# Impairment in updating spatial representations in Parkinson's disease correlates with dopaminergic deficiency

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Patients with Parkinson's disease (PD) depend on visual feedback in their behavior more than healthy individuals, suggesting deficits in monitoring their own movements. During eye movements, internal monitoring signals (corollary discharge, CD) are relayed to the cortex via subcortical structures whose function is compromised in PD due to deficits in the dopaminergic system. We studied early-stage PD patients (N=14), and age-matched healthy control participants (N=14) using a double-saccade task. In the task, participant fixates two targets in succession. In order to accurately fixate the second target, the participant must correct for the displacement caused by the first saccade. PD patients showed systematic deficits in fixating the second target although their ability to fixate the first target was not significantly impaired. The deficit in fixating the second target was observed especially when the patients made saccades towards the side with primary motor symptoms. Across patients, the impairment in fixating the second target correlated with the integrity of the dopaminergic system: Patients with lower striatal dopamine transporter binding made larger errors. The direction of the errors suggests that the CD signal may be amplified in PD patients relative to the motor signal. Furthermore, the results suggest that deficits in the dopaminergic system may contribute to updating of spatial representations after movement. This could in part aggravate motor symptoms, and explain frequently occurring visual symptoms in PD.

Keywords: Parkinson's disease, corollary discharge, spatial remapping, dopamine, dopamine transporter binding, saccadic eye movement

57 Motor behavior requires the brain to update spatial representations to take into account
58 changes that are produced by self-induced movements. This requirement is apparent in eye
59 movements: several times per second we sample the environment by rapidly relocating our eyes
60 using saccadic eye movements during which the image on the retina is displaced. Yet we experience a
61 stable visual world and precisely know the locations of objects in the world because changes in
62 perception that are due to the eye movements have been eliminated by the brain. This internal
63 monitoring of movements and updating of the spatial representation is assumed to rely on corollary
64 discharge (CD) signals that relay a copy of the motor command to sensory areas (Figure 1A; 1).
65 Patients with Parkinson's disease (PD) are known to depend on visual feedback in controlling
66 their movements, more so than healthy individuals, suggesting that the brain mechanisms that
67 internally monitor movements (e.g. CD) are deficient: When visual feedback is restricted PD patients
68 tend to undershoot the target 2,3. Previous research has hypothesized that PD patients have defects
69 in kinesthesia 2,3, and CD 4,5, but studies have not examined this issue in detail. We examined PD
70 patients' ability to monitor their own eye movements using a *double-saccade task* which has been
71 widely utilized to examine CD and spatial updating (e.g. 1,6,7). In the task, a participant must take into
72 account the image displacement caused by a first saccade to accurately perform a second saccade
73 (Figure 1B).
74 Saccadic eye movements are triggered by neurons in the superior colliculus, which projects to
75 oculomotor burst neurons in the pons 8. The superior colliculus receives driving input from various
76 cortical areas that mediate voluntary control of eye movements, and nuclei of the basal ganglia that
77 filter out appropriate saccade targets 9. During the initiation of eye movements, the superior
78 colliculus is assumed to relay the CD to the cortex via medial thalamus 1,10. In other words, as

saccades are triggered by the superior colliculus, cortical systems are updated by the CD signal through the thalamus. The CD shifts the receptive fields of visually responsive neurons to the location where the saccade is going to land 1,11. Studies done on monkeys demonstrate that inactivation of the medial thalamus both disrupts the shift in the receptive field 12 and impairs the monkey's ability to monitor its own eye movements 13.

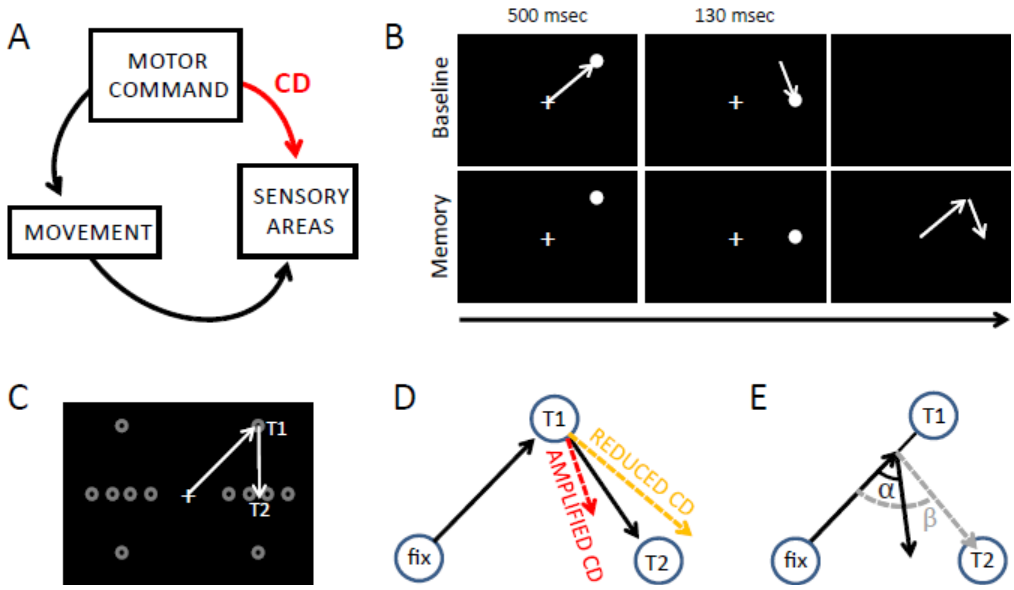


Figure 1. A) A simplified presentation of CD signals (red arrow). CD signals are predictions from motor commands sent to the sensory areas. B) The double-saccade task. In the baseline condition the participants made two sequential saccades (white arrows) to targets. In the Memory condition, the they made saccades to memorized target locations. C) The grey circles show the possible positions of the targets. For data analysis, the coordinates of the targets/eye positions were transposed to correspond to the case where the first target was at the upper right corner of the screen and the second target directly below it (arrows represent eye movements). D) Predictions concerning the double saccade task. If CD is diminished relative to the strength of the motor signal, the participants fail to fully take into account the first eye movement they have performed – hence, their second saccades are biased outward (orange dashed line). Amplified CD (relative to the strength of the motor signal) produces the opposite pattern of results: the second saccade is biased inward (red dashed line). Note that deficits in CD may affect both the angle and the amplitude of the second saccade. E) The efficacy of sensorimotor control can also be examined on a trial-by-trial basis by measuring how well the participants take into account errors in the first saccade 14. In the example, the participant's first saccade falls short of the target T1. The grey line shows what would be the optimal amplitude (length of arrow) and angle (β) of the second saccade to compensate for the error in the first saccade.

The second black arrow shows an example where the amplitude (length) and angle (α) of the second saccade are sub-optimal (i.e. participant overestimates the length of the first saccade, for example, due to amplified CD).

