

Dynamic Characteristics of Saccade Trajectory and Velocity Profile, a Road to New Bio-markers for Parkinson's Disease

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Keywords

Parkinson's Disease;
Pro-saccade;
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Abstract

While Parkinson's disease (PD) is widely recognized for its motor symptoms, it also significantly impacts eye movements. Consequently, researchers are exploring saccade parameters as potential diagnostic biomarkers. However, current literature suggests that standard metrics—specifically latency, amplitude, and peak velocity—lack the sensitivity to serve as standalone diagnostic tools. This limitation likely stems from the inherent complexity of PD, coupled with the high intra-trial variability and the demanding "high-speed, high-accuracy" nature of saccadic movements.

This study investigated pro-saccade parameters in 15 individuals with PD (on medication) and 15 age- and sex-matched neurologically healthy controls (HC). Aimed to explore dynamic characteristic of saccades, landing-error-to-amplitude ratio, amplitude and area under curve (AUC) of saccade displacement trajectory, along with peak, median, and average velocity, and high-velocity-percentage (HVP), i.e. percent of saccade duration with velocity above median, were examined in distinguishing PD patients from HC group.

We found that high-velocity-percentage (HVP) was significantly higher ($p = 0.015$) and landing-error-to-amplitude ratio was significantly lower ($p = 0.002$) in the HC group. However, peak, median and average velocity, amplitude and AUC of saccade displacement did not show significant differences between the two groups. Although sensitivity and specificity values were not high, the two introduced parameters provided some discriminatory ability compared to standard metrics with no discrimination. These findings suggest that parameters offering a holistic perspective on saccadic position and velocity profiles may be more effective at distinguishing between PD patients and healthy controls (HC).

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, second only to Alzheimer's disease [1,2]. PD patients suffer a lot of movement symptoms including eye movement abnormalities [3,4].

Since saccade circuitry in brain is relatively known to the researchers, saccades are widely studied in PD patients in an attempt to better understand how PD affects the brain and its performance. Also, saccade parameters are being investigated as potential diagnostic biomarkers of PD [5-9].

However, in spite of extensive research, based on current literature, saccadic parameters such as duration, latency, amplitude, peak and average velocity are not sensitive and specific enough to serve as a standalone diagnostic tool for PD [10]. Prolonged latency, decreased average velocity and amplitude in saccades are the most commonly reported eye movement abnormalities in PD patients [11-14]. However, there are numerous studies which reported insignificant changes in these parameters for PD [15-17]. Simultaneous high speed and high accuracy nature of the saccade, high intra-trial variability of saccades, multifactorial nature of the disease, development of hallmark motor symptoms at different stages of the disease, and existence of several subtypes of PD could be few reasons for this insufficiency.

Given the rapid dynamics of saccadic eye movements, the underlying control mechanisms are likely too complex and multifaceted to be fully characterized using conventional parameters such as latency, mean velocity, and amplitude. Metrics that capture the temporal evolution of the system throughout the movement may provide a more comprehensive description of saccade dynamics, potentially improving the discrimination between PD patients and healthy controls (HC). Although several studies have proposed control-theoretic models to characterize these complex dynamics [18-20], these approaches have not yet achieved the diagnostic maturity required for reliable subject classification or quantitative assessment of disease severity. Nevertheless, a small number of studies investigating saccade trajectories and velocity profiles suggest that these dynamic features may be more sensitive for distinguishing PD from HC. Particularly, compared with HC, saccades in PD have been reported to be less smooth and more segmented [21-23]. In addition, whereas saccades in healthy individuals typically exhibit a single velocity peak, PD saccades frequently display multiple velocity peaks, reflecting a more fragmented movement profile [23].

In the present study, we aimed to investigate dynamic performance of saccades during reflexive saccades (pro-saccade task) in individuals with PD compared to age- and sex-matched neurologically healthy controls. We compared both basic but commonly used parameters of saccade and more complex ones between the two groups. We hypothesized that parameters with more holistic view on the saccade kinematics such as how the saccade trajectory differs from a straight line, or how much the average amplitude deviates from the desired target amplitude are more capable of characterizing the saccade performance and better differentiating between PD and healthy participants.

