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A highly efficient detection model for early-stage Parkinson's disease using non-contact, multi-modality measurement and artificial intelligence

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Abstracts

Early diagnosis of Parkinson's disease (PD) is challenging due to the difficulty in identification of various early motor signs. We aimed to develop and validate a highly efficient detection model for early-stage PD using an optimal modality (OM) selection strategy. 151 off-medication, early-stage PD patients and 138 controls were divided into a development cohort and a validation cohort at 5:1 ratio. 186 features from 11 motor tasks were collected in all participants via a non-contact, multi-modality pipeline, using deep learning algorithms, covering saccade, facial expression, hand and foot movements, gait, and voices. In the development cohort, features were screened for each modality by between-group comparison, and OMs were selected following steps of Shapley Additive Explanations analysis, assessments of unimodal model classification performance and stability. Saccade, facial expression during passage reading, and gait were identified as OMs, comprising 39 features. Using the Multilayer Perceptron, the model integrating the three OMs demonstrated the best classification performance, comparable to the model using 11 modalities with 78 features in both the development cohort (AUC: 0.87 vs. 0.89) and validation cohort (AUC: 0.84 vs. 0.88). In conclusions, integrated features from saccade, facial expression during passage reading, and gait could efficiently detect early-stage PD patients.

Keywords: Parkinson's disease; early-stage; detection; multi-modality; artificial intelligence;

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, with the fastest-growing prevalence among the neurological diseases ^[1]. It is characterized by progressive motor impairment, primarily due to dopaminergic neuron loss in the substantia nigra. As one of the leading causes of neurological disability ^[2], PD underscores the importance of early diagnosis, as timely symptomatic treatment could significantly alleviate motor disability and prevent fall-related injuries, improving the living quality and extending life expectancy for patients. Moreover, early diagnosis within the initial years from onset would facilitate the recruitment of eligible patients with milder dopaminergic loss into cohorts for disease-modifying therapy trials ^[3].

Early diagnosis of PD still faces challenges. Clinical diagnosis of PD has centered on a defined motor syndrome of bradykinesia in combination with either rest tremor, rigidity, or both ^[4]. At the early stage of PD, compared with tremor, bradykinesia-related signs, which manifest as a reduction in the amplitude, frequency or velocity during repetitive voluntary and spontaneous movements, are more commonly unnoticeable or misattributed to aging due to the insidious onset mode and slight functional impairment ^[4, 5]. PD patients (PDs) are more likely to seek medical help when they are disabled in the advanced stages. Therefore, implementing screening in communities or primary care settings for these early motor signs is critical to enable early diagnosis of PD. Given the need for large-scale populations assessment, a simple, low-cost, and time-efficient screening tool is required in real clinical practice, which, however, remains unmet.

Increasing studies have utilized various motor modalities with machine learning methods to measure

featured motor signs, identify the motor digital biomarkers, thereby building detection models for PD^[6-9], given the digital biomarkers' advantages of easy accessibility, non-invasiveness, and low cost. Notably, motor signs are highly variable among early-stage PDs during the initial years from onset due to the clinical heterogeneity in both affected body regions and initial motor symptoms^[10, 11]. Although rest tremor is a hallmark feature of PD, it is present in only 52.0–68.5% of patients and may occasionally appear at the very early stage^[12]. In contrast, bradykinesia is common and a required condition for clinical diagnosis of PD^[4]. Given an efficient detection model should have the capability of identifying the common and core motor features of PD, we targeted bradykinesia-related motor signs as the source for obtaining key motor digital biomarkers to build such a model. Among early-stage PD patients, bradykinesia-related features (e.g., hypomimia, dysphagia, reduced flexibility of distal extremities, gait changes, and abnormal eye saccade) vary with the affected body regions^[13-15]. However, existing detection models were mostly built using the unimodal analysis of isolated motor signs, based on data from treated PDs with longer disease durations^[6-9]. Additionally, the selection of motor modalities in these studies was based on clinical experience instead of using data-driven methods. These limitations might compromise the utility of these models as screening tools in real clinical practice.

To address these problems, we designed this case-control study in which off-medication, early-stage PDs within five years from onset were recruited. As illustrated by the Figure 1, we performed a comprehensive motor measurement on multiple body regions using a non-contact, multi-modality AI pipeline that integrated visual and acoustic signal perception algorithms, covering eye saccades, face expression, gait, hand and foot movements, and voices. We aimed to use multiple machine learning methods

to identify the optimal modalities (OM) with the best classification performance, thereby establishing a simple, time-efficient detection model for early-stage PDs with good generalizability and interpretability.

Results

Demographic and Clinical Characteristics

The development cohort included 239 participants (127 PDs and 112 HCs) and the validation cohort included 50 participants (25 PDs and 25 HCs). Detailed characteristics of participants were displayed in Table 1. Age and gender ratio were equally distributed between PDs and HCs in both two cohorts. However, PDs had significant lower MoCA scores in the validation cohort ($p < 0.001$). For PDs in the two cohorts, the median age was 69(64~74) and 72(67~75) years, the median disease duration was 20(12~34) and 23(7~35) months, the median MDS-UPDRS-III score was 25(19~34) and 30(23~41).

PDBs for Early-stage PDs

A total of 78 PDBs from the 11 motor modalities were identified for early-stage PDs through between-group comparison in the development cohort, including 8 saccade features, 2 spontaneous eye blinking features, 14 facial features during passage reading, 18 facial features during monologue, 17 gait features, 3 hand movement features, 1 foot movement feature, and 15 vocal features (Table 2). Reduced movement amplitude was the most prominent feature for early-stage PDs in multiple modalities of the saccades, facial expression, and gait. Slower velocity was observed in early-stage PDs for some modalities, including the saccades, stride during walking, and the finger tapping ($p < 0.05$). However, the change trend of amplitude and velocity in finger and toe tapping were not significantly different between PDs and HCs. Different

vocal features were identified across four modalities in early-stage PDs, except for the sound intensity parameters which showed both increased mean and reduced variability during passage reading and monologue tasks. Table S6~S11 show the detailed comparison results of each modality.

Classification performance of the full-modality Model

We built full-modality classification models integrating the 78 PDBs from all modalities. The models performed excellently with the four classifiers in the development cohort, with AUC exceeding 0.85. Additionally, the full-modality models outperformed all the unimodal models in all metrics, which was independent of classifiers (Table S12). MLP demonstrated superior performance among all classifiers, achieving the highest AUC of 0.89 (95%CI, 0.86-0.92) (Figure 2A and B).