Defects in CD have been observed in neurological patients with lesions to the CD system 15,7. Using the double-saccade task, Thakkar et al. 6 observed that in schizophrenia patients the errors in the angle of the second saccade suggested reduced CD relative to motor signals. As schizophrenia has been associated with hyperactive striatal dopamine neurotransmission 16, this raises the question whether PD patients – who characteristically have nigrostriatal dopaminergic defects 17 – display a reverse effect (i.e. amplified CD relative to motor signals). Thus, assuming that the dopaminergic system contributes to the CD, PD patients should show signs of amplified CD when assessed with the double-saccade task. While dopamine is not *per se* assumed to relay the CD information, it is crucial in modulating the activity of basal ganglia and thereby motor behavior 18, and it is hypothesized to meditate the integration of bottom-up sensory information and contextual information such as previously performed movements (e.g. CD) 19,20. The two possible outcomes of CD deficits (reduced vs. amplified CD relative to the motor signals) are displayed in Figure 1D. Furthermore, as shown in Figure 1E, impaired CD should also lead to systematic variation in the angle of the second saccade on trial-to-trial basis 14,20.

Abnormal CD is also predicted by the site of neuronal dysfunction in PD. The decrease of dopaminergic projections from the substantia nigra pars compacta (SNc) leads to an excessive inhibition in basal ganglia, thalamus, superior colliculus, and cortex 21,22,23. This is assumed to explain in large part the characteristic motor symptoms of PD 18, which often also affects eye movements 24,25,26. Dopaminergic deficit in PD also results in abnormal functioning of the structures assumed to relay the CD to cortex, most importantly the thalamus. In PD, the medial dorsal

126 nucleus of the thalamus – which is assumed to relay the saccade CD signal to the cortex 12 – displays
127 abnormal bursting activity, which is assumed to disturb the information flow to the cortex 27. It is also
128 possible that in PD the strength of the CD signal may be amplified *relative to the strength of the motor*
129 *signals*, due to inhibition in the neural mechanisms that produce eye movements in PD. That is, one
130 may assume that, when compared to the inhibition in the actual motor signals, the neural
131 mechanisms that mediate the CD signals are less affected in PD.
132 Deficits in CD could lead to problems in visual stability and contribute to the motor symptoms of
133 PD, such as posture and gait, as the patient's internal spatial model does not accurately reflect the
134 world. Abnormal CD could also contribute to visual symptoms observed in PD 28, such as
135 hallucinations 5,29.
136
137 **Results**
138 *Visual symptoms*
139 PD patients reported more visual symptoms compared to healthy controls, although this
140 difference was statistically non-significant (Mann-Whitney test; Table 1). The patient group reported
141 numerically more symptoms especially concerning general confusion about locations of objects, and
142 experiencing spatial shifts or jerks during saccades.
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**Table 1. Visual symptoms (mean and SD)**

| | | Controls | PD | Z | p |
|---|---|---|---|---|---|
| General | Nausea | 0.07 (0.25) | 0.06 (0.24) | -0.05 | 0.96 |
| | Spatial confusion | 0.00 (0.00) | 0.13 (0.34) | -1.39 | 0.16 |
| | Hallucinations | 0.00 (0.00) | 0.00 (0.00) | 0.00 | 1.00 |
| Saccade | Vertigo | 0.14 (0.51) | 0.13 (0.33) | -0.45 | 0.65 |
| | Spatial shift | 0.00 (0.00) | 0.13 (0.33) | -1.39 | 0.16 |
| | Motion | 0.07 (0.25) | 0.13 (0.33) | -0.57 | 0.36 |
| Smooth pursuit | Vertigo | 0.00 (0.00) | 0.00 (0.00) | 0.00 | 1.00 |
| | Spatial shift | 0.00 (0.00) | 0.00 (0.00) | 0.00 | 1.00 |
| | Motion | 0.00 (0.00) | 0.00 (0.00) | 0.00 | 1.00 |
| Total | | 0.03 (0.09) | 0.07 (0.11) | -1.13 | 0.26 |

*Saccadic suppression*

Visual thresholds did not differ between the control group and the PD group during fixation (t = -.13), saccade (t = .15), or after saccade (t = -.91). These factors were hence removed from the linear model used to analyze visual threshold. The pruned model showed that both groups displayed clear saccadic suppression as visual thresholds increased during saccades ($\beta$ = 1.96, 95% CI = [1.48, 2.44], t = 8.06) and right after saccades ($\beta$ = 0.78, CI = [0.30, 1.25], t = 3.21) when compared to thresholds during fixation (see Figure 2). This indicates that the patients' visual sensitivity was similar to the control group.

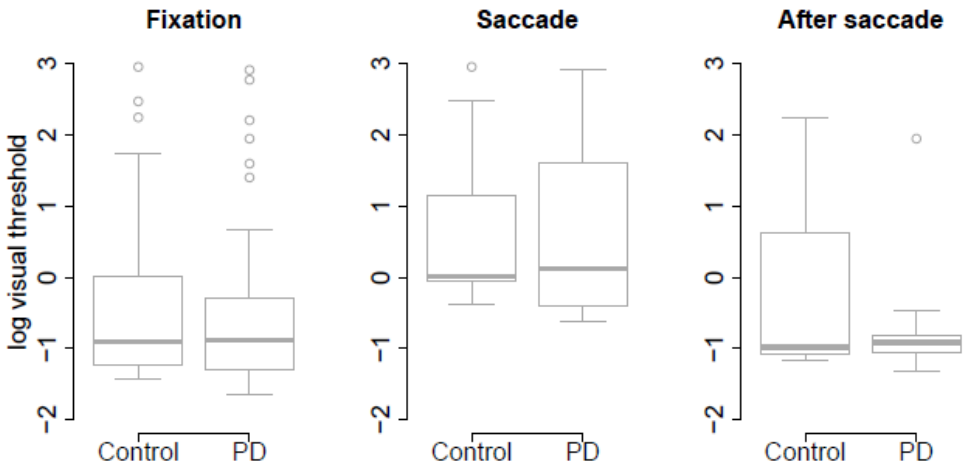



Figure 2. Visual thresholds during fixation, saccade, and after saccade for each group. The unit of the y axis is the logarithm of Michelson contrast of the stimulus.

*Double-saccade task*

*Horizontal and vertical errors*

Figure 3A shows the participants' accuracy in fixating the first and second targets. The data was analyzed using linear mixed-effects models that included the predictors group (Control vs. PD), condition (Baseline vs. Memory), group × condition interaction, and the running trial number (centered). The models were pruned by removing predictors that did not significantly ($t < |2|$) contribute to the model. Horizontal and vertical errors were modelled separately.

*Saccades to the first target.* Although the fixations to the first target concentrated around the actual target position (Fig. 3A upper panels), saccades towards the first target were, on average, somewhat hypometric (i.e. they did not quite reach the target) in the Baseline condition in both groups (*x error*: $\beta$ = -23. 49, CI = [-31.19, -15.83], t = -6.11; *y error*: $\beta$ = -48.19, CI = [-64.33, -32.00], t = -5.82; in the results, the $\beta$ values show the size of the average effect in pixels). In the Memory condition, fixations to the first target became horizontally more accurate in both groups ($\beta$ = 12.26, CI

= [0.59, 23.76], t = 2.11). However, in PD patients the saccades became vertically more hypometric in the Memory condition (y error, PD × Memory: $\beta$ = -42.47, CI = [-78.05, -7.00], t = 2.33), whereas in control group vertical errors somewhat decreased in the Memory condition (t = 1.61).

