Dopamine and eye movement control in Parkinson's disease: deficits in corollary discharge signals

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During motor behavior the brain has to predict the sensory consequences of movements to enable accurate perception of the world. This process is assumed to rely on corollary discharge signals sent through the basal ganglia and dopaminergic system, both of which malfunction in Parkinson's disease (PD). We studied early-stage PD patients (N=14), and age-matched healthy control participants (N=14) to examine whether PD patients reveal deficits in updating their sensory representations after eye movements. The participants performed a double-saccade task where, in order to accurately fixate a second target, the participant must correct for the displacement caused by the first saccade. PD patients showed systematic deficits in fixating the second target, especially when they made saccades towards the body side with predominant motor symptoms. Across PD patients, the impairment in fixating the second target correlated with the integrity of the dopaminergic system as measured with [^{123}I]FP-CIT SPECT: Patients with lower striatal dopamine transporter binding made larger errors. The direction of the errors suggests that the corollary discharge indicated a larger movement than was actually made by the patients. Dopamine transporter binding did not correlate with the accuracy of the first saccade. This deficit in internal monitoring of movements could aggravate motor symptoms, and explain frequently occurring visual symptoms in PD.

Keywords: Parkinson's disease, corollary discharge, efference copy, predictive coding, dopamine, dopamine transporter binding, saccadic eye movement

57 Motor behavior requires the brain to update sensory representations to take into account
58 changes that are produced by self-induced movements. How the brain accomplishes this remains
59 open, but theories assume that the basal ganglia, thalamus, and the dopaminergic system contribute
60 to this process (Crutcher & DeLong, 1984; Wurtz, 2008; Friston, et al., 2012). The present study
61 examined this little studied hypothesis in Parkinson's disease (PD), which is a neurodegenerative
62 disease characterized by a deficiency in dopaminergic neurons which leads to malfunction of the basal
63 ganglia and thalamus (DeLong & Wichmann, 2007; Albin, et al., 1989). We examined PD patients'
64 ability to monitor their own eye movements using a *double-saccade task* which has been widely
65 utilized to examine internal monitoring of movements (Wurtz, 2008; Ostendorf, et al., 2010; Thakkar,
66 et al., 2015). During eye movements the image on the retina changes place, and yet we precisely
67 know the locations of objects in the world because changes in perception that are due to the eye
68 movements have been taken into account by the brain. In the double-saccade task a participant must
69 take into account the displacement caused by a first saccade to accurately perform a second saccade
70 (Figure 1B). This is assumed to rely on corollary discharge (CD) signals that relay a copy of the motor
71 command to sensory areas (Figure 1A) via medial thalamus (Sommer & Wurtz, 2008; Wurtz, 2008).
72 Dopaminergic deficit in PD (DeLong & Wichmann, 2007; Albin, et al., 1989) results in abnormal
73 functioning of the structures assumed to relay the CD to cortex, most importantly the thalamus. In
74 PD, the medial dorsal nucleus of the thalamus displays abnormal bursting activity which is assumed to
75 disturb the information flow to the cortex (Pifl, et al., 2012). The CD signal can be seen as a part of a
76 more general mechanism that integrates bottom-up sensory information and contextual information.
77 This is clearly formalized in the predictive coding framework which assumes that the brain is