In the validation cohort, the model with MLP achieved AUC value of 0.88 (Figure 4B) and it demonstrated a higher AUC in female patients than in patients (0.92 vs 0.84), with comparable performance between younger (<70 years) and older (≥ 70 years) patients (0.90 vs 0.89) (Figure 4C and 4E). The detailed performance metrics were displayed in Table S13.

Classification performance of the streamlined-modality Model

We performed OM selection following the predefined steps. In the importance evaluation, 4 of 11 modalities were identified as key contributors to the full-modality model due to their importance scores exceeding the threshold of 0.36, including gait, FEDM, FEDPR, and saccade (Figure 3B). When evaluating the classification ability and stability, the modality of FEDM (with LR) were excluded from OMs for its higher CV value (0.17) (Figure 3A and Table S14). Finally, gait, FEDPR, and saccade were identified as OMs,

involving 17 gait PDBs, 14 FEDPR PDBs, and 8 saccade PDBs. Detailed PDBs from OM_s were shown in Table 3.

We compared the modal performance across different OM combinations and classifiers in the development cohort. The binary model integrating facial expression during passage reading, and gait outperformed other binary models and all unimodal models in metrics of the AUC (Figure 3C), accuracy, precision, and specificity across all classifiers (Table S12). When using MLP, it demonstrated the best classification performance (AUC = 0.87) (95%CI, 0.83-0.91) (Figure 3C), comparable to the full-modality model (AUC = 0.89). When the saccade modality was integrated, the ternary model (with MLP) achieved a higher sensitivity (0.81 vs 0.77) with a lightly lower specificity (0.75 vs 0.77), while the AUC remained unchanged (Figure 3C). Given the need of high sensitivity for a screening tool, we suggest that the MLP model integrating gait, facial expression during passage reading, and saccade as the streamlined model. In the Delong test, the streamlined model demonstrated a statistically different AUC compared to either the unimodal model (gait or saccade) or the binary model integrating gait and saccade ($p < 0.05$) (Table S12).

In the validation cohort, this streamlined model achieved an AUC of 0.84 (Figure 4B), with better performance for female (0.84 vs 0.79) and younger PD patients (< 70 years) (0.86 vs 0.82) (Figure 4D and 4F). It performed well both in the calibration curve and the DCA (Figure S1). The detailed performance metrics were displayed in Table S13.

Discussion

This is the first study to compare different motor modalities in discriminating early-stage PDs from HCs. The OM_s outperformed other commonly used motor modalities for detecting early-stage PDs, given their

stronger and more stable classification performance. Integration of the three OMs enables the streamlined model to demonstrate discrimination power comparable to that of the full-modality model in both the development and validation cohorts, greatly shortening the detection time within several minutes. Additionally, these biomarkers within the OMs well characterized the motor impairment patterns, providing high interpretability for this model. Given its excellent classification performance, high efficiency, simple operation and low-cost, we suggest the streamlined model might serve as a screening tool for early-stage PDs in community or primary care settings.

By using the non-contact, marker-less vision and acoustic system, we detected more gait features for the off-medication, early-stage PDs during the go-and-back walking task, compared with the previous studies that used wearable sensors, plantar pressures and light markers ^[16, 17]. The ecologically valid assessment conditions with a large sample size might contribute to the high richness of gait features, including reduced distal limb movement amplitude, greater interarm asymmetry, slower stride velocity, wider stride width, and longer turning duration. These features are primarily linked to limb bradykinesia and rigidity, following an asymmetric progression pattern ^[18]. The unimodal model exhibited medium classification power across all classifiers, achieving a comparable accuracy (0.70) to the previous studies (0.68~0.71) using different motion capture systems ^[17, 19].

Using facial features during passage reading, the unimodal model achieved the highest AUC of 0.82 with MLP, which was better than a prior facial features-based model (the highest AUC is 0.67 with RF) ^[8]. The better performance might be attributed to the use of more fine-grained facial markers to capture the movement of the eyebrows, palpebral apertures, upper and lower lips, and mouth corners during passage

readings. These PDBs well characterized the hypomimia, manifested by symmetrically diminished movements in both upper and lower facial muscles ^[6]. Although the modality of facial features during monologue demonstrated comparable discrimination performance to the modality of facial features during passage reading, it was excluded from the OMs for its higher variability. During monologues, we observed significant variations in pause duration and emotional expression in both early-stage PDs and HCs, which was primarily associated with individual personality traits and educational levels. These factors might enhance the variability of facial features among participants, decreasing the model's classification stability. We observed a general improvement in models' classification performance when integrating facial and gait features, with the bimodal models outperforming each unimodal models across all classifiers. Given the distinct striatal somatotopic representations of facial and limb movements ^[20], we propose that combining facial and gait features might enhance the models' classification power in addressing the clinical heterogeneity in affected body regions and dominant motor phenotypes in our study (Table 1).

In our study, the modality with eight saccade PDBs also demonstrated important and stable diagnostic capacity for early-stage PDs. It achieved the highest AUC of 0.75 with MLP, which was superior to a recent model that used different eyeball movement features (AUC=0.689) ^[21]. These PDBs supported the features of hypometric saccades and impaired saccade inhibition in early-stage PDs, which was attributed to the striatal dopamine deficiency, leading to both excessive inhibition of the superior colliculus by the basal ganglia and impaired dorsolateral frontal-striatal circuit ^[22]. Integrating saccade features with facial and gait features, the multimodal model achieved higher sensitivity (0.81 vs 0.77) at the cost of a slight specificity reduction (0.75 vs 0.77) in the development cohort, indicating these saccade features were common but

non-specific to early-stage PDs. Additionally, we observed inferior classification performance for male PD patients in both the full-modality (0.84 vs 0.92) and streamlined models (AUC:0.79 vs 0.84) in both the development and validation cohorts, indicating gender might be a potential influencer for the model performance. Further investigation based on large-sample scale is required for clarify the relationship between genders and these modality features. If necessary, gender-specific models would be developed for improving the detection of early-stage PDs.

