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RESEARCH

Eye movement parameters as biomarkers for diagnosis and levodopa responsiveness in patients with Parkinson's disease

Qibing Luo[1,2] · Ziqi Gao[2] · Qi Qi[2] · Siming Rong[2] · Rui Yang[2] · Chentao He[2] · Mengfei Cai[2] · Piao Zhang[2] · Yuhu Zhang[1,2]

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Abstract

Background Abnormalities in characteristic eye movements have been identified in Parkinson's disease (PD) patients.

Aim To determine if eye movement parameters can serve as biomarkers for diagnosing PD and predicting therapeutic responses to levodopa.

Methods We enrolled 128 PD patients and 28 healthy controls, assessing eye movements before and after levodopa administration.

Results Specific eye movement parameters robustly differentiated PD patients from controls, with an AUC of 0.856, and maintained robustness post-levodopa. Correlations were found between changes in eye movement parameters and motor symptom improvements, leading to a predictive model for levodopa responsiveness with an AUC of 0.783.

Discussion and conclusions Eye movement assessments offer an objective tool for PD diagnosis and levodopa responsiveness prediction.

Keywords Parkinson's disease · Prosaccades · Antisaccade · Biomarkers · Levodopa

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease [1]. Despite the availability of established diagnostic criteria and guidelines [2], early diagnosis of PD remains challenging. The accurate identification rate is only 26% in untreated patients or those with minimal response to treatment, and 53% in patients who respond well to levodopa [3]. In recent years, eye movement has emerged as a promising objective, easy to operate and non-invasive tool for characterizing motor and cognitive dysfunction [4]. Characteristic abnormalities in eye movement parameters, such as prolonged saccade latency and decreased saccade velocity in both the prosaccade test and the antisaccade test, are commonly observed in PD [5–8]. Prior studies have identified a correlation between eye movement and motor symptom in PD [9], however, the diagnostic value of eye movement parameters in PD remains to be fully elucidated.

The acute levodopa challenge test is a widely accepted procedure for assessing the therapeutic response to dopaminergic treatment in patients with PD [2, 10]. Despite the involvement of experienced evaluators, this test is still susceptible to subjective bias. Recent research on PD has suggested levodopa treatment may exacerbate saccadic parameters, resulting in prolonged saccade latency and diminished saccade velocity [8, 9, 11], which apparently contrasts with levodopa's beneficial effects on motor symptoms in PD. However, the relationship between these changes in eye movement and the improvement of motor symptoms is not well defined. Additionally, it remains unclear whether eye movement parameters can serve as objective markers of levodopa responsiveness in PD patients.

This study aimed to ascertain whether eye movement parameters can be employed as biomarkers for the diagnosis of PD and for predicting the therapeutic response to levodopa in PD patients. Since previous studies have reported an effect of levodopa on eye movements in PD, we

✉ Yuhu Zhang
zhangyuhu@gdph.org.cn

1 Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong Province 510080, China

2 Department of Neurology, Guangdong Neuroscience Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, No. 106 Zhongshan Er Road, Guangdong ProvinceGuangzhou 510080, China

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also investigated the effect of levodopa on the performance of eye movements in diagnosing PD.

Methods

Study design and participants

PD patients and healthy controls (HC) were prospectively enrolled from our neurology department in Guangdong Provincial People's Hospital between August 2022 and August 2024. The PD patients were recruited from in-patients and out-patients at our hospital during the study period. The HC were also recruited from our hospital, primarily consisting of relatives of the PD patients and non-medical staff. Inclusion criteria for PD: Patients who met the diagnostic criteria of no red flags and absolute exclusion criteria formulated by the International Parkinson and Movement Disorders Society (MDS) in 2015 [2] were considered as clinically established PD after evaluation by two neurologists; Mini-Mental State Examination (MMSE) > 24 (for those received more than 6 years of schooling (junior high and above)) or MMSE > 20 (for those received 6 years of schooling or less (primary school education)) [12]. Exclusion criteria for PD: other central nervous systemic diseases; patients with developmental disorders (such as visual and auditory problems), high myopia, hearing abnormalities, color blindness, and other eye diseases that affect vision. The healthy controls had no history of neurological or psychiatric disorders. Finally, 28 eligible HC and 128 PD were selected for the study.

