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# Involuntary saccades and binocular coordination during visual pursuit in Parkinson's disease

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# Eye movement control during visual pursuit in Parkinson’s disease

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33 **Abstract:**

34 **Background.** Prior studies of oculomotor function in Parkinson's disease (PD) have either  
35 focused on saccades without considering smooth pursuit, or tested smooth pursuit while  
36 excluding saccades. The present study investigated the control of saccadic eye movements  
37 during pursuit tasks and assessed the quality of binocular coordination as potential sensitive  
38 markers of PD.

39 **Methods.** Observers fixated on a central cross while a target moved toward it. Once the  
40 target reached the fixation cross, observers began to pursue the moving target. To further  
41 investigate binocular coordination, the moving target was presented on both eyes (binocular  
42 condition), or on one eye only (dichoptic condition).

43 **Results:** The PD group made more saccades than age-matched normal control adults (NC)  
44 both during fixation and pursuit. The difference between left and right gaze positions  
45 increased over time during the pursuit period for PD but not for NC. The findings were not  
46 related to age, as NC and young-adult control group (YC) performed similarly on most of the  
47 eye movement measures, and were not correlated with classical measures of PD severity  
48 (e.g., Unified Parkinson's Disease Rating Scale (UPDRS) score).

49 **Discussion:** Our results suggest that PD may be associated with impairment not only in  
50 saccade inhibition, but also in binocular coordination during pursuit, and these aspects of  
51 dysfunction may be useful in PD diagnosis or tracking of disease course.

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## 57 1. Introduction

58 Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the  
59 cardinal motor signs of tremor, rigidity, bradykinesia, disordered gait, balance, and posture  
60 (Massano & Bhatia, 2012; Rodriguez-Oroz et al., 2009). Individuals with PD have difficulty  
61 in moving the limbs and trunk, as well as in controlling oculomotor function. It has been  
62 known for some time that those with PD show prolonged saccadic latency (Rascol et al.,  
63 1989) and reduced smooth pursuit gain relative to healthy age-matched individuals (White,  
64 Saint-Cyr, Tomlinson, & Sharpe, 1983). Uc et al. (2006) found visual search performance  
65 was impaired in PD during driving, and Toner et al. (2012) showed that impaired visual  
66 search in PD could be attributed to sensory deficit. Many other studies have also reported  
67 perceptual and visuospatial disturbance in PD (Bodis-Wollner, 2003; Cronin-Golomb, 2010;  
68 Davidsdottir, Cronin-Golomb, & Lee, 2005; Davidsdottir, Wagenaar, Young, &  
69 Cronin-Golomb, 2008; Diaz-Santos et al., 2015). It is still unclear whether these oculomotor  
70 symptoms may co-occur with, or even arise before, the disease-characteristic motor  
71 symptoms in limbs and trunk.

72 Among the oculomotor functions, smooth pursuit eye movements serve an important  
73 role in vision by maintaining fixation on the selected moving object as it moves across visual  
74 field. Conventionally, smooth pursuit has been studied using small targets that produce either  
75 local or global motion signals to initiate and maintain pursuit (Santos, Gnan, & Kowler,  
76 2012). Although there are higher-level signals such as prediction, anticipation and symbolic  
77 cues that may elicit anticipatory pursuit (Kowler, Aitkin, Ross, Santos, & Zhao, 2014), these  
78 high-level signals are not sufficient to maintain pursuit after its initial onset. Unlike other  
79 types of eye movements such as saccades, the quality of smooth pursuit highly relies on  
80 motion signals. The dependence of smooth pursuit on motion perception highlights the  
81 connection between the oculomotor and perceptual systems. Accordingly, the pattern of eye  
82 movements may reveal the quality of perception. Support for this possibility is provided by  
83 the existence of brain regions (such as middle temporal area [MT]) that are important for both  
84 motion perception and the generation of smooth pursuit (Keller & Heinen, 1991). Prior  
85 studies have shown that lesions of MT led to impairment in pursuing a moving target  
86 (Newsome & Wurtz, 1985), which suggests that the motion signal processed in MT is also  
87 supplied to the pursuit system. Hence, studying smooth pursuit eye movements could be a  
88 useful tool for understanding the disorders that feature both perceptual and motor  
89 dysfunction, such as PD.

90 Studies of oculomotor control in PD have often focused on smooth pursuit without  
91 considering the effect of saccades occurring during the pursuit (Keller & Khan, 1986; Ladda,  
92 Valkovic, Eggert, & Straube, 2008), or on saccade tasks in which no smooth pursuit was  
93 initiated (Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Crawford, Henderson, &  
94 Kennard, 1989). When analyzing smooth pursuit, saccades are usually discarded or replaced  
95 with the results of linear interpolation (Ke, Lam, Pai, & Spering, 2013). By contrast, a  
96 number of studies have pointed to the interrelation of smooth pursuit and saccades. Erkelens  
97 (2006) asked observers to make a saccade and then engage in pursuit of a series of moving  
98 targets in various locations. When the targets appeared one at a time, pursuit latencies were  
99 shorter than saccade latencies. But when a new moving target appeared before the currently  
100 pursued target was removed, pursuit and saccadic latencies became similar. This result raises  
101 the possibility that pursuit eye movements and saccades share a single preparatory input and  
102 may be governed by a common decision process (Joiner & Shelhamer, 2006; Krauzlis &  
103 Miles, 1996; Krauzlis, Zivotofsky, & Miles, 1999). Krauzlis & Dill (2002) further found that,  
104 in superior colliculus, the activity of the same set of neurons represents target selection not  
105 only for saccades but also for smooth pursuit. Behavioral studies have also indicated a tight  
106 correlation between saccades and smooth pursuit in predicting object motion in the natural  
107 environment (Diaz, Cooper, Rothkopf, & Hayhoe, 2013). Together these findings suggest

108 that investigating smooth pursuit without taking into account the effect of saccades may miss  
109 the opportunity to evaluate their coordination, which may itself serve as a new measure of  
110 eye movement disturbance in PD. It may also be important for understanding of the observed  
111 changes in motor behaviors that depend upon the integration of visual signals, such as noted  
112 above for visual search while driving, and further for daily locomotion (including avoidance  
113 of falls).

114 Prior studies have investigated the effect of PD on saccades since one of the hallmarks of  
115 PD is the dysfunction of the basal ganglia, which also control the generation of saccades  
116 (Bergman et al., 1998; Hikosaka, Takikawa, & Kawagoe, 2000). Clark, Nearing, &  
117 Cronin-Golomb (2010) found that observers with PD had impaired performance on an  
118 antisaccade task but not on prosaccades (reflexive saccades), as predicted by the dependence  
119 of antisaccades on frontal-lobe function, which is compromised in PD. Helmchen et al.  
120 (2012) studied the effect of PD on both pursuit and saccades. They found that the ability to  
121 anticipate future events before pursuit initiation was impaired in PD, but the latency of  
122 saccades did not differ from that seen in the control group. Although both saccades and  
123 smooth pursuit were investigated in this study, they were tested in separate tasks and  
124 therefore it is still unclear how well saccades are inhibited during pursuit or how the  
125 saccades are triggered.

126 In addition, very little research has investigated the effect of PD on binocular  
127 coordination. Binocular coordination keeps the lines of sight from two eyes aligned for the  
128 process of fusion. It has been established that individuals with PD suffer from several visual  
129 deficits, such as diplopia (Armstrong, 2011). It is possible that individuals with PD may also  
130 have impaired binocular coordination which leads to a deficit of convergence, as prior study  
131 found that children with dyslexia also show the deficit of binocular coordination (Kirkby,  
132 Blythe, Drieghe, & Liversedge, 2011). Evaluating binocular coordination in PD may provide  
133 useful insight into any dysfunction of oculomotor control.