The other modalities in our study demonstrated less contribution to the early-stage PDs detection than the OMs. Moreover, these modalities exhibited higher CV values across multiple classifiers, indicating significant variation in their corresponding motor functions among early-stage PDs. These limitations might hinder these modalities from building models with strong classification power and good generalization. Notably, our findings differed from Lim's reports, where vocal features outperformed facial and gait features in classification performance^[8,9]. In this study, we applied the recommended vocal parameters to assess vocal function in early-stage PDs who were strictly defined as having disease durations of <5 years and HY stage ≤ 2 at the off-medication state. In Lim's studies, more complicated vocal parameters were used in early-stage PDs who were defined as HY stage <3. The disparity in the parameters and patient inclusion criteria might contribute to the divergent model classification performance between studies. However, a recent European multicenter study reported that a model utilizing a combination of recommended vocal features from four vocal tasks achieved an AUC of 0.80^[23], comparable to our result (0.79), in diagnosing early-stage PDs whose inclusion criteria were consistent with those in our study. Given our SHAP analysis for modality importance, we suggest that recommended vocal parameters might be

suboptimal for detecting early-stage PDs with shorter disease durations. Notably, our model is limited by its inability to detect resting tremor. Because bradykinesia related motor features are required for clinical diagnosis of PD ^[4, 24], this limitation might not significantly impair this model's ability to identify early-stage PD patients whose symptoms and signs meet the diagnosis criteria of PD. Additionally, the sample size of the validation cohort is relatively small. Despite a 5:1 ratio between training and validation datasets, a larger validation cohort would improve the diversity of motor features, enhancing the validation ability for the model.

In summary, this streamlined model integrating features from gait, facial expression during passage reading, and saccade, demonstrates promising capability for screening early-stage PDs. While the large-scale validation is still required, our study provides valuable insights for advancing the early diagnosis of PD.

Methods

Participants

All early-stage PDs were recruited from the movement disorders clinics of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Healthy controls (HCs) were spouses of PDs and community residents. A development cohort (127 PDs and 112 HCs) was enrolled between April 2023 and July 2024, and a validation cohort (25 PDs and 25 HCs) was recruited between September 2024 and November 2024. The inclusion criteria for early-stage PDs included willingness to cooperate with tests, a diagnosis of clinically probable PD according to MDS criteria ^[4], the disease duration (time since initial motor symptom) was < 5 years, Hoehn-Yahr (H&Y) stage at medication off status was ≤ 2 ^[25] (Figure

1A). The exclusion criteria included having other neurological diseases that might interfere with motor measurement, having histories of vocal cord diseases, serious visual or hearing impairment, osteoarthritic diseases, cognitive impairment that led participants unable to perform tests. All participants underwent baseline assessment, including demographic data, cognitive function evaluation by the Montreal Cognitive Assessment (MoCA) and PD disease information (for PD patients). Notably, early-stage PDs underwent motor assessments and the

following motor tasks at off-medication status (at least 12 hours after the last medication). Motor assessment tools included the Movement Disorder Society Unified Parkinson Rating Scale-III (MDS-UPDRS-III) and H&Y stage. Details of motor phenotype classifications, affected body part distribution and total MoCA scores were shown in Table S1. MDS-UPDRS-certified, experienced clinicians performed clinical assessments. A neurological exam of cranial nerves was conducted before all the assessments to ensure all participants perform the following motor tasks. In accordance with the Declaration of Helsinki, the study received approval from the research ethics committee on human experimentation of Xinhua hospital before the study and obtained written consent for research from all participants (M2024-001/2024.01.09). All data were acquired during standard clinical care.

Motor feature collection

A multi-modality AI pipeline was designed to automatically measure motor features from different motor tasks, incorporating both visual and acoustic devices with deep learning-based perception algorithms, using an in-house developed motor measurement machine (Figure 1B). Specifically, the binocular camera with two 1280×960 resolution cameras at a 30-cm baseline was utilized to capture visual signals at 30-fps and a

microphone (CM379-10934) was used to record acoustic signals. Notably, the proposed pipeline did not depend on this specific machine; rather, the essential requirements were that the input videos and audio recordings meet the predefined acquisition specifications, particularly in terms of video resolution, frame rate, camera configuration, and audio recording quality. The features of gait, hand and foot movement were extracted based on the detected participants' 3D human poses estimated by RSB-Pose^[26, 27]. Facial features were extracted from 98 2D-facial keypoints obtained using PFLD, based on faces detected by MTCNN from videos^[28, 29]. Vocal features were extracted from audio recordings using speech signal processing technologies with Python's parselmouth-and pyaudioanalysis packages^[30, 31].

11 motor tasks were carefully designed based on clinical expertise and published studies^[32-37], with totally 186 motor features, to characterize the motor signs of early-stage PDs (Figure 1B). Each task lasted up to 1 minute and was followed by a rest period of about 30 seconds. Character instruction and example videos were displayed on the screen before each task to help participants finish the task. An instructor would provide movement demonstrations to participants when necessary. Motor features and tasks were outlined below, and feature definitions were displayed in Table S2~S5.

In the task of spontaneous eye blinking (SEB), participants sat in a relaxed position with their heads stabilized by a U-shaped fixator to minimize head movement, positioned 0.55m from the camera and 0.7 m from the display. They were instructed to look at a gray dot located at the center of the white-background display in a silent room under natural lighting conditions for 2.5 minutes. Features were extracted for the last 2 minutes of the recording, including spontaneous eye blink rate (sEBR), spontaneous eye blink cycle (sEBC), the durations for eyelid closing and reopening, negative and positive amplitude-velocities^[32, 33]. In

the saccade task, participants, sitting with the same position to the eye blinking task, were instructed to perform the prosaccade and antisaccade tasks in sequence. The procedures referred to a previous study in which a high-speed video system was used to measure eye saccade movements ^[34]. The latter 20 times of both the pro-saccade and anti-saccade were included in the analysis. A total of 16 features were extracted from 98 2D-facial keypoints, including reaction time, amplitude, velocity, times of correct-reaction, error-reaction and non-reaction and error rate. In the task of facial expression during passage reading (FEDPR), participants read a given popular nursery rhyme of 92 words displayed on the screen at a comfortable pitch and loudness. 31 facial features were detected and extracted during the task, including sEBR, eyebrow elevation, eyebrow tilt, eyebrow shape, palpebral aperture, upper and lower lip elevation, mouth height and mouth corner adduction/abduction ^[6]. Then, participants spoke freely for 1 minute on one of three topics (childhood memories, hobbies, or family) that were displayed on the screen. Features from facial expression during monologue (FEDM) were detected and extracted following the same procedures in the reading passage task ^[6].

Four tasks were performed to collect vocal features. In the task of sustained vowel (SV), participants firstly performed took a deep breath and then perform sustained phonations of vowel “ah” (a vowel in mandarin) three times, then “a” (a vowel in English) three times. Vocal features from this task included $F0_{SD}$, Jitter, Shimmer, CPP_{median} , CPP_{P25} , CPP_{P75} , RFA, HNR ^[26/35]. In the task of sequential and alternating motion rates (SAAMR), participants were asked to repeat the syllables "pa/-/ta/-/ka/" as quickly and accurately as possible within one breath, completing at least 12 cycles per trial, three trials. Vocal features were collected, including DDK rate, DDK regularity, VOT, RFA ^[35]. In the task of passage reading (PR),

participants completed this task in the aforementioned procedures. Eight vocal features were extracted from each task, including sound intensity, $F0_{SD}$, NSR, DPI_{median} , DPI_{P25} , DPI_{P75} , and RFA [35, 36]. The detailed procedures of monologue were displayed above. Nine vocal features were extracted from this task, including speech duration, sound intensity, $F0_{SD}$, NSR, DPI_{median} , DPI_{P25} , DPI_{P75} , and RFA [35, 36].