All participants underwent eye movement assessments. A flowchart of the eye movement data acquisition process and study design is shown in Fig. 1. PD patients were divided into two cohorts (cohort 1 ($n = 50$) and cohort 2 ($n = 78$)) based on whether they consented to the acute levodopa challenge test. Patients in cohort 1 underwent the acute levodopa challenge test, with eye movement assessments conducted both before and after administration of the medication. Within this cohort, we explored the potential of eye movement indicators as biomarkers for diagnosing PD and predicting levodopa responsiveness.

Cohort 2 was used to validate the diagnostic performance of eye movement indicators for PD in a more clinically representative setting. This cohort comprised PD patients in distinct states: medication-naïve, OFF or ON. The ON state was defined as the period of dopamine replacement therapy being effective and symptoms being controlled. The OFF state was defined as the period of poor symptom control. In this validation phase, the eye movement assessment of PD patients was performed only once.

Details of PD patients in the study can be found in the supplemental data. The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital. Signed informed consents were acquired from all participants.

Eye movement assessments

An eye-tracking system (Beijing CAS-Ruiyi Information Technology Co., Ltd) was used to record eye movement parameters at a sampling rate of 90 Hz.

Eye-tracking paradigms: (1) Gap prosaccade test: In this paradigm, a central fixation point is presented for an initial duration of 0.8 s, after which it disappears. Following a gap of 0.2 s, the fixation point reappears in a randomly selected direction. Participants are instructed to make a rapid saccade toward the newly presented point. This sequence is repeated 20 times. (2) Overlap prosaccade test: This saccade assessment begins with the presentation of a central fixation point, which remains visible for 1.2 s. However, 0.2 s prior to the disappearance of the fixation point, a target point appears randomly in one of the cardinal directions (up, down, left, right). Participants are directed to execute a rapid eye movement (saccade) toward the target as soon as it becomes visible. This procedure is also conducted for a total of 20 trials. (3) Antisaccade test: Initially, a fixation point is displayed centrally for 1 s before it disappears. Subsequently, a target point appears in one of the four cardinal directions. Participants are instructed to make a saccade in the direction opposite to that of the target, necessitating the voluntary inhibition of the reflexive saccade towards the target. This trial is repeated 20 times.

In each of these paradigms, the recorded parameters include saccade latency (ms) and average saccade velocity (°/s).

Acute levodopa challenge test

PD patients in cohort 1 were pretreated with 20 mg domperidone 1 h before the test to prevent side effects. For drug-naive patients, the levodopa dose was 250 mg levodopa/benserazide in the morning and the fasting state. For patients receiving long-term treatment, long-acting dopamine agonists were discontinued 72 h before the evaluation date and all anti-Parkinson's drugs were discontinued 12 h before the test date. Besides, levodopa dose was levodopa/benserazide 1.5 times the individual morning levodopa dose [13]. Motor scores were evaluated using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) before and 1 h after medication [14]. According to the total improvement rate, PD patients were divided into two groups: the definite response group, which corresponds to an improvement of 24.5% or more,

