheap methodology enabling an accurate diagnosis of PD. A relevant finding here is that our machine learning algorithm can recognize PD even in the *early-stage* of the disease, track the disease severity and evaluate the symptomatic effect of L-Dopa using a safe, easy, and cheap methodology. Accordingly, the data reported in the present study would suggest the possible use of machine learning voice analysis as an innovative biomarker in PD.

A final comment deserves the specific speech tasks here used to assess voice in PD. In agreement with our previous studies (19, 22), when comparing voice samples during the emission of a vowel and a standardized sentence, our analysis disclosed similar ROC curves in PD. We therefore demonstrated a similar degree of PD-related voice impairment regardless of the complexity of the speech tasks used. Accordingly, given that the sustained emission of the vowel represents a language- and culture-free speech task, we suggest the voluntary emission of a vowel as the preferred speech task for the worldwide assessment of PD (19, 22).

We recognize that the present study has several limitations. As we have not recorded vocal samples in each patient serially, we cannot exclude the possibility of daily fluctuations in vocal features in PD. Also, in this study *early-stage* patients were slightly younger than *mid-advanced-stage* patients and HS. Hence, we cannot exclude that age differences between *early-stage* and *mid-advanced-stage* patients or HS would have contributed at least in part to the high accuracy achieved in the discrimination between the two subgroups of patients (19). Concerning the clinical-instrumental correlations, given that machine learning analysis requires a large amount of data, we speculate that future studies with larger sample size will report higher r values than those here reported. Furthermore, the uncertain association between specific aspects of *hypokinetic dysarthria* in PD (i.e., hypophonia, mono-pitch and mono-loudness speech) and the specific voice features selected by the machine learning algorithm requires further investigation in depth.

In conclusion, in the present study in a large and clinically well-characterized cohort of patients, we provide clinical and instrumental evidence supporting voice changes occurring early in PD and worsening significantly over the course of the disease. Also, L-Dopa improves but does not restore voice in PD. Overall, given that machine learning objectively recognizes PD even in the *early-stage* of the disease, tracks the disease severity and detects the effect of L-Dopa with previously unreported high diagnostic accuracy, we speculate that machine learning-based voice analysis would represent in a near future an innovative disease biomarker able to support the clinical management of PD. Lastly, we speculate that our study would promote the future homebound application of machine learning voice analysis for telemedicine approaches in PD.

DATA AVAILABILITY STATEMENT

All clinical and instrumental data are stored offline and are available on reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB of Tor Vergata University of Rome, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS, GC, FA, and GS: research project—conception and organization. FA, PDL, MSA-W, GDL, and SS: research project—execution. AS, GC, FA, and PL: statistical analysis—design. AS, FA, and PL: statistical analysis—execution. GC, AP, and GS: statistical analysis—review and critique. AS, GC, and FA: manuscript preparation—writing of the first draft. AP and GS: manuscript preparation—review and critique. All authors contributed to the article and approved the submitted version.

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Brain Functional Connectivity in *de novo* Parkinson's Disease Patients Based on Clinical EEG

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In Parkinson's disease (PD), cortical–subcortical interplay plays a relevant role in affecting clinical performance. Functional MRI sequences described changes in functional connectivity at different stages of disease. Scarce are, instead, the investigations examining brain connectivity in patients with PD at early stages of disease. For this aim, here we analyzed the differences in functional connectivity between *de novo*, never treated, PD patients and healthy controls. The analyses were based upon custom-written scripts on the Matlab platform, combined with high-level functions of Fieldtrip, Brainstorm, and Brain Connectivity toolboxes. First, we proceeded to the spectral analysis of the EEG data in the five frequency bands (δ-θ-α-β-γ). Second, we calculated functional connectivity matrices based on both coherency (COH) and imaginary part of coherency (iCOH), in the δ-θ-α-β-γ frequency bands. Then, four network measures (density, transitivity, global efficiency, and assortativity) were computed in identified connectivity matrices. Finally, we compared the spectral density, functional connectivity matrices, and network measured between healthy controls and *de novo* PD patients through two-samples *T*-test. A total of 21 *de novo* PD patients and 20 healthy subjects were studied. No differences were observed in spectral analysis between the two groups, with the exception of the γ band where a significant increase in power density was found in PD patients. A reduced connectivity in the main EEG frequency bands (α-β frequency bands) was observed in PD patients compared to controls, while a hyperconnectivity was found in PD patients in γ band. Among the network measures, a reduced assortativity coefficient was found in *de novo* PD patients in α frequency band. Our results show the occurrence of early EEG functional connectivity alterations from the initial stages of PD. From this point of view, connectivity analysis may ease a better understanding of the complexity of PD physiopathology.

Keywords: Parkinson's disease, EEG, functional connectivity, graph theory, assortativity

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder whose hallmark is the degeneration of dopaminergic neurons of pars compacta of substantia nigra, leading to the classic motor symptoms. However, the concept centered on an exclusive basal ganglia involvement does not completely explain the heterogeneous complexity of disease motor and non-motor symptoms spectrum.

Therefore, new models, mainly based on prion-like spreading of misfolded α-synuclein from brainstem to subcortical and later cortical structures, were developed, suggesting a multisystem involvement in PD (1). Nevertheless, the clinical presentation of PD not necessarily follows the spatiotemporal pattern indicated by neuropathological findings. Underlying effects on brain networks by neuropathological changes might contribute to explain this phenomenon, even in the earliest stages of the disease.

In recent years, brain connectivity analysis was used successfully to better define the pathophysiology of dementias, mainly in Alzheimer's disease (2), with a predictive value (3). In this framework, cerebral connectivity analysis could be useful to improve the understanding also of the pathophysiological mechanisms of PD. So far, functional brain networks are usually examined by measuring the temporal correlations in functional MRI (fMRI) of blood oxygen level dependent (BOLD) signal between different brain regions (4). Electroencephalography (EEG) is a non-invasive and accessible method to evaluate the cortical electrical activity through scalp electrodes, routinely used in clinical practice for diagnoses of epilepsy or disturbances of consciousness. This technique may be used to estimate the functional interactions between brain areas, through different connectivity measures (5). Compared to fMRI, EEG has the advantage of direct measuring of electrical activity with high temporal resolution.

The aim of this study is to explore if dysfunctions in brain functional connectivity may feature PD since the early, off-therapy disease stages. For this purpose, we analyzed the EEG resting-state connectivity in *de novo* PD patients, compared to healthy controls, using a custom-written scripts on the Matlab platform, combined with high-level functions of Fieldtrip (6) and Brainstorm (7) toolboxes, common EEG analysis software, and Brain Connectivity toolbox, usually utilized for graph theory analysis (8). Preliminary data were presented at "7 Congresso Accademia LIMPE-DISMOV 2021"—December 15–17, 2021, Bologna, Italy.

MATERIALS AND METHODS

Study Recruitment

We recruited patients diagnosed with idiopathic PD, according to the MDS clinical diagnostic criteria (9). Patients were required to meet the following criteria: (1) disease duration <24 months; (2) no history of taking therapy with dopaminergic drugs (iMAO, L-Dopa, Dopamine agonists, iCOMT, anticholinergic agents, amantadine); (3) no history of epilepsy or other conditions that could cause pathological alterations of EEG recording (i.e., brain tumors, stroke, infections, etc.); (4) no cognitive impairment, as defined by a Mini-Mental State Examination (MMSE) score above 25 (10); (5) morphological MRI without brain parenchymal lesions; and (6) no other neurological diseases except PD.

All included PD patients underwent the EEG recording session and, on the same day, they were clinically evaluated using the Unified Parkinson Disease Rating Scale motor section (UPDRS part III) (11).

As control group, we enrolled age-matched healthy subjects, without history of epilepsy or other conditions that could justify alterations of EEG, as described above for PD patients. Control cohort was composed of subjects under EEG scrutiny as part of diagnostic tests, which excluded epilepsy or other neurological diseases.

EEG Acquisitions and Removal of Artifacts

EEG data were recorded for 10 min at a sampling rate of 128 Hz and band-pass filtered at 0.5–50 Hz using a 19-channel EEG system. Scalp electrodes were positioned according to 10–20 International System (12). Recording was performed during awake-resting state. Subjects were instructed to keep their eyes closed while staying awake. During the EEG acquisition, we monitored the level of vigilance of patients by visual inspection of EEG traces: in case of slowing of the EEG activity, sleepiness was avoided by giving instructions to the subjects once again.

After the acquisition, we selected a 100-s poor-artifact segment of each EEG recording. We used a cleaning algorithm for EEG data. First, as other authors have previously suggested, we applied detrending and re-reference to each channel (13). Then, we used independent component analysis (ICA), to remove EEG artifacts due to eye-blinks, muscle activity, cardiac signals, and line noise sources (14).

Spectral Analysis

We proceeded to the spectral analysis of the EEG data. We applied the Welch's method, which consists in averaging consecutive Fourier transform, calculated using the Fast Fourier Transform (FFT) algorithm, of small windows of signal, with or without overlapping. In the present study, the EEG data were divided into segments of 1 s length, with overlap of 50%.

Then, we computed the power spectral density or periodogram for each subject in the five frequency bands (δ 0.5–4, θ 4–8, α 8–13, β 13–30, and γ 30–50 Hz).

Connectivity Analysis

Coherency (COH) is a measure of the linear relationship of two EEG channels at a specific frequency. If $x_m(f)$ and $x_n(f)$ are the complex Fourier transforms of the time series $x_m(t)$ and $x_n(t)$ of the channel m and n, the cross-spectrum is defined as:

$$G_{mn}(f) = \left\langle x_m(f) x_n^*(f) \right\rangle \tag{1}$$

Where * indicates the complex conjugation and $\langle \ldots \rangle$ means the average value. Then, COH can be defined as the normalization of cross-spectrum:

$$COH_{mn} = \frac{\left|G_{mn}(f)\right|^2}{G_{mm}(f) G_{nn}(f)} \tag{2}$$

Where $G_{mm}(f)$ and $G_{nn}(f)$ are the power spectral density of m and n, respectively.

Coherency is widely used as a measure of EEG functional connectivity (15). In the present study, we considered COH and the imaginary part of coherency (iCOH), which is known to reduce the volume conduction artifacts, compared to COH (16).

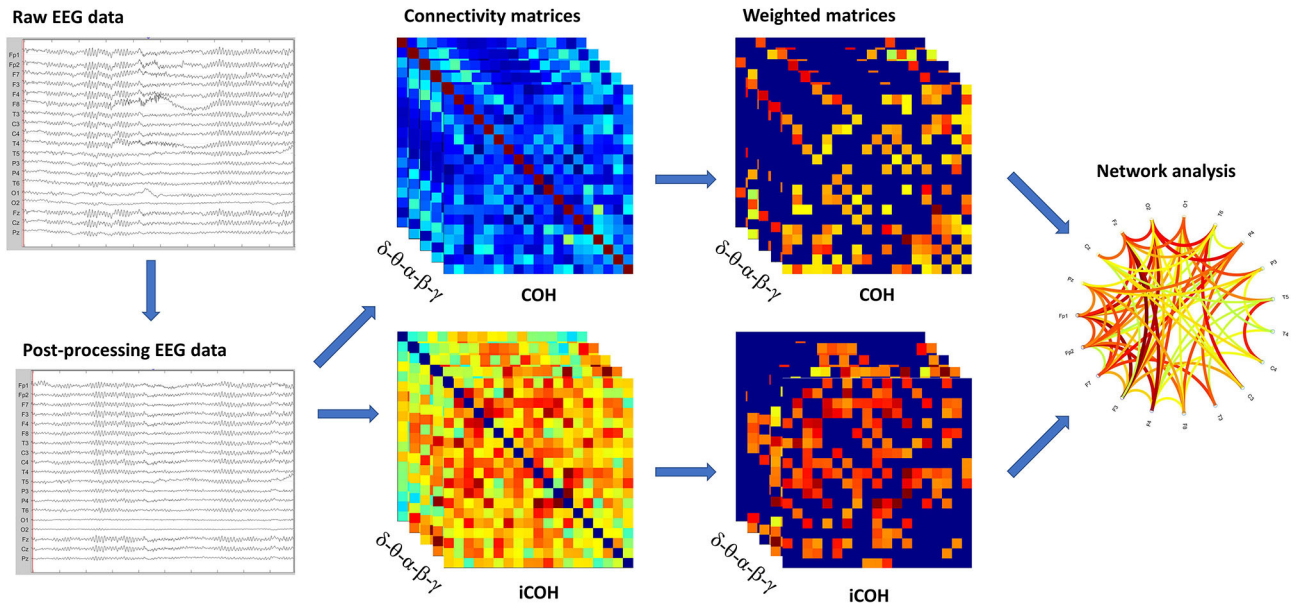

FIGURE 1 | Schematic representation of the analysis. In sequence, we showed: raw EEG data filtered and cleaned using Independent Component Analysis (ICA); the functional connectivity matrices based on COH and iCOH for each frequency band; weighted undirected matrices based on coherency (COH) and imaginary part of coherency (iCOH) for each frequency band; graph representation of network.

Functional connectivity matrices of all subjects were obtained by calculating the values of COH and iCOH between any pair of channels in the five fundamental frequency bands on segments of 1 s length, with overlap of 50%, according to the Welch's method.

Network Measures

At this point, we analyzed the network properties. For this purpose, we computed the mean connectivity matrices of COH and iCOH of all subjects over the five frequency bands and calculated a cut-off value, so that 30% of all edges were considered significant. We thresholded the individual connectivity matrices by absolute weight, in order to generate weighted undirected networks.

We used four global metrics to measure network properties of all subjects [an extended description on measures of brain connectivity can be found on this paper (8)].

- Density: it represents the fraction of present edges to possible edges or "wiring cost" of the network.
- Transitivity: it is the ratio of triangles to triples in the network and represents a collective normalization of clustering coefficient (17). Transitivity is a classical measure of functional segregation in brain network, which can be define as the ability for specialized processing to occur within interconnected group of regions.
- Global efficiency: the functional integration in brain network represents the ability to rapidly combine information from different brain regions. Measures of integration are commonly based on the concept of a path: shorter paths imply stronger functional integration. Global efficiency can be define as the average shortest path length between all pairs of nodes in the network and it is commonly used as measure of functional integration (18).
- Assortativity: it is a correlation coefficient between the degrees of all nodes on two opposite ends of an edge (19). Networks with positive assortativity coefficient are likely to have a resilient core of mutually interconnected high-degree hubs, while networks with a negative assortativity coefficient are likely to have widely distributed and vulnerable high-degree hubs. Hence, assortativity represents an indirect measure of resilience, which reflects the network's vulnerability to insults.

A schematic representation of the different steps in the analysis is shown in **Figure 1**.

Statistical Analysis

Since Kolmogorov–Smirnov test showed that variables followed a normal distribution, we performed parametric statistical tests. We analyzed the differences in the magnitude of power spectral density [i.e., sqrt (power)] for each EEG channel in the five frequency bands (δ-θ-α-β-γ) between *de novo* PD patients and healthy controls using two sample *T*-test. We analyzed the differences in the functional connectivity matrices based on COH and iCOH measures between *de novo* PD patients and healthy controls groups. We compared each cell of the matrices in the five frequency bands (δ-θ-α-β-γ) by two samples *T*-test. Finally, we compared global network measures of calculated connectomes (density, transitivity, global efficiency, and assortativity) between PD patients and controls using two samples *T*-test.

A preventive Levene's test was used for each *T*-test in order to verify if the populations examined had the same variance. Null-hypothesis was rejected at p-value < 0.05. The statistical analysis was performed using Matlab 2020a.

TABLE 1 | Demographic and clinical characteristics of *de novo* Parkinson's Disease (PD) patients and healthy controls.

	***De novo* PD**	**Controls**
N	21	20
Sex (% male)	76.2	70.0
Age (years)	60.95 ± 10.47	60.45 ± 13.96
Disease duration (months)	8.48 ± 7.26	/
UPDRS III	14.4 ± 5.7	/

Data are mean ± SD. UPDRS III, Unified Parkinson's Disease Rating Scale part III (motor symptoms).

RESULTS

Subjects

We used a population of 21 PD patients, who met the inclusion criteria of the study. They were consecutive patients, followed up to the Neurological Clinic of the University of "Tor Vergata," Rome, between January 2020 and July 2021.

As control group, we enrolled 20 healthy subjects (see methods), who underwent the same EEG recordings of patients. The demographics and clinical characteristics of both groups are summarized in **Table 1**.

Comparison in Spectral Analysis

Comparisons in spectral analysis between PD patients and healthy controls are reported in detail in **Figure 2**. The spectral analysis documented an increased power density in PD patients compared to controls in δ-θ-γ frequency bands. In particular, we found a modest but statistically significant (p-value < 0.05) increase in power density in PD *de novo* patients in Fp1 channel in δ band and in Fp1 and Pz channels in θ band. A more extensive increase in power density was found in the γ band, affecting Fp1, C3, Cz, C4, and P3 channels. No statistically significant differences were found in α and β frequency bands.

Comparison in Functional Connectivity

First, we analyzed the functional connectivity based on COH (**Figure 3**). In the δ-θ frequency bands, there is no clear predominance of functional connectivity in controls or in PD patients. In α and β, we observed a significant reduced functional connectivity or hypoconnectivity in PD patients compared to healthy controls. Instead, we found a widely increased functional connectivity in PD patients compared to controls in the γ frequency band.

Similar results were also observed in functional connectivity based on iCOH (**Figure 4**). Compared to the connectivity based on COH, a clear increase in connectivity can be found in controls in δ band, while no substantial differences were observed in θ band. A clear hyperconnectivity is confirmed in healthy controls compared to PD patients also in connectivity based on iCOH in α and β, as well as an increased connectivity was observed in PD patients in γ frequency band, even if it appeared statistically significant in a smaller number of pairs of channels compared to connectivity based on COH.

Differences in Network Measures

We compared four network measures (density, transitivity, global efficiency, and assortativity) between controls and PD patients of functional connectivity matrices based on COH and iCOH. Comparisons can be found in detail in **Figure 5**.

No significant differences were observed between control and PD groups in δ and θ bands in COH- and iCOH-based connectomes. In α band, a higher assortativity coefficient was found in controls than in PD patients both in COH (p-value 0.002) and in iCOH (p-value 0.046) based connectomes. In COH-based connectivity increased density (p-value 0.028) and global efficiency (p-value 0.015) in controls were found in β band, while the assortativity coefficient resulted higher in controls than in patients with p-value at the limits of significance (p-value 0.064). No significant differences were found in β band in iCOH-based connectomes.

An inverse result was observed in γ frequencies. In iCOH based-connectivity, all four network measures resulted higher in PD patients compared to controls (density-transitivity-global efficiency-assortativity; p-value 0.014, 0.002, 0.023, 0.041). In COH-based connectivity increased density, transitivity and global efficiency were found in PD patients (p-value 0.012, 0.028, 0.011), while assortativity coefficient resulted higher in control group (p-value 0.004).

DISCUSSION

Dysfunction in α-β Bands Functional Connectivity

The aim of this study was to assess the functional connectivity integrity in *de novo* PD patients compared to healthy controls. We found that PD patients in the early stages of disease have a reduced connectivity in the main EEG frequency bands (α-β), contrary to the spectral analysis, which did not reveal any significant differences in α-β bands. These data seem to suggest that changes in functional connectivity may precede alterations in spectral analysis in PD patients. Indeed, a previous study showed a reduced power spectral density in α-β bands in advanced PD patients (20). We can, therefore, hypothesize that spectral analysis modifications do not characterize the initial stages of disease, contrary to the reduced functional connectivity.

Previous studies based on fMRI have reported functional connectivity alterations in PD patients, mainly in sensorimotor network (SMN) and in default-mode network (DMN). SMN is a large-scale brain network, involved in performing and coordinating motor tasks (21), and its alteration has been largely reported in PD (22–25). The DMN is a network consistently active during resting-state or task-negative conditions, and it is involved in a large number of functions, such as thinking about themselves or others, remembering past events or perception of time (26), and dysfunction in DMN has been observed in cognitively impaired patients with PD (27–29).

Compared to the previous fMRI studies, our study is based on EEG recordings, non-invasive and accessible method to evaluate cortical electrical activity. Our data are, therefore, interesting considering the pathophysiology of PD, since we analyzed PD

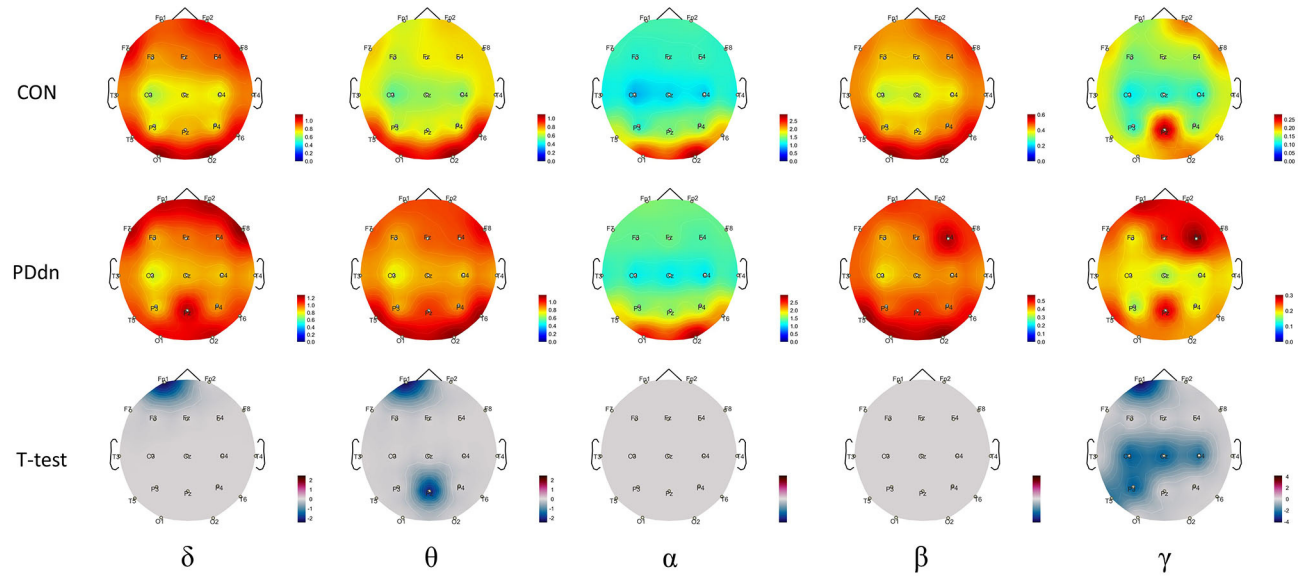

FIGURE 2 | First and second rows show magnitude of power spectral density for each channel, respectively, in control and in PD de novo groups at δ-θ-α-β-γ frequency bands. Third row reports t-values between magnitudes of power spectral density of Controls and Parkinson's disease (PD) patients (CON-PDdn) for each channel at δ-θ-α-β-γ frequency bands. Only t-values with p-value < 0.05 are shown.

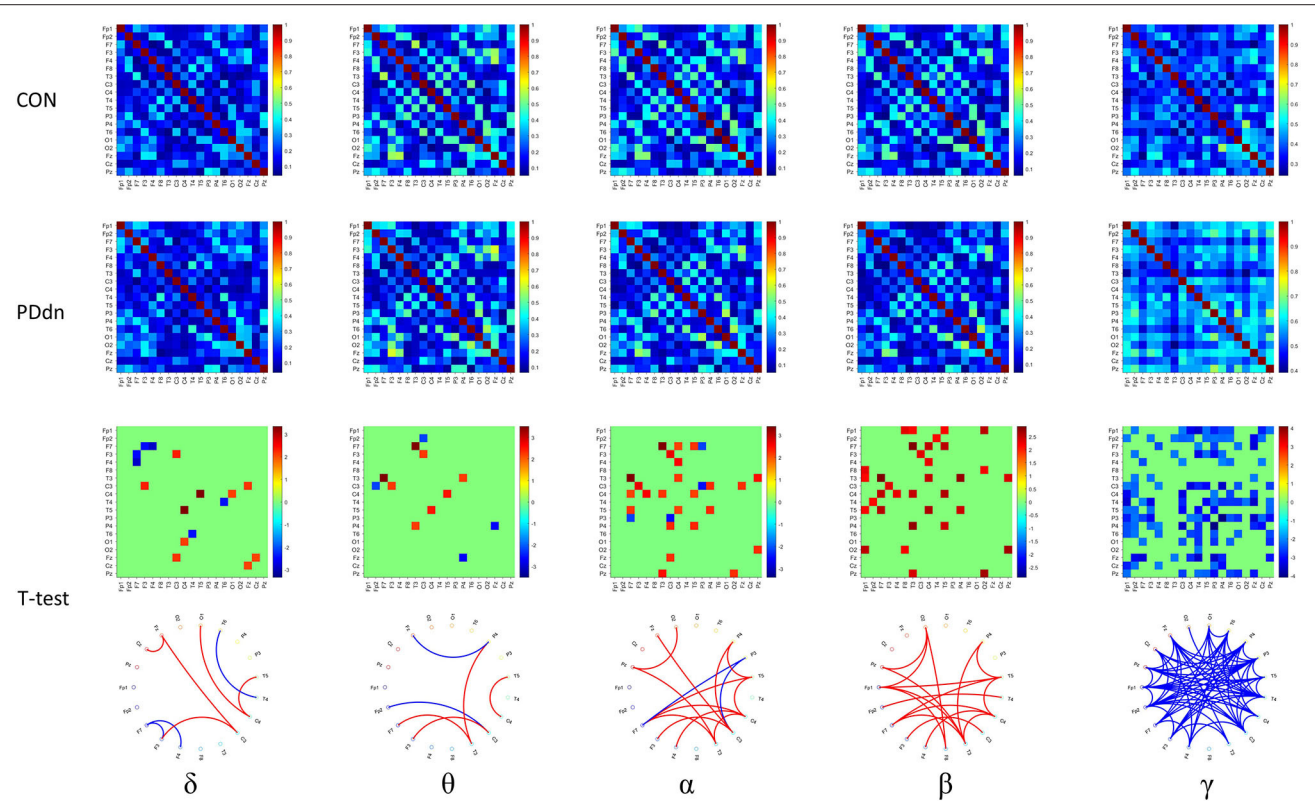

FIGURE 3 | First and second rows show functional connectivity for each pair of channels based on COH, respectively, in healthy controls and in PD de novo patients at δ-θ-α-β-γ frequency bands. Third row shows t-values (CON-PDdn) and fourth row shows the graph representation of different functional connectivity for each pair of channels with a p-value < 0.05 at δ-θ-α-β-γ frequency bands between controls and PD patients (red indicates higher connectivity in healthy controls, while blue in PD patients).

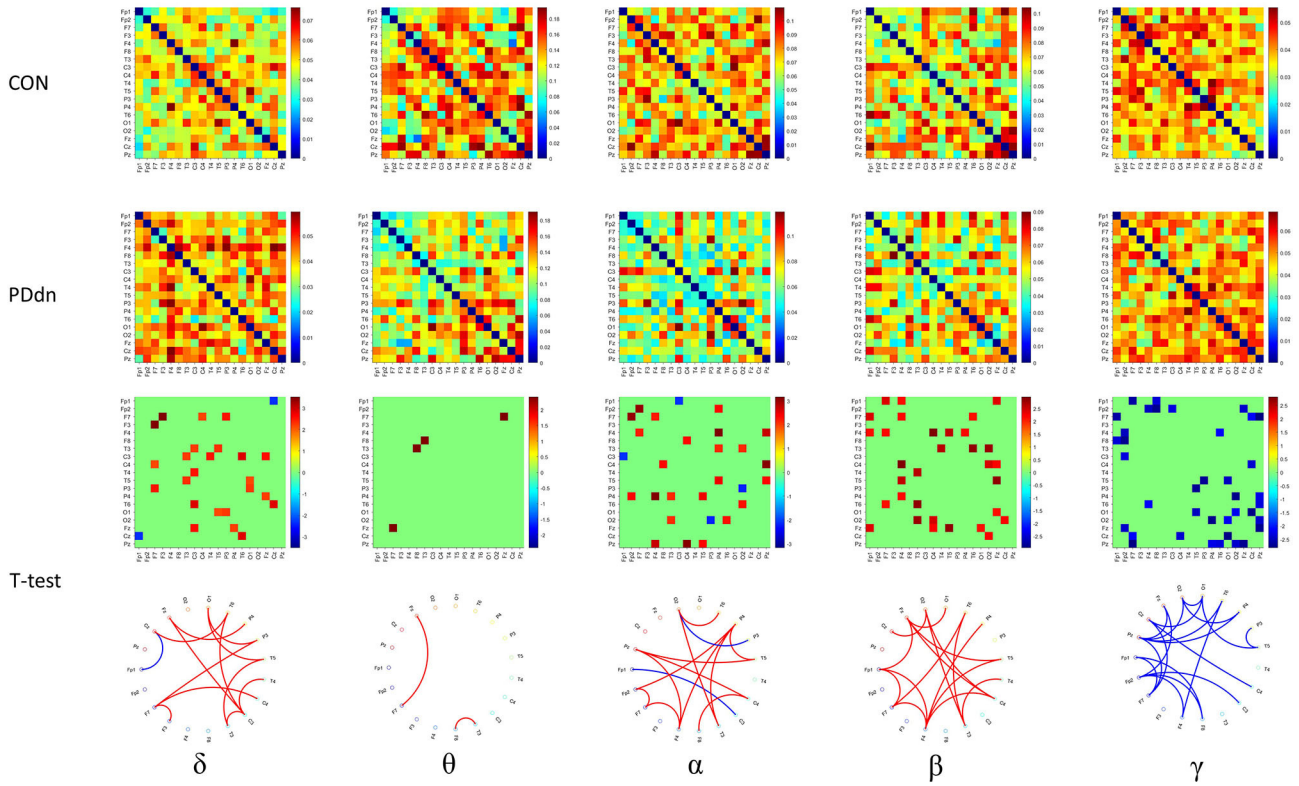

FIGURE 4 | First and second rows show functional connectivity for each pair of channels based on iCOH, respectively, in healthy controls and in PD de novo patients at δ-θ-α-β-γ frequency bands. Third row shows t-values (CON-PDdn) and fourth row shows the graph representation of different functional connectivity for each pair of channels with a p-value < 0.05 at δ-θ-α-β-γ frequency bands between controls and PD patients (red indicates higher connectivity in healthy controls, while blue in PD patients).

patients in the first stages of disease in which the synucleinopathy should not have reached the cortical areas, according to the Braak theory (1). In first hypothesis, the dysfunction we observed in EEG functional connectivity may be related to downstream remote effects, i.e., through striatal-thalamocortical circuits (30), rather than local cortical involvement. This is in line with previous studies demonstrating that synucleinopathy can alter the resting-state functional networks as consequence of deficits in other brain regions (22). On the other hand, recent hypothesis of top-down cortical pathogenesis of PD was proposed (31), as opposed to Braak's theory of bottom-up progression. Therefore, from this point of view, the alteration of EEG functional connectivity documented in our study could be evidence of cortical involvement since the early stages of PD.

Assortativity Coefficient in *de novo* PD Networks

Among the network measures, interesting results derive from the analysis of the assortativity coefficient, which was found to be reduced in *de novo* PD patients in α frequency band both in COH- and iCOH-based connectivity. Assortativity coefficient represents the correlation between degrees of all nodes on two opposite sides of an edge, and is an indirect measure of the network resilience (19).

In assortative networks, nodes with higher degrees tend to be connected together, so the disturbed connections of one node can be compensated by other high-degree nodes. Indeed, in assortative networks, high-degree and low-degree vertices tend to link to other high-degree and low-degree vertices, respectively. When the assortativity coefficient decreases, this order is altered, and some nodes start establishing new connections with vertices with less similar degrees to their own degrees. The lower assortativity coefficient, we observed in PD patients, might indicate that some cortical regions start establishing or increasing connections with other regions to compensate an initial deficiency. However, an analysis of the sources is necessary to corroborate this hypothesis.

Compensatory Hyper-Connectivity in γ Frequencies

A further result of our research is that PD patients showed a hyper-connectivity in γ frequency band, when compared to other frequency bands. Previous studies have demonstrated that γ oscillations of cortical neurons are generated by interactions between pyramidal cells and inhibitory interneurons, and reflect synchronization phenomena (32, 33). The γ oscillations have been associated with movements executions and with planning of movements (33–37). The γ band has also been related to sensory

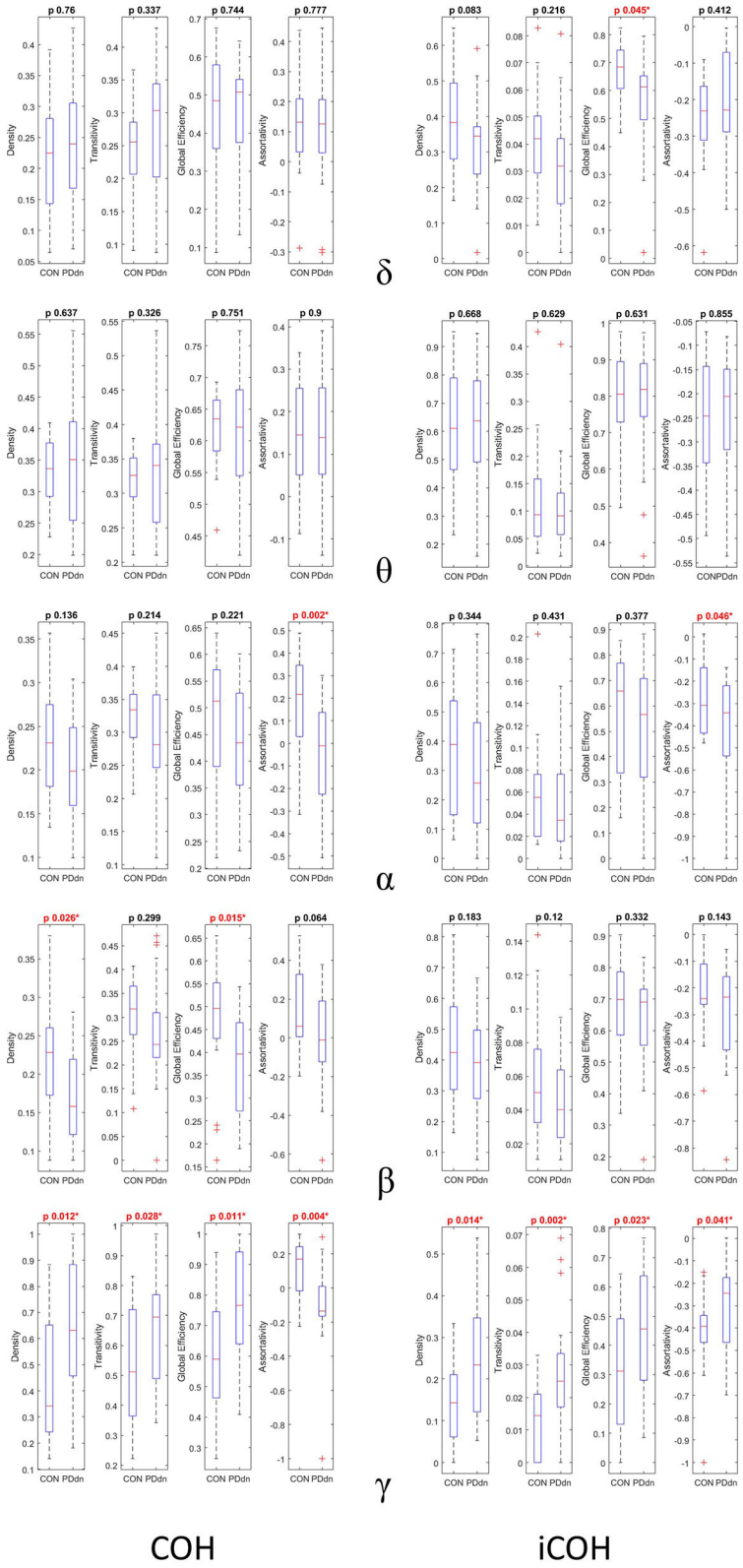

FIGURE 5 | First and second columns show box plots and p-value of two samples T-test (CON-PDdn) of four network measures (density–transitivity–global efficiency–assortativity) between healthy controls and PD patients at δ-θ-α-β-γ frequency bands of functional connectivity matrices based on, respectively, COH and iCOH. Red color indicates a p-value < 0.05).

and cognitive processing, long-term memory, and language tasks (38, 39).

In our opinion, the observed γ hyper connectivity may be interpreted as compensatory mechanism performed by cortical neurons still not affected by synucleinopathy. In other words, it should be presented in the early stages of PD and be lost as the disease progresses, accompanied with a worsening of the motor symptoms. Actually, a previous study based on extracellular recordings of subthalamic nucleus neurons of advanced PD patients during surgery for deep brain stimulation, has demonstrated that percentage of units oscillating at γ frequency was negatively correlated with the bradykinesia scores (40). Moreover, it was observed a positive correlation between γ band power and the improvement of symptoms with Levodopa administration (41), which could indicate a better response to dopaminergic therapy in PD patients due to the integrity of the cortical γ connectivity. Furthermore, a recent intermittent theta burst stimulation (iTBS) study emphasized the role of cortical γ oscillations in the pathophysiology of the abnormal long-term potentiation (LTP)-like plasticity in PD patients (42), indicating a positive correlation of cortical γ oscillations with synaptic plasticity.

Finally, a previous experimental study that analyzed cortical and pallidal γ frequency in hemiparkinsonian rats with unilateral 6-hydroxydopamine (6-OHDA) lesion, showed that γ band increased only in animals manifesting levodopa-induced dyskinesias (LIDs) (43). Future studies are needed to demonstrate the potential predictive role of early γ hyperconnectivity in the subsequent development of LIDs.

Limitations of the Study

The study is limited by relatively small number of PD patients and healthy controls. This limitation is partly due to the strict inclusion criteria, restricted to *de novo* drug-naive PD patients, and with exclusion of cognitive impairment history. However, a larger number of patients may ensure a better representation of the statistical sample.

As mentioned earlier, the study is limited by the low resolution of the EEG, as the study is based on standard recordings, which can only allow sensor-based connectivity analysis, and it is not possible to carry out an adequate reconstruction of the brain sources due to the number of channels (44). However, it has the advantage of allowing a functional connectivity analysis through an easily accessible and safe tool in the Neurology departments.

Finally, the present study is not longitudinal, yet. It may be useful to follow-up patients over time to observe further changes in EEG brain functional connectivity.

Conclusions

Functional connectivity analysis may ease a better understanding of the complexity of PD physiopathology, from the earliest stages of disease. We found a reduced functional connectivity in *de novo* PD patients in α and β frequency bands both in COH and in iCOH-based connectivity analysis, suggesting their dysfunction in a disease stage, in which LP should not have reached the brain cortical areas. We also found a paradoxical hyperconnectivity in the γ band, which we interpreted as an initial compensation mechanism by brain areas spared by extensive LP. Future studies are needed to unleash the potential of a widespread functional connectivity analysis on 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 Ethical Committee of Policlinico Tor Vergara. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC: conceptualization, data curation, formal analysis, methodology, software, and writing – original draft. RB: formal analysis and methodology. EG: data curation. TS: visualization. FP: validation. NM: visualization. RC: resources. MP: writing – review & editing. AS: supervision and writing – review & editing. All authors contributed to the article and approved the submitted version.

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REVIEW
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Clinical Intervention Using Focused Ultrasound (FUS) Stimulation of the Brain in Diverse Neurological Disorders

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Various surgical techniques and pharmaceutical treatments have been developed to improve the current technologies of treating brain diseases. Focused ultrasound (FUS) is a new brain stimulation modality that can exert a therapeutic effect on diseased brain cells, with this effect ranging from permanent ablation of the pathological neural circuit to transient excitatory/inhibitory modulation of the neural activity depending on the acoustic energy of choice. With the development of intraoperative imaging technology, FUS has become a clinically available noninvasive neurosurgical option with visual feedback. Over the past 10 years, FUS has shown enormous potential. It can deliver acoustic energy through the physical barrier of the brain and eliminate abnormal brain cells to treat patients with Parkinson's disease and essential tremor. In addition, FUS can help introduce potentially beneficial therapeutics at the exact brain region where they need to be, bypassing the brain's function barrier, which can be applied for a wide range of central nervous system disorders. In this review, we introduce the current FDA-approved clinical applications of FUS, ranging from thermal ablation to blood barrier opening, as well as the emerging applications of FUS in the context of pain control, epilepsy, and neuromodulation. We also discuss the expansion of future applications and challenges. Broadening FUS technologies requires a deep understanding of the effect of ultrasound when targeting various brain structures in diverse disease conditions in the context of skull interface, anatomical structure inside the brain, and pathology.

Keywords: clinical focused ultrasound, MRgFUS, high-intensity focused ultrasound (HIFU), low-intensity focused ultrasound (LIFU), thermoablation, neuromodulation, blood-brain barrier (BBB) opening

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INTRODUCTION

Focused ultrasound (FUS) is a transformative tool that can be used to noninvasively create lesions or temporarily modify the function of targeted brain tissue while minimally affecting all intervening tissues carrying the ultrasound energy. Because FUS can be used to create these lesions remotely from the source, with well-defined margins and precise localization, this technology is an attractive option for noninvasive neurosurgery (1).

The field of FUS was created in 1927 by Wood and Loomis, who first documented the effects of ultrasound on living biological tissue (2). Therapeutic applications for high-intensity focused

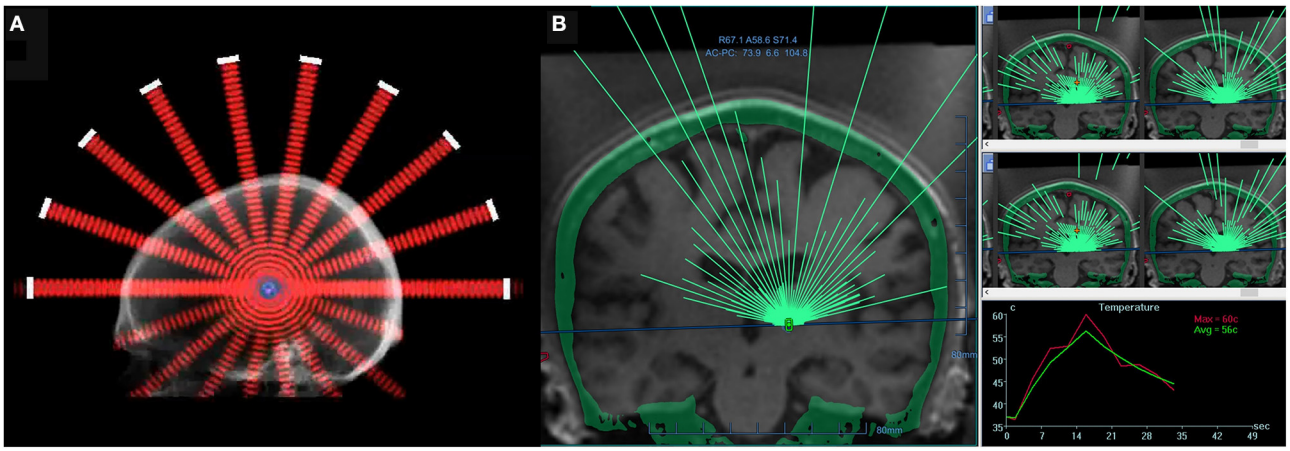

FIGURE 1 | (A) A 2-dimensional schematic of a hemispherical phased-array transducer, showing multiple beams converging at a geometric focus. **(B)** A screen image of a commercial software MRgFUS with >1,000 individual transducer elements (ExAblate; InSightec, Israel). All transducer elements use a phase shift algorithm to account for individual skull effects. Transducer elements are individually electronically steered to ensure precise, submillimeter targeting. For the treatment of essential tremor, a typical device operates at approximately 650 kHz, achieving a focal spot size of approximately 6 mm and a target temperature of 55°C (right bottom panel: real-time temperature monitoring via MR thermometry), thus allowing for thermoablation of a deep-seated brain structure.

ultrasound (HIFU) often use a lower frequency (300 kHz – few MHz) with maximum ultrasound intensity at a beam focus of approximately 1,500 W/cm^2, whereas a high frequency range (2–15 MHz) and low intensity (0.1 W/cm^2) are typical for diagnostic ultrasound (3). A drawback of the early animal experiments in the field of HIFU was the considerable tissue damage caused along the ultrasound pathway from the skin to the target. This damage was partly due to the use of a single source, which provided no geometric gain when compared with current technology. A further complication in the creation of brain lesions was the presence of the skull, which is a source of sound wave reflection, scatter, and absorption; all of these factors reduce power deposition at the target. Although the source power could be sufficiently increased to overcome this loss and create deep brain lesions, the increased power would also increase collateral damage to the scalp and skull. Thus, early animal work necessitated removal of skull flaps, thereby limiting clinical application of this technology.

Considerable progress in human brain HIFU was made in the 1950s by the Fry brothers, who developed a 4-beam technology and demonstrated the therapeutic potential of FUS for treating neurological disorders by creating lesions deep inside a primate brain (4). Although these advances demonstrated the great potential of HIFU for treating diverse neurological diseases, successful clinical application would require real-time imaging to accurately visualize and verify target location. To this end, a multi-element phased-array system (**Figure 1**) was combined with magnetic resonance imaging (MRI), thus allowing for MR-guided FUS (MRgFUS) (5–7). Starting with *in vitro* studies in 1998, this technique permitted simultaneous visualization of anatomical and temperature maps and provided the feedback needed to perform a completely incisionless and closed-loop procedure.

In 1998, Hynynen and Jolesz (8) reported using pretreatment computed tomography (CT) scans to inform a phased-array HIFU system with phase-correction methods to further mitigate skull attenuation by tightening the focus, thereby increasing the energy deposition density. This approach led to Food and Drug Administration (FDA)–approved MRgFUS system that uses thermoablation to treat essential tremor (ET) and tremor-dominant Parkinson's disease (PD) in 2016, and more recently FDA approved thermoablation of internal globus pallidus, pallidotomy, as an alternative MRgFUS treatment for PD dyskinesia in November 2021. Research to expand the clinical application of FUS technology to other neurological disorders has since increased greatly (**Figure 2**).

Because of the diverse biophysical properties of ultrasound, the effects of FUS on biological tissue may include heat, cavitation (both stable and unstable), histotripsy, microbubble interactions, and both low-intensity and high-intensity microstreaming. Various therapeutic FUS applications can exploit these bioeffects, allowing clinicians to perform thermoablation, immunotherapy, histotripsy, opening of the blood-brain barrier (BBB), and neuromodulation. Many *in vitro* and *in vivo* studies have evaluated the feasibility and safety of these applications for a variety of diverse neurological conditions (**Figure 2**). In this review, we will discuss the well-established clinical use of MRgFUS for the treatment of ET, PD, and obsessive-compulsive disorder (OCD), as well as current clinical trials assessing the use

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CRST, Clinical Rating Scale for Tremor; CT, computed tomography; DBS, deep brain stimulation; ET, essential tremor; FDA, Food and Drug Administration; FUS, focused ultrasound; GBM, glioblastoma multiforme; HIFU, high-intensity focused ultrasound; HU, Hounsfield unit; LIFU, low-intensity focused ultrasound; MDD, major depressive disorder; MRgFUS, MR-guided FUS (MRgFUS); MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PD, Parkinson's disease; SDR, skull density ratio; SEEG, stereo-electroencephalography; Vim, ventral intermediate nucleus; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

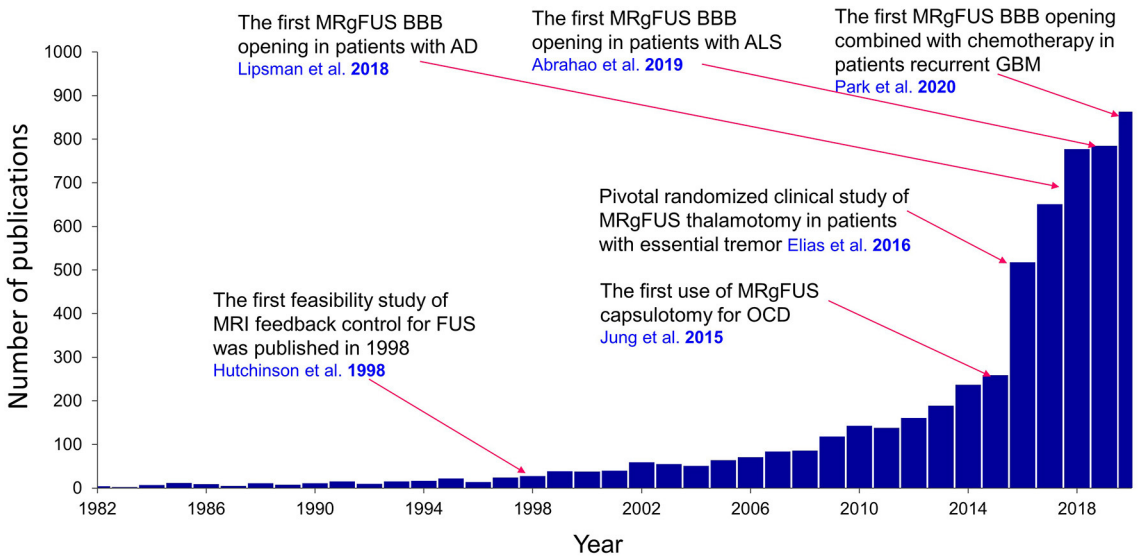

FIGURE 2 | Publications regarding the clinical application of FUS in neurological disorders. A landmark study for each clinical application is overlaid on the graph. Results were obtained from PubMed. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier; GBM, glioblastoma multiforme; OCD, obsessive-compulsive disorder.

of FUS methods for the treatment of glioblastoma, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and epilepsy.

FUS-MEDIATED THERMAL ABLATION

Effect of the Physical Properties of the Skull on MRgFUS Thermal Ablation

If a high enough temperature can be reached to create a thermoablative lesion of the correct size and at the correct location, considerable clinical efficacy can be obtained for conditions such as PD (9), ET (10), OCD/major depressive disorder (MDD) (11), and epilepsy (12). Although modern MRgFUS techniques generally allow high spatial and temporal resolution of temperature characterization and effective control of temperature distribution in the brain, several studies have reported difficulties in achieving a temperature that reaches the ablative level in patients with ET and PD because of the physical properties of the skull (13, 14).