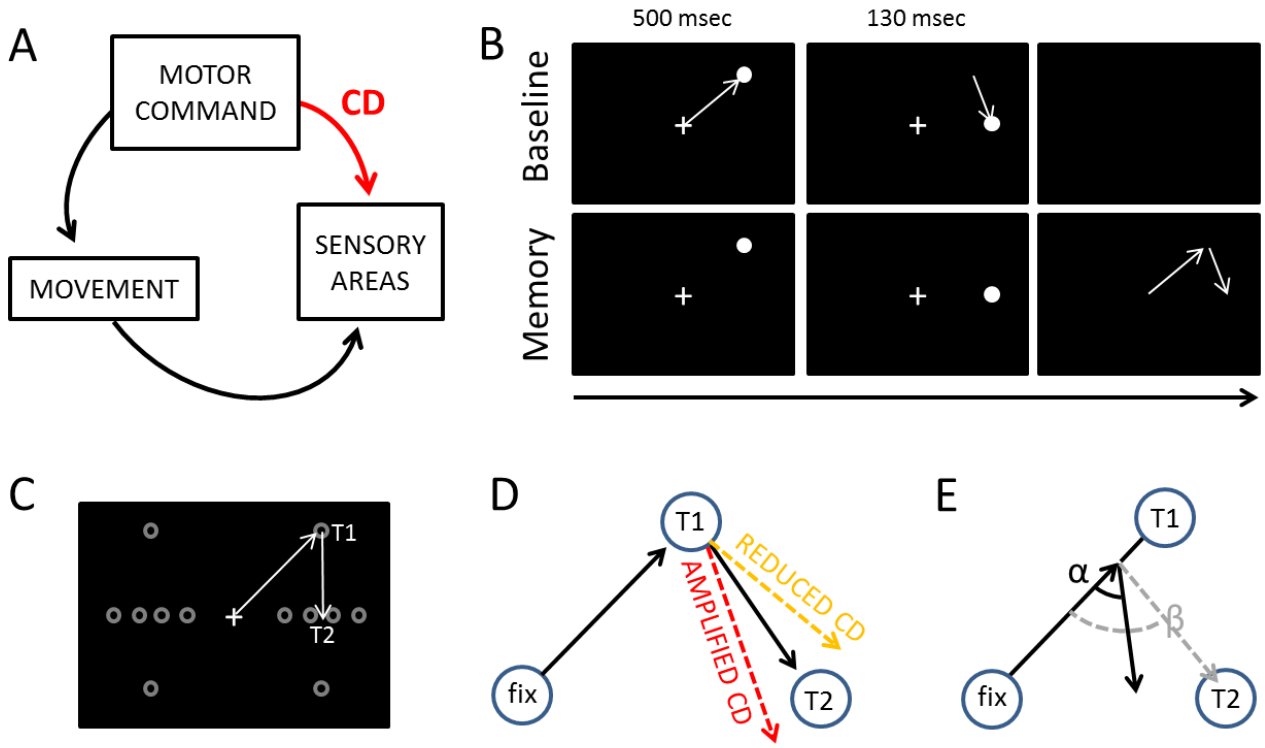


Figure 1. A) A simplified presentation of CD signals (red arrow). CD signals are predictions from motor commands sent to the sensory areas. B) The double-saccade task. In the baseline condition the participants made two sequential saccades (white arrows) to targets. In the Memory condition, the they 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) Hypothesis concerning the double saccade task. If CD is diminished relative to the strength of the motor command, 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 command) produces the opposite pattern of results: the second saccade is biased inward (red dashed line). 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 (Joiner, et al., 2010). In the example, the participant's first saccade falls short of the target T1. The grey dashed 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 angle (α) and amplitude of the second saccade is sub-optimal (i.e. participant overestimates the length of the first saccade, for example, due to amplified CD relative to the actual motor output).

constantly attempting to predict (model) incoming sensory information based on previous experiences (Hohwy, 2013; Clark, 2016). The CD signal is a prediction about the sensory consequence of a movement. According to this framework, during (eye) movements the brain compares its current model of the world (predictions) against incoming sensory information (Friston, et al., 2012). Friston et al. have hypothesized, and using dopamine depletion simulations provided evidence, that the dopaminergic system mediates sensorimotor integration by adjusting the how much the brain relies on the predictions (Friston, et al., 2012). Specifically, they have proposed that the dopaminergic deficiency in PD causes the patients to rely more on their internal predictions (e.g. CD) than bottom-up sensory information (Friston, et al., 2012).

Defects in CD have been observed in neurological patients with thalamic lesions (Bellebaum, et al., 2005; Ostendorf, et al., 2010). Using the double-saccade task, Thakkar et al. (2015) 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 (Howes & Kapur, 2009), this raises the question whether PD patients – who characteristically have nigrostriatal dopaminergic defects (Kordower, et al., 2013) – display a reverse effect (i.e. amplified CD relative to motor commands). Previous studies have not tested whether the integrity of the dopaminergic system correlates with performance in the double-saccade task. While dopamine is not *per se* assumed to relay the CD information, it is assumed to mediate the integration of bottom-up sensory information and contextual information such as previously performed movements (e.g. CD) (Friston, et al., 2012). The two possible outcomes of CD deficits (reduced vs. amplified CD relative to the motor signals) are displayed in Figure 1D. As shown in Figure 1E, CD also

allows for taking into account variation in the endpoint of the first saccade on a trial-to-trial basis to produce accurate saccades to the second target (Joiner, et al., 2010; Munuera, et al., 2009).

Deficits in sensorimotor integration could lead to problems in visual stability and contribute to the motor symptoms of PD, such as posture and gait, as the patient's internal model of the world does not accurately reflect world (Friston, et al., 2012). Abnormal CD could also contribute to visual symptoms observed in PD (Weil, et al., 2016), such as hallucinations (Diederich, et al., 2014; Thakkar, et al., 2017). For the present study, participants at an early stage of PD without visual symptoms were recruited to examine if deficits in visuomotor integration can be observed even when the patients do not themselves report experiencing visual deficits.

Methods

Participants

Fourteen PD patients (8 women; M_{age} = 62, range: 45–75 years, 13 right-handed and one ambidextrous) and fourteen right-handed neurologically healthy control participants (7 women; M_{age} = 67, range 44–78) took part in the experiment. PD patients were diagnosed using the UK Brain Bank criteria, all diagnoses were supported by marked striatal defects in dopamine transporter SPECT and none of the patients presented features suggestive of atypical parkinsonism. All participants had normal or corrected-to-normal vision. Three control participants had to be excluded from the analysis due to technical problems during testing. In most cases the control participants were the spouses of the PD patients. The duration of motor symptoms in PD patients was on average 24 months (range: 3–72 months), and the Hoehn-Yahr stages of the patients were as follows: Six patients at stage I, seven patients at stage II, and one patient at stage III. The patients had a mean motor MDS-UPDRS

142 score of 37 (range 11–95, SD = 20). In eight patients the motor symptoms were primarily on the left
143 side, in four patients in the right side, and two patients had nearly symmetrical motor symptoms.
144 None of the patients had depression (mean BDI = 3.8, range 1-12, SD = 2.8), and none showed signs of
145 abnormal cognitive abilities as measured by the Mini-Mental State Examination (mean 27.6, range 26-
146 30).