134 The goal of the present study was to understand the eye movement control during  
135 smooth pursuit in PD and investigate the possible effect of PD on binocular coordination. To  
136 do this, we used a simple pursuit task while varying the viewing conditions in which the  
137 moving target could be seen by both eyes or by only one eye. This pursuit task consisted of  
138 two periods (fixation period then pursuit period), which required observers to maintain their  
139 gaze first on the stationary fixation and later on a moving target. During the fixation  
140 period, the later pursuit target would keep approaching observers' gaze position so that it  
141 would serve as a distractor to increase the difficulty of holding their fixation. Normal  
142 observers should be able to maintain their fixation even when the distractor was heading to  
143 their gaze and then keep their fixation on the moving target during the pursuit. We assessed  
144 the observers' ability to inhibit saccades both during fixation and during the pursuit within the  
145 same task. Aging has been found to have effects on the gain of pursuit (Moschner & Baloh,  
146 1994), the dynamics and metrics of saccades, such as peak velocity and saccadic duration  
147 (Munoz, Broughton, Goldring, & Armstrong, 1998), and also the inhibitory control of  
148 saccades (Butler, Zacks, & Henderson, 1999). Considering the effects of aging motivated a  
149 novel aspect of the present study of participants with PD and age-matched normal control  
150 adults (NC) by the inclusion of a young-adult control group (YC) in order to investigate  
151 whether aging has an effect on the control of eye movements. We were also interested in  
152 examining whether aging affects the coordination between saccades and smooth pursuit eye  
153 movements during pursuit.

## 154 **2. Methods**

### 155 *2.1 Participants*

156 Thirty observers participated in the study. Ten (8 men and 2 women) had been diagnosed  
157 with idiopathic Parkinson's disease (PD) without dementia (mean age 64.5 years [ $SD = 7.2$ ],  
158 mean education 17.5 years [ $SD = 2.4$ ]) and another ten (5 men and 5 women) were healthy  
159 normal control adults (NC) (mean age 61.2 [ $SD = 7.3$ ], mean education 16.3 [ $SD = 1.8$ ]). All  
160 participants with PD were screened for dementia using an extensive neuropsychological  
161 assessment that assessed multiple cognitive domains. The NC group was matched for age and  
162 education to the PD group (age,  $t(18) = 1.01$ ,  $p = 0.32$ ; education,  $t(18) = 1.28$   $p = 0.22$ ). A  
163 further ten observers were young control adults (YC, 7 men and 3 women), all of whom were  
164 undergraduates at Boston University (age range 18-22). Members of the PD and NC groups  
165 were assessed for overall mental status using the modified Mini-Mental State Examination  
166 (MMSE; score converted to standard MMSE) (Stern, Sano, Paulson, & Mayeux, 1987).  
167 Mean MMSE for those with PD was 28.8 ( $SD = 0.7$ ) and for NC was 29.2 ( $SD = 0.5$ ).  
168 Participants with PD were recruited from Parkinson Disease Clinic at the Boston Medical  
169 Center and the Fox Foundation Trial Finder, and NC were recruited from the community.  
170 The PD and NC participants were compensated for their time. The YC participants received  
171 course credit. All procedures were approved by the Boston University Charles River Campus  
172 Institutional Review Board (1204E), and consent was obtained according to the Declaration  
173 of Helsinki.

174 Diagnosis of idiopathic PD was made by the participants' neurologists, using United  
175 Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes,  
176 Daniel, Kilford, & Lees, 1992). They met criteria for mild to moderate stages of the disorder  
177 (stages 1-3 on the Hoehn and Yahr scale (Hoehn & Yahr, 1967)). Disease severity was  
178 determined with the use of the Unified Parkinson's Disease Rating Scale (UPDRS, 4  
179 sections; (Fahn, Elton, Committee, & others, 1987; Levy et al., 2005), Table 1).

## 180 *2.2 Apparatus*

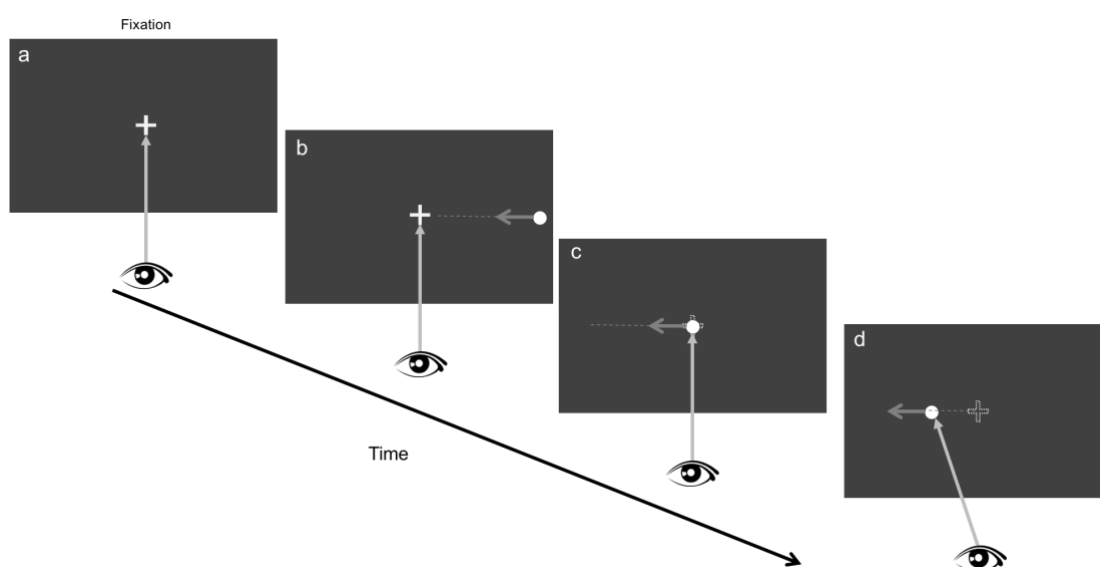
181 Movements of the left and right eyes were tracked and recorded using an SR Research  
182 Eye-Link II head mounted eye tracker, sampling at 250 Hz. A chin rest was used to stabilize  
183 the head. The stimulus was presented by a 3D projector (Optoma HD25, HD, 1080p, 2000  
184 ANSI Lumens) with a frame rate of 120 Hz through a polarized active shutter (Smart Crystal  
185 Pro, Intelligent 3D Polarization Modulator). The active shutter polarization oscillated at 120  
186 Hz in synchrony with the projector frame update and was placed in front of the projector.  
187 Through this method, the left and right eye images could be assigned to different  
188 polarizations at each consecutive time frame. Observers wore passive polarizing glasses  
189 (Volfoni Intelligent 3D Eyewear, VP-101) throughout the experiment and the eye  
190 movements were recorded through the glasses. Observers saw only the left eye frame with  
191 the left eye for 8.3 ms and then saw only the right eye frame with the right eye for the next 8.3  
192 ms. In this way, we achieved stereoscopic and dichoptic displays with passive polarizing  
193 glasses while avoiding interruption of the eye tracking signals.