The skull's acoustic properties are different from those of soft tissue. The intrinsic attenuation of ultrasonic waves in the skull is ∼20 dB/cm*MHz, which is higher than the attenuation of waves in brain tissue (∼0.8 dB/cm*MHz) (15). Attenuation arises from acoustic absorption and scattering in all directions in the medium. Acoustic scattering refers to that part of an incident acoustic wave that is reflected from interfaces between different tissues due to inhomogeneities in their density and compressibility (16, 17). This scattering can be substantial at major interfaces, such as between bone and soft tissue. Reflection is also high at interfaces between the outer/inner tables of cortical bones and the central cancellous bone because of their different bone structures (18). Increased attenuation implies decreased heating power available at the target, in addition to increased deposition at nontarget soft tissues such as the scalp and skull. Such unwanted heating is exacerbated if the total incident power is increased to compensate for increased attenuation and maintain the desired temperature at the target. There can be great variability in attenuation between portions of a single skull and also between the skulls of different patients. Some patients are effectively untreatable with this method because of potential scalp burns or damage to the underlying bone, in addition to the painful heating of nontarget tissues. Thus, a practical simple measure that can predict which patients may benefit from HIFU is needed.

Along any ultrasound ray traversing the skull, one can calculate the ratio of skull density between the mean cortical and mean cancellous bone using the Hounsfield units (HUs) that result from a CT scan with high resolution and using a bone kernel for image reconstruction. These ratios can be averaged over all rays traversing the skull in a HIFU configuration to provide a single measure called the skull density ratio (SDR), which is a useful global index for identifying patients who are eligible to undergo MRgFUS-mediated lesion creation (**Figure 3**). Although currently used MRgFUS techniques can compensate for skull factors with CT-based phase-correction software on multiarray systems, some patients will still demonstrate sufficiently low SDR to restrict them from treatment. To this end, practice guidelines from the American Society for Stereotactic and Functional Neurosurgery state that patients with an SDR <0.4 should not undergo MRgFUS for lesion creation (19), as insufficient heating at the intracranial target will lengthen the time needed to achieve ablative temperatures and lead to excessive heating at nontarget tissues.

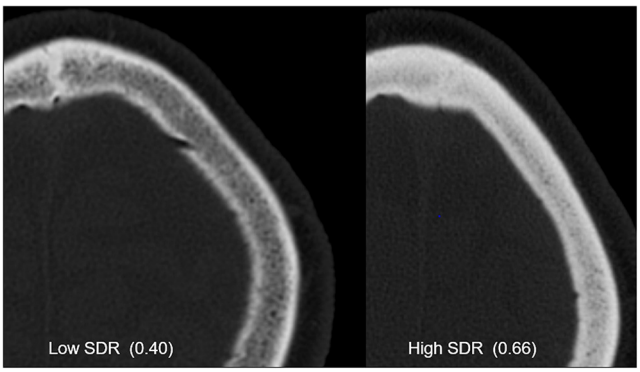

FIGURE 3 | CT images from patients with low and high skull density ratios (SDRs). Both images are windowed the same way, and the skull with high SDR clearly shows increased Hounsfield units.

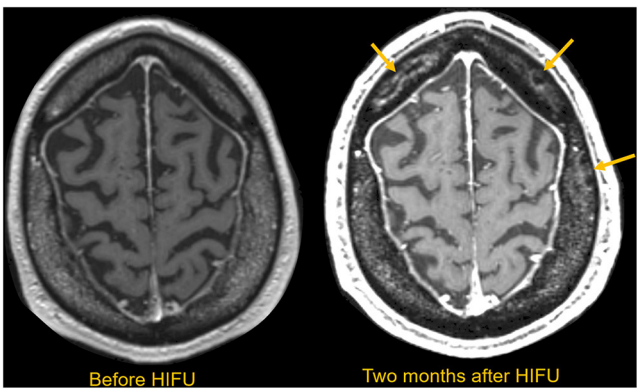

FIGURE 4 | MRI scan obtained before and 2 months after HIFU in a patient requiring extended sonications to make a durable thalamic lesion. Multiple serpiginous marrow lesions compatible with infarctions are subsequently seen in the marrow space, as indicated with yellow arrows. These lesions are asymptomatic, but notable.

Researchers have also assessed other factors such as skull morphology (20) and volume (21) as potential predictors of MRgFUS treatment success. For instance, in a retrospective analysis of 189 patients who underwent MRgFUS, D'Souza et al. (22) found that patients across different SDR categories (SDR<0.4, 0.4 $\leq$ SDR $<$ 0.45, and SDR $\geq$ 0.45) demonstrated similar improvements in clinical outcomes indexed by 1-year follow-up Clinical Rating Scale for Tremor (CRST) scores even though the percentage of patients achieving the peak temperature of 54°C was substantially higher in patients with SDR $\geq$ 0.45 (91%) than in those with 0.4 $\leq$ SDR<0.45 (64%) and those with SDR<0.4 (55%). Several other studies have reported cases of patients with low SDR in whom permanent ablation was still achieved (23, 24). Thus, there is an urgent clinical need to investigate factors such as skull thickness, incidence angle, and skull heterogeneity as potential predictors of treatment success, thereby identifying new metrics that may be more accurate in predicting success among patients with low SDR.

For patients with low SDR, the thalamic target energy deposition will be inefficient, leading to an increased risk of overheating the scalp and skull at the expense of therapeutic heating in the thalamic target. This unwanted heating will cause the patient pain and could lead to irreversible tissue damage (**Figure 4**). In addition, the efficiency of energy deposition decreases over the course of multiple treatment cycles, potentially due to effects from skull heating (25). A recent study of patients treated with MRgFUS reported that seven out of 30 patients demonstrated multiple new asymptomatic calvarial marrow injuries 3 months after attempted treatment (26). This study found no correlation between SDR and the presence of skull lesions, but the maximum power used was substantially higher for patients with lesions than for those without. For instance, one patient with a skull lesion had undergone prolonged sonication for 31 s with 1,100 W maximum power, but the maximum temperature achieved was only 48°C. There is a well-established time-temperature relationship that can change various time-temperature profiles into a standardized single measurement to estimate the degree of the thermal dose while allowing for tissue necrosis (27). For future MRgFUS procedures, clinicians must be able to tailor parameters such as maximum energy, sonication duration, and number of sonication sessions so that they can prevent thermal hotspots in the skull and thus prevent long-term skull injuries, especially for patients with unfavorable skull bone characteristics.

InSightec's hemispheric phased array system is composed of 1,024 element of transducers, and besides the skull bone property, i.e., SDR and thickness, the successful delivery of ultrasound beam from each transducer depend on the angle of incidence to the skull surface. Since the shape of the skull is not spherical, if the targeting brain structure is located far from the center of the brain, some of the ultrasound rays may likely have an incidence angle to the skull of >25°. The increased angle of incidence will deactivate the corresponding transducer and lead to a less cumulative number of active elements as the incidence angle of >25° will increase reflection and thereby likely decrease energy deposition inside of the planned target and increase deposition in the scalp. As a specific example, a recent study by Jung et al. (28) showed that an increased number of elements were deactivated when targeting globus pallidus interna (Gpi) and anterior limb of the internal capsule (ALIC), which are more lateral brain structures from the center of the brain compared to the thalamus. Several simulation studies have suggested that significant attenuation may be attributed from longitudinal-shear (transverse) mode conversion (29, 30); however, another study also reported that the conversion of longitudinal waves to shear waves inside the skull is insignificant when the incidence angle is <20°, with the assumption that amplitude loss during shear wave conversion from incident rays at the skull is not critical (31). An investigation using an *ex vivo* human skull demonstrated a significant reduction (nearly 31% loss of normal incidence) in transmitted amplitude when the incident angle was 31° at 0.548 MHz (32). In the study by Jung et al. (28), at an incidence angle >25°, energy transmission sharply decreased when the SDR was <0.6, but the energy transmission started to recover when the SDR was >0.6, indicating that a high SDR compensates for

the influence of a higher incidence angle. This study highlights that even though SDR provides a useful standard value for screening eligible patients, the role of incidence angle also must be considered, especially when the focal region is distant from the transducer's geometric focus as in cases of capsulotomy (33) and pallidotomy (34).

Jung at al. (28) also demonstrated higher energy transmission (by a factor of ∼3) at a lower frequency (230 kHz) than at a mid-frequency (680 kHz) for all SDR and incidence angle ranges. These findings helped to initiate subsequent studies developing a low-frequency system to circumvent skull limitations at higher frequencies, in addition to broadening the regions in the brain accessible to lesion creation.

Recent studies have used computer simulations to better predict the temperature increase in targets in individual skulls by modeling the skull efficiency with properties extracted from CT, in particular the HU (36, 37), an arbitrary unit of radio density. Although the HU has widespread applicability, it is still dependent on various other factors (38), and so standardization of CT parameters should optimize the use of HU as a rigorous diagnostic tool for evaluating skull adequacy for MRgFUS lesioning. Recently, researchers reported the use of a novel method employing microbubbles as an ultrasound contrast agent; this technique allowed acoustic echoes to modify phase corrections and thereby narrow the acoustic focus. This method, called "echo focusing," provided sonication efficiency for lesion formation that was superior to that obtained with CT-based aberration correction (24, 39). In these studies, an echo-focusing phase aberration correction technique was incorporated by measuring returning acoustic signals from intravenously injected microbubbles around the intended target region during sonication (40, 41). With echo focusing, successful lesion formation was achieved in 12 patients with ET, including 3 patients in whom MRgFUS thalamotomy treatment using CT-based aberration correction had failed (24). In another study, 8 patients with low SDR (mean SDR = 0.35) were successfully treated using the echo-focusing method by raising the temperature to >54°C in patients with ET and to >52°C in patients with PD; these temperatures were sufficient for lesion formation (39). This echo-focusing technique could be particularly beneficial for patients with low SDR and for those with a target that is more lateral than the thalamus, as this research demonstrated permanent lesion formation in cases of pallidotomy in patients with an SDR <0.4.

Intraoperative MRI and Accelerometer Measurements to Guide Treatment

Similar to deep brain stimulation (DBS), FUS has features that confer "closed-loop" status. Specifically, during the staged procedure, repeated examinations of the effect of increasing sublesional temperatures on the patient's tremor (as measured with continuous MR thermometry; **Figure 5**) (35) provide near–real-time feedback to verify targeting, monitor outcome, and update the treatment plan. Additionally, because the patient does not need to be placed under general anesthesia for FUS, the effect of treatment on tremor can be observed immediately after each sonication both from the accelerometer and the patient's handwriting (**Figure 6**). Approaches such as the use of an intraoperative accelerometer to quantify the tremor response in real time are necessary and will help to complete closed-loop feedback procedures in a patient-specific manner (**Figure 7**).

Research should continue to focus on developing a reliable method to identify the target, reduce lasting side effects, and enhance durability. For instance, during the course of the MRgFUS thalamotomy, different MR sequences can provide information about lesion volume and diameter changes over time (**Figure 8**). Only T2-weighted sequences can show the lesion shortly after it is created; however, the lesion may not be apparent on T2-weighted images obtained up to 180 days after the procedure. Susceptibility-weighted images, on the other hand, can demonstrate the lesion up to 180 days after treatment (42). Fast gray matter acquisition T1 inversion recovery imaging can be used for surgical planning, as this method offers superior visualization of the target and is especially effective in differentiating between the internal capsule and thalamus (**Figure 9**). Furthermore, T1-weighted 7T images can depict lesion shrinkage and shifting up to 65 days after treatment (**Figure 10**).

Movement Disorders

Disabling movement disorders such as ET and PD are often diagnosed in patients of advanced age, and the incidence of these disorders is increasing due to a growing and aging world population. The effect of movement disorders on daily life is considerable, impairing routine functions such as holding a glass of water, writing a check, or using a hand-held device. Safe and effective treatment options are therefore needed so that patients can maintain independent function. Although medications such as beta-blockers may adequately control mild upper extremity tremor, they are practically inconsequential for slowing moderate to severe tremor. Propranolol and primidone (beta-Blockers) are the most common choice of drugs in medical therapy for treating moderate to severe functional disability in ET. However, if the patient has a contraindications to beta-blockers or inadequate tremor control, other drugs such as Mysoline, Benzodiazepines, gabapentin, topiramate, zonisamide can be used as add-on therapy or monotherapy. Surgeries such as FUS-mediated Vim thalamotomy or DBS are considered last when medical treatment does not help suppress tremor. On the other hand, PD has more complex features encompassing both motor and non-motor disabilities. Most PD patients initiate treatment with levodopa therapy, the most effective drug in treating PD. However, the long-term use of levodopa frequently leads to dyskinesia (43) and wearing-off phenomenon. Patients with levodopa resistance or with rapid progression motor symptoms seek surgical treatment such as bilateral DBS, or unilateral FUS-mediated Vim thalamotomy. They could also benefit from recently approved FUS-mediated pallidotomy for bradykinesia and drug-induced dyskinesia, etc.

DBS of targets such as the ventral intermediate nucleus (Vim) of the thalamus (44), subthalamic nucleus (45), and internal globus pallidus (46) is a well-established option for the treatment

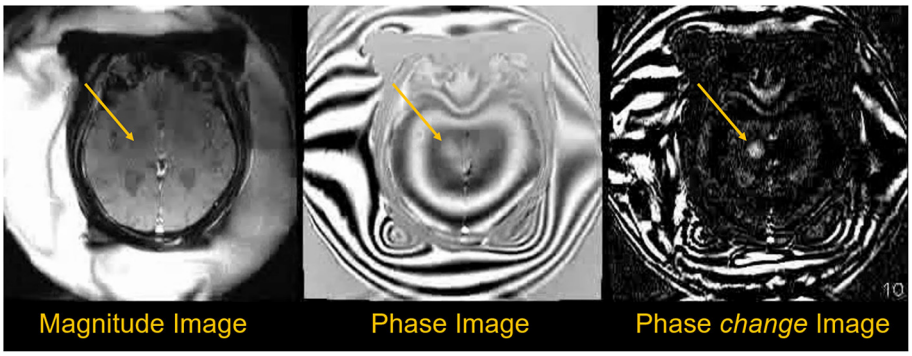

FIGURE 5 | Phase data used to obtain temperature information during sonication. The magnitude image shows little change during treatment, but the phase images show more measurable changes. Temperature difference maps (ΔT) can be created using phase-change images obtained every ∼6 s during treatment, with temperature changes proportional to cumulative phase shift (35).

FIGURE 6 | Drawings from a patient with essential tremor during MRgFUS left thalamotomy. The patient's handwriting, spiral, and line drawing were checked after each sonication in their supine position inside the MR suite **(A–G)**, and we received 2-year follow-up mail of handwriting sheet from the patient **(H)**. Note the handwriting of the patient's name after HIFU has been blocked for deidentification purposes because it is now sharp enough to read.

of movement disorders. The benefits of this treatment are long-lasting and the risk profile is low; however, the procedure is costly and invasive and requires permanently implanted hardware. Because FUS circumvents these surgical complications, there was early enthusiasm that this technique might appeal to patients reluctant to undergo DBS. Radiosurgery using Gamma Knife had

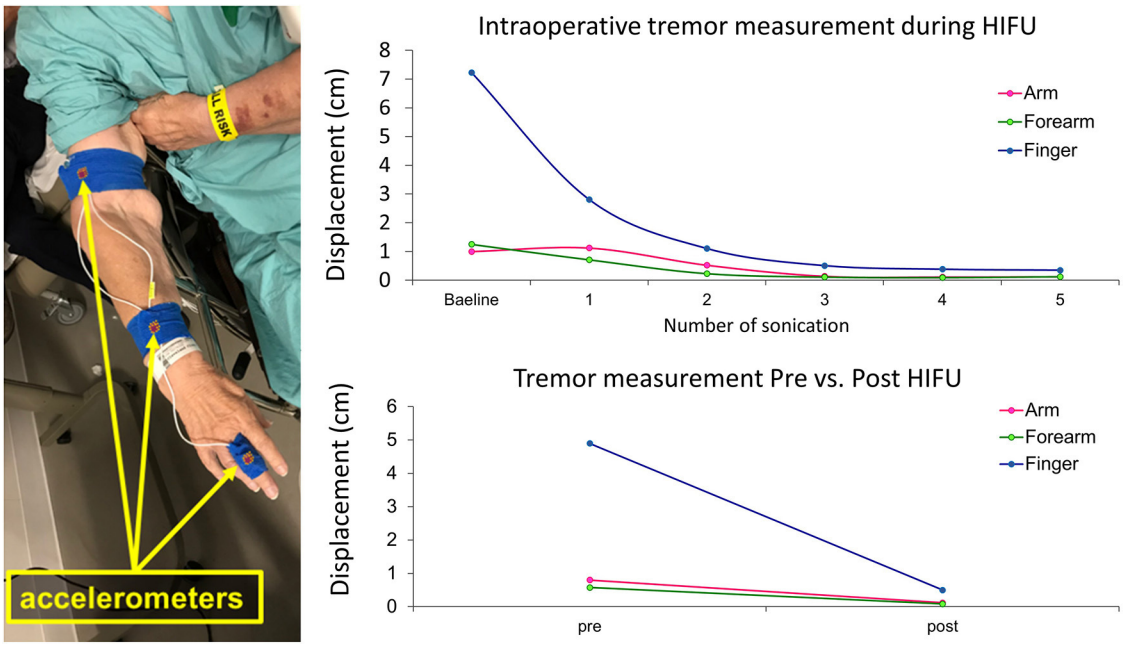

FIGURE 7 | Intraoperative monitoring of treatment response using accelerometer recordings. Accelerometer sensors are placed on the patient's finger, forearm, and upper arm during MRgFUS thalamotomy. With the patient in the MR machine, displacements of the finger, forearm, and upper arm during tremor are plotted after each sonication measure (upper graph). With the patient sitting upright in the preparation room, postural tremor is measured before and after the thalamotomy procedure (lower graph).

a similar appeal, but this procedure was limited by an absence of intraoperative validation (47) and a lack of reliable methods for targeting.

The overall outcomes of FUS and radiosurgical thalamotomy for tremor are related to the size and location of the lesion; these factors also govern potential side effects. While the durability and efficacy of treatment may be greater with larger lesions, so too is the probability of adverse effects (10). Radiosurgical thalamotomy has a shallower temperature gradient than HIFU (48), which consequently increases the uncertainty of the lesion's margins and increases the risk of extending the lesion beyond the planned target. Although the temperature range with HIFU may be easier to control, there is a small lag (2–3 s) in MRI thermometry maps, which may partially offset this advantage.

In 2016, based on data from a clinical trial by Elias et al. (14), the FDA approved the use of HIFU for ablation of the Vim in patients with ET, and this indication was expanded in 2018 to include ablation of the Vim in patients with tremor-dominant PD. With this technique, high-intensity ultrasound waves irreversibly create lesions in the target structures *via* coagulative necrosis in the tissue secondary to the heat resulting from frictional forces (49, 50). The temperatures typically need to exceed 55°C for this treatment to be effective (51). In the first proof-of-concept clinical study testing HIFU in a randomized controlled trial, ablation of the thalamic Vim with MRgFUS significantly suppressed tremor, with patients demonstrating improvements in finger-to-nose pointing tasks (14). In addition, scores on the CRST were reduced by 81.3% at 3 months after HIFU treatment compared with baseline scores. A follow-up study published in 2018 (52) demonstrated a sustained effect at 2 years in most patients with ET, and another follow-up study highlighted continued benefit from the unilateral thalamotomy after 3 years (53). It is also noteworthy that patients who benefited from the unilateral MRgFUS thalamotomy without experiencing any side effects wished to extend the lesioning procedure for bilateral thalamotomy to improve on the other side. Although a few case reports of bilateral thalamotomy state that staged second treatment were successful without severe adverse events (54–57), bilateral thalamotomy is not currently approved as standard treatment as the research of bilateral thalamotomy in relation to the tremor etiology, adjustment of the second lesion, and overall incidence of adverse events are still under investigation (NCT04112381, https://clinicaltrials.gov/ct2/show/NCT04112381).

Since this initial research was published, multiple other studies have demonstrated similar findings. For instance, Bond et al. (9) used MRgFUS to perform unilateral Vim thalamotomy in patients with PD refractory to levodopa and reported a 62% improvement in CRST scores for hand tremor contralateral to the treatment side. In another study, MRgFUS of the Vim led to a 55.9% improvement in tremor score at 3 months after treatment in 6 patients with diverse tremor types including PD, dystonia, dystonia gene–associated tremor, and writer's cramp (58). Two patients experienced lasting side effects of hemitongue numbness and hemiparesis with hemihypoesthesia, suggesting the need for long-term safety evaluation with a larger sample size. In 2020, researchers assessed the feasibility of using MRgFUS for unilateral pallidotomy in PD patients

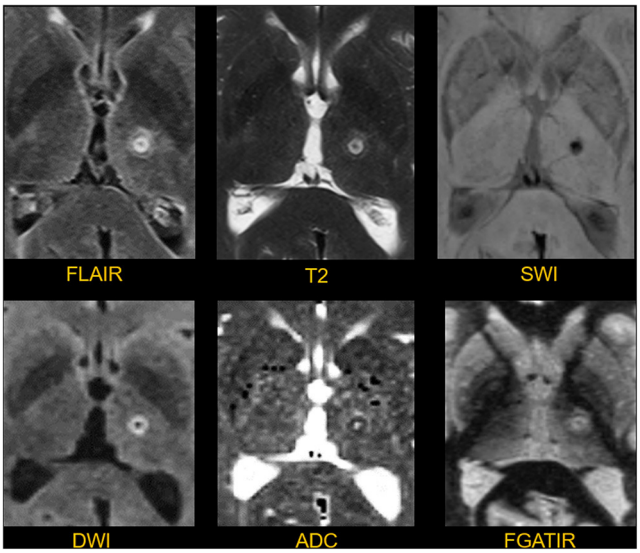

FIGURE 8 | Appearance of a thalamic lesion on postoperative day 1. The lesion in the left thalamus is manifest as a T2/FLAIR spherical hyperintense focus with a diameter of about 6 mm. There is hemosiderin clearly shown in the susceptibility weighted image (SWI). There is a rim of restricted diffusion with a core of facilitated diffusion shown on the DWI and ADC images. The FGATIR sequence shows the relationship between the lesion, thalamus, and adjacent internal capsule.

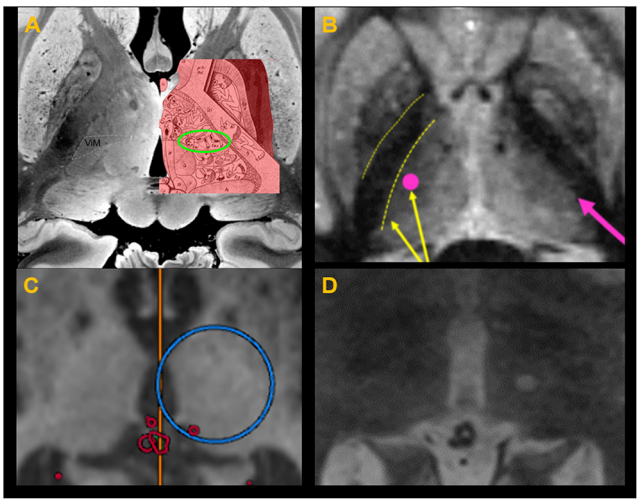

FIGURE 9 | (A) Thalamic homunculus superimposed over the thalamus in post mortem ultra–high-resolution images obtained at 7T. The green circle indicates the location of the ventral intermediate nucleus (Vim). **(B)** Fast gray matter acquisition T1 inversion recovery scan shows sharp demarcation between the IC (internal capsule) and thalamus, allowing adjustment of the target selection to avoid lesion spread into the IC. **(C)** Target coordinate selection during treatment planning using the anterior commissure–posterior commissure as standard references for localizing the target. **(D)** A successful lesion is created at the Vim, confirmed with a T2-weighted image obtained immediately after sonication with the ablative temperature.

with dyskinesia induced by the long-term use of levodopa (34). The study demonstrated a 43% improvement from baseline in Unified Dyskinesia Rating Scale score, an effect that persisted through 12 months. As the pathophysiology of PD is different from that of ET, patients show distinct cardinal signs such as rest tremor, rigidity, and bradykinesia, which has prompted researchers to explore novel therapeutic targets for PD. In November 2021, FDA extended the therapeutic target for PD and approved MRgFUS for pallidotomy. Additionally, a clinical trial assessing bilateral ablation of the pallidothalamic tract for PD is currently ongoing (NCT04728295, https://clinicaltrials.gov/ct2/show/NCT04728295). Furthermore, researchers in Madrid assessed lesioning the subthalamic nucleus for PD with markedly asymmetric signs and found that the Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor score (i.e., part III) was decreased by approximately 50% from baseline to 4 months after treatment (59).

Although early research studied the response of tremor to HIFU targeting of the Vim, other targets are also under investigation for the treatment of disabling movement disorders. For example, the internal globus pallidus is a preferred target when patients' symptoms are dominated by dyskinesia and dystonia. Previous research has demonstrated that pallidotomy and pallidal DBS lead to marked improvements in the symptoms and motor dysfunctions of PD (60).

The current evidence suggests that HIFU is a safe and effective option for patients with disabling ET or PD who are not candidates for DBS or are reluctant to undergo surgery. However, more studies are needed to address the nontremor motor symptoms of movement disorders. Additionally, questions regarding durability, the safety of bilateral treatment, and novel therapeutic targets for tremor are currently being investigated in clinical trials.

OCD

OCD is a common psychiatric disorder characterized by repetitive behaviors, compulsions, and urges detrimental to health and quality of life (61). Selective serotonin reuptake inhibitors are currently the first-line pharmacotherapy for management of OCD. Because of the chronic nature of this disease, medical therapy is often combined with cognitive and behavior therapy to increase the durability of treatment. However, 20% to 30% of patients do not respond to medication and could potentially benefit from neurosurgical options such as DBS (62, 63), radiosurgery (Gamma Knife) (64), and MRgFUS (33). Of these techniques, MRgFUS has the advantage of being noninvasive, with the added benefit of lack of general anesthesia and associated surgical complications. In addition, with MRgFUS, the lesion size and location can be controlled in real time.

The study of MRgFUS in psychiatric disorders dates back to the 1950s, when neurosurgeon Petter Aron Lindstrom first removed brain tissue using MRgFUS as an alternative to prefrontal invasive craniotomy and lobotomy (65). Lindstrom introduced the concept of MRgFUS-mediated lobotomy to his colleague Lars Leksell, who then set out to study the use of MRgFUS for treating psychiatric disorders (Steiner L. Personal communication. 2007). Leksell designed a custom stereotactic

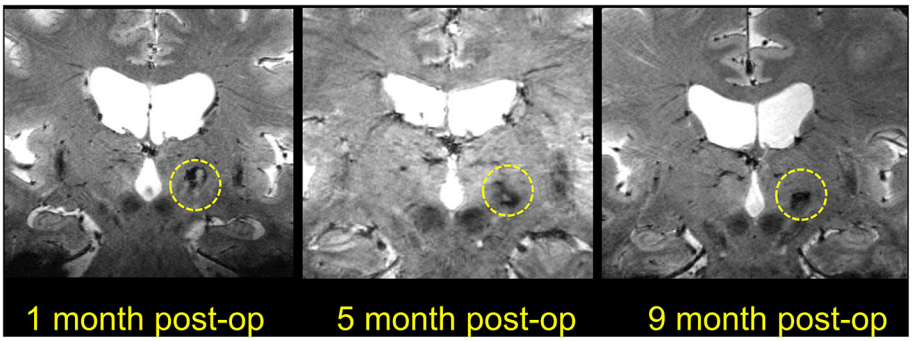

FIGURE 10 | Coronal T1-weighted 7T images showing lesions at different time points after MRgFUS thalamotomy. The three images are all from different patients, as the postoperative MR images were obtained at different time points.

headframe as a precise lesioning tool but was unable to complete his MRgFUS investigations because of the challenges imposed by the transmission of ultrasound through the skull. However, his contributions to developing a noninvasive modality for the treatment of functional brain disorders laid the foundation for the development of the first Gamma Knife model.

Research into the pathological brain networks responsible for OCD has focused on the cortico-striatal-thalamo-cortical pathway (33), and recent neuroimaging studies suggest involvement of the orbitofrontal cortex, the dorsal anterior cingulate cortex, and the amygdalo-cortical circuit (66, 67). In a study of 4 patients with OCD, bilateral MRgFUS was used to create lesions in the anterior limb of the internal capsule. This dense white matter tract consists of afferent and efferent fibers of the affect network and reward network that run their course up to the orbitofrontal cortex (68) and form a target for medication-resistant OCD. The patients treated with this procedure demonstrated a gradual improvement in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), with a mean improvement of 33% over a 6-month follow-up (33). In addition, depression and anxiety levels after MRgFUS capsulotomy were almost immediately improved (mean reductions of 61.1 and 69.4%, respectively). Similarly, Kim et al. (69) used MRgFUS bilateral capsulotomy to treat 7 patients with medication-refractory OCD and measured the patients' Y-BOCS scores at 1 week and at 1, 3, 6, 12, and 24 months. Significant improvement (38%) from baseline was seen at the 24-month follow-up, without any severe adverse events. In addition, OCD symptoms started to improve as early as 1 week after MRgFUS capsulotomy, and depression and anxiety levels were also reduced at 1-week follow-up (−47.4% on the Hamilton Rating Scale for Depression and −53.6 % on the Hamilton Rating Scale for Anxiety). The improvement in Y-BOCS score seen in this study was comparable to the improvement reported in a meta-analysis of DBS studies (45.1% reduction in Y-BOCS score among 116 patients) (70). In another recent study, 10 patients (5 with refractory OCD, 5 with MDD) underwent MRgFUS anterior capsulotomy (71). In these patients, reduced symptoms of OCD (measured with Y-BOCS scores) and MDD (measured with Hamilton Rating Scale for Depression scores) were highly correlated with self-reported frontal function measured with the Frontal Systems Behavior Scale (72), thus indicating successful disruption of pathological function within the frontal-striatal networks by both up-regulating frontal-executive function and down-regulating OCD symptoms. However, this study reported no cognitive impairment after treatment, and therefore could not provide information regarding the upper limit of safety for lesion size. The results from these studies warrant large-scale and sham-controlled clinical trials to broaden our understanding of MRgFUS for the treatment of OCD.

Epilepsy

Several clinical trials are ongoing to assess the use of FUS for the treatment of epilepsy, with some using low-intensity focused ultrasound (LIFU) to induce a neuromodulatory effect on the area with the highest epileptogenic activity within the temporal lobe and others using HIFU for thermoablation of a hypothesized epileptogenic focus using MRgFUS. Previous studies regarding FUS neuromodulation have led to the establishment of safe sonication parameters for reversible mechanical disruption of the neural circuit (73–75), and these induced neuromodulatory effects could be stimulatory and inhibitory depending on the targeted brain regions and pulsing schemes. In one clinical trial (NCT03657056, https://clinicaltrials.gov/ct2/show/NCT03657056), the BX Pulsar 1002 is being used to precisely target the epileptic focus in patients who are scheduled for temporal lobe resection. The feasibility and safety of the treatment with both excitatory and inhibitory LIFU parameters will be examined by assessing BOLD functional MRI signal changes throughout the LIFU procedure. Investigators in another clinical trial (NCT03868293, https://clinicaltrials.gov/ct2/show/NCT03868293) are also using the LIFU neuromodulatory effect to treat drug-resistant temporal lobe epilepsy. In this study, patients are undergoing a total of 8 LIFU treatment sessions within 1 month, with researchers assessing treatment efficacy by comparing the number of seizure episodes during and after treatment with the number of episodes in the pretreatment period. Investigators also hope to identify the electrophysiological changes in the epileptic tissue after LIFU neuromodulation and expect to reduce the frequency and/or attenuate the amplitude of epileptiform discharges recorded in electroencephalography data. The unique bimodal modulatory

effect of LIFU intervention on the neuronal circuits that may initiate seizure activity may provide an important mapping strategy to identify the seizure focus when combined with electrophysiology or brain imaging readout. In another clinical trial assessing LIFU (NCT 02151175, https://clinicaltrials.gov/ct2/show/NCT02151175), investigators are again using the BX Pulsar 1002 device to study the excitatory and inhibitory effects of stimulation on patients with nondominant mesial temporal lobe epilepsy. The primary endpoint in this study is the safety of the device, which will be assessed by identifying any histological tissue changes. Secondary outcomes include changes in seizure frequency, neurological status, neuropsychological profile, and psychological profile. An initial publication from this group reported that among 8 patients who underwent LIFU sonication of the temporal lobe followed by resection of the affected side, no abnormal histological or neuropsychological changes were observed (76).

The results of another clinical study regarding the use of LIFU in the seizure onset zone were recently published (77). In this study, seizure focus was determined once patients had experienced at least 3 confirmed seizures after stereo-electroencephalography (SEEG) implantation. Patients then underwent LIFU using burst tone and nonthermal parameters with a 10-min exposure time. Sonication occurred while the SEEG electrodes were still implanted; they were removed 3 days later. Of the six patients who underwent treatment, three had no change in seizure frequency, two had a decrease in seizure frequency, and one had an increase in seizure frequency. More cases will need to be evaluated to determine the efficacy of LIFU as a treatment for patients with epilepsy. However, the use of LIFU should not be limited to treatment alone; variations in seizure activity can also aid in diagnosis and confirm the epileptogenic focus.

HIFU is also being investigated for the treatment of epilepsy. Patients with focal epilepsy are currently being recruited for a multicenter clinical trial (NCT02804230, https://clinicaltrials.gov/ct2/show/NCT02804230) that aims to evaluate the feasibility, safety, and initial efficacy of MRgFUS ablation of epileptic foci (defined in this study as temporal sclerosis, dysplasias, and heterotopias). Two other trials (NCT03417297, https://clinicaltrials.gov/ct2/show/NCT03417297 and NCT05032105, https://clinicaltrials.gov/ct2/show/NCT05032105) are assessing the feasibility and safety of using HIFU to ablate the anterior nucleus of the thalamus. One of the trials is focused on determining whether this ablation will help to prevent secondary generalization. The other is assessing the effect of ablation on focal seizure-related anxiety, using functional MRI to evaluate the reactivity of the amygdala to threat.

One of the challenges involved in treating epileptogenic lesions with HIFU is the size limitation of the ablation. Usually $<$1 cm in any diameter, the convergence of ultrasound waves in HIFU cannot completely ablate a large epileptogenic lesion in a single session. For instance, Yamaguchi et al. (78) described the use of HIFU to ablate a hypothalamic hamartoma in a 26-year-old man with medically refractory epilepsy and gelastic seizures. The hamartoma was too large for ablation, and so the case report details the authors' approach to achieve disconnection. First, electroencephalography was used to identify the location of the patient's seizure activity (right frontal lobe). Diffusion tensor tractography identified connectivity between the hypothalamus and right frontal lobe in the right posterior portion of the hamartoma. This boundary area was subsequently ablated with HIFU, creating a lesion with dimensions of 4.73 mm by 6.46 mm by SI (superior-inferior) 7.73 mm. The patient had no seizures after the ablation and remained seizure free over 1 year of follow-up. This case demonstrates the limitation of HIFU ablation size in epilepsy. However, with the integration of structural connectivity imaging, a disconnective approach could be the optimal treatment strategy.

Another challenge is that the most common type of epilepsy, mesial temporal lobe epilepsy, typically requires ablation of the anterior hippocampus and/or amygdala. Due to the incident angles of the ultrasound beam and the skull at this location, it is very difficult to achieve a high enough treatment efficiency to cause thermal ablation. One group in Japan published the first case report in thermal lesioning at the hippocampus for treating mesial temporal lobe epilepsy (12). Even with the maximum energy and high SDR (0.56), the temperature did not exceed ablative level, and postoperative MRI did not indicate any viable lesion. The patient remained seizure free after 12 months, and the authors theorized that there was a potential neuromodulatory effect due to the subablative temperature.

Neuropathic Pain

The International Association for the Study of Pain defines the chronic pain indication as "persistent or recurrent pain lasting longer than 3 months" (79), at which point the pain network will no longer serve as a protective and healing mechanism but will be a pathological condition. Acute pain can occur in any part of the body, but as the pain evolves into a chronic state, pain information from the periphery to the thalamus will drive changes in higher-order brain areas, including reward, motivation, and cognition (80). Altering these widespread brain networks will change the biochemistry of pain transduction and affect the patient's cognitive and emotional experience in pain perception. Unfortunately, the current status of pain management using pharmacotherapy alone is limited to achieving satisfactory pain relief, and the conventional noninvasive brain stimulation modality is still controversial and lacks good scientific data to prove the effectiveness of the treatment (80).

MRgFUS has therapeutic potential for pain management using ablative therapy. In one sham-controlled randomized clinical study (NCT05122403), patients with medication-refractory neuropathic pain are undergoing MRgFUS central lateral thalamotomy followed by a double-blinded assessment regarding treatment effects and adverse events 3 months after treatment. Another ongoing clinical trial (NCT03309813) is targeting bilateral thalamic nuclei with MRgFUS to reduce pain and increase quality of life in patients with chronic trigeminal neuropathic pain. The goal of this randomized, sham-controlled, crossover study is to evaluate the safety and feasibility of treating chronic pain using the MRgFUS lesioning procedure.

FUS-MEDIATED BBB OPENING

Brain Tumor

Among brain tumors, glioblastoma multiforme (GBM) is the most aggressive and is known to respond poorly to conventional chemotherapies. Contributing to this difficulty is the presence of the BBB, the tight junctions of which impair access of the macromolecular agents into the cellular environment. Additionally, the integrity of the BBB is highly heterogeneous due to the tumor microenvironment (81). Researchers initially found that HIFU could modify the BBB through the use of high intensities similar to those used to create lesions in normal tissue; however, this also led to an increased frequency of hemorrhage and edema (82, 83). Later research demonstrated that a reduction in the acoustic intensity could still achieve BBB opening with a lower incidence of unwanted side effects (84). In 2001, Hynynen et al. (85) found that with the intravenous injection of microbubbles, low-power FUS (ie, within the range of diagnostic ultrasound level, <1.5–2 MPa) could induce transient, reproducible, and localized BBB opening in rabbits without producing any associated neuronal damage. This study opened the door to improved chemotherapy delivery for patients with malignant brain tumors, with this technique allowing successful delivery of chemotherapeutic agents and thereby improving on the low (5%) efficacy of conventional systemic administration (86, 87). The FDA-approved use of concurrent microbubbles as contrast agents in diagnostic imaging thus permits safe doses of FUS intensity to disrupt the BBB (88, 89).

The first-in-human BBB opening was achieved using a transducer surgically implanted into the epidural space superficial to the tumor in patients with recurrent GBM (**Table 1**) (90). Patients received monthly FUS treatments coupled with intravenous injection of microbubbles for BBB opening. The pressure amplitude began at 0.5 MPa and increased to 1.1 MPa through 5 different doses (0.5, 0.65, 0.8, 0.95, 1.1 MPa), and BBB disruption was found to occur at pressure amplitudes >0.8 MPa. Disruption of the BBB was quantified with gadolinium-enhanced T1-weighted MR images; this technique was chosen based on data from a previous BBB opening study in nonhuman primates (91). Carboplatin, a common chemotherapeutic agent, was used in this study to control the recurrent GBM. This study was limited by the need to surgically implant the ultrasound transducer. Additionally, the transducer was unfocused and unable to electronically steer the beam after surgical implantation.

A few years later, researchers performed a first-in-human trial of noninvasive MRgFUS BBB opening in patients with malignant glioma, using concurrent systemic administration of temozolomide chemotherapy (**Table 1**) (92). T1-weighted MR images demonstrated a 15% to 50% increase in signal enhancement, indicating transient BBB opening in the target tissue (**Figure 11**). Approximately 24 h after FUS and chemotherapeutic administration, the patients underwent craniotomy and tumor resection. Sonicated and unsonicated peritumor tissue samples were collected and the tissue chemotherapy concentrations were measured. Note that during the trial, the chemotherapy agent was switched from

TABLE 1 | FUS and microbubble parameters for BBB opening.

Condition	Study	FUS system	FUS frequency	FUS intensity	MB dose	Sonication duration	Follow-up	Outcome
Recurrent GBM	Carpentier et al. (90)	SonoCloud	1.05 MHz	0.5–1.1 MPa (>0.8 MPa opened the BBB)	Sonovue (0.1 mL/kg, with a maximum dose of up to 8.7 mL)	2.38% duty cycle for 150 s	6 mo	BBB of each patient was disrupted monthly using pulsed ultrasound in combination with systemically injected microbubbles
	Mainprize et al. (92)	The ExAblate Neuro	0.22 MHz	4–15 W	Definity (4 µL/kg); did not exceed 20 µL/kg	0.74% duty cycle for 50 s	3 mo	Reversible and safe opening of the BBB
	Park et al. (93)	The ExAblate Neuro	0.22 MHz	Maximum power did not exceed 40 W	Definity (4 µL/kg); did not exceed 20 µL/kg	5% duty cycle for 90 s	1 mo	Repetitive MRgFUS at the same target with standard chemotherapy
	Chen et al. (94)	NaviFUS	0.5	0.5–1.1 MPa (equates to 4, 8, 12 W)	Sonovue (0.1 mL/kg)	10 ms burst duration for 120 s. PRF of 9 Hz	36 ± 3 d	Feasibility and the tolerated dose of transient opening of the BBB
AD	Lipsman et al. (95)	The ExAblate Neuro	0.22 MHz	3–10 W	Definity (4 µL/kg); did not exceed 20 µL/kg	0.74% duty cycle for 50 s	2 mo	Reversible, safe, and repeated opening of the BBB

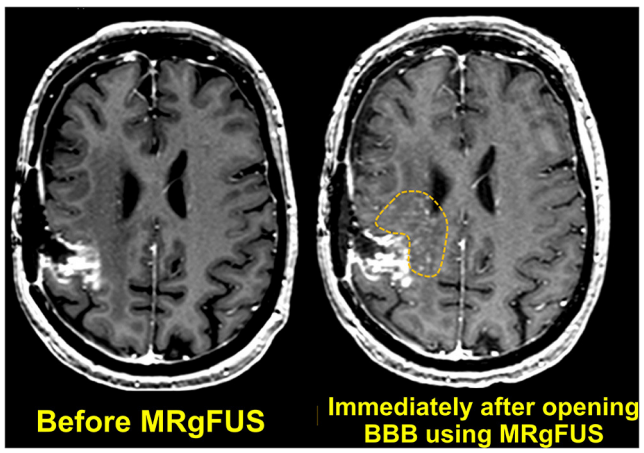

FIGURE 11 | Axial T1-weighted MR images obtained before and immediately after MRgFUS was used to open the BBB. Localized extravasation (inside the dotted yellow circle) can be seen in the predefined targeted brain tissue.

liposomal doxorubicin to temozolomide, and limited resectable tumor volume in three of five patients prevented statistical analysis of the tumor samples. Nevertheless, the researchers observed a chemotherapy concentration that was 7.7 times higher in the sonicated peritumor tissue than in the unsonicated peritumor tissue in one patient.

Another group of researchers subsequently tried to enhance the treatment effect by creating multiple BBB openings with MRgFUS (**Table 1**) (93). In this study, 6 patients who underwent a gross total resection of malignant glioma received 6 cycles of temozolomide with associated FUS BBB opening performed at the beginning of each 4-week cycle. Patients underwent follow-up MRI 1 year after the first chemotherapy cycle (6 months after the last chemotherapy cycle), and there was no evidence of any FUS-related adverse effects.

In 2021, another study demonstrated the feasibility and safety of using NaviFUS, a frameless novel device that integrates neuronavigation and an FUS system, in patients with GBM (94). Six patients were assigned to one of three different ultrasound doses in the mechanical index (0.48, 0.58, or 0.68) to temporarily open the BBB. The lowest dose used (0.48) was previously identified as the threshold of BBB opening in nonclinical studies (96); the maximum dose of 0.68 was chosen based on Good Laboratory Practice safety tests (97). Dynamic contrast-enhanced MRI was performed immediately after and 24 h after the BBB opening procedure and demonstrated the efficacy of NaviFUS BBB opening. T2-weighted images were obtained to evaluate any hemorrhages associated with BBB opening. All patients were scheduled for tumor resection surgery within 2 weeks after the FUS BBB opening, and clinical visits for follow-up were performed routinely until the third week after BBB opening to assess physical and neurological functions.

AD and ALS

AD represents an enormous societal and healthcare burden as the population ages. Still, the development of new pharmacotherapeutics provides diminishing returns, as these drugs are restricted from entering the brain by the BBB. FUS temporarily loosens the BBB tight junction, allowing the delivery of therapeutic agents to the sonicated brain area. However, even without these therapeutics, studies have reported that BBB opening alone triggers a significant reduction of Aβ deposition through microglia activation (98, 99). Therefore, researchers have assessed the use of potential therapeutics such as a GSK-3 inhibitor and RN2N as an additive strategy that can further increase the therapeutic benefit of BBB opening (100). These preclinical studies using transgenic mouse models of AD have demonstrated improvements in Aβ plaque clearance and up-regulation of cognitive function in AD pathology after opening of the BBB. Based on these findings, researchers assessed the use of FUS in 4 patients with AD, and clinical and radiographic evaluations in these patients demonstrated reversible, repeatable, and safe noninvasive opening of the BBB with FUS (**Table 1**) (95). The researchers in this study targeted the superior frontal gyrus white matter of the dorsolateral prefrontal cortex to reduce the risk of adverse events. Note that a [18F]-florbetaben positron emission tomography scan performed 1 week after both the first and second sonication could not demonstrate a clear effect of BBB opening on Aβ clearance. Additionally, the small sample size limited the conclusions that could be drawn regarding the safety and efficacy of this treatment, as well as whether FUS BBB opening affected the clinical and pathological symptoms of AD.

Another research group developed a novel strategy in which FUS was delivered to deep brain regions without tissue ablation or BBB opening (101). The researchers used single ultra-short pulses (3 μs) instead of conventional pulses (100 ms) (75, 102) at 5-Hz pulse repetition frequency, and used 6,000 pulse numbers per session. This approach was found to be safe and effective in a preclinical study using an energy level of 0.3 mJ mm^{-2}; the energy level was decreased to 0.2 mJ mm^{-2} for clinical purposes. In this study, 35 patients with mild AD treated at 2 separate clinics underwent FUS. In patients from clinic 1, researchers targeted the AD brain network, which included the dorsolateral prefrontal cortex, inferior frontal cortex, and language areas extending to Broca's and Wernicke's areas. In patients from clinic 2, researchers performed global cortical stimulation by distributing the total sonication energy over all brain areas by moving the headpiece probe over the scalp in a circular trajectory. Neuropsychological changes after therapy were evaluated with Consortium to Establish a Registry for Alzheimer's disease (CERAD) scores. Study patients demonstrated significant improvements in CERAD corrected total scores and logistic regression scores after treatment, and these improvements remained consistent over 3 months. Principal component analysis was also performed to assess CERAD-derived cognitive measurements of learning and memory, verbal skills, and visuospatial processing. Patients from clinic 1 demonstrated improvements in learning/memory and verbal skills lasting up to 3 months, and showed a decline in visuospatial processing. However, patients from clinic 2 demonstrated no significant change in visuospatial processing. This absence of stimulation effect could be due to the lack of stimulation of the occipito-parietal region in patients from clinic 2.

FUS also holds potential for the treatment of ALS. ALS is a devastating and incurable neurological illness, and medical advances have been incremental. As with brain tumors, the BBB is a pharmacologic barrier to potentially effective treatments for ALS. To this end, researchers assessed the use of MRgFUS to open the BBB in patients with ALS and demonstrated successful results (103). In this research, the brain region targeted for BBB opening was the eloquent primary motor cortex, and the process was found to be safe, feasible, and reversible. For patients with ALS, BBB opening is used to introduce agents such as nonviral vectors that transport therapeutic genetic elements into neurons; it is therefore essential that these agents are not damaged as they travel through the BBB (104).

LIFU FOR PSYCHIATRIC DISORDERS AND IMPAIRED CONSCIOUSNESS

The introduction of LIFU, an incisionless brain stimulation modality that influences brain activity through subthermal temperature increases, presented a new opportunity to reversibly explore psychiatric disorders related to perception, emotion, and cognition along with altered states of consciousness. One of the first reports of the effects of transcranial ultrasound was published in 2013 and involved a double-blind crossover study of patients with chronic back pain (105). In this study, patients underwent either FUS or a sham session on a LOGIQe ultrasound imaging system with an 8-MHz probe placed over the frontal-temporal cortex contralateral to the side of maximal pain for 15 s. Forty minutes later, patients were switched to the opposite treatment arm (FUS or sham) for the second session. The parameter selection produced a mechanical index of 0.7 and a thermal index of 0.5, well below the FDA guidelines of 1.9 for mechanical index and 6.0 for thermal index. Patients in this study reported significant improvements in mood (measured with the Global Affect score derived from the Visual Analog Mood Scale) both 10 min and 40 min after FUS compared to the sham session.

Small animal studies using LIFU have suggested that targeted ultrasound could be used to restore consciousness after injury, although translating these results to humans is challenging because of the vast differences in scale between the awake state of humans and animals. The thalamus is often the target of choice in this research given its perceived role in the coordination of awake and sleep states. For example, Yoo et al. (106) demonstrated that performing thalamic LIFU led to a faster recovery time from ketamine/xylazine anesthesia in rats. In 2016, a case study was published reporting improvements in Glasgow Coma Scale and Coma Recovery Scale-Revised scores in a patient suffering from a posttraumatic disorder of consciousness (107). In this case, 10 pulsed sonications using a frequency of 650 kHz, an intensity of 720 mW/cm^2 (I_{SPTA}), and a pulse duration of 0.5 ms were applied to the thalamus. Each pulse train continued for 30 s with a subsequent 30-s interval. Five days after the sonication treatment, the patient attempted to walk and showed new motor responses and vocalization. The sonication parameters used in this study to stimulate the human thalamus were adapted from a previous rodent study where thalamic stimulation reduced the time under anesthesia (106). Except for the acoustic intensity being increased from 300 mW/cm^2 to 720 mW/cm^2 when translated to the human, fundamental frequency (650 kHz), duty cycle (5%), and pulse-repetition frequency (100 Hz) stayed the same. Based on the study in Plaskin et al. (108), a simulation model called neuronal intramembrane cavitation excitation (NICE) showed that thalamic reticular neurons display cell-type-specific inhibitory response to FUS parameters comprising 5% duty cycle and 100 Hz pulse-repetition frequency (PRF) driven by the particular membrane property of mechanosensitive T-type calcium channels. Those particular thalamic neurons are hypersensitive to a discontinuous pulsed mode of ultrasound stimuli compared to continuous mode as the T-type voltage-gated calcium channels show strong response during the hyperpolarization phase, and the depolarization phase results in increased calcium currents during the ultrasound off-period. Furthermore, the slow deactivation of the T-type calcium channel after the hyperpolarization allows charge accumulation during the ultrasound-off period and makes them more sensitive for re-excitation for repeated short-bursts of ultrasound pulses. Therefore, the authors believe that the neuromodulation effect on thalamic nuclei could modulate thalamocortical communication. In contrast, lesioning procedure uses continuous (100 % duty cycle) FUS parameters with the acoustic intensity at the thermoablation level. The researchers in this case sonicated the thalamus to modulate the cortico-striato-pallido-thalamo-cortical circuit; this decision was based on previous research in which the thalamus was targeted via pharmacological intervention (109), DBS (110), or transcranial direct current stimulation (111). The neuromodulatory effect, targeting, and safety of applying FUS to deep subcortical human brain was further assessed by Legon et al. (102). In this study, the authors found that sonicating the human thalamus reduced the amplitude of somatosensory evoked potentials and induced measurable behavior changes.