2. Methods

2.1. Participants

This study included two age- and sex-matched groups: 15 individuals with Parkinson's disease (PD) and 15 neurologically healthy control (HC) participants. All participants had normal or corrected-to-normal vision. PD participants were evaluated in the ON-medication state.

Inclusion criteria for the PD group were a clinical diagnosis of idiopathic Parkinson's disease based on the UK Parkinson's Disease Society Brain Bank criteria, Hoehn and Yahr [24] stages 2 or 3, and the ability to understand and follow task instructions. Exclusion criteria included the presence of any neurological disorder other than PD, a history of deep brain stimulation or other neurosurgical procedures, or changes in L-DOPA medication dosage within the month preceding the test.

The study protocol was approved by the local Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

2.2. Experimental Protocol

Participants completed an eye-movement task consisting of 40 trials of reflexive (pro-saccade) eye movements at three target amplitudes (5° , 10° , and 15°). Each trial (Fig. 1) began with the presentation of a blue fixation circle (0.6° diameter) centered on a gray background. After a randomized fixation interval ranging from 1000 to 2500 ms (mean = 1500 ms), the fixation stimulus disappeared and a black circular target (0.6° diameter) appeared randomly to the left or right of fixation (gap condition). The target remained visible for 1500 ms, after which it disappeared, followed by a 500 ms inter-trial interval. Another block including 20 trials of pro-saccades with 10° target amplitude was completed by each subject in the same session to provide data for test-retest reliability analysis.

Eye movements were recorded using an EyeLink 1000 Plus binocular head-mounted video-oculography system (SR Research Ltd., Ottawa, Canada). The system was calibrated for each participant using a nine-point grid calibration procedure (biquadratic with corner correction [25]). Binocular eye position data were sampled at 1000 Hz for 1500 ms beginning at target onset.

Visual stimuli were presented on a 24-inch LCD monitor. Participants were seated approximately 70 cm from the display, which was positioned at eye level. A chin rest was used to minimize head movements during data acquisition.

2.3. Data Processing

Initial data inspection and extraction were performed using Data Viewer software (SR Research Ltd.). Subsequent analyses and saccade detection were conducted using custom-written scripts in MATLAB (R2017b, MathWorks Inc., Natick, MA), following a standardized protocol for quantifying saccadic eye movements [26]. Raw eye-position signals were filtered using a zero-phase, second-order maximally flat low-pass filter with a cut-off frequency of 100 Hz (10% of the sampling frequency). The filtered signal was further smoothed using a nine-sample edge-enhancing kernel to reduce noise and facilitate velocity estimation. Data segments from 100 ms before to 250 ms after blink events were excluded to eliminate blink-related artifacts.

A saccade was classified as valid if it was initiated between 50 and 1000 ms following target onset, thereby excluding anticipatory and excessively delayed responses. Additionally, saccades were required to originate within 2.5° of visual angle from the central fixation point, proceed in the correct direction, and reach at least 50% of the target amplitude. Although, saccades were excluded if there was a discrepancy greater than 2 degrees in amplitude or more than 20 ms in onset time between the two eyes.

Saccade displacement was computed from the horizontal and vertical eye position signals recorded from both eyes and averaged within each trial. The resulting displacement signal was modeled using a fifth-order polynomial and subsequently differentiated to derive the corresponding velocity profiles. A fifth-degree polynomial was selected because it represents the lowest-order model that allows enforcement of standard saccade boundary conditions—namely, smooth onset and offset with zero velocity and zero acceleration—while yielding the physiologically expected bell-shaped velocity profile (with the derivative being a fourth-degree polynomial). As demonstrated by Wang et al. [27], polynomial models of order higher than five produce comparable residual errors; therefore, increasing the polynomial degree does not meaningfully improve modeling accuracy and increases the risk of over-smoothing physiologically meaningful variability in the data.

Because saccade duration varied across trials, the fitted polynomial functions were used to resample saccade displacement and velocity over a normalized time base ranging from 0% to 100% of saccade duration for each trial. Mean saccade displacement trajectories were then obtained for each target amplitude and direction (right or left) by averaging displacement values at each normalized time point across corresponding trials. The same procedure was applied to derive mean velocity profiles for each amplitude and direction. Similarly, data from second block of pro-saccades were processed.