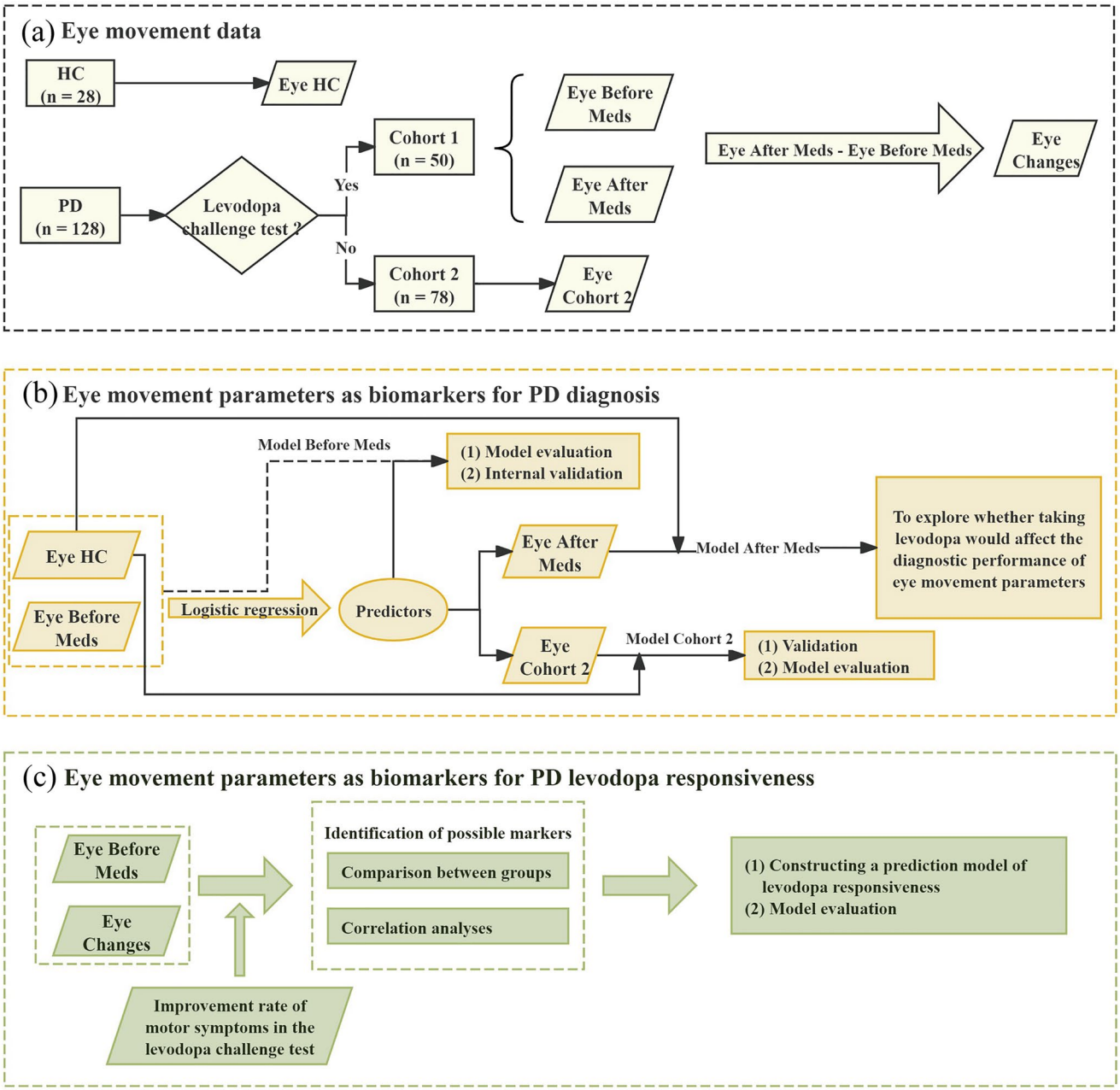

Fig. 1 Flowchart of eye movement data acquisition process and study design. (**a**) PD were divided into two cohorts depending on whether they consented to an acute levodopa challenge test. The study evaluated the eye movement of HC and PD in cohort 2 once, and the eye movement of PD in cohort 1 twice. (**b**) We explored and validated the ability of eye movement parameters to diagnose PD: (1) We first used the eye movement parameters before levodopa administration to screen the predictors and construct the PD diagnostic model and model evaluation; (2) Another PD diagnostic model was constructed using eye movement parameters after levodopa administration to determine whether taking levodopa would affect the performance of the PD diagnostic model; (3) To verify the robustness of our selected predictors in the diagnosis of PD in cohort 2. (**c**) In this section, we searched for eye movement parameters that could predict levodopa responsiveness in PD

and the limited response group, which corresponds to less than 24.5% improvement [15, 16]. This 24.5% threshold is equivalent to a 30% change in the UPDRS III score. The score of each sub-symptom was calculated both before and after medication, including rigidity, bradykinesia, rest tremor, gait impairment, and axial impairment [17].

Statistical analysis

Demographics and clinical characteristics were compared between PD and HC groups using t-test or Mann-Whitney U test for continuous variables, and chi-square test for categorical variables. The independent-samples t-test or

Mann-Whitney U test was employed to compare the eye movement parameters between the PD groups and the HC group, and between the PD definite response group and limited response group, while the paired-samples t-test or Wilcoxon signed rank test was utilized to compare the eye movement parameters between before and after medication in PD patients.