The use of LIFU has also been assessed for the treatment of mood disorders, in part because of the high prevalence of these disorders in the general population and inconsistent benefits with pharmacological treatment. Recently, researchers investigated whether FUS of the right inferior frontal gyrus (rIFG), a brain area associated with emotional regulation (112), could affect the mood of healthy participants in a randomized, placebo-controlled, double-blind study (113). Analysis of the participants' functional MRI results and self-reported moods demonstrated that FUS applied to the rIFG significantly enhanced mood for up to 30 min and significantly reduced specific brain connectivity between the rIFG and subgenual cortex for 20 min after sonication. These findings support previous research suggesting that interconnectivity between diverse brain regions is involved in the regulation of emotional and cognitive function (114–116). Previous research has also found that hyperactivity in the subgenual cortex is correlated with negative emotional states and might contribute to mood disorders such as depression (117). This study of FUS applied to the rIFG also demonstrated

a decrease in default mode network connectivity (113). It is hypothesized that overexcited default mode network connectivity is associated with a lack of self-referential processing and the rumination that is frequently observed in patients with depression (118, 119). Therefore, depressive symptoms may be improved by down-regulating the activity of the rIFG with FUS. This research group subsequently reported research in which the same brain location was targeted in patients diagnosed with mild to moderate depression (120). In this study, they lowered the intensity of the ultrasound treatment from 130 to 71 mW/cm^2 (I_{SPTA}) delivered over 5 days. Patients who were treated with FUS self-reported a decrease in worry and an increase in happiness; however, the mood change was not consistent throughout the treatment period. The authors stated that the lower ultrasound intensity might be the reason for the inconsistent treatment effect and suggested that future studies should address parameter optimization to balance safety and efficacy. Nevertheless, this study shows that FUS may be a potential therapeutic intervention for depression, as only slight increases in worry and anxiety increase depression severity and the likelihood of refractory depression (121, 122).

FUTURE OUTLOOK

Over the past 5 years, we have witnessed a global surge of publications regarding the clinical use of FUS across diverse neurological disorders, and this exponential growth of interest in the therapeutic potential of this modality has laid the foundation to optimize current technologies for human research. For instance, MR thermometry is crucial in MRgFUS lesioning procedure, as it provides real-time feedback of both anatomical location of the sonicated tissue and imposed thermal dose at the focus, which allow us to estimate the target accuracy and the degree of tissue damage for achieving thermal necrosis with precise spatial resolution. On the other hand, FUS can deliver exceptionally safe and stable opening of the BBB using passive cavitation detection, which is incorporated in MRgFUS system to real-time monitor the bubble activity provided by passive cavitation maps. Furthermore, functional connectivity is another modality of MRI often for examining the effect of FUS-mediated neuromodulation on network levels.

Besides the different types of MR tools coupled with the FUS system, each thermoablation therapy and BBB opening uses different FUS systems of MRgFUS. Although both FUS systems have hemispherical phased-array transducers consisting of thousands of elements, each is operated at different fundamental frequencies. 650 kHz FUS and 220 kHz systems are optimized for thermoablation and BBB opening, respectively. Using a high frequency of 650 kHz with a short wavelength and high intensity in a continuous waveform is useful when strategizing heat accumulation for irreversible tissue ablation. Using 650 kHz with 2.3 mm wavelength (assuming a speed of sound as 1,500 m/s in the brain) in a phased-array system enables tight focus and sharp demarcation within Vim, which is approximately 6–10 mm. On the other hand, using a low frequency of 220 kHz with a larger wavelength (6.8 mm) and burst-type of low-intensity in the pulsed waveform is beneficial when transiently opening the BBB within a large and complex target volume.

Researchers are also increasingly interested in the development of treatment methods that use the mechanical bioeffects of FUS, as there is a lower risk of thermal damage. Research in animal models has shown that fine-tuning of the pulse repetition frequency and the pulse duration with extremely high energy of ultrasound can create microbubble clouds to fractionate soft tissue (123–125), a method know as histotripsy. However, the mechanism of mechanical ablation is still poorly understood compared to the mechanism of thermoablation, and additional examinations of safety are still needed. Nevertheless, mechanical ablation is currently being explored for the treatment of stroke/intracranial hemorrhage (126–129). As with past research in this field, future studies will again require the expertise of the medical physics, imaging, engineering, and neuroscience communities.

CONCLUSION

In conclusion, since the early attempts to use FUS-induced heating as a direct surgical approach in neurosurgery, acoustic energy in therapeutic applications has been widely attractive in diverse central nervous system diseases. Subsequently, therapeutic ultrasound has been under active investigation in preclinical and clinical studies for the last few decades. These research efforts marked the first successful culmination as experts in medical physics and engineers demonstrated the clinical feasibility of harnessing ultrasound energy by designing a transducer that can produce a focused beam of concentrated energy into the size of a grain of rice. This tight focus of concentrated acoustic energy allows FUS-induced heating to create a lesion at the particular region of the brain circuits responsible for pathological indications to normalize its function. Following the FDA approval of MRgFUS unilateral thalamotomy for ET in 2016 and MRgFUS unilateral pallidotomy for PD 5 years later, MRgFUS became a commercially available treatment option in the clinic for both ET and PD. Researchers and teams of clinicians—neuroradiologists, neurologists, and neurosurgeons—now envision extending FUS-mediated thermal ablation to treat a broader range of central nervous system diseases such as epilepsy, OCD, and neuropathic pain. FUS-mediated BBB opening combined with drug delivery is another promising modality requiring a team effort of broad interdisciplinary collaborations to fill the translation gap. Potentially, BBB opening technology could be developed into a localized therapeutic delivery and cellular delivery platform releasing chemotherapeutics, drug-encapsulated nanoparticles, stem cells, and immune cells for treating diverse neurological diseases.

Here we have reviewed the current clinical application of MRgFUS in treating brain disease in terms of thermoablation and BBB opening and discussed a growing number of clinical studies on FUS neuromodulation.

AUTHOR CONTRIBUTIONS

HB wrote the original draft of this review. SJ conceptualized and created all figures. SJ and SN substantively reviewed the final manuscript. All authors made contributions to sections, were involved in revising and editing the manuscript, and they all approved the final version of the manuscript.

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REVIEW
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A New Paradigm in Parkinson's Disease Evaluation With Wearable Medical Devices: A Review of STAT-ON™

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In the past decade, the use of wearable medical devices has been a great breakthrough in clinical practice, trials, and research. In the Parkinson's disease field, clinical evaluation is time limited, and healthcare professionals need to rely on retrospective data collected through patients' self-filled diaries and administered questionnaires. As this often leads to inaccurate evaluations, a more objective system for symptom monitoring in a patient's daily life is claimed. In this regard, the use of wearable medical devices is crucial. This study aims at presenting a review on STAT-ON™, a wearable medical device Class IIa, which provides objective information on the distribution and severity of PD motor symptoms in home environments. The sensor analyzes inertial signals, with a set of validated machine learning algorithms running in real time. The device was developed for 12 years, and this review aims at gathering all the results achieved within this time frame. First, a compendium of the complete journey of STAT-ON™ since 2009 is presented, encompassing different studies and developments in funded European and Spanish national projects. Subsequently, the methodology of database construction and machine learning algorithms design and development is described. Finally, clinical validation and external studies of STAT-ON™ are presented.

Keywords: wearables, accelerometer, machine learning (ML), Parkinson's disease, medical device

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INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative disorder, presenting a wide range of motor and non-motor symptoms. It is estimated that at least 10 M people have been diagnosed around the world (1), and some studies indicate that this number will keep rising drastically (2). The disease is characterized by different cardinal symptoms (tremor at rest, rigidity, bradykinesia (BKS), and postural instability), as well as non-motor symptoms (3). The detailed and accurate evaluation of the disease is of interest in the management of daily medical practice. Dopamine treatments have been shown to improve motor symptoms and quality of life (4). However, after a certain time undergoing this therapy, some motor complications may appear, such as motor fluctuations (MF), including end-of-dose deterioration (wearing-off) and dyskinesia (DKS) (5), or freezing of gait (FoG). Apart from the motor symptoms, non-motor fluctuations are also

present, which make disease management complex (6). It is well-known that MF can appear early in the course of PD. Thus, its early identification is crucial to keeping an optimal quality of life (7, 8). The diagnosis of early fluctuations and dyskinesia is delayed in many cases due to multiple circumstances, such as the short neurology visits and the lack of optimal tools, which can allow for precise symptom identification. This circumstance is also present in advanced stages, where there is also an infradiagnosis of advanced symptoms (9, 10). So far, the identification and quantification of MF can be measured through patient diaries (e.g., Hauser diaries) and/or by a set of validated scales, such as the Unified Parkinson's Disease Rating Scale (UPDRS) (11, 12). Nevertheless, the subjectivity and cognitive state of the patients play an important role in the results. Furthermore, the interrater and intrarrater variability of the UPDRS is significant, leading to confusing evaluation results and highlighting this method's subjectivity (13, 14). On the other hand, Hauser diaries require a great effort and major time consumption from the patients' side. Furthermore, reduced compliance, recall bias, and patient fatigue are also variables to take into account when the Hauser diary is set as a clinical endpoint (15).

Symptoms' evaluation during consultancy results is complicated. The average clinical visits occur around every 6–9 months with about 20 min of time duration (16). Considering this scenario, clinicians are faced with major difficulties in detecting patients who need special care or concrete therapies. In addition to this, medication intake usually happens before going to the doctor's visit, and therefore, real symptoms are not shown in front of clinicians. Thus, the anamnesis performed by the clinician tends to be quite subjective as the symptoms' distribution information is mainly obtained from the patient's point of view. Furthermore, the white coat effect and the Hawthorne effect (behavioral change due to awareness of the patient by being evaluated) affect the symptoms' severity presented at the clinical visit, consequently affecting the whole assessment of healthcare professionals, too (17). Thus, this scenario results in incorrect therapy prescriptions, so decreasing patients' quality of life (QoL). Hence, objective home and daily symptoms monitoring is the key to better understanding the patient's symptoms severity in real life and therefore, prescribing the correct therapy.

Recently, the introduction of targeted tools such as wearable sensors in clinical practice has provided a new approach to collecting motor symptoms in real environments during long-term monitoring in a more precise and objective manner. This new paradigm enables the neurologist to observe clinical symptoms without depending on subjective methods, which come with self-perception bias, or third parties' evaluation, resulting in a non-adequate knowledge or training (18). Furthermore, due to the new social scenario of COVID-19, patients have difficulties and barriers to accessing healthcare facilities and maintaining the usual relationship with their medical service. These technologies allow the patients to overcome these obstacles by being remotely monitored and continuing their relationship with the clinician. Thus, wearable medical devices can become of great support for neurologists to manage movement disorders, especially motor symptoms associated with PD, and consequently improve the QoL and drug treatment of patients (19, 20).

In literature, there have been many approaches to evaluate PD motor symptoms with wearable systems. First, it is important to define the ON and OFF states as the levodopa-related response (5). The ON state is associated with a good levodopa response, while the OFF state is when symptoms re-emerge. One of the most important symptoms that represent an OFF state in PD is bradykinesia. According to Jankovic et al., this is the most characteristic clinical feature of PD (3). Bradykinesia is characterized by slowness in movements, and, in consequence, affects general movement, such as gait. Gait is possibly the best characteristic where a bradykinetic patient can be differentiated from a medicated-ON patient. In a patient affected with bradykinesia, gait is altered by reducing the cadence and the step length, a part of having problems of instability. Bradykinetic gait is affected by levodopa (21, 22), and some studies have focused on bradykinetic gait as a crucial symptom to analyze the behavior of motor fluctuations along the day (23, 24). Due to the motor complications of the disease, the patient takes the medication before the doctor's visit for reaching the healthcare center without mobility problems. However, when the patients take their medication, it hides the main symptoms of bradykinesia, making it difficult to determine the actual condition of the patient.

Another major symptom to be assessed in PD is FoG. This symptom is considered the fifth cardinal symptom of Parkinson's disease (25) and is defined as a "brief, episodic absence or marked reduction of forwarding progression of the feet despite the intention to walk" (26–28). There is an evident correlation between falls and FoG, which leads to a need to accurately treat the symptom (26). FoG is a key symptom for determining a correct therapy prescription, and as some patients do not respond well to levodopa, they need to have a comprehensive evaluation. Given the difficulty to elicit a FoG episode in clinical environments, Nonnekes et al. propose an algorithm for the treatment of FoG and finally, suggest as a solution the use of wearable systems (29).

FoG is very difficult to understand, although several conclusions have been drawn by the scientific community. There are specific conditions where FoG is elicited. This symptom is usually shown in patients with an OFF state, although, in some cases, it can also appear in the ON state (30). The fact that FoG is context-dependent is the reason why it is very difficult to assess it in clinical practice. Thus, in order to measure and quantify this symptom, the freezing of gait questionnaire (FoGQ) (31) and the new freezing of gait questionnaire (NFOG-Q) (32) were designed. Nevertheless, there are some discrepancies in rating FoG with different scales (33), and the NFOG-Q seems to be unsuitable as an outcome in clinical trials according to some experts (34). In this last work, the authors also claim that the use of objective tools such as wearable is essential thanks to their usefulness.

In another study, the issue with FoG assessment in current clinical practice is pointed out. Mancini et al. provide three main arguments in this regard (35). Firstly, FoG disappears

while patients walk focusing on goals provided by the clinician. Gait improves when patients consciously focus on walking rather than performing automatic gait. FoG occurs in home environments and real living conditions, not in clinical practice, where the patient is assessed while being observed by a healthcare professional. Secondly, clinical environments are often free of obstacles, not being a space where it is easy to provoke a FoG episode. Thirdly, patients tend to go to the clinical evaluation subsequent to medication intake or in the ON state. The latter affects the physician's evaluation as patients with PD tend to suffer FoG in the OFF state, or, at least, more severe episodes. Mancini et al. claim that wearable systems will be crucial for accurate FoG monitoring.

Regarding PD tremors, it needs to be considered that they differ in types and that not all of them have a dopaminergic response (36). This means that, in many patients, tremor is not correlated with motor fluctuations and can often appear in the ON state. Although there is evidence that some types of tremors are responsive to dopaminergic therapies (37), the same work also remarks that it is not effective for other types of tremors. Thus, tremor monitoring motor state detection (ON or OFF) is often unclear or confusing. Nonetheless, as tremor is manifested in the upper limbs, certainly, wrist-worn devices are a good solution for this symptom evaluation.

On the other hand, levodopa-induced dyskinesias are motor complications caused by the continuous intake of levodopa. These motor complications affect the mobility of the patient, causing involuntary movements in the upper limbs, lower limbs, neck, and trunk. Dyskinesias are related to a decreased QoL (38), as it is a motor complication that should be diminished by adjusting the medication correctly. However, some dyskinesia motor complications are episodic due to the so-called peak-dose dyskinesia, provoked by the L-dopa intake, being difficult to be accurately observed in the doctor's office. In order to evaluate dyskinesia, some questionnaires are administered. However, some articles show that the Unified Dyskinesia Rating Scale is more reliable than other questionnaires (39, 40). Nonetheless, questionnaire administration takes time during consultancy, and, although interrater and intrarrater correlations are moderate according to (40), the questionnaire is administered every so often/occasionally. Among these, the most used questionnaire, the UPDRS, is very dependent on the patient's opinion and does not provide real accurate information about daily symptoms' severity and distribution. This information is key for therapeutic tailoring.

This study aims at presenting a technology solution, which meets the clinical needs of filling the aforementioned lack of objectivity in patients' data in order to quantify the PD motor symptoms during regular ambulatory activity and non-controlled conditions. We present STAT-ON^{TM}: a medical device Class IIa based on a single wearable system and able to monitor, measure, hold in internal memory, and finally, generate a report on the temporal evolution of motor symptoms in daily living conditions. First, the state of the art on wearable systems for monitoring PD motor symptoms is presented. Subsequently, related scientific background and assessment of STAT-ON^{TM} in clinical trials, pilots, and algorithm validation processes are explained. Then, the STAT-ON^{TM} system is described, encompassing hardware and software descriptions. Finally, a set of performed clinical validations performed so far is presented.

STATE OF THE ART

There are multiple initiatives and research works on the identification of motor symptoms (13, 14, 41–46), where accelerometers are the most widely used sensors, although gyroscopes (47), skin conductivity systems (48), electromyography (49), pressure insoles (50), and pressure platforms are also used, such as GaitRite (51, 52). Unfortunately, many of these investigations or solutions do not reach the market, mainly due to three barriers: firstly, the poor usability due to a lack of portability of some of these systems, thus making it difficult to incorporate into the daily life of the patient as they are not wearable; secondly, the necessary industrialization process; and, thirdly, the required certification process as a medical device. These last two factors are long, complex, and expensive processes. As mentioned, the most extended solutions are based on inertial systems (47, 53–56), but at present, there is no complete and definitive solution yet. It is necessary to advance in the investigation and development of methods focused on the following points:

- The medical device must provide reliable information from algorithms that have been designed with rigorous methodologies;
- Key and clear information for the healthcare professionals must be presented;
- The design must be focused on the usability of the system in order to maximize the patient's adherence.

The reliability of a monitoring system mainly depends on the following aspects: the number of sensors used, their position on the body, and the robustness in the design of the employed processing algorithm. Brognara et al. (57) state that a trade-off between the number of sensors and the usability of a system should be required. Li et al. (58) also report that a high number of sensors complicate the setting up of a study. Several sensors cause difficulties in synchronizing data, following a timestamp. Furthermore, the number of input features in a machine learning algorithm is increased, consequently increasing the computational burden. However, sensors placed on different parts of the body capture a clearer signal from specific movements and contribute to a better characterization of a symptom (59).

Many of the existing systems for monitoring PD-related motor symptoms rely on a supervised machine learning approach. Algorithms are developed through a learning process based on a specific and representative database. In this way, the dataset employed to build an algorithm is of crucial importance. The dataset must be representative of the problem looking to be solved, and, for this reason, it must be labeled by clinical experts and well synchronized with raw data of the sensors (60). The number and variety of patients with PD that participate in the dataset construction are also the key for the learning of the

machine learning method. A good generalization means having a representative dataset, without exceeding the number of patients included, which will introduce noise or repetitive information, but including as many different patients as possible for the generalization of the algorithm against a new input (61).

Apart from increasing the sensitivity or capacity to correctly detect a symptom, having a large heterogeneous database also minimizes the number of false positives and, thus, improves the specificity of a classifier. This is the main reason why a dataset also needs data that do not contain the symptom to be detected. The algorithm will learn what is not the symptom with the aim of maximizing its specificity. Therefore, the experimental protocol must be formed by activities that elicit a symptom so that the raw data (the signal) contain parts with the target symptoms to be analyzed and, also, parts where other activities are included. To do so, the appropriate method is to construct the dataset in home environments, where unforeseen conditions are continuously present (62). Once the dataset is constructed, specific and key features will be extracted and selected from the data and a random part of the data will be used for training the classifier; the other part of the dataset will be used for validating the model. Then, a supervised machine learning technique will be applied (neural networks, support vector machines, etc.), and an automatic classifier model will be obtained that will be cross-validated against the evaluation dataset.

On the other hand, providing key information for the professionals is essential for acquiring an accurate state of motor complications. A medical device should provide information that healthcare professionals do not have in consultancy, that is, the severity and time distribution of motor symptoms in home environments. The report obtained has to be easy and quick to read, embedding self-explanatory graphics. One of the main targets is to increase the usability of the system for healthcare professionals to facilitate a dynamic patient's visit with quality information on key symptoms. In (46), some graphical examples of different commercialized devices are shown. On the other hand, usability for patients is also essential. Usability will define the patient's adherence to the use of the technology. Wrist-worn devices have been shown to be devices prone to very high usability (63). They are comfortable, and the patient does not feel stigmatized. However, in order to analyze bradykinetic gait, freezing of gait, or dyskinesia (which is manifested in upper and lower limbs, trunk, or neck), an inertial wrist-worn device is not able to capture accurately these symptoms, and other devices would be better, such as the waist or chest-worn devices from where body movements are better characterized due to being close to the center of mass of the human body. The main issue with wrist-worn devices is the high degrees of freedom of movements made by the arm, in addition to their high randomness of execution, provoking an elevated rate of false positives, causing a decrease in the specificity (64). Several studies point to serious errors in this type of system for the characterization of steps or momentum (65, 66).

Taking a look into the global market, there are, at least, four commercialized tools with a Medical Certification (CE Certificate with the Directive 93/42/EEC or with Regulation 2017/745, FDA, or other regional certificates, such as CFDA, TFA, etc.) able to monitor Parkinson's disease symptoms: Personalized Kinetigraph™ (67), Kinesia 360™ (68), PD Monitor™ (69), and STAT-ON™ (70). There are other solutions, such as MM4PD (55) or NEPTUNE (71); both are wrist-worn devices in different stages of technology readiness but, still, without medical certification. Furthermore, so far, no clear evidence or article has been published on the algorithm methods used in these last two devices. In the review performed in (72), different algorithms are also proposed as techniques to be embedded in hardware solutions in order to detect motor fluctuations. Other solutions focus more on gait, which can be also interesting (73–78), but they do not provide continuous monitoring at home with a complete mapping of the different symptoms of PD.

Table 1 presents a comparison between the aforementioned identified solutions, including the list of the different symptoms monitored by each solution.

An important point is the analysis of the algorithms developed by each manufacturer and the validation performed. While PD MONITOR™ and STAT-ON™ are based on advanced machine learning techniques, Kinesia360™ bases its algorithms on multiple regression methods and PKG™ on a statistical analysis of two variables.

PKG™'s algorithm was published in 2012 by Griffiths et al. (79). The authors presented a method based on the analysis of the accelerometer signals obtained from the wrist during 2-min windows. From this window, they analyzed frequency features between 0.2 Hz and 4 Hz, the maximum acceleration achieved, and the time without movement, from which the two indexes are generated. One is associated with bradykinesia (BKS), and the other with dyskinesia (DKS), which are then represented in a chart with interquartile ranges to then determine the severity of a symptom or the other. There is no evidence of a training-evaluation data method, thus not being considered a machine learning algorithm. The validation was performed through the median of all the BKS samples in 9 h along 10 days and was correlated with the UPDRS, obtaining a significant $r = 0.64$, $p < 0.0005$. A third score called FDS was designed to measure motor fluctuations (80). This score, which is expressed as an algebraic combination of BKS and DKS, determines whether a patient is fluctuating. However, the method cannot determine the "ON" state without dyskinesia (81). Although there are no data that confirm the performance of an algorithm with blind data, the device has been widely tested under clinical conditions and compared to UPDRS (82) or diaries (80, 81). For instance, the work from Santiago et al. (83), determines that PKG™ provides more information to classical routine visits after analyzing 3 user cases. In a work performed by Nahab et al., the authors also denote utility in clinical practice (84). Finally, the system has shown good results in usability (85). According to Monje et al. (13), the PKG™ has been extensively validated but needs more independent validation.

Kinesia 360™ is another device to monitor Parkinson's disease. The algorithm is more complex than the PKG™ one and uses a gyroscope to add information value. The system is composed of two sensors, a wrist-worn

TABLE 1 | Parkinson's disease continuous monitoring systems.

Manufacturer		Global Kinetics Corporation	Great Lakes Neurotech.	Pdneuro-Technology	Apple	Orbit Health	Sense4Care
Device name		PKG® or Kinetigraph®	KINESIA360™	PDMONITOR®	MM4PD	NEPTUNE	STAT-ON™
Device Location		1 wrist sensor	2 sensors (wrist/ankle)	5 body-worn sensors	1 wrist sensor	1 wrist sensor	1 waist sensor
Detected symptoms	ON/OFF	Yes	Yes	Yes	No	No	Yes
	Bradykinesia	Yes	Yes	Yes	No	Yes	Yes
	Dyskinesia	Yes	Yes	Yes	Yes	Yes	Yes
	Tremor	Yes	Yes	Yes	Yes	No	No
	Freezing of Gait	No	No	Yes	No	No	Yes
	Gait Parameters	No	Yes	Yes	No	No	Yes
	Inactivity/Rest	Yes	Yes	Yes	No	No	Yes
	Falls	No	No	No	No	No	Yes
Medical device certification		Yes	Yes	Yes	No	No	Yes

device, and an ankle-worn system, which, on the one hand, obtains information about gait. The latter is crucial to understanding the state of a patient with PD; nonetheless, the dual system reduces usability for the patient.

Kinesia 360™ offers outcomes from tremor, dyskinesia, slowness, mobility, posture, and steps (68). The quantification of bradykinesia, which was performed in an ankle-mounted device (86, 87), relies on the analysis of some specific features coming both from the accelerometer and gyroscope and is computed through linear regression models, which are correlated with the UPDRS scores. The dyskinesia algorithm is also based on a linear regression model, and the sensors are worn on the most affected side of the body. The correlation obtained is significant ($R = 0.77$) and is performed with the modified Abnormal Involuntary Movement Scale (mAIMS). The models are evaluated through a Leave-One-Subject-Out method. The system has been widely evaluated with different therapies, such as levodopa (53), rotigotine patch (88), deep brain stimulation (89), or subthalamic stimulation (90).

Finally, PDMonitor™ is a five-device system in which the main aim is to characterize all the motor symptoms of a patient with PD coming from any part of the body. In this way, it is not necessary to select the most affected side of the body, and it is possible to get movements from the upper limbs, lower limbs, and trunk. The system was designed in the PERFORM project (46), and its algorithms are based on the training of an expert database and using advanced machine learning algorithms. The complete system is presented in (47), and the algorithms are briefly described, such as tremor (91), dyskinesia (92), bradykinesia (93), and FoG (94). All the algorithms employ different classification methods. For instance, tremor is based on hidden Markov models, obtaining an 87% of accuracy; dyskinesia algorithm is based on a decision tree, reaching 85.4% on classification accuracy. The bradykinesia algorithm uses support vector machines, with a 74.5% on classification accuracy, and the FoG algorithm relies on a random forest classifier, getting a significant accuracy of 79%. Although the PERFORM project is well documented, and the algorithms are transparent, as far as the authors know, there is no evidence that the system has been validated in clinical practice.

In summary, it can be understood that it is not possible to directly compare the four devices, given the different locations in the body, the number of sensors, or the algorithmic used methodology (learning-based or statistical-based). The only work found so far with a direct comparison between devices is a work from Grahn, which compares the agreement between PKG™ and STAT-ON™ with 2 physicians (95). The agreement between the clinical opinion and STAT-ON™ was found to be significantly higher than PKG's™; on the other hand, both devices show to be usable by patients. Although STAT-ON™ shows superiority in this work, further studies are needed with more consistent data.

The following section presents a compilation of the methodology used in the case of the STAT-ON™ solution.

BACKGROUND ON STAT-ON™-EMBEDDED ALGORITHMS

The STAT-ON™ device is the result of a long research process and development based on different and complementary achievements gathered in several research projects managed and participated by the authors. The base of the algorithms to detect and monitor the relevant PD motor fluctuations relies on gait parameters analysis, complemented with another set of specific algorithms dedicated to the identification of concrete symptoms and characteristics: bradykinesia, dyskinesia, FoG, detection of falls, or the signal magnitude area (SMA), for the assessment of the quantity of movement.

A starting point for this activity was the publication in 2009 of the hypothesis about the possibility of adjusting the necessary dose of apomorphine pumps by detecting motor fluctuations with wearable sensors (96). Continuing with the study of motor symptoms in PD, new lines of research, focused on ambulatory monitoring of specific motor symptoms, were mainly performed in the projects *Monitoring the Mobility of Parkinson's Patients for Therapeutic Purposes* (MoMoPa Project) (97), *Home-Based Empowered Living for Parkinson's Disease* (HELP project) (98, 99), *Personal Health Device for the Remote and Autonomous Management of Parkinson's Disease* (REMPARK project) (24, 100, 101), the MoMoPa-2 project (102), and the MASPARK project (103). Within these projects, the resultant algorithmic set was validated by introducing new patients. Finally, once a consistent clinical validation was achieved, *Unobtrusive, Continuous, and Quantitative Assessment of Parkinson's disease: Hard Evidence for Optimal Disease Management with Information Technologies* (PARK-IT2) project (104) was performed in order to redesign the existing prototype, embed the developed algorithms, industrialize and certify it as Medical Device Class IIa. The final device was considered clinically usable by a group of neurologists (54), and it is being validated in different pilots and clinical trials (105, 106).

At the starting point of the described research, a preliminary decision was considered on the number of sensors to be used and their location in the body for optimal detection of the PD motor symptoms, along with an optimal usability characteristic. After analyzing different parts of the body, the waist was selected, given that it is very close to the mass center of the body and many movements are reflected there in some way. This situation provided very clear inertial signals from the gait, upper and lower limbs movements, and trunk or neck dyskinesia. Concerning the number of used sensors, the decision was very clear, and the objective was to use a unique sensor located in the waist, as has been mentioned.

Following this decision, a coherent and strict methodology was developed, including a very complete analysis of the gait. Initial gait parameter algorithms were achieved by selecting specific features using accelerometer signals from the waist by combining them with different kernel methods (107). This algorithm was improved in posterior research projects, such as MoMoPa-2 (102), or MASPARK (103) by improving the methodology for gait characterization, focusing on the bradykinetic gait (108, 109). The estimation of bradykinesia severity relies on a specific methodology mainly based on the detection and characterization of gait. Several filters were implemented, and the first one is formed by a Support Vector Machine classifier (SVM), which detects if the patient is walking or not by analyzing specific features, which have been selected by means of the Relief algorithm. The detection of walking is followed by the detection of strides in terms of walking bouts. This stride is then characterized with different features in order to linearly separate "*bradykinesia*" from "*no bradykinesia*" through a threshold β, whose value is set by means of an ϵ-Support Vector Regression (ϵ- SVR) model with RBF kernel (110, 111). The ϵ-SVR model depends on a set of parameters extracted from stride fluidity (m): the mean, standard deviation, minimum, maximum, and median. Other inputs of the ϵ- SVR model are the Hoehn and Yahr stage and the age of the patient, which are factors that show the advance of the disease and limit the movement fluidity of the patient. All these seven variables will be inputs of the ϵ-SVR model whose output is the threshold β. The ϵ- SVR model is then trained and evaluated following a Leave-One-Subject-Out methodology. Results obtained show an average sensitivity of 0.925 and 0.891 of specificity, with an accuracy of 0.918 on bradykinetic gait detection (109).

As it is described in (112), a self-adapting bradykinesia detection algorithm is incorporated. The threshold β enables the recognition of bradykinesia in terms of ON and OFF. For instance, a young patient without motor complications provides a high β threshold; however, a patient with advanced-staged PD with motor complications would provide low β values. Therefore, ON and OFF states are patient-dependent, and first, the algorithm needs to understand and learn the stage of the patient. To do so, and considering the input variables for the ϵ- SVR algorithm, a concrete patient self-adapted algorithmic part was developed, requiring minimum information from the person's movement in order to establish the correct parameters. It has been stated that 3 days of monitoring are enough to get enough stride fluidity values and to learn how the patient walks, fluctuates, and behaves within his or her motor fluctuations. From the 3rd day on, the healthcare professional could obtain the data and see the ON and OFF state in the downloaded data. If the data are downloaded on the 5th day, it means that the β value has been computed with these 5-day data. The main obtained advantage of the inclusion of this part is the minimization of the external parameters to be manually introduced and a new evaluation of the necessary threshold β for every new use of the device. This allows the reuse of the sensor among different patients and allows easier disease evolution monitoring.

The main goal of the algorithmic set, as established in the REMPARK project, is the identification and registration of the ON and OFF states of affected people. The final decision to determine an ON or OFF state is conditioned to the sustainability of this β threshold along time. Another crucial factor for the decision of the ON and OFF algorithm is the detection of levodopa-induced dyskinesia symptoms, which considerably increases the probability of establishing an ON state.

Dyskinesia algorithm was first designed in (113), where frequency power was extracted in the considered frequency band of dyskinesia (1–4 Hz), defined by Manson et al. (114), and, also,

analyzing the frequency band up to 20 Hz in order to remove false positives if the patient was walking. The algorithm was simple, but thresholds were optimized by maximizing positive predictive value and negative predictive value. The algorithm was improved significantly by using machine learning in the optimization of thresholds and other features, such as the inclusion of the postural transitions' frequency band (115). The final model was not patient dependent, being general and valid for any patient with PD. The database used to train and validate the algorithms was composed of 102 patients. The presented algorithm showed a performance of 0.39 on sensitivity and 0.95 on specificity on mild dyskinesia, but a 0.93 on sensitivity in any strong dyskinesia and trunk mild dyskinesia, keeping the 0.95 on specificity. This specific work was performed in the frame of the REMPARK project (24). In the same framework, the algorithm was validated clinically against the Unified Dyskinesia Rating Scale (UDysRS) (40), considering the severity of the dyskinesia. The algorithm correlated 0.7 with all the UDysRS questionnaires, but the correlation increased up to 0.91 when only sub-items from the UDysRS were considered for dyskinesia in the trunk and legs (116).

The developed ON/OFF algorithm is a hierarchical structure of classifiers that get together the outcomes of specific algorithms, such as the bradykinesia and dyskinesia, and observe the behavior at regular slots of time (1, 10, and 30 min). The output data rate of the ON/OFF algorithm provided by STAT-ON^{TM} is precisely 30 min. The complete explanation of this algorithm is given in (112). However, a third state was introduced and was called *"Intermediate."* This state stands for that motor state where the patient is not walking in his or her better condition, but the stride fluidity is better than his or her OFF state.

In REMPARK's project, this proposed ON/OFF algorithm achieved a 0.92 both on specificity and sensitivity (112). This study contains the presentation of the methodology to detect the motor fluctuations, and the results were compared to a specific Hauser diary. The patient had to fill in the Hauser diary, but a researcher performed a supervision call to the patient every 2 h to confirm the motor state in order to maximize the confidence of a correct diary annotation. This algorithm was then validated against the opinion of direct observers, UPDRS (117), and Hauser diaries (118). In a work by Rodriguez-Molinero et al. (119), 20 patients participated in a database from which the algorithm model was trained, following the methodology explained in the aforementioned work by Pérez-López et al. (112). The algorithm model was then validated by employing 15 new patients, and the results of the algorithm were compared against the opinion of trained observers who stayed with the patients the whole time during the validation test. The results obtained were 0.96 on sensitivity and 0.94 on specificity, showing significant robustness.

In another published work from Rodriguez-Molinero et al. (20), the ON/OFF algorithm was validated against UPDRS subscales (UPDRS-III), with the participation of new 75 patients with PD. The correlation with all UPDRS-III was moderate, achieving a rho $= -0.56$ ($p < 0.0001$); however, the correlation with the gait item increased to 0.73 $p < 0.001$, and a correlation with Factor I item on UPDRS (axial function, balance, and gait) was -0.67 ($p < 0.01$), considered as a significant correlation. The algorithm was also validated against Hauser diaries to compare the method with other gold standards.

In a work performed by Bayes et al. (19), a total of 41 patients with PD participated in a 3-day test, where the patients were asked to fill in the Hauser diary. In this experiment, and with the aim of having rigorous control, the researchers called the patients in order to verify their motor state. Only when the result of the diary and the call were equal, then it was considered "comparable" to the sensor. This condition elevated the rigorousness of the Hauser diary, given the reduced compliance and recall bias that this method uses to present (15). A total of 0.97 on sensitivity and .88 on specificity were achieved following this method.

Finally, the ON/OFF algorithm was also validated against the Hauser diary in (120), where a total of 23 patients participated. One of the most important conclusions was to realize that a total of 37% records more were achieved by the sensor in the pilot, showing the reduced compliance obtained with the diaries. Also, it must be noted that, in these experiments, clinicians tried to minimize the rejection rate by filling the diaries by administering MoCA or MMSE questionnaires. This fact is the key because the patient does not need any interaction with the sensor. In this study, the accuracy (0.92) was provided along with positive (0.92) and negative (0.94) predictive values.

Complementing the ON/OFF, bradykinesia, and dyskinesia algorithms, the FoG algorithm was also embedded within STAT-ON^{TM}. The algorithm is based on a machine learning approach based on SVM (62). The database was performed in home environments with 21 patients performing semi-guided activities in ON and OFF states. The fact that data were collected at each patient's home provoked different situations and FoG episodes in their real daily living activities, not in clinical settings. All the FoG episodes (except the akinetic ones) were video-recorded and labeled by experts. The inertial signal associated with this label and the generated database was used for training the algorithm with supervised machine learning methods, including SVM. The generated algorithm was evaluated through a strict method, which balanced the true negative episodes, which could be given in long-term activities where FoG episodes were not possible to appear, such as sleeping, sitting, or standing still. This detail is the key and showed a more reliable specificity compared to other evaluation methods. Specificity depends on true negatives and false positives. If a true negative was considered as the evaluation of the algorithm every second, then in 30 min, we would have 1,800 true negatives, falsely increasing the specificity of the algorithm, although there were 10 false positives in those 30 min. Thus, we only counted a single true negative episode every 30 s, giving a more realistic specificity in this concrete time frame. The classifier designed analyses, filters, and processes 3.2 s-windowed signals overlapped at 50% with the aim of not losing information that occurred between windows (**Figure 1**). Then, specific features are extracted from each window, and a set of characteristics is organized by assigning a label y_w for each w window.

The $y_w$label was set to "*1*" if that window contained a FoG episode regardless of its length. For instance, if the FoG episode was 1-s long, then that window was considered to have a FoG

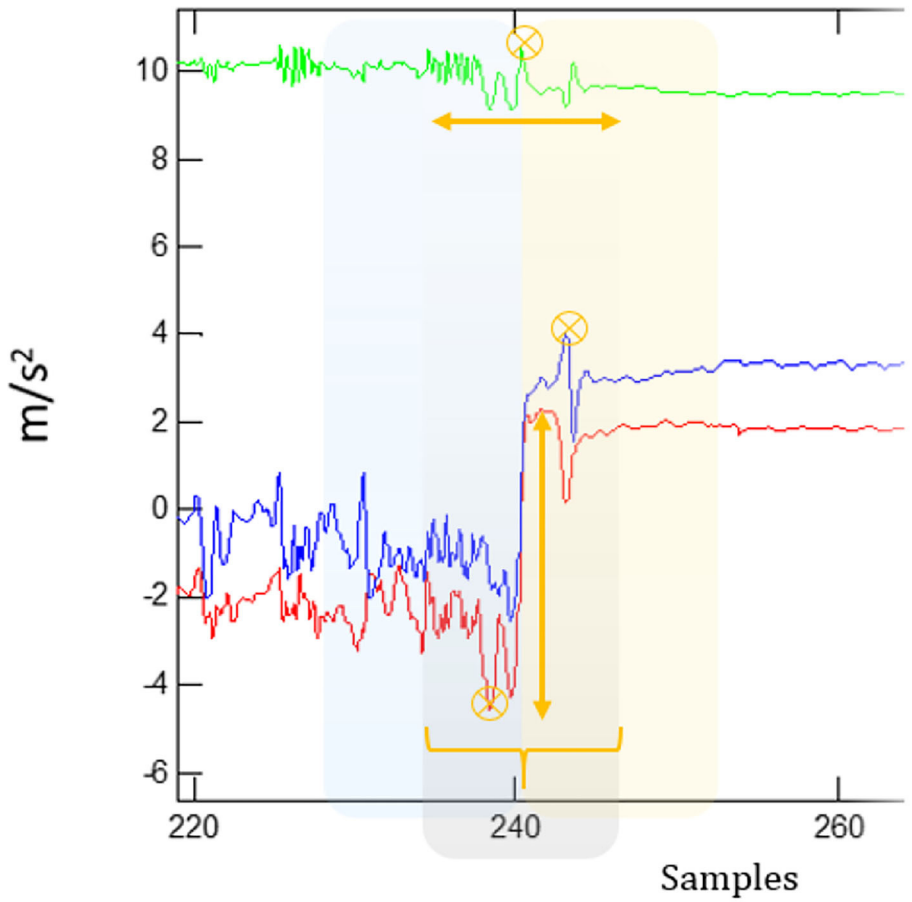

FIGURE 1 | Windowing of a signal at 50% overlapping and feature extraction.

episode and was labeled as "*1*." If the window did not contain any FoG episode, then it was labeled with a "*-1*" value (62).

Each window contains a total of 55 features, which were employed as an input of an SVM classifier in which the used kernel was a Gaussian radial basis function (RBF) due to its good performance and generalization capacity. Following this method, it was achieved a general classifier model with 0.75 on sensitivity and 0.79 on specificity for the detection of FoG episodes. However, the method was then improved by applying a feature selection and deleting noise (121). In this work, several classifiers, such as logistic regression, neural networks, or SVM with different hyperparameters, were tested, and it was shown that SVM with RBF kernel worked better with optimal resources. Finally, the new and optimized method achieved a 0.92 on sensitivity and 0.87 on specificity and was compared in the same conditions with other published methods, showing a significant improvement. The embedded algorithm was evaluated by clinicians with 12 patients in (122), where a 0.82 on sensitivity and a 0.97 on specificity were achieved. The model was not self-adaptive, being general for all the patients.

Additional gait parameters, such as stride fluidity, step length, cadence, and stride speed, are obtained based on the algorithm presented by Sayeed et al. (108), where 28 patients with PD participated, and an accuracy of 0.96 was obtained in the detection of gait. One of the most important patient characteristics is energy expenditure or the quantity of movement. The STAT-ON^{TM} provides the quantity of movement through the Signal Magnitude Area (SMA parameter), which was first tested in the sensor in (123), employing the accelerometer signals in the 3 axes to analyze the variability of the signal in a concrete period.

On the other hand, the STAT-ON^{TM} also incorporates an algorithm to detect falls; the algorithm, which was tested in the FATE project for a whole year with 200 patients, was embedded within the device (124, 125). The fall algorithm achieved 0.95 on sensitivity and 0.99 on specificity. Finally, a postural classifier and posture transition algorithm is incorporated in order to achieve specific information about the patient's activity (123, 126).

The conditions and results obtained in each algorithm embedded within STAT-ON^{TM} are presented below in **Table 2**. In Year/Project column, the project is presented from which the data were trained and validated. *M1* stands for MoMoPa-1 (97), *M2* stands for MoMoPa-2(102), *M3* stands for MoMoPa-3 (127), *RE* stands for the REMPARK project (101), *MA*

TABLE 2 | A summary of the main results obtained in the included algorithms.

	References	Year/project	Evaluation reference	Number of patients	Evaluation result	Result
ON/OFF algorithm	Pérez-López et al. (112)	2016/M2	Hauser diaries with patient calls every 2 h	15	Sensitivity/specificity	0.92/0.92
	Rodriguez-Molinero et al. (119)	2015/M1	Hauser diaries with patient calls every 2 h	35	Sensitivity/specificity	0.94/0.96
	Bayes et al. (19)	2018/RE	Hauser diaries with patient calls every 2 h	41	Sensitivity/specificity	0.97/0.88
Bradykinesia estimation	Samà et al. (109)	2017/M1,M2	Video recording	12	Sensitivity/specificity	0.925/0.891
			UPDRS subscales		Pearson correlation	UPDRS (item 22) : −0.912; $p < 0.001$
					Pearson correlation	UPDRS (item 24): −0.808 $p < 0.001$
					Pearson correlation	UPDRS (Factor I): −0.834; $p < 0.001$
	Rodriguez-Molinero et al. (20)	2017/RE,M2	UPDRS subscales	75	Spearman correlation	UPDRS (part III): −0.56; $p < 0.001$
						UPDRS (Item 22): −0.73; $p < 0.001$
						UPDRS (Factor I): −0.67; $p < 0.01$
Levodopa induced dyskinesia	Pérez-López et al. (115)	2016/RE	Video recordings	102	Sensitivity/specificity	No-trunk, mild dyskinesia: 0.39 / 0.95
						Trunk, mild dyskinesia: 0.78 / 0.95
						No-trunk, strong dyskinesia: 0.90/0.95
						Trunk, strong dyskinesia: 1 / 0.95
	Rodriguez-Molinero et al. (116)	2019/RE,M3	UDysRS	13	Spearman correlation	UDysRS score: 0.70; $p = 0.01$
						UDysRS sub-item (trunk and leg): 0.91; $p \leq 0.001$
Freezing of Gait	Rodríguez-Martin et al. (62)	2017/RE,MA	Video recordings	21	Sensitivity/specificity	0.75/0.79
	Samà et al. (121)	2017/MA	Video recordings	15	Sensitivity/specificity	0.92/0.87
	Rodríguez-Martin et al. (122)	2017/MA	Video recordings	12	Sensitivity/specificity	0.82/0.97
Gait	Sayeed et al. (108)	2015/RE	Video recordings	28	Accuracy	0.96
Falls	Cabestany et al. (124, 125)	2013/SP	Patients' case report forms	205	Sensitivity/specificity	0.95/0.99
Postural transitions	Rodríguez-Martin et al. (123)	2013/M1,SP	Video recordings	39	Sensitivity/specificity	0.86/0.98
	Rodríguez-Martin et al. (126)	2015/RE,SP	Video recordings	87	Sensitivity/specificity	0.90/0.91

stands for MASPARK (103), and *SP* stands for specific expert databases.

STAT-ON™, THE HOLTER FOR PARKINSON'S DISEASE MOTOR SYMPTOMS

The STAT-ON™ Hardware

STAT-ON™ is an inertial wearable medical device Class IIa. Concretely, the STAT-ON™ system consists of a monitoring device as shown in **Figure 2**, a base charger, a belt, and a mobile application. The system provides numerical and graphical information of the motor symptoms' presence and distribution associated with Parkinson's disease based on a real-time processing embedded version of the algorithms referred to in Section Background on STAT-ON™-Embedded Algorithms. Furthermore, data related to the general motor activity of the patient are also computed according to the concepts introduced in the precedent Section Background on STAT-ON™-Embedded Algorithms.

The sensor measures 90 mm^3 x 62.5 mm^3 x 21.2 mm^3 and weighs 86 grams. Internally, the system is composed of two ultra-low triaxial nano-accelerometers, two microcontrollers, and a Bluetooth Low Energy system, among other parts. The sensor has a battery life of 7 days for a continuous operation in normal conditions (8 h per day). The system is waterproof with IP65 protection. The enclosure is formed by two pieces that fit each other by a specifically designed sealing strip, which is included for waterproofing purposes. The material selected for the enclosure is POLYLAC ® FR-ABS, an acrylonitrile butadiene styrene (ABS) material. Some of the main features are flame rated, RoHS compliant, and heat and weather resistant.

As shown in **Figure 3**, the sensor is formed of two microcontrollers: the main one is an nRF51822 that manages all the internal processes of the system and that has incorporated internally a Bluetooth (BLE) system (128). The second microcontroller is the STM32F415 microcontroller, which has a Cortex™ M4 core (with a floating-point unit) running at 168 MHz for operating complex mathematical models, such as the SVM classifiers, or the signal filtering and featuring required by the described algorithms (129).

The main microcontroller manages the user interface (LEDs, event button, buzzer, and vibrator), and stores the outcomes of the algorithms in the internal flash memory. This microcontroller also manages the states of the medical device, such as the sleeping state in case of a lack of movement, or active state in case the patient is performing some movement. The necessary flags for the definition of these conditions are provided by the secondary accelerometer, which detects the absence of movement or wakes up the system in case of movement detection (128).

The communication part of the system is based on Bluetooth Low Energy (BLE) and is used only when the clinicians configure the system or when the healthcare professional requires the downloading of the data monitored and internally stored after the processing phase. The microcontroller STM32F415 is responsible for computing all the inertial signals provided by the main accelerometer, an LIS3DH that provides a 50-Hz signal to the microcontroller. In parallel, the system provides the possibility to store the raw complete data from the accelerometer inside a microSD card.

The system includes a vibrator and a buzzer to send alarms to the patient or caregiver, such as medication reminders, which can be configured with the STAT-ON™ app. The user can also find the event button, whose target is to indicate a concrete event. This event will be registered internally and will be shown in the graphs generated by the STAT-ON™ app. There are two LEDs: the first one indicates the state of the battery (charging or not), and the second provides different color codes to inform the user of the state of the system, such as "connected," "capturing data," "low battery alarm," "error alarm," "synchronizing," and "configuring."

The management of power consumption is very important. For this reason, the power system is divided into three separated electrical zones: analogic, digital, and power system zones. Different regulators manage each zone, being isolated by specifically designed grounds and ferrite beads, as shown in **Figure 4**.

The power system includes a fuel gauge (BQ27441) for controlling the voltage level and managing the battery. Also, it includes the BQ51050B, a Qi-compliant wireless power receiver with an integrated Li-Ion/Li-Po battery charge controller. The power system is connected to a specific coil that sets the communication with any commercial wireless Qi-compliant chargers in order to charge the device wirelessly.

The system has been certified as Medical Device Class IIa and has successfully passed the electromedical equipment tests under IEC60601-1, including the EN ISO 60601-1-11 for home environments use. The device is manufactured under ISO 13485 for medical devices. The software explained in the next section has been certified under EN 62304 for medical software.

STAT-ON™ Software

In the frame of the project PARK-IT2 (104), where the redesign and industrialization phases of STAT-ON™ were done, the algorithmic set described in Section Background on STAT-ON™-Embedded Algorithms was completely embedded in the aforementioned hardware, and a new software layer for the management, interfacing, and correct usability of the sensor was created. A specific app is required to be installed on a smartphone/tablet, which is the current operative interface with the user (a healthcare professional).