194

## 195 *2.3 Stimulus display and procedure*

196 The horizontal and vertical spans of the projected display on the screen were 47 and 27  
197 degrees, respectively. Two viewing conditions were tested separately. Each condition started  
198 with a five-point calibration procedure, followed by presentation of a small fixation cross in  
199 the center of the screen. Then observers would press the space bar to start the trial. In  
200 binocular viewing conditions, both eyes saw identical stimuli. In dichoptic viewing  
201 conditions, one eye would see the moving target and the selection of which eye seeing the  
202 target was randomly chosen. Figure 1 shows the experimental procedure in the binocular  
203 condition. Observers were instructed to fixate on a marker after the trial began (the central  
204 cross in Figure 1a). A chin rest was used to maintain head stability. After a short duration,

205 randomly selected in a range of 200-400 ms, a target, which was a red disc with the diameter  
 206 of 0.5 deg, appeared at one of two possible locations (left/right edge) in the peripheral visual  
 207 field (with 22° of eccentricity) and started to move towards the fixation point with the speed  
 208 of 10 deg/s. Observers were instructed to keep fixating on the central marker (Figure 1b)  
 209 before the target hit the marker. When the target reached the central marker (trigger moment),  
 210 the marker would disappear and the target kept moving along the same direction. Observers  
 211 were asked to pursue the moving target as soon as the target reached the central fixation. As  
 212 the target moves with a constant speed, the pursuit start time would be predictable and  
 213 observers would keep pursuing the target until it reaches the edge of the display (22°). To  
 214 familiarize observers with the task, we conducted a set of practice trials before the  
 215 experimental trials. After the practice trials, observers conducted 10 trials in the binocular  
 216 viewing condition, followed by 20 trials in the dichoptic viewing condition. Each trial lasted  
 217 approximately 6 seconds.



218  
 219 **Figure 1.** (a) Fixation period (200-400 ms, randomly chosen to avoid observer's anticipation  
 220 of target appearance). (b) A target appears in the peripheral visual field (e.g., at the right edge  
 221 of the display) and starts to move towards the fixation point; (c) At the trigger moment, the  
 222 fixation point for each eye disappears and the target keeps moving in the same direction at the  
 223 original speed. (d) The observer's task is to maintain fixation during the fixation period and  
 224 to pursue the moving target once it hits the central fixation point.

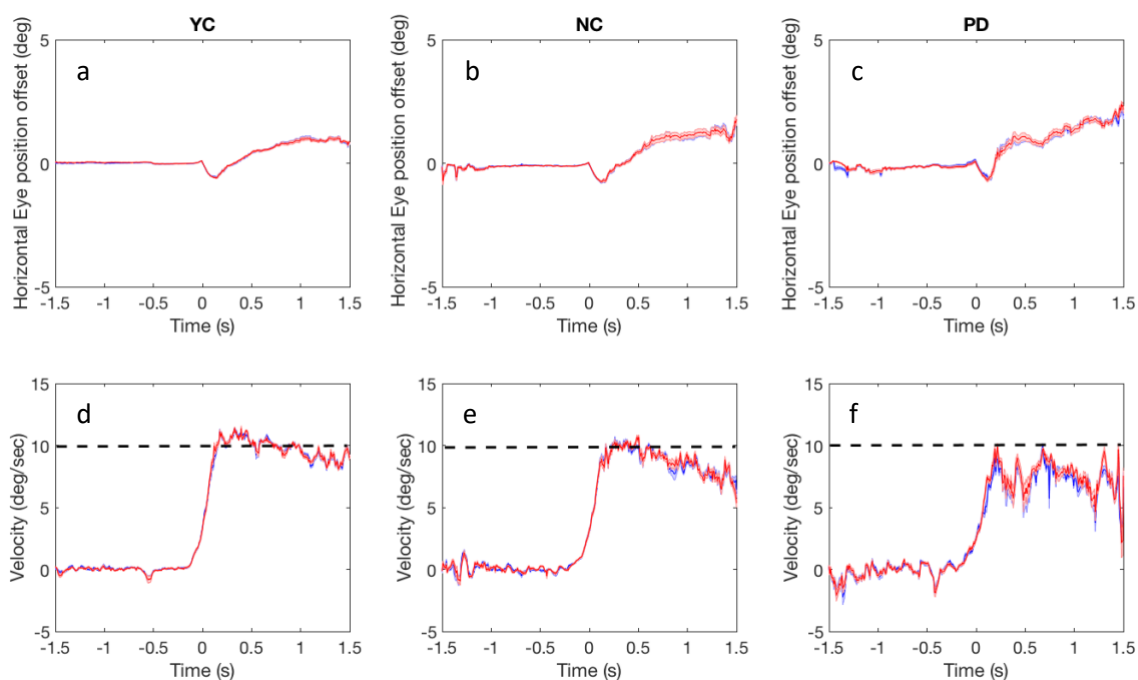
#### 225 2.4 Data Analysis

226 Gaze positions for individual trials were stored for offline analysis. Horizontal eye  
 227 velocity was calculated from the time course of horizontal gaze positions. Each velocity  
 228 sample is the slope of the regression line of the gaze position samples within a sliding  
 229 window of 100 ms (which is similar to Santos et al., (2012) but the current study had a wider  
 230 window). Saccade onsets and offsets were detected offline using the Eyelink velocity  
 231 algorithm with a minimum amplitude criterion (1.5 deg). Saccades were excluded (along  
 232 with blinks) in the velocity trace and pursuit velocity analysis, and the gaps were filled by  
 233 interpolating the data adjacent to the gaps. Pursuit velocity was analyzed during the steady  
 234 state pursuit, which was the interval 500-700 ms after pursuit starting point (Heinen, Jin, &  
 235 Watamaniuk, 2011). To avoid artifacts due to the edge of the display, the analysis focused on  
 236 the 3-second interval from one and half second before to one and half second after the  
 237 moving target reached the central fixation marker.

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### 239 3. Results

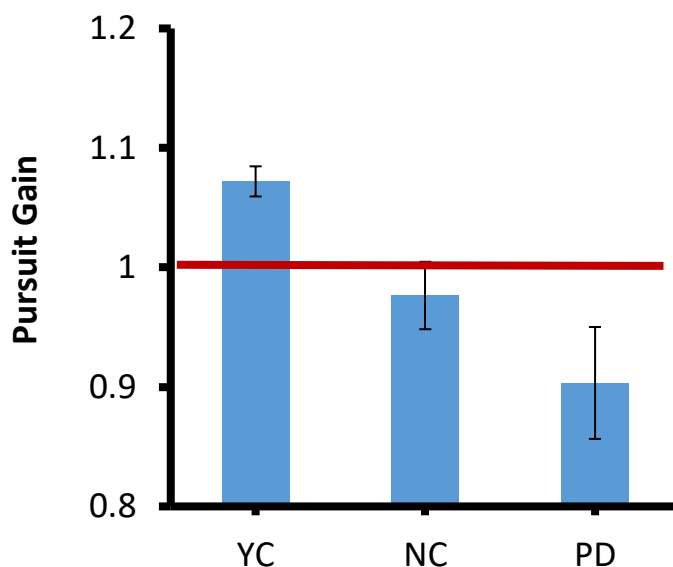
240 Figures 2a-c show the mean horizontal eye offset from the ideal fixating position and  
 241 Figures 2d-f show mean horizontal eye velocity over time. In Figures 2a-c, the gaze position  
 242 relative to the ideal fixating position is shown as a function of time, with zero indicating the  
 243 moment of the target crossing the initial gaze position (trigger moment) and observers  
 244 needing to start pursuing the target. Observers fixated on the central fixation point and started  
 245 pursuing the horizontal moving target at time zero. Thus, the eye offset before time zero is  
 246 the gaze position relative to the fixation point and the offset after time zero is the gaze  
 247 position relative to the moving target. Negative numbers on position difference (vertical axis)  
 248 indicate that the gaze positions were behind the target position, and positive numbers indicate  
 249 that the gaze positions were ahead of the moving target. The intervals containing saccades  
 250 during the fixation or smooth pursuit were excluded.