Three tasks were designed for collecting limb and walking motor features. Firstly, participants performed the finger-tapping task (FT), following the procedures of the MDS-UPDRS-III item 4. Features were measured bilaterally, including velocity, velocity change trend, amplitude, amplitude change trend and ASA [37]. Then, participants underwent the toe-tapping task, following the procedures of the MDS-UPDRS-III item 7. Extracted features were consistent to those in the finger tapping task. Finally, in the gait task, participants stood at a start point with back towards the camera with a distance of 1.5 m, then walk straightly for a 4 m distance, then turn and return to the start point, at a preferred walking speed. Gait features included shoulder tilt, hand-ground gap, arm swing amplitude, arm swing angle, arm swing velocity, calf swing range, foot elevation, stride cycle, stride length, stride velocity, cadence, stride width, and turning duration. These features were extracted for both the left and right limbs, with asymmetry (ASA) and coefficient of variation (CV) also quantitatively assessed, resulting in a total of 38 features characterizing walking.

Model structure, development and validation

Firstly, we performed feature selection for each motor task in the development cohort, following the condition of P values < 0.05 when comparing PDs with HCs (Figure 1C). Selected features were considered as potential digital biomarkers (PDBs) for PDs. Each modality containing PDBs would be used in the following model development and validation. We then performed optimal modality Selection. In this part,

we constructed a full-modality classification model incorporating all modalities and separate unimodal models in the development cohort through machine learning algorithms. Four classifiers would be used in model training and validation, including logistic regression (LR), support vector machine (SVM), random forest (RF), and multilayer perceptron (MLP). Modal performance was evaluated in the development cohort using 10-fold cross-validation method. Optimal modalities (OM) were selected following the three sequential criteria: 1) being important in decision-making of full-modality model; 2) being capable to distinguish PDs from HCs; 3) having stable classification performance (Figure 1C). Shapley additive explanations (SHAP) analysis was first conducted to assess the modality importance^[38]. We defined the importance score of each modality in a classifier for one fold as the ratio of the sum of its PDBs' absolute SHAP values to the total SHAP values of all PDBs^[39]. A modality would be considered important if its sum of 10-fold average importance score among four classifiers exceeds 0.36, corresponding to the expected average contribution of one modality among the 11 evaluated modalities ($0.36 \approx 4 * 1/11$). Unimodal models achieving an average area under the receiver operating characteristic curve (AUC) of higher than 0.6 were deemed capable of distinguishing PDs from HCs, and those with CV of AUC below 0.15 were considered to have stable classification performance. These two thresholds were specified a priori based on previous methodological experience^[40]. Finally, multiple classification models were developed by combining OM in different configurations to identify the streamlined-modality model with the best performance. The performance of both the full-modality model and the streamlined model were evaluated in the validation cohort (Figure 1D).

Model Classification performance was evaluated through five metrics: accuracy, precision, recall,

specificity, and area under the receiver operating characteristic curve (AUC)^[29-31]. Calibration curves and decision curve analysis (DCA) were applied in the validation cohort to evaluate the calibration and clinical usefulness of the streamlined model for early-stage PD detection.

Statistical Analysis

Continuous variables in normal distribution were described as mean (standard deviation, SD), continuous variables in skewed distribution were described as median (interquartile range), and categorical variables were described as counts. T-Test or Mann-Whitney test was used in continuous variables comparison, ANOVA was used in categorical variables comparison. DeLong's test was used to compare the AUCs between the streamlined model and the other combinations of OMs. Data description and comparison were performed using SPSS 27. We performed 10-fold cross-validation to evaluate the performance in each model training process. Performance metrics were presented as mean (SD) in the tables, with 95% confidence intervals (CIs) reported in the results. All models were implemented by Python, version 3.8.

Data Availability

The datasets analyzed during the current study consist of video and audio recordings are collected from human participants and are not publicly available due to privacy and ethical restrictions. The dataset, study protocol, and statistical analysis methods are available from the corresponding author upon reasonable request and subject to appropriate ethical.

Code Availability

The underlying code for this study is available in the PD_early repository and can be accessed via this link:

https://github.com/sherrywan/PD_early/tree/main.

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Author Contributions

ZG.L. and X.Z. designed the study; Y.W. and XY.W. designed the detailed scheme; YW. Z. and SL.Y. finished clinical assessments and motor tasks; W.C., J.G., C.Q., N.W., L.L., L.S., Y.Z. recruited the participants; Y.W., YW. Z. and L.R. performed participants screening; L.R. and ZH.L. completed the data collation; Y.W. and YW. Z. performed the clinical data analysis; X.Z. and XY. W. designed the algorithm framework; ZR.L. implemented the software pipeline; XY. W. and BZ.D. completed the instructional video; YH.C. realized the perception and measurement algorithm of facial expression muscle and eyeball movement modalities and extracted features; BZ. D., YX.L. and ZX.Z. completed the algorithm and feature extraction of limb and laryngeal modalities respectively; XY.W. completed the training and validation of detection models and the analysis of the OMs; Y.W. and XY.W. wrote the manuscript; ZG.L. and X.Z.

revised the manuscript. All authors reviewed the manuscript and approved the submission.

Competing Interests

The authors declare no competing financial or non-financial interests.