The regular use of the STAT-ON™ consists of wearing the device in home environments with the aim of capturing activities of daily living of the patient and the fluctuations of the disease, as well as the severity and frequency of PD's motor symptoms. Firstly, the healthcare professional, with a specific smartphone app, will configure the device with just three parameters crucial for the algorithms of walking and bradykinesia estimation: age, H&Y stage, and leg length. Then, the device is provided for the patient, who should wear it during wakening hours and in normal conditions (the sensor must not be used while taking a shower, traveling, or doing sports except hiking) for 5–7 days approximately. After the monitoring period, the healthcare professional will download, using the same smartphone/tablet

FIGURE 2 | STAT-ON™ and its location and orientation.

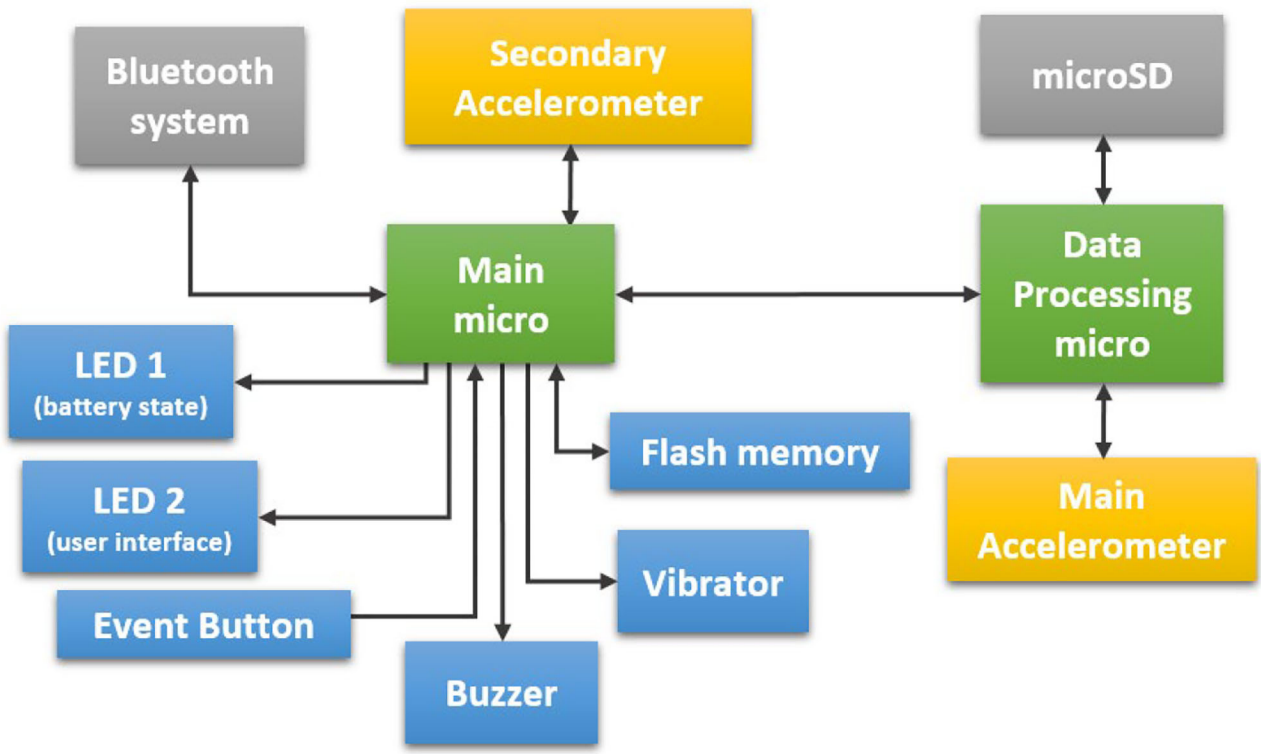

FIGURE 3 | STAT-ON™'s internal structure.

app, all the outcomes computed and stored by the sensor. These outcomes are organized as a complete report of the activity and the symptoms' presence and their evolution. The healthcare professional can also decide to download a more complete report generated by the device, where details are more explicit, together with comprehensive gait information during the monitored period.

Data are presented with different graphs with a fixed temporal resolution of 30 min and 24 h for weekly data graphs. The structure of the report consists of the first page, reporting the summary of the monitoring period, and then the distribution graph is presented (**Figure 5**).

The software offers the possibility to download a basic report with the previous graphs and also with quick information about the percentage of OFF hours per day and the total amount of OFF hours per day. Finally, a graph reporting the number of FoG episodes per day is presented. An example of both graphs is shown in **Figure 6**.

For an extended analysis, there is the possibility to obtain an extended report with the rest of the information. Then, weekly graphs are shown followed by detailed daily graphs of each variable. The values presented in the temporary format of 24 h are: cadence, number of steps, step length, SMA (quantity of movement), stride fluidity, dyskinesia, ON state, OFF state, INT

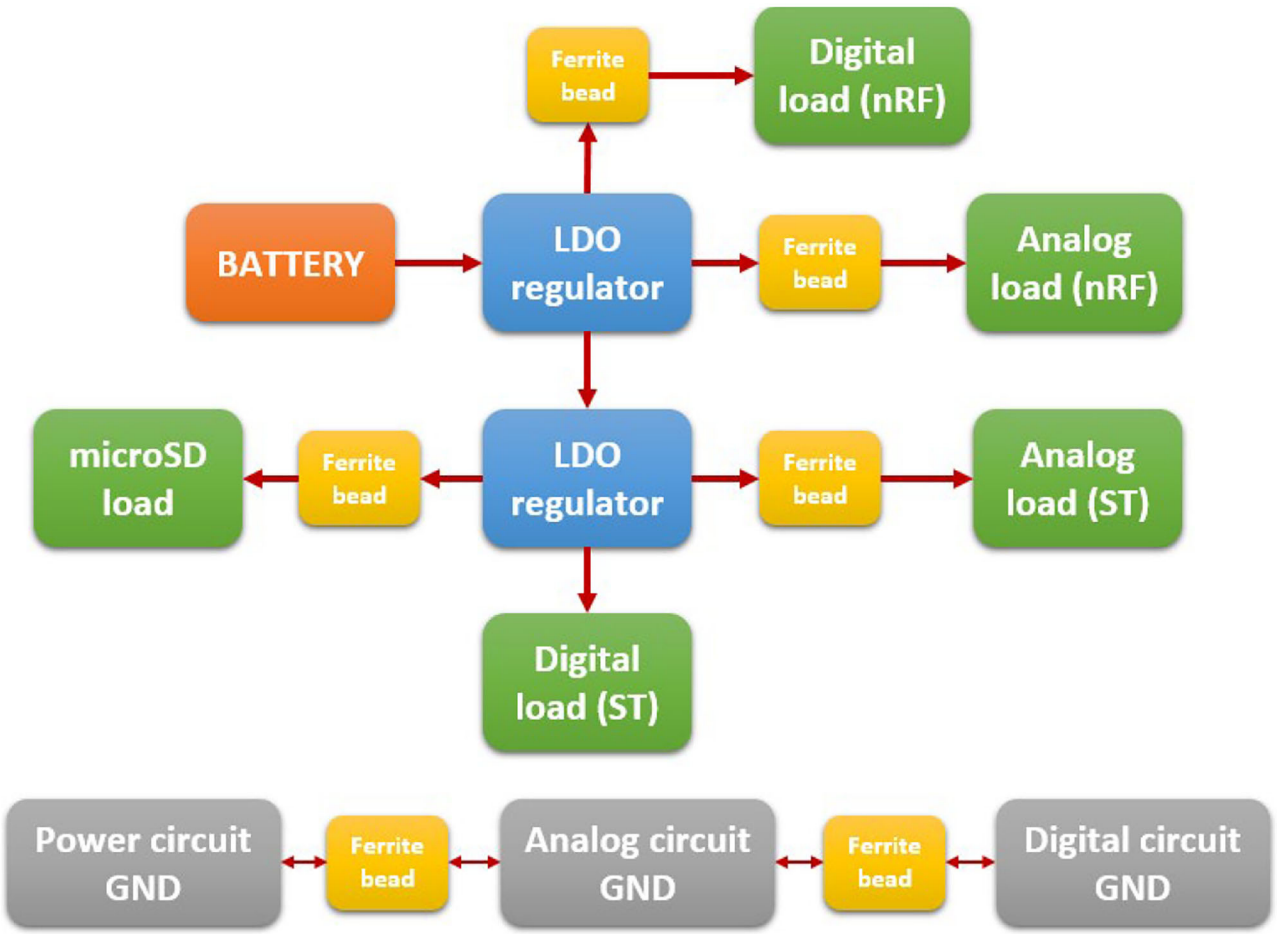

FIGURE 4 | Power system and regulator managing.

state, number of FoG episodes, duration of FoG episodes, falls, and events generated through the sensor button.

Figure 7 shows the stride fluidity graph, which is one of the most important graphs and offers the severity of the bradykinetic gait. Scores obtained in this graph are based on the algorithm of bradykinesia estimation (109). In this case, it is shown a patient with fluctuations passing from ON to OFF and inversely. Two clear OFF zones are detected in the morning and the evening. At midday, the patient has low scores, but the OFF seems not to be very significant. The objective information creates a quick picture of the state of the patient. In this Figure, the two thresholds are determined after having learned how the patient walks for 3 days based on the self-adaptive algorithm described in Section Background on STAT-ON^{TM}-Embedded Algorithms.

Figure 8 shows possible graphs provided by STAT-ON^{TM}, such as energy expenditure, step length, cadence, or the number of steps. It must be noted that more information is provided, such as stride speed, weekly summaries, and detailed daily motor states (70). Given that these graphs are filtered every 30 min, for more detailed information and for research purposes, it is better to use the CSV file, with the detailed information per minute. The graphs are mainly used in clinical practice.

CLINICAL VALIDATION OF STAT-ON^{TM}

STAT-ON^{TM} started its commercialization in June 2019, when the CE mark was obtained. It was then that the validation (from the regular clinical praxis point of view) of the commercialized device started. So far, the device has been validated in several studies.

A series of questionnaires were performed within the PARK-IT2 project in order to understand the acceptability of the device (130). A total of 107 questionnaires were performed, involving 17 neurologists, 19 health professionals, 30 caregivers, and 41 patients. A significant 88% of neurologists thought that STAT-ON^{TM} was able to detect advanced PD symptoms, and the average score of the sensor was 7.9/10. Healthcare professionals gave a score of 8.6/10 to the sensor. On the other hand, 80% of caregivers found STAT-ON^{TM} a good or very good solution and no one disliked the sensor. Moreover, 76% thought that it was easy to use, and no caregiver reported the belt was difficult to wear and adjust. The patients also rated the sensor an 8.5/10, and 77.5% thought that it was very easy to use. The belt was rated 8.1/10.

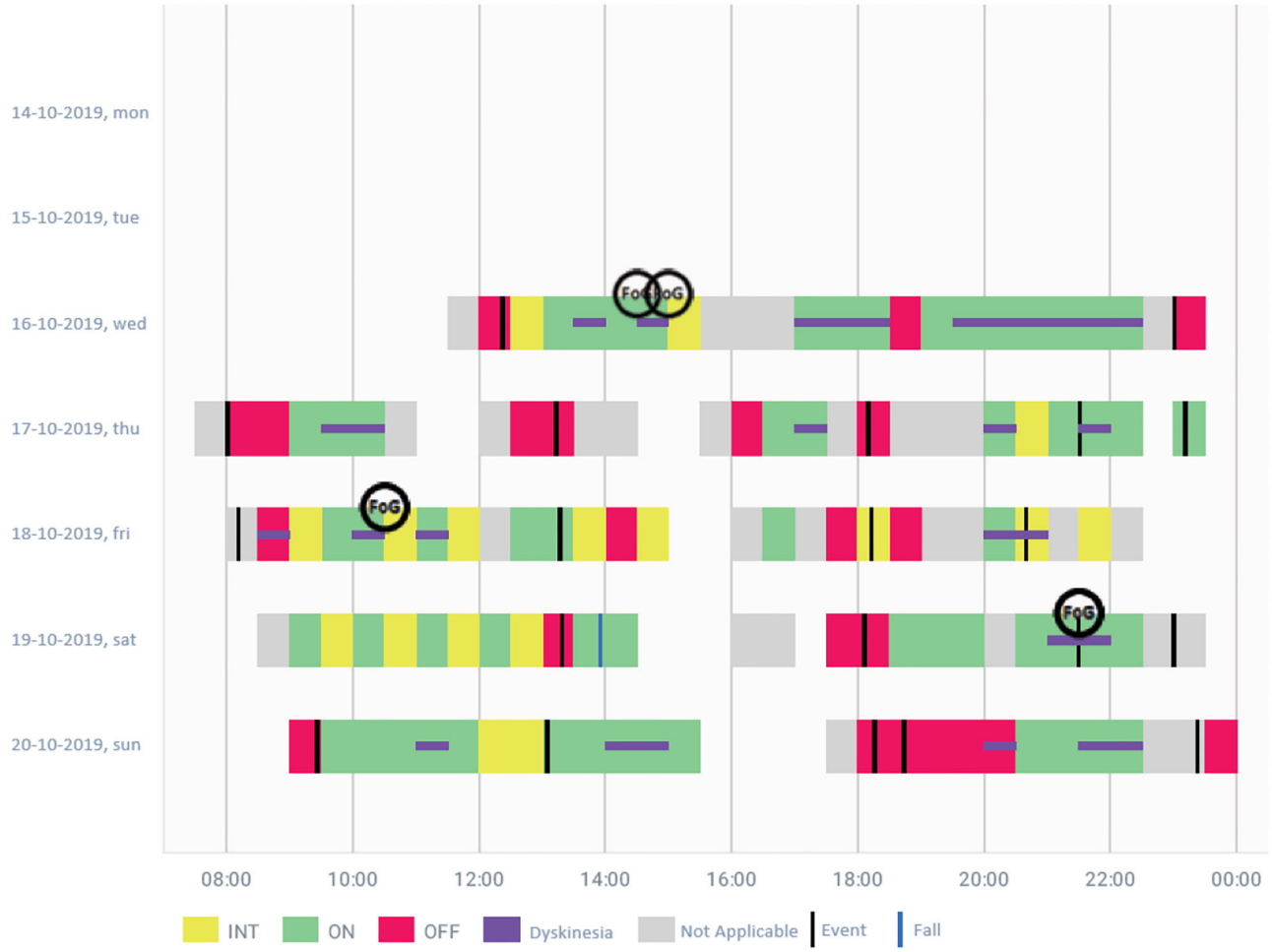

FIGURE 5 | An example of the distribution of symptoms (hourly distribution of symptoms along different days following the established color code), one of the graphics generated by STAT-ON™. This patient has a concurrent OFF zone every day around 18:00. It is clear when the patient rests at 15:00 or 16:00 every day. The OFF and dyskinesia are significant, but the FoG only appears 4 times, being practically insignificant and should be contrasted with the patient. The black line is when the button was pushed, in this case when the patient took the medication.

FIGURE 6 | An example of the percentage of OFF hours and total OFF hours and the number of FoG episodes per day.

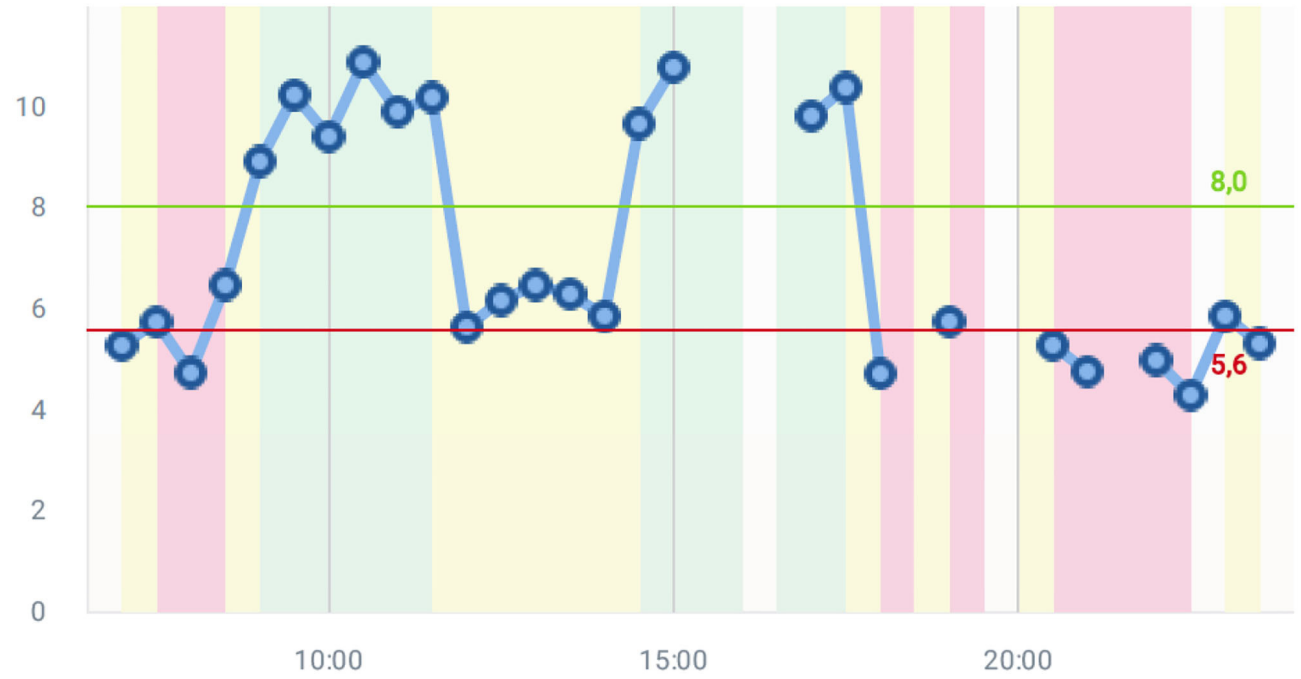

FIGURE 7 | A stride fluidity example.

FIGURE 8 | Some graph examples of the extended report.

In 2020, Santos et al. published the opinion of 27 clinical experts in movement disorders about STAT-ON™ after having tested the device in clinical practice (54). The general opinion of the neurologists was promising and with some important conclusions. A total of 119 evaluations were performed with different patients with PD using a STAT-ON™ sensor. In conclusion, STAT-ON™ was considered better than diaries by 70.3% of neurologists, and it was also considered a useful tool to detect advanced Parkinson's disease by 81.5% of the involved neurologists. The device was considered "quite" to "very useful" by 74% of the participants, and a moderate correlation between the use of the sensor and the opinion of the physician was obtained ($r = 0.403$; $p = 0.046$). A total of 89% of neurologists would use STAT-ON™ in their clinical practice.

A clinical trial has been proposed to test the device against other considered gold standards, such as the Hauser diary and the UPDRS (106). This clinical trial is a single-blinded randomized controlled trial. The neurologists who participated in this study were randomly assigned to one of the three branches of the study in which a therapeutic adjustment would be performed based on different sources of information: the STAT-ON™ reports, the patient diary of motor fluctuations, or the clinical information collected at the consultancy.

A total of 162 patients were participating in this study for 6 months, and the main outcome is to compare the efficiency of STAT-ON™ against classical clinical practice methods in terms of OFF-time reduction. Other symptoms will be also evaluated, such as dyskinesia and FoG, and the non-inferiority of the sensor against the diary of motor fluctuations will be also evaluated (https://clinicaltrials.gov/ct2/show/NCT04176302) (106).

On the other hand, a pilot is being led by the Movement Disorders Unit, "UParkinson" from Centro Médico Teknon, Grupo Hospitalario Quirón in Barcelona, Spain (105). The pilot consists of analyzing the agreement in detecting motor fluctuations, dyskinesia, and FoG using the STAT-ON™, based on a patient's opinion, and a neurologist's opinion in the home environment. The first preliminary results showed that the sensor can increase the awareness of motor fluctuations in patients with PD and help healthcare professionals detect them earlier. The level of satisfaction (QUEST questionnaire) achieved significant results (all items over 4 out of 5). The System Usability Scale (SUS) questionnaire results were considered high.

In another study, which was presented at the Annual Meeting of the Spanish Neurology Society, Caballol Pons et al. (131) discussed a multi-centric work, considering a high number of STAT-ON™ reports (in concrete, 237) in different use cases. The most frequent reason given by the neurologists for using STAT-ON™ was the ON/OFF time quantification, followed by the detection of FoG/falls and dyskinesias. The device is being used in patients with both initial and advanced PD for the diagnosis of motor complications and/or treatment optimization.

Due to the COVID-19 pandemic, telehealth systems are also important tools to be considered, and STAT-ON™ meets the requirements to be classified as a helpful system for the remote monitoring of patients with PD. Currently, the device is used in a clinical trial where patients with PD are being monitored remotely with video calls and STAT-ON™ (https://clinicaltrials.gov/ct2/show/NCT04694443).

In an Argentinian study, a team of neurologists tested the device with 11 patients and reached some interesting conclusions. The comparison against diaries showed that the Holter registers were bigger than diary registers, showing one of the main issues of the diary: low patient compliance. Also, the study highlights the enhanced patient's awareness of FoG episodes, as the sensor detected them while the patient did not report them. The sensor information was useful as neurologists could see objectively the real behavior of FoG episodes. It is also important to note that the authors emphasize the importance of the sensor in guiding therapeutic decisions in clinical practice. This was reported in patients who need second-line therapies, and the decision is based on questionnaires and the doctor's office evaluation. Finally, the authors conclude that these tools were useful to obtain an objective measure of the patients' motor state who were in advanced stages of the disease, with difficulty controlling motor symptoms, inconsistencies in their daily reports, and suspicion of inappropriate medication intake (due to lack or excess medication) (132).

The device has been also validated with advanced-stage PD patients with levodopa-carbidopa intestinal gel. Bougea et al. demonstrated the better detection of ON/OFF motor fluctuations, dyskinesia, and falls against patients' diaries with 51 patients with PD. All the sensitivities and specificities were higher with the sensor rather than with the diary, concluding that STAT-ON™ can be a promising tool for monitoring patients with advanced disease (133).

STAT-ON™ was also used in patients that were administered PERCEPT™, a deep brain stimulator that also registers the signal perceived from the subthalamic nucleus field, remarkably aligning their signals in the appearance of OFF states, ON states, dyskinesia, and FoG episodes. This case study suggests that STAT-ON™ can be a useful tool for the optimization of this kind of therapy (134).

Finally, in a Swedish study, STAT-ON™ was tested and compared against PKG™ through resident physician criteria. A significant agreement was obtained between STAT-ON™ and the physician (kappa = 0.783, $p = 0.014$), and none was found between PKG and the physician (95).

CONCLUSIONS

Currently, technology offers multiple possibilities for interaction and monitoring of patients with chronic diseases. In the field of PD, the main drawbacks are the lack of objective information obtained by the physician and the fact that the consultancy or hospital is not the most convenient environment for a correct patient evaluation. They should be evaluated, when possible, in normal living conditions in their home environments.

There are wearable tools that provide objective information about the severity and distribution of PD motor symptoms that could improve the evaluation of clinical experts. However, all devices in the market have their pros and cons. The strongest point of STAT-ON is, undoubtedly, the accuracy of the algorithms, which have been designed with precise data obtained in home environments and with a sensor located in a very specific part of the body, very close to the center of the human body. The waist has been shown to be akin to human movement,

and also many movements can be characterized from there. However, this strong point could be also a weak point, given that the usability that a wrist-worn device will always be higher due to the lower invasiveness of the device. Nevertheless, the devices that are worn on the wrist are conditioned to the random movements in the arm that should be considered for maximizing specificity. This point is of key importance to get high accuracies, and this problem has not been already solved. On the contrary, these devices are socially accepted and might be very useful for obtaining approximate measurements of basic movements.

Concerning other sensors, there has to be a trade-off between the number of sensors, usability of the wearable system, and the accuracy of a system. In this paper, we presented a complete review of STAT-ON^{TM}, a wearable medical device that provides objective information on motor symptoms, such as bradykinesia, dyskinesia, ON-OFF fluctuations, FoG, and gait parameters, falls, the quantity of movement, and postural activity. The purpose of use of this device is focused on home environments in order to get the missing data, which a healthcare professional cannot obtain in his or her consultancy. A complete review of the algorithms is performed, opening up the possibility to improve the outcomes by combining different machine learning approaches, enlarging the database or using deep learning or other more advanced methods.

The clinical evaluation in real clinical practice with STAT-ON^{TM} has already started, although the first results have been achieved by having a great acceptance rate by different stakeholders: patients with PD, caregivers, neurologists, and healthcare professionals. The utility and acceptability in clinical practice are promising (54), and, although further research and validation should be carried out, results show the potential of an easy-to-use tool. The STAT-ON^{TM} has achieved great results in user satisfaction and usability (105) and has been used in many cases (131), such as detection of motor fluctuations, dyskinesia, freezing of gait, therapy optimization, or second-line treatments' patients' selection. Nonetheless, further studies are needed for early symptoms detection and to demonstrate the effectiveness of the device with different therapies. However, it seems that there is a consensus on using the device for the detection of candidates for second-line therapies (54, 132). The Antonini et al. consensus for the selection of patients for advanced therapies seems to align with the outcomes of STAT-ON^{TM}, but additional findings are required to confirm this (135). The fact that the main database in REMPARK was composed of patients with fluctuations and Hoehn & Yahr >2 in ON state (24), the algorithms have been focused on mid and advanced stages of PD. This is particularly beneficial as a tool for an appropriate selection of the patient for second-line therapies and for adjusting these therapies (continuous subcutaneous apomorphine infusion, levodopa-carbidopa intestinal gel, or deep brain stimulation). However, a challenge is to see if STAT-ON^{TM} works fine for earlier stages. In the work performed by Caballol et al. (105), they detected morning fluctuations, which are the first OFF episodes in early fluctuating patients, but more studies are needed. One of the limitations of STAT-ON^{TM} is that the ON-OFF algorithm does not work in patients who are unable to walk, and 3 days of data are necessary for learning the way the patient walks. The accuracy of the ON-OFF algorithm has been shown but takes too much time to achieve results. Also, according to the user manual, it is recommended to use the device between 5 and 7 days (70). Although the patient can wear the device for more time, it is enough between 5 and 7 days to see patterns, severity of symptoms, and their distribution.

Another point and limitation is the understanding of the FoG algorithm. In (54), the FoG algorithm was considered one of the weaker algorithms. However, it has to be taken into account that this algorithm output is given every 1.6 s, while the ON-OFF is given every 30 min and the possibility to provide a false positive increases. The specificity presented in (121) is 0.87, which is considered optimal. However, some false positives could appear in festinating gaits, by tripping, traveling by car or public transport, and doing sports. Nevertheless, the device could identify properly the FoG in ON and OFF states, and help the healthcare professionals to understand this symptom in patients with PD as was shown by Perrote et al. (132).

The utility of wearable devices is increasing widely in the field of PD. In a Spanish study discussing the future of Parkinson's evaluation, 94% of 75 experts in movement disorders think that the use of wearables will increase (136). The conjunction of complement devices is a topic of discussion for achieving the best evaluation of patients with PD. For example, non-motor symptoms detection, such as depression, anxiety, fatigue, orthostatic hypotension, and sleep disturbance, have not been investigated deeply (137, 138). Nevertheless, there are some approaches for sleep disorders, such as electroencephalograms and eye tremor analysis (139). Also, heartbeat and blood pressure (140), or even skin conductance (141), have been used for non-motor symptoms. All these systems need further evaluation and more studies. In the same line, telemedicine is also a future challenge, and pilots and further tests are needed to validate the system for this purpose, which is crucial in post-pandemic times.

Another point is the use of the achieved data to continue improving the algorithms: several machine learning techniques will be published in the future, and even additional data could be obtained through STAT-ON^{TM} in future projects for refining the algorithms based on the opinion of physicians.

According to the first hypothesis performed by some of the authors in 2009 (96), STAT-ON^{TM} and other monitoring devices could be used in a closed-loop system to automatically adjust the therapy; this idea is closer to the appearance of new medical devices but needs accurate devices, with well-validated algorithms both in computer science and medical journals and in controlled clinical trials.

STAT-ON^{TM}, which is a marketed medical device, is the result of 12 years of research, including algorithmic development based on machine learning and offering a complete solution in clinical practice, trials, and research. The device can be used for adjusting and personalizing therapies, selecting patients for specific therapies, following up on specific symptoms, and seeing objectively the severity and distribution of PD motor symptoms. Although more validation is needed in the future, the system has been shown to be useful for healthcare professionals and suggests a new paradigm in the clinical evaluation of patients with PD.

AUTHOR CONTRIBUTIONS

DR-M and JCab: conceptualization, methodology, and project administration. DR-M, CP-L, and MP: hardware and firmware. MP, AS, and CP-L: software. CP-L and MP: validation. DR-M, CC, and JCab: formal analysis. DR-M, CP-L, and AS: investigation. DR-M, CC, AR-M, AC, and CP-L: resources. DR-M and CP-L: data curation. DR-M: writing the original draft preparation. CC, JCab, CP-L, MP, JCal, AC, and AS: writing, reviewing, and editing. CC, DR-M, JCab, CP-L, and MP: visualization. JCab, CC, AC, and AR-M: supervision. JCab, DR-M, and JCal: funding acquisition. All the authors have read and agreed to the published version of the manuscript.

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ORIGINAL RESEARCH
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A New Application of Functional Zonal Image Reconstruction in Programming for Parkinson's Disease Treated Using Subthalamic Nucleus–Deep Brain Stimulation

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Objective: Programming plays an important role in the outcome of deep brain stimulation (DBS) for Parkinson's disease (PD). This study introduced a new application for functional zonal image reconstruction in programming.

Methods: Follow-up outcomes were retrospectively compared, including first programming time, number of discomfort episodes during programming, and total number of programming sessions between patients who underwent image-reconstruction-guided programming and those who underwent conventional programming. Data from 142 PD patients who underwent subthalamic nucleus (STN)-DBS between January 2017 and June 2019 were retrospectively analyzed. There were 75 conventional programs and 67 image reconstruction-guided programs.

Results: At 1-year follow-up, there was no significant difference in the rate of stimulus improvement or superposition improvement between the two groups. However, patients who underwent image reconstruction-guided programming were significantly better at the first programming time, number of discomfort episodes during programming, and total number of programming sessions than those who underwent conventional programming.

Conclusion: Imaging-guided programming of directional DBS leads was possible and led to reduced programming time and reduced patient side effects compared with conventional programming.

Keywords: Parkinson's disease, deep brain stimulation, programming, subthalamic nucleus, image reconstruction

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative syndrome involving multiple motor and non-motor neural circuits in the basal ganglia. Subthalamic nucleus (STN) deep brain stimulation (DBS) is an effective treatment for patients with advanced PD and motor complications (1–3). Common DBS targets for PD include the *globus pallidus pars interna* (GPi), the STN and, less often, the ventral intermediate nucleus of the thalamus. A recent review concluded that GPi-and STN-DBS provide similar and consistent benefits with subtle target differences (4, 5). Target selection should

be tailored to each patient's clinical presentation. Numerous factors contribute to positive outcomes of DBS, including careful patient selection, lead placement, and effective programming (6). Only DBS programming can be modified after patient implantation; therefore, DBS programming plays a crucial role in improving clinical outcomes (7).

Nevertheless, for three decades, programming has remained a manual and time-consuming process that requires highly trained and experienced clinicians to achieve maximal therapeutic benefit in each patient (8, 9). Other sessions are often organized during follow-up visits to manage stimulation-induced side effects (e.g., speech problems and stimulation-induced dyskinesias) or worsening of the underlying parkinsonism. While the utility of these reprogramming sessions is well-established, no guidelines are available, and most of these changes rely on the results of a few open-label studies (10–12). In fact, although DBS has been used for almost three decades, systematic programming protocols remain lacking, leading to inconsistent and inefficient stimulation adjustments, as well as numerous or unnecessary patient visits. Our center used image reconstruction technology to reconstruct the nuclei and electrodes, and used this to guide programming and obtained satisfactory results.

METHODS

Patients

This study and the STN-DBS protocol were approved by the Ethics Institutional Committee of the First Hospital affiliated with USTC (China). All patients provided informed consent to participate in the study. Records from 142 patients with PD undergoing STN-DBS, performed by the same surgeon between January 2017 and January 2021, were analyzed. Between January 2017 and June 2019, 75 patients comprising the control group underwent conventional programming, and 67 were guided to a program based on functional zonal image reconstruction after improved programming methods from June 2019 to January 2021.

Image Reconstruction

First, imaging data from the patients were obtained, including postoperative computed tomography (CT; thin layer, 0.62 pitchless scan 5 mm) and preoperative localization magnetic resonance imaging (MRI; 3.0 Tesla, 2 mm pitchless scan). Next, the lead DBS was installed through the MATLAB platform and, after successful installation, imaging data were imported. Second, postoperative CT data were aligned with preoperative MRI data. Third, preoperative MRI data were standardized into the cranial model to obtain transformation parameters. Fourth, target reconstruction was performed. Finally, the electrode contact position was stimulated.

Programming Process

Programming was not initiated immediately after surgery but 4 weeks later, when the initial microlesion benefits faded. At the appointed time, patients visited the outpatient clinic. Programming sessions were performed in the "OFF" medication state after the overnight withdrawal of all dopaminergic medications for at least 12 h. The pulse width was standardized to 60 ms and the stimulation frequency was set to 130 Hz for both DBS programming sessions. The physician was able to query and record patient medical history. The patients' motor symptoms were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS III, except for rigidity and postural stability). The physician placed the programmer close to the patient's skin surface where the stimulator had been implanted. After the programmer was connected to the stimulator, the physician was able to view current parameters, adjust parameters (including voltage, pulse width, frequency, stimulated contact, and electrode configuration adjustment), set limits of the patient programmer, start up and shut down the stimulator, and to check impedance. According to functional zonal image reconstruction, the electrode contacts located in the STN sensorimotor region were defined as the optimal contact of the image, and the optimal contact of the image was preferentially selected for programming. Programming without using functional zonal image reconstruction as guidance is referred to as conventional programming.

Outcome Evaluation

All patients were assessed for PD severity using the UPDRS III drug on (i.e., with drugs), UPDRS III (without drugs), and UPDRS IV, while Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores were used to assess the cognitive status of the patients. The first programming time, discomfort episodes during programming, and total number of programming sessions were recorded. Discomfort during programming included dizziness, headache, blurred vision, numbness in the limbs, speech difficulties, and palpitation. Surgical outcome was assessed according to the stimulus improvement rate (UPDRS III score improvement compared to pre-operation when stimulated alone without the drug) and superposition improvement rate (UPDRS III improvement compared to pre-operation when stimulated with the drug) at 1 year after surgery.

Statistical Analyses

All statistical analyses were performed using Empower(R) (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) and R (http://www.R-project.org). Initially, the Kolmogorov–Smirnov test was performed to examine data distribution of the variables. Subsequently, data conforming to a normal distribution were evaluated using a two-tailed Student's *t*-test or one-way analysis of variance (ANOVA). Non-parametric data between different groups were compared using the Mann–Whitney test. Differences with two-tailed $P < 0.05$ were considered to be statistically significant.

RESULTS

Demographic data of the patients and scale scores were comparable between the two groups (**Table 1**). The mean ($\pm$ SD) age of the control group was 59.17 $\pm$ 8.77 years and 59.37 $\pm$ 8.42 years for the image reconstruction group. As shown in **Table 1**,

TABLE 1 | Characteristics of the patients with image reconstruction group and conventional programming group.

	Conventional programming group	Image reconstruction group	*P*-value
Number of patients	75	67	
Age (years)	59.17 ± 8.77	59.37 ± 8.42	0.987
Duration (years)	8.01 ± 3.38	8.54 ± 3.78	0.590
Gender			0.916
Male	52 (69.33%)	47 (70.15%)	
Female	23 (30.67%)	20 (29.85%)	
UPDRS III med off	7.04 ± 1.53	6.99 ± 1.69	0.608
UPDRS III med on	21.85 ± 12.52	24.51 ± 11.64	0.195
UPDRS IV	6.83 ± 1.80	6.94 ± 1.58	0.691
MMSE	26.01 ± 3.28	26.33 ± 3.09	0.558
MoCA	20.88 ± 5.39	20.73 ± 5.31	0.869

TABLE 2 | Comparison of stimulus improvement rate, superposition improvement rate between conventional programming group and image reconstruction group at 1 year after surgery.

	Conventional programming group	Image reconstruction group	*P*-value
Improvement rate med off	0.46 ± 0.15	0.40 ± 0.18	0.384
Improvement rate med on	0.63 ± 0.15	0.64 ± 0.16	0.978

there were no significant differences in age, sex, duration, UPDRS III, UPDRS IV, MMSE, and MoCA scores between the control and image reconstruction groups.

In terms of surgical outcome, the mean stimulation improvement rate was 0.46 ± 0.15 in the control group and 0.40 ± 0.18 in the imaging reconstruction group—a difference that was not statistically significant. Similarly, the superposition improvement rate was 0.63 ± 0.15 in the control group and 0.64 ± 0.16 in the image reconstruction group, which was also not a significant difference (**Table 2**).

Regarding programming, the first programming time was 32.77 ± 8.57 min in the control group and 23.15 ± 7.90 min in the image reconstruction group. The mean number of discomfort episodes during programming was 1.64 ± 0.91 in the control group and 0.70 ± 0.67 in the image reconstruction group. The total number of programming sessions was 8.34 ± 0.29 in the control group and 5.42 ± 0.16 in the image reconstruction group (**Table 3**). Therefore, the image reconstruction group exhibited obvious advantages in the first programming time, the number of discomfort episodes during programming, and the total number of programming sessions (**Figure 1**).

DISCUSSION

DBS is an established and effective treatment for PD. After electrode(s) implantation, connection wires are internalized and connected to an implantable pulse generator (IPG) in the upper chest. Patients then participate in a number of extensive programming sessions to define the best stimulation parameters for optimal symptom management. The aim of this study was to compare conventional clinical DBS programming with an individualized image reconstruction-based programming approach.

The preferential target is the sensorimotor portion of the subthalamic nucleus (STN) which is often located within its dorsolateral part (13–15). Yet, the existence and location of a potential anatomical sweet spot within the STN remains a much debated question (16). Effective symptom control has been associated with active contacts being located around the dorsolateral border of the STN, indicating that not stimulation of the nucleus itself, but of adjacent white matter tracts might be accountable for symptom relief (17). Although STN discharges can be recorded by microelectrodes during operation, it is still impossible to distinguish the functional regions of STN from the microelectrode records. Therefore, postoperative image reconstruction of electrode and STN is helpful to guide postoperative stimulation contact selection and turn-on voltage for "visualization and predictability" guidance (**Figure 2**).

Despite accurate lead placement in the anatomical target, identification of optimal stimulation settings requires in-depth evaluation of all available contacts of the DBS lead and often even individualized settings for pulse frequency or width. Programming sessions may hence extend to several hours of time and be therefore exhausting for patients and clinicians, likewise. Furthermore, the evaluation of therapeutic and side effects of stimulation relies on high levels of training and experience of the performing clinician, making computer-based support highly desirable.

The need for further aid when it comes to DBS programming has been accentuated with modern DBS systems. While traditionally DBS leads consisted of four circular contacts, more sophisticated designs introduced lately to clinical routine

TABLE 3 | Comparison of first programing time, number of discomfort during programming between conventional programming group and image reconstruction group.

	Conventional programming group	Image reconstruction	*P*-value
First programing time(min)	32.77 ± 8.57	23.15 ± 7.90	<0.001
Number of discomfort during programming	1.64 ± 0.91	0.70 ± 0.67	<0.001
Total number of programming	8.34±0.29	5.42 ± 0.16	<0.001

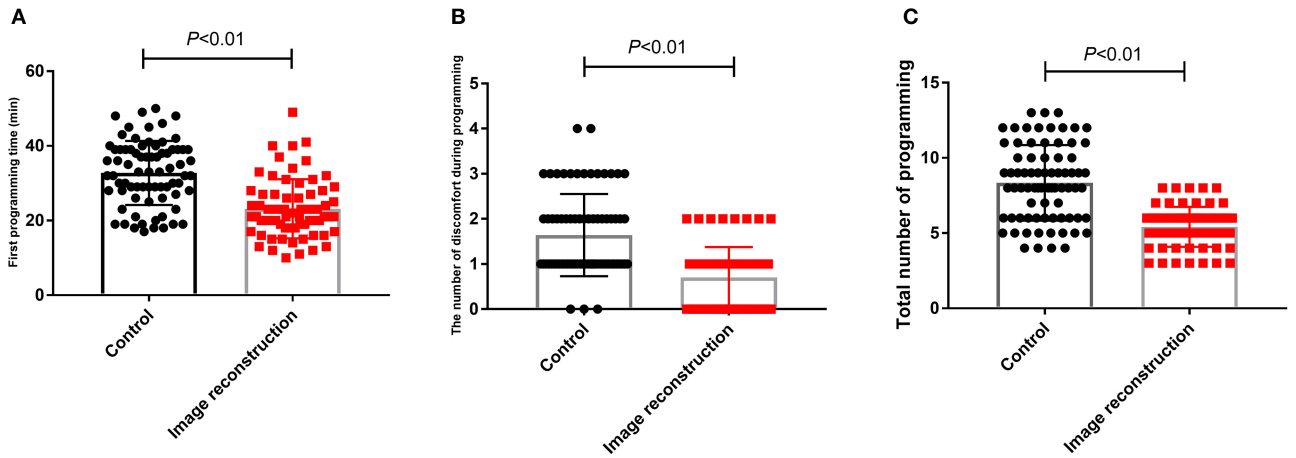

FIGURE 1 | Comparison of first programming time **(A)**, number of discomfort episodes during programming **(B)** and total number of programming during 1 year after surgery **(C)** between control group and image reconstruction group.

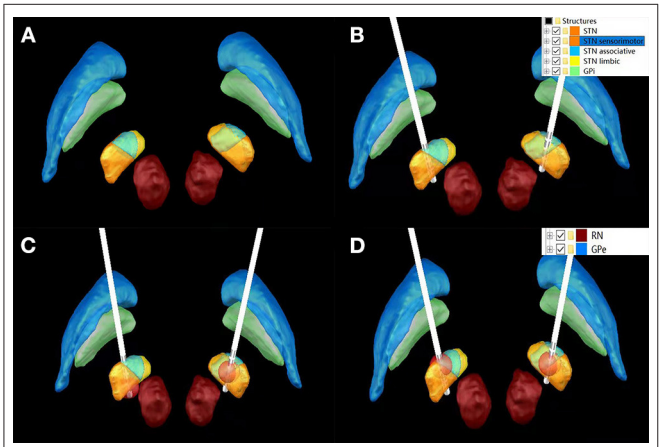

FIGURE 2 | Bilateral STN morphology without Lead implantation **(A)**; Lead implantation on bilateral STN **(B)**; 1.5 V stimulation of K1 contact of left Lead involved sensorimotor, associative and limbic regions, while 1.5 V stimulation of K8 contact of left Lead only stimulated sensorimotor regions **(C)**; 1.5 V stimulation of K1 contact of lead on the left and K10 contact of lead on the right involved sensorimotor, Associative and limbic functional areas **(D)**.

allow further shaping of the electrical field achieving an increased therapeutic window (18, 19). This extension of the parameter space resulted, however, in an exponential increase of duration of clinical programming due to the almost uncountable potential parameter combinations. There have been considerable efforts to develop tools using imaging data to ascertain where stimulation might be most effective (20). Nevertheless, these advances have been restricted to a small number of highly specialized centers with a strong computational background and, so far, such tools have not been implemented into or approved for clinical use. At the same time, efforts are being undertaken to develop user-friendly software which may foster a more pointed search strategy for personalized stimulation settings.

In this study, we used commercially available software tool (lead DBS, matlab) to visualize DBS leads and to simulate potentially effective stimulation settings, that is those resulting in a volume of the electrostatic field located in or within the immediate vicinity of the STN. There was no significant difference in symptom control between the image-based programming and the conventional programming. This finding is consistent with a pilot study including ten PD-patients with octopolar unidirectional DBS which demonstrated equality in motor improvement (21). However, it has obvious advantages in saving programming time and alleviating patients' side effects during programming.

In this study, we could show that image reconstruction techniques may facilitate more targeted testing. We therefore advocate for imaging-based parameters serving as baseline settings (i.e., lead level and directionality) which may be refined based on clinical effects. By this means, the proposed approach or similar techniques may still reduce the total time needed for clinical DBS programming sessions, given the approximate time of 10–20 min at the computer and 20 min with the patient. Particularly, the efforts required for

satisfying symptom control may be reduced using image reconstruction initial DBS settings. In general terms, image reconstruction may hence play a role in improving efficiency of DBS programming.

The present study had some limitations, the first of which was its small sample size. Second, this was a retrospective study, and future prospective studies will be designed to investigate the effects of image-reconstruction-guided programming. Third, this study did not determine the long-term effects of DBS in individuals with PD.

In summary, imaging-guided programming of directional DBS leads is possible and leads to save programming time and reduce patient side effects compared with clinical programming. Taking patient-specific anatomy into consideration, this technique or similar approaches may promote more efficient programming of DBS. Given that determination of the lead direction is an indispensable presupposition for successful clinical use of directional DBS, reliable visualization of DBS leads including their rotation angle is possible with image reconstruction with comparable results.

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 Ethics Institutional Committee of the First Hospital Affiliated with USTC (China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM and BC jointly completed the experiment and the writing. CX and MJ followed up patients. CN took overall control of the whole study. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Feasibility, Safety, and Effectiveness of Telerehabilitation in Mild-to-Moderate Parkinson's Disease

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Introduction: Parkinson's disease (PD) patients frequently engage in rehabilitation to ameliorate symptoms. During the Coronavirus disease 2019 (COVID-19) pandemic, access to rehabilitation programs has been markedly limited, consequently, telerehabilitation gained popularity. In this prospective, open-label, and pilot study, we aimed to investigate feasibility, safety, and efficacy of telerehabilitation in mild-to-moderate PD patients.

Materials and Methods: Twenty-three PD patients, with Hoehn and Yahr stage <3, without gait disturbances or dementia and capable of using the televisit platform, were recruited for a 5-week telerehabilitation program, consisting of 1 remote visit with a therapist and a minimum of two sessions of >30-min of self-conducted exercises per week. Patients received video tutorials of exercises and were asked to keep a diary of sessions. At baseline (T0), at the end of the intervention (T1), and 1 month after the end of treatment (T2), patients were remotely assessed with MDS-UPDRS part I-III, PDQ-39, Functional Independence Measure (FIM), and Frontal Assessment Battery scales, respectively. Acceptable compliance to the program was defined as >60% matching of frequency and duration of sessions, whereas optimal compliance was set at >80% matching.

Results: The dropout rate was 0%. Over 85% of patients reached acceptable adherence cut-off and around 70% reached optimal one. No adverse events were reported during sessions. The repeated measure analysis of variance (rANOVA) showed a significant effect of factor "time" for MDS-UPDRS-III ($p < 0.0001$) with a mean reduction of 4.217 points between T0 and T1 and return to baseline at T2. No significant effect was found for other outcome measures.

Conclusion: Our findings demonstrate that telerehabilitation is safe, feasible, and effective on motor symptoms in mild-to-moderate PD patients.

Keywords: neurorehabilitation, Parkinson's disease, physiotherapy, remote treatment, telehealth, telemedicine, telerehabilitation

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in terms of prevalence and burden of disability (1). The primary symptoms of PD include bradykinesia, rigidity, and resting tremor. Additional and more disabling motor symptoms, such as postural instability and gait disturbances, frequently occur with disease progression and carry heavy impact on independence and quality of life (QoL) (2, 3). Moreover, PD patients may experience a variety of non-motor symptoms (NMS), such as sensory alterations, dysautonomia, sleep disturbances, mood disorders, and cognitive impairment, which may precede the motor onset or arise along disease course, and further deteriorate the QoL of patients (4). The management of PD relies mostly on symptomatic pharmacological therapy with L-Dopa or other dopaminergic agents (5). Several drugs are available for treating NMS as well (6). However, even with optimal pharmacological management, most PD patients engage in rehabilitation to reduce disability in daily activities. Physiotherapy is the most widely used rehabilitation approach and has the most solid result evidence, in particular on motor symptoms of PD (5–7). In this respect, the European Physiotherapy Guidelines for PD offer a useful tool for clinicians to evaluate patients and refer them to physiotherapists. Moreover, these guidelines represent the evidence-based supports to physiotherapists for identifying treatment goals and intervention strategies tailored to the management of disease staging and severity (8).

The recent Coronavirus disease 2019 (COVID-19) pandemics widely disrupted most of our daily life aspects and forced administrations to lockdown and strict social distancing measures. This had a heavy impact on the healthcare systems as well, with chronic disease patients being the most affected. Indeed, reports of worsening of some NMS, in particular anxiety, in PD patients have accumulated in the last 2 years (9–18). This was associated mostly with difficulties in accessing clinical services and medications (19), reduction of physical activity, and inability to access rehabilitation clinics (20), with up to 88% of patients reporting the interruption of physiotherapy during lockdown (16). To overcome these limitations, a transition from in-person to remote visits has been supported by several PD centers for implementing telemedicine and telehealth management of PD patients (21–24).

Telemedicine represents an interface in a virtual patient–physician relationship to provide primary and secondary care for a variety of neurological disorders (25). With respect to PD, telemedicine has been applied to assist remote management of devices for advanced therapies, teleconsultation, telerehabilitation, and monitoring of motor and non-motor parameters in an ecologically valid environment (26). In the field of rehabilitation, the call for implementing telemedicine instruments to ensure continuity in the management of neurological patients was strong (27–31). In Italy, the Italian Society for the Neurological Rehabilitation published a guideline containing urgent measures to face limitations imposed by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)-pandemics, including the use of remote assessments and management solutions (32). The remote administration of physiotherapy in PD patients is rather challenging, and the feasibility of treatment is hampered by the fear of adverse events (AEs), particularly falls without the possibility of prompt intervention by the operator. Despite these concerns, there is growing evidence in favor of the efficacy of telerehabilitation to sustain physical activity, mobility, and emotional wellbeing (23, 29, 33–39). Most reports dated before the COVID-19 pandemics were focused on cognitive training, speech therapy, and dance therapy in small cohorts of patients affected by different neurological disorders. In the present study, we sought to investigate the feasibility, safety, and efficacy of telerehabilitation in mild-to-moderate PD patients. The program was originally designed and carried out during the lockdown due to the COVID-19 pandemics in Italy, then maintained after the reopening of rehabilitation facilities.