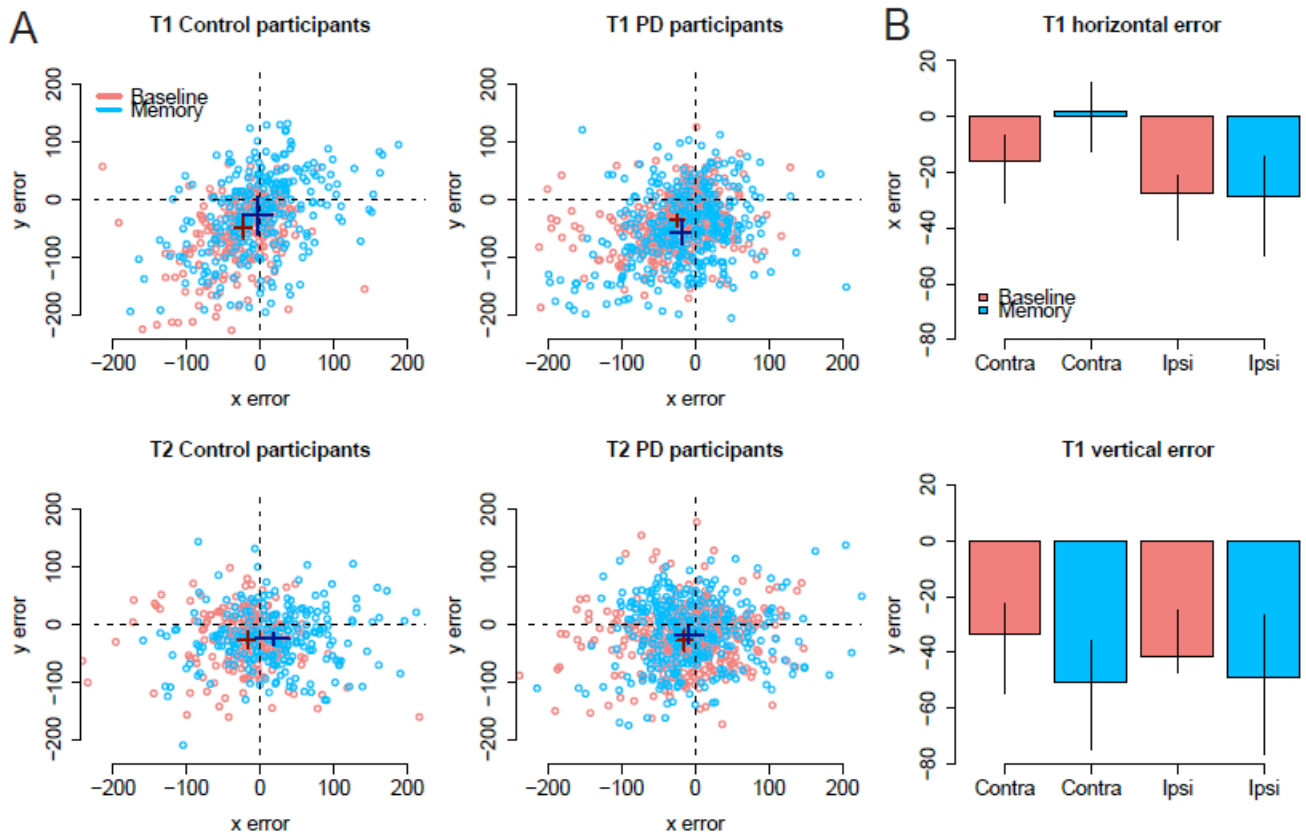



Figure 3. A) Fixation maps for the first target (T1, upper panels) and second target (T2, lower panels), separately for control participants (left) and patients (right). The red and blue dots denote individual fixations in the Baseline and Memory conditions, respectively. The red and blue crosses show the respective group averages; the lengths of the lines is 95% confidence interval of the mean. B) Amount of error as a function of laterality in the PD group. Ipsilateral refers to targets that were presented at the same side as the motor symptoms. Error bars are the 95% CIs of means. Unit of error is pixels (22 pixels is ~1$^{o}$).

As motor symptoms in PD are often asymmetric, we analyzed if the accuracy of fixations was modulated by whether the targets were presented ipsi- or contralaterally with respect to the

194 predominant motor symptoms. This analysis was restricted to PD patients who showed asymmetric
195 symptoms (N=12). The results, displayed in Figure 3B, revealed that fixations to the first target were
196 more inaccurate (horizontally and vertically) when the target was ipsilateral with respect to symptoms
197 (*x error*: *β* = -11.71, CI = [-21.48, -1.93], t = -2.34; *y error*: *β* = -19.71, CI = [-19.85, -1.55], t = -2.29).
198 Moreover, as shown in Fig. 3B (upper panel), in the Memory condition horizontal error was reduced
199 when the targets were contralateral to motor symptoms (Memory × Laterality: *β* = -18.91, CI = [-
200 33.95, -3.87], t = -2.46). Vertical error revealed also an interaction between Memory condition and
201 target laterality: In the Baseline condition vertical errors increased at ipsilateral locations, whereas
202 the effect reversed in the Memory condition (*β* = 16.36, CI = [2.27, 30.40], t = 2.27), but as seen from
203 Fig. 3B (lower panel) the size of this effect is negligible. In summary, these results show that PD
204 patients have selective deficits especially in making horizontal saccades to memorized targets that are
205 at the same side as their primary motor symptoms.
206
207 *Saccades to the second target.* Fixations to the second target (Fig. 3A lower panels) were also on
208 average hypometric in the Baseline condition in both groups (*x error*: *β* = -15. 48, CI = [-23.87, -7.14], t
209 = -3.68; *y error*: *β* = -26.10, CI = [-44.91, -32.00], t = -7.33). During the Memory condition, fixations
210 became hypermetric, on average, i.e. they were biased away from the center of the screen in the
211 horizontal direction in both groups (*β* = 18.32, CI = [0.94, 35.70], t = 2.10). Although Fig. 3A suggests
212 that this effect was smaller in PD patients, this Group × Condition interaction did not reach statistical
213 significance (t = -1.83). A further analysis performed on the patient group showed that when the
214 targets were presented at the same side as motor symptoms, fixations to the second target were on
215 average biased towards the center of the screen in horizontal direction in both conditions (*β* = -14.44,

216 CI = [-22.46, -6.38], t = -3.52). This means that the PD patients show errors consistent with amplified
217 CD when they make saccades towards the side with primary motor symptoms. However, these results
218 should be taken with caution as the bias observed in the fixations to the second target could be in
219 part caused by biases in fixating the first target. To control for this possible confound, the analyses
220 concerning the bias in the second saccade were also performed in trial-by-trial basis (see Fig. 1E) in
221 section *Compensation in angle and amplitude following the first saccade.*
222
223 *Modulation by DAT binding.* Finally, we wanted to see if the accuracy of fixations correlated
224 with striatal dopamine transporter (DAT) binding in PD patients. This analysis focused on mean striatal
225 DAT binding. In addition to the condition (Baseline vs. Memory) and trial number factors, the model
226 included a predictor labelling whether or not the targets were presented contralaterally with respect
227 to the hemisphere with smaller DAT binding (Contralateral factor), the overall DAT binding in the
228 more affected hemisphere (i.e. the one with lower binding), the motor MDS-UPDRS score of the
229 patient, and the interactions of these four predictors.
230 Horizontal or vertical errors of fixations to the *first target* were not modulated by DAT.
231 Horizontal errors of fixations to the *second target* become somewhat more accurate as mean
232 striatal DAT binding increased. This main effect was not statistically significant ($\beta$ = 24.84, CI = [-3.30,
233 52.0499], t = 1.7), but as shown in Figure 4A, the interaction between laterality and DAT suggested
234 that it was only observed for fixations performed to targets presented ipsilaterally to the more
235 affected hemisphere (contralateral × DAT: $\beta$ = -23.94, CI = [-44.65, -3.23], t = -2.3). Figure 4A shows
236 the averaged result across both memory and baseline condition, because no statistically significant
237 effect was observed for condition. UPDRS scores did not significantly modulate fixation errors (t <