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

152 The experiment was approved by the Ethics committee of the hospital district of South-West
153 Finland, and a written informed consent was obtained prior the study. The study was conducted
154 according to the principle of the Declaration of Helsinki.

155

156 *Tasks, stimuli and procedure*

157 In addition to performing the double saccade task, we also measured the strength of saccadic
158 suppression in the participants by measuring visual thresholds during saccades and fixation. Previous
159 studies have reported increased visual threshold in PD (Silva, et al., 2005; Diederich, et al., 2002), and
160 saccadic suppression has been hypothesized to be triggered by extra-retinal (e.g. CD) signals (Ross, et
161 al., 2001). Finally, the participants were queried about their subjective experience of visual stability
162 using a questionnaire described below. We assumed that deficits in CD and visual updating may lead
163 to subjectively experienced symptoms of unstable vision.

To assess whether the participants experience symptoms of unstable vision they were asked whether they perceived motion, experienced vertigo, or had feelings that the world has “changed position” during saccadic or smooth pursuit eye movements. Smooth pursuit eye movements were included in the questionnaire as control questions, since we hypothesized that possible impairments in visual stability selectively affect saccades. In addition participants were asked if they had trouble estimating the positions of objects, had experienced visual hallucinations, or had experienced any other visual symptoms. Answers were given on a four step scale (0 = never … 3 = often).

In the double saccade task a participant is asked to shift her gaze to two briefly presented targets. In the traditional form of the task the targets are presented so briefly that when the participant initiates the first saccade, both visual targets have disappeared from the screen. Thus the participant must use her internal monitoring signals (i.e. CD) to take into account the spatial change produced by the first saccade in order to correctly fixate the second target (Hallett & Lightstone, 1976; Sommer & Wurtz, 2008; Thakkar, et al., 2015). Pilot experiments for the present study showed that the traditional double saccade task was too challenging for the elderly participants (the participants had trouble perceiving and making saccades to the locations of the briefly presented target stimuli). In order to make the task easier for the participants, we modified the task so that each target stimulus is presented for a longer duration, but the participants were instructed to initiate the saccades only after both targets had disappeared from the screen (Memory condition; Figure 1B). While this means that short-term visuospatial memory may contribute to performance more in our modified version than in the traditional form of the task (which taxes the sensory memory more), the key idea behind the double saccade task remains unchanged: the participants need to take into account the spatial change produced by the first saccade in order to correctly fixate the second

target. In the Baseline condition (Fig. 1B), which was physically identical to the experimental condition, the participants were not required to wait until the targets have disappeared and could initiate their eye movements voluntarily.

For the double saccade task, round (.6°) white target stimuli were presented on a black background. The double saccade task began with a nine point calibration of the eye-tracker (i.e. whole screen was calibrated). After calibration, each trial began with a white fixation point presented at the center of the screen. This fixation point was also used as a (eye-tracking) drift-correction point in the beginning of each trial. After the participants correctly fixated the center of the screen for 1.2-1.5 sec, the two target stimuli were presented. The first stimulus was always presented in one of the four quadrants of the screen (e.g. upper right quadrant as in Fig. 1B) for 500 msec ~16 degrees from the fixation point. Right after the first target, a second target was presented for 130 msec on the horizontal meridian at the same side of the screen as the first target. However, the exact horizontal position of the second target varied from trial to trial (there were four equally likely positions, separated by a minimum of ~2.4 degrees). The possible locations of the saccade targets are presented in Figure 1C. Each participant performed the baseline and memory conditions once. Thirty trials were collected for each condition. Before the experimental runs, each participant performed at least 10 practice trials without eye-tracking.

Visual 81% thresholds were measured by presenting a horizontally oriented, low-frequency, luminance modulated Gabor grating (diameter ~12°, 0.33 cycles per degree, phase varied randomly on each trial) in the upper or lower visual field (center of the Gabor was 7 degrees from the center of the screen) for one screen refresh (11.8 msec). The stimuli were presented on mid-grey background. Participants' task was to report whether the Gabor stimulus was presented in the upper or lower

visual field using the up and down arrow keys. The detection threshold was determined by adaptively varying the Michelson contrast of the Gabor using a Bayesian staircase method QUEST (Watson & Pelli, 1983). This procedure is similar to previously reported means of measuring saccadic suppression (Burr, et al., 1994). Each participant performed three different conditions during which visual thresholds were measured: during fixation, during saccade, and right after saccade. When the thresholds were measured during fixations participants kept fixating to a fixation dot, presented in the middle of the screen. In the 'saccade condition', the visual threshold was determined for Gabor stimuli presented while participants performed ~19 degree saccades from a fixation point on the left side of the screen to a black dot at the center of the screen. In the 'after saccade' condition the Gabor stimulus was presented ~100 msec after the saccade had ended. Participants always initiated the saccades voluntarily after a brief period of fixation during which the eye tracker was drift corrected. To enable accurate tracking of horizontal eye-position, the eye-tracker was calibrated by three calibration points presented on the horizontal meridian (left side, right side and center of the screen).