PD diagnostic model construction and evaluation

In cohort 1, we constructed and evaluated a PD diagnostic model using eye movement parameters. According to the Akaike information criterion (AIC), multiple stepwise regression (direction = "both") was performed to establish the diagnostic model. The variance inflation factor (VIF) was used to evaluate the multicollinearity among variables (VIF > 10 was considered strong collinearity) [18]. The diagnostic accuracy of eye movement parameters was determined using the Receiver Operating Characteristic (ROC) curve. DeLong's test was applied to compare the performance of the diagnostic models by examining variations in the area under the curve (AUC) [19]. Hosmer-Lemeshow (H-L) test and calibration curve were used to assess calibration. Decision Curve Analysis (DCA) was used to evaluate the clinical usefulness and net benefit. The internal validation of the diagnostic model was performed using bootstrap with 500 replicates to obtain an AUC. In cohort 2, validation of the diagnostic model was performed using the AUC, H-L test, calibration curve, and DCA.

Identification of eye movement markers and development of predictive models for levodopa responsiveness in PD patients

In cohort 1, correlation analyses were conducted to identify biomarkers that predict levodopa responsiveness by examining the relationships between eye movement parameters (before medication), changes in eye movement (after medication – before medication), and motor symptom improvement rates in the acute levodopa challenge test. Spearman or Pearson correlation tests were employed as appropriate, with false discovery rate (FDR) correction applied for multiple comparisons. The logistic regression analysis method mentioned above was utilized to develop a prediction model of eye movement parameters for PD levodopa responsiveness and to construct the corresponding ROC curve.

Statistical analyses and graphical representation were conducted utilizing R version 4.3.2. The statistical significance level was set at a two-sided P-value < 0.05.

Results

Clinical characteristics of participants

The clinical characteristics of all subjects are shown in Table 1. A total of 128 PD patients and 28 HC were included in this study. Although PD patients in our study had no cognitive impairment, the education years ($p < 0.01$) and MMSE ($p < 0.05$) of PD patients in both cohorts were lower than those in HC. PD in cohort 2 had a longer disease duration, higher MDS-UPDRS III scores, higher MMSE scores, and higher LEDD than PD in cohort 1 ($p < 0.05$).

Effects of levodopa on eye movement parameters in PD patients

In cohort 1, the latency of prosaccade tests was significantly increased in PD compared to HC ($p < 0.001$), and the difference was further increased after levodopa administration (compared with before medication, $p > 0.05$) (Fig. 2a and b).

Table 1 Clinical characteristics of participants

	HC ($n = 28$)	PD in cohort 1 ($n = 50$)	PD in cohort 2 ($n = 78$)
Gender = Female (%)	16 (57.1)	26 (52.0)	29 (37.2)
Age, years	63.50 [56.75, 68.00]	62.50 [58.00, 67.00]	61.00 [54.00, 67.00]
Disease duration, years	NA	2.00 [1.00, 2.50]	3.00 [1.50, 5.00] [f]
Education, years	12.07 (2.61) [a]	9.20 (4.74) [a, d]	9.00 [8.00, 12.00] [d]
MMSE	29.00 [28.00, 29.00]	27.00 [25.00, 28.75] [d]	28.00 [27.00, 29.00] [e, g]
Hoehn and Yahr	NA	2.00 [2.00, 2.00]	2.00 [2.00, 2.00]
MDS-UPDRS III	NA	26.50 [22.25, 34.75] [b]	33.00 [24.25, 45.00] [c, g]
LEDD, mg	NA	62.50 [0.00, 284.38]	300.00 [0.00, 471.25] [g]

Values represent Median [IQR]

[a] Mean (SD); [b] before medication; [c] Medication-naïve ($n = 15$), OFF ($n = 25$) or ON ($n = 38$) status