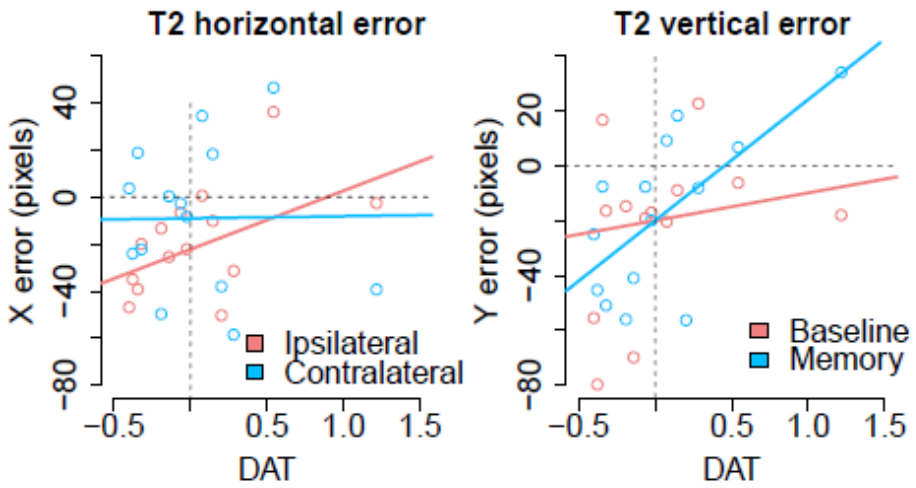
238 |1|), and the modulatory effects by DAT binding were observed even though UPDRS main effect and

239 the contralateral × UPDRS interaction were also included in the model. A further three-way

240 interaction (Condition × UPDRS × DAT) indicated that in the Memory condition, the modulatory effect

241 by DAT binding (Fig. 4A), was reduced in participants with higher UPDRS scores ($\beta$ = -4.20, CI = [-8.17, -

242 0.24], t =-2.1).




243

244 Figure 4. Relationship between average striatal dopamine transporter binding and accuracy of
245 fixations to the second target. A) Horizontal error was modulated by average DAT binding for targets
246 ipsilateral (red line) to the more affected hemisphere (blue line = contralateral). B) Vertical error was
247 modulated by DAT binding, and this effect was stronger when the patients made fixations to
248 memorized targets (blue = Memory). DAT binding variable has been centered (i.e. zero represented
249 the mean). The dots represent the observed data, and the lines represent the modelled results.

250

251 Vertical errors in fixations to the *second target* were more clearly modulated by DAT binding, as

252 shown in Figure 4B. In the Memory condition the vertical accuracy of fixations increased as DAT

253 increased (Memory × DAT: $\beta$ = 44.00, CI = [13.63, 74.38], t = 2.8). No such effect was observed in the

254 Baseline condition (t = 0.4). Target laterality did not modulate this effect, and therefore Fig. 4B shows

255 the average of ipsi- and contralateral data. Again, UPDRS scores did not significantly predict fixation

256 accuracy (t < |1|), suggesting that the observed modulation by DAT does not simply reflect the

severity of the PD. Altogether these results suggest that dopamine specifically contributed to the accuracy of the *second* saccades. This effect was most clearly observed in vertical errors, and in the Memory condition (Fig. 4B) where the saccades are performed without external visual guidance (i.e. they are based on CD).

*Compensation in angle and amplitude following the first saccade*

As explained in Fig. 1E we also examined how well the participants took into account the trial-by-trial variability in the first saccade when executing the second saccade. In the regression models, the predictor variables were the centered optimal angle/amplitude of the saccade (see Fig. 1E), group, condition, all interaction between these three variables, and running trial number (centered).

As shown in Figure 5A-B, the trial-to-trial variability in the *angle* of the second saccade was strongly predicted by the optimal angle required to perfectly fixate the second target ($\beta$ = 0.71, CI = [0.67, 0.76], t = 29.62). In other words, the participants clearly had information about the error in the endpoint of the first saccade which they could use to correctly aim to the second target. In the Memory condition, the angle of the second saccade was smaller than in the Baseline condition. That is, participants' saccades were biased towards the center of the screen (i.e. the initial fixation point; $\beta$ = -4.69, CI = [-7.75, -1.67], t = -3.09). Furthermore, in the Memory condition, the larger the optimal angle, the larger was the bias towards the center of the screen (interaction: $\beta$ = -0.13, CI = [-0.20, -0.02], t = -4.32). PD patients were not statistically significantly different from control participants ($t \leq |1|$).

Also the *amplitude* of second saccade strongly correlated with the optimal amplitude ($\beta$ = 0.87, CI = [0.78, 0.96], t = 19.46). Moreover, although the amplitudes of the second saccades did not differ

between groups (t = 0.04), there was an interaction between group and optimal amplitude: Patients' second saccades become more hypometric as the optimal amplitude required to reach the target increased (Fig. 5C-D, blue line: $\beta$ = -0.15, CI = [-0.27, -0.04], t = 2.61).