In both tasks (double saccade and visual threshold) the stimuli were presented using Psychtoolbox (Brainard, 1997) running on Matlab 2014b. Eye movements were recorded using EyeLink 1000 eye-tracker (SR Research) that was operated using the EyeLink Toolbox (Cornelissen, et al., 2002). The eye movement registration was done monocularly, typically for the right eye, using 1000 Hz sampling frequency. The stimuli were presented on a 19″ CRT screen with a screen resolution of 1024 × 768 pixels and 85Hz refresh rate. Participants were seated 70 cm from the screen and a head rest was used to stabilize the head.

SPECT imaging

230 To image dopamine transporter (DAT) binding, all PD patients underwent brain [^{123}I]FP-CIT
231 ([^{123}I]N- ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane) SPECT. The interval
232 between the scanning and behavioural testing (e.g. double saccade task) was 8-29 months. Prior to
233 scanning, thyroidal update of the ligand was blocked by administering oral potassium perchlorate
234 (250 mg) 60 minutes before the injection of [^{123}I]FP-CIT. An 185 MBq bolus of [^{123}I]FP-CIT was
235 administered and scanning performed 3 hours after the injection. Imaging was performed as
236 described earlier (Kaasinen, et al., 2014). The images were reconstructed and analysed using BRASS
237 (Hermes Medical Solutions AB, Stockholm, Sweden). Specific binding rations (SBRs) for the caudate
238 nucleus and the putamen were quantified using occipital cortex as the reference region SBR_{ROI} = (ROI
239 – OCC) / OCC, where ROI refers to the uptake in the region of interest and OCC in the occipital cortex.
240 Although occipital cortex may contain minute concentrations of DAT, it has been shown to be a valid
241 reference region in [^{123}I]FP-CIT imaging (Joutsa, et al., 2015). Mean striatal values (caudate, anterior
242 putamen and posterior putamen) in the left and right hemisphere were used for correlation analyses.
243 In statistical analysis of the relationship between DAT binding and behavioural performance, the
244 analyses always included a factor that indicated whether saccades were made ipsilaterally or
245 contralaterally with respect to the hemisphere with lower binding.
246
247 *Data analysis*
248 Single-trial eye movement data (accuracy of fixations) was analyzed using linear mixed-effects
249 models using the lme4 package (Bates, et al., 2014) in R statistical software (R Development Core
250 Team , 2014). Because the analysis is performed on a single-trial basis rather than on aggregated
251 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 (Baayen, et al., 2008), 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 (Cumming, 2012). Error bars in all the figures are 95% CIs calculated from 1000 bootstrap samples.

In the double-saccade task, separate models were built for horizontal and vertical errors (relative to the target location). Only trials where the first saccade was directed towards the first target and where the participants made a following saccade towards the second target were included in the analysis (5.8% of trials were excluded). For each participant, the first fixation to the first and second targets were included in the analysis, except for cases were the first fixation was very brief and rapidly followed by a corrective saccade towards the correct location. Before the analysis of fixation accuracy, the data was 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 (Fig. 1C). These preprocessing steps were performed in Matlab 2014b.

Datasets can be downloaded from the Open Science Framework (https://osf.io/bqnzh).

Results

Visual symptoms

PD patients reported more visual symptoms compared to healthy controls, although this difference was statistically non-significant (Mann-Whitney test; Table 1). The patient group reported numerically more symptoms especially concerning general confusion about locations of objects, and experiencing spatial shifts or jerks during saccades.

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 (β = 1.96, 95% CI = [1.48, 2.44], t = 8.06) and right after saccades (β = 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.

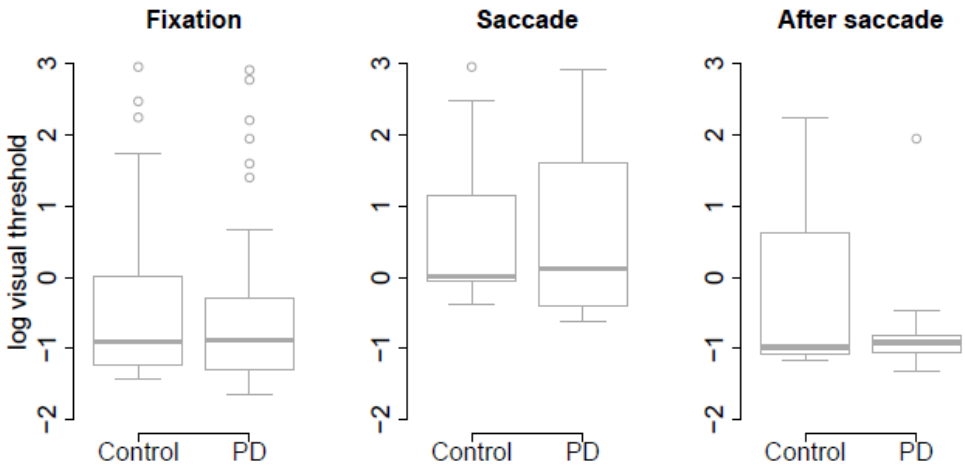


Figure 2. Visual thresholds during fixation, saccade, and after saccade for each group. The unit of the y axis is the logarithm of Michelson contrast of the stimulus.