The averaged saccade displacement trajectories and velocity profiles for each amplitude and direction were used to compute the outcome parameters. Subsequently, values obtained for rightward and leftward saccades of the same amplitudes (5° , 10° , or 15°) were averaged to yield a single parameter value for each amplitude and block.

2.4. Outcome Measures

From the saccade displacement profiles, saccade amplitude, the area under the curve (AUC) of saccade displacement and the landing-error-to-amplitude ratio were calculated. AUC of saccade displacement was defined as the signed area between the saccade displacement curve and the straight line connecting the start and end points of that curve (Fig. 2). The area was considered positive when the displacement curve lay above the straight line and negative when it lay below it. This parameter (AUC) is used to determine the dominant direction and magnitude of the curvature [28]. Landing error was defined as the absolute difference between the averaged saccade amplitude and the target amplitude for each amplitude and direction (right or left). The landing-

error-to-amplitude ratio was calculated by dividing the landing error by the target amplitude for each amplitude and direction (right or left). Although landing error has been used in literature before [16], but landing-error-to-amplitude ratio was not.

In addition, peak velocity, median velocity, average velocity, and High-velocity-percentage (HVP), were derived from the saccade velocity profiles. HVP was defined as the proportion of saccade duration during which velocity exceeded the median velocity for the corresponding amplitude and direction (right or left). To the best of our knowledge, this parameter was defined here for the first time.

2.5. Statistical Analysis

Statistical analyses were performed using SPSS (version 26; IBM Corp., Armonk, NY). Comparisons between the two groups were conducted using independent-samples t-tests for normally distributed variables and Mann–Whitney U-tests for variables that were not normally distributed. Normality was assessed using the Shapiro–Wilk test. Statistical significance was defined as $\alpha = 0.05$ for all analyses and Bonferroni correction was applied to adjust for the risk of Type I error inflation (i.e., significance level = $\alpha/3 = 0.017$).

Test–retest reliability of parameters was evaluated using intraclass correlation coefficients (ICCs), calculated via a two-way mixed-effects ANOVA model (single measures and absolute agreement). ICC values were interpreted according to established criteria: excellent (ICC > 0.90), good (0.75–0.90), moderate (0.50–0.75) and poor (< 0.50) [29–30].

2.6. Classification Analysis

Classification analyses (ROC/AUC, sensitivity, specificity) were performed using SPSS (version 26; IBM Corp., Armonk, NY) and MATLAB (R2017b, MathWorks Inc., Natick, MA). The Receiver Operating Characteristic (ROC) curve was used to investigate the power of calculated saccade parameters in discriminating PD from HC subjects. In general, an area under the curve (AUC) of 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the disease or condition based on the test), 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding. The Youden's index was used to determine optimal cut-off value. The classification performance was reported using sensitivity and specificity metrics [31–33].

3. Results and Discussion

3.1. Statistical Analysis's Results

Demographics and clinical characteristics of the subjects are presented in Table 1. There was no significant difference in age between the two groups ($t = 0.451$, $p = 0.656$).

HVP of both groups is presented in Fig. 3. The HC group had higher percent of high velocity compared to PD group. These differences reached significance in saccades with 15-degree amplitude ($p = 0.003$) and the average of saccades with different amplitudes ($p = 0.015$).

Peak velocity, median velocity and average velocity for both groups are presented in Fig. 4. There were no significant differences between two groups in these parameters.

Landing-error-to-target-amplitude ratio for both groups is presented in Fig. 5. In this parameter, the PD group had higher values compared to HC group. These differences reached significance in all comparisons except saccades with 5-degree amplitude ($p = 0.004$; $p = 0.012$; $p = 0.002$; respectively).

At last, averaged saccade amplitude and AUC are shown in Fig. 6 for each group. No significant differences were seen in averaged saccade amplitude or AUC of saccade displacement profiles.

To evaluate the test-retest reliability, ICCs were calculated for all parameters between the results of trials with a 10-degree target amplitude in the first block and the results of second block trials (all had 10-degree target amplitudes). The results of second block were used only in test-retest reliability analysis.

ICCs were excellent for HVP (high-velocity-percentage) and good for landing-error-to-amplitude ratio in both groups. Remaining parameters demonstrated excellent or good reliability for both PD and HC groups. These values are comparable to those previously reported for parameters based on saccade velocity and trajectory in the neurologically healthy individuals [26].