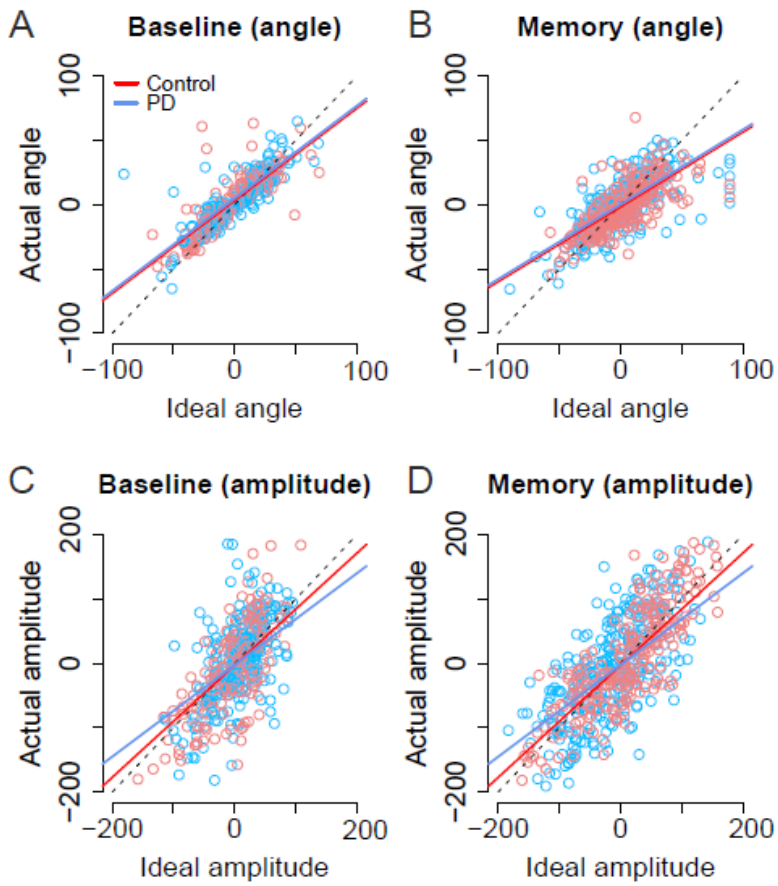



Figure 5. Actual saccade angles (A-B) and amplitudes (C-D) as a function of ideal angle/amplitude. Left panels show the baseline condition, and the right panel the Memory condition. Red color denotes the healthy control participants, and the blue color the patient group. Dots show the observed data (individual saccades) and lines the fitted linear models. Note that angle/amplidute variables are centered, i.e. negative values show that angle/amplitude was smaller than average. Unit is pixels (22 pixels is ~1$^{o}$).

As with previous analyses, we examined whether the laterality of the motor symptoms correlated with the angles/amplitudes of the second saccades. As shown in Figure 6, when the targets were presented at the same side as the motor symptoms the compensation in saccade angle was

worse than when the targets were presented on the side with less motor symptoms – the second saccades become biased towards the center of the screen, consistent with amplified CD ($\beta$ = -0.11, CI = [-0.19, -0.033], t = -2.78). In other words, although the PD group did not in general as a group differ from healthy controls in compensating for variability in the endpoint of the first saccade, such an effect was observed when the laterality of the symptoms was considered. In other words, this means that since in some patients the symptoms are predominantly on the right side, and in other patients on the left side, the deficit is only observed when the laterality of the symptoms is taken into account.

Target side relative to motor symptoms did not modulate the precision of compensation for saccade *amplitudes*.

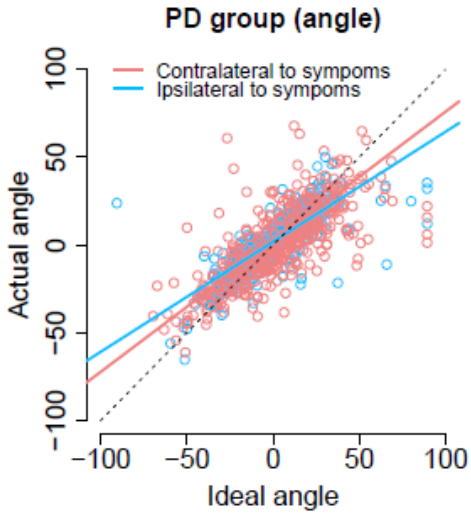



Figure 6. The angle of the second saccade as a function of ideal angle. Compensation for variation in the endpoint of the first fixation is worse for targets that are at the same side as motor symptoms.

*Modulation by DAT binding.* We also examined whether the success of compensating for variability in the endpoint of the first fixation correlated with dopamine transporter binding in PD patients. As previously, the model included condition, target laterality (with respect to the more affected

312 hemisphere), the amount of DAT binding, the optimal angle to perfectly fixate the second target, and
313 the motor MDS-UPDRS score of the participant (and the interactions between these regressors).
314 As previously stated the actual *angles* of the saccades were strongly predicted by the optimal
315 angle required to reach the second target ($\beta$ = 0.74, CI = [0.67, 0.81], t = 20.3). As shown in Figure 7A
316 (blue dashed line) patients with lower DAT transporter binding values were more inefficient in taking
317 into account for the trial-to-trial variability in the endpoint of the first saccade and their saccades
318 become more biased towards the center of the screen (Ideal angle × DAT: $\beta$ = 0.17, CI = [0.070, 0.28],
319 t = 3.2). Furthermore, the modulation of the angle of the second saccade by DAT is not explained by
320 the severity of PD as the motor MDS-UPDRS score revealed similar modulatory effect (Ideal angle ×
321 UPDRS: $\beta$ = 0.0030, CI = [0.00081, 0.0053], t = 2.6). Note that although the $\beta$ coefficient of the Ideal
322 angle × UPDRS interaction (0.0030) is much smaller than the $\beta$ coefficient of the Ideal angle × DAT
323 interaction (0.17), the relative size of this effect is in fact very similar (due to the fact that the range of
324 motor MDS-UPDRS scores is much higher than DAT values). The modulatory effect by motor MDS-
325 UPDRS is visualized in Figure 7A as the red dotted line which overlaps the blue dashed line that
326 depicts modulation by DAT. In addition to the above mentioned two-way interactions, a Ideal angle ×
327 motor MDS-UPDRS × DAT interaction was observed ($\beta$ = 0.014, CI = [0.004, 0.025], t = 2.8). This three-
328 way interaction indicates that the modulation by DAT binding was stronger in participants with more
329 severe PD (i.e. higher UPDRS scores).
330 Next we examined whether DAT binding was associated with the ability to modulate the
331 *amplitude* of the second saccade to compensate for trial-to-trial variability in the first saccade.
332 Although patients were in general successful in making a second saccade whose amplitude closely
333 resembled the ideal amplitude required to perfectly fixate the second target ($\beta$ = 0.73, CI = [0.65,

0.81], t = 17.7), patients with lower DAT binding made more hypometric saccades ($\beta$ = 53.94, CI = [19.23, 88.65], t = 3.0), as shown in Figure 7B. UPDRS score did not statistically significantly modulate saccade amplitudes in general (main effect of UPDRS: t = -0.3). However, patients with higher motor MDS-UPDRS scores were more inefficient in making a close-to-ideal amplitude saccade to the second target (Ideal amplitude × motor MDS-UPDRS: $\beta$ = -0.010, CI = [-0.015, -0,0050], t = -3.7). Surprisingly, as shown in Figure 7C, this effect was only observed when the targets were presented ipsilaterally with respect to the hemisphere with lower DAT binding (Contralateral × Ideal amplitude × motor MDS-UPDRS: $\beta$ = 0.012, CI = [0.0048, 0,020], t = 3.1).

