BRIEF REPORT

Where Do Parkinson's Disease Patients Look while Walking?

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ABSTRACT: Background: Parkinson's disease (PD) is associated with gait and visuomotor abnormalities, but it is not clear where PD patients look during ambulation.

Objective: We sought to characterize the visual areas of interest explored by PD patients, with and without freezing of gait (FOG), compared to healthy volunteers (HVs).

Methods: Using an eye-tracking device, we compared visual fixation patterns in 17 HVs and 18 PD patients, with and without FOG, during an ambulatory and a nonambulatory, computer-based task.

Results: During ambulation, PD patients with FOG fixated more on proximal areas of the ground and less on the target destination. PD patients without FOG displayed a fixation pattern more similar to that of HVs. Similar patterns were observed during the nonambulatory, computer-based task.

Conclusions: Our findings suggest increased dependence on visual feedback from nearby areas in the environment in PD patients with FOG, even in the absence of motor demands. © 2022 International Parkinson and Movement Disorder Society

Key Words: visual sampling; freezing of gait; Parkinson's disease

Parkinson's disease (PD) is characterized by tremor, rigidity, bradykinesia, and gait disturbances,[1] as well as dysfunction in eye movements and high-level visuospatial processing.[2-6] Interestingly, freezing of gait (FOG), one of the most disabling complications of PD, is known to be induced by visual stimuli.[7] Understanding specific patterns of visual exploration in this subpopulation may help characterize the mechanistic underpinnings of FOG and lead to the design of circuit-targeted therapies.[8,9] Using an eye-tracking device, we aimed to compare the visual areas of interest (AOIs) explored by PD patients, with and without FOG, during ambulatory and nonambulatory tasks.

Patients and Methods

Participants

Participants were recruited at the National Institutes of Health (NIH) between 2014 and 2015. PD patients were evaluated by a movement disorders neurologist (C.L.) and met the UK Brain Bank Criteria[10] for idiopathic PD. FOG was defined by self-reported FOG not limited to start hesitation or freezing during turns, and at least one witnessed freezing event during the screening visit. Exclusion criteria included requirement of visual aids for ambulation, ocular pathology affecting eye movements, blepharospasm, structural brain abnormalities, and Montreal Cognitive Assessment scale (MoCA) below age 22. All participants provided written informed consent, and the study was approved by the NIH Institutional Review Board.

Procedures

Patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), with the motor subscale (Part III) performed in the *off* medication state ≥12 hours after the last dose. The MoCA was

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Nora Vanegas-Arroyave, Denise F. Chen, Codrin Lungu, and Mark Hallett contributed equally to this work.

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performed in the *on* medication state ~30 minutes after the last dose. PD participants with FOG were denominated the "PDf" group, whereas those without FOG were the "PD" group. PDf also completed the New Freezing of Gait Questionnaire.[11] Eye movements were recorded using eye-tracking glasses (SensoMotoric Instruments, Berlin, Germany).

Tasks were performed during the *off* medication state. During the ambulatory task, subjects walked down a 10.24-m corridor to reach a wall (target destination, Fig. S1), turned, and walked back to the starting position, passing through a doorway 5.73 m from the starting position. Healthy volunteers (HVs) completed three trials; PD and PDf patients completed two to three trials as permitted by their level of fatigue. During the nonambulatory task, participants viewed a set of 25 photographs twice, in randomized order. The set of photographs contained full-color scenes of real-world environments with elements anecdotally described to cause gait difficulty in PDf patients (Fig. S2).

Eye movement metrics included average duration of fixations and percentage of time spent on fixations, saccades, and blinks. Fixation locations were mapped in the BeGaze software suite (SensoMotoric Instruments) to predetermined AOIs (Fig. S1) and composite AOI groups by category, comprised of several individual AOIs. The primary outcome of interest—AOI fixation percentage—was defined as the percentage of total fixation time spent on a specific individual or composite AOI. The number of unique AOIs fixated on during the task ("AOI variability") was also evaluated.