[d] Lower in PD than in HC, $p < 0.01$

[e] Lower in PD than in HC, $p < 0.05$

[f] Longer in cohort 2 than in cohort 1, $p < 0.01$

[g] Higher in cohort 2 than in cohort 1, $p < 0.05$

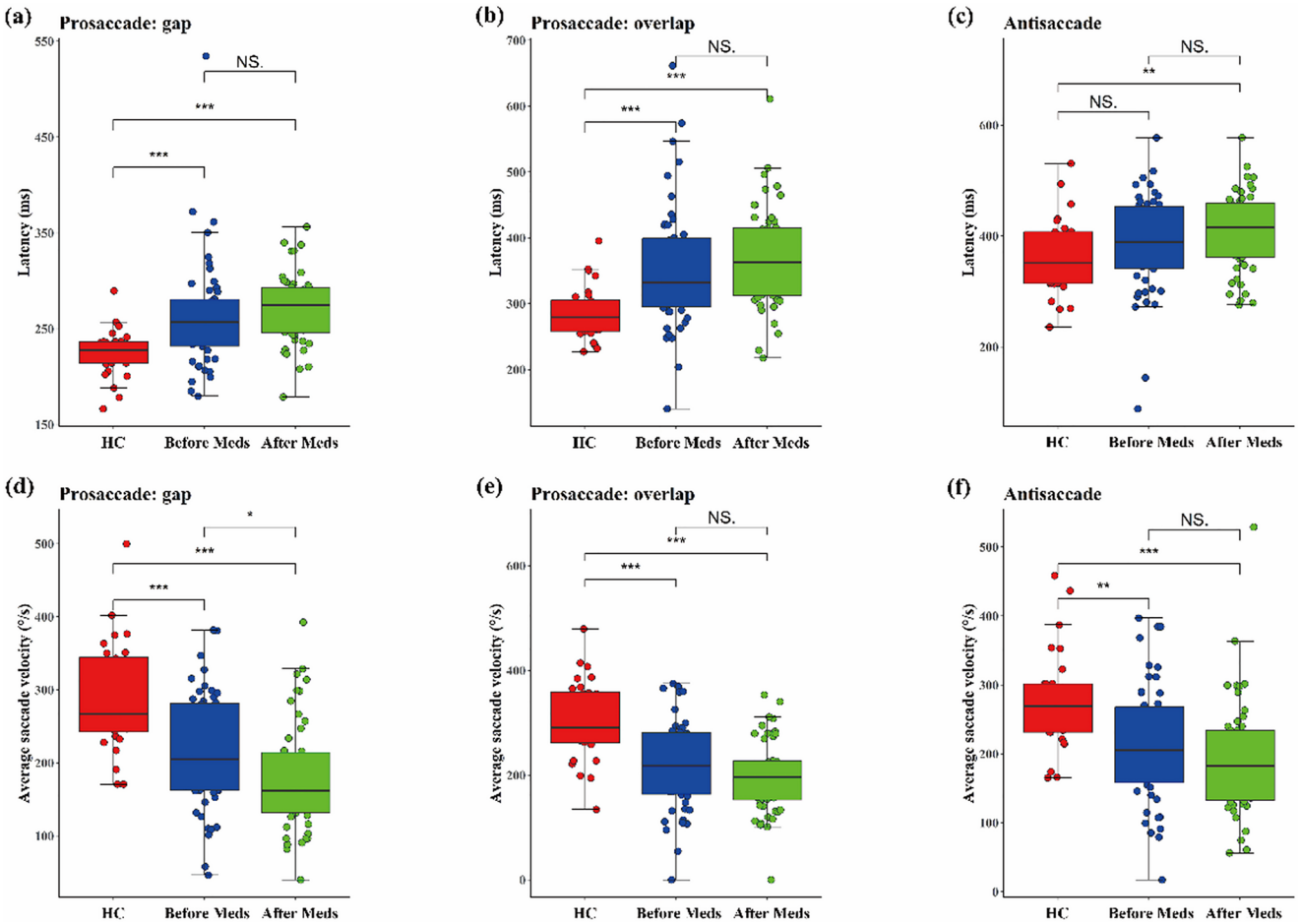

Fig. 2 Effects of levodopa on eye movement parameters in PD patients. (**a**) Latency in the gap prosaccade test. (**b**) Latency in the overlap prosaccade test. (**c**) Latency in the antisaccade test. (**d**) Average saccade velocity in the gap prosaccade test. (**e**) Average saccade velocity in the overlap prosaccade test. (**f**) Average saccade velocity in the antisaccade test. HC: healthy controls; Before Meds: eye movements were assessed before administration of the medication in the acute levodopa challenge test; After Meds: eye movements were assessed after administration of the medication in the acute levodopa challenge test. *$p<0.05$; **$p<0.01$; ***$p<0.001$; NS: no significance

The latency of antisaccade was also increased in PD compared with HC ($p>0.05$), and the difference was statistically significant after levodopa administration ($p=0.006$; compared with before medication, $p>0.05$) (Fig. 2c). The average saccade velocity of the gap prosaccade test, overlap prosaccade test and antisaccade test in PD group was lower than that in HC group ($p<0.001$, $p<0.001$, $p=0.002$, respectively), and further decreased after levodopa administration (Fig. 2d, e and f). Detailed results are in Supplementary Table 1. In the cohort 2, the same eye movement characteristics were observed in PD (Supplementary Table 2).