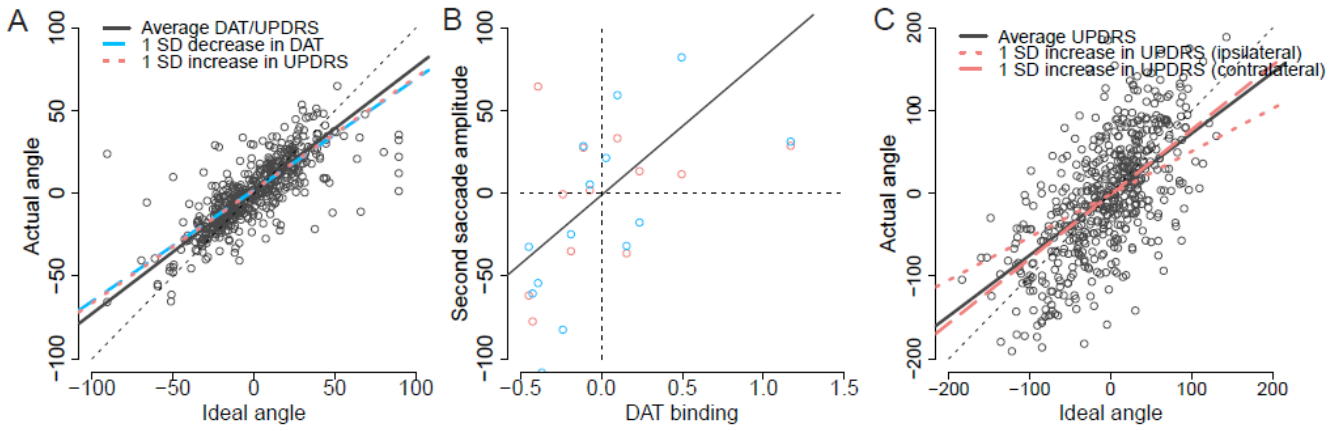



Figure 7. Modulation of compensation in the amplitude of the second saccade. A) Compensation for variation in the endpoint of the first fixation is modulated by DAT binding (blue dashed line) and MDS-UPDRS (red dotted line). The visualized effects represent 1 SD decrease (DAT) or increase (MDS-UPDRS) relative to the patient group average, which is plotted as a grey solid line. The circles represent the observed data. B) Correlation between the amplitude of the second saccade and DAT binding. The red and blue circles represent the (average) observed data in the Baseline and Memory condition respectively. The grey line shows the modelled results (Baseline and Memory conditions pooled, as no Condition × DAT interaction was observed). C) Participants with higher MDS-UPDRS scores were more inefficient in compensating for the trial-to-trial variability in the endpoint of the first saccade, but this effect was only observed when the patients made saccades to targets presented ipsilaterally with respect to the hemisphere with lower DAT binding (dotted red line). The grey solid line shows the modelled performance of the patients on average.

357 **Discussion**

358 We examined how well early PD patients can update their spatial representations during eye
359 movements, and whether this ability correlates with the integrity of the dopaminergic system. The
360 participants were asked to make eye movements to two targets presented in succession. The results
361 showed that while the patients' general ability to fixate the first target was relatively intact, they
362 showed systematic deficits in shifting their gaze to the second target when compared to age-matched
363 neurologically healthy controls. This effect was most prominent when the patients made saccades
364 towards the side with primary motor symptoms. The deficit in fixating the second target correlated
365 with the integrity of the dopaminergic system: patients with lower dopamine transporter binding
366 showed more marked deficits in fixating the second target, and their eye movements were biased
367 towards the center of the screen (i.e. towards the starting point of the first saccade).

368 The results are consistent with the assumption that PD patients show an amplified CD relative
369 to the motor signals: the brain systems that internally monitor the eye movements of the patients
370 signal that the extent of the movement was larger than what was actually the case. Hence, when the
371 patients make a second saccade quickly after the first one, they tend to undershoot the target of the
372 second saccade. The present findings are especially interesting as previous research has shown that
373 deficits in CD are associated with *reduced* CD relative to motor signals 13,6. However, there is no
374 reason to assume that abnormal CD always results in reduction of the CD signal (although this is
375 obviously the case when an area that conveys the CD signal is lesioned; 1).

376 The interpretation that PD patients show an amplified CD which correlates with the integrity of
377 the dopaminergic system is consistent with the finding that schizophrenia patients reveal the reverse
378 pattern of results when performing the double-saccade task: in contrast to the present results,

379 schizophrenia patients underestimate the size of the first saccade 6. Because schizophrenia has been
380 associated with increased basal ganglia dopamine neurotransmission 16, PD patients (who have
381 dopamine deficiency) should show an opposite effect assuming that the dopaminergic system
382 contributes to the CD. Previous studies have not tested whether the integrity of the dopaminergic
383 system correlates with performance in the double-saccade task. Our results suggest that the
384 dopamine system contributes to spatial remapping. Crucially, correlations between dopamine
385 transporter binding and saccade performance were observed only for fixations to the *second* target,
386 implying that the dopaminergic system contributes specifically to spatial remapping and not to
387 performing saccades in general. Furthermore, the modulation by DAT binding was observed even
388 when motor symptom severity of PD was controlled by including the motor MDS-UPDRS score to the
389 model, suggesting that the effect is not simply due to variation in the motor symptoms of PD, but
390 rather a specifically dopaminergic phenomenon.

391 The present results do not imply that the dopamine system per se carries the CD, but that
392 dopamine modulates the functioning of the network of brain regions that mediate the CD, or
393 otherwise mediates spatial remapping after saccades. The present study does not specify whether the
394 possible deficits in the CD system result from 1) the amplification of the CD signal, or 2) the decrease
395 in the strength of the "output" motor signal relative to CD. The crucial claim is that there may be a
396 mismatch between internal monitoring signals (CD), and output motor signals in PD. According to a
397 widely held view, the degeneration of neurons in the SNc 30,31 leads to an inhibition in subcortical
398 structures 21,23 that take part in relaying the CD to the cortex (basal ganglia, thalamus, superior
399 colliculus; 1). However, there could also be independent striatal changes in the dopamine system as
400 the nigral cell counts do not seem to correlate with striatal DAT binding 32. Also, cortical systems and

401 cortico-subcortical-systems in general, are affected in PD 33, and the spatial remapping after
402 movement are assumed to rely on computations performed on cortical level 11,34.

403 Amplified CD signal is not the only possible explanation for the present results. Previous studies
404 have emphasized the role of kinesthetic feedback in PD 3,2, and it could be argued that the errors in
405 fixating the second target are due to impaired kinesthetic feedback from the extra-ocular muscles. As
406 with CD, this interpretation assumes that kinesthetic feedback is amplified. Future studies should
407 attempt to disentangle the contributions of CD and kinesthetic feedback to spatial remapping in PD.
408 Furthermore, because the present study focused on the spatial accuracy of fixations, it remains to be
409 tested whether the proposed deficit in CD is also reflected in saccadic latencies, or whether spatial
410 biases are accompanied by changes in saccade latencies.

411 The present study employed a modified version of the double-saccade task. In the classical
412 version (e.g. 35,13,6) the visual targets are presented so briefly that they are removed from the
413 screen before the eye movements begin; hence the saccades cannot be guided by sensory
414 information. Because the classical double-saccade task-set up proved too demanding for elderly
415 subjects, we used a modified task where the targets were presented for a longer duration. We
416 expected that the PD patients would show deficits especially in the Memory condition, where the
417 saccades to the two target locations are performed solely based on memory. However, the present
418 results show that PD patients are impaired in their second saccade also when the first saccade could
419 be directed based on visual information. This observation speaks against the interpretation that the
420 observed results are solely due to impaired CD or kinesthetic feedback. On the other hand, it could be
421 argued that if CD or kinesthesia is impaired, the bias in their internal spatial representation may
422 contribute to performance even when sensory information can be used to guide behavior because

423 behavior and perception are based on the interplay between incoming sensory information and
424 internal models (predictions such as the CD). The fact that performance was deteriorated both in
425 Baseline and in Memory condition suggest that the impairment in PD may be related to more general
426 difficulties in updating spatial representations, or binding sensory information with current internal
427 spatial representation. The dopamine system may thus be part of a more general prediction system
428 that estimates the uncertainty of internal models of the world 19,20. Consistent with the present
429 findings, dopamine contributes to encoding and updating spatial representations in hippocampal
430 neurons 36,37.