MATERIALS AND METHODS

This was a prospective, open-label pilot study, aimed to investigate the feasibility, safety, and efficacy of telerehabilitation in mild-to-moderate PD patients. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Approval was granted by the Local Ethical Committee of the Sapienza University of Rome. Data collection and processing followed the current European regulation for data protection. Patients with PD, referring to our Movement Disorder Outpatient Service in the period between January 2020 and August 2021 were screened for enrollment with a 1:10 ratio according to the visit schedule. The inclusion criteria were: (i) diagnosis of idiopathic PD according to the MDS criteria (40); (ii) disease stage <3 according to the modified Hoehn and Yahr (H&Y) scale (41); (iii) stable antiparkinsonian treatment in the previous 3 months; (iv) availability of technical instruments for remote video-call (tablet, laptop, or computer/webcam) and ability to use them by patients and/or caregiver; (v) availability and motivation of patients to participate to a 5-weeks telerehabilitation program; and (vi) attendance of a caregiver during remote and self-conducted sessions for patients with H&Y score >1. The exclusion criteria were: (i) contraindications to rehabilitation treatment; (ii) patients already undergoing rehabilitation treatment; (iii) co-morbidity with non-stabilized major medical illnesses; (iv) cognitive impairment as defined by a Mini-Mental State Examination (MMSE) score <24; and (v) presence of freezing of gait (FOG).

Enrolled patients matching inclusion and exclusion criteria underwent a 5-week telerehabilitation program consisting of a remote session with a physiotherapist once weekly and at least two self-conducted sessions per week. In the 1st week of the treatment, an additional assisted remote session was scheduled for further training and exercise feedback. Moreover, patients had free access to video tutorials, showing the exercises performed with physiotherapists and were instructed to exercise at least twice weekly with a minimum of 30 min for each session. Areas of intervention included general mobility, static, and dynamic

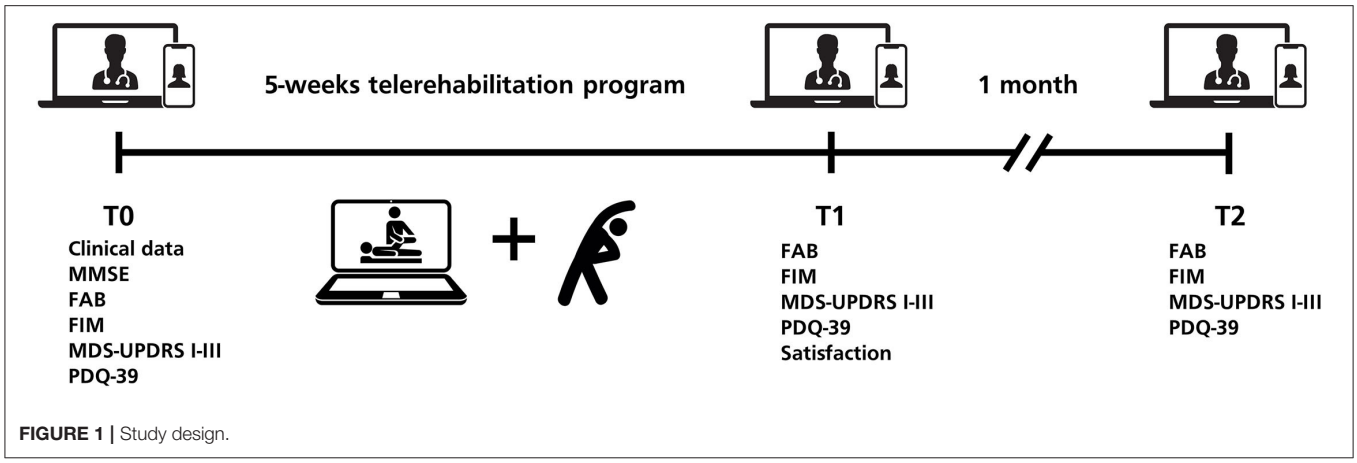

FIGURE 1 | Study design.

balance, coordination, dexterity, postural transitions, and facial mobility. Mobility and postural transition exercises focused mainly on sit-to-stand and lying mobility to address in-bed turning difficulties. A number of exercises ranging from 8 to 12, for duration of 40–60 min were included in each session depending on the patients' condition, functional demands, and reported difficulties. Examples of video tutorials are available in the **Supplementary Material**.

To evaluate compliance, patients were instructed to keep a diary of self-conducted sessions. Patients were evaluated before treatment (T0), at the end of the 5-week treatment program (T1) and 1 month after the end of treatment (T2). All evaluations were performed remotely on a digital platform for telemedicine freely available by Regione Lazio, named "Salute Digitale" (42). The platform consists of an easy-to-access audio/video remote conference call interface based on the open-source set Jitsi Meet. A unique room for teleconsultation is generated by the healthcare provider and the private link for participation is communicated to the patient. The teleconsultation room is canceled automatically at the end of the call. The platform is compliant with GDPR and current regulations for web and software privacy and security.

The primary outcome measures of the present study were feasibility and safety of telerehabilitation. To assess them, we investigated three variables: dropout rate, adherence to the program, and occurrence of AEs. Dropout rate was defined as the rate of patients who did not complete the study from enrollment to post-training evaluation. The *a priori* criterion for adherence was set at a 20% dropout rate. Patient adherence to the telerehabilitation program was defined as the rate of training sessions matching frequency ($\geq$3 sessions per week) and duration ($\geq$30 min). This was considered acceptable for at least 60% and optimal for at least 80% rate, respectively. Falls during the telerehabilitation program were considered the primary AEs. The *a priori* criterion was set at 0 falls. Moreover, any other possible AE occurring during the training program was recorded. Six secondary outcome measures were collected to evaluate the patients' status.

The MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I-III were used to assess the motor symptoms

TABLE 1 | Demographic and clinical characteristics of enrolled patients.

	PD patients ($N = 23$)	
Age (years)		64.1 ± 8.9
Sex	F	10 (43.5%)
	M	13 (56.5%)
Disease Duration (years)		6.5 ± 3.8
H&Y		2 (2–2; 1–2.5)
MMSE		30 (29–30)
LEDD (mg)		581.5 ± 210.2
Therapy	DA or iMAO-B monotherapy	4 (17.4%)
	L-DOPA monotherapy	3 (13%)
	L-DOPA + Add-on	16 (69.6%)

DA, dopamine agonist; iMAO-B, MAO-B inhibitors; LEDD, levodopa equivalent daily dose. Variables are shown as Mean ± SD or Median (Q1–Q3; Min–Max) for numerical variables and N (%) for categorical variables.

severity and the impact of motor and non-motor symptoms on daily life (43). The Parkinson's Disease Questionnaire-39 (PDQ-39) was used to evaluate patients QoL (44). The Functional Independence Measure (FIM) was used to assess functional independence in daily life activities (45). The Frontal Assessment Battery (FAB) was employed to evaluate the frontal cognitive abilities of enrolled patients (46). At the end of the telerehabilitation program, patients were administered a questionnaire composed of five questions constructed as a 7-items Likert scale, investigating the satisfaction for the telerehabilitation program (Q1), the usefulness of the program for PD patients (Q2), the satisfaction for the remote visit modality (Q3) and the willingness to participate again in the same telerehabilitation protocol or other telemedicine programs (Q4 and Q5; **Figure 1**).

Due to the exploratory nature of the study, a rigorous sample size calculation was not carried out. However, we predicted high compliance for telerehabilitation programs with a low dropout rate. Therefore, we fixed the number of enrolled patients at 25, considering a dropout rate of 20%. All statistical analyses were carried out using the SPSS version 23 software

for Windows. The normality of distribution of the variables was assessed using the Shapiro–Wilk test. To assess the effect of the telerehabilitation program across the different time-points on the evaluated variables, repeated measure analysis of variance (rANOVA) was performed. Greenhouse–Geisser correction for non-sphericity and Bonferroni's correction for multiple tests were applied when needed. To evaluate the effect size of our intervention partial η^2 (η^2_p) was reported and a *post-hoc* analysis to compute achieved power was performed using G*Power software 3.1.9.7 for Windows. The level of significance was set at $p < 0.05$. All data are reported as Mean ± *SD* or Median (Q1–Q3; Min–Max).

RESULTS

Forty-seven patients were screened for eligibility for the study and 23 (48.9%) were enrolled based on inclusion and exclusion criteria (**Supplementary Figure 1**). Demographic and clinical features of enrolled patients are shown in **Table 1**. All patients completed the study, resulting in a dropout rate of 0%. A total of 452 training sessions were completed, 380 of which (83.9%) reached the duration cut-off of 30 min. In 94 out of 115 training weeks (81.7%), the *a priori* criteria of at least 3 sessions/week for minimum 30 min each were reached. When considering single patients, 20/23 (87%) patients reached the cut-off for acceptable adherence of at least 60% of matching frequency and duration, and 16/23 patients (69.6%) reached the optimal cut-off of 80%. No falls or other AEs were reported and no interventions by caregivers were necessary during supervised or self-conducted sessions. Repeated measure ANOVA showed a significant effect of the factor "time" for the MDS-UPDRS-III score across the different time points ($F_{2,44} = 10.539$; $p < 0.0001$). The *post-hoc* analysis showed a motor severity score significantly reduced right after the treatment with a mean decrease of 4.217 (95% CI, 1.637–6.798; $p = 0.001$), with a return to baseline values at 1-month evaluation (T1 vs. T2 $p = 0.036$; T0 vs. T2 $p = 0.147$; **Figure 2**). No significant effect of factor "time" was found for the other secondary outcome measures, which remained stable from the beginning to the end of the study. Variables values across time points, the values of η^2_p and achieved power are shown in **Table 2**. Over 90% of patients were "extremely satisfied" or "very satisfied" for the telerehabilitation and remote visit modality and considered the intervention "extremely useful" or "very useful" for PD patient. Furtherly, all except a single patient were highly interested in undergoing again the telerehabilitation program or other telemedicine projects (**Supplementary Figure 2**).

DISCUSSION

In this open-label pilot study, we investigated the feasibility, safety, and efficacy of telerehabilitation in mild-to-moderate PD patients. Telemedicine has been applied recently under specific circumstances, for specific indications and eligible patients. Despite the potential relevance of telemedicine for diagnosis, consultation, monitoring and treatment management, availability, and diffusion of telemedicine is still limited by the clinical and sociodemographic features (24, 25). The issue of telerehabilitation in PD has been promoted during the lockdown for COVID-19 pandemics; however, it appears promising for the management of early stages of PD under normal conditions as well. Safety is a major concern to remote physiotherapy, in particular because of the limited possibility of direct intervention by the operator if the case of AEs. Based on the previous reports that 35–90% of PD patients experience at least 1 fall/year, and 2/3 of cases are recurrent fallers (47), the occurrence of falls was the main safety measure in our study. The *a priori* criterion of no falls was matched in our cohort, indicating the high safety of our telerehabilitation program in mild-to-moderate PD patients. Moreover, there was no report of any other AE, in line with the results of previous studies underlying the safety of remote rehabilitation in PD patients (33). Dropout rate and adherence to the program were considered as measures of feasibility. All participants completed the program and the post-training evaluation (dropout rate 0%), confirming that duration and complexity of exercises were accessible to all participants. Despite the potential bias due to lockdown, we would like to point out that participation in our program remained absolute after the reopening of rehabilitation structures as well. The present findings are, therefore, much more promising compared to those of previous studies showing a 20% dropout rate in elderly subjects engaging in a rehabilitation program (48), and confirm the awareness and willingness of PD patients toward rehabilitation. This concept is further supported by the high adherence to the protocol, as almost 85% of patients reached the acceptable cut-off and 70% reached the optimal cut-off for participation. Thus, the present results indicate that telerehabilitation is a feasible, accessible, and likely rewarding intervention in mild-to-moderate PD patients. However, among screened patients, less than half-matched inclusion and exclusion criteria. This at least partially reflects the strict enrollment criteria used in the present studies and must be taken into account when considering the general applicability of remote physiotherapy intervention in PD. Finally, the high rate of satisfaction and willingness to engage in similar programs among our patients demonstrates that PD subjects are interested in the rehabilitation program and can ensure notable compliance and adherence to treatment.

As to motor outcome measures, we found a significant reduction of MDS-UPDRS-III after telerehabilitation. Despite being a secondary outcome measure, *post-hoc* power analysis demonstrated a statistical power >98% with high effect size, confirming the reliability of the finding. Moreover, the previous studies showed a minimum clinical impact for MDS-UPDRS-III between 2.4 and 3.25 (49), thus the score reduction of 4.22 in our study had a clinically significant impact on the patient's motor symptoms severity. In the literature, the efficacy of physiotherapy on motor symptoms is widely demonstrated (7). Moreover, preliminary studies showed efficacy of non-conventional remote administered rehabilitation strategies, including dance or virtual reality training, on motor and non-motor outcomes in PD patients (33). Our study confirms this extended knowledge to the efficacy of remote administered physiotherapy program on motor symptoms of PD, as measured by the MDS-UPDRS-III score. No significant variation was, however, found

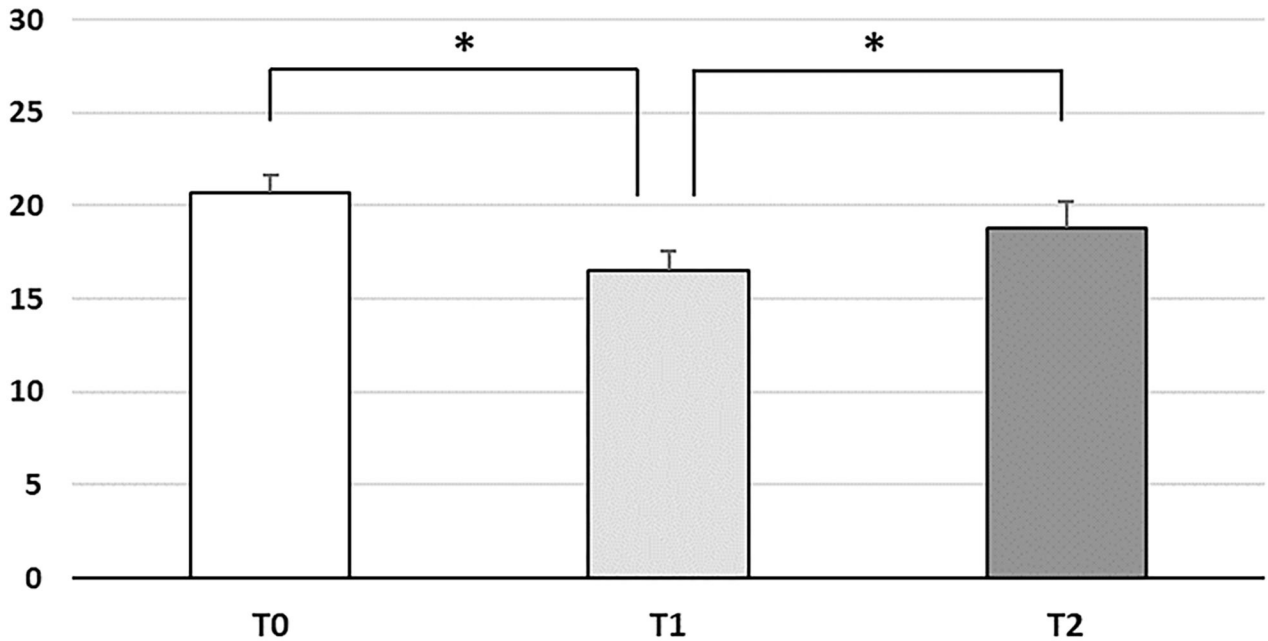

FIGURE 2 | Histogram showing the MDS-UPDRS-III score across time points. Standard error of the mean is shown by vertical bars. Statistically significant differences are marked with an asterisk. The *post-hoc* analysis showed a reduction between T0 and T1 and a return to baseline at T2.

TABLE 2 | Secondary outcome measures scores at T0–T2.

	T0	T1	T2	rANOVA	*p*	η^2_p	Power%
MDS-UPDRS-I	8.87 ± 3.98	7.74 ± 3.67	8.17 ± 3.8	F (2, 44) = 2.002	0.147	0.083	39.1%
MDS-UPDRS-II	6.87 ± 4.2	6.3 ± 3.31	6.57 ± 3,68	F (1.559, 34.292) = 0.430	0.604	0.019	10.8%
MDS-UPDRS-III	20.7 ± 4.73	16.48 ± 5.32	18.78 ± 6.75	F (2, 44) = 10.539	**<0.0001***	0.324	98.4%
PDQ-39	17.87 ± 10.86	17.26 ± 11.99	15.52 ± 9,96	F (1.424, 31.333) = 1.031	0.345	0.045	18.8%
FIM	122.09 ± 5.25	122.39 ± 4.27	122.35 ± 4.27	F (2, 44)= 0.073	0,929	0,003	6%
FAB	14 (13–15); (7–15)	14 (13–15); (6-15)	14(13-15); (10–15)	F (2, 44) = 1.526	0.229	0.065	30.7%

For repeated measures ANOVA, F-statistics, effect sizes, and power are reported. Statistically significant results are marked in bold with an asterisk. η^2_p*, partial eta squared. Variables are shown as Mean ± SD or Median (Q1–Q3; Min–Max).*

regarding functional independence, QoL, NMS, and executive cognitive functions in mild-to-moderate PD patients. This lack of significance may depend on several reasons. First, we enrolled PD patients with a modified Hoehn and Yahr score <3. In particular, patients using ambulation aids, with postural instability or reporting FOG were excluded, primarily for safety reasons. Balance and gait disturbances are among the most disabling impairments in PD patients, strongly limiting functional independence and having a strong impact on QoL (4, 47–50). Secondly, the enrolled patients were mostly cognitively stable and patients with significant cognitive impairment were excluded. The previous studies demonstrated an effect of physical exercise on cognitive function and some effect on NMS (7, 51–54), but the relatively good cognitive and NMS status of our patients could have masked the improvement with a roof effect on our secondary outcome measures.

Beyond these considerations, we acknowledge that this exploratory study suffers from limitations due to the open-label and non-controlled design, the small cohort, the relatively good status of our patients, and the remote motor evaluation. Regarding the number of subjects, this was a pilot study, thus a precise sample size calculation was not carried out. However, the *post-hoc* power analysis confirms the reliability of the reported results. Again, the characteristics of enrolled patients could limit the generalizability of our data due to the relatively good functional and cognitive status and a roof effect in outcome measures. Further studies, including intermediate-to-advanced patients with balance and gait disturbances, cognitive

impairment and using ambulation aids could help addressing this issue. Finally, the remote motor evaluation could somehow limit the reliability of our data. MDS-UPDRS-III items 3 and 12 (rigidity and postural instability) cannot be performed during remote visits and some evidence showed the reduced validity of tremor assessment when performed through video (55). However, recent studies demonstrated the feasibility and reliability of MDS-UPDRS-III remote administration (22, 55). Thus, we decided remote evaluation of our patients, also to address the difficulties to access medical services during lockdowns and COVID-19 related restrictions. Future studies, implementing remote evaluation instruments, such as wearable devices, could help overcome this limitation.

CONCLUSION

Our findings demonstrate that telerehabilitation is safe, feasible, and effective on motor symptoms in mild-to-moderate PD patients. Thus, remote physiotherapy programs could be viable and useful tools to overcome situations with limited access to healthcare services. Further controlled studies with greater sample size, including patients with higher disease severity, cognitive impairment, and implementing remote assessment instruments could help further expand our results.

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 Ethical Committe Sapienza. 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

EB, CO, and FP designed the study and wrote the first draft of the manuscript. CO and CM performed the physiotherapy treatment. EB and MA evaluated patients and collected data. EB performed data analyses. DR, PA, AM, and MS reviewed the manuscript draft. All authors contributed to the article and approved the submitted version.

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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.2022.909197/full#supplementary-material

Supplementary Figure 1 | Flow chart of participants trough the study.

Supplementary Figure 2 | Results of satisfaction and willingness to re-engage in similar telemedicine programs.

Supplementary Video 1 | Video tutorial showing one of the exercises for lying mobility.

Supplementary Video 2 | Video tutorial showing one of the exercises for postural transition from lying to sitting position.

Supplementary Video 3 | Video tutorial showing one of the exercises combining coordination and dynamic balance.

Supplementary Video 4 | Video tutorial showing one of the exercises for facial mobility.

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BRIEF RESEARCH REPORT
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Objective Observer vs. Patient Motor State Assessments Using the PD Home Diary in Advanced Parkinson's Disease

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Background: The Parkinson Disease (PD) Home Diary (HD) is a commonly used clinical outcome measure, but it has not been extensively compared to direct assessments by experienced observers.

Objective: Validation of patient-reported HD by investigating the agreement between motor state assessments by patients and observers.

Methods: This observational study included patients with PD and motor fluctuations. Observers were physicians or research nurses. Patients completed a screening visit, one day of diary ratings at home, and then two days of ratings on-site during which patients and observers simultaneously judged the participants' motor state.

Results: Observers and 40 patients completed 1,288 pairs of half-hourly blinded motor state assessments. There were significant differences between observer and patient ratings ($P < 0.001$) and the temporal agreement was poor (Cohen's $\kappa = 0.358$). The agreement between patient and observer ratings was 71.1% for observed "On without dyskinesia", 57.3% for observed "Off", and 49.4% for observed "On with dyskinesia". Daily times spent in the three motor states as aggregated diary data showed fair to excellent reliability with intraclass coefficient values ranging from 0.45 to 0.52 for "On" and 0.77 for "Off".

Conclusion: There were significant differences between observer and patient ratings. Patients and observers generally agreed on when the patients was in the "On" state (with or without dyskinesia). Patient ratings on the hour level seem to be influenced by other aspects of the patients' experience than the observed motor state, but assessment of daily time spent in the different motor state provides reasonable reliability.

Keywords: motor fluctuations, Parkinson disease, patient reported outcome (PRO) measures, clinical trials, Parkinson disease home diary

INTRODUCTION

In the early 2000's Hauser et al. developed the Parkinson Disease (PD) Home Diary (HD), or "Hauser diary", for use as an outcome measure of motor function in clinical trials (1–3). Previous to the HD, trials relied on the reduction of time spent in "off" as an indicator of improved motor function and did not address any potential increase of dyskinesia. In addition to "On" and "Off", Hauser et al. added "On with non-troublesome dyskinesia" and "On with troublesome dyskinesia" to better reflect the patient's motor state.

The HD was validated through correlation between patient self-assessment of "On" or "On without troublesome dyskinesia" with "good" time, then "Off" or "On with troublesome dyskinesia" with "bad" time (2). The predictive validity was reasonable when testing the correlation between HD ratings and patients' responses to questions about their motor state and the HD subsequently showed a good test-retest reliability (1). Patients often have limited knowledge of motor state terminology and may therefore benefit from training prior to the use of the HD (3).

Since the development of the HD, data collected using this method have been used as a central endpoint of many clinical trials on PD (4), primarily due to its usefulness during long-term follow-up and limited clinician bias. However, despite widespread use, the HD assessments have not been compared to what is considered the gold standard for objective measurement of motor function in PD: assessment by an experienced observer.

The aim of this study was thus to validate the HD by investigating the agreement between observer and HD ratings.

MATERIALS AND METHODS

Study Protocol Approvals and Patient Consents

This observational study was conducted at the Neurology Research Unit, Skåne University Hospital, Lund, Sweden ("the site") as part of an international collaboration on symptom fluctuations in PD, VALIDATE-PD. The study was approved by the Regional Ethics Review Board, Lund, Sweden (2017/936) and informed written consent was obtained from study participants.

Participants

Participants were recruited at the Department of Neurology, Skåne University Hospital or through the Swedish Parkinson Registry. Potential participants received information about the study in the mail and were then contacted by phone. Potential participants were invited to a screening visit that included the signing of an informed consent, evaluation of participation criteria, and documentation of baseline demographic and clinical information.

The inclusion criteria were: diagnosis of PD according to the United Kingdom PD Society Brain Bank criteria, age $\geq$30 years, motor fluctuations documented in patient records and/or on the revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the ability to sign an informed consent.

The exclusion criteria were: signs of secondary/atypical Parkinsonian syndromes, inability to complete patient questionnaires, lack of cooperation during study, signs of dementia [Montreal Cognitive Assessment (MoCA) $\leq$21] (5) or psychotic symptoms, and current device-aided treatment, as well as conditions interfering with the patient's ability to consent, adherence to the study protocol, or clinical evaluation.

Instruments and Assessments

The MoCA was used for screening for cognitive impairment (maximum 30 points, lower scores indicate more cognitive impairment) (6). The MDS-UPDRS was used for characterization of the study sample (maximum 260 points, higher scores indicate more PD symptoms) (7).

The motor states that were selectable for observers and in the HD were identical: "Asleep", "Off", "On without dyskinesia", "On with non-troublesome dyskinesia", and "On with troublesome dyskinesia". "On with dyskinesia" replaced the latter two categories in the analyses unless otherwise noted.

Procedures

Each participant attended one screening visit on-site, completed one day of HD recording at home, and then two office-hour days on-site. Participants were instructed in the use of a HD and received oral ($\sim$10 min) and written instructions including pictograms on the HD motor states. No instruction videos or concordance thresholds were used. Participants were asked to use the HD for 24 h while at home and were then allowed to clarify any issues regarding the rating procedure with study personnel before starting on-site ratings. Only the on-site ratings were used in the analyses.

During the two days on-site, participants were asked every 30 min between 8 am and 4 pm to rise from a chair, walk seven meters, and note their motor state in the HD. Meanwhile, the observer made a simultaneous assessment blinded to the HD rating. The observer assessment was based on observations during preparation for and execution of the seven-meter walk. Aggregated diary data consisted of percentage daily times spent in the three motor state calculated as the mean from the two on-site days. In between the half-hourly assessments, participants were typically socializing, solving crossword puzzles, playing cards, reading magazines, listening to radio, having lunch, and drinking coffee.

Authors JT, SC, and three research nurses functioned as observers and the median experience of working with clinical PD research was about 5 years. All observers had completed the MDS-UPDRS training program prior to the study.

Statistical Analyses

The McNemar-Bowker test was used to test for symmetry of disagreements between the rating procedures, while Cohen's κ was used to estimate the agreement between the observer and HD data (8). The McNemar test with Bonferroni adjustment for multiple comparisons was performed as *post-hoc* comparisons of the different motor states. The McNemar test was used to compare dyskinesia occurrence and severity between observer and HD assessments. Pearson's correlation test

and intraclass correlation coefficient (ICC) estimation were used for correlations of daily times spent in the various motor states on the participant level. A Pearson's correlation coefficient $|r| <$ 0.3 was considered a weak, $|r| = 0.3$–0.59 a moderate and $|r| \geq$ 0.6 a strong agreement/correlation. ICC estimates and their 95% confidence intervals (95% CIs) were calculated based on single-rating, absolute-agreement, 2-way mixed-effects models with two rating instruments across all participants. According to the guideline by Cichetti (9), we interpreted κ values or ICC < 0.40 as poor, κ/ICC $= 0.40$–0.59 as fair, κ/ICC $= 0.60$–0.74 as good and κ/ICC $= 0.75$–1.00 as excellent reliability. The Wilcoxon signed-rank test was used for ancillary comparison of the estimations from the MDS-UPDRS of time spent in "Off" and "On with dyskinesia" to the observer and HD assessments. The effect size of the Wilcoxon signed-rank test was calculated using $r = \frac{Z}{\sqrt{N}}$. $P < 0.05$ was considered significant. IBM SPSS Statistics version 26.0 was used for statistical analyses.

RESULTS

Cohort Characteristics

Eighty-one potential participants received written information about the study and 41 (50.6%) agreed to participate. One participant declined further participation due to undisclosed reasons after the screening visit, while 40 participants completed the study (for demographic and clinical characteristics, see **Table 1**). No participant failed to comply with diary ratings.

TABLE 1 | Demographic data, disease characteristics, and clinical instruments ($n = 40$).

Male/female	22 (55%)/18 (45%)
Age, in years, median (IQR)	70 (62–76)
Disease duration, in years, median (IQR)	7 (6–12)
Symptom duration, in years, median (IQR)	10 (7–14)
Duration of motor fluctuations, in months, median (IQR)	51 (25–79)
Hypokinetic fluctuations	46 (20–74)
Hyperkinetic fluctuations	36 (21–59)
MDS-UPDRS total, median (IQR)	45 (30–57)
Part I	8 (5–11)
Part II	8 (5–14)
Part III	20 (15–29)
Part IV	5 (3–8)
Hoehn & Yahr stage, median (IQR)	2 (2–3)
Motor fluctuation symptoms	
Nightly "off"	31 (78%)
"Wearing off"	30 (75%)
Delayed "on" or no "on"	9 (23%)
"On-off" phenomena	25 (64%)
Peak dose dyskinesia	27 (69%)
Biphasic dyskinesia	5 (14%)
Off-dose dystonia	12 (33%)
MoCA total	26 (24–28)
Cognitive Impairment	
Normal	22 (55%)
Mild Cognitive Impairment	18 (45%)
Dementia	0 (0%)
Antiparkinson medication	
Levodopa	40 (100%)
Catechol-*O*-methlytransferase (COMT) inhibitors	24 (60%)
Monoaminoxidase B (MAO-B) inhibitors	26 (65%)
Dopamine agonists	32 (80%)
Levodopa dose per day in mg, median (IQR)	525 (456–769)
Levodopa equivalent dose per day in mg, median (IQR)	941 (763–1187)

Values are provided as numbers (percentages) or median with interquartile range (IQR); Mild cognitive impairment was defined as having a MoCA score of 22–25 points. MoCA, Montreal Cognitive Assessment; MDS-UPDRS, revised Unified Parkinson's Disease Rating Scale. Levodopa equivalent doses were calculated according to Tomlinson et al. (10).

Comparisons of Observer Ratings and HD on the Half-Hour Level

Out of 2,720 expected half-hour ratings, 89 (3.3%) were missing. A total of 1,322 observer and 1,309 patient diary ratings resulted in 1,288 complete pairs of ratings. As displayed in **Figure 1A**, ratings in observer diaries and PD Home diaries were distributed between "Off", "On without dyskinesia" and "On with dyskinesia" with a significant difference between observers and patient diary ratings in the distribution between the different motor states ($P < 0.001$), which was also illustrated by a Cohen's κ of 0.358. *Post-hoc* analyses comparing the various motor states revealed significant differences between the two ratings for "Off" ($P = 0.033$; McNemar test with Bonferroni adjustment) with a corresponding Cohen's κ of 0.562 and for "On without dyskinesia" ($P = 0.045$; McNemar test with Bonferroni adjustment) with a corresponding Cohen's κ of 0.314. Although there was no significant difference in the number of dyskinesia ratings between observers and HDs independent of their "troublesomeness" (**Figure 1A**, $P = 1.000$; Cohen's κ of 0.289), dyskinesia was significantly less often seen as "troublesome" in observer (2.1%) than patient diary ratings (10.9%, $P < 0.001$).

The agreement between observers and participants, using the observer ratings as the gold standard, ranged from 71.1% in "On without dyskinesia" to 49.4% in "On with dyskinesia" (**Figure 1B**). Patients considered themselves to be "On without dyskinesia" in 25.7% of the intervals with observed Off (**Figure 1C**). Even more strikingly, patients chose "On without dyskinesia" in 47.3% of those intervals in which the observer had actually noted "On with dyskinesia".

Comparisons of Observer Ratings and HD on the Participant Level

The HD have been repeatedly used as the primary outcome measure to assess effects of novel treatments on motor fluctuations in advanced PD with the aggregates measure of daily times spent in the three different motor states as the most frequent read-outs (4). We therefore also analyzed the daily percentage times spent in the three different motor states (8 am to

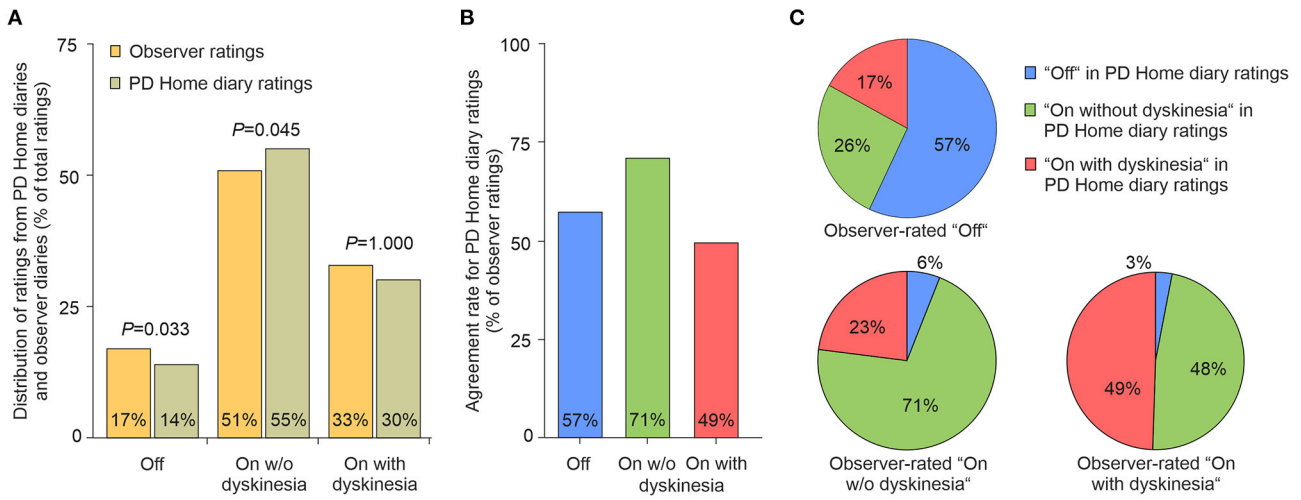

FIGURE 1 | Proportion and temporal agreement of motor states assessed by observer diaries and PD Home diaries. **(A)** Proportion of "Off", "On without dyskinesia" and "On with dyskinesia" as assessed by observer and patient diaries. *P*-values are from *post-hoc* McNemar test with Bonferroni adjustment. **(B)** Temporal agreement rate for all motor states as well as "Off", "On without dyskinesia" and "On with dyskinesia" with the observer ratings as the reference for comparison. **(C)** Participants' choices on the PD Home diary in each respective observed motor state. Number of observations in each observed motor state: "Off": $n = 218$, "On without dyskinesia": $n = 651$, "On with dyskinesia": $n = 419$. PD, Parkinson's disease.

4 pm) on the participant level from all 40 participants. As shown in **Figure 2A**, we detected similar percentage daily times spent in all three motor states when comparing observer diary data and HD with no significant differences between the two diary ratings for all motor states ($P \geq 0.05$, Friedman test with *post-hoc* Wilcoxon Rank test with Bonferroni adjustment). Pearson correlation analyses of the individual times spent in the three different motor states revealed a strong correlation of percentage daily times spent in "Off", but only a moderate correlation of "On without dyskinesia" and "On with dyskinesia" between observer and patient diary data (**Figures 2B–D**). Reliability analyses using ICC calculation revealed excellent reliability for HD data for "Off" when correlated with observer diary data [ICC = 0.77 (95% CI: 0.60–0.87)], and fair reliability for "On without dyskinesia" [ICC = 0.52 (95% CI: 0.26–0.72)] and "On with dyskinesia" [ICC = 0.45 (95% CI: 0.16–0.67)], respectively.

Using the participants' estimation of waking hours spent in "On with dyskinesia" from the MDS-UPDRS item 4.1 for ancillary analyses, dyskinesia was found to be underreported in the MDS-UPDRS (median 12.5%) when compared to observer (median 27.9%, $P < 0.001$, $r = -0.43$) and HD (median 22.4%, $P < 0.013$, $r = -0.28$). There were no significant differences between the estimation of time spent in "Off" in the MDS-UPDRS item 4.3 (median 6.7%) and neither observer assessment (median 13.6%, $P = 0.066$, $r = -0.21$) nor HD ratings (median 3.4%, $P = 0.852$, $r = -0.02$).

The temporal agreement on the participant level of HD data with the observer-rated diary data were estimated using the temporal agreement rate and Cohen's κ for each participant (**Figures 3A,B**). Taking the observer diary as gold standard criterion, temporal agreement rates for HD data showed a very high variability within the cohort with median agreement rates of 56.3% of observer-rated "Off", 68.8% of "On without dyskinesia", and 28.3% of "On with dyskinesia" (**Figure 3A**). The corresponding median Cohen's κ values ranged from 0.15 for "On without dyskinesia" and "On with dyskinesia" to 0.55 for "Off" (**Figure 3B**).

DISCUSSION

The primary finding of this study is that the temporal agreement between simultaneous observer and HD assessments of the participants' PD motor state can be characterized as poor. Indeed, we found that as few as 49% of HD ratings in observed "On with dyskinesia" and 57% in observed "Off" were in agreement with the simultaneous observer assessment, while 71% of ratings in observed "On without dyskinesia" were in agreement. Analyses of temporal agreement on the participant levels resulted in very high variability of agreement rates between the participants, but in general similar results as on the time level. In contrast, for daily time spent in the three motor states as a major outcome measure in clinical studies (4), the HD show fair reliability for both "On" either with or without dyskinesia and even an excellent reliability for "Off" when using the observer diary data as the outside criterion.

As the HD and observer data was nominal, Cohen's κ was chosen over other possible methods for studying validity. The poor agreement between observers and participants (κ = 0.358) indicates that there were conflicting assessments of the participant's motor state (9). Participants were most successful at recognizing "On without dyskinesia" and least successful at recognizing "On with dyskinesia". Participants and observers were largely in agreement regarding when the participant was in "On" if the severity of dyskinesia was not taken into account, but

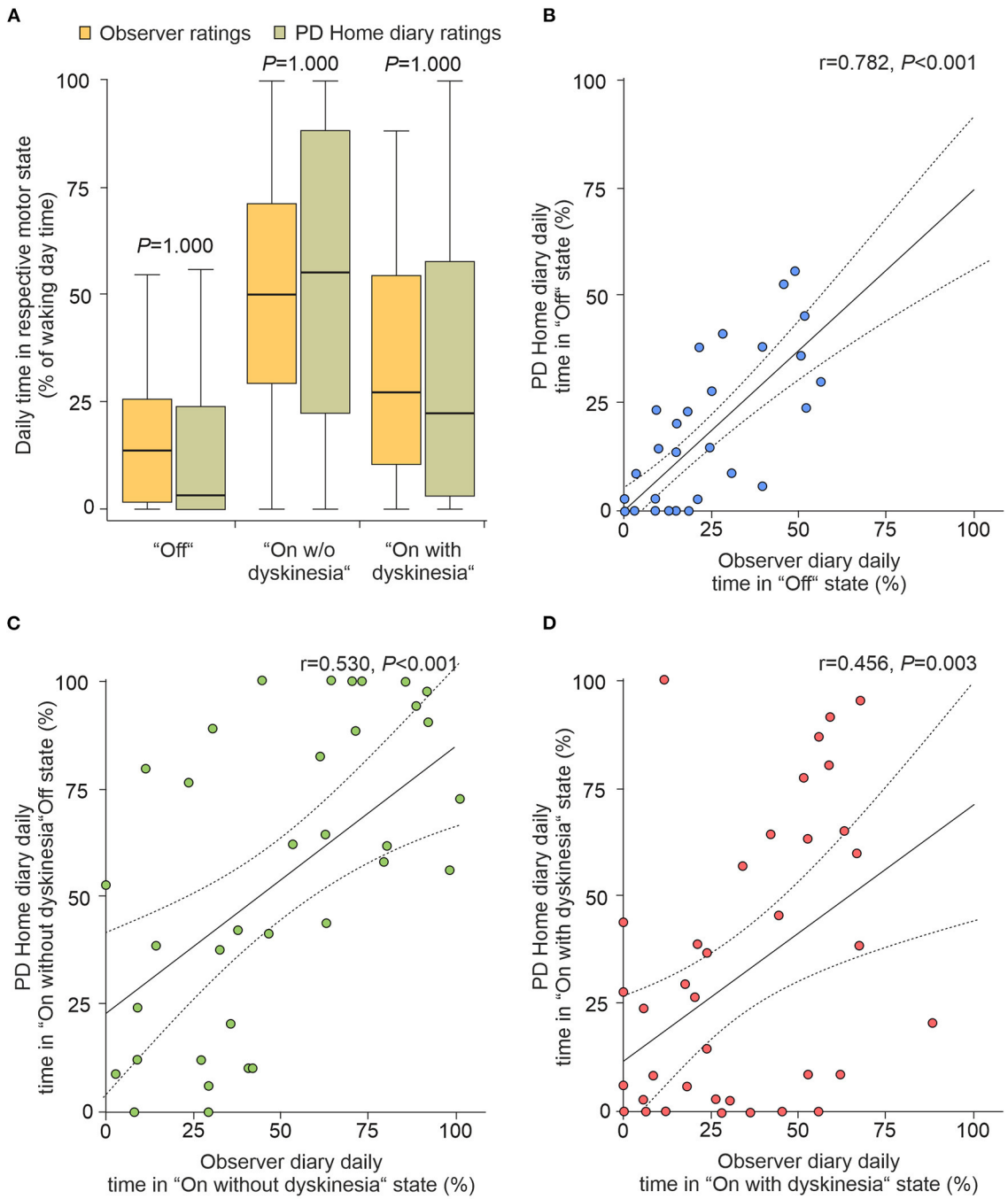

FIGURE 2 | Proportions for time spent in motor states assessed by observer diaries and PD Home diaries on participant level. **(A)** Distribution of daily time proportions of "Off", "On without dyskinesia" and "On with dyskinesia" based on the simultaneous, half-hourly performed diary ratings from 40 participants from two consecutive days (8 am to 4 pm). Boxplots are shown with a central mark at the median, bottom, and top edges of the boxes at 25th and 75th percentiles, respectively, whiskers out to the most extreme points within 1.5 times the interquartile range. Displayed *P*-values are from Friedmann tests with *post-hoc* Wilcoxon signed-rank tests with Bonferroni correction for multiple comparisons. **(B–D)** Correlation analyses of mean proportions of "Off" **(B)**, "On without dyskinesia" **(C)** and "On with dyskinesia" **(D)**. Solid lines in represent the regression line with 95% CI (dotted lines). Values in upper right corner are the correlation coefficients and *P*-values from Pearson's correlation tests. PD, Parkinson's disease; CI, confidence interval.

in observed "Off" 42.7% of the HD ratings were instead "On" either with or without dyskinesia (**Figure 1C**). The motor state is likely to overlap with other symptoms that are not noticeable to an observer but nonetheless make up a significant part of the patient's experience. This has historically led to difficulties with establishing a widely used practical definition of "Off"

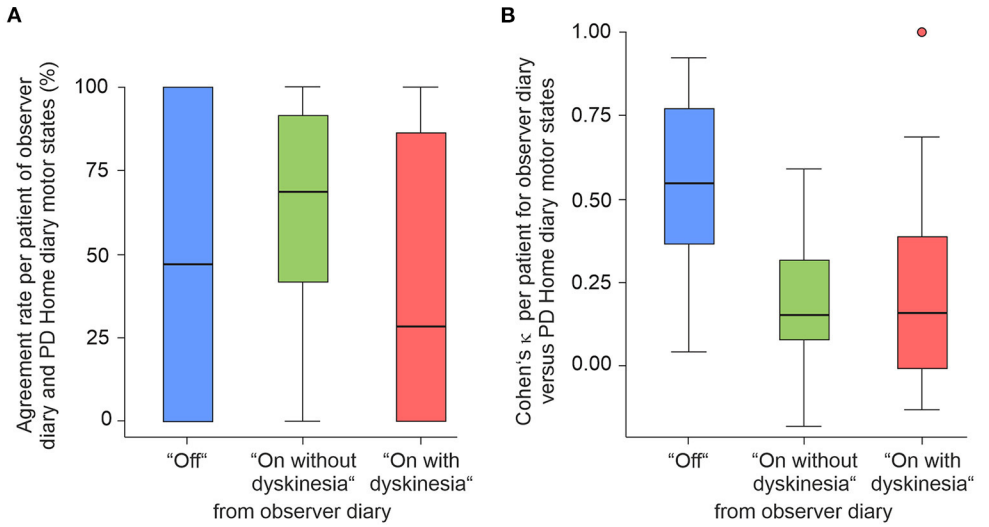

FIGURE 3 | Temporal agreement of observer-documented and PD Home diary ratings on the participant level. Agreement rates **(A)** and Cohen's κ values **(B)** for "Off", "On without dyskinesia" and "On with dyskinesia" based on simultaneous half-hourly ratings of 40 participants from two consecutive days (8 am to 4 pm) and independent observer ratings serving as reference for the comparison. Boxplots are shown with a central mark at the median, bottom, and top edges of the boxes at 25th and 75th percentiles, respectively, whiskers out to the most extreme points within 1.5 times the interquartile range, and outliers scoring more than 1.5 × IQR but at most 3 × IQR outside the quartiles. PD, Parkinson's disease; IQR, interquartile range.

(11). Fluctuations of neuropsychiatric, sensory, and autonomic symptoms are generally present among PD patients with motor fluctuations (12). It is possible that such non-motor fluctuations could have influenced HD ratings.

Patients often prefer dyskinesia to hypokinesia (13) and the clinical impression is that observers are more likely to notice mild dyskinesia than patients themselves are. We did not find any significant difference in the number of "on with dyskinesia" ratings between HD and observer ($P = 0.192$) and cannot, based on our findings, support that notion. Instead, we show that participants rated dyskinesia as "troublesome" more often than observers did ($P < 0.001$). We refrained from further analysis regarding dyskinesia severity as it is an inherently subjective dichotomization. It is noteworthy that in observed "Off", "On with dyskinesia" made up 17% of HD ratings, which may indicate a lack of understanding among participants of the PD motor states' characteristics, such as confusing tremor with dyskinesia.

Daily times spent in the three different motor states calculated from the HD have been repeatedly used as the primary outcome measures to assess effects of novel treatments on motor fluctuations in advanced PD (4). In reasonable agreement with Löhle et al. (14), the aggregated HD data showed fair to excellent reliability with ICC values ranging from 0.45 for "On with dyskinesia" over 0.52 for "On without dyskinesia" to 0.77 for "Off". This rather good reliability of the aggregated data stand in contrast to the limited temporal agreement between HD and observer ratings. It is likely that the timing of motor and non-motor fluctuations in conjunction with their ratings limit the temporal agreement together with the differences in motor state perception between the patient and the objective observer (15). During further ancillary analyses, we found dyskinesia to be underreported in the MDS-UPDRS item 4.1, but the time spent in "Off" estimated in MDS-UPDRS item 4.3 did not significantly differ from neither the observer nor HD ratings. Although this is an interesting exploratory finding, our on-site ratings did not include the night-time, during which especially "Off" is common, and further investigation is warranted.

This study has several limitations. Firstly, all observers had experience of movement disorders and were certified in the use of MDS-UPDRS, but were not Movement Disorder Specialists and could thus be considered less accurate than the gold standard. Furthermore, using multiple observers may have influenced the results and, as each patient was rated by a single observer, no calculations of the inter-rater reliability between observers were performed (e.g., the Fleiss' kappa). However, findings from a single-rater German cohort are in many aspects in agreement with the present results (14). It is also possible that participants were more inactive than they would have been in a home setting and therefore were less likely to notice "Off" and troublesome dyskinesia due to a limited number of activities available at the site. Lastly, the participant instructions for the use of the HD could have been more rigorous and included the recommended instruction video (3), which might have increased the agreement with observer assessments. However, the level of instructions to participants in this study was representative of how the HD is often used in clinical trials and in clinical practice.

The Movement Disorders Society Technology Task Force has identified a number of limitations among the currently available PD patient diaries and proposed a comprehensive development plan for a new eDiary (16). The Task Force has for example highlighted the need for capturing partial

medication states, medication intake, non-motor fluctuations, and functional assessments in the eDiary to better reflect the dynamic PD symptomatology. The eDiary is therefore intended to be an electronic diary/tracker interface that puts together the complementary information from patient ratings and wearable sensors.

The eDiary is certainly warranted, but the HD is likely to serve as a mainstay in clinical trials for several years to come. Based on our findings, and if observer assessments are held as the gold standard, the HD does not seem to be an accurate depiction of a patient's motor state at a given time point. However, that does not imply that the HD is not a useful tool since the daily time spent in the various motor states seems to reflect the observer times in a reliable manner. The HD should still be regarded as an important patient reported outcome, albeit a composite that is likely to be influenced by timing and other factors of the patient's experience than strictly the observed motor state. There is a potential complementary role for wearable sensors and other technology-based objective measures in the monitoring of PD, but it needs further study and we want to highlight the need for validation against observer ratings before implementation. Furthermore, it is warranted to investigate the effect of more extensive patient training on the agreement between HD and observer ratings. Notably, the limited temporal agreement might be particularly relevant in standard clinical use of the HD, wherein it is routinely applied to adapt the timing of antiparkinsonian medication.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request that is in line with local data protection regulations.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethics Review Board, Lund, Sweden. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JT, ML, AB, AS, and PO: conception and organization of research project, design and execution of statistical analysis, and review and critique of manuscript. JT, ML, AB, and SC: execution of research project. SC, FG, GE, ÖD, SI, and MN: review and critique of statistical analysis and review and critique of manuscript. JT: writing of the first draft. All authors contributed to the article and approved the submitted version.

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Does Executive Function Influence Walking in Acutely Hospitalized Patients With Advanced Parkinson's Disease: A Quantitative Analysis

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Introduction: It is well-known that, in Parkinson's disease (PD), executive function (EF) and motor deficits lead to reduced walking performance. As previous studies investigated mainly patients during the compensated phases of the disease, the aim of this study was to investigate the above associations in acutely hospitalized patients with PD.

Methods: A total of seventy-four acutely hospitalized patients with PD were assessed with the delta Trail Making Test (ΔTMT, TMT-B minus TMT-A) and the Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III). Walking performance was assessed with wearable sensors under single (ST; fast and normal pace) and dual-task (DT; walking and checking boxes as the motor secondary task and walking and subtracting seven consecutively from a given three-digit number as the cognitive secondary task) conditions over 20 m. Multiple linear regression and Bayes factor BF_{10} were performed for each walking parameter and their dual-task costs while walking (DTC) as dependent variables and also included ΔTMT, MDS-UPDRS III, age, and gender.