251 **Figure 2.** (a-c) show the average horizontal eye-fixation offset from the requested central  
 252 fixation/ the moving target and (d-f) represent the average eye velocity over time in the  
 253 blank background condition for YC (a, d), NC (b, e) and PD (c, f). (a-c) show the gaze offset  
 254 from target and (d-f) show the eye velocity. The offset before time = 0 is the eye-fixation  
 255 difference. The offset after time = 0 is the eye-target offset. Observers started to pursue the  
 256 horizontally moving target at time = 0. The black dashed line in d-f represents target velocity  
 257 (10 deg/s). Red and blue lines represent data from the right and left eyes, respectively.  
 258 Shading indicates +/- standard error across all ten observers per group.  
 259

260  
 261 After the pursuit start time (trigger point, time = 0), there was a lag behind the target for  
 262 all YC, NC and PD. Even though the eye-fixation offset for PD was similar to NC and YC  
 263 during the fixation period (negative time), the eye velocity trace became unstable for PD  
 264 during fixation. By contrast, both NC and YC were able to keep their fixation on the fixation  
 265 point. This pattern can be shown by the number of saccades generated during the fixation  
 266 period in the later analyses.

267 To evaluate the quality of pursuit performance, we computed the gain of smooth pursuit,  
 268 which was the average pursuit velocity during the steady-state pursuit phase (the interval  
 269 500-700 ms after pursuit starting point, see Data Analysis section), divided by the target  
 270 velocity. Figure 3 shows the pursuit gain for all three subject groups.



**Figure 3.** Pursuit Gain in binocular viewing condition.

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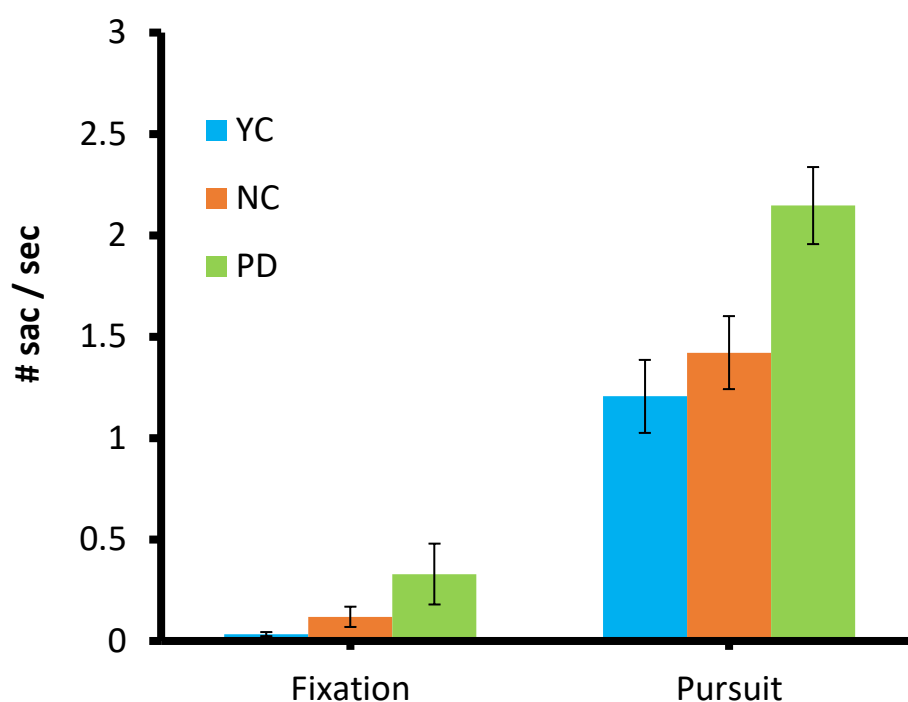
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A one-way ANOVA revealed a main effect of participant group ( $F(2,27) = 6.81, p = 0.004, \eta_p^2 = 0.3$ ). However, a post-hoc Tukey test showed no difference either between PD and NC ( $p = 0.26$ ) or between YC and NC ( $p = 0.11$ ).

Figure 4 shows the average saccade rates during fixation (-1.5 sec to 0) and during smooth pursuit (0 to 1.5 sec) for all PD, NC, and YC participants. A one-way ANOVA indicated that during the pursuit, the saccade rates were different across subject groups ( $F(2,27) = 7.2, p = .003, \eta_p^2 = 0.35$ ). A post-hoc Tukey test indicated that saccade rates were different between PD and NC ( $p = 0.03$ ) and there was no difference between NC and YC ( $p = 0.69$ ). The saccades were analyzed separately during pursuit initial phase (0-500 ms) and during steady phase (500-1500 ms) and PD participants made more saccades than NC and YC in both initial phase ( $F(2,27) = 4.73, p = .017, \eta_p^2 = 0.26$ ) and the steady phase ( $F(2,27) = 7.08, p = .003, \eta_p^2 = 0.34$ ). During fixation, there was no significant difference found in saccade rates ( $F(2,27) = 2.75, p = .08, \eta_p^2 = 0.17$ ).



289  
 290 **Figure 4.** Average saccade rates during fixation (-1.5 to 0 sec) and smooth pursuit (0 to 1.5  
 291 sec) for the YC (blue), NC (red) and PD (green) groups in the binocular viewing condition.  
 292 The error bars indicate +/- standard error. A value of zero in fixation indicates that there was  
 293 no saccade during the fixation period.

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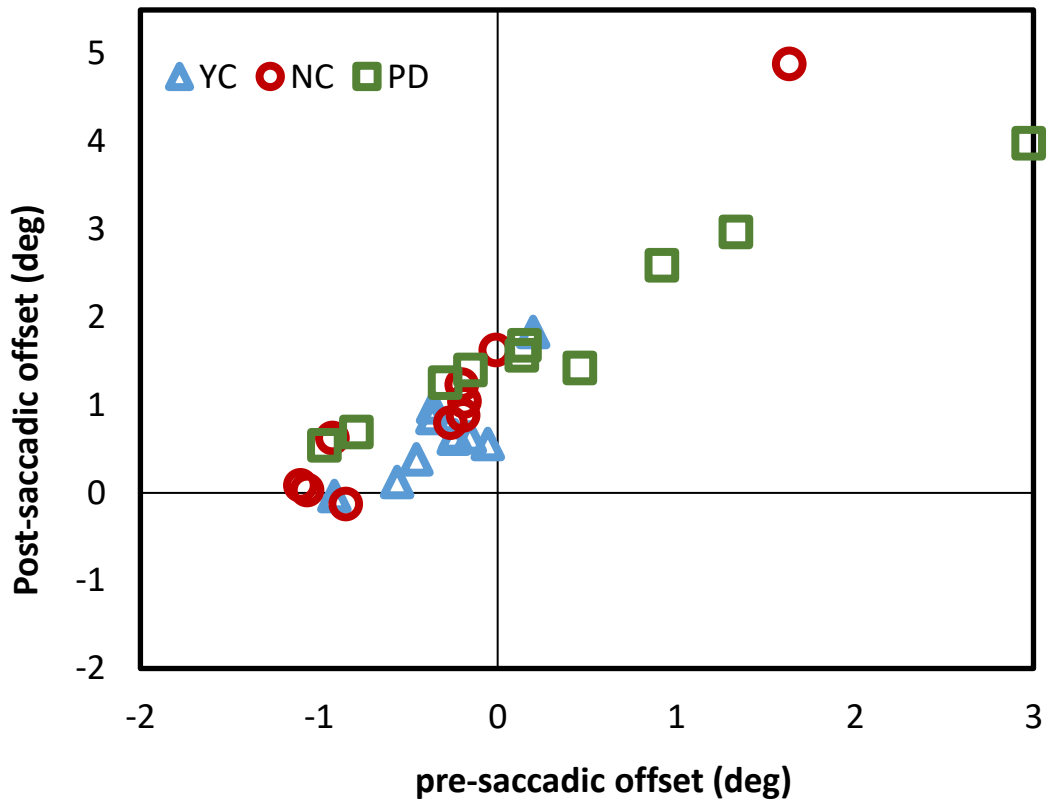
295 The results above show that individuals with PD had higher saccade rates during the  
 296 pursuit. It is possible that the increasing saccade rate during the pursuit was an attempt of  
 297 correcting offset between fixation and the moving target as some prior study has shown  
 298 (Stuart, Alcock, Galna, Lord, & Rochester, 2014). To evaluate this possibility, we compared  
 299 the offset error before and after saccades during the pursuit. Figure 5 shows the post- versus  
 300 pre-saccadic offset for each observer in all three groups. The offset was calculated by  
 301 subtracting the target position from the eye position. Thus, the negative offset means the eye  
 302 was behind the target and positive offset means the eye was ahead of the moving target.