431 PD patients are known to undershoot targets when performing eye movements 25,24, and
432 studies have also reported that PD affects saccadic response times 38. The present results showed
433 that the patient group was relatively unimpaired in making spatially accurate saccades to the first
434 target. This may be due to the fact that the patients were at an early stage of PD. The main difference
435 in the performance in the two groups was that the PD patients' performance (in making the first
436 saccade) deteriorated in the Memory condition, which is consistent with previous reports 39,25,24.
437 Altogether, this suggests that the patients' deficits in the present task were not simply related to
438 difficulties in executing eye movements in general. Our results replicate the finding that deficits in
439 saccades are typically worse on the side with larger primary motor symptoms 26. Importantly, the
440 deficits in spatial remapping were also dependent on the laterality of the primary motor symptoms:
441 the hypothesized deficits in the trial-to-trial variability in the angle of the second saccade were only
442 observed when the laterality of motor symptoms was taken into account (see Fig. 6). This is consistent
443 with the observation that thalamic lesions (that interfere with the CD) produce lateralized defects
444 (e.g. 12). However, we also observed some more surprising – and perhaps counterintuitive – findings

445 related to lateralization. First, the modulation of the horizontal error in fixations to the second target
446 by dopamine transporter binding was observed only for saccades *ipsilateral* to the hemisphere with
447 lower DAT binding (Fig. 4A; although note that this effect was weak). Secondly, PD patients with
448 higher motor symptoms severity scores made larger errors in fixating the second target, but again this
449 only applied to saccades *ipsilateral* to the hemisphere with lower DAT binding (Fig. 7C). While these
450 findings could be false positive findings due to limited sample size (Fig. 4A), or they may also suggest
451 that the laterality effects of dopaminergic deficits are not straightforward (Fig. 7C). PD patients
452 sometimes display motor symptoms ipsilateral to the dopaminergic deficit 40,41. Another possibility
453 is that while DAT function in the contralateral striatum is affected severely already in early PD
454 (possibility due to floor effect), correlations can be more easily detected in the ipsilateral side.
455 The PD patients in the present study were at the early stages of PD, generally did not report
456 visual symptoms, and the visual sensitivity of the patients was similar to the control group. It is
457 important to note that with the double-saccade task we were able to detect subclinical deteriorating
458 visual functions that the patients were unaware of. These disturbances, together with the shown
459 associations with DAT binding suggest that, as the disease progresses and the dopaminergic deficit
460 deepens, relevant clinical CD-associated motor and visual symptoms will emerge. Advanced PD
461 patients have many visual symptoms 28 and abnormal CD may lead to deficits in experienced visual
462 stability in PD. More generally, the present study suggests that motor deficits in PD are partly
463 produced by difficulties in internal monitoring of movements. Studies with patients with more
464 progressed PD and other dopaminergic diseases are required to confirm these findings.
465
466 **Method**

467 *Participants*

468 Fourteen PD patients (8 women; $M_{age}$ = 62, range: 45–75 years, 13 right-handed and one
469 ambidextrous) and fourteen right-handed neurologically healthy control participants (7 women; $M_{age}$
470 = 67, range 44–78) took part in the experiment. PD patients were diagnosed using the UK Brain Bank
471 criteria, all diagnoses were supported by marked striatal defects in dopamine transporter SPECT and
472 none of the patients presented features suggestive of atypical parkinsonism. All participants had
473 normal or corrected-to-normal vision. Three control participants had to be excluded from the analysis
474 due to technical problems during testing. In most cases the control participants were the spouses of
475 the PD patients. The duration of motor symptoms in PD patients was on average 24 months (range:
476 3–72 months), and the Hoehn-Yahr stages of the patients were as follows: Six patients at stage I,
477 seven patients at stage II, and one patient at stage III. The patients had a mean motor MDS-UPDRS
478 score of 37 (range 11–95, SD = 20). In eight patients the motor symptoms were primarily on the left
479 side, in four patients in the right side, and two patients had nearly symmetrical motor symptoms.
480 None of the patients had depression (mean BDI = 3.8, range 1-12, SD = 2.8), and none showed signs of
481 abnormal cognitive abilities as measured by the Mini-Mental State Examination (mean 27.6, range 26-
482 30).

483 Eleven patients underwent a voluntary break in medication before the experiment, and did not
484 take medication on the morning of the test session. One patient did not have any medication, and
485 two participants did not go through a break in medication. Three patients were on levodopa, nine
486 patients were treated with MAO-B inhibitors and/or dopamine agonists and medication was unknown
487 for one patient.

488 The experiment was approved by the Ethics committee of the hospital district of South-West
489 Finland, and a written informed consent was obtained prior the study. The study was conducted
490 according to the principle of the Declaration of Helsinki.
491
492 *Tasks, stimuli and procedure*
493 In addition to performing the double saccade task, we also measured the strength of saccadic
494 suppression in the participants by measuring visual thresholds during saccades and fixation. Previous
495 studies have reported increased visual threshold in PD 42,43, and saccadic suppression has been
496 hypothesized to be triggered by extra-retinal (e.g. CD) signals 44. Finally, the participants were
497 queried about their subjective experience of visual stability using a questionnaire described below.
498 We assumed that deficits in CD and visual updating may lead to subjectively experienced symptoms of
499 unstable vision.
500 To assess whether the participants experience symptoms of unstable vision they were asked
501 whether they perceived motion, experienced vertigo, or had feelings that the world has "changed
502 position" during saccadic or smooth pursuit eye movements. Smooth pursuit eye movements were
503 included in the questionnaire as control questions, since we hypothesized that possible impairments
504 in visual stability selectively affect saccades. In addition participants were asked if they had trouble
505 estimating the positions of objects, had experienced visual hallucinations, or had experienced any
506 other visual symptoms. Answers were given on a four step scale (0 = never … 3 = often).
507 In the double saccade task a participant is asked to shift her gaze to two briefly presented
508 targets. In the traditional form of the task the targets are presented so briefly that when the
509 participant initiates the first saccade, both visual targets have disappeared from the screen. Thus the

510 participant must use her internal monitoring signals (i.e. CD) to take into account the spatial change
511 produced by the first saccade in order to correctly fixate the second target 35,1,6. Pilot experiments
512 for the present study showed that the traditional double saccade task was too challenging for the
513 elderly participants (the participants had trouble perceiving and making saccades to the locations of
514 the briefly presented target stimuli). In order to make the task easier for the participants, we modified
515 the task so that each target stimulus is presented for a longer duration, but the participants were
516 instructed to initiate the saccades only after both targets had disappeared from the screen (Memory
517 condition; Figure 1B). While this means that short-term visuospatial memory may contribute to
518 performance more in our modified version than in the traditional form of the task (which taxes the
519 sensory memory more), the key idea behind the double saccade task remains unchanged: the
520 participants need to take into account the spatial change produced by the first saccade in order to
521 correctly fixate the second target. In the Baseline condition (Fig. 1B), which was physically identical to
522 the experimental condition, the participants were not required to wait until the targets have
523 disappeared and could initiate their eye movements voluntarily.