3.2. Classification Analysis's Results

ROC curve analysis confirmed both HVP and landing-error-to-amplitude ratio had power to discriminate PD and HC groups (Table 2). All other parameters showed values below 0.7 for AUC of ROC curve, which suggests no discrimination ability.

Based on Youden's index, a threshold level of 79.3 for HVP and a threshold level of 0.073 for landing-error-to-amplitude ratio was obtained. Meaning, subjects with HVP lower than 79.3 were classified in PD group and subjects with higher HVP values were classified in HC group. Also, subjects with landing-error-to-amplitude ratio higher than 0.073 were classified in PD group and subjects with lower landing-error-to-amplitude ratio values were classified in HC group.

Although sensitivity and specificity of these two new parameters were not considerable, their ability to discriminate PD and HC groups were higher than traditional saccade parameters which showed no discrimination ability.

3.3. Discussion

In this study, we examined the trajectory and velocity profiles of saccades with three different amplitudes to find characteristics that can distinguish between individuals with Parkinson's disease (PD) and neurologically healthy controls (HC) based on their dynamic performance during saccades. To do so, we calculated both traditional saccade parameters (amplitude, peak velocity, median velocity, and average velocity) and more complex parameters (AUC of saccade displacement, landing-error-to-target-amplitude ratio, and high-velocity-percentage).

According to our results, traditional saccade parameters (i.e. peak velocity, median velocity, average velocity and amplitude) failed to show the differences of saccadic performance between PD and HC groups in any of the target amplitudes.

On the other hand, the new parameters showed a higher discriminant validity. HVP showed significantly higher values in HC compared to PD group. Also, landing-error-to-target-amplitude ratio showed significantly higher values in PD compared to HC group. In contrast, AUC of saccade displacement profiles did not present any significant differences between two groups. Note that AUC was used successfully to evaluate the dominant direction and magnitude of a curvature [28]. However, in our results, AUC was positive in both groups for all amplitudes, and also there were no significant differences in the magnitude of AUC between them. As a result, it seems reasonable to conclude that the general shape of the saccade trajectory in terms of deviation from the straight line is similar between PD and HC groups.

Our findings suggest that, although PD group can generate the same peak velocity as HC group, and PD's average velocity is not significantly different from that of HC, they are unable to maintain the high velocity for sufficient portion of the saccade duration. As a result, while both groups have similar general saccade displacement trajectory, PD group significantly falls behind the target amplitude compared to the HC group.

Dopamine depletion in Parkinson's disease increases inhibitory output from the basal ganglia, resulting in excessive inhibition of the superior colliculus [10, 34], weakening and destabilizing the excitatory drive to the brainstem saccadic burst generator. Consequently, the descending motor command is thought to become less temporally stable, resulting in segmented saccade trajectories, interrupted velocity profiles, and, in some patients, multiple velocity peaks [21-23]. As a result, it is reasonable to assume the saccade spends less time in a continuous high-velocity state and proportionally more time in slower phases of the movement. The proportion of time spent above the median velocity (i.e. HVP) therefore reflects the integrity and temporal continuity of the saccadic motor command, providing a physiologically plausible marker of basal ganglia dysfunction that is not captured by conventional measures such as latency, amplitude, or peak velocity.

To further examine the validity and potential of HVP and landing-error-to-target-amplitude ratio to be used as Parkinson's disease biomarkers, test-retest reliability and classification analysis were conducted. ICCs were excellent for HVP (high-velocity-percentage) and good for landing-error-to-amplitude ratio in both groups. These values are comparable to those previously reported for parameters based on saccade velocity and trajectory in the neurologically healthy individuals [26]. Based on classification analysis's results, HVP showed a 68.89% sensitivity and a 55.56% specificity. Also, landing-error-to-amplitude ratio showed a 64.44% sensitivity and a 77.78% specificity. Although sensitivity and specificity of these two new parameters were not outstanding, their ability to discriminate PD and HC groups were higher than traditional saccade parameters which showed no discrimination ability with values below 0.7 for AUC of ROC curve. However, since dopaminergic medication is known to affect saccadic performance, the lack of OFF-medication assessment in PD group should be considered as a major limitation of this study. Also, relatively small sample size (15 subject in each group) should be considered before generalizing the results for PD patients.