303

304 There are two possible reasons for generating saccades during pursuit: 1) observers  
 305 produced catch-up saccades to compensate for the offset when the eye was behind the  
 306 moving target; 2) observers failed to inhibit saccades when there was no need to initiate  
 307 them. Figure 5 shows that, unlike most of NC and YC who made saccades when their  
 308 fixations were behind the moving target in attempt to catch up with the moving target, about  
 309 half of PD observers made the saccades when the eyes were not behind the target or even  
 310 when the eyes have been ahead of the target and the saccades they made did not reduce the  
 311 overall offset from the moving target. This implies that the high saccade rates in PD (Figure  
 4) were not due to the attempt of correcting the pursuit error, but due to the other factors.

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317 **Figure 5.** Post- versus pre-saccadic offset for the YC (blue), NC (red) and PD (green) groups  
318 in the binocular viewing condition. Each data point represents the average data for an  
319 individual observer.

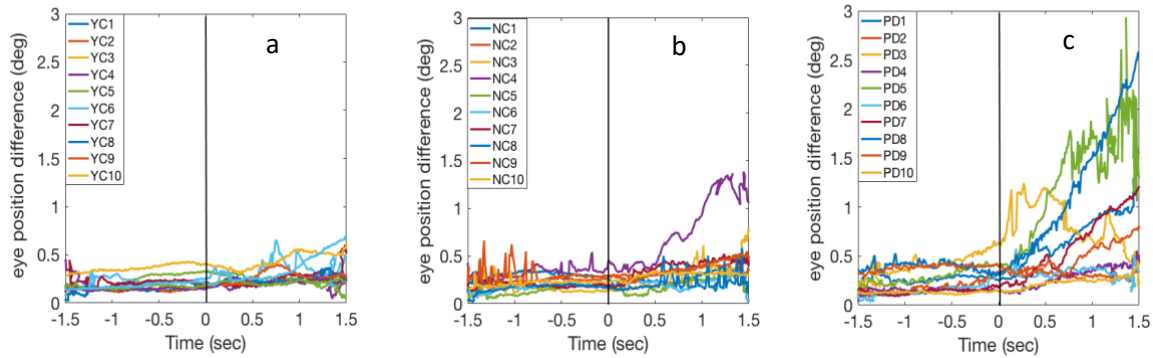
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321 Taken together, these results suggest that participants with PD were more likely to have  
322 difficulty in maintaining their fixation on the moving target during pursuit. This deficit was  
323 not due to aging since the saccade rates and the cause of making saccades for the NC group  
324 were indistinguishable from those of the YC group.

325

### 326 *3.1 Binocular coordination*

327 To test the possible deficit of binocular coordination, we analyzed the difference  
328 between left-right gaze positions during a 3-second interval from 1.5 second before to 1.5  
329 second after the moving target reached to the fixation. Figure 6 shows the left-right eye  
330 divergence (the absolute difference of the left and right eye gaze positions on the screen).



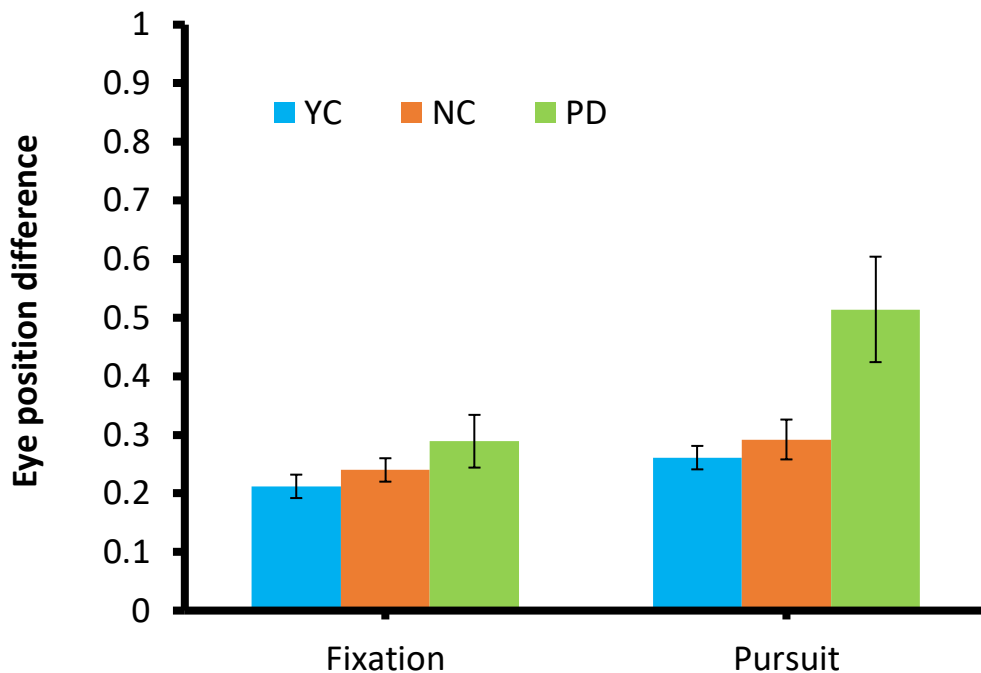
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332 **Figure 6.** Left-right gaze position difference over time in the binocular blank background  
 333 condition for YC (a), NC (b) and PD (c). Each line represents the average data from a single  
 334 observer. Observers started pursuit at time = 0.

335

336 While the vergence during fixation did not show a large difference for any of three  
 337 groups, about half of PD participants showed an overall increasing cross-ocular difference  
 338 when they started to pursue the moving target. To quantitatively examine the left-right eye  
 339 divergence, we compared the average gaze position differences before and after the start of  
 340 pursuit. Figure 7 shows the average binocular eye position difference during fixation and  
 341 during pursuit.

342



343

344 **Figure 7.** Left-right eye divergence during fixation and during pursuit.

345

346 During fixation, there was no difference in binocular divergence ( $F(2,27) = 1.51$ ,  $p =$   
 347  $0.24$ ). Of note, during pursuit, there was a significant difference in binocular divergence  
 348 across different groups ( $F(2,27) = 5.82$ ,  $p = .008$ ,  $\eta_p^2 = 0.3$ ). Post-hoc testing revealed a  
 349 significant difference between PD and NC ( $p = 0.03$ ) but no difference was found between  
 350 NC and YC ( $p = 0.92$ ).