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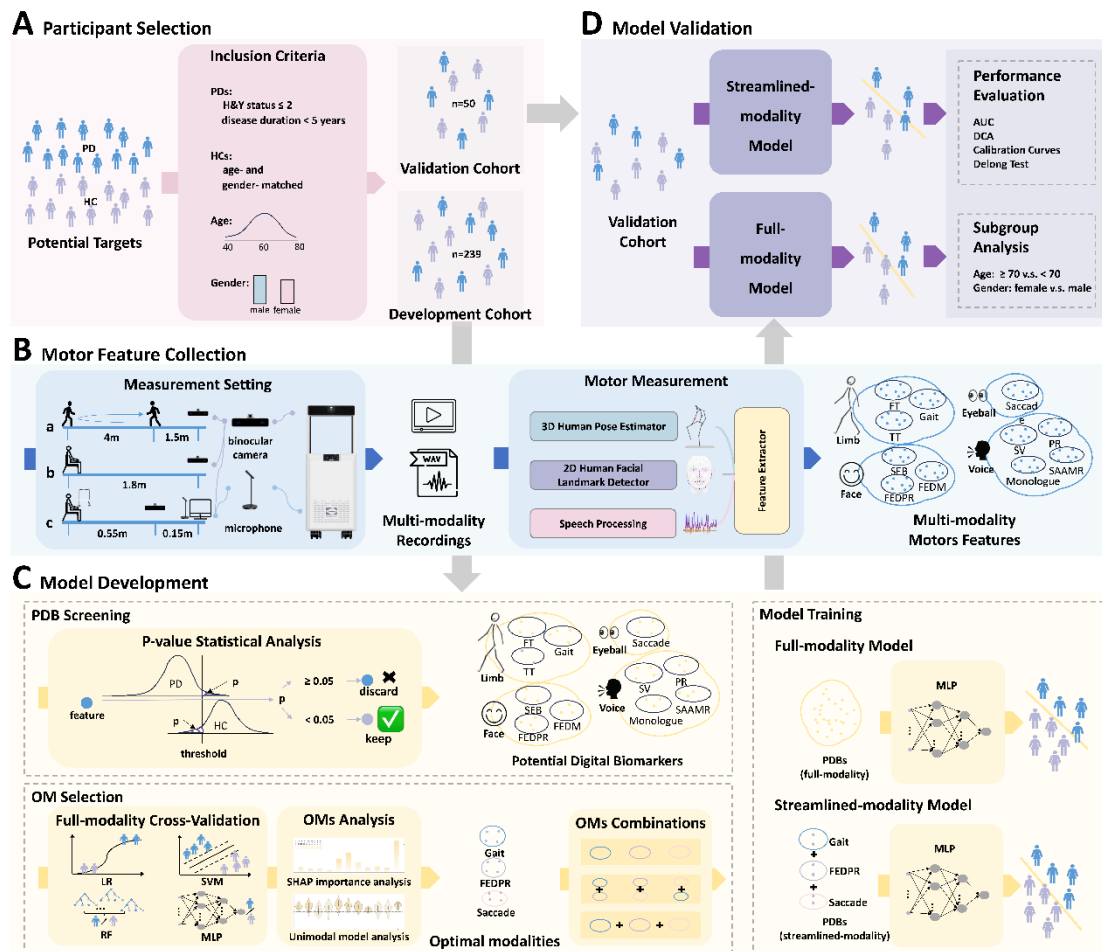


Figure 1 Workflow Pipeline. A. Participant Selection B. Motor Feature Collection C. Model development. PDBs, screened by between-group comparison, were used to build each modality. All modalities were used to develop full-modality models. OMs were selected following steps of SHAP analysis, assessments of unimodal model classification performance and stability. Multiple classification models were developed by combining OMs in different configurations to identify the streamlined-modality model with the best performance. D. Model validation. PD: Parkinson's disease; H&Y Stage: Hoehn-Yahr (H&Y) stage; SEB: spontaneous eye blinking; FEDPR: facial expression during passage reading; FEDM: facial expression during monologue; SV: sustained vowel; SAAMR: Sequential and alternating motion rates; PR: passage reading; FT: finger tapping; TT: toe tapping; PDB: potential digital biomarkers; OM: optimal modalities; AUC: area under the receiver operating

characteristic curve; DCA: decision curve analysis; MLP: multilayer perceptron.

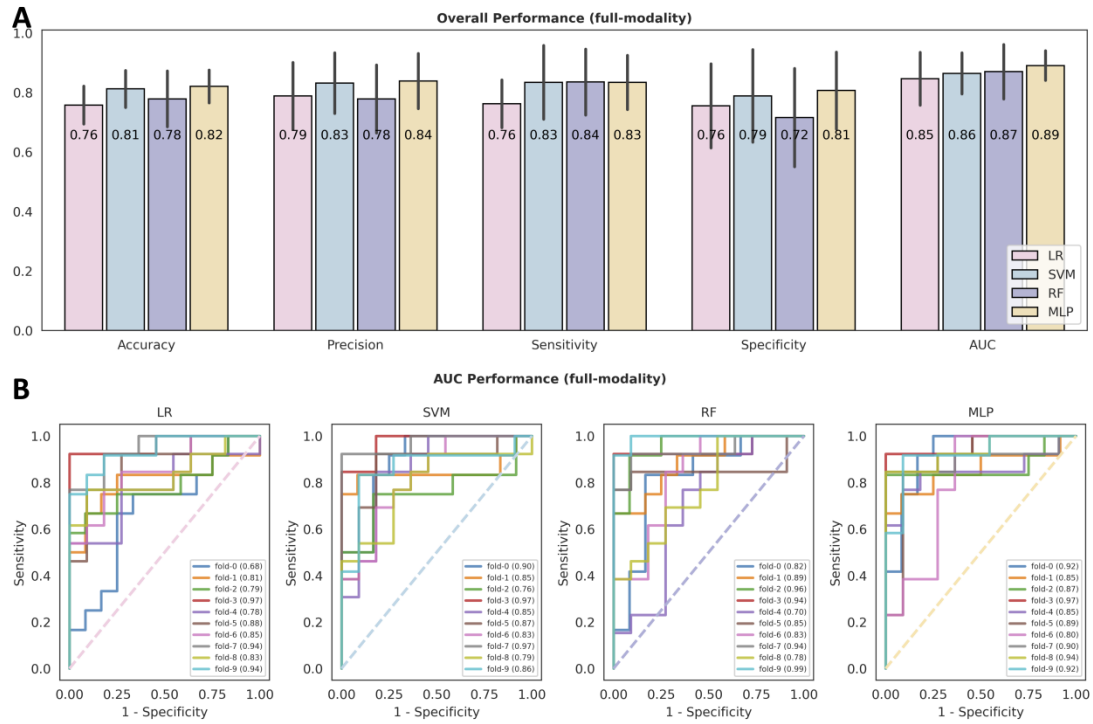


Figure 2 Model performance in the development cohort. A. Overall results of 10-fold cross-validation for full-modality models. B. 10-fold cross-validation AUC of full-modality models. AUC: area under the receiver operating characteristic curve; LR: logistic regression; SVM: support vector machine; RF: random forest; MLP: multilayer perceptron.