Development and validation of the PD diagnostic model

After stepwise selection, the latency of the gap prosaccade test and the average saccade velocity of the overlap prosaccade test were chosen as predictors and included in the logistic model (VIF = 1.166). The AUC of the model was 0.856 (0.845 in the internal validation), with a sensitivity of 68.0% and a specificity of 92.9%, as illustrated in Fig. 3. Moreover, the AUC value of the constructed model of these two eye movement parameters increased after medication (AUC = 0.941; Delong's test, $p=0.093$). There was no statistical difference between the AUC values of our model and the model constructed by all the eye movement parameters in the study ($p=0.375$).

The H–L test and calibration curve showed that calibration was adequate ($p=0.482$; Supplementary Fig. 1a). From the clinical decision curve, it can be seen that the net benefit value of our model is high (Supplementary Fig. 1b).

In the validation of our diagnostic model, AUC was 0.863 (95% CI: 0.793–0.933) (Supplementary Fig. 2), and the H-L test and calibration curve showed good calibration ($p=0.488$; Supplementary Fig. 3a). In the DCA, our model

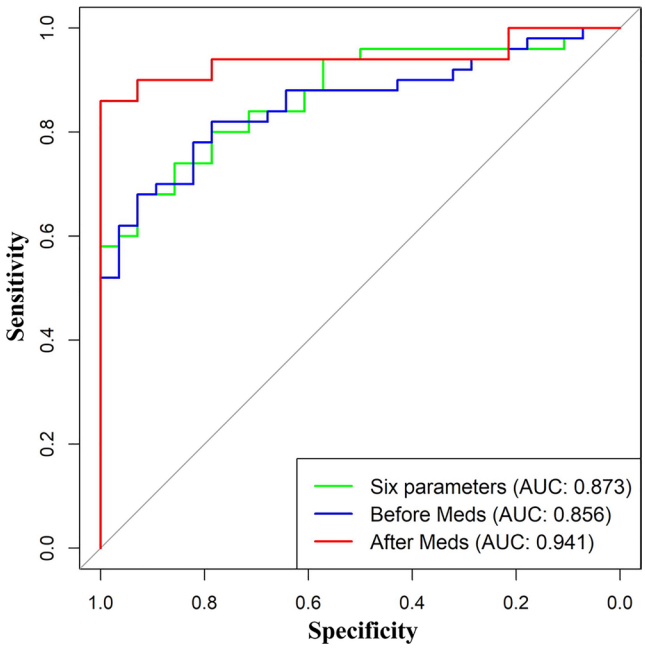

Fig. 3 ROC curves. Six parameters: including all eye movement parameters we collected; Before Meds: eye movements were assessed before administration of the medication in the acute levodopa challenge test; After Meds: eye movements were assessed after administration of the medication in the acute levodopa challenge test

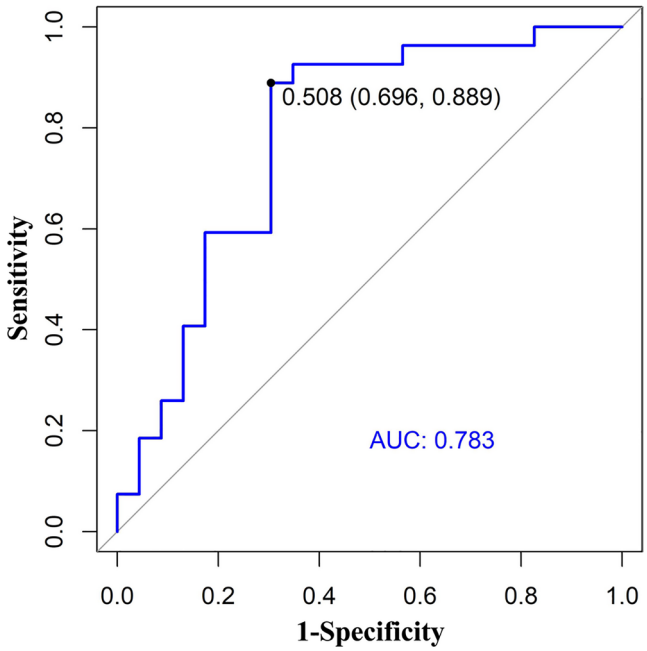

Fig. 4 The ROC curve of eye movement parameters (after – before medication) for predicting levodopa responsiveness in PD patients

had a higher net benefit than "All line" or "None line" for ≥34% of the probability of PD (Supplementary Fig. 3b).