351 Within the PD group, we also examined whether the impairment of binocular  
 352 coordination was related to any particular clinical characteristic, in order to establish whether  
 353 our measures were sensitive to more severe disease. To do this, we computed the Spearman  
 354 correlation between the eye position difference during pursuit and scores on the Unified  
 355 Parkinson's Disease Rating Scale (UPDRS), the standard clinical measure of PD severity,  
 356 including motor and other aspects of PD; the Hoehn and Yahr index of stage of disease; and  
 357 the Columbia Modified Mini-Mental State Examination (MMSE), a measure of overall  
 358 cognitive status (Table 1). The MMSE had a very restricted range in our sample, who were  
 359 not demented. There was no correlation between eye position difference and UPDRS total  
 360 score ( $\rho = -0.09, p = 0.8$ ), UPDRS motor score ( $\rho = 0.12, p = 0.73$ ), Hoehn and Yahr stage ( $\rho =$   
 361  $-0.16, p = 0.7$ ), or MMSE ( $\rho = 0.13, p = 0.72$ ). The lack of correlation between UPDRS score  
 362 with gaze position difference is comparable to what has been found in previous studies  
 363 (MacAskill et al., 2012; Stuart, Galna, Delicato, Lord, & Rochester, 2017). In addition, no  
 364 correlation was found between eye gaze position difference and saccade rates ( $\rho = 0.07, p =$   
 365  $0.85$ ) or between disease duration and saccade rate during pursuit ( $\rho = -0.22, p = 0.54$ ) or  
 366 between disease duration and other eye movement characteristics ( $\rho = 0.19, p = 0.6$  for  
 367 pursuit gain;  $\rho = -0.24, p = 0.51$  for eye position difference).

368  
 369

**Table 1.** Participant characteristics of individuals with Parkinson's disease

| Subject                         | Age           | Gender | Education<br>(years) | Disease<br>duration<br>(years) | Far acuity<br>(4m)     | MM<br>SE | UPDRS<br>motor | UPDRS<br>total | Hoehn<br>and<br>Yahr<br>stage | LED<br>(mg<br>per<br>day) | Duration<br>between<br>tests of eye<br>movement<br>s and<br>UPDRS<br>(years) |
|---------------------------------|---------------|--------|----------------------|--------------------------------|------------------------|----------|----------------|----------------|-------------------------------|---------------------------|--|
| PD1                             | 71            | F      | 18                   | 9.4                            | 20/25                  | 29.2     | 5              | 21             | 1.5                           | 770                       | < 0.25   |
| PD2                             | 64            | M      | 16                   | 10.3                           | 20/20                  | 27.7     | 34             | 44             | 3                             | 750                       | < 0.25   |
| PD3                             | 56            | M      | 12                   | 3.1                            | 20/16                  | 28.7     | 17             | 27             | 2.5                           | 225                       | < 0.25   |
| PD4                             | 71            | M      | 18                   | 2.7                            | 20/16                  | 27.7     | 14             | 35             | 1.5                           | 225                       | < 0.50   |
| PD5                             | 73            | M      | 21                   | 5.2                            | 20/20                  | 28.7     | 9              | 20             | 1                             | 10                        | NA   |
| PD6                             | 69            | M      | 19                   | 2.1                            | 20/16                  | 29.2     | 4              | 10             | 1                             | 100                       | < 0.25   |
| PD7                             | 59            | M      | 16                   | 1.3                            | 20/25                  | 28.7     | 19             | 36             | 2                             | 600                       | < 0.25   |
| PD8                             | 64            | M      | 18                   | 21                             | *                      | *        | 39             | 63             | 3                             | 1675                      | < 0.25   |
| PD9                             | 67            | M      | 18                   | 1.3                            | 20/20                  | 29.7     | 33             | 48             | 2                             | 0                         | < 0.25   |
| PD10                            | 51            | F      | 19                   | 1.1                            | 20/25                  | 29.2     | 16             | 28             | 3                             | 0                         | < 0.25   |
| <b>Group<br/>Mean,<br/>SD**</b> | 64.5<br>(7.2) |        | 17.3<br>(2.4)        | 5.7<br>(6.3)                   | 20/20<br>[20/16-20/25] |          | 14.8<br>(12.4) | 25.4<br>(15.5) | 2<br>[1.5-3]                  | 382.1<br>(530.8)          | < 0.5  |

370 \* Formal acuity assessment not available. The observer was able to easily see, detect, and locate the fixation  
 371 point and moving target.

372 \*\*Means, SDs except for Snellen acuity (for those available) and Hoehn and Yahr scale, which are medians  
 373 and ranges.

374 MMSE: Mini-Mental State Examination. UPDRS: Unified Parkinson's Disease Rating Scale. LED:  
 375 Levodopa equivalent dose of medication, per Tomlinson conversion formula (Tomlinson et al., 2010).

376 Although we did not find that PD pursuit gain was significantly smaller than NC, our  
 377 results show that PD made more saccades than NC or YC during pursuit but not necessarily  
 378 due to the need of correcting offset error during the pursuit. Moreover, binocular divergence  
 379 for PD increased over time during pursuit, which was not the case for NC or YC.

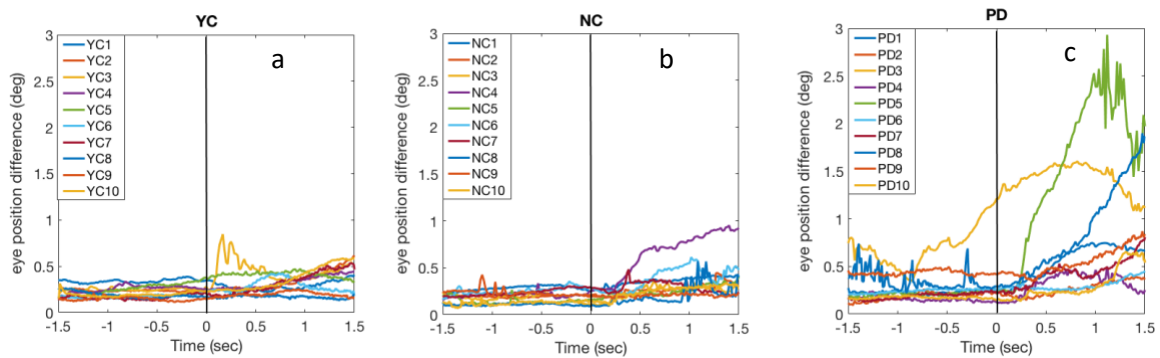
380  
381

### 382 3.2 Dichoptic Conditions

383 As shown above, it is possible that the coordination of the eyes may be impaired in  
384 individuals with PD and this could explain why we saw an increasing position difference  
385 between the eyes over time once the PD participants started the pursuit. If this is the case, we  
386 may see a similar or even larger deviation between the two eyes when each eye sees a  
387 different image. To investigate this possibility, the same observers participated in an  
388 experiment composed of trials with a dichoptic condition in which one eye could see only the  
389 moving target and the other eye could see only the background. Likewise during the fixation  
390 period (before observers start pursuing while the gaze is on the fixation point), the dichoptic  
391 condition (in which only one eye can see the fixation point), may reveal binocular divergence  
392 during the fixation period.