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*: β = -23. 49, CI = [-31.19, -15.83], t = -6.11; *y error*: β = -48.19, CI = [-64.33, -32.00], t = -5.82; in the results, the β 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 (β = 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: β = -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). This means that when the saccades were performed without visual guidance (Memory condition), the patients' first saccades were biased towards the second target location.

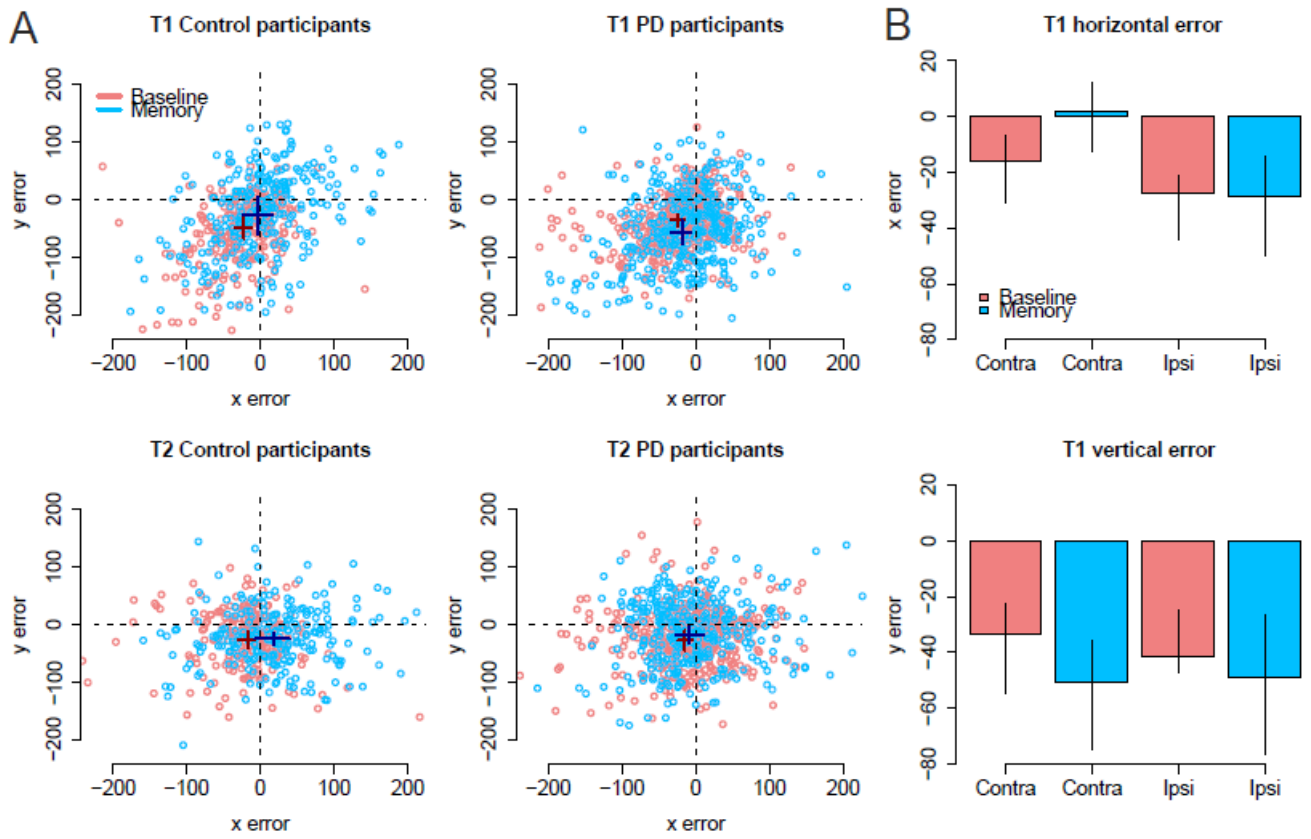


Figure 3. A) Fixation maps for the first target (T1, upper panels) and second target (T2, lower panels), separately for control participants (left) and patients (right). The red and blue dots denote individual fixations in the Baseline and Memory conditions, respectively. The red and blue crosses show the respective group averages; the lengths of the lines are 95% confidence intervals 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°).

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 predominant motor symptoms. This analysis was restricted to PD patients who showed asymmetric symptoms (N=12). The results, displayed in Figure 3B, revealed that fixations to the first target were more inaccurate (horizontally and vertically) when the target was ipsilateral with respect to symptoms (*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). Moreover, as shown in Fig. 3B (upper panel), in the Memory condition horizontal error was reduced when the targets were contralateral to motor symptoms (Memory × Laterality: β = -18.91, CI = [-33.95, -3.87], t = -2.46). Vertical error revealed also an interaction between Memory condition and target laterality: In the Baseline condition vertical errors increased at ipsilateral locations, whereas the effect reversed in the Memory condition (β = 16.36, CI = [2.27, 30.40], t = 2.27), but as seen from Fig. 3B (lower panel) the size of this effect is negligible. In summary, these results show that PD patients have selective deficits especially in making horizontal saccades to memorized targets that are at the same side as their primary motor symptoms.