Eye movement parameters in different Levodopa response groups

Neither the eye movement parameters before levodopa administration nor the changes in these parameters (after medication – before medication) showed a statistically significant difference between the definite response group and the limited response group ($p>0.05$) (Supplementary Table 3).

Association between eye movement parameters and the degree of improvement in motor symptoms

The average saccade velocity (before medication) in all eye-tracking paradigms we analyzed correlated negatively with the rate of improvement of axial symptoms (r range = -0.324 - -0.355, $p<0.05$). The average saccade velocity (after – before medication) in the gap and overlap prosaccade tests correlated negatively with the rate of improvement of bradykinesia symptoms (r = -0.291, $p=0.041$; r = -0.407, $p=0.003$, respectively). Moreover, the average saccade velocity (after – before medication) in the gap prosaccade test, overlap prosaccade test, and antisaccade test also correlated negatively with the rate of improvement of axial symptoms (r = -0.481, $p<0.001$; r = -0.503, $p<0.001$; r = -0.391, $p=0.005$, respectively). After FDR correction, the average saccade velocity (after – before medication) in the gap and overlap prosaccade test still correlated negatively with the rate of axial symptoms improvement (both p(FDR)=0.014) (Supplementary Table 4). Considering the disease duration and motor symptoms severity may affect the improvement rate of motor symptoms and eye movement, we adjusted the following covariates: age, gender, education, disease duration and MDS-UPDRS III (before medication). After adjustment for confounders, the correlation between the average saccade velocity (after – before medication) in the gap and overlap prosaccade test and the improvement rate of axial symptoms remained (r = -0.381, $p<0.01$; r = -0.441, $p<0.01$, respectively).

A predictive model of levodopa responsiveness in PD was constructed using eye movement parameters (after – before medication)

After stepwise selection, the latency of the overlap prosaccade and antisaccade tests and the average saccade velocity of the overlap prosaccade test were included in the model (Supplementary Table 5). The AUC of the model was 0.783, with a sensitivity of 88.9% and a specificity of 69.6%, as illustrated in Fig. 4.

Discussion

In this study, we endeavored to explore the clinical utility of eye movement parameters in both diagnosing PD and predicting levodopa responsiveness. Our findings suggest that these parameters are not only effective for diagnosing PD but also maintain their diagnostic robustness regardless of levodopa treatment. This implies that eye movement assessments can be applied to both medication-naïve patients and those undergoing treatment, a claim further substantiated by the validation in cohort 2. The diagnostic potential of eye movement tools in PD is indeed promising, as evidenced by our results.

We conducted between-group comparisons and correlation analyses to identify eye movement markers predictive of levodopa responsiveness in PD patients. We observed that alterations in eye movement parameters were significantly correlated with the improvement rates of motor symptoms following levodopa administration. Building upon these findings, we developed and evaluated a predictive model, demonstrating that changes in eye movement can serve as predictive indicators of the therapeutic response to levodopa in PD patients. Collectively, these outcomes underscore the dual utility of eye movement indicators in both diagnosing PD and forecasting the efficacy of levodopa treatment.

In the prosaccade tests, PD patients showed prolonged latency and decreased average saccade velocity compared to healthy controls. Saccade deficits in PD patients have been confirmed in many studies [7, 9], which is most likely due to dual excessive suppression of the superior colliculus, resulting from direct downstream inhibition by the internal segment of the globus pallidus and substantia nigra, and a deteriorated pre-oculomotor drive via the frontal-basal ganglia circuit. In our study, we demonstrated levodopa had a negative effect on latency and average saccade velocity in the prosaccade tests. This negative effect was consistent with findings from previous studies [8, 11, 20]. One potential explanation is a dopamine overdose in dopaminergic regions not typically depleted in PD, such as the superior colliculus [21]. Specifically, when dopamine is flushed onto D2-expressing neurons in the superior colliculus, neural activity is suppressed, which in turn prolongs latency and slows down saccade speed. In addition, increased inhibition from the prefrontal cortex to subcortical structures (the superior colliculus) may be the other reason [20]. Frontal activity helps promote planned saccades by suppressing reflexive rapid saccades [22]. There was evidence that increased dopamine levels in the prefrontal cortex led to prolonged saccade latency [23].