4. Conclusions

Eye movements are repeatable and easy to collect data that may help better understand and identify PD patients. In this study, we observed significant differences in HVP and landing-error-to-target-amplitude ratio between PD and HC groups. However, there were no significant differences between two groups in peak velocity, median velocity, average velocity, amplitude and AUC of saccade displacement.

These findings suggest that, while commonly used traditional saccade parameters were unable to differentiate the saccadic performance of the two groups, more complex parameters seemed to be more successful in this regard.

According to our results, PD group had similar peak velocity (345.84 deg/s) compared to HC group (335.77 deg/s), and average velocity did not differ meaningfully between them (247.61 deg/s in PD vs 248.26 deg/s in HC). Also, based on AUC values, general trajectory of saccades was similar between PD (+2.62 deg) and HC (+2.58 deg) groups. PD group, however, had lower HVP (70.79%) compared to HC group (76.46%), meaning PD did not maintain a high velocity for sufficient portion of the saccade duration. As a result, they fell behind the HC group in their attempt to reach the intended target amplitude and as a result, PD had almost twice landing-error-to-amplitude ratio (0.115) compared to HC group (0.060). Test-retest reliability (ICC) was excellent for HVP (0.917 in HC; 0.924 in PD) and good for landing-error-to-amplitude ratio (0.752 in HC; 0.0776 in PD) in both groups. Based on ROC curve analysis, both HVP (AUC of ROC curve = 0.811) and landing-error-to-amplitude ratio (AUC of ROC curve = 0.844) had power to discriminate PD and HC groups. While, all other parameters showed values below 0.7 for AUC of ROC curve, which suggests no discrimination ability.

To further investigate the validity of the proposed parameters, one need to look into other variables such as the effects of levodopa and differences between ON- and Off-medication states [35-37], freezer versus non-freezer subjects, and other stages of the disease.

Authors' Credit

Fatemeh S. Daeinejad: Conceptualization; Methodology; Data curation; Data analysis; Data interpretation; Writing – Original draft

Mahmoud Saadat Foumani: Conceptualization; Methodology; Data interpretation; Writing – review & editing

Laila Alibiglou: Conceptualization; Methodology; Data interpretation; Writing – review & editing

Saeed Behzadipour: Conceptualization; Methodology; Data interpretation; Writing – review & editing

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of Captions

Figure 1. Reflexive saccades (pro-saccade) experimental protocol

Figure 2. Definition for AUC of saccade displacement

Figure 3. High-velocity-percentage (HVP). HC group had significantly higher values compared to PD group in saccades with 15-degree amplitude ($p = 0.003$) and the average of saccades with different amplitudes ($p = 0.015$). (*:Significant difference between two groups).

Figure 4. The common temporal saccade parameters showed no significant difference (a) Peak velocity (b) Median velocity, (c) Average velocity

Figure 5. Landing error/ target amplitude. PD group had significantly higher values compared to HC group in saccades with 10-degree amplitude ($p = 0.004$), saccades with 15-degree amplitude ($p = 0.012$) and the average of saccades with different amplitudes ($p = 0.002$). (*:Significant difference between two groups).

Figure 6. (a) Amplitude, and (b) AUC of saccade displacement. There were no significant differences between two groups.