Saccades to the second target. Fixations to the second target (Fig. 3A lower panels) were on average biased towards the center of the screen and somewhat hypermetric in the Baseline condition in both groups (*x error*: β = -15. 48, CI = [-23.87, -7.14], t = -3.68; *y error*: β = -26.10, CI = [-44.91, -32.00], t = -7.33). During the Memory condition, fixations were on average biased away from the center of the screen in the horizontal direction in both groups (β = 18.32, CI = [0.94, 35.70], t = 2.10). Although Fig. 3A suggests that this effect was smaller in PD patients, this Group × Condition interaction did not reach statistical significance (t = -1.83) in the linear model. A further analysis

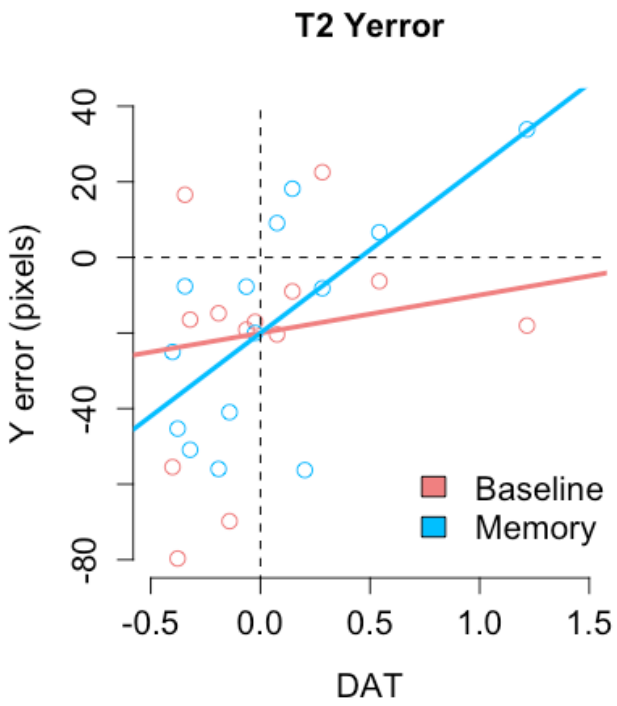
347 performed on the patient group showed that when the targets were presented at the same side as
348 motor symptoms, fixations to the second target were on average biased towards the center of the
349 screen in horizontal direction in both conditions (β = -14.44, CI = [-22.46, -6.38], t = -3.52). This means
350 that the PD patients show errors whose direction is consistent with amplified CD (relative to motor
351 command) when they make saccades towards the side with primary motor symptoms. Furthermore,
352 the bias observed in the fixations to the second target could be in part caused by biases in fixating the
353 first target. To control for this possible confound, the analyses concerning the bias in the second
354 saccade were also performed in trial-by-trial basis (see Fig. 1E) in section *Compensation in angle and*
355 *amplitude following the first saccade.*
356
357 *Modulation by DAT binding.* Finally, we wanted to see if the accuracy of fixations correlated
358 with striatal dopamine transporter (DAT) binding in PD patients. This analysis focused on mean striatal
359 DAT binding. In addition to the condition (Baseline vs. Memory) and trial number factors, the model
360 included a predictor labelling whether or not the targets were presented contralaterally with respect
361 to the hemisphere with smaller DAT binding (Contralateral factor), the overall DAT binding in the
362 more affected hemisphere (i.e. the one with lower binding), the motor MDS-UPDRS score of the
363 patient, and the interactions of these four predictors.
364 Horizontal or vertical errors of fixations to the *first target* were not modulated by DAT.
365 Horizontal errors of fixations to the *second target* become somewhat more accurate as mean
366 striatal DAT binding increased. This main effect was not statistically significant (β = 24.84, CI = [-3.30,
367 52.0499], t = 1.7). Interaction between laterality and DAT suggested that it was only observed for
368 fixations performed to targets presented ipsilaterally to the more affected hemisphere (contralateral

369 × DAT: *β* = -23.94, CI = [-44.65, -3.23], t = -2.3). However, although the interaction reached statistical

370 significance, due to the small size of this correlation this result is not discussed further (DAT binding

371 vs. horizontal error for ipsilateral targets, *β = .9,* when the main effect of DAT binding is taken into

372 account).



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374 Figure 4. Vertical error was modulated by DAT binding, and this effect was stronger when the patients
375 made fixations to memorized targets (blue = Memory). DAT binding variable has been centered (i.e.
376 zero represented the mean). The dots represent the observed data, and the lines represent the
377 modelled results.
378

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

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

381 binding increased (Memory × DAT: *β* = 44.00, CI = [13.63, 74.38], t = 2.8). No such effect was observed