393

394 Figure 8 shows the difference between left-right gaze positions for the dichoptic  
395 condition. Similar to what we found in the binocular condition (Figure 6), many PD showed  
396 an increase in the binocular divergence after pursuit was initiated, whereas most of NC and



397 YC remained at the same level (except NC4).

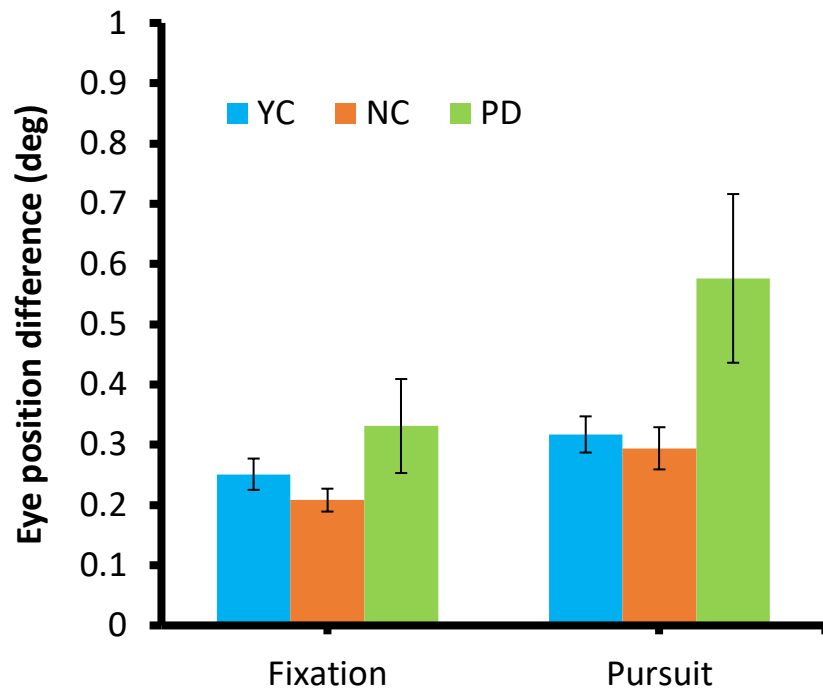
398

399 **Figure 8.** Binocular divergence over time in the dichoptic condition for YC (a), NC (b) and  
400 PD (c). Each line represents the average data from a single observer. Observers maintained  
401 their fixation then started pursuit at time = 0. Observers were same as those in Experiment 1.

402

403 Figure 9 shows the average binocular eye position difference during fixation and during  
404 pursuit. Similarly, there was no binocular divergence difference across subject types during  
405 fixation ( $F(2,27) = 1.63, p = 0.2, \eta_p^2 = 0.11$ ), but there was a significant position difference  
406 during pursuit ( $F(2,27) = 3.4, p = 0.048, \eta_p^2 = 0.2$ ). Nevertheless, Tukey post-hoc testing  
407 showed only nonsignificant marginal difference in binocular divergence between PD and NC  
408 ( $p = .07$ ), or between PD and YC ( $p = 0.1$ ). A repeated measure ANOVA also shows that  
409 there was no difference in eye position difference between binocular and dichoptic viewing  
410 conditions ( $F(1,27) = 2.72, p = 0.11$ ).

411



412  
 413 **Figure 9.** Binocular divergence during fixation and during pursuit in the dichoptic viewing  
 414 condition.

415  
 416

417 The relation between binocular divergence during pursuit and the clinical characteristic  
 418 were also examined. Similar to the result in the binocular condition, there was no correlation  
 419 between eye position difference and UPDRS total score ( $\rho = -0.006$ ,  $p = 0.99$ ), UPDRS motor  
 420 score ( $\rho = 0.12$ ,  $p = 0.76$ ), MMSE ( $\rho = 0.087$ ,  $p = 0.83$ ), or Hoehn and Yahr stage ( $\rho = -0.18$ ,  $p$   
 421  $= 0.62$ ).

422 The saccade rates in dichoptic conditions were also analyzed. As found in Experiment  
 423 1, there were significant differences in saccade rates during the pursuit across groups  
 424 ( $F(2,27) = 4.42$ ,  $p = 0.02$ ). A post-hoc testing showed that there was some difference in  
 425 saccade rates between PD and NC ( $p = 0.02$ ) and no difference was found between NC and  
 426 YC ( $p = 0.66$ ). Similarly, no correlation was found between saccade rates during pursuit and  
 427 eye position difference in dichoptic condition ( $r = -0.17$ ,  $p = 0.63$ ).

428 The result of Experiment 2 shows that binocular coordination was not different across  
 429 viewing conditions (binocular vs. dichoptic). That is, the eye position deviation was not  
 430 larger when each eye saw different images than when both eyes saw identical images.  
 431 Nevertheless, some of the participants with PD still showed an increased binocular  
 432 divergence after pursuit was initiated and this increase was not seen in NC.

#### 433 4. Discussion

434 The present study examined the role of saccades during pursuit and fixation in PD, in  
 435 healthy adults matched to the PD group for age, and in younger control adults. Saccades are  
 436 often excluded from smooth pursuit analysis as seen in many previous studies, yet they not  
 437 only reveal how attention may be distributed during pursuit (Heinen et al., 2011; Jin, Reeves,  
 438 Watamaniuk, & Heinen, 2013), but also provide valuable information about the control of the  
 439 oculomotor system in PD, as we show with the present experimental results. If the saccadic  
 440 inhibitory system for PD is impaired (Chan et al., 2005; Kitagawa, Fukushima, & Tashiro,

441 1994), those with PD may fail to maintain their fixation and initiate saccades while  
 442 attempting to fixate a stationary point or pursue a moving target. Our results showed that  
 443 individuals with PD made more saccades during pursuit (Figure 4). These detected saccades  
 444 are not simply the square wave jerks as saccade rates during fixation were too low to be  
 445 conjugate. And the average magnitude of saccades during pursuit is about 2.4 deg, which is  
 446 much larger than the average square wave jerks reported in previous studies (Kapoula et al.,  
 447 2013; Otero-Millan, Schneider, Leigh, Macknik, & Martinez-Conde, 2013). In addition,  
 448 this frequent occurrence of saccades did not seem to be due to the effect of age since control  
 449 adults who were age-matched to the PD group were able to maintain their fixation on the  
 450 moving target better than PD, and their eye movements were similar to those of the young  
 451 adult control group.

452 During pursuit, the occurrence of saccades often serves to compensate the offset error  
 453 arose from the slower pursuit velocity shown in the past studies. Some observers with PD in  
 454 the current study, however, made more saccades even when the fixation was not behind or  
 455 even ahead of the moving target and this caused the eyes to be ahead of the moving target,  
 456 as shown in Figure 2, despite the overall lower pursuit velocity.

457 It is noteworthy that the increasing binocular divergence after pursuit initiation was  
 458 mostly observed in PD, not in NC or YC, and this eye-position difference was similar in the  
 459 binocular and dichoptic viewing conditions and was not associated with saccade rates. This  
 460 suggests that the occurrence of saccades in PD observers may not be an attempt for correcting  
 461 the fixation-target offset. Moreover, the differences were not correlated with the result of a  
 462 standard motor test for PD (UPDRS). In addition, even with larger binocular eye gaze  
 463 position difference, our PD observers did not report motion diplopia, which could follow  
 464 the disconjugate gazes during smooth pursuit (Kaski, Domínguez, & Bronstein, 2013). This  
 465 indicates that the higher saccade rates during pursuit and the increasing left-right eye  
 466 divergence may form a new dimension independent of classical measures of PD.