524 For the double saccade task, round ($.6^{o}$) white target stimuli were presented on a black
525 background. The double saccade task began with a nine point calibration of the eye-tracker (i.e.
526 whole screen was calibrated). After calibration, each trial began with a white fixation point presented
527 at the center of the screen. This fixation point was also used as a (eye-tracking) drift-correction point
528 in the beginning of each trial. After the participants correctly fixated the center of the screen for 1.2-
529 1.5 sec, the two target stimuli were presented. The first stimulus was always presented in one of the
530 four quadrants of the screen (e.g. upper right quadrant as in Fig. 1B) for 500 msec ~16 degrees from
531 the fixation point. Right after the first target, a second target was presented for 130 msec on the

532 horizontal meridian at the same side of the screen as the first target. However, the exact horizontal
533 position of the second target varied from trial to trial (there were four equally likely positions,
534 separated by a minimum of ~2.4 degrees). The possible locations of the saccade targets are presented
535 in Figure 1C. Each participant performed the baseline and memory conditions once. Thirty trials were
536 collected for each condition. Before the experimental runs, each participant performed at least 10
537 practice trials without eye-tracking.

538 Visual 81% thresholds were measured by presenting a horizontally oriented, low-frequency,
539 luminance modulated Gabor grating (diameter ~12°, 0.33 cycles per degree, phase varied randomly
540 on each trial) in the upper or lower visual field (center of the Gabor was 7 degrees from the center of
541 the screen) for one screen refresh (11.8 msec). The stimuli were presented on mid-grey background.
542 Participants' task was to report whether the Gabor stimulus was presented in the upper or lower
543 visual field using the up and down arrow keys. The detection threshold was determined by adaptively
544 varying the Michelson contrast of the Gabor using a Bayesian staircase method QUEST 45. This
545 procedure is similar to previously reported means of measuring saccadic suppression 46. Each
546 participant performed three different conditions during which visual thresholds were measured:
547 during fixation, during saccade, and right after saccade. When the thresholds were measured during
548 fixations participants kept fixating to a fixation dot, presented in the middle of the screen. In the
549 'saccade condition', the visual threshold was determined for Gabor stimuli presented while
550 participants performed ~19 degree saccades from a fixation point on the left side of the screen to a
551 black dot at the center of the screen. In the 'after saccade' condition the Gabor stimulus was
552 presented ~100 msec after the saccade had ended. Participants always initiated the saccades
553 voluntarily after a brief period of fixation during which the eye tracker was drift corrected. To enable

554 accurate tracking of horizontal eye-position, the eye-tracker was calibrated by three calibration points
555 presented on the horizontal meridian (left side, right side and center of the screen).
556 In both tasks (double saccade and visual threshold) the stimuli were presented using
557 Psychtoolbox 47 running on Matlab 2014b. Eye movements were recorded using EyeLink 1000 eye-
558 tracker (SR Research) that was operated using the EyeLink Toolbox 48. The eye movement
559 registration was done monocularly, typically for the right eye, using 1000 Hz sampling frequency. The
560 stimuli were presented on a 19″ CRT screen with a screen resolution of 1024 × 768 pixels and 85Hz
561 refresh rate. Participants were seated 70 cm from the screen and a head rest was used to stabilize the
562 head.
563
564 *SPECT imaging*
565 To image dopamine transporter (DAT) binding, all PD patients underwent brain [$^{123}$I]FP-CIT
566 ([$^{123}$I]N- ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane) SPECT. The interval
567 between the scanning and behavioural testing (e.g. double saccade task) was 8-29 months. Prior to
568 scanning, thyroidal update of the ligand was blocked by administering oral potassium perchlorate
569 (250 mg) 60 minutes before the injection of [$^{123}$I]FP-CIT. An 185 MBq bolus of [$^{123}$I]FP-CIT was
570 administered and scanning performed 3 hours after the injection. Imaging was performed as
571 described earlier 49. The images were reconstructed and analysed using BRASS (Hermes Medical
572 Solutions AB, Stockholm, Sweden). Specific binding rations (SBRs) for the caudate nucleus and the
573 putamen were quantified using occipital cortex as the reference region $SBR_{ROI}$ = (ROI – OCC) / OCC,
574 where ROI refers to the uptake in the region of interest and OCC in the occipital cortex. Although
575 occipital cortex may contain minute concentrations of DAT, it has been shown to be a valid reference

region in [$^{123}$I]FP-CIT imaging 50. Mean striatal values (caudate, anterior putamen and posterior putamen) in the left and right hemisphere were used for correlation analyses. In statistical analysis of the relationship between DAT binding and behavioural performance, the analyses always included a factor that indicated whether saccades were made ipsilaterally or contralaterally with respect to the hemisphere with lower binding.

*Data analysis*

Single-trial eye movement data (accuracy of fixations) was analyzed using linear mixed-effects models using the lme4 package 51 in R statistical software 52. Because the analysis is performed on a single-trial basis rather than on aggregated means, mixed-effects models enable taking into account individual differences, in addition to group-level effects. Participants were included in the model as random variables, that is, each individual participant's data was fitted with individual intercepts and slopes (concerning the Baseline/Memory condition). The fixed-effect predictors included in the models are described in the Results section. The models were pruned by removing fixed-effects predictors that did not significantly ($t < |2|$) contribute to the model. The visual detection thresholds (saccadic suppression) were analyzed using linear mixed effects models with separate intercepts for each subject. As there is no standardized way to calculate the degrees of freedom and the corresponding p values in mixed-effects models 53, we do not report p values. However, the statistical significance of an effect can be checked from the confidence intervals (CI): whenever the value zero is included in the CI, the effect is not considered statistically significant. Another reason to not report p values is to draw the reader’s attention to the size of the effect 54. Error bars in all the figures are 95% CIs calculated from 1000 bootstrap samples.

598 In the double-saccade task, separate models were built for horizontal and vertical errors
599 (relative to the target location). Only trials where the first saccade was directed towards the first
600 target and where the participants made a following saccade towards the second target were included
601 in the analysis (5.8% of trials were excluded). For each participant, the first fixation to the first and
602 second targets were included in the analysis, except for cases were the first fixation was very brief
603 and rapidly followed by a corrective saccade towards the correct location. Before the analysis of
604 fixation accuracy, the data was transposed to correspond to the case where the first target was at the
605 upper right corner of the screen and the second target directly below it (Fig. 1C). These preprocessing
606 steps were performed in Matlab 2014b.
607 Datasets can be downloaded from the Open Science Framework (https://osf.io/bqnzh).
608
609 **Additional information**
610 *Competing Interests*
611 The authors declare that they have no competing interests.
612
613 *Author contributions*
614 H.R. and V.K. designed the research. H.O. and H.R. programmed the eye-tracking experiments.
615 E.E. and O.P. collected the eye movement and questionnaire data. V.K. and J.J. collected and analyzed
616 the SPECT data. H.R. analyzed the eye-movement data and wrote the first draft of the manuscript.
617 V.K., H.O. and J.J. reviewed and edited the manuscript.
618
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626

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628

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629

630