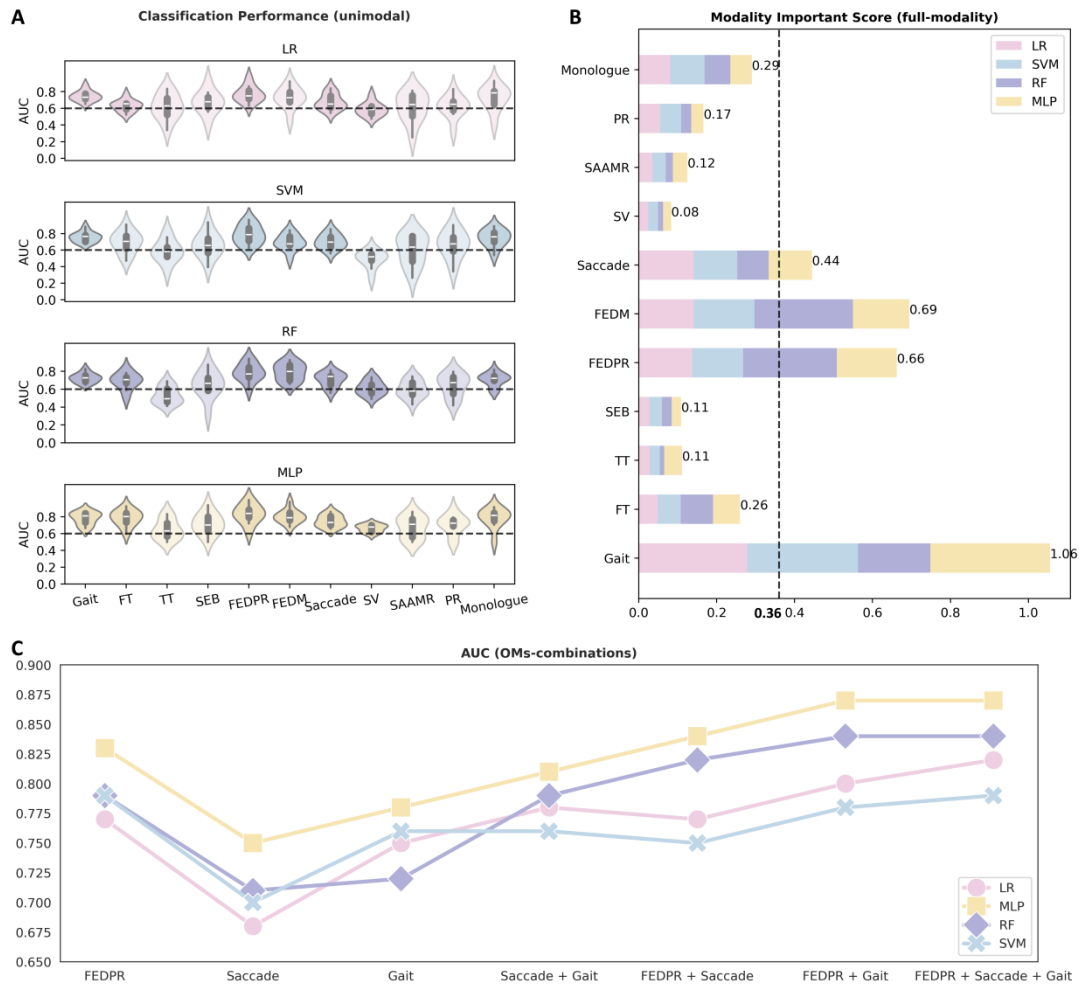


Figure 3 Modality analysis. A. 10-fold cross-validation AUC of unimodal models, with thresholds of AUC mean = 0.6 and CV = 0.15; lighter shading denotes instability (CV > 0.15). B. Sum of 10-fold average importance scores across four classifiers for modalities in full-modality models, with a threshold of 0.36. C. 10-fold cross-validation AUC mean of OMs-combination models. AUC: area under the receiver operating characteristic curve; LR: logistic regression; SVM: support vector machine; RF: random forest; MLP: multilayer perceptron; SEB: spontaneous eye blinking; FEDPR: facial expression during passage reading; FEDM: facial expression during monologue; SV: sustained vowel; SAAMR: Sequential and alternating motion rates; PR: passage reading; FT: finger tapping; TT: toe tapping.

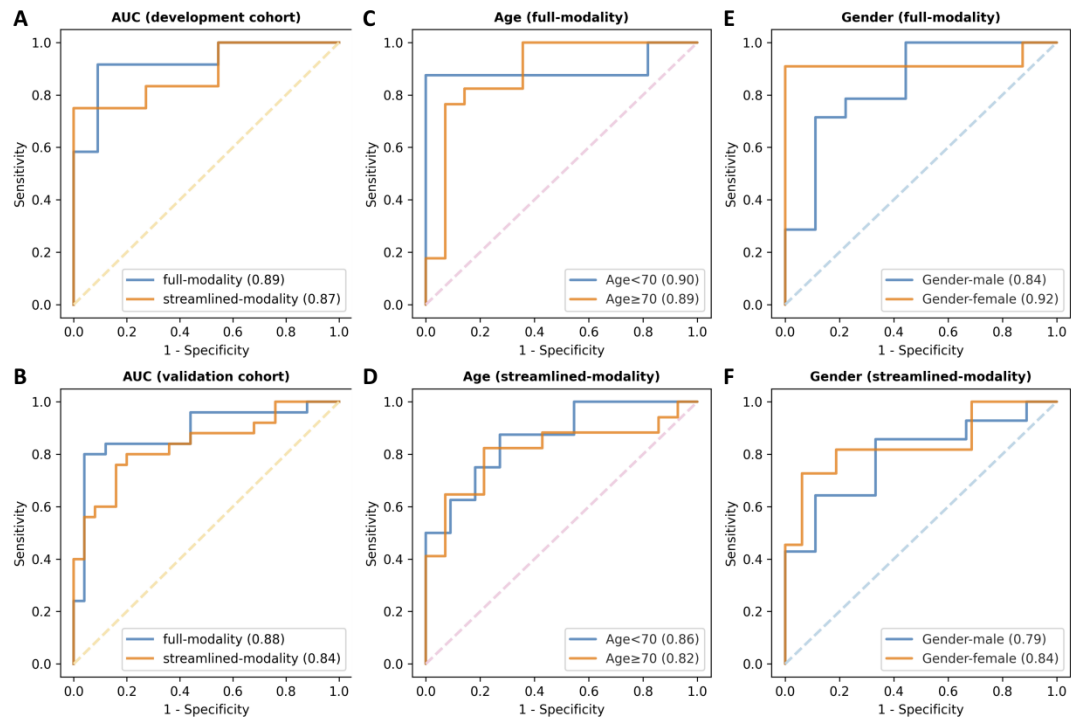


Figure 4 Model Performance and subgroup analysis. A: AUCs of the two different models in the development cohort. B: AUCs of the two different models in the validation cohort. C~F: AUCs of the MLP full-modality model and streamlined-modality model across specific subgroups identified by age and gender in the validation cohort.