Statistical Analysis

Normally distributed data were analyzed using one-way analysis of variance or two-sample t test. Nonnormally distributed data were analyzed using Kruskal–Wallis and Wilcoxon rank sum tests. For the dynamic task, AOI fixation percentages were analyzed using linear mixed models, with separate models based on corridor location for before and after crossing the doorway and for the entire length of the corridor. AOI variability was modeled using linear mixed models, also stratified by corridor location. For the stationary task, composite AOI fixation percentages were modeled using linear regression models. Relationships between AOI fixation percentages and clinical characteristics were analyzed using Spearman's correlation. All statistical tests were two-sided and implemented in R (version 4.0.0, R Core Team, Vienna, Austria) with $\alpha = 0.05$.

Results

Demographic and Clinical Characteristics

Demographic and clinical data are presented in Table 1. Nine PD patients without FOG (PD group), 9 PDf patients with FOG (PDf), and 17 HVs participated in the study. Only a subgroup of participants (13 HVs, 7 PD, and 8 PDf patients) performed the stationary task due to time availability. The PDf group had a higher Hoehn & Yahr (H&Y) score compared to the PD group (PDf $= 3.4 \pm 0.7$, PD $= 2.4 \pm 0.8$, $P = 0.01$). There were otherwise no significant demographic or clinical differences among groups.

Eye Movement Characteristics

Eye movement characteristics are presented in Table 1. Of the three groups, PDf patients had the longest fixation durations. HV and PD groups spent more time making saccades compared to the PDf group, but this difference was statistically significant only between the HV and PDf groups (HV $= 25.8 \pm 6.6$, PDf $= 20.1 \pm 5.3$, $P < 0.001$). HVs spent a higher percentage of time blinking compared to PD and PDf patients ($P < 0.001$).

Fixation Patterns: Ambulatory Task

PDf patients fixated more on the floor (ground AOI) compared to the other subject groups ($P < 0.001$, Fig. 1A). The PDf group also fixated less on the target destination compared to HVs ($P < 0.001$) and the PD group ($P = <0.0001$, Fig. 1B). A post hoc analysis showed that PDf subjects fixated proportionately more on proximal compared to distal areas of the ground ($P < 0.001$, Fig. S3). Fixation percentages on the doorway were found to be lower in the PD and PDf groups compared to HVs, but this difference was significant only for the PD group ($P = 0.02$). Regardless of fixation length, PDf patients fixated on more unique AOIs compared to the HV (PDf $= 7.3 \pm 2.5$, HV $= 6.3 \pm 1.6$, $P = 0.01$) and PD groups (PDf $= 7.3 \pm 2$, PD $= 6.4 \pm 1.6$, $P = 0.01$).

Clinical Correlation Analyses

In the PD group, the target destination AOI fixation percentage was negatively correlated with UPDRS, Part III ($r = -0.53$, $P < 0.02$), and positively correlated with MoCA scores ($\rho = 0.54$, $P = 0.02$), whereas the ground AOI fixation percentage was positively correlated with UPDRS III score ($P = 0.46$, $P < 0.050$), Table S1. In the PDf group, H&Y score was negatively correlated with fixation percentage on the target destination AOI ($\rho = -0.72$, $P < 0.02$) but positively correlated with fixation percentage on the ground AOI ($\rho = 0.73$, $P < 0.02$).

Fixation Patterns: Nonambulatory Task

AOI fixation percentages for larger composite AOI groups across multiple pictures are summarized in Table S2. HVs and PDs spent significantly more time fixating on the large "destination" AOI compared with PDf subjects (HV $= 39.91 \pm 8.5$, PD $= 38.5 \pm 10.6$,