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

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

384 fixation accuracy (t < |1|), suggesting that the observed modulation by DAT does not simply reflect
385 the severity of the PD. Altogether these results suggest that dopamine specifically contributed to the
386 accuracy of the *second* saccades. This effect was most clearly observed in vertical errors, and in the
387 Memory condition (Fig. 4B) where the saccades are performed without external visual guidance (i.e.
388 they are based on CD). The direction of the errors is consistent with the interpretation that (perhaps
389 due to abnormal CD) the participants overestimated the size of the first saccade (see Fig. 1E).
390 However, as already noted, this effect could also be caused by biases in fixating the first target. Thus,
391 following analyses examined how the participants compensated for the variability in the endpoint of
392 the first saccade when making the second saccade.
393
394 *Compensation in angle and amplitude following the first saccade*
395 As explained in Fig. 1E we also examined how well the participants took into account the trial-
396 by-trial variability in the first saccade when executing the second saccade. In the regression models,
397 the predictor variables were the centered optimal angle/amplitude of the saccade (see Fig. 1E), group,
398 condition, all interaction between these three variables, and running trial number (centered). Models
399 were pruned by removing non-significant regressors.
400 As shown in Figure 5A-B, the trial-to-trial variability in the *angle* of the second saccade was
401 strongly predicted by the optimal angle required to perfectly fixate the second target (β = 0.71, CI =
402 [0.67, 0.76], t = 29.62). In other words, the participants clearly had information about the error in the
403 endpoint of the first saccade which they could use to correctly aim to the second target. In the
404 Memory condition, the angle of the second saccade was smaller than in the Baseline condition. That
405 is, participants' saccades were biased towards the center of the screen (i.e. the initial fixation point; β

= -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: β = -0.13, CI = [-0.20, -0.02], t = -4.32). PD patients were not statistically significantly different from control participants (t ≤ |1|).

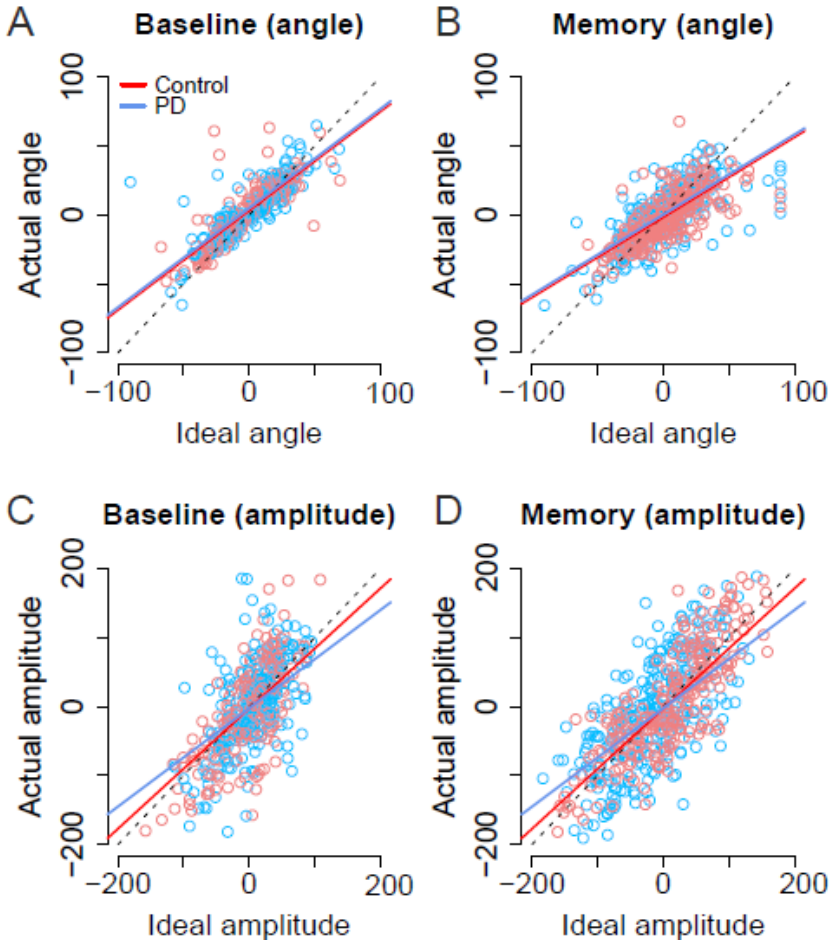

Figure 5. Actual saccade angles (A-B) and amplitudes (C-D) as a function of ideal angle/amplitude. Left panels show the baseline condition, and the right panel the Memory condition. Red color denotes the healthy control participants, and the blue color the patient group. Dots show the observed data (individual 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°).

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 (β = -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.

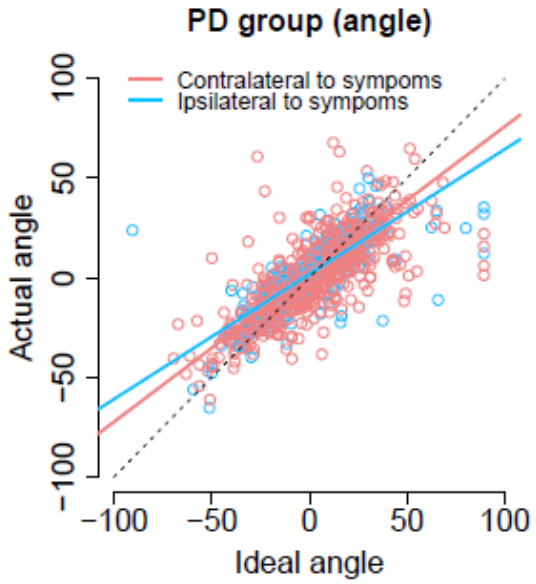

Figure 6. The angle of the second saccade as a function of ideal angle. Compensation for variation in the endpoint of the first fixation is worse for targets that are at the predominant side of motor symptoms.