To perform the antisaccade task, patients were required to: initiate a reflexive saccade; inhibit the saccade; and initiate voluntary antisaccades in the opposite direction [4]. Unlike reflex saccades, previous studies have proposed that levodopa intake may reduce the latency of antisaccades [22]. However, despite their agreement, Lu et al. [11] did not replicate the reduced effect of levodopa on antisaccade latency in their study. Similar to some research [20], we found in this study levodopa also prolonged the latency and decreased the average saccade velocity of antisaccade. The priming of antisaccade is seen as a frontal-based task primarily provided by the frontal eye fields (FEF) and dorsolateral prefrontal cortex (DLPFC) [24]. Two mechanisms are involved in the execution of this task: top-down suppression of reflex saccades towards targets, provided by the DLPFC; the trigger of intentional saccades in the opposite direction provided by the FEF [25]. At present, the effect of levodopa on the latency and average saccade velocity of antisaccade is controversial, and the mechanism is not clear. More studies are needed to validate our results and to elucidate the mechanism by which levodopa induces prolonged antisaccade latency and decreased antisaccade average saccade velocity.

Although previous studies have suggested the presence of abnormal eye movement parameters in PD patients, the efficacy of eye movement parameters in PD diagnosis has not been confirmed. We developed a diagnostic model utilizing eye movement parameters and assessed its robustness against the influence of levodopa administration in PD patients by comparing the AUC values before and after administration. Our results showed that the diagnostic performance of the model was not affected by levodopa and performed well. The diagnostic ability of this model was ideal with AUC values all greater than 0.85 in two cohorts. The well-performed calibration and clinical net benefits of the model were also demonstrated in both cohorts, suggesting that this diagnostic tool could be effectively applied to PD patients, irrespective of their medication status, and holds promising prospects for clinical use.

Historically, the assessment of levodopa responsiveness has been marred by subjectivity and reliant on clinical evaluations, which are susceptible to the biases of evaluators and the physical limitations of patients, such as motor deficits that impede task performance. Our study addressed this shortcoming by introducing eye movement metrics as an objective alternative. The observed correlation between changes in eye movement and improvements in specific motor symptoms, notably axial and bradykinesia symptoms, suggests a sensitivity of these metrics to dopaminergic therapy-induced changes. This is particularly relevant given that not all PD patients respond equally to levodopa, and some patients may exhibit resistance or a diminished response over time. The ability to predict levodopa responsiveness using eye movement parameters, as indicated by our ROC curve analysis, could revolutionize the way clinicians assess

treatment efficacy, potentially leading to more personalized and effective treatment plans for PD patients. However, our study noted no significant differences in eye movement parameters between patients with definite and limited levodopa responses. This may be attributed to the intricate relationship between eye movement changes and specific motor symptoms, which complicates the differentiation between groups based on overall improvement rates, as levodopa's effects on symptoms are not uniform.

In this study, we confirmed that eye movement parameters can effectively distinguish PD from HC, and in subsequent research, we aim to further validate the ability of these eye movement parameters to differentiate PD from atypical parkinsonian syndromes, including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). In addition, in this study, we found for the first time that eye movement parameters may be objective markers of levodopa responsiveness. More research is needed to further confirm and extend our findings in the future.

Conclusion

Eye movement is not only an objective indicator for PD diagnosis but also can be used to predict the response of PD patients to levodopa treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-025-03089-2.

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Author contributions Qibing Luo: Conceptualization, Methodology, Data curation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. Ziqi Gao and Qi Qi: Data curation. Siming Rong, Rui Yang, and Chentao He: Writing – review & editing. Piao Zhang and Mengfei Cai: Supervision, Software. Yuhu Zhang: Supervision, Funding acquisition, Conceptualization, Writing – review & editing, Resources.

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Data availability The data supporting the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital.

Informed of consent Signed informed consents were acquired from all participants.

Competing interests The authors declare no competing interests.

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