Results: Under ST, significant negative effects of the use of a walking aid and MDS-UPDRS III on gait speed and at a fast pace on the number of steps were observed. Moreover, depending on the pace, the use of a walking aid, age, and gender affected step time variability. Under walking-cognitive DT, a resolved variance of 23% was observed in the overall model for step time variability DTC, driven mainly by age ($\beta = 0.26$, $p = 0.09$). Under DT, no other significant effects could be observed. ΔTMT showed no significant associations with any of the walking conditions.

Discussion: The results of this study suggest that, in acutely hospitalized patients with PD, reduced walking performance is mainly explained by the use of a walking aid, motor symptoms, age, and gender, and EF deficits surprisingly do not seem to play a significant role. However, these patients with PD should avoid walking-cognitive DT situations, as under this condition, especially step time variability, a parameter associated with the risk of falling in PD worsens.

Keywords: Parkinson's disease, straight walking, wearable sensors, executive functions, dual task, aged

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INTRODUCTION

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by specific motor symptoms, such as bradykinesia and rigidity, and several non-motor symptoms, such as cognitive impairment and depression (1, 2). The progression of these symptoms and the associated limitations, particularly deteriorated walking performance, can lead to reduced quality of life (3). Due to this progressive aggravation of both motor and non-motor symptoms accompanied by the effects of age as well as a history or risk of falls, patients with advanced PD may increasingly require inpatient medical treatment (4). However, these vulnerable patients are often not included in the studies (5, 6). Furthermore, the association between specific non-motor symptoms and walking performance in patients with PD is not fully understood. Hence, an important open question is how motor and specific non-motor symptoms are related in the advanced stage of the disease in acutely hospitalized patients.

Typical motor symptoms can be accompanied by reduced walking performance, i.e., decreased gait speed, increased asymmetry, and impaired rhythmicity and stability of gait (5). These symptoms lead to daily life-relevant limitations, especially concerning mobility. As motor impairments progress, the risk of falls increases and patients become more dependent (for example, being in need of using walking aids). Both factors are associated with reduced quality of life (4, 7). To detect motor impairment in PD, wearable devices have been increasingly used in recent years as a flexible and cost-effective option in clinical settings (7–10).

Among the non-motor symptoms in patients with PD, cognitive impairment, namely, deficits in cognitive flexibility, set shifting, and working memory (the so-called fronto-striatal associated executive functions, EFs), as well as in divided attention and keeping attentional focus, play an important role [reviewed in (23, 24)]. Even in the early stages of the disease and also in patients with PD without dementia, deficits in internal attentional control, cognitive flexibility, and planning actions have been reported (16). Cognitive impairment and dementia in PD are associated with an increased risk of falls (25) and reduced quality of life (6).

In everyday situations, walking is not merely a simple task but rather requires the ability to manage multiple tasks simultaneously. This complex process requires a high degree of cognitive flexibility and integration of movement sequences and external stimuli, depending on environmental demands. In light of this, recent studies have investigated a possible link between limited walking performance and deficits in EF and attention both in older healthy individuals and in patients with PD (12–15, 17, 22, 26–35). These studies typically examined walking under both single task (ST) and dual-task (DT) conditions, with different methods, paradigms, and outcome parameters. A meta-analysis showed negative associations between age and cognitive status, as well as age and gait speed under DT in healthy older adults (21). In addition, in a longitudinal study over 6 years with healthy older adults ($n = 583$, aged 65 and older), reduced cognitive flexibility [measured by the Trail Making Test, TMT (36)] was identified as a predictor for increasing mobility impairment and mortality (20). Another study found associations between poor TMT performance and changes in DT prioritization during walking at the expense of gait speed in older adults (11). Overall, the existing evidence suggests that healthy older adults under DT strategically adapt to increased demands, e.g., by reducing gait speed or requiring increased reaction time during cognitive tasks, but do not exhibit extensive changes in walking performance (32). In contrast, patients with PD appear to need higher levels of attention, executive control, and cognitive flexibility for actions such as walking. During the course of the disease, coping with increasing task complexity becomes more difficult for patients with PD (23, 32, 37–39). Comparative studies have shown that EF performance and associated walking impairment (primarily reduced gait speed and increased gait variability) are worse in patients with PD than in healthy controls, especially under DT conditions (15, 22). In addition, studies in patients with PD have shown that spatio-temporal walking parameters, such as gait speed and stride length, gait variability, and postural control, may be differently affected by impaired EF (14, 18, 34, 38, 40). These findings suggest that deficits in EF and divided attention in PD are associated with impaired walking performance and altered task prioritization as cognitive demands increase. The complexity of the (gait) situation is particularly evident with regard to higher dual-task costs (DTCs) while walking (14, 38, 41).

However, the studies mentioned above could not identify EF and divided attention as a relevant predictor for specific walking parameters and mainly focused on single walking parameters or used group comparisons or simple correlations (14, 34, 38). Cognitive impairment, advanced disease stage, severe motor symptoms, and needing a walking aid were the exclusion criteria (either combined or single) in most of the studies. Also, acutely hospitalized patients were often not included. However, these aspects are highly relevant for treatment indications, risks as well as quality of life, and patients' ability to cope with everyday life (5–7). Thus, it remains unclear to what extent EF and divided attention have an influence on specific aspects of gait for patients with advanced PD in acute need of inpatient care. Furthermore, many studies are conducted under laboratory conditions, which means that the results are not necessarily transferable to clinical diagnostics or the home environment (19). Further investigation focusing on the understanding and clinical considerations that follow from these findings is important. Therefore, the aim of this study was to investigate the association between EF, divided attention, and walking performance under ST and DT conditions in acutely hospitalized patients with advanced PD. We also included patients with severe symptoms (e.g., cognitive impairment and reduced walking performance). In doing so, different requirements under ST as well as under DT with both congruent (i.e., predominantly motor) and divergent (i.e.,

Abbreviations: ASYM, Mean step time asymmetry; ComOn, Cognitive and Motor Interaction in the Older Population; DIA-S, *Depression im Alter* Scale; DLS, Mean double limb support; DT, Dual task; $DTC_{Walking}$, Dual-task costs while walking; FOG, Freezing of gait; LEDD, Levodopa equivalence daily dose; MCI, Mild Cognitive Impairment; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; ST, Single task; STV, Mean step time variability; TMT, Trail Making Test; MDS UPDRS, Revised version of the Unified Parkinson's Disease Rating Scale.

TABLE 1 | Descriptive characteristics of demographic, clinical, and walking parameters over all four walking conditions and of $DTC_{Walking}$ over both DT walking conditions.

demographic and clinical parameters	ST normal pace		ST fast pace		DT walking-cognitive		DT walking-motor	
	n	M (SD) [min; max] {Median; IQR}	*n*	M (SD) [min; max] {Median; IQR}	*n*	M (SD) [min; max] {Median; IQR}	*n*	M (SD) [min; max] {Median; IQR}
age [years]	74	72 (8.39) [48;87] {75; 12}	60	73 (8.78) [48;83] {77; 12}	45	72 (9.55) [48;83] {77; 12}	34	71 (10.0) [48;81] {76.5; 14}
Women [*n* (%)]		25 (11)		17 (12)		12 (13)		7 (14)
Education [years]		10 (1.88) [6;14]		10 (1.79) [6; 14]		10 (1.89) [6;14]		10 (2.12) [6;14]
Disease duration [years]		10 (6.85) [0;25]		10 (7.02) [0;25]		9 (6.48) [0;24]		8 (5.68) [0;20]
Hoehn & Yahr		{3; 1}		{3; 1}		{3; 1}		{3; 0}
LEDD [mg]		748 (370.7) [100;1811]		717 (368.5) [100;1811]		707 (389.8) [100;1811]		648 (373.9) [100;1811]
MoCA		23 (3.27) [15;29]		23 (3.36) [15;29]		24 (3.30) [17;29]		23 (3.57) [15;29]
DIA-S		3 (2.3) [0;9]		2 (2.35) [0;9]		2 (2.47) [0;9]		2 (2.55) [0;9]
ΔTMT [s]		129 (81.5) [16;399] {104; 116}		128 (81.5) [16;399] {104; 88}		111 (78.2) [16;399] {83; 55}		125 (79.3) [16;303] {83.5; 116}
MDS-UPDRS III		30 (14.8) [4;60] {28.5; 25}		30 (14.4) [4;60] {28; 23}		28 (14.9) [4;60] {26; 23}		24 (14.0) [4;60] {22; 18}
Occurrence of dyskinesia [*n* (%)]		15 (14)		11 (15)		6 (16)		5 (17)
Impact of dyskinesia [*n* (%)]		5 (7)		3 (5)		2 (4)		0 (0)
Occurrence of FOG		29 (18)		25 (19)		15 (20)		9 (13)
Walking aid [*n* (%)]		23 (21)		17 (12)		11 (22)		0
Walking parameters								
Number of steps	74	41.2 (11.7) [20;80]	60	39.2 (11.6) [23; 77]	45	45.1 (16.8) [23; 104]	34	46.5 (17.8) [27; 106]
Gait speed		0.78 (0.21) [0.34;1.25]		0.98 (0.29) [0.38; 1.64]		0.74 (0.25) [0.26; 1.25]		0.76 (0.29) [0.29; 1.33]
DLS		0.37 (0.1) [0.14; 0.82]		0.39 (0.06) [0.3; 0.72]		0.4 (0.12) [0.23; 0.87]		0.38 (0.07) [0.22; 0.53]
ASYM		0.03 (0.05) [−0.05; 0.23]		0.04 (0.03) [−0.005; 0.16]		0.05 (0.04) [0.0006; 0.15]		0.04 (0.03) [0.004; 0.13]
STV		0.04 (0.05) [−0.04;0.2]		0.07 (0.04) [−0.02;0.2]		0.06 (0.05) [0.0001; 0.34]		0.06 (0.03) [0.02; 0.13]
$DTC_{Walking}$								
$DTC_{Walking}$ Number of Steps [%]					44	6.35 (20.6) [−84.0; 58.6]	33	13.4 (16.8) [−22.2; 43.2]
$DTC_{Walking}$ gait speed [%]						8.14 (25.5) [−97.2; 61.2]		9.55 (33.3) [−136; 63.1]
$DTC_{Walking}$ DLS [%]						4.22 (18.9) [−42.6; 54.7]		0.30 (13.8) [−30.9; 34.4]
$DTC_{Walking}$ ASYM [%]						−0.41 (161) [−620; 348]		−40.1 (165) [−515; 209]
$DTC_{Walking}$ STV [%]						46.9 (139) [−191; 589]		−5.11 (82.7) [−281; 129]

ASYM, asymmetry; DIA-S, Depression im Alter Scale; DLS, double limb support; DT, dual task; $DTC_{Walking}$, dual-task costs for walking while doing a second task (in percentage, %); FOG, Freezing of gait; IQR, interquartile range; LEDD, levodopa equivalence daily dose (in milligram, mg); M, mean; max, maximum; MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; min, minimum; MoCA, Montreal Cognitive Assessment total score; n, sample size; s, seconds; SD, standard deviation; ST, single task; STV, step time variability; ΔTMT, delta of Trail Making Test (part B minus part A).

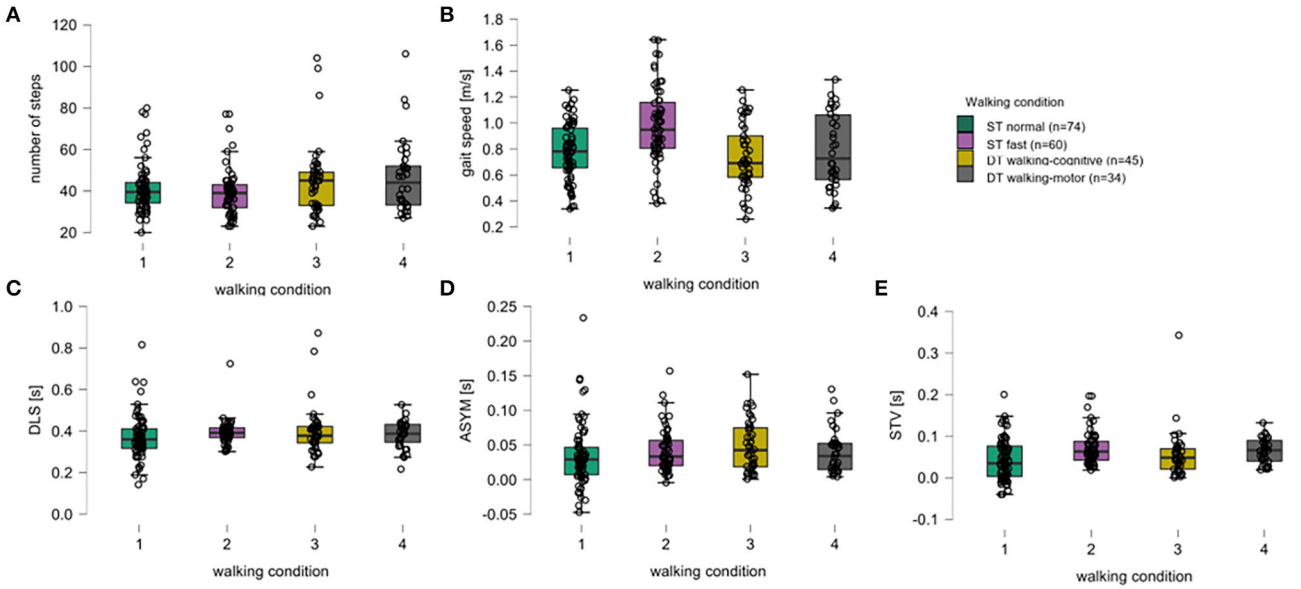

FIGURE 1 | Box plots for all walking parameters over all walking conditions. For the five walking parameters, **(A)** number of steps, **(B)** gait speed (meters per second), **(C)** double limb support (DLS, seconds), **(D)** asymmetry (ASYM, seconds), and **(E)** step time variability (STV, seconds), the medians (thick black horizontal lines), the interquartile range (IQR, black-bordered boxes), and lower and upper whiskers (values within ±1.5xIQR), single-subject data points (black circles) are given for walking conditions of a single task normal pace (green, 1), a single task fast pace (violet, 2), the dual-task walking-cognitive (yellow, 3), and the dual-task walking-motor (gray, 4).

cognitive) additional demands during straight walking were investigated. Walking performance was assessed using spatio-temporal walking parameters to identify those associated with EF and divided attention in PD. Outcomes were measured with assessments integrated into the clinical routine on a neurogeriatric ward.

METHODS

This study was a part of the exploratory, observational multicenter study "COgnitive and Motor interaction in the Older populatioN" (ComOn). In the ComOn study, participants aged 50 years and older with at least one chronic disease are included. The main aim of the study was to gain a better understanding of the multifaceted symptoms of this cohort and their complex interactions using quantitative and digital parameters. Therefore, a comprehensive examination protocol to assess cognitive, motor, behavioral, and other clinical parameters was conducted. For the full examination protocol, we referred a previous study (42). The focus of these analyses is on the influence of EF and divided attention on straight walking performance in patients with advanced PD.

The data presented here were collected between October 2017 and November 2020 at the Department of Neurology, University Hospital Schleswig-Holstein Campus Kiel (Germany). Informed oral and written consent was obtained from all participants and, if necessary, their legal representative or assistance (e.g., due to cognitive impairment or dementia). The study was reviewed by the ethics committee of the Medical Faculty of the University of Kiel (ethics application number D 427/17).

Participants

The study included geriatric inpatients diagnosed with PD ($n = 119$) according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (43) and the Movement Disorder Society (MDS) clinical diagnostic criteria for PD (44, 45). All participants fulfilled the inclusion criteria of the ComOn study protocol (42). Briefly summarized, participants were included if they were 50 years or older, able to walk at least 3 m independently with or without walking aid, and had sufficient hearing and visual acuity as well as sufficient speech comprehension as judged by the investigator. Main reasons for inpatient admission were deterioration in mobility and walking ability or general condition, recent falls, or medication adjustment due to reduced drug effects. Patients with severe motor symptoms measured by the MDS-revised motor part of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS III, (46)] as well as patients with previously described mild cognitive impairment (MCI) or mild to moderate dementia were included (refer to Section Demographical and Clinical Parameters). Patients were excluded if they scored <5 points in the Montreal Cognitive Assessment [MoCA, (47)] as a cutoff value for severe dementia in PD (48). Patients with more than two falls in the past week were excluded due to safety reasons in the motor assessment.

Procedure

Assessments took place in a clinical setting within the first 2 days after admission to the neurogeriatric ward. On the day of admission, a detailed medical history was conducted, and participants were given self-reporting questionnaires on various behavioral and clinical aspects. On the first day of treatment, a detailed neuropsychological examination was carried out, followed by a comprehensive movement analysis using inertial measurement units (IMUs, see Section IMU System). The duration of the two latter assessments was about 60 to 90 min each. Between the assessments, participants had a break of at least 60 min. The movement analysis was carried out on the ward corridor (>3 m broad, well-lit) in a designated area for this purpose. For this study, the data for straight walking over 20 m in ST and DT conditions were considered. To examine the patients in their best mobility condition possible, the medication was to be administered at a suitable time interval prior to the measurement after consulting with the medical staff.

Measures

Demographical and Clinical Parameters

Age, gender, years of education [total number of years in school plus standard time period for any completed professional education (49)], and current disabilities (e.g., care level, frailty, vision, and hearing impairments and urinary incontinence) were collected *via* interview using geriatric screening tools which are described in detail in the ComOn study protocol (42, 50, 51). From the medical records, PD duration and aspects of previously described cognitive deficits were extracted. In addition, the MoCA was performed to assess global cognitive performance (47). Depressive symptoms were assessed using the screening questionnaire *Depression im Alter* Scale [DIA-S, (52)]. Based on the medication schedule at admission, the levodopa equivalent daily dose [LEDD (53)] was determined.

The MDS-UPDRS III (46) was used to evaluate the severity of motor symptoms. We scored values below 30 as mild, between 30 and 60 as moderate, and values above 60 as severe PD motor stage [adapted from (54)]. Moreover, the modified Hoehn & Yahr Scale (46) was assessed. Furthermore, the occurrence of dyskinesia (according to the MDS-UPDRS definition as involuntary, random movements) during the examination as well as their impact on the rating of the MDS-UPDRS III and the occurrence of freezing of gait (FOG) were recorded using the three related items of the MDS-UPDRS III (55, 56).

Executive Functions and Divided Attention

Executive function and divided attention were measured by the Trail Making Test (36). The TMT is a widely used neuropsychological paper-pencil test consisting of two parts, TMT A and TMT B (57). Both tasks captured the components of perceptual tracking as well as the processing speed. The TMT B also captured more complex executive functions such as alternating sequencing and set shifting (as a part of cognitive flexibility) and divided attention (57–59). In TMT A, circles with the numbers "1" to "25" must be connected as quickly as possible in ascending order. In TMT B, circles with the numbers "1" to "13" and the letters "A" to "L" must be connected alternately, again as quickly as possible. For both tasks, a test run with eight items was carried out in advance. The required time to complete each task was measured in seconds. Errors were corrected in a standardized way while time continued to run (57). In this study, the difference index ΔTMT (TMT B minus TMT A) was calculated. Several authors recommend using this derived score as it corrects for processing speed and therefore provides a better index of EF (11, 20, 59–62).

Straight Walking Performance

Walking Conditions

For the gait analysis, the participants were asked to walk a marked straight distance of 20 m four times. A different condition was set for each walk with increasing motor difficulty. During all four walks, participants wore an IMU system. It was documented whether patients completed the task with or without a walking aid. In condition one, *ST normal pace*, the distance was to be covered at a self-selected comfortable gait speed. In condition two, *ST fast pace*, participants were asked to walk as fast as possible without running. In condition three, *DT walking-cognitive*, participants were asked to subtract seven consecutively from a given three-digit number as fast as possible while walking at a fast pace. In condition four, *DT walking-motor*, predetermined boxes on a sheet of paper were to be crossed as quickly as possible with a pen while walking at a fast pace. Condition four was only possible for patients without a walking aid. Walking conditions were performed in the following order if patients had the capacity: ST fast pace, ST normal pace, DT walking-motor, DT walking-cognitive.

IMU System

Velcro straps were used to attach the RehaGait® IMU [Hasomed, Magdeburg, Germany (63)] to the patient's lower back at the level of the fifth lumbar vertebra before the gait assessment. The IMU is CE-certified and includes a triaxial accelerometer (±16 g) and a triaxial gyroscope (±2,000/s). Data were collected at a sampling frequency of 100 Hz and transmitted during the measurement *via* Bluetooth to a tablet with the RehaGait® application modified for the ComOn study in cooperation with the manufacturer.

Extraction and Analysis of Walking Parameters

Walking performance data were analyzed by an algorithm that has been validated for step detection in PD (64). From the raw data, the spatio-temporal parameters, number of steps and gait speed (m/s), double limb support time (DLS, s), mean step time asymmetry (ASYM, s; difference between mean step time difference between both feet), and step time variability (STV, s; square rooted sum of variance of step time for each foot divided by two) were calculated. A linear correction of DLS, ASYM, and STV to normalize for gait speed (to 1 m/s) was applied, as recommended in previous biomechanical studies on sensor-based walking parameters (41).

For the two DT conditions, the DTCs for walking ($DTC_{Walking}$) were calculated for each of the parameters according to the formula $DTC = (ST - DT)/ST \times 100$ (65), with positive DTC indicating deterioration of gait performance under DT compared to ST (31).

TABLE 2 | Multiple linear regression models and Bayes factors for significant walking parameters and their $DTC_{Walking}$.

	Gait Speed					**STV**					**Number of steps**				
						ST normal pace ($n = 74$)									
Walking parameters	**$R^2_{adj.}$**	**F**	**BF_{10}**	**β**	**p**	**$R^2_{adj.}$**	**F**	**BF_{10}**	**β**	**p**					
	0.24	4.31	0.12[a]		0.002**	0.16	2.55	0.13[a]		0.04*					
Age				−0.12	0.32				−0.12	0.09					
Gender				−0.04	0.71				−0.13	0.25					
MDS-UPDRS III				−0.21	0.06				0.04	0.73					
Walking aid				−0.35	0.004**				−0.25	0.05*					
ΔTMT				0.02	0.89				−0.06	0.63					
						ST fast pace ($n = 60$)									
	$R^2_{adj.}$	**F**	**BF_{10}**	**β**	***p***	***$R^2_{adj.}$***	**F**	**BF_{10}**	**β**	***p***	***$R^2_{adj.}$***	**F**	**BF_{10}**	**β**	***p***
	0.22	3.10	0.14[a]		0.02*	0.18	3.51	0.13[a]		0.008**	0.19	2.60	0.14[a]		0.04*
Age				−0.17	0.21				−0.17	0. 21				0.17	0.22
Gender				0.05	0.69				−0.24	0.06				−0.04	0.75
MDS-UPDRS III				−0.27	0.04*				0.09	0.45				0.25	0.06
Walking aid				−0.27	0.06				−0.30	0.03*				0.24	0.09
ΔTMT				0.05	0.72				−0.02	0.87				−0.04	0.76
$DTC_{Walking-cognitive}$ [%] ($n = 44$)			**STV [%]**												
	$R^2_{adj.}$	**F**	**BF_{10}**	**β**	***p***										
	0.23	3.50	0.18[a]		0.01**										
Age				0.26	0.09										
Gender				0.20	0.16										
MDS-UPDRS III				0.18	0.25										
Walking aid				0.26	0.12										
ΔTMT				0.08	0.58										

[a]*moderate evidence for H0; BF_{10}, Bayes factor as a measure of strength of model evidence; β, standardized regression weights; DT, dual-task; $DTC_{Walking}$, dual-task costs for walking while doing a second task (in percentage, %); F, test statistic from ANOVA used for testing significance of the multiple regression models; MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; m/s, meter per seconds; n, sample size; $p \leq 0.05^{*}$, significant on level of significance $\alpha \leq 0.05$; $p \leq 0.01^{**}$, significant on level of significance $\alpha \leq 0.01$; $R^2_{adj.}$, multiple regression coefficients adjusted for sample size; s, seconds; ST, single task; STV, step time variability; ΔTMT, delta of Trail Making Test (part B minus part A).*

Statistics

To address the question to which extent EF and divided attention are associated with quantitative walking parameters in PD, both multiple linear regression models and Bayesian regression models were calculated in all four walking conditions for each of the five walking parameters (number of steps, gait speed, DLS, ASYM, and STV) as well as their $DTC_{Walking}$ in both DT conditions as outcome variables. Each model included ΔTMT as the predictor and MDS-UPDRS III, the use of a walking aid (except for DT walking-motor), age, and gender as covariates (using the forced entry method). Outliers, defined as ±3SD, were excluded. In detail, ΔTMT scores of two patients and $DTC_{Walking}$ parameters of two patients (one in each of the two DT walking conditions) were excluded (**Table 1**). Model assumption multicollinearity (with variance inflation factor and tolerance), homoscedasticity, linearity and normality of residuals (with Q-Q-Plots), and independence of residuals (with Durbin-Watson) were checked (66). For the multiple linear regression models, the goodness of fit of each overall model using the R^2_{adj} [adjusted for sample size n and multiple predictors using McNemar (66)] and the standardized regression weights β were determined and tested for significance (level of significance $\alpha < 0.05$). *Post-hoc* Spearman's rho (ρ) correlation coefficient was calculated. For each Bayesian regression model, the Bayes factor BF_{10}, as a measure for the strength of evidence in favor of one of two competing scientific theories (here, influence vs. no influence of EF and divided attention on walking performance) provided by the data (67, 68), was estimated using the Bayesian information criterion (BIC, (69). BF_{10} was classified, according to Lee and Wagenmakers (70), as follows: with BF_{10} above ten (for H1, here: EFs are associated with walking parameters) but below 0.03 (for H0, here: EFs are not associated with walking parameters) as "strong evidence" BF_{10} between three and ten (H1), respectively, of 0.10 and 0.03 (H0) as "moderate evidence" BF_{10} between one and three (H1), respectively, of 0.33 and 0.10 as "anecdotal evidence" (for H0), and $BF_{10} = 1$ as no evidence (70). Differences between the four walking conditions were calculated for ΔTMT, MDS-UPDRS III, age (using Kruskal–Wallis H test), and gender [using χ^2 test, (66)]. As an additional explorative analysis, differences in ΔTMT, MDS-UPDRS III, age, and gender between patients with and without walking aid were calculated for the ST normal pace, the ST fast pace, and the DT walking-cognitive conditions [using the Mann–Whitney U test for continuous variables and Fisher's exact test for gender as dichotomous (66)].

Data were preprocessed using MATLAB [version 2020b, (71)] and Python [version 3.9.1., (72)] Statistical analysis was conducted using JASP [version 0.14.1, (73)].

RESULTS

Descriptive Characteristics

Out of the 119 (*n*) patients with PD who participated in the ComOn study and performed the TMT, a total of 74 participants with complete IMU-based data were included for this analysis ($n = 45$ did not perform the 20-m walking tasks due to the lack of capacity or motivation). In this overall group, the mean age was 72 years (SD = 8), 34% ($n = 25$) of participants were women, and the mean period of education was 10 years (SD = 2). Mean disease duration was 10 years (SD = 7), the median Hoehn & Yahr stage was 3 (IQR = 1), mean MDS-UPDRS III was 30 points (SD = 15), and mean LEDD was 748 mg (SD = 371). According to the medical records, cognitive impairment was previously reported in 17.7% of the cohort, of which 8.8% were diagnosed with dementia. The mean MoCA score was 23 points (SD = 3.2) and thus was below the diagnostic cutoff for MCI in PD [26 points, (74)]. The mean score of the DIA-S was three points (SD = 2.3) and thus below the cutoff for suspected depressive mood [≥4 points, (52)], with 23% of the patients showing a depressive mood.

Complete data on IMU-based walking measurement were available from 74 participants for ST normal pace, $n = 60$ for ST fast pace, $n = 45$ for DT walking-cognitive, and $n = 34$ for DT walking-motor. The decrease in sample size is due to the fact that not all subjects were capable of participating in every condition, which can be explained by the increasing demands per condition and the prioritized order of the tasks (e.g., due to reduced physical capacity not necessarily, all subjects who passed the ST normal pace condition could also perform ST fast pace, etc.). In general, over all four walking conditions, participants were comparable with respect to age ($H = 0.72$ (3), $p = 0.87$, **Table 1**), gender ($\chi^2 = 2.13$ (3), $p = 0.55$, **Table 1**), and ΔTMT performance ($H = 2.18$ (3), $p = 0.54$, **Table 1**). A walking aid was used by one-quarter (DT walking-cognitive) to one-third (ST normal pace) of the participants. Dyskinesia occurred during the measurement in 13% (DT walking-cognitive) to 21% (ST normal pace) and had an impact on the MDS-UPDRS III ratings in 0 (DT walking-motor) to 7% (ST normal pace). FOG occurred in 27 (DT walking-motor) to 42% (ST fast pace) of the participants during the MDS-UPDRS III examination. DT walking-motor was only feasible for participants who did not require a walking aid, as the checking box task while walking required the use of both arms. This group also had a lower MDS-UPDRS III score, but there was no significant difference between the walking conditions ($H = 3.84$ (3), $p = 0.28$). **Table 1** provides descriptive characteristics across all four walking conditions.

Concerning descriptive aspects of the walking parameters, the study participants used slightly fewer steps under ST conditions than under DT conditions. Under ST normal pace, the lowest values for mean DLS, mean ASYM, and mean STV were obtained. Under ST fast pace, participants had the lowest mean number of steps, walked the fastest on average, and showed the highest mean STV. Under DT walking-cognitive, they walked the slowest and had the highest mean DLS and mean ASYM (**Figure 1**, **Table 1**).

Under the DT walking-cognitive condition, higher DTCs were found for the number of steps, gait speed, DLS, and STV. For ASYM, DTCs were approximately zero. The highest DTCs were observed in the STV (46.9%). Under the DT walking-motor condition, higher DTCs were found in the parameters such as the number of steps and gait speed. Again, DLS did not show relevant DTC. Both ASYM (by about 40%) and STV (by about 5%) showed negative DTC (**Table 1**).

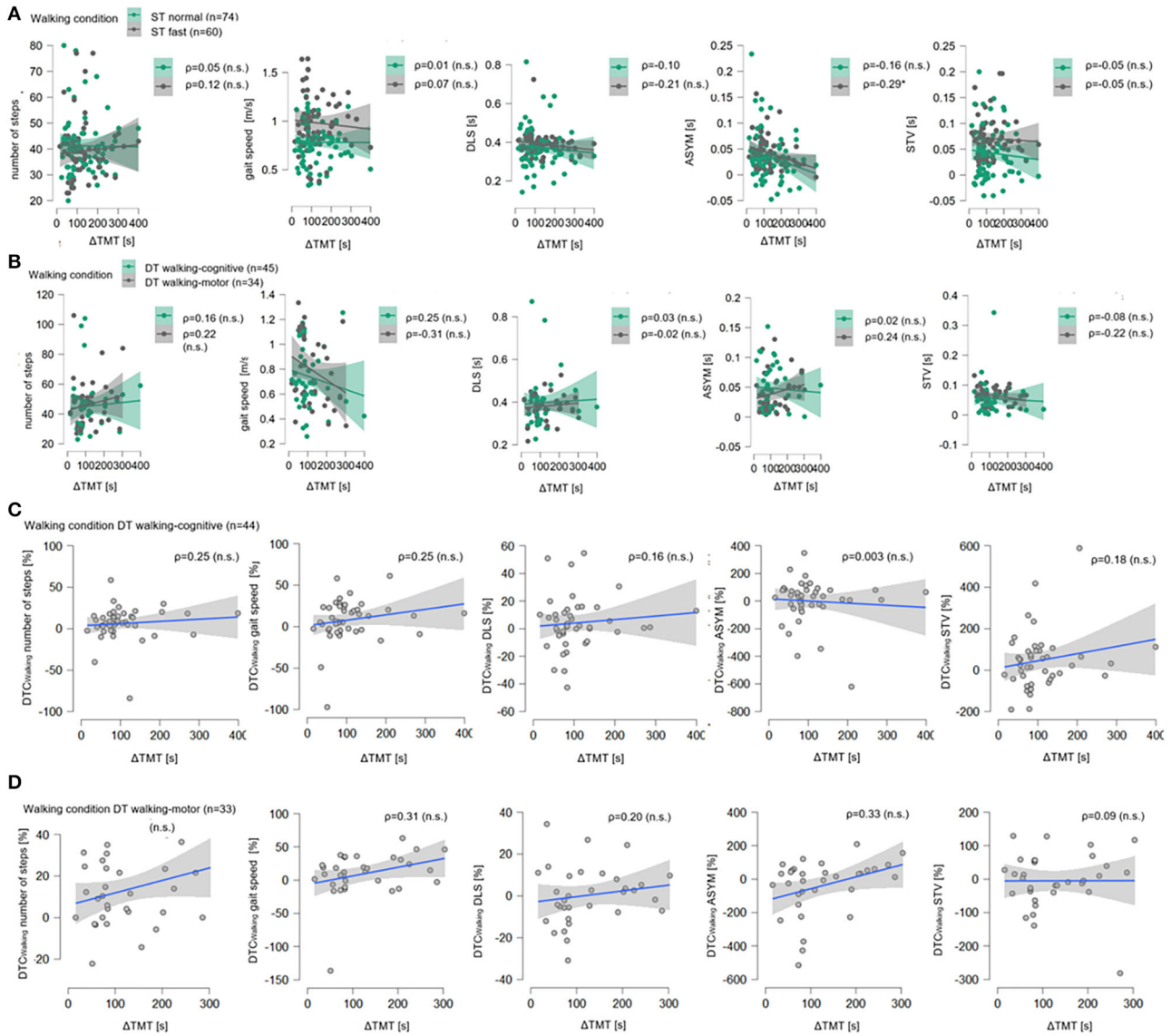

FIGURE 2 | Correlation plots for ΔTMT with all walking parameters. In **(A)**, for the single-task normal pace walking condition (ST Normal, green) and the single-task fast pace condition (ST Fast, gray), all five walking parameters, i.e., number of steps, gait speed (in meter per seconds, m/s), double limb support (DLS), asymmetry (ASYM), and step time variability in seconds (STV, s) are shown on the ordinates, the delta of Trail Making Test (part B minus part A, ΔTMT) is on the abscissas. Sample size N is given as well as Spearman's rank correlation (ρ) between ΔTMT and each walking parameter, significant correlation coefficients are marked with * (level of significance $p \leq 0.05$), non-significant ones are marked with (n.s). For each condition, data points (dots) and regression lines with confidence intervals (lines with surrounding boxes) are shown. In **(B)** the same is shown for the dual-task motor-cognitive walking condition (DT motor-cognitive, green) and the dual-task motor-motor condition (DT motor-motor, gray). In **(C)**, for DT motor-cognitive walking condition the dual-task costs while walking in percentage ($DTC_{Walking}$, %) for all five walking parameters are shown on the ordinates, the delta of Trail Making Test (part B minus part A, ΔTMT) are on the abscissas as well as Spearman's rank correlation (ρ) between ΔTMT and each $DTC_{Walking}$. Data points (gray dots) and regression lines with confidence intervals (blue lines with surrounding gray boxes) are shown for each parameter. The same is shown in **(D)** for the DT motor-motor walking condition.

In the exploratory group comparison, patients who required a walking aid had significantly higher scores in the MDS-UPDRS III than patients without a walking aid in all three walking conditions (ST normal pace: W = 391, $p = 0.02$, ST fast pace: W = 244, $p = 0.005$, DT walking-cognitive: W = 77, $p = 0.004$) as well as lower gait speed (ST normal pace: W = 901, $p = 0.001$, ST fast pace: W = 534.5, $p = 0.006$, DT walking-cognitive: W = 278, $p = 0.02$) and STV (St normal pace: W = 353, $p = 0.004$, ST fast pace: W = 575, $p < 0.001$, DT walking-cognitive: W = 297, $p = 0.02$). Under the DT walking-cognitive condition, patients with walking aid showed higher $DTC_{Walking}$ at ASYM (median = 78.1 vs. median = 7.44, W = 69, $p = 0.003$) and STV (median = 108 vs. median = −3.88, W = 69, $p = 0.003$) than patients without walking aid. Under ST fast

pace condition, patients with walking aid were older (median = 79 vs. median = 74, W = 215, $p = 0.01$) and took more steps (median = 42 vs. median = −36, W = 193.5, $p = 0.005$). There were no significant differences regarding ΔTMT, DLS, and ASYM and in gender distribution between these groups. **Supplementary Table 1** provides detailed information.

Regression Analyses

Single Task Walking Conditions

Under the ST normal pace condition, the overall multiple linear regression model with gait speed as the outcome parameter was significant ($p = 0.002$) with a coefficient of the determination of $R^2_{adj} = 24\%$. Therefore, the overall model, including age, gender, MDS-UPDRS III, walking aid, and ΔTMT, significantly explains 24% of gait speed variance. The effect was mainly driven by the use of a walking aid ($\beta = -0.35$, p=0.004) with a moderately negative *post-hoc* correlation ($\rho = -0.43$, $p = 0.0001$, **Figure 3A**) and, to less extent, by the MDS-UPDRS III ($\beta = -0.21$, $p = 0.06$) with a moderately negative *post-hoc* correlation ($\rho = -0.32$, $p = 0.005$, **Figure 3A**). ΔTMT ($\beta = 0.02$, $p = 0.89$), age ($\beta = -0.12$, $p = 0.32$), and gender ($\beta = 0.04$, $p = 0.71$) had no significant effect in the model. Also, the overall multiple regression model for STV was significant ($p = 0.04$) with R^2adj = 16%. Here, the effect was again mainly driven by the use of a walking aid ($\beta = -0.25$, $p = 0.05$) with a moderately negative *post-hoc* correlation ($\rho = -0.34$, $p = 0.003$, **Figure 3B**) and, to less extent, by age ($\beta = -0.12$, p=0.09) with a low negative *post-hoc* correlation ($\rho = -0.27$, $p = 0.09$, **Figure 3B**). Despite the parametric regression models being significant, the Bayesian regression suggested moderate evidence for H0, indicating no relevant association of ΔTMT with neither gait speed ($BF_{10} = 0.12$) nor STV ($BF_{10} = 0.13$). Similarly, the Bayesian regressions provided moderate evidence for H0 with regard to the number of steps ($BF_{10} = 0.13$), DLS ($BF_{10} = 0.13$), and anecdotal evidence for H0 for ASYM ($BF_{10} = 0.36$). Therefore, individually significant effects were not further interpreted. **Table 2** provides detailed information on the significant multiple regression models.

For the ST fast pace, the multiple linear regression model for gait speed was significant ($p = 0.02$, **Table 2**), with a variance resolution of $R^2_{adj} = 22\%$, driven by the MDS-UPDRS III ($\beta = -0.27$, $p = 0.04$) with a moderately negative *post-hoc* correlation ($\rho = -0.31$, $p = 0.02$, **Figure 3A**) and a negative trend for use of a walking aid ($\beta = -0.27$, $p = 0.06$) with a moderate negative *post-hoc* correlation ($\rho = -0.36$, $p = 0.004$, **Figure 3A**). For STV, the overall model was also significant ($p = 0.008$) with a variance resolution of $R^2_{adj} = 18\%$. Here, the model was driven by the use of a walking aid ($\beta = -0.30$, $p = 0.03$) with lower STV in patients without walking aid compared to patients with a walking aid, with a moderately negative *post-hoc* correlation ($\rho = -0.45$, $p = 0.0003$, **Figure 3B**), and a trend toward significance in the gender parameter with lower STV in women compared to men ($\beta = -0.24$, $p = 0.06$), with a moderately negative *post-hoc* correlation ($\rho = -0.36$, $p = 0.005$, **Figure 3B**). For the number of steps, the overall model was also significant ($p = 0.04$, **Table 2**) with a variance resolution of $R^2_{adj} = 19\%$, with no significant effect of a single predictor but trends toward significance for the use of a walking aid ($\beta = -0.24$, $p = 0.09$), with a moderately negative *post-hoc* correlation ($\rho = -0.37$, $p = 0.004$, **Figure 3C**) and the MDS-UPDRS III ($\beta = -0.25$, $p = 0.06$) with no significant *post-hoc* correlation ($\rho = -0.23$, $p = 0.08$, **Figure 3C**). Similarly, in the Bayesian regressions, there was moderate evidence for H0 for gait speed ($BF_{10} = 0.14$), STV ($BF_{10} = 0.13$), number of steps ($BF_{10} = 0.14$), and DLS. For DLS ($BF_{10} = 0.23$), there were no significant effects for the overall model of the multiple linear regression analyses. There was no significant effect for ΔTMT in any of the models. However, there was a significant negative correlation with ASYM ($\rho = -0.29$, $p = 0.03$, refer to **Figure 2A**), but Bayesian Regression again indicated anecdotal evidence for H0 for ASYM ($BF_{10} = 0.40$, no relevant association with gait speed with the ΔTMT included in the model).

Dual-Task Walking Conditions

For both DT conditions, there were no significant effects in any of the multiple linear regression models. There was no significant effect for ΔTMT in any of the models (**Figure 2B**). In the Bayesian regressions, there was moderate evidence for H0 under DT walking-cognitive for all walking parameters (BF_{10} between 0.15 and 0.19). The same was true for the multiple linear regression and Bayesian regression models, including ΔTMT, MDS-UPDRS III, age, and gender, but not for the use of a walking aid under DT walking-motor for the number of steps ($BF_{10} = 0.19$), gait speed ($BF_{10} = 0.19$), and STV ($BF_{10} = 0.26$). For ASYM ($BF_{10} = 0.37$) and DBL ($BF_{10} = 0.36$), however, there was again anecdotal evidence for H0.

Dual-Task Costs

With the cognitive task added, the overall multiple linear regression model was significant for $DTC_{Walking}$ of STV ($p = 0.01$, **Table 2**) with a resolved variance of $R^2_{adj} = 23\%$, driven by a trend for age ($\beta = 0.26$, $p = 0.09$) with a significant moderately positive *post-hoc* correlation ($\rho = 0.32$, $p = 0.04$, **Figure 3D**). There were no further significant results for $DTC_{Walking}$ of any other walking parameter.

With the motor task added, there were no significant results for $DTC_{Walking}$ in the multiple linear regression models. Under both DT walking conditions, ΔTMT did not show a significant association with $DTC_{Walking}$ in any of the regression models or significant correlations (**Figure 2D**). In the Bayesian regression, there was moderate evidence for H0 for all $DTC_{Walking}$ under DT walking-cognitive conditions (BF_{10} between 0.16 and 0.31) as well as for all $DTC_{Walking}$ of all walking parameters except ASYM (where there was again anecdotal evidence for H0, $BF_{10} = 0.83$) under DT walking-motor condition (BF_{10} between 0.19 and 0.26).

Figure 2 illustrates the results using correlation plots for all walking parameters with the ΔTMT for both ST conditions (A) and DT conditions (B) as well as for all $DTC_{Walking}$ under both DT conditions [(C), (D)]. As for the walking parameters, the flat slopes of the regression lines and the wide dispersion of the data points suggest a lack of linear associations between ΔTMT and any of the walking parameters in all four conditions or the $DTC_{Walking}$ in both

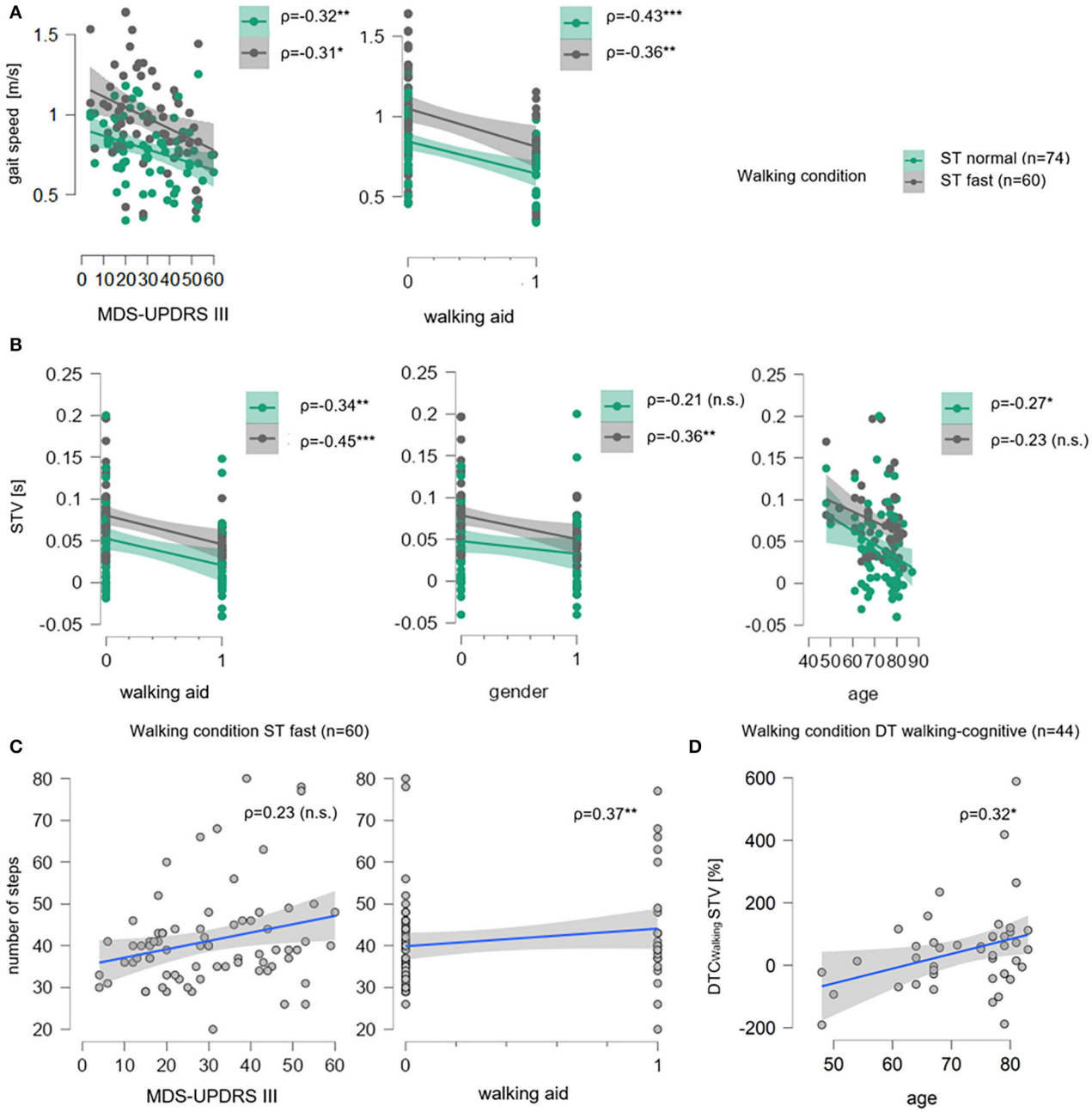

FIGURE 3 | Correlation plots for significant multiple linear regression models for gait speed, STV, number of steps and $DTC_{Walking}$ for STV. In **(A)**, for single task normal pace walking condition (ST Normal, green) and single-task fast pace condition (ST Fast, gray), gait speed (in meter per seconds, m/s) is shown on the ordinates, the total score of the Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) and walking aid (0 = "no walking aid," 1 = "walking aid") are on the abscissas. Sample size n is given as well as Spearman's rank correlation (ρ) between gait speed and each parameter. For each condition, data points (dots) and regression lines with confidence intervals (lines with surrounding boxes) are shown, and significant correlation coefficients are marked with * (level of significance $p \leq 0.05$), ** (level of significance $p \leq 0.01$), and *** (level of significance $p \leq 0.001$), non-significant ones are marked with (n.s.). In **(B)**, the same is shown for step time variability (STV in seconds, s) on the ordinates, and walking aid, gender (0= "men," 1= "women"), and age on the abscissas. In **(C)** for ST fast pace number of steps is shown on the ordinates, MDS-UPDRS III and walking aid are on the abscissas. Here, data points (gray dots) and regression lines with confidence intervals (blue lines with surrounding gray boxes) are given for each parameter. In **(D)**, the same is shown for DT walking-cognitive walking condition for dual-task costs while walking in percentage ($DTC_{Walking}$, %) of STV on the ordinate and age on the abscissa.

DT conditions. *Post-hoc* Spearman's ρ correlation coefficients were also reported. Other than the abovementioned low negative correlation with ASYM under ST fast pace, there were no significant correlations to be found between the ΔTMT and any of the other walking parameters nor their $DTC_{Walking}$.

Figure 3 illustrates the effects of the MDS-UPDRS III total score and the use of a walking aid on gait speed (A) and on STV (B) in the multiple linear regression models using correlations plots for both ST conditions. The slope of the regression degrees and the condensed location of the data points indicate a linear relationship between gait speed and both predictors. The trends of the MDS-UPDRS III total score and the use of a walking aid on a number of steps are similarly seen (C) as well as the age trend on $DTC_{Walking}$ of STV under DT walking-cognitive condition (D).

DISCUSSION

The aim of this study was to investigate to which extent EF and divided attention (measured by ΔTMT performance) are related to specific aspects of walking performance in acutely hospitalized participants with advanced PD under ST and DT walking conditions. To our best knowledge, this is the first study to analyze several IMU-based spatio-temporal walking parameters and their DTC in this vulnerable cohort. Other studies either focused on single walking parameters (14), excluded patients with advanced PD and cognitive impairment (14, 22, 33, 34, 38), used different statistical methods [e.g., only correlation analyses (40)], or calculated group comparisons for ST and DT conditions (35), which addresses different scientific questions. Our results suggest that, especially, the severity of motor symptoms, the use of a walking aid, age, and gender have a relevant influence on walking performance in these patients. Concerning specific walking parameters, especially, gait speed and STV were significantly influenced, mainly under ST conditions. Furthermore, with an added cognitive task, increasing $DTC_{Walking}$ of STV was also significantly influenced. Surprisingly, EF and divided attention do not seem to play a significant role.