TABLE 1 *Demographic, clinical, and eye movement characteristics*

Demographic and clinical characteristics				
Group (n)	**HV (17)**	**PD (18)**	**PDf (9)**	***P*-value**
Age (y)	61.3 (6.3)	62.7 (4.6)	66.6 (6.5)	n.s.[a]
Gender (% male)	61	65	73	n.s.[b]
MoCA	27.6 (1.6)	27.7 (2.8)	28.0 (1.9)	n.s.[c]
Disease duration (y)		10.8 (6.2)	11.4 (7.1)	n.s.[a]
UPDRS III		32.4 (9.3)	35.8 (13.8)	n.s.[a]
Hoehn & Yahr		2.4 (0.8)	3.4 (0.7)	0.01[d]★
NFOGQ			22.6 (3.5)	
Eye movement characteristics				
Group (n)	**HV (17)**	**PD (18)**	**PDf (9)**	***P*-value[d]**
Fixation percentage (SD)	67.9 (8.3)	73.4 (9.9)	78.3 (5.8)	0.001★, <0.001★, 0.035★
Fixation duration (SD)	244 (60.8)	290 (107.8)	303 (71.9)	0.024★, 0.001★, n.s.
Saccade percentage	25.8 (6.6)	23.8 (9.5)	20.1 (5.3)	n.s., <0.001★, n.s.
Blink percentage	6.3 (6.5)	2.8 (4.2)	1.7 (2.4)	<0.001★, <0.001★, n.s.

Data are presented as mean (SD). Percentage of blinks, saccades, or fixations was calculated as the percentage of total eye events for the duration of a complete testing session. Duration is expressed in milliseconds. *P*-values refer to comparisons between HV versus PD, HV versus PDf and PD versus PDf, respectively.
★Significant difference between groups ($P < 0.05$); n.s., no significant difference between groups.
[a]One-way analysis of variance test.
[b]Pearson's χ^2 ± Fisher's exact test where group frequency <5.
[c]Kruskal–Wallis test.
[d]Mann-Whitney *U* test.
Abbreviations: HV, healthy volunteers; PD, Parkinson's disease patients without freezing of gait; PDf, Parkinson's disease patients with freezing of gait; MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III (motor score); NFOGQ, New Freezing of Gait Questionnaire; SD, standard deviation.

PDf = 23.1 ± 15.2, $P < 0.05$). Overall, fixations on "above ground" areas predominated in HVs and PD subjects compared to PDf patients (HV = 74.8 ± 8.1, PD = 77.4 ± 9.2, PDf = 57.8 ± 20.5, $P = 0.02$). In contrast, PDf patients fixated more on "ground" areas, but this difference was not significant (HV = 23 ± 8, PD = 19 ± 10, PDf = 36 ± 20).

Discussion

To our knowledge, this is the first study to examine specific locations of visual fixations during ambulation in PD patients with and without FOG. Our findings suggest a unique tendency of PDf patients to have a "ground-focused" visual fixation pattern in contrast to