467 The current study found that individuals with PD made more saccades during smooth  
 468 pursuit than the two control groups. It is known that during pursuit, normal observers  
 469 typically make catch-up saccades to decrease the gaze offset when pursuit was slower than  
 470 the moving target (de Brouwer, Missal, Barnes, & Lefèvre, 2002, Collewijn & Tamminga,  
 471 1984). In our study, unlike the two control participants who made saccades during pursuit  
 472 mostly when the fixation was behind the pursuit target, more than half of the observers with  
 473 PD made saccades when the fixation was not behind or even ahead of the moving target  
 474 (Figure 5). This may suggest that these saccades made by PD were not triggered by the  
 475 signal of spatial offset. Instead, they may just indicate a failure of saccade inhibition.

476 PD has been associated with dopaminergic disruption in the basal ganglia, which plays a  
 477 critical role in saccade inhibition (Hikosaka, Matsumura, Kojima, & Gardiner, 1993;  
 478 Hikosaka et al., 2000). It is possible that the depletion of dopamine in PD also affects the  
 479 superior colliculus (Basso & Evinger, 1996). As a consequence, the inhibition signal to the  
 480 superior colliculus is not sustained so that saccades are made involuntarily during fixation  
 481 and during pursuit.

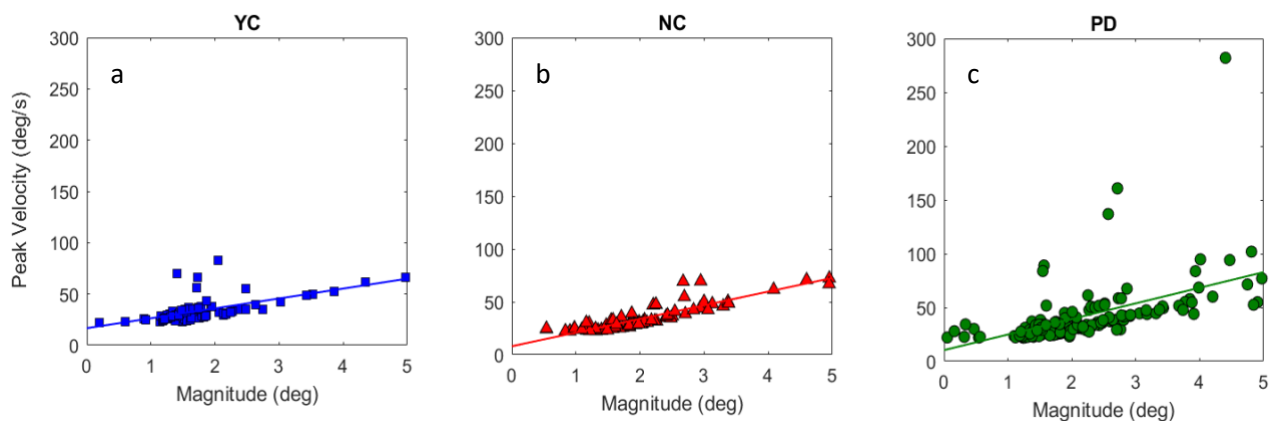
#### 482 *Binocular coordination during pursuit*

483 Problems in binocular coordination during reading have been found in people with  
 484 dyslexia and also in people with Huntington's disease (Bucci, Brémond-Gignac, & Kapoula,  
 485 2008; Collewijn, Went, Tamminga, & Vegter-Van der Vlis, 1988), though little is known  
 486 about this condition in PD. Hanuška et al. (2015) asked observers to continuously fixate a  
 487 target either moving toward or moving away from them. They found that observers with PD  
 488 indeed had longer latencies in their vergence eye movement and this implies a possible  
 489 impairment of binocular synchronization. Our study provides a possible new insight into  
 490 binocular coordination in PD. One important finding is that some observers with PD showed

491 an increasing binocular divergence once they started to pursue, indicative of a potential  
 492 deficit in binocular coordination while tracking a moving target. This result is unlikely due to  
 493 measurement error because the gaze position of both eyes aligned well during fixation for all  
 494 three groups. Once smooth pursuit was initiated, observers with PD were more likely to show  
 495 an increased binocular positional offset over time. The same pattern of binocular offset was  
 496 found across both binocular and dichoptic viewing conditions.

497 The original rationale for using dichoptic viewing was to further test whether binocular  
 498 gaze offset would increase if the two eyes perceived different visual inputs as the larger  
 499 binocular eye gaze position difference may have been resulted not only from the impaired  
 500 motor control, but also from the impaired perception of visual signal. If this is the case, the  
 501 manipulation of unseeing eye in the dichoptic condition would introduce larger visual  
 502 disturbance and therefore may result in a bigger binocular offset. First, our result shows that  
 503 in both viewing conditions, those with PD were more likely to show the binocular  
 504 misalignment when they started to pursue. Second and more importantly, the gaze offset for  
 505 PD in the dichoptic viewing condition is not larger than in the binocular viewing condition  
 506 during the pursuit. This may suggest that the impaired coordination was not due to the  
 507 processing of visual input but rather due to motor processing. Whether the perceived visual  
 508 signal has different effects on the seeing eye and unseeing eye in PD would need further  
 509 studies and investigation.

510 In addition, the quality of calibration may also contribute to the observed results. That is,  
 511 the impaired binocular coordination may be attributed to the poor calibration in PD.  
 512 Nevertheless, the quality of calibration should affect fixations, saccades and smooth pursuit  
 513 in a similar way. That is, if the larger binocular eye gaze position difference was due to the  
 514 poor calibration quality, we should see the similar deviation vectors with regard to disparity  
 515 at any time point during the trial. To better validate the detected saccades during pursuit in  
 516 the current study, we compared the relationship between saccadic peak velocity and  
 517 magnitude across different groups. Figure 10 shows the pattern of saccade main sequence  
 518 for each group, which indicates that saccade detection in the current study was not caused  
 519 by noise. Thus, any difference in saccade rate, change in saccadic offset or binocular gaze  
 520 position difference cannot simply be caused by the difference in calibration quality.



521

522

523 **Figure 10.** Relation between saccade peak velocity and magnitude for YC (a), NC (b), and

524 PD (c).

525

526

527 *Limits of the current study*

528 The current study only contained limited numbers of trials and observers, and the signal  
529 noise resulted in some degree of variation as indicated in the results section. Therefore, we  
530 also presented the data of individual observers along with the main results to ensure that our  
531 readers could directly observe and access the variations of measured metrics within and  
532 across groups.

533

534 **5. Conclusions**

535 The current study reexamined the ability of individuals with PD to track a moving target.  
536 We found that those with PD produced more saccades during pursuit than the control groups.  
537 We also observed that some of those with PD showed impaired binocular coordination when  
538 they started pursuit. This deficit appears to arise from abnormalities in the oculomotor system  
539 rather than the perceptual systems, as the group differences emerged under both the binocular  
540 and the dichoptic conditions. Our measures may provide extra dimensions for PD diagnosis  
541 in addition to the standard and classic measures since the eye movement difference between  
542 the individuals with PD and age-matched NC in the present study was not correlated with  
543 classical measures of PD severity (e.g., UPDRS score or MMSE). Whether these  
544 abnormalities in eye movements occurred before the other PD-related abnormalities will  
545 need to be further investigated in the future. The current study was conducted with  
546 participants with mild-moderate PD rather than very recently diagnosed individuals because  
547 we estimated that any effect would be more likely to occur in the former group; once  
548 established, such an effect could be sought in earlier-onset cases. By pursuing these studies,  
549 we hope to achieve a better understanding of the impairment of eye movement mechanisms  
550 in PD, which may be of relevance to the understanding of oculomotor function in other  
551 neurodegenerative disorders as well.

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559

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