Although some previous studies were able to reveal correlative and predictive relationships between EF and walking parameters, in this study, TMT performance has no significant predictor of specific spatio-temporal walking parameters, neither under ST nor under DT conditions. In one study that compared moderately affected patients with PD and healthy controls under ST and various DT walking conditions, EF performance was correlated significantly with gait variability (15). The authors concluded that gait variability and rhythmicity represent automated processes in healthy older adults but are more attention-demanding for patients with PD in the context of EF deficits in complex walking situations. In addition, studies have shown that different walking performance factors, such as spatio-temporal control, postural control, and variability, underlie different mechanisms that may also be differently affected by EF deficits in PD (18). For example, there is evidence that gait speed and stride length correlate positively with cognitive processing speed, whereas step width variability correlates positively with EF and attentional functions [as a calculated factor out of several cognitive tasks, (34)]. Also, patients with PD with poorer EF showed higher DTC, with EF accounting for 5% of the total DTC for gait speed and being identified as the best predictor of DTC (14), along with motor symptoms. However, compared with the results presented here, the authors could not uncover a significant relationship among EF, divided attention, and gait speed in any of the walking conditions. EFs were assessed with a different paradigm than the TMT and the walking distance was shorter, which would explain the different results in our study. In another study of advanced patients with PD (suffering from motor fluctuations) using comparable walking conditions and secondary tasks to this study, EF performance (measured by ΔTMT) was identified as a relevant predictor of DTC of gait speed (38). However, there were also differences in the methodology and characteristics of the subjects, which would explain the different results in our study. The walking distance was also four times longer than usual in our study and DTCs were calculated differently. Furthermore, participants were on average 8 years younger than the participants reported here, showed less severe motor symptoms (mean MDS-UPDRS III total score was 11 points lower), did not use a walking aid, and did not suffer from clinically relevant cognitive impairment. Our results match with the findings of another study on patients with advanced PD without cognitive impairment (40). The duration of a 3 m Timed-Up and Go Test (TUG) and EF (also measured by the TMT) was correlated moderately under both ST and DT, but TMT performance was not a significant predictor. This data and our findings suggest that performance in EF and divided attention tasks may not necessarily be linked linearly to common spatio-temporal walking parameters, such as gait speed, of these patients. Rather, the severity of PD-specific motor symptoms seems true to inflict the walking performance in this and other PD cohorts. Specifically, under ST, the increase in motor symptoms explains a decrease in spatio-temporal walking parameters, e.g., gait speed, which is also consistent with previous studies (14, 75). Moreover, our results suggest that patients with a walking aid are more affected by the underlying disease. Hence, being in need of a walking aid, which can be seen as an indicator of vulnerability, is another relevant factor with regard to a better understanding of deficits in walking performance in patients with advanced PD. Therefore, these factors should be prioritized regarding the diagnostics and treatment of walking performance deficits in an acute neurogeriatric setting.

Nevertheless, our results also provide evidence that cognitive aspects should not be disregarded in this vulnerable cohort. This may be particularly relevant for patients with dementia. Consistent with the literature, the results shown here indicate that patients with advanced PD show partly high costs in spatio-temporal walking parameters in situations where an additional demand is placed on them (14, 38). Depending on the secondary task type (convergent vs. divergent, i.e., walking-cognitive, respectively walking-motor) and motor difficulty, the costs vary (38). In the study presented here, DTCs are most pronounced in STV. Patients in both divergent (walking-cognitive) and convergent (walking-motor) DT conditions exhibited increased $DTC_{Walking}$ for the number of steps and gait speed but not necessarily for DLS, STV, and ASYM. These findings fit with a previous study showing that, during walking under DT, patients with PD exhibited reduced gait speed and stride frequency compared to healthy controls (22). Interestingly, for the number of steps and gait speed, $DTC_{Walking}$ tends to be higher in the convergent condition. This suggests that accomplishing another

motor task while walking might require a higher level of brain capacity in similar areas and thus be more demanding on speed than an additional divergent task. In contrast to that, the highest $DTC_{Walking}$ was found for STV (47%) in the divergent condition. For $DTC_{Walking}$ of STV, the overall model explained about 23% of the variance. This suggests that, in this cohort, step time variability decreases when older patients with advanced PD are demanded to split attention between walking and a demanding cognitive task. This is also in line with a previous study (15), in which it was detected that gait variability was impaired under DT only in the PD group. Together, this suggests that gait variability needs to be brought into clinical focus as a diagnostic parameter, especially when assessing the ability to cope with more complex walking situations. This is particularly relevant given that increased STV is associated with falls in patients with PD (4, 8). Therefore, these patients should avoid those situations. This also can result in possible new implications for multimodal therapeutic interventions with regard to the trainability of STV under DT walking-cognitive condition. Interestingly, ASYM proved to be 40% better under DT than under ST in the presence of an additional convergent (i.e., predominantly motor) task. A possible explanation could lie in the specific execution of the motor task using a clipboard. The carrying of the clipboard and the demanded visual focus on the clipboard while checking boxes during walking could contribute to the compensation in the asymmetric walking performance. In addition, checking boxes themselves, as an external rhythm generator, could support step time symmetry. However, this requires further investigation on the underlying pathophysiological mechanisms. Nonetheless, if this is true, it might be relevant with regard to clinical diagnostics as well as the design of multimodal interventions, where this specific kind of additional task could be promising in the training of symmetrical walking. In addition, for the DT walking-motor condition, only patients without walking aid could be considered by definition. This makes comparability with the other three walking conditions (which included also patients with walking aids) difficult. Future studies should further focus on this aspect, using other secondary motor tasks that can also be performed with a walking aid. However, we believe that our study provides new insight regarding important factors influencing walking performance in acutely hospitalized patients with advanced PD. As so far there has been a lack of knowledge regarding this cohort that deserves special attention due to its vulnerability, our results contribute to the optimization of diagnostics and treatment in the neurogeriatric setting.

Limitations

First, the influence of acute factors (e.g., infections, worsening of PD or other symptoms, and recent fall events) on the overall condition of the patients cannot be completely ignored. However, we argue that, as this group of patients requires special attention in treatment due to their health condition, a specific investigation of this cohort is justified. Second, the number of participants decreased successively with increasing the motoric task difficulty. Therefore, data of more severely affected patients are not included in the more complex gait tasks. Furthermore, randomization of the tasks was not possible for reasons of feasibility and to reduce errors in performance, as they were integrated into a comprehensive movement protocol [more detailed information provides (42)]. The decrease in the number of subjects in successful task performance with higher cognitive and motor complexity can be taken as an additional indication that these demands, as required in everyday life, can be increasingly poorly mastered by patients with advanced PD. Third, the tasks were adapted to the individual coping ability (with or without a walking aid) of the patients. This was done with the rationale of realistically representing a neurogeriatric PD cohort and achieving the most meaningful sample size possible. Fourth, patients were tested during the "ON" phase to collect data on the patients' best possible condition. Therefore, we cannot draw any conclusions regarding the un-medicated ("OFF") status. Fifth, cognitive flexibility and divided attention were assessed with a previously established paradigm (TMT), which, however, only measures specific aspects of EF and attentional processes. It was selected because the purpose of the study was to detect associations using clinically established, well-validated (refer to Method section) and economically feasible methods. Sixth, due to the small sample size of this pilot, a more granular analysis of the severity of dyskinesia, the influence of freezing of gait or walking aids was not possible. Future studies with larger cohorts should focus on these aspects specifically for patients with advanced PD. Finally, our sample did not include healthy controls nor age-matched in-patients with other diseases as controls, which would allow more direct conclusions regarding pathology-specific aspects and to correct for effects of age and acute illness.

CONCLUSION

To our knowledge, this is the first study to predict spatio-temporal walking parameters in acutely hospitalized patients with advanced PD. Therefore, these results provide new insights regarding walking performances in situations where an additional demand is placed on. A relevant predictive value of EF and divided attention for deficits in walking performance cannot be inferred from our study. However, our analyses provide evidence that more severe motor symptoms, being in need of a walking aid (and age), are associated with a reduced gait speed and higher STV, especially under ST conditions as well as with increasing $DTC_{Walking}$ in STV when an additional cognitive task requires to split attention. Thus, for clinical diagnostics and treatment in an acute neurogeriatric setting, it remains essential to consider clinical symptoms. Furthermore, potential cognitive influences under DT walking situations, which can pose limitations and hazards (such as increased falls due to distraction), also need to be taken into consideration when evaluating new assessment methods for walking performances such as IMU data. Future studies should investigate to what extent deficits in EF and attentional functions may influence the benefit of therapeutic interventions for patients with PD in acute need of hospital care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commitee of the Medical Faculty of the Christian-Albrechts-University of Kiel. The patients/participants and, if necessary, their legal representative or assistance provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG and WM made substantial contributions to the conception and design of all parts of the study, trained and supervised the examiners, were responsible for acquisition, analysis, and interpretation of data and in drafting as well as revising the manuscript. JW, CH, MH, JK, and ME made substantial contributions to the conception and design and training and supervision of the examiners. NB and AS made substantial contributions to the conception and design, analysis, and interpretation of the data. CM together with JG, JW, CH, and JK was responsible for the implementation of the database and organization of data. MH, ME, JK, AA, CS, and JH made substantial contributions to the conception and design regarding clinical data for their involved Department of Neurology in Kiel (Germany). All authors revised the manuscript critically for important intellectual content, given their final approval of the version to be published, and has participated sufficiently in the work and takes public responsibility for appropriate portions of the content and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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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.2022.852725/full#supplementary-material

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Single- and dual-task gait performance and their diagnostic value in early-stage Parkinson's disease

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Background: Gait parameters are considered potential diagnostic markers of Parkinson's disease (PD). We aimed to 1) assess the gait impairment in early-stage PD and its related factors in the single-task (ST) and dual-task (DT) walking tests and 2) evaluate and compare the diagnostic value of gait parameters for early-stage PD under ST and DT conditions.

Methods: A total of 97 early-stage PD patients and 41 healthy controls (HC) were enrolled at Hwa Mei hospital. Gait parameters were gathered and compared between the two groups in the ST and DT walking test, controlling for covariates. Utilizing the receiver operating characteristic curve, diagnostic parameters were investigated.

Results: In the ST walking test, significantly altered gait patterns could be observed in early-stage PD patients in all domains of gait, except for asymmetry ($P < 0.05$). Compared to the ST walking test, the early-stage PD group performed poorly in the DT walking test in the pace, rhythm, variability and postural control domain ($P < 0.05$). Older, heavier subjects, as well as those with lower height, lower level of education and lower gait velocity, were found to have a poorer gait performance ($P < 0.05$). Stride length (AUC = 0.823, sensitivity, 68.0%; specificity, 85.4%; $P < 0.001$) and heel strike angle (AUC = 0.796, sensitivity, 71.1%; specificity, 80.5%; $P < 0.001$) could distinguish early-stage PD patients from HCs with moderate accuracy, independent of covariates. The diagnostic accuracy of gait parameters under ST conditions were statistically noninferior to those under DT conditions($P>0.05$). Combining all gait parameters with diagnostic values under ST and DT walking test, the predictive power significantly increased with an AUC of 0.924 (sensitivity, 85.4%; specificity, 92.7%; $P < 0.001$).

Conclusion: Gait patterns altered in patients with early-stage PD but the gait symmetry remained preserved. Stride length and heel strike angle were the two most prominent gait parameters of altered gait in early-stage of PD that could serve as diagnostic markers of early-stage PD. Our findings are helpful to understand the gait pattern of early-stage PD and its related factors and can be conducive to the development of new diagnostic tools for early-stage PD.

KEYWORDS

gait analysis, dual task, wearable sensors, Parkinson's disease, diagnosis

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder and represents a raising cause of disability worldwide and a growing burden on society (1). PD is characterized by bradykinesia, rigidity, and tremor; as the disease progresses, these symptoms worsen and result in severe disability. Therefore, it is crucial to diagnose PD as soon as possible in order to improve its clinical management and attempt to slow down its progression. Currently, the diagnosis of PD is primarily based on clinical evaluation. However, the limited accuracy and low repeatability of clinical evaluation make the early diagnosis of PD challenging, thereby increasing direct and indirect medical costs (2). New imaging examinations, such as positron emission tomography/computed tomography, can be used for the early diagnosis of PD but due to the radiation exposure risk, they are not generally applicable (3). In the past decade, numerous candidate biomarkers for the diagnosis of PD have been identified but most of them are limited in clinical practice due to their low accuracy (4). Consequently, it is crucial to develop safe, reliable, and effective clinical diagnostic markers to improve the clinical management of PD (5).

Gait impairment is one of the primary motor symptoms of PD and it will worsen as the disease progresses, even leading to falls and subsequent disability (6). In prodromal PD, studies have indicated that the nuclei and fibers involved in postural gait regulation could be impaired (7). Previous studies have suggested subtle changes in gait could be detected in prodromal PD, especially in rapid eye movement sleep behavior disorder (8–10). In addition, a previous study demonstrated that quantitative gait alterations could be observed ∼4 years before PD diagnosis, indicating that certain gait parameters have the potential to serve as early diagnostic markers of PD (11). Mild gait disorders, such as reduced gait velocity, stride length, arm swing amplitude, greater interlimb asymmetry, and gait variability, may be one of the earliest indicators of PD (12–14). In early-stage PD, slower gait velocity and shorter stride length are indicative of bradykinesia, rigidity, and diminished motion range (13). Reduced heel height is associated with a dragging gait in PD patients (15). The greater variability and asymmetry of gait, reflect gait instability and the unilateral onset of PD (13, 16). In addition, an increasing number of studies have implemented the gait paradigm of PD patients under dual-task (DT), in which subjects were required to perform a cognitive task while walking (17–20). In DT walking test, when additional cognitive resources are mobilized for gait planning and management, PD patients can exhibit more severe gait impairment (17, 18, 21). These studies suggest that the DT gait test widens the gap between PD and healthy populations, indicating that it may be a viable method for investigating gait perturbations in PD and detecting early-stage PD.

Clinically, it can be difficult to observe these subtle gait changes with the naked eye, and traditional Gait Analysis requires large equipment that is not always available (13). With the development of technology, new gait analysis tools based on inertial sensors enable the quantitative detection of mild gait changes in PD patients and reduce evaluator discrepancies (22). The quantitative gait analysis can therefore be implemented in clinical practice and may contribute to the early diagnosis of PD (11). However, previous studies also have some limitations. First, though numerous spatiotemporal and dynamic characteristics have been studied in PD patients, the gait characteristics vary with no consistency across studies, the lack of control over covariates makes it difficult to compare gait parameters between studies, and it is still unclear which of the many gait parameters is best for the early diagnosis of PD (13, 23–26). To solve these problems, Lord et al. have proposed a structured approach to the measurement of gait in PD to standardize the study's quality, and the spatiotemporal gait characteristics of PD have been divided into five modal domains: pace, rhythm, variability, asymmetry, and postural control (23). Studies using structured gait measurement and controlling for covariates are needed to increase the comparability of different studies and explore diagnostic gait markers for early-stage PD. Second, most of the previous studies have focused on spatiotemporal gait parameters, while few studies have analyzed kinematic parameters in PD patients and the results are controversial in the limited studies (12, 27–29). Further studies validating changes in kinematic gait parameters in early-stage PD are needed. Third, it is unclear whether walking under DT conditions has a negative effect on kinematic parameters other than spatiotemporal gait parameters (30). Establishing the effect of DT on various gait parameters and their associated factors may aid in identifying risks associated with DT. Besides, though patients with early-stage PD present a more impaired gait pattern in the DT gait test, rare studies have investigated the advantage of using the DT walking test to diagnose early-stage PD (13).

Consequently, this study aims to: (1) evaluate the potential influences of confounders on standard measured gait parameters; (2) compare the gait performance between early-stage PD patients and healthy adults in a single task (ST) and DT walking test, controlling for covariates; and (3) evaluate and compare the diagnostic value of gait parameters for early-stage PD patients under ST and DT condition. Our findings may be helpful to understand the gait pattern of early-stage PD and its related factors and provide a low-cost, feasible, and effective method for early diagnosis of PD, accordingly allowing for early disease intervention.

Materials and methods

Participants

From September 2019 to December 2021, 97 patients with early-stage PD were enrolled at Hwa Mei hospital, University

of Chinese Academy Of Sciences, with the following inclusion criteria: (1) diagnosis of PD according to Movement Disorder Society (MDS) criteria (31); (2) Hoehn and Yahr (H&Y) scale stages 1-2; (3) able to walk independently; (4) stable recent symptoms and medication. The following were the criteria for exclusion: (1) other diseases that may affect gait performance; (2) unable to comply with the doctor's instructions. A total of 41 healthy subjects from the community were enrolled in the healthy control (HC) group. The HC group matched the early-stage PD group in terms of age and gender, and the inclusion criteria were as follows: (1) no history of diseases that could impact gait performance, such as PD, cerebrovascular disease, depression, dementia, vestibular diseases, or orthopedic disease; and (2) able to comply with doctor's instructions.

The research was conducted in accordance with the Helsinki Declaration. All participants voluntarily participated and signed an informed consent form before the study. Hwa Mei hospital and the Chinese Academy of Sciences granted ethical approval for the research (approval number: PJ-NBEY-KY-2020-023-01).

Clinical data collection

All participants' demographic characteristics were collected. The same specialist collected medical data and performed physical examinations on patients with early-stage PD. Part III of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) was employed to assess the severity of motor symptoms. The Berg Balance Scale (BBS) and Mini-Balance Evaluation Systems Test (Mini-BEST) were used to assess balance function and fall risk. The H&Y scale was used to assess the severity of the disease, while the Activity of Daily Living Scale (ADL) was utilized to assess the quality of daily life. The Mini-Mental State Examination (MMSE) was used to assess cognitive function, whereas the Hamilton Depression Rating Scale-24 (HMAD) was used to assess depression. All PD patients were evaluated in the OFF state (the antiparkinsonian medication was stopped for 18 h).

Gait evaluation

Using the JiBuEn® gait analysis system, gait data was collected (32). This system consisted of shoes and modules with Micro-Electro-Mechanical System sensors on the waist, thigh, lower limb, and heel bottom of the shoe, and it transmitted motion data to a computer. The high-order low-pass filter and hexahedral calibration technique are employed in data preprocessing, which reduces high-frequency noise interference and installation errors produced by sensor devices. Moreover, the accumulative errors are also corrected based on the zero-correction algorithm. The final gait parameters are obtained by fusing acceleration data and posture, which is calculated using the quaternary complementary filtering technique. The validation of the JiBuEn® system in measuring gait parameters has been evaluated (33).

All participants were required to complete two walking tests: (1) ST walking test: All participants walked in a straight line on a 10 m footpath at their preferred "natural" gait velocity, and gait parameters were collected during natural walking; (2) DT walking test: All participants walked in a straight line on the same 10 m footpath under DT. They were instructed to perform serial subtraction of 7 beginning with 100 while walking at their usual pace. During DT walking, they were instructed to focus on both tasks. Before the walking tests, all participants received one practice trial for walking under both ST and DT without data collection with the JiBuEn®.

Spatiotemporal gait parameters were determined as follows based on at least 40 steps: gait velocity (GV), stride length (SL), stride time, swing time, and stance time (23). The stance phase was calculated. Toe-off angle (TO) and heel strike angle (HS) were also obtained as kinematic parameters using this system. As reported, HS and TO are associated with postural instability in PD patients; consequently, we categorized them into the postural control domain (34). The variability of the left and right gait parameters was calculated separately and then combined to form the coefficient of variation (CV) (35). We calculated the variability of GV (CV-GV), SL (CV-SL), stride time (CV-stride time), swing time (CV-swing time), stance time (CV-stance time), TO (CV-TO), and HS (CV-HS). Using the asymmetry index (AI), the symmetry of SL (AI-SL), stride time (AI-stride time), swing time (AI-swing time), and stance time (AI-stance time) were evaluated (36).

Statistical analysis

SPSS 26.0 software (IBM, Armonk, NY, USA) was used to analyse the data. The comparison of measured data between groups was evaluated by using the independent *t*-test for normally distributed data expressed as mean differences ± standard deviation (x ± s), and the Mann-Whitney *U* test for non-normally distributed data expressed as medians (interquartile ranges, IQRs). The χ^2 test was used to evaluate the count data. The correction between GV and other gait parameters was analyzed using Spearman's correlation. The correlation values were considered very high (0.90–1.00), high (0.70–0.90), moderate (0.50–0.70), low (0.30–0.50), or negligible (0.00–0.30) (37). The level of significance was set to 0.05. In all analyses including gait parameters, the significance level was adjusted by Benjamini-Hochberg multiple testing correction with a prespecified false discovery rate of 0.05.

The Generalized Linear Mixed Model (GLMM) was used to analyse the data at two levels (level 1: task conditions, intra-individuals; Level 2: subjects, individuals) (38). To fit the model, task conditions (ST and DT) were assigned as repeated variables,

and each gait parameter was used as a dependent variable. The initial model for gait parameters contained the following explanatory variables as fixed effects: grouping (e.g., early-stage PD group and HC group), task status (e.g., ST and DT), grouping * task status, and covariates (age, gender, education levels, height, weight, the score of MMSE and HAMD, with or without GV). Additionally, intercept and task status were regarded as random effects. GLMM was also used to control covariates in the comparison of groups. Using the regression coefficient test, the effects of grouping, task status, clinical parameters, and non-motor symptoms on gait parameters were analyzed.

The receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of gait parameters using the pROC package of R language version 4.0.3 (39). The area under the curve (AUC) was calculated and compared using the bootstrap method with 2,000 iterations. Youden index was used to determine the optimal threshold for predicting early-stage PD. Figures were configured using Graph Pad Prism Software version 8.0.1.

Results

Demographic characteristics

This study included a total of 97 patients with early-stage PD. The mean disease duration of the early-stage PD group was 4.36 ± 4.50 years, the mean score of MDS-UPDRS III was 30.7 ± 14.41, and the median levodopa equivalent daily dose in the early-stage PD group was 309.38 (350) mg. In addition, 41 participants were assigned to the HC group. There were no statistically significant differences in age, gender, height, weight, or education level between the two groups (all $P>0.05$), but the score of MMSE score in the PD group was slightly lower than that of the HC group. In the early-stage PD group, the score of HAMD was higher than in the HC group ($P < 0.05$). Table 1 displays the clinical characteristics of all participants.

TABLE 1 Clinical characteristics of participants.

	PD	HC	*P*
N	97	41	
Age (years)	66.46 ± 9.20	62.49 ± 12.00	0.623
Male (%)	55 (56.70)	17 (41.50)	0.105
Height (cm)	163.00 (10.00)	165.00 (10.00)	0.362
Weight (kg)	62.00 (15.00)	65.00 (12.00)	0.180
Education (years)	6.00 (6.00)	9.00 (3.00)	0.278
MMSE	27.00 (5.00)	28.00 (3.00)	**0.012**
HADM	6.00 (8.00)	3.00 (7.00)	**0.005**
Duration of PD (years)	4.36 ± 4.50		
LEDD (mg)	309.38 (350.00)		
H-Y stage 1 (%)	22 (22.68)		
MDS-UPDRS III	30.70 ± 14.41		
BBS	52.74 ± 5.68		
Mini-BEST	24.57 ± 3.38		
ADL	96.74 ± 8.97		

Values are expressed as n (%), mean ± standard deviation or median (interquartile range). Independent t test, the χ^2 test, or the Mann–Whitney U-test were performed for comparisons.
$P < 0.05$ were considered statistically significant.
Bold values highlight the significant difference.
PD, Parkinson's Disease; HC, healthy control; MMSE, Mini-Mental State Examination; HAMD, Hamilton Depression Rating Scale; LEDD:Levodopa Equivalent Daily Dose; H-Y stage, Hoehn and Yahr stage; MDS-UPDRS III, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part III; BBS, the Berg Balance Scale; Mini-BEST, Mini-Balance Evaluation Systems Test; ADL, Activity of Daily Living Scale.

Influences of confounders on gait performance

In all subjects, SL, stance time, stance phase, TO and HS were strongly correlated with GV in both walking tests ($P <$ s0.001). Stride time, CV-SL, AI-SL, and CV-TO showed a moderate correlation with GV in all walking tests, although only a low or negligible correlation with GV could be observed in other parameters (Supplementary Table 1). After controlling for covariates, GV was significantly correlated with all gait parameters except for AI-GV and AI-stance time ($P < 0.05$, Table 2; Supplementary Table 2).

In patients with early-stage PD, male subjects had a longer SL, a greater CV-GV, CV-ST, CV-stance time, and AI-ST compared to female subjects ($P < 0.05$). In addition, as the education year lengthens, a longer SL, faster GV, bigger TO and HS, shorter ST, smaller AI-GV and AI-SL could be observed ($P < 0.05$). However, the score of MMSE and HAMD only had a weak effect on gait parameters in patients with early-stage PD ($P < 0.05$), as shown in Table 3; Supplementary Table 3.

Gait parameters in DT walking test compared with ST walking test

In the DT walking test, patients with early-stage PD demonstrated significantly impaired pace, rhythm, variability, and postural control domain than in the ST walking test ($P < 0.05$, Figure 1). After controlling for covariates (age, gender, height, weight, levels of education, MMSE scores, HAMD scores, and UPDRS-III scores), all the differences remained significant ($P < 0.05$, Table 3; Supplementary Table 3). However, compared to ST, no significant changes in gait parameters were observed in the HC group under DT conditions ($P > 0.05$, Figure 2).

Gait parameters in the early-stage PD patients compared with healthy controls

In both ST and DT walking tests, patients with early-stage PD exhibited a slower GV, a shorter SL, a bigger stance phase,

TABLE 2 Results of the generalized linear mixed models for each gait parameter controlling for gait velocity.

	Task (ref ST)	Group (ref controls)	Group* Task	GV
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
SL (m)	0.028 (0.007,0.05)	**−0.087 (−0.12,−0.055)**	−0.006 (−0.031,0.019)	**0.634 (0.573,0.696)**
CV-Swing time (%)	−0.071 (−2.444,2.302)	−2.581 (−5.306,0.143)	0.973 (−1.844,3.790)	**−12.748 (−18.210,−7.287)**
Stride time (s)	0.019 (−0.023,0.062)	**−0.148 (−0.199,−0.097)**	0.017 (−0.034,0.067)	**−0.697 (−0.804,−0.590)**
Stance time (s)	0.012 (−0.019,0.043)	**−0.113 (−0.151,−0.075)**	0.012 (−0.024,0.048)	**−0.642 (−0.718,−0.566)**
Swing time (s)	0.007 (−0.004,0.018)	**−0.032 (−0.044,−0.02)**	0.004 (−0.009,0.017)	**−0.065 (−0.091,−0.039)**
Stance phase (%)	−0.066 (−0.221,0.352)	**−0.937 (−1.450,−0.424)**	0.023 (−0.314,0.359)	**−13.645 (−14.571,−12.719)**
CV-GV (%)	−2.48 (−5.45,0.49)	−1.857 (−6.363,2.649)	−0.818 (−4.354,2.717)	**−10.303 (−16.198,−4.408)**
CV-SL (%)	−0.011 (−2.212,2.191)	−0.043 (−1.853,1.767)	−0.442 (−3.070,2.186)	**−11.439 (−14.967,−7.91)**
CV-Stride time (%)	−0.72 (−4.184,2.745)	−4.569 (−8.687,−0.451)	2.267 (−1.850,6.383)	**−12.897 (−20.532,−5.261)**
CV-Stance time (%)	−0.178 (−1.734,1.377)	−1.362 (−3.212,0.489)	0.774 (−1.072,2.621)	**−3.947 (−7.541,−0.352)**
AI-GV (%)	**−5.538 (−8.367,−2.709)**	2.446 (−4.482,9.375)	0.154 (−3.141,3.449)	−4.553 (−15.180,6.075)
AI-Swing time (%)	−2.182 (−7.729,3.365)	−3.828 (−10.705,3.048)	2.895 (−3.683,9.474)	**−22.859 (−36.160,−9.558)**
AI-Stride time (%)	−2.723 (−8.622,3.175)	−8.746 (−15.444,−2.047)	4.271 (−2.741,11.282)	**−13.485 (−26.216,−0.754)**
AI-Stance time (%)	−0.535 (−2.966,1.896)	−1.323 (−4.324,1.677)	0.899 (−1.984,3.782)	−5.762 (−11.604,0.080)
AI-SL (%)	−0.234 (−5.035,4.568)	0.618 (−3.432,4.668)	−1.431 (−7.164,4.302)	**−19.583 (−27.274,−11.892)**
TO (°)	0.64 (−77.569,78.85)	0.023 (−93.867,93.914)	−0.320 (−94.199,93.559)	**22.451 (18.169,26.733)**
HS (°)	0.489 (−0.194,1.173)	**−3.471 (−5.025,−1.917)**	−0.288 (−1.086,0.509)	**20.257 (17.762,22.751)**
CV-TO (%)	−0.193 (−2.791,2.405)	−2.917 (−5.599,−0.236)	0.955 (−2.142,4.053)	**−19.419 (−24.459,−14.378)**
CV-HS (%)	0.399 (−2.499,3.298)	−1.350 (−4.062,1.362)	0.413 (−3.045,3.871)	**−17.390 (−22.639,−12.142)**

The Generalized Linear Mixed Model was used to analyze the effects of group, task, group* task.
The models were controlled by gender, age, height, weight, education level, score of Mini-Mental State Examination and Hamilton Depression Rating Scale, gait velocity.
All of the P-values were corrected using Benjamini–Hochberg multiple testing correction.
P < 0.05 were considered statistically significant and highlighted in bold.
CI, confidence intervals; β, beta; ref, reference; Group*Task: The interaction between group and task; ST, single task; GV, gait velocity; SL, stride length; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index.

a greater AI-SL and CV-SL, a smaller TO and HS, and a greater CV-HS than HCs ($P < 0.05$). After controlling for GV, compared with HC group, a shorter SL, longer stance phase, and smaller HS could be observed in the early-stage PD group in both walking tests, while a smaller swing time only in the ST walking test ($P < 0.05$), as shown in Table 4.

After controlling for covariates (age, gender, height, weight, levels of education, the scores of MMSE and HAMD), some of the differences were no longer statistically significant, including stance phase, CV-SL, AI-SL, and CV-HS in the ST walking test ($P>0.05$). During the DT walking test, only the differences of GV, SL, TO, and HS remained significant after controlling for covariates ($P < 0.05$), as shown in Table 4. The interaction between task status and grouping was statistically significant in HS and TO ($P < 0.05$, Table 5; Supplementary Table 4).

After additional controlling for both covariates and GV, significant differences in SL, stride time, swing time, stance time, and TO could be observed between the early-stage PD group and HC group in all walking tests, while a difference of CV-GV could only be observed between groups in the DT walking test ($P < 0.05$), as shown in Table 4. No interaction between task status and grouping could be observed after further controlling for GV ($P > 0.05$, Table 2; Supplementary Table 2).

Diagnostic value of gait parameters for early-stage PD patients under ST and DT

For all gait parameters with significant differences between the early-stage PD and HC groups, ROC curve analysis was performed to determine their diagnostic utility. Nine gait parameters from the ST walking test and eleven gait parameters from the DT walking test had significant predictive values for early-stage PD ($P < 0.05$, Supplementary Table 5). The AUC value indicated that GV, SL, TO, and HS in both walking tests, and the Stance phase in the DT walking test had a moderate ability to distinguish early-stage PD from HC (AUCs > 0.700, $P < 0.001$) (Supplementary Table 5; Figure 3). At a cut-off of 1.083, the AUC value, sensitivity and specificity of SL were 0.823, 68.0% and 85.4%, respectively, in the ST walking test ($P < 0.001$, Supplementary Table 5; Figure 3). Following HS with an AUC of 0.796 in the ST walking test, at a threshold of 30.025, the

TABLE 3 Influences of clinical features on the gait parameters in early-stage PD group.

	Intercept	Task (ref ST)	Age (y)	Gender (ref female)	Height (cm)	Weight (kg)	Education (y)	HADM	MMSE	MDS–UPDRS III
GV (m/s), β	**1.364**	**−0.112**	**−0.004**	0.030	0.002	−0.003	**0.011**	−0.004	−0.007	**−0.006**
SL (m), β	**1.640**	**−0.048**	**−0.006**	**0.083**	0.002	**−0.003**	**0.009**	−0.002	**−0.010**	**−0.007**
CV-Swing time (%), β	**69.565**	**2.431**	0.076	3.274	**−0.306**	−0.001	−0.127	0.050	−0.062	−0.053
Stride time (s), β	**1.215**	**0.114**	0.001	0.050	−0.001	0.001	−0.006	0.003	−0.001	0.001
Stance time (s), β	0.689	**0.096**	0.001	0.026	−0.001	0.002	**−0.006**	**0.003**	0.001	0.001
Swing time (s), β	**0.466**	**0.018**	−0.001	0.018	0.001	−0.001	−0.001	0.001	−0.001	−0.001
Stance phase (%), β	**55.474**	**1.607**	0.044	−0.878	−0.013	**0.076**	**−0.128**	**0.074**	0.089	**0.058**
CV-GV (%), β	**73.646**	**−2.112**	0.097	**4.187**	−0.242	0.019	−0.319	−0.016	−0.260	0.102
CV-SL (%), β	14.318	0.949	**0.136**	0.989	−0.027	−0.030	−0.178	0.090	0.087	**0.109**
CV-Stride time (%), β	**84.951**	**3.189**	0.143	**6.772**	**−0.405**	−0.034	−0.260	0.044	−0.043	−0.123
CV-Stance time (%), β	**52.311**	**1.104**	0.043	**2.732**	**−0.216**	−0.023	−0.051	0.022	−0.057	**−0.060**
AI-GV (%), β	**177.328**	**−4.540**	0.169	5.986	**−0.833**	0.260	**−1.174**	0.130	−0.304	0.107
AI-Swing time (%), β	**122.038**	3.731	0.256	7.416	**−0.680**	−0.056	−0.525	0.202	0.036	−0.102
AI-Stride time (%), β	**115.241**	3.500	0.318	**11.098**	**−0.690**	−0.052	−0.506	0.123	0.132	−0.152
AI-Stance time (%), β	**55.145**	1.167	0.118	3.418	**−0.291**	−0.056	−0.204	0.080	0.045	−0.051
AI-SL (%), β	33.040	0.985	**0.265**	4.131	−0.239	−0.016	**−0.650**	0.113	0.331	**0.199**
TO (°), β	**99.358**	**−2.214**	**−0.345**	0.719	−0.103	**−0.129**	**0.495**	−0.129	−0.258	**−0.206**
HS (°), β	**87.382**	**−2.087**	**−0.253**	2.848	−0.184	−0.070	**0.275**	−0.107	−0.171	**−0.243**
CV-TO (%), β	11.641	**2.929**	0.116	1.698	−0.014	0.005	−0.193	0.083	−0.022	**0.107**
CV-HS (%), β	32.701	**2.746**	0.132	3.006	−0.109	−0.004	−0.168	0.046	−0.026	**0.094**

The Generalized Linear Mixed Model was used to analyze the influence of clinical features on the gait parameters in early-stage PD group.
P < 0.05 were considered statistically significant and highlighted in bold.
β, beta; ref, reference; ST, single task; GV, gait velocity; SL, stride length; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index; MMSE, Mini-Mental State Examination; HAMD, Hamilton Depression Rating Scale; MDS-UPDRS III, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part III.

sensitivity of HS was 71.1%, whereas the specificity was 80.5% ($P < 0.001$, Supplementary Table 5; Figure 3).

In DT walking test, the AUC value of all gait parameters increased, but not significantly ($P > 0.05$, Figure 3, Supplementary Tables 5, 6). SL demonstrated the most accurate predictive performance in the DT walking test, with an AUC value increased to 0.836, a sensitivity of 78.4%, and a specificity of 78.0% at the cut-off of 1.083, followed by HS with an increased AUC value of 0.830, a sensitivity of 73.2%, and a specificity of 82.9% at the cut-off of 28.700 ($P < 0.001$, Supplementary Table 5; Figure 3).

In addition, we attempted to combine the 9 diagnostic gait parameters in the ST walking test and discovered that the accuracy of prediction increased significantly, with an AUC of 0.869, a sensitivity of 70.8%, and a specificity of 92.7%. Combining the 11 diagnostic gait parameters under DT increased the predicted AUC to 0.909, with a sensitivity of 89.7% and a specificity of 82.9%. After combining all gait parameters with diagnostic values under ST and DT, the predictive power significantly increased compared with the combination of diagnostic parameters under ST, with an AUC increased to 0.924 ($P < 0.001$, Supplementary Tables 5, 6; Figure 3).

After adjusting for GV, 5 gait parameters from the ST walking test and 4 gait parameters from the DT walking test had significant predictive values for early-stage PD ($P < 0.05$, Supplementary Table 5). Interestingly, in both walking tests, after controlling for GV, the predictive power of the combined diagnostic parameters was statistically noninferior to that of the parameters without adjusting for GV ($P > 0.05$, Supplementary Tables 5, 6; Figure 3).

Discussion

This cross-sectional, single-center, observational study aimed to identify gait parameters with a high degree of accuracy for early diagnosis of PD and to comprehend the gait pattern of early-stage PD patients in the ST and DT walking tests. Our results showed that: (1) demographic covariates and the score of HAMD, and GV could impact various gait parameters of PD; (2) In the DT walking test, the early-stage PD group demonstrated impaired pace, rhythm, variability, and postural control domain compared to the ST walking test. (3) SL and HS could distinguish early-stage PD and HC, independent of differences in GV; (4) The diagnostic accuracy of gait parameters increased, but not significantly, under DT condition as compared with those under ST. The diagnostic accuracy of the gait parameters significantly increased when ST and DT walking tests were combined.

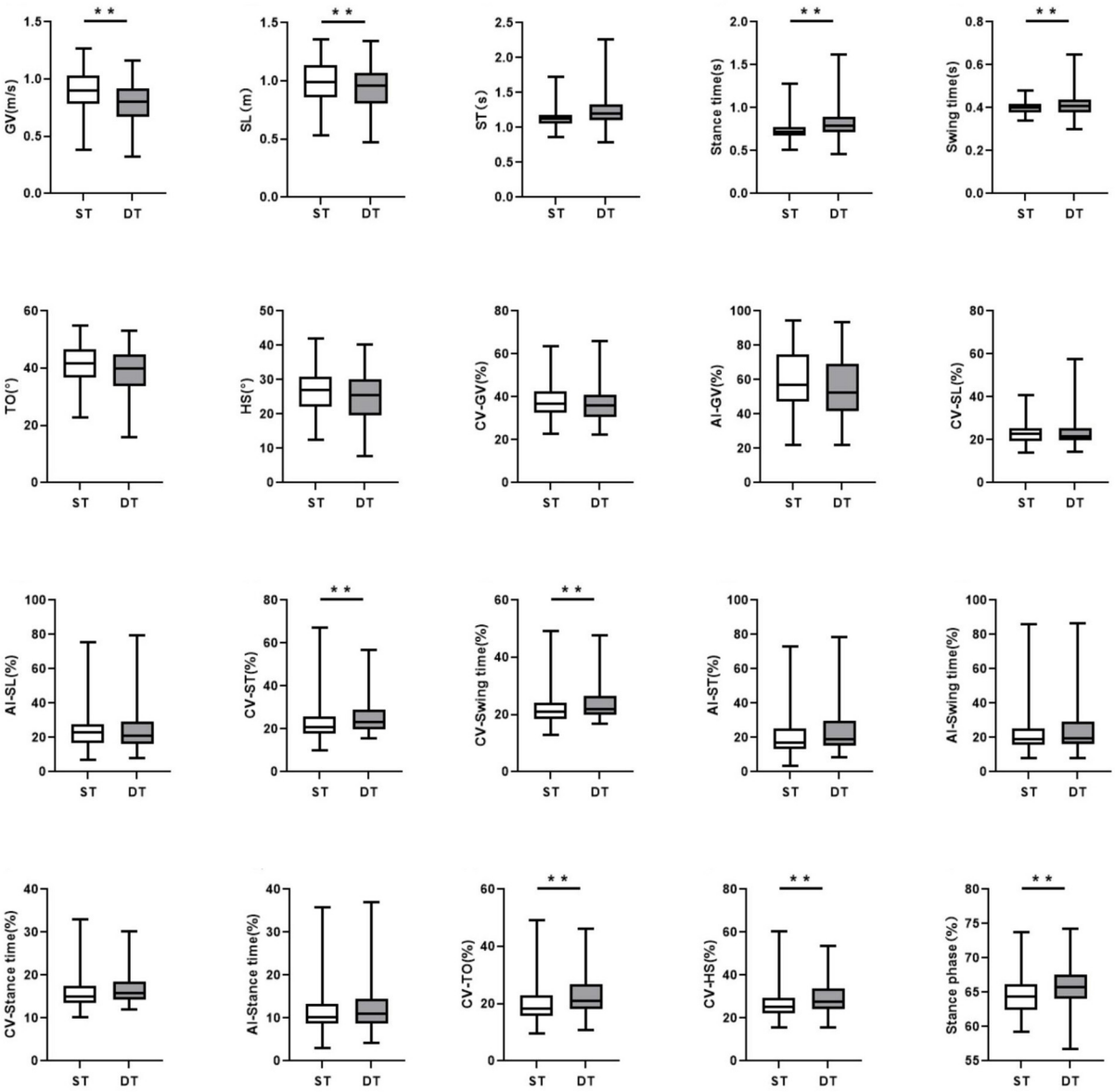

FIGURE 1
The comparisons of gait characteristics of Parkinson's Disease in single task walking and dual task walking. ST, single task; DT, dual task; PD, Parkinson's Disease; HC, healthy control; GV, gait velocity; SL, stride length; ST, stride time; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index. All of the P-values were corrected using Benjamini–Hochberg multiple testing correction. $^{**}p \leq 0.05$.

Influences of GV and confounders on gait performance

A recent systematic review has suggested that the spatiotemporal gait parameters and joint kinematics decreased at slower speeds (24). Particularly, for the older individuals, when they walked slower, the cadence and step length decreased (24). Consequently, the lower spontaneous walking speed of patients with early-stage PD may impact gait parameters, leading to an overestimation of pathological gait impairment (40). In this study, lower GV was highly associated with shorter SL, longer stance time, stride time, stance phase, smaller TO, and HS in all walking tests, in line with previous studies (40–42). A previous study has suggested that in patients with PD, the variability of stride time and swing time were independent of gait speed (43). In line with the previous

TABLE 4 Comparison of gait characteristics of patients with early-stage PD and healthy controls.

	ST					DT				
	HC	PD	*P*	Adj.*P*	Adj.*P'*	HC	PD	*P*	Adj.*P*	Adj.*P'*
Pace										
GV (m/s)	1.06 ± 0.20	0.89 ± 0.19	**<0.001**	**0.005**	**0.005**	0.99 ± 0.19	0.78 ± 0.19	**<0.001**	**<0.001**	**<0.001**
SL (m)	1.19 ± 0.14	0.99 ± 0.18	**<0.001***	**<0.001**	**<0.001**	1.17 ± 0.12	0.93 ± 0.20	**<0.001***	**<0.001**	**<0.001**
CV-Swing time (%)	19.49 (5.36)	20.99 (5.16)	0.558	0.903	**0.155**	20.23 (4.09)	21.98 (6.63)	**0.044**	0.749	0.567
Rhythm										
Stride time (s)	1.11 (0.12)	1.12 (0.13)	0.872	0.114	**<0.001**	1.17 (0.15)	1.20 (0.23)	0.366	0.610	**<0.001**
Stance time (s)	0.70 (0.13)	0.72 (0.11)	0.290	0.255	**<0.001**	0.74 (0.12)	0.79 (0.18)	0.087	0.910	**<0.001**
Swing time (s)	0.42 (0.03)	0.40 (0.04)	**0.004***	**<0.001**	**0.004**	0.42 (0.04)	0.41 (0.06)	0.054	0.740	**<0.001**
Stance phase (%)	62.67 (3.72)	64.32 (3.84)	**0.006***	0.280	**0.006**	63.67 (3.55)	65.71 (3.50)	**<0.001***	0.084	**0.001**
Variability										
CV-GV (%)	37.64 (10.50)	36.63 (9.99)	0.631	0.913	**0.026**	35.38 ± 7.84	36.18 ± 7.31	0.676	0.343	0.381
CV-SL (%)	20.08 ± 4.21	22.96 ± 5.28	**0.005**	0.122	0.496	19.38 (4.82)	21.79 (5.73)	**0.004**	0.640	0.733
CV-stride time (%)	22.95 (11.71)	20.77 (7.95)	0.208	0.508	0.241	22.73 (11.55)	23.37 (9.07)	0.692	0.641	0.347
CV-Stance time (%)	15.01 (3.96)	15.09 (3.87)	0.783	0.877	0.381	15.00 (3.00)	15.89 (4.18)	0.299	0.613	0.733
Asymmetry										
AI-GV (%)	59.80 (33.48)	58.00 (28.20)	0.256	0.662	0.894	53.00 (32.54)	52.54 (27.54)	0.189	0.486	0.804
AI-Swing time (%)	16.67 (13.14)	18.75 (8.54)	0.195	0.951	0.640	16.67 (7.00)	19.51 (13.00)	**0.010**	0.747	0.733
AI-Stride time (%)	20.0 (29.16)	17.19 (12.14)	0.262	0.281	0.175	17.74 (30.07)	19.14 (14.39)	0.530	0.249	0.226
AI-Stance time (%)	10.15 (7.03)	10.29 (4.35)	0.430	0.877	0.567	8.70 (3.58)	10.96 (5.72)	0.053	0.853	0.958
Postural control										
AI-SL (%)	16.28 (9.37)	22.92 (10.98)	**0.004**	0.131	0.638	16.67 (8.02)	21.05 (13.01)	**0.004**	0.613	0.638
TO (°)	45.97 ± 5.76	40.97 ± 7.02	**<0.001**	**0.027**	0.825	44.99 ± 5.57	38.83 ± 7.58	**<0.001**	**0.020**	0.880
HS (°)	34.07 ± 6.05	26.67 ± 6.68	**<0.001***	**<0.001**	**<0.001**	33.09 ± 5.51	24.66 ± 6.73	**<0.001***	**<0.001**	**<0.001**
CV-TO (%)	16.81 (6.01)	18.26 (7.25)	0.085	0.692	**0.383**	17.34 (6.28)	21.02 (8.61)	**0.006**	0.303	0.057
CV-HS (%)	21.63 (7.13)	25.15 (7.51)	**0.007**	0.850	0.733	24.59 (9.59)	27.44 (9.66)	0.010	0.174	0.401

Variables are expressed as mean ± standard deviation or median (interquartile range). Independent t test or the Mann–Whitney U-test were performed for comparisons.
Adj.P, P-value were controlled for gender, age, height, weight, education level, score of Mini-Mental State Examination and Hamilton Depression Rating Scale.
Adj.P', P-value were controlled for gender, age, height, weight, education level, score of Mini-Mental State Examination and Hamilton Depression Rating Scale, GV.
All of the P-values were corrected using Benjamini–Hochberg multiple testing correction. Bold values highlight the significant difference.
*The significant difference after adjusting for GV.
ST, single task; DT, dual task; PD, Parkinson's Disease; HC, healthy control; GV, gait velocity; SL, stride length; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index.

study, the correlation between GV and CV-GV, CV-stride time, and CV-stance time, was low to negligible in this study, indicating the increased gait variability in PD was disease-related, and not simply a consequence of bradykinesia (43). Future research is needed to investigate the interaction of the central structure or function with the variability of gait in early-stage PD.

Non-motor symptoms of PD are reported to be associated with gait disturbances in PD (25, 26). Interestingly, this study suggested that cognitive function didn't have a significant influence on the gait performance of patients with early-stage PD, except for a minor impact on SL, inconsistent with previous studies (25, 44). We analyzed that the early-stage PD patients enrolled in this study were not suffered with severe cognitive impairment, and MMSE might not be sensitive enough to assess the mild cognitive impairment. To be considered, however, there are limitations of the MMSE in detecting attention and executive function responsible for gait performance in PD (45, 46). Future research using more precise assessments, such as extensive neuropsychological tests, is needed. As reported, depression was associated with gait disturbances in PD, including a lower GV and greater variability of stride time (26, 47). However, in this study, after controlling for the score of MDS-UPDRS III, only a mild influence of the HAMD score on stance time and stance phase could be observed in patients with early-stage PD. We attribute it to the fact that the higher score of HAMD was associated with poorer motor symptoms in PD patients (48). In addition, we only enrolled early-stage PD patients, while the majority of these patients did not have depression (31). Future studies

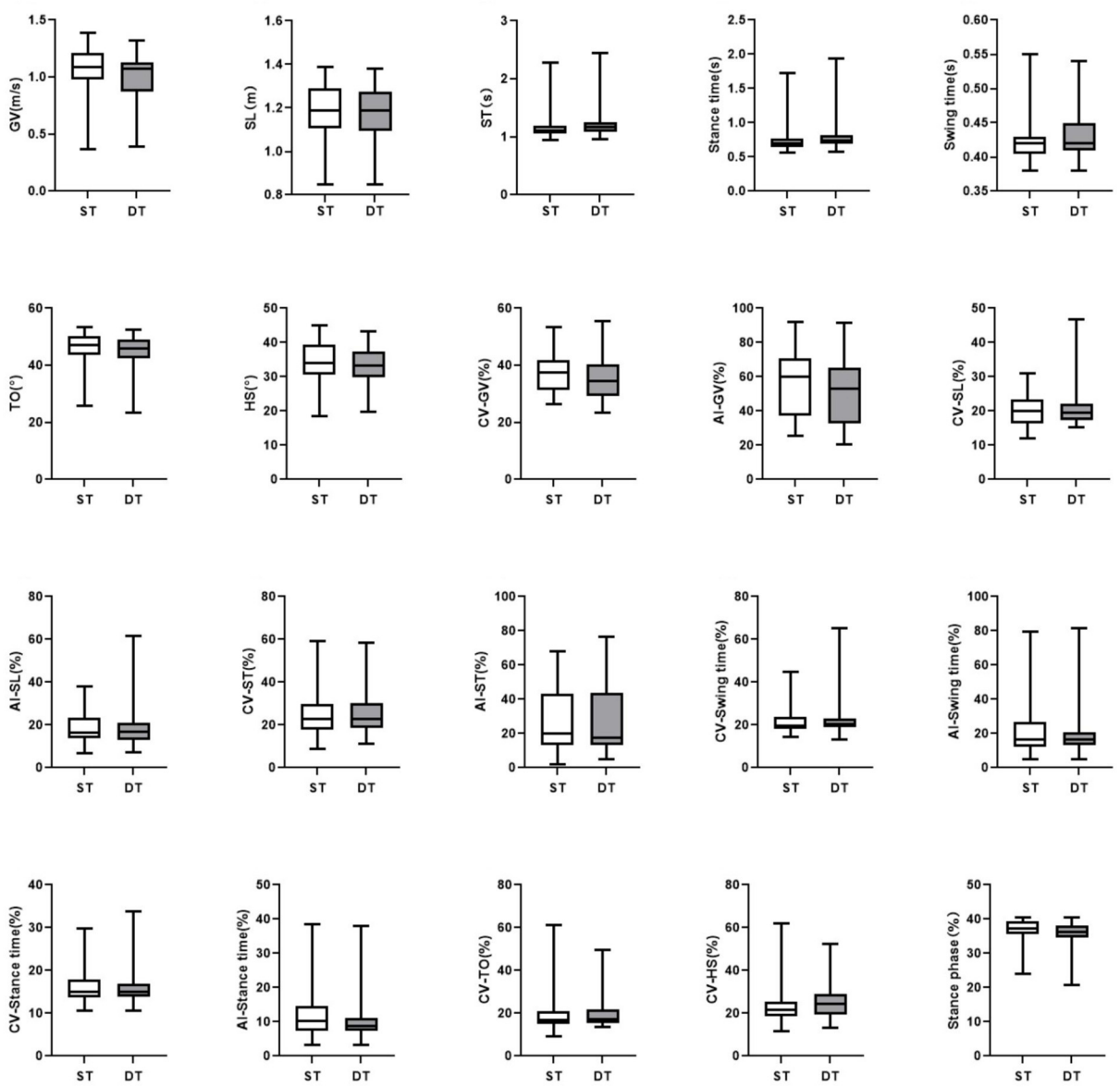

FIGURE 2
The comparisons of gait characteristics of healthy adults in single task walking and dual task walking. ST, single task; DT, dual task; PD, Parkinson's Disease; HC, healthy control; GV, gait velocity; SL, stride length; ST, stride time; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index. All of the P-values were corrected using Benjamini–Hochberg multiple testing correction. $^{**}p \leq 0.05$.

should investigate the relationship between depression, motor symptoms and gait performance.