Table 1 Comparison on the clinical characteristics between PDs and HCs

	Development cohort			Validation cohort		
	PDs (n=126)	HCs (n=113)	P value	PDs (n=25)	HCs (n=25)	P value
age, years	69(64~74)	68(61~72)	0.051 ^a	72(67~75)	71(63~74)	0.45 ^a
gender(male/female), n	61/65	48/65	0.39 ^b	14/11	9/16	0.16 ^b
Moca score	24(21~26)	23(22~26)	0.21 ^a	25(22~26)	27(26~28)	<0.001 ^{a,c}
Disease duration (time since onset of motor symptoms), months	20(13~34)	NA	NA	23(7~35)	NA	NA
Initial motor symptom (tremor/stiffness/bradykinesia/gait change), n	76/9/30/11	NA	NA	13/0/9/1	NA	NA
Side of onset (right/left/both/head), n	56/38/28/4	NA	NA	9/9/5/1	NA	NA
MDS-UPDRS-III score	25(19~34)	NA	NA	30(23~41)	NA	NA
HY stage (1/2), n	52/74	NA	NA	9/14	NA	NA
Motor phenotype, n (TD/PIGD/Indeterminate)	29/79/18	NA	NA	6/14/5	NA	NA
Affected body part at assessment (upper/lower/both), n	8/0/118	NA	NA	3/0/22	NA	NA

a: Comparison by Mann-Whitney test; b: Comparison by ANOVA; c: $p < 0.05$; PDs: PD patients; HCs: healthy controls; Moca: Montreal Cognitive Assessment; MDS-UPDRS-III: Movement Disorder Society Unified Parkinson Rating Scale-III; HY: Hoehn-Yahr; TD: tremor dominant phenotype; PI GD: postural instability/gait difficulty phenotype.

Table 2 Feature Screening by between-group comparison

	PDs (n=126)	HCS (n=113)	P value
Saccade			
pro-saccade			
amplitude, %	0.067(0.060~0.085)	0.079(0.067~0.094)	0.002 ^{a,c}
velocity, %/s	0.017(0.013~0.026)	0.023(0.017~0.038)	0.001 ^{a,c}
no reaction times, times	7(4~12)	6(3~10)	0.003 ^{b,c}
anti-saccade task			
amplitude, %	0.070(0.060~0.08)	0.082(0.070~0.098)	<0.001 ^{a,c}
velocity, %/s	0.018(0.013~0.025)	0.025(0.016~0.038)	<0.001 ^{a,c}
correct reaction times, times	5(2~8)	7(5~10)	<0.001 ^{a,c}
no reaction times, times	8(5~13)	5(2~11)	0.003 ^{a,c}
error rate, %	52.48(25.79)	44.07(25.69)	0.007 ^{c, d}
SEB			
sEBR, times	16(4~31)	29(14~52)	<0.001 ^{a,c}
sEBC_sum, ms	3750.00(866.67~17716.67)	7700.00(2866.67~15766.6)	<0.001 ^{a,c}
FEDPR			
blinking rate, times/min	4.67(0.75~24.79)	21.24(6.58~48.58)	<0.001 ^{a,c}
eyebrow elevation SD, %	0.0021(0.0012~0.0036)	0.0044(0.0022~0.0095)	<0.001 ^{a,c}
eyebrow tilt, °			
left SD, °	0.033(0.021~0.049)	0.058(0.042~0.11)	<0.001 ^{a,c}
right SD, °	0.039(0.022~0.063)	0.078(0.044~0.18)	<0.001 ^{a,c}
eyebrow shape, °			
left mean,	39.45(36.61~41.57)	40.28(38.39~42.80)	0.046 ^{a,c}
left SD	1.83(1.30~3.31)	3.86(2.26~6.48)	<0.001 ^{a,c}

right SD	2.08(1.45~4.82)	4.18(2.44~8.79)	<0.001 ^{a,c}
palpebral aperture, pixel ²			
left SD	1273.43(540.76~2342.54)	2250.27(821.15~5136.78)	0.001 ^{a,c}
right SD	1152.39(511.76~2202.86)	2223.35(844.56~4913.59)	<0.001 ^{a,c}
upper lip elevation SD, %	0.00089(0.00059~0.0014)	0.0011(0.00086~0.0017)	<0.001 ^{a,c}
lower lip elevation SD, %	0.0067(0.0040~0.010)	0.0096(0.0067~0.014)	<0.001 ^{a,c}
mouth height SD, %	0.0067(0.0040~0.0097)	0.0083(0.0054~0.011)	0.003 ^{a,c}
mouth corner adduction, %			
left SD	0.0022(0.0014~0.0037)	0.0040(0.0029~0.0066)	<0.001 ^{a,c}
right SD	0.0018(0.0013~0.0030)	0.0033(0.0024~0.0053)	<0.001 ^{a,c}
FEDM			
blinking rate, times/min	29.66(11.65~58.75)	68.00(45.0~95.00)	<0.001 ^{a,c}
eyebrow elevation, %			
mean	1.40(0.19)	1.35(0.22)	0.048 ^{c, d}
SD	0.0046(0.0022~0.010)	0.010(0.0053~0.019)	<0.001 ^{a,c}
eyebrow tilt, °			
left SD	0.035(0.026~0.072)	0.12(0.050~0.32)	<0.001 ^{a,c}
right SD	0.047(0.027~0.13)	0.17(0.060~0.30)	<0.001 ^{a,c}
eyebrow shape, °			
left mean	39.54(3.71)	41.19(3.48)	0.001 ^{c,d}
left SD	3.23(2.10~5.43)	5.38(3.09~11.07)	<0.001 ^{a,c}
right SD	3.85(2.26~6.48)	5.37(2.98~11.67)	0.001 ^{a, c}
mean_ASA_3	-0.05(-0.13~-0.00026)	-0.022(-0.062~0.023)	0.002 ^{a,c}
palpebral aperture, pixel ²			
left SD	2659.23(1248.59~4999.72)	3919.14(1776.77~9633.53)	0.007 ^{a,c}
right SD	2205.53(931.94~4527.60)	4260.83(2090.71~9875.62)	0.001 ^{a,c}
upper lip elevation, %			
SD	0.0012(0.00073~0.0020)	0.0017(0.0011~0.0028)	0.001 ^{a,c}