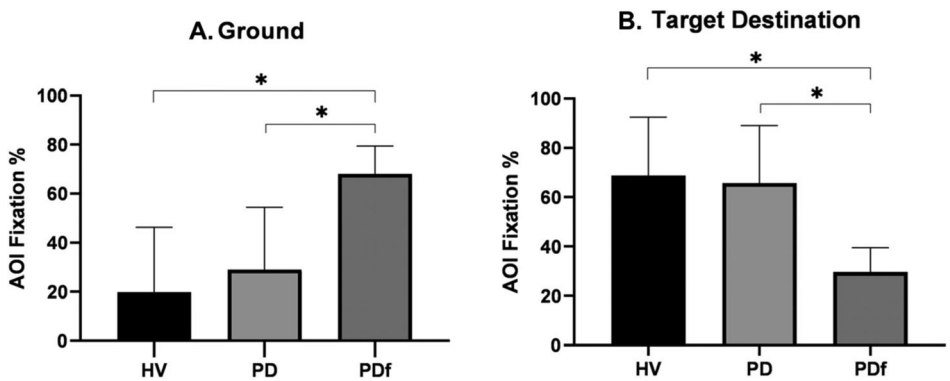

FIG.. 1. Comparison of average fixation percentages between subject groups for (**A**) ground and (**B**) target destination—areas of interest (AOIs). AOI fixation percentage is defined as the fixation time on a specific AOI divided by total fixation time during the trajectory. The PDf group fixated significantly more on the ground AOI (**A**) compared to PD subjects without freezing ($P < 0.001$) and controls (PDf 68.0 ± 11.3, PD 29.0 ± 25.5, HV 19.8 ± 26.5, $P < 0.001$). In contrast, the PDf group fixated less on the target destination AOI (**B**) compared to PD subjects without freezing (PDf 29.7 ± 9.8, PD 65.7 ± 23.2, HV 68.8 ± 23.6, $P < 0.001$) and controls ($P = 0.001$). AOIs, areas of interest; HV, healthy volunteers; PD, Parkinson's disease without freezing of gait; PDf, Parkinson's disease with freezing of gait. *Significant difference between groups ($P < 0.05$).

the "destination-focused" fixation pattern of healthy controls. This finding in the PDf group correlated with functional disability (H&Y) but was independent of other measures of disease severity (UPDRS III and MoCA). PD patients without FOG displayed an intermediate visual fixation pattern more similar to that of controls but which correlated with MoCA and UPDRS III scores. Importantly, similar group-specific patterns were observed in the absence of motor demands during the nonambulatory task.

The integration of visual information and motor outputs during locomotion relies on interactions among a variety of central pathways.[12-14] Degeneration of the basal ganglia has been particularly related to gait dysfunction,[15,16] leading to an increased reliance on cortical structures sensitive to environmental visual cues, such as the premotor area.[17] In our study, the ground-focused visual fixation observed in the PDf group might reflect increased dependence on specific visual stimuli and feedback from AOIs most relevant to the task at hand. Increased reliance on visual cues may in turn cause an inappropriate dependence on these cues[18,19] and, in conjunction with an inability to "de-emphasize" abnormally heightened visual input, produce inappropriate motor responses such as FOG.[20,21] Interestingly, the fixation patterns observed in the PDf population were similar in the computer-based task, so the findings did not depend on actual walking. These similar findings between the stationary and the walking tasks could argue against the idea that the observed visual exploration patterns were simply a compensatory behavior. However, the patients have likely been looking down for a long time before our study, and this pattern of visual behavior may now be well learned. Thus, although the observed visual fixation patterns in the PDf group may reflect compensatory mechanisms, this response may be also maladaptive. Of note, although we had anticipated that PDf patients would fixate more on the doorway due to this structure's anecdotal reputation as a trigger for FOG, we found that PDf subjects actually spent less time looking at the doorway. The mechanisms explaining why patients become more dependent on certain stimuli and which stimuli are more likely to successfully cue ambulation remain to be elucidated.

In addition, the ability to intermittently take a glance at the ground during ambulation depends on the capacity to retain information in spatial memory. Studies of memory-guided eye movements in PD patients have suggested a disruption in short-term working memory[22,23] and the ability to transform spatial mnemonic information into motor responses.[24] These impairments in visuospatial memory may manifest as an increased need for frequent visual feedback from nearby areas, leading to the ground-focused fixations observed in PDf patients.

Our study has several limitations. Our PDf sample size was small due to our strict selection criteria for FOG, and we did not distinguish between levodopa-responsive and nonresponsive FOG, limiting interpretation with regard to these specific FOG phenotypes. In addition, we could not reproduce freezing episodes in PDf patients during the ambulatory task, an issue that has been previously described.[25,26] Despite this limitation, PDf patients still exhibited distinct patterns of visual exploration that were independent of motor and cognitive disease severity and present, both, during locomotion and in the absence of motor demands.

Conclusion

During ambulation, PDf patients demonstrate a unique "ground-focused" pattern of visual exploration compared to a more "destination-focused" visual exploration in healthy controls and PD patients without FOG. These distinct fixation patterns were observed during locomotion and in the absence of motor demands during a nonambulatory task. Future studies investigating visual fixation patterns in specific phenotypes of PD and the effects of dopaminergic medications are warranted.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

N.V-A.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
D.F.C.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
P.M.L.: 1C, 2A, 2C, 3B
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Nora Vanegas-Arroyave has served as chair of Neurocrine advisory boards.