Table 1. Demographics and Clinical Characteristics of Study Participants

Table 2. Receiver Operating Characteristic (ROC) Curve Analysis

Figures and Tables

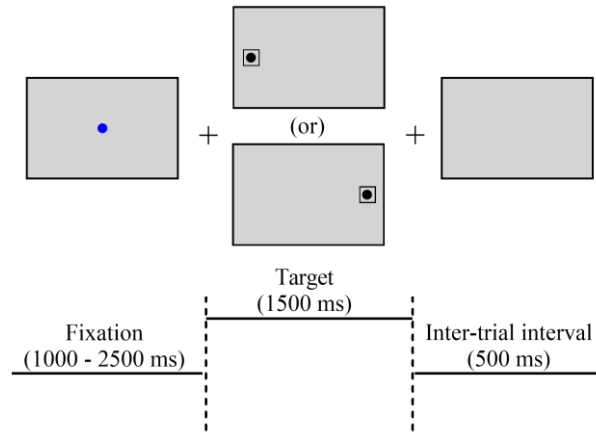


Figure 1

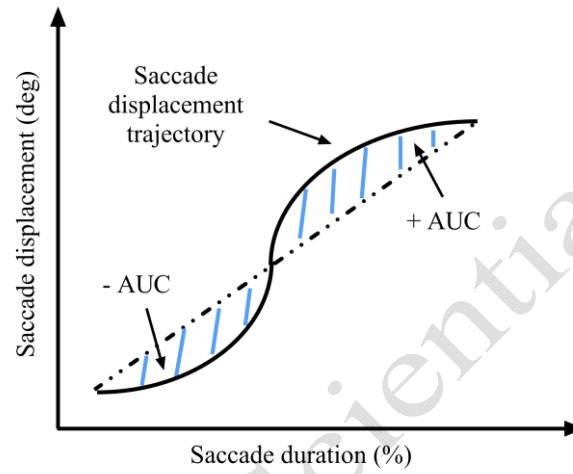


Figure 2

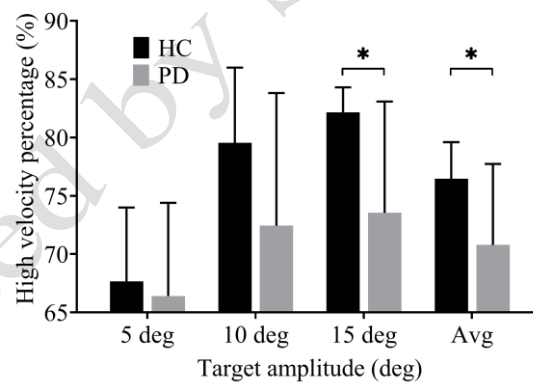


Figure 3

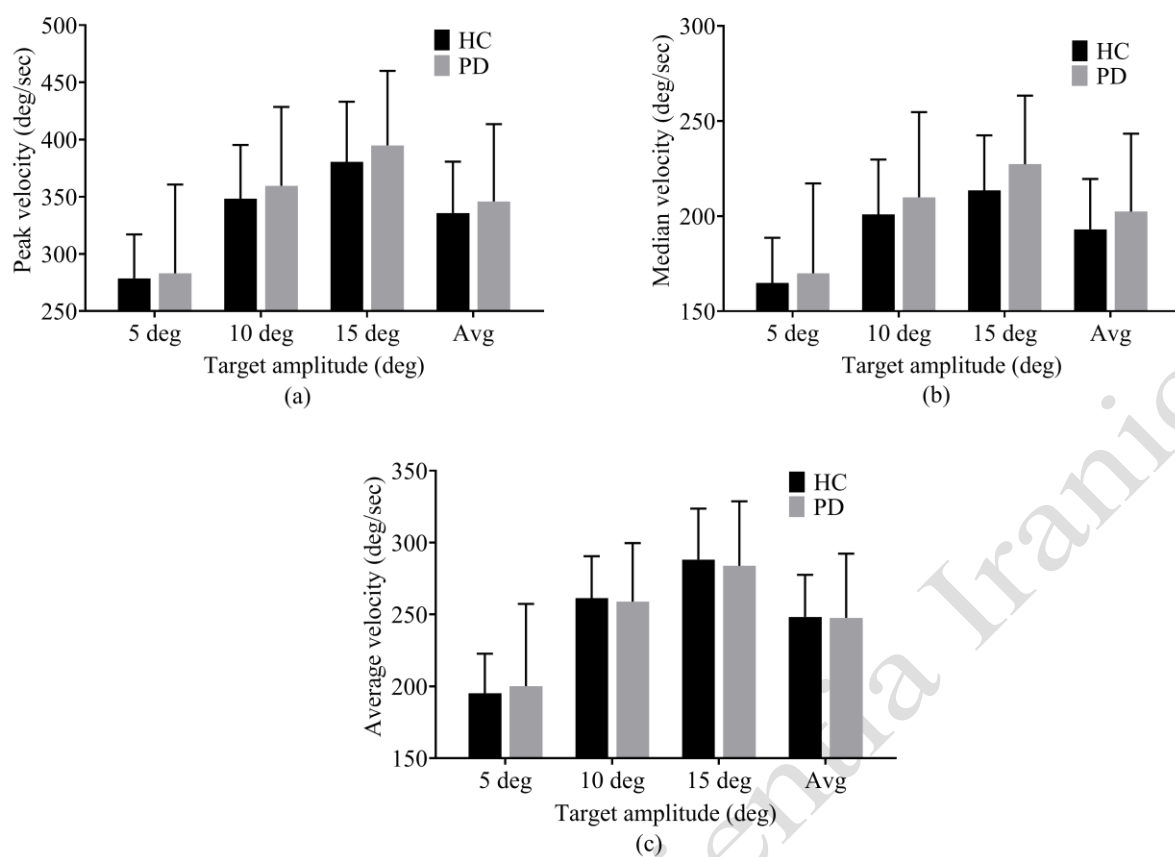


Figure 4

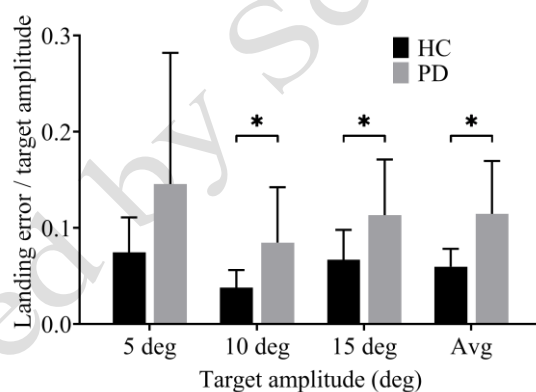


Figure 5

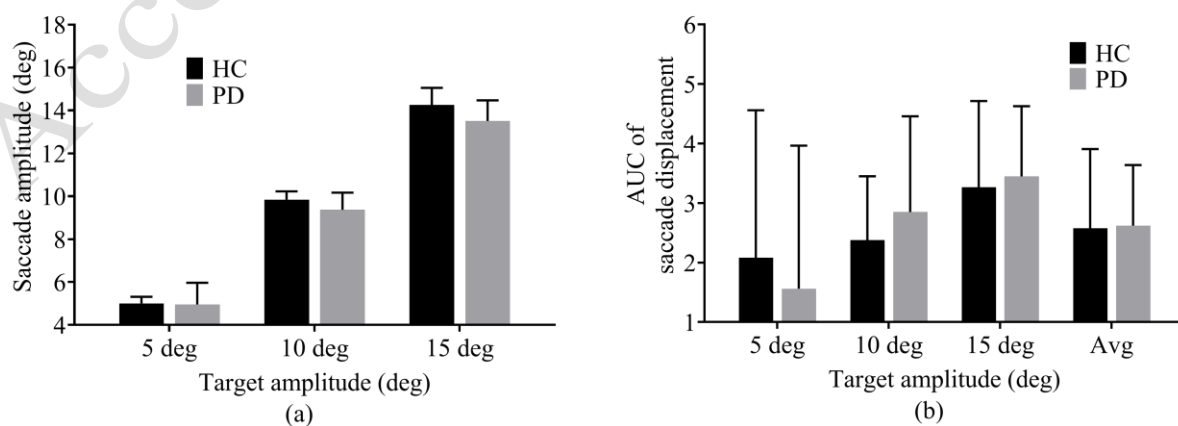


Figure 6

Table 1

	HC group	PD group
Number of subjects	15	15
Age	59.40 ± 8.28	60.53 ± 5.11
Gender (male/female)	11/4	11/4
UPDRS Score (Part III)	-	34.40 ± 9.14
Hoehn and Yahr	-	2.40 ± 0.51
Years since diagnosis	-	4.80 ± 2.21

Table 2

	HVP	Landing Error/Amplitude
AUC	0.811	0.844
95% CI for AUC	0.655 to 0.967	0.698 to 0.991
<i>P</i> -value	0.004	0.001
Optimal Cut-off Value	79.3	0.073
Sensitivity	68.89	64.44
Specificity	55.56	77.78

Biographies

Fatemeh Sadat Daeinejad received her BSc and MSc in Mechanical Engineering from Sharif University of Technology, Tehran, Iran, in 2011 and 2015, respectively. She is currently a PhD candidate in Sharif University of Technology. Her research interests include eye movement abnormalities, Parkinson's disease, modeling and analysis of biomedical data, design and control of medical systems and devices.

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