Consistent with the previous studies, we found demographic factors could impact the gait performance in subjects with early-stage PD, necessitating adjustment for these variables in order to standardize the study's quality and investigate the robust diagnostic markers of PD (49, 50). Among these, weight and education level are controllable variables. A previous study of healthy adults has shown that being overweight had a negative effect on gait performance, as evidenced by a shorter SL, a longer stance time, and a reduction in postural stability (51). Our study also showed that weight had a slight effect on SL and TO. Particularly, this study revealed that the year of education could improve gait performance in the pace, rhythm, asymmetry, and postural control domains, with the GV increasing by 0.011 m/s for each additional year of education. It can be explained by the contribution of education to increased cognitive reserve, which is linked to both milder motor deficits and cognitive impairment (52, 53). Controllable variables, such as weight and education, should be investigated in greater depth in the future and can

TABLE 5 Results from the generalized linear mixed models for each gait parameter not controlling for gait velocity.

	Intercept	Task (ref ST)	Group (ref controls)	Group*Task
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
GV (m/s)	**1.678 (0.686, 2.671)**	**−0.072 (−0.107, −0.037)**	**−0.130 (−0.200, −0.060)**	−0.039 (−0.081, 0.003)
SL (m)	**1.540 (0.665, 2.414)**	−0.017 (−0.044, 0.009)	**−0.171 (−0.231, −0.111)**	−0.031 (−0.062, 0.001)
CV-Swing time (%)	**58.934 (22.532, 95.335)**	0.849 (−1.581, 3.279)	−0.971 (−3.676,1.734)	1.472 (−1.445, 4.389)
Stride time (s)	0.826 (−0.206, 1.857)	**0.070 (0.002, 0.137)**	−0.061 (−0.140,0.017)	0.044 (−0.037,0.125)
Stance time (s)	0.254 (−0.605, 1.112)	**0.058 (0.001, 0.115)**	−0.034 (−0.095, 0.027)	0.038 (−0.031, 0.106)
Swing time (s)	**0.403 (0.223, 0.583)**	0.011 (−0.002,0.025)	**−0.022 (−0.035, −0.010)**	0.006 (−0.010, 0.022)
Stance phase (%)	**48.617 (33.635, 63.600)**	**1.051 (0.476, 1.626)**	0.852 (−0.182,1.885)	0.558 (−0.132, 1.247)
CV-GV (%)	**68.461 (32.271, 104.650)**	**−1.736 (−2.836, −0.636)**	−0.846 (−3.424, 1.733)	−0.414 (−1.735, 0.906)
CV-SL (%)	15.994 (−8.085, 40.074)	0.815 (−1.393, 3.024)	1.380 (−0.569, 3.328)	0.007 (−2.645, 2.658)
CV-Stride time (%)	82.906 (33.096, 132.715)	0.211 (−3.269, 3.692)	−3.073 (−7.132, 0.986)	2.772 (−1.405, 6.950)
CV-Stance time (%)	47.913 (24.733, 71.092)	0.107 (−1.447, 1.661)	−0.930 (−2.730, 0.871)	0.929 (−0.936, 2.794)
AI-GV (%)	**146.536 (48.215, 244.856)**	**−5.209 (−7.920, −2.498)**	2.151 (−4.662, 8.963)	0.332 (−2.922, 3.587)
AI-Swing time (%)	101.891 (13.291, 190.491)	−0.531 (−6.106, 5.043)	−1.058 (−7.878, 5.763)	3.791 (−2.900, 10.483)
AI-Stride time (%)	132.064 (50.680, 213.449)	−1.750 (−7.610, 4.111)	−7.143 (−13.708, −0.577)	4.799 (−2.235, 11.834)
AI-Stance time (%)	51.493 (13.196, 89.789)	−0.119 (−2.532, 2.293)	−0.621 (−3.550, 2.308)	1.125 (−1.771, 4.021)
AI-SL (%)	25.984 (−24.341, 76.310)	1.180 (−3.597, 5.957)	3.176 (−1.024, 7.376)	−0.663 (−6.397, 5.071)
TO (°)	**91.091 (57.836, 124.346)**	−0.980 (−1.974, 0.013)	**−3.144 (−5.464, −0.825)**	**−1.200 (−2.392, −0.008)**
HS (°)	**79.249 (47.393 to 111.105)**	**−0.973 (−1.838 to −0.109)**	**−6.981 (−9.266 to −4.695)**	**−1.035 (−2.066 to −0.003)**
CV-TO (%)	6.194 (−29.564, 41.952)	1.209 (−1.503, 3.922)	−0.730 (−3.596, 2.137)	1.696 (−1.563, 4.956)
CV-HS (%)	24.711 (−11.438, 60.860)	1.655 (−1.283, 4.593)	0.643 (−2.219, 3.506)	1.071 (−2.459, 4.601)

The Generalized Linear Mixed Model was used to analyze the effects of group, task, group* task.
The models were controlled by gender, age, height, weight, education level, score of Mini-Mental State Examination and Hamilton Depression Rating Scale.
All of the P-values were corrected using Benjamini–Hochberg multiple testing correction.
$P < 0.05$ were considered statistically significant and highlighted in bold.
CI, confidence intervals; β, beta; ref, reference; Group*Task: the interaction between group and task; ST, single task; GV, gait velocity; SL, stride length; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index.

be used to design future effective treatments to improve the gait pattern of people with PD (54).

Influences of DT on gait performance of early-stage PD

Under DT, the walking task and the cognitive task compete for the limited information processing resources, resulting in a decline in task performance (55). Consistently with previous studies, patients with early-stage PD in this study demonstrated worse gait performance in the DT walking test in four domains, including pace, rhythm, variability, and postural control, when compared to the ST walking test (17–20). Overall, the influence of DT on the variability domains was significant across the biggest number of variables and the influence was highest compared to other domains in our study, in line with previous research (18). Reduced movement automaticity and increased conscious control can explain the phenomenon (55, 56). In addition, this study added some new findings: in the DT walking test, the variability of TO and HS were greater in the early-stage PD compared with ST, and a smaller TO and HS could be observed after further controlling for covariates. TO and HS are measured at the beginning or end point of the swing phase and can reflect the foot clearance and dragging gait in PD patients (57). A recent work, using a word-color interference test as the cognitive task, also suggested significant reductions in lower limb kinematics during toe-off and heel-strike could be observed in PD patients in DT walking when compared to ST walking (58). However, a previous study using forward digit span as the cognitive task suggested that TO was adversely affected by DT in PD patients, while HS was not (27). We attribute the difference in the results to the different complexity of the cognitive task and the different walking speed in the two studies, which will impact the performance of DT walking (21, 41). In future studies, the effects of DT on PD gait should be investigated in greater depth, which will facilitate the development of DT training to improve DT gait performance in patients with PD (59).

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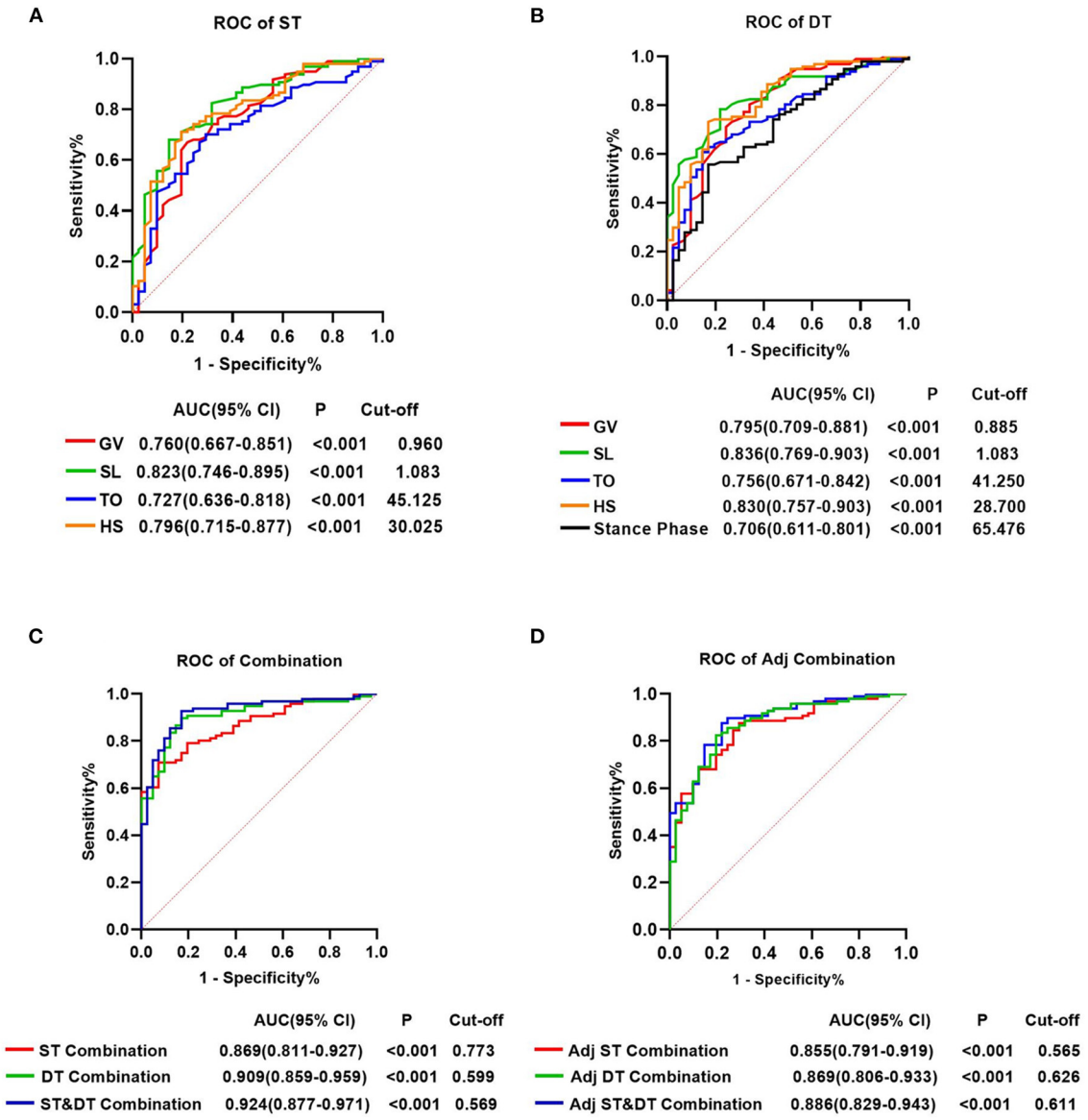

FIGURE 3
Receiver operating characteristics analysis plots for gait parameters distinguishing the individuals with early-stage Parkinson's Disease and healthy controls. **(A)** GV, SL, TO, and HS for identifying patients with PD in the single task walking test. **(B)** GV, SL, TO, HS and stance phase for identifying patients with PD in the single task walking test. **(C)** ST-Combination, receiver operating characteristics (ROC) analysis for the combination of GV, SL, TO, HS, swing time, stance phase, CV-HS, CV-SL, and AI-SL under ST; DT-Combination, DT-Combination, ROC analysis for the combination of GV, SL, TO, HS, stance phase, CV-SL, AI-SL, CV-TO, CV-HS, CV-Swing time and AI-Swing time under DT; ST&DT-Combination, ROC analysis for the combination of all gait parameters with diagnostic values under ST and DT. **(D)** Adj ST-Combination, ROC analysis for the combination of GV, SL, swing time, stance phase, and HS under ST. Adj DT-Combination, ROC analysis for the combination of GV, SL, stance phase, and HS under DT. Adj ST& DT-Combination, ROC analysis for the combination of ST-GV, ST-SL, ST-swing time, ST-stance phase, ST-HS, DT-GV, DT-SL, DT-stance phase, and DT-HS. AUC, area under the curve; CI, confifidence interval; cut-off, cut-off point; ST, single task; DT, dual task; GV, gait velocity; SL, stride length; TO, toe-off angle; HS, heel strike angle; CV, coefficient of variation; AI, asymmetry index.

Gait parameters in the early-stage PD patients compared with healthy controls

In line with previous studies, this study revealed that patients with early-stage PD presented impaired pace, rhythm, variability, and postural control domains of gait in the ST walking test, and an impaired pace, variability, asymmetry, and postural control domain in the DT walking test (12, 14, 19). Among these, gait variability was disease-related, and not significantly associated with GV according to previous research (43). Greater gait variability suggested increased conscious control, decreased automaticity, increased gait instability, and the beginning of impaired gait control (18). Due to the significant influence of DT on the variability of gait, the risk of falls in PD patients under DT should be considered and avoided (60). The regulation of steps is impaired in PD patients, and the asymmetry of gait can be a sensitive measure of gait instability (61). However, this study revealed that the gait symmetry remained preserved in early-stage PD, which is not consistent with previous studies (62, 63). We attribute the disparity to more advanced patients with PD were enrolled in previous studies. Consistent with our hypothesis, previous studies involving patients within H&Y stages 1-2 showed that the gait symmetry was not significantly altered in early-stage PD (12, 64). Future research is needed to examine how asymmetrical gait pattern varies with disease progression, and investigate the relationship between gait symmetry and symmetrical function of the motor cortex, the supplementary motor cortex and dopaminergic circuit in patients with early-stage PD to verify our hypothesis.

After controlling for demographic covariates and scores of MMSE and HAMD, differences in the TO, HS, SL and GV between the early-stage PD and HC groups remained statistically significant in both walking tests. The acquisition of the pace domain of gait is simple, so the GV and SL have been routinely measured in prior research (13). GV and SL reflect the bradykinesia and amplitude control of PD, both of them are dopa-responsiveness and change with disease progression (13). In line with previous studies, we discovered that SL was the most prominent parameter of altered gait in patients with early-stage PD under both ST and DT conditions (12, 13, 64). While lower GV is not unique to patients with PD, many other diseases including Alzheimer's disease can reduce GV, and GV may also be affected by age (13).

In line with previous studies, the HS was smaller in the early-stage PD group than in the HC group during both the ST and DT walking tests in this study (15, 27–29). A previous study suggested in patients with PD, the DT condition increased the attention required for joint flexion, extension, and muscle strength of the ankle (27). This study extended previous findings in showing that the DT gait test widened the gap of HS between the early-stage PD population and the HC, suggesting a more dragging gait when walking under DT conditions. Therefore, even early-stage PD patients should avoid performing complex cognitive tasks while walking on uneven terrain. Particularly, after adjusting for GV, the difference in HS and SL between groups was still significant, indicating these two parameters were disease-related. While in previous studies, the changes in TO in patients with early-stage PD remain controversial (12, 28, 29, 61). We attribute it to the inclusion of PD patients with different spontaneous GV and various stages in these studies (12, 28, 29, 61). In this study, TO was smaller in the early-stage PD group, but after adjusting for GV, the difference was not significant, consistent with previous research enrolling early-stage PD patients (15). This result indicated that altered TO in patients with early-stage PD was due to the slower spontaneous GV. Further research on TO and HS in early-stage PD under different speeds is required to explain the disparity in results.

Diagnostic gait markers of early-stage PD

Recently, a growing number of studies aimed to distinguish PD patients from healthy individuals using gait features (65, 66). However, the classification accuracy for older adults and early-stage PD can be much more difficult than for advanced patients, as the gait impairment in PD patients worsens with progression (6). Based on the ROC curve analysis, 9 parameters in the ST waking test and 11 parameters in the DT walking test had predictive values for early-stage PD, especially SL, GV, TO, and HS had a moderate predictive value (AUC $>$ 0.700). When the predictive parameters under both ST and DT conditions were combined, the AUC for early-stage PD prediction increased to 0.924, suggesting a combination of DT and gait analysis by wearable sensors could conduce to the early diagnosis of PD. While after adjusting for GV, HS, SL, swing time and stance phase had predictive values for early-stage PD. Interestingly, after combining these parameters, the diagnostic value of the combined markers was non-inferior to that of combined gait parameters not adjusting for GV. This finding is important because these disease-related markers controlled the influence of GV, making it easy to compare between studies, thus these gait parameters can be candidate gait markers for the early diagnosis of PD (24).

Strengths and limitations of this study

The strengths of this study can be summarized as follows: (1) Using wearable sensors and controlling for covariates, we performed a comprehensive analysis of the gait impairment in early-stage PD patients compared with HC in ST and DT walking tests. (2) We extended previous studies by investigating the changes in kinematic gait parameters in early-stage PD under

ST and DT conditions. (3) We compared the diagnostic value of gait parameters to distinguish early-stage PD from HC under ST and DT conditions.

As reported, dopaminergic treatment improves certain aspects of gait, including GV, SL, and foot dynamics (67–69). In addition, improved DT walking can be observed in patients in the ON state compared to those in the OFF state (68). Levodopa can also improve depression in a proportion of patients with PD (70). This study aimed to understand gait pattern of early-stage PD and its related factors, so we assessed PD patients in the OFF condition to exclude the influence of levodopa on gait performance, DT and other potential confounders. However, the limitation should be considered in that the different gait parameters' responsiveness to levodopa could not be evaluated to investigate their diagnostic values for PD. Consequently, the results of the study may not transfer to the ON stage of medication administration. In particular, patients with early-stage PD are mostly in the ON state, as they usually have a good response to dopaminergic medications. It is inconvenient to stop the antiparkinsonian medication to reveal OFF state before performing gait analysis in clinical practice, so the applicability of this potential paradigm to support the diagnosis of patients with early-stage PD is limited. In the future, the gait parameters of early-stage PD patients in both ON and OFF states should be investigated.

This study also has some other limitations. First, the participants were recruited from a single center, leading to potential selection biases. However, the consecutive recruitment and the large sample size of this study decreased the biases. Second, the additional information of the AUC is limited without the training set and testing set. So the results of our study could not be used for the diagnosis of PD in clinical practice yet. Future multi-center studies recruiting a larger sample of subjects should be conducted to collect more gait data for validation and tests. Third, the study was a cross-sectional study, while longitudinal data were unavailable, limiting the study of pathological gait signatures of PD. Fourth, the reliability of the ST and DT gait measures of PD patients could not be provided in this study, due to both walking tests were only performed once.

Conclusion

In conclusion, the gait pattern altered in patients with early-stage PD, but the gait symmetry remained preserved. PD gait impairments may be exacerbated by modifiable factors such as DT, weight gain, and low education level. Gait parameters could distinguish early-stage PD patients from healthy controls. Among these, SL, and HS were the two most prominent gait parameters and had moderate predictive values for early-stage PD. Combining gait parameters under ST and DT can improve the accuracy of early-stage PD diagnosis and facilitate early intervention. Our findings contribute to understanding the gait pattern in patients with early-stage PD gait, are helpful in the future designs of effective treatments of gait impairment in PD and can be conducive to the development of new diagnostic tools for early-stage PD. Further multi-center, longitudinal studies are needed to evaluate the evolution of PD gait patterns and determine the diagnostic value of gait parameters for early-stage 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

The studies involving human participants were reviewed and approved by the Ethics Committee of Hwa Mei Hospital, University of Chinese Academy of Science. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ contributed to the collecting clinical data, statistical analysis, and drafting the manuscript. WF, HY, and LL contributed to the recruitment of subjects and recording clinical data. QG and ZC revised the manuscript and conceived and supervised the work. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

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Facial muscle movements in patients with Parkinson's disease undergoing phonation tests

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Purpose: Parkinson's disease (PD) is a serious neurodegenerative disease affecting the elderly. In general, the locomotion deficit, which seriously affects the daily life of patients with PD, usually occurs at a later stage. The mask face symptom meanwhile progressively worsens. However, facial muscle disorders and changes involved in the freezing mask are unclear.

Method: In this study, we recruited 35 patients with PD and 26 age- and sex-balanced controls to undergo phonation tests, while the built-in camera on the laptop recorded their facial expressions during the whole pronunciation process. Furthermore, FaceReader (version 7.0; Noldus Information Technology, Wageningen, Netherlands) was used to analyze changes in PD facial landmark movement and region movement.

Results: The two-tailed Student's *t*-test showed that the changes in facial landmark movement among 49 landmarks were significantly lower in patients with PD than in the control group ($P < 0.05$). The data on facial region movement revealed that the eyes and upper lip of patients with PD differed significantly from those in the control group.

Conclusion: Patients with PD had defects in facial landmark movement and regional movement when producing a single syllable, double syllable, and multiple syllables, which may be related to reduced facial expressions in patients with PD.

KEYWORDS

Parkinson's disease, facial dystonia, phonation tests, facial expression, stiff muscle

Introduction

Parkinson's disease (PD) is a common neurological degenerative disease. From 1990 to 2016, the standard incidence ratio of PD increased by 21.7% (1). The cost of patients with PD in China exceeds the average economic capacity, especially anti-Parkinson medication and caring costs (2).

Decreased facial movement is a clinical feature of PD, known as "masked syndrome." Approximately 39–65% of patients with PD experience freezing mask (3). Freezing mask is associated with dysarthria and dysphonia. Dysarthria is caused by neurologic damage to the motor components of speech, which may involve any or all of the speech processes, including respiration, phonation, articulation, resonance, and prosody. Our previous studies demonstrated that dysarthria was primarily manifested by sound quality changes, poor clarity, decreased volume, trembling, and hoarseness (4). In addition, dysphonia refers to disordered sound production at the level of the larynx, classically seen as hoarseness. It may have a neurologic, structural, or functional etiology (5). Fluorographic studies have demonstrated that the most common progression of vocal tract symptoms begins with laryngeal dysfunction, followed by changes in tongue and lip function (6). Stiffness of the laryngeal muscle tissue usually increases the hardness of the vocal cords, thereby affecting the closure of the vocal cords and increasing muscle tone (7). In addition, freezing mask may occur when muscle stiffness extends to the face. The main manifestation of mask face is the movement of the eyebrows, eyes, cheeks, and lips, and other movements have serious obstacles in speed, elasticity, and coordination. The facial muscles consequently become increasingly stiff (8, 9), which is caused by the inhibition of muscle activity responsible for facial expressions (10).

The face contains 44 muscles. The interaction of these organizations creates abundant facial expressions, including happiness, anger, despair, and other emotions (11). Happy and fearful faces activate the amygdala bilaterally, whereas sad faces only activate the right amygdala; disgust seems to preferentially activate the anterior insula (12) and fear preferentially activates the amygdala (13). A smile is accompanied by raised cheeks in the upper half of the face (14). Surprise is usually manifested as stretched eyebrows and an open mouth, whereas anger is manifested as an open mouth and frown (15).

These dominant facial expressions are accompanied by facial muscle activation (stretching or shrinking). However, facial muscle stiffness in patients with PD reduces these expressions. Numerous studies (16, 17) have validated the difficulty in identifying the expressions of sadness, anger, and fear in patients with PD. Gunnery et al. (18) measured spontaneous facial expressions across 600 frames in patients with PD and found that, if the severity of facial expression deficit was increased, the number, duration, intensity, and coactivation of facial muscle action was decreased. In addition, another study (19) demonstrated that, compared to healthy individuals, patients with PD had more difficulty identifying negative emotions (e.g., anger, disgust, fear, and sadness) than identifying relatively positive emotions (e.g., happiness, surprise). Accumulative evidence has shown that the ability of patients with PD to recognize aversive and neutral facial expressions in the early stages of the disease is significantly lower than that of the control group. Identifying other facial expressions (e.g., fear, sadness) is also weaker among patients with PD than among the control group (20, 21).

A freezing mask generally occurs early in the course of PD because of the loss of spontaneous facial expression and dystonic contraction of the facial muscles (10). Marneweck et al. (22) reported that facial muscle autonomic control was impaired in most patients with PD and was positively and highly correlated with disease severity (22). With regard to motor symptoms, patients experience hypomimia (e.g., spontaneous blinking and reduced facial expressions), which often occurs in the early phase of the disease. In stage IV PD, facial muscles become increasingly rigid; therefore, the richness of facial expressions is significantly decreased (23). In 2016, Livingstone et al. (24) found that the frontal muscles of patients with PD had a weakened response to a sad expression. In 2019, Okamoto et al. used FaceReader (Noldus Information Technology) and surface electromyography to conduct a three-dimensional facial expression analysis of patients with PD to evaluate facial expression and muscle activity, respectively. Patients with PD in the intervention group were treated with facial rehabilitation exercises. Patients with PD had a lower "happy" index and a higher "sad" index. Facial rehabilitation exercises affected the emotions, facial expressions, and facial muscle activity of patients with PD (25).

Therefore, facial expression loss in patients with PD often manifests before motor symptoms and occurs in the early stage. However, little is known about how coordinated movements across regions of the face are impaired in PD. Furthermore, at present, the micro-stiffness of the facial muscles in the freezing mask is difficult to recognize—that is, no software can recognize facial muscle movements more sensitively. In this study, we used facial landmarks to identify the micro-movement of each facial muscle during the phonation test to explore facial region movement.

Materials and methods

Ethics statement

The Institute of Institutional Review Board and Ethics Committee of the First Affiliated Hospital of

Abbreviations: PD, Parkinson's disease.

Chengdu Medical College (Sichuan, P.R. China) approved this study. Written informed consent was provided by all participants.

Participants

From January to December 2019, two groups of participants were recruited: patients with PD and healthy individuals (i.e., the control group). The PD group consisted of 35 patients, including 21 men and 14 women, the average age was 67.57 ± 8.78 years. The control group consisted of 26 age- and sex-balanced healthy participants, which included 11 men and 15 women, and the average age was 66.46 ± 7.02 years. The severity of PD was evaluated, based on the Hoehn–Yahr Scale (H&Y) and the Unified Parkinson's Disease Rating Scale III (UPDRS III), and the duration of the disease was recorded. In addition, profession, alcohol consumption, smoking habits, and education level of all participants were recorded. The entire recording and evaluation process was conducted by a neurologist. All patients with PD included in the study met the following main inclusion criteria: (1) the patient's neurologist had undergone PD and other movement disorder management training and had diagnosed the patient as having idiopathic PD; and (2) during the first 3 months of the study, the patient had not participated in other clinical trials. The exclusion criteria for all participants were as follows: (1) a history of other neurological diseases; (2) severe mental disorders or cognitive disorders that may hinder speech; (3) mental illness or major systemic diseases; (4) clinical problems such as aphasia; (5) a medical history of acute stroke, sports injury, or mental illness; (6) failure to complete the learning task accurately; and (7) participation in other rehabilitation projects. Patients with PD stopped taking levodopa on the morning of the phonation test but continued to take other anti-Parkinson's drugs. All patients were in the "ON" stage. If a patient had severe motor symptoms, the experiment was not conducted.

Phonation tests

Vowels have an important role in Chinese Pinyin. The pronunciation of vowels requires the tongue, lip, and jaw to form an oropharyngeal resonance cavity. When vowel sounds are produced, the airflow exhaled from the lungs passes through the mouth with minimal resistance and no friction sound (26). This process is suitable for studying patients with PD who have low oral pressure and dysphonia. In this study, we chose the vowels /a/, /o/, and /e/ to form the syllables "lā lā lā," "duǒ," and "fēi é," respectively, for the phonation test. Furthermore, our previous research has verified its feasibility and accuracy (27).

Face muscle movements recording and analysis

The participants were guided through playing the slides of "lā lā lā," "duǒ," and "fēi é" on a laptop. The built-in camera on the laptop recorded facial movement during the entire test process. FaceReader (version 7.0; Noldus Information Technology, Wageningen, Netherlands) was used to analyze detail parameters, including landmarks of key points on the face, head orientation, mouth, eye, and eyebrow open or closed status. Clinicians cross-validated and ensured quality control of the video recording. Ensuring that a participant's face had even lighting was important. The participant maintained normal intonation and loudness in a relaxed state. All participants were under the guidance of clinicians. If a participant felt tired, the test was suspended until the participant was satisfied with completing the rest of the test.

Statistical analysis

All data were stored in Excel (Microsoft Corporation, Redmond, WA, USA). All analyses were conducted using STATA15.0 (Stata Corporation, College Station, TREATMENT,

TABLE 1 Baseline characteristics of the participants.

Variable	Patients with PD	Control group	*P*-value
Number	35	26	
Age, y*	67.57 ± 8.78	66.46 ± 7.02	$P = 0.70$
Sex, M/F#	21/14	11/15	$P = 0.17$
Duration of disease, y	4.59 ± 3.75	-	
H&Y Scale score	2.60 ± 0.81	-	
UPDRS III score	35.60 ± 20.39	-	
Alcohol consumption, N/Y#	27/8	23/3	$P = 0.26$
Smoker, N/Y#	26/9	23/3	$P = 0.17$
Profession#			$P = 0.04$
Retired	10	1	
Farmer	17	18	
Worker	8	7	
Education#			$P = 0.03$
Primary school	19	23	
Middle school	10	1	
High school	5	2	
Master's degree	1	0	

The data are presented as the number or as the mean ± standard deviation.
#Based on the Chi-square test.
*Based on the two-tailed Student's t-test.
PD, Parkinson's disease; M, male; F, female; H&Y, Hoehn–Yahr Scale; UPDRS III, Unified Parkinson's Disease Rating Scale III; N, no; Y, yes.

USA). The Chi-square test was used to compare the distribution of the participant's sex, profession, alcohol consumption, smoking habit, and education level between the two groups. The data were expressed as the mean ± standard deviation. The two-tailed Student's *t*-test was used to assess whether differences existed between the two groups in age, landmark movement, and facial region movement. A value of $P < 0.05$ was considered statistically significant.

Results

General information

In this study, the demographic characteristics of 35 patients with PD and 26 control individuals were compared. Table 1 displays no significant difference between the two groups in age ($t = 0.5305$, $df = 59$, $P = 0.7011$) and sex ($\chi^2 = 1.874$, $df = 1$, $P = 0.171$). In addition, the duration of PD was 4.59 ± 3.75 years, and the average scores on the H&Y and UPDRS III were 2.60 ± 0.81 and 35.60 ± 20.39, respectively. However, no significant difference existed in alcohol consumption and smoking habits between the two groups. The results revealed a significant difference in profession ($\chi^2 = 6.2674$, $df = 2$, $P = 0.044$) and education level ($\chi^2 = 8.8961$, $df = 3$, $P = 0.03$) between the two groups.

Landmark movement

Changes in landmark movement between patients with PD and the controls were compared during the phonation test. Details of the landmarks on the face are listed in Figure 1. The data revealed that changes in 49 landmarks were significantly lower in patients with PD than in the controls (Table 2). This finding was consistent with the manifestation of stiff facial muscles in patients with PD. Interestingly, patients with PD had a significantly higher mean of the landmarks in "duǒ" and "lā lā lā." This result contrasted with that of the controls, who had a significant decreased mean of landmarks in "duǒ" than "lā lā lā." This finding indicated that different pronunciations may have different effects on facial muscle movements in patients with PD.

Facial region movement

We also compared facial region movement between the two groups. Both eyes and the upper lip were interestingly significantly different between the two groups. In particular, when pronouncing "lā lā lā," the average movement of the left and right eyes of patients with PD was significantly lower than that of the controls ($P < 0.05$). The average movement of the right eye with the syllable "duǒ" was similarly significantly lower in patients with PD than in the controls ($P < 0.05$). This

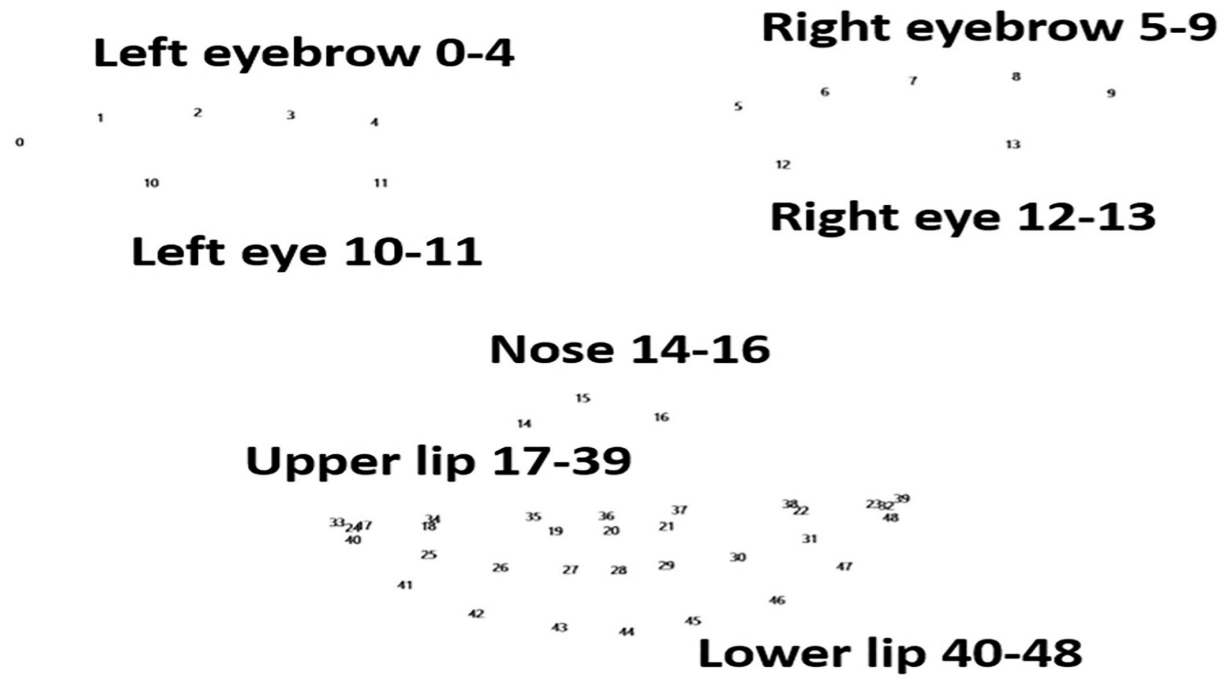

FIGURE 1
Landmarks of the face. Numbers 0–48 represent the 49 landmarks in the face, involving the eyebrows, eyes, nose, upper lip, and lower lip. These are the points recognized by FaceReader (version 7.0; Noldus Information Technology, Wageningen, Netherlands).

TABLE 2 Comparison of landmark movements in groups due to syllable pronunciation.

Landmarks	Pronunciation "lā lā lā"			Pronunciation "duǒ"		
	Patients with PD	Control	*P*-value	Patients with PD	Control	*P*-value
	Mean ± S.Dev	Mean ± S.Dev		Mean ± S.Dev	Mean ± S.Dev	
L0	0.0059 ± 0.0037	0.0231 ± 0.0285	0.0211*	0.0065 ± 0.0085	0.0227 ± 0.0300	0.0403*
L1	0.0058 ± 0.0040	0.0236 ± 0.0290	0.0194*	0.0064 ± 0.0077	0.0231 ± 0.0302	0.0344*
L2	0.0059 ± 0.0041	0.0242 ± 0.0295	0.018*	0.0063 ± 0.0072	0.0235 ± 0.0307	0.0316*
L3	0.0059 ± 0.0042	0.0247 ± 0.0299	0.0167*	0.0063 ± 0.0068	0.0238 ± 0.0311	0.0308*
L4	0.0057 ± 0.0042	0.0249 ± 0.0303	0.0164*	0.0062 ± 0.0069	0.0240 ± 0.0317	0.0309*
L5	0.0059 ± 0.0046	0.0257 ± 0.0315	0.0168*	0.0066 ± 0.0081	0.0251 ± 0.0338	0.0361*
L6	0.0061 ± 0.0047	0.0259 ± 0.0316	0.0172*	0.0069 ± 0.0084	0.0254 ± 0.0341	0.0381*
L7	0.0060 ± 0.0045	0.0258 ± 0.0315	0.017*	0.0068 ± 0.0085	0.0254 ± 0.0344	0.0385*
L8	0.0059 ± 0.0044	0.0256 ± 0.0315	0.0173*	0.0067 ± 0.0085	0.0254 ± 0.0347	0.0392*
L9	0.0058 ± 0.0041	0.0253 ± 0.0314	0.018*	0.0066 ± 0.0085	0.0254 ± 0.0351	0.0406*
L10	0.0056 ± 0.0037	0.0233 ± 0.0291	0.0199*	0.0063 ± 0.0087	0.0230 ± 0.0309	0.0394*
L11	0.0054 ± 0.0038	0.0239 ± 0.0300	0.0183*	0.0060 ± 0.0080	0.0236 ± 0.0321	0.0364*
L12	0.0055 ± 0.0041	0.0248 ± 0.0310	0.0174*	0.0061 ± 0.0077	0.0246 ± 0.0341	0.0374*
L13	0.0057 ± 0.0041	0.0252 ± 0.0314	0.0179*	0.0064 ± 0.0081	0.0253 ± 0.0349	0.0383*
L14	0.0055 ± 0.0044	0.0261 ± 0.0324	0.0156*	0.0063 ± 0.0078	0.0253 ± 0.0344	0.0343*
L15	0.0059 ± 0.0048	0.0271 ± 0.0329	0.0148*	0.0067 ± 0.0084	0.0260 ± 0.0346	0.0332*
L16	0.0055 ± 0.0045	0.0265 ± 0.0328	0.0154*	0.0063 ± 0.0082	0.0256 ± 0.0350	0.0353*
L17	0.0054 ± 0.0035	0.0251 ± 0.0317	0.0177*	0.0062 ± 0.0071	0.0247 ± 0.0349	0.0407*
L18	0.0055 ± 0.0038	0.0255 ± 0.0321	0.0178*	0.0063 ± 0.0072	0.0250 ± 0.0350	0.0394*
L19	0.0057 ± 0.0044	0.0262 ± 0.0328	0.017*	0.0064 ± 0.0077	0.0256 ± 0.0355	0.0374*
L20	0.0056 ± 0.0044	0.0263 ± 0.0329	0.0168*	0.0064 ± 0.0079	0.0257 ± 0.0356	0.0375*
L21	0.0056 ± 0.0043	0.0264 ± 0.0331	0.0164*	0.0064 ± 0.0081	0.0258 ± 0.0358	0.0377*
L22	0.0056 ± 0.0044	0.0263 ± 0.0331	0.0171*	0.0064 ± 0.0082	0.0259 ± 0.0364	0.0393*
L23	0.0057 ± 0.0045	0.02630 ± 0.033	0.0175*	0.0063 ± 0.0082	0.0259 ± 0.0366	0.0394*
L24	0.0055 ± 0.0036	0.0252 ± 0.0317	0.0175*	0.0062 ± 0.0071	0.0248 ± 0.0349	0.0402*
L25	0.0056 ± 0.0037	0.0260 ± 0.0320	0.0156*	0.0064 ± 0.0072	0.0253 ± 0.0352	0.0386*
L26	0.0058 ± 0.0039	0.0266 ± 0.0322	0.0146*	0.0065 ± 0.0073	0.0257 ± 0.0354	0.0371*
L27	0.0059 ± 0.0040	0.0269 ± 0.0325	0.0143*	0.0066 ± 0.0076	0.0260 ± 0.0357	0.0365*
L28	0.0059 ± 0.0041	0.0270 ± 0.0327	0.0142*	0.0066 ± 0.0077	0.0261 ± 0.0359	0.0365*
L29	0.0059 ± 0.0041	0.0271 ± 0.0328	0.0143*	0.0066 ± 0.0079	0.02620 ± 0.036	0.0366*
L30	0.0058 ± 0.0042	0.0271 ± 0.0329	0.0145*	0.0066 ± 0.0080	0.0262 ± 0.0362	0.0367*
L31	0.0057 ± 0.0043	0.02670 ± 0.033	0.0155*	0.0064 ± 0.0081	0.0261 ± 0.0364	0.0378*
L32	0.0057 ± 0.0045	0.0264 ± 0.0330	0.0167*	0.0063 ± 0.0082	0.0260 ± 0.0365	0.0382*
L33	0.0055 ± 0.0035	0.0251 ± 0.0316	0.0178*	0.0062 ± 0.0071	0.0247 ± 0.0348	0.0406*
L34	0.0057 ± 0.0040	0.0257 ± 0.0322	0.0176*	0.0064 ± 0.0073	0.02520 ± 0.035	0.0384*
L35	0.0057 ± 0.0044	0.0263 ± 0.0327	0.0167*	0.0065 ± 0.0077	0.0256 ± 0.0351	0.037*
L36	0.0058 ± 0.0045	0.02650 ± 0.033	0.0167*	0.0066 ± 0.0080	0.0258 ± 0.0354	0.0373*
L37	0.0058 ± 0.0045	0.0266 ± 0.0331	0.0167*	0.0066 ± 0.0083	0.0259 ± 0.0357	0.038*
L38	0.0056 ± 0.0044	0.0265 ± 0.0331	0.0164*	0.0064 ± 0.0083	0.0259 ± 0.0362	0.038*
L39	0.0057 ± 0.0045	0.02640 ± 0.033	0.0169*	0.0063 ± 0.0083	0.0260 ± 0.0366	0.0388*
L40	0.0055 ± 0.0036	0.0253 ± 0.0317	0.0174*	0.0063 ± 0.0071	0.0248 ± 0.0350	0.0402*
L41	0.0058 ± 0.0038	0.0262 ± 0.0323	0.0161*	0.0065 ± 0.0072	0.0255 ± 0.0355	0.039*
L42	0.0059 ± 0.0039	0.0268 ± 0.0325	0.0148*	0.0067 ± 0.0074	0.0260 ± 0.0358	0.0376*
L43	0.0061 ± 0.0041	0.0273 ± 0.0329	0.0144*	0.0068 ± 0.0077	0.0264 ± 0.0361	0.0369*

(Continued)

TABLE 2 (Continued)

Landmarks	Pronunciation "lā lā lā"			Pronunciation "duǒ"		
	Patients with PD	Control	*P*-value	Patients with PD	Control	*P*-value
	Mean ± S.Dev	Mean ± S.Dev		Mean ± S.Dev	Mean ± S.Dev	
L44	0.0061 ± 0.0041	0.0275 ± 0.0332	0.0142*	0.0069 ± 0.0079	0.0266 ± 0.0364	0.037*
L45	0.0061 ± 0.0042	0.0277 ± 0.0333	0.014*	0.0069 ± 0.0081	0.0267 ± 0.0366	0.0368*
L46	0.0060 ± 0.0043	0.0275 ± 0.0334	0.0147*	0.0067 ± 0.0082	0.0267 ± 0.0368	0.0374*
L47	0.0058 ± 0.0044	0.0271 ± 0.0334	0.0157*	0.0066 ± 0.0083	0.0264 ± 0.0368	0.0382*
L48	0.0057 ± 0.0044	0.0265 ± 0.0331	0.0166*	0.0063 ± 0.0083	0.0261 ± 0.0366	0.0384*

L0 to L48 indicates Landmark 0 to Landmark 48.
*A value of $P < 0.05$ is significant.
PD, Parkinson's disease; S.Dev, standard deviation.

TABLE 3 Comparison of face regions in groups, based on syllable pronunciation.

Face region	Pronunciation	Patients with PD (mean ± S.Dev)	Control (mean ± S.Dev)	*P*-value
Left eye	lā lā lā	0.0829 ± 0.0468*	0.1421 ± 0.0996*	0.0329
Right eye	lā lā lā	0.0778 ± 0.0310*	0.1321 ± 0.0879*	0.0227
	duǒ	0.0604 ± 0.0306*	0.1214 ± 0.1018*	0.0246
Upper lip	fēi é	0.0459 ± 0.0186*	0.0322 ± 0.0181*	0.0373

*A value of $P < 0.05$ is significant.
S.Dev, standard deviation; PD, Parkinson's disease.

finding may be related to the fact that patients with PD blink less frequently than healthy individuals. However, when patients with PD pronounced "fēi é," their upper lip movement was significantly higher than that of the control group ($P < 0.05$), (see Table 3).

Discussion

One of the most common movement symptoms of PD is a facial muscle movement disorder, including the reduction and slowing of facial muscle movement, which may affect the upper and lower parts of the face: in the upper part, it is shown that the blink rate and blink range decreases. In the lower part, the displacement amplitude of the jaw and upper lip decreases (9, 10). In addition, facial muscle movement disorder makes PD patients to have serious problems such as speech disorder, dysphagia, and salivation (10, 28). In this study, the movement of the 49 landmarks in patients with PD was significantly decreased, compared to the movements in the control group. This finding indicated that the movements of the left and right eyebrows, left and right eyes, nose, and upper and lower lips of patients with PD were weakened. This finding was consistent with the symptoms of facial freezing in patients with PD. The freezing mask is usually manifested by the reduction of the voluntary movement of the facial muscle group and the obvious reduction of the movement range, so that the facial expression becomes not obvious, resulting in facial expression disorder. This is mainly caused by damage to the nervous system of speech motor components.

Both groups had significant differences in the left eye, right eye, and upper lip movements when they pronounced the same syllable. During the phonation test, patients with PD in our present study had smaller eye muscle movements than did those in the control group. This factor may be the reason why PD patients usually have mild to obvious facial expression reduction and spontaneous blinks/minute, which usually represents an early motor symptom of PD (29).

Furthermore, a lack of movement in certain parts of the patient's body, including the face, neck, and arms, can also be an early sign of the disease. PD is a neurodegenerative disease caused by the loss of dopaminergic neurons in the dense part of the substantia nigra of the brain (30). The loss of these neurons leads to the reduction of dopamine neurotransmission in the basal ganglia, resulting in excessive inhibition of some facial movements and cognitive pathways (31). When PD damages dopamine-producing nerve cells, the ability of nerves to control muscles is affected, resulting in the appearance of facial movement symptoms (32). Basal ganglia dysfunction associated with PD may contribute to orofacial movement disorders. An abnormal increase in driving neuromotor activity mediated by lower motor neuron centers translates to an increase in

muscle stiffness, which is the clinical correlate of muscular rigidity in PD. The main manifestations of freezing mask are serious obstacles in the speed, elasticity, and coordination of the eyebrows, eyes, cheeks, lips, and so on (9).

Taken together, patients with PD presented significantly different facial muscle movements during the phonation test. The pronunciation of different syllables requires a different coordination mechanism, such as the breath muscle movement-induced vocal cord vibration. Because the spontaneous and non-spontaneous movements of the face depend on the fine coordination between the complex facial nervous and muscular systems. According to the observation of facial muscle movement, it is a useful attempt to diagnose and monitor PD patients at an early stage. Therefore, these valuable evidence are helpful for the early diagnosis and monitoring of PD.

Limitations

The patients with PD in this study stopped taking levodopa before the experiment but continued to take other anti-Parkinson's disease drugs. Thus, the patients were in the "ON" stage. In addition, this experiment did not conduct a facial electromyographic study. Furthermore, the larger sample size in further studies could be the strength of the conclusion, and consequently, consider the interesting findings as preliminary.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Chengdu Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FX, L-qY, and G-gX developed the study concept and drafted the manuscript with X-wZ. X-wZ and Q-hG recruited the subjects and collected the phonation test and facial expression data. JZ performed the Noldus FaceReader 7.0 operation, and conducted the statistical analysis with Q-hG. XW and S-cM proofread the manuscript. All authors contributed to the article and approved the submitted version.

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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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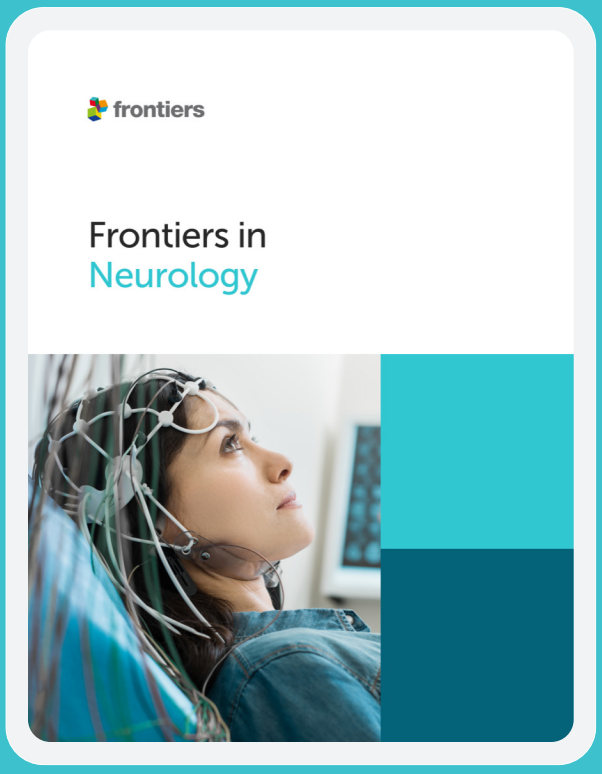

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