lower lip elevation SD, %	0.0060(0.0038~0.010)	0.0081(0.0055~0.012)	<0.001 ^{a,c}
mouth height SD	0.0058(0.0035~0.0085)	0.0070(0.0048~0.010)	0.025 ^{a,c}
mouth corner adduction, %			
left SD	0.0024(0.0013~0.0055)	0.0037(0.0021~0.0073)	0.001 ^{a,c}
right SD	0.0026(0.0014~0.0046)	0.0049(0.0025~0.0085)	<0.001 ^{a,c}
mean_ASA_3	0.053(0.058)	0.032(0.064)	0.013 ^{c,d}
SD_ASA_3	-0.037(-0.032~0.40)	-0.20(-0.56~0.12)	0.007 ^{a,c}
SV_"ah"			
CPP _{p25} , dB	0.0043(0.0021~0.0076)	0.0025(0.0013~0.0066)	0.017 ^{a,c}
HNR, %	8.36(2.98)	9.43(3.10)	0.011 ^{c,d}
SV_"a"			
Jitter, %	0.078(0.15)	0.073(0.016)	0.019 ^{c,d}
SAAMR			
DDK regularity, s	0.10(0.082~0.15)	0.098(0.071~0.12)	0.031 ^{a,c}
VOT, s	0.060(0.053~0.067)	0.062(0.056~0.069)	0.036 ^{a,c}
RFA, Hz	1741.94(344.10)	1595.76(333.01)	0.002 ^{c,d}
PR			
sound intensity, dB			
mean	53.82 (50.11~56.44)	51.42 (48.07~54.74)	0.006 ^{a,c}
SD	15.01 (13.16~16.74)	16.74 (14.59~19.07)	<0.001 ^{a,c}
DPI _{p25} , s	0.045 (0.040~0.070)	0.058 (0.046~0.081)	0.016 ^{a,c}
Monologue			
pause interval, s			
sum	12.50(5.94~21.80)	5.56(1.82~12.61)	<0.001 ^{a,c}
mean	2.90(2.05~4.01)	2.00(1.60~2.66)	<0.001 ^{a,c}
sound intensity, dB			
mean	72.03(2.78)	71.01(2.60)	0.007 ^{c,d}
SD	11.53(10.20~12.67)	12.20(10.99~13.15)	0.006 ^{a,c}

DPI _{P25} , s	0.046(0.041~0.065)	0.058(0.046~0.070)	0.009 ^{a,c}
DPI _{P75} , s	0.60((0.42~0.86)	0.48(0.32~0.68)	<0.001 ^{a,c}
Gait			
arm swing range, °			
left mean	0.029 (0.020~0.041)	0.040(0.028~0.055)	<0.001 ^{a,c}
right mean	0.028(0.020~0.043)	0.040(0.030~0.060)	<0.001 ^{a,c}
left SD	0.013(0.010~0.017)	0.016(0.012~0.022)	0.001 ^{a,c}
right SD	0.012(0.0092~0.016)	0.016(0.012~0.020)	<0.001 ^{a,c}
left CV	48.94(35.99~61.96)	41.90(29.27~55.87)	0.012 ^{a,c}
right CV	44.47(32.77~57.21)	40.05(30.24~50.35)	0.025 ^{a,c}
ASA_1	11.68(5.07~19.38)	7.32(4.02~12.15)	<0.001 ^{a,c}
arm swing angle, °			
left mean	48.30(38.62~58.79)	55.97(43.93~69.51)	<0.001 ^{a,c}
right mean	36.8430.93~43.57)	39.25(33.72~48.22)	0.016 ^{a,c}
calf swing angle, °			
left mean	67.15(61.43~71.80)	69.80(66.44~75.00)	0.001 ^{a,c}
right mean	62.73(7.30)	65.02(5.76)	0.003 ^{c,d}
foot elevation, %			
left mean	0.083(0.016)	0.089(0.017)	0.010 ^{c,d}
right mean	0.086(0.075~0.094)	0.092(0.085~0.10)	<0.001 ^{a,c}
stride length, mm	530.00(407.69~588.89)	588.89(481.82~662.50)	<0.001 ^{a,c}
stride velocity, mm/s	474.15(404.00~589.89)	558.29(478.00~686.20)	<0.001 ^{a,c}
stride width, %	0.092(0.023)	0.077(0.024)	<0.001 ^{c,d}
turning duration, s	1.62(1.47~1.84)	1.40(1.30~1.53)	<0.001 ^{a,c}
FT			
velocity, times/min			
left	1.40(0.58)	1.66(0.39)	<0.001 ^{c,d}
right	1.40(0.54)	1.60(0.38)	<0.001 ^{c,d}

amplitude ASA_2	0.48(0.20~0.99)	0.32(0.14~0.59)	0.005 ^{a,c}
TT			
velocity ASA-2, times/min	0.34(0.16~0.57)	0.19(0.11~0.36)	0.001 ^{a,c}

^a: Comparison by Mann-Whitney test; ^c: p<0.05; ^d: Comparison by T-Test; PDs: PD patients; HCs: healthy controls; sEBR: spontaneous eye blink rate. sEBC: spontaneous eye blink cycle; FEDPR: facial expression during passage reading; FEDM: facial expression during monologue; SD: standard deviation; SV: sustained vowel; SAAMR: Sequential and alternating motion rates; PR: passage reading; FT: finger tapping; TT: toe tapping. ASA_1: asymmetry_1; Cepstral Peak Prominence; HNR: Harmonic Noise Ratio; DDK: Dysphonia Detection Kit; VOT: Voice Onset Time; RFA: Relative Formant Amplitude; DPI: Duration of pause intervals; CV: coefficient of variation; ASA_2: asymmetry_2

Table 3 Digital biomarkers within optimal modalities

OMs	PDBs
Saccade	Pro-saccade: amplitude, velocity, no reaction times of pro-saccade; Anti-saccade: amplitude, velocity, correct reaction times, no reaction times, error rate.
FEDPR	blinking rate, eyebrow elevation SD, left and right eyebrow tilt SDs, left eyebrow shape mean and SD, right eyebrow shape SD, left and right palpebral aperture SDs, upper and lower lip elevation SDs, mouth height SD, left and right mouth corner adduction SDs
Gait	left and right arm swing range means, SDs and CVs, arm swing range ASA_1, left and right arm swing angle means, left and right calf swing angle means, left and right foot elevation means, stride length, stride velocity, stride width, turning duration

OM: optimal modality; PDB: potential digital biomarkers; FEDPR: facial expression during passage reading; SD: standard deviation; ASA_1: asymmetry_1; CV: coefficient of variation.

SUPPLEMENTARY INFORMATION

The online version contains the supplementary material.