Also the *amplitude* of second saccade strongly correlated with the optimal amplitude (β = 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: β = -0.15, CI = [-0.27, -0.04], t = 2.61). In other words, the patients had trouble making long saccades.

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

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 hemisphere), the amount of DAT binding, the optimal angle to perfectly fixate the second target, and the motor MDS-UPDRS score of the participant (and the interactions between these regressors).

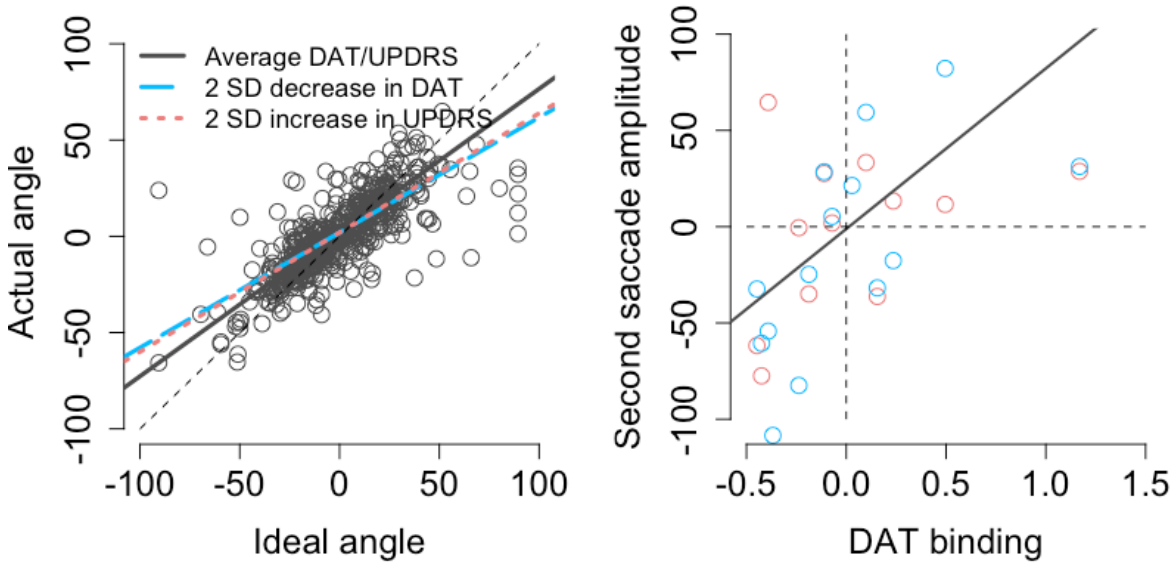

Figure 7. Modulation of compensation in the amplitude of the second saccade. A) Compensation for variation in the endpoint of the first fixation is modulated by DAT binding (blue dashed line) and MDS-UPDRS (red dotted line). The visualized effects represent 2 SD decrease (DAT) or increase (MDS-UPDRS) 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).

As previously stated the actual *angles* of the saccades were strongly predicted by the optimal angle required to reach the second target (β = 0.74, CI = [0.67, 0.81], t = 20.3). As shown in Figure 7A (blue dashed line) patients with lower DAT transporter binding values were more inefficient in taking into account for the trial-to-trial variability in the endpoint of the first saccade and their saccades become more biased towards the center of the screen, consistent with stronger reliance on CD than bottom-up visual information (Ideal angle × DAT: β = 0.17, CI = [0.070, 0.28], t = 3.2). Furthermore, the modulation of the angle of the second saccade by DAT was not explained by the severity of PD as the motor MDS-UPDRS score revealed similar modulatory effect (Ideal angle × UPDRS: β = 0.0030, CI =

467 [0.00081, 0.0053], t = 2.6). Note that although the *β* coefficient of the Ideal angle × UPDRS interaction
468 (0.0030) is much smaller than the *β* coefficient of the Ideal angle × DAT interaction (0.17), the relative
469 size of this effect is in fact very similar (due to the fact that the range of motor MDS-UPDRS scores is
470 much higher than DAT values). The modulatory effect by motor MDS-UPDRS is visualized in Figure 7A
471 as the red dotted line which overlaps the blue dashed line that depicts modulation by DAT. In addition
472 to the above mentioned two-way interactions, a Ideal angle × motor MDS-UPDRS × DAT interaction
473 was observed (*β* = 0.014, CI = [0.004, 0.025], t = 2.8). This three-way interaction indicates that the
474 modulation by DAT binding was stronger in participants with more severe PD (i.e. higher UPDRS
475 scores).

476 Next, we examined whether DAT binding was associated with the ability to modulate the
477 *amplitude* of the second saccade to compensate for trial-to-trial variability in the first saccade.
478 Although patients were in general successful in making a second saccade whose amplitude closely
479 resembled the ideal amplitude required to perfectly fixate the second target (*β* = 0.73, CI = [0.65,
480 0.81], t = 17.7), patients with lower DAT binding made more hypometric saccades (*β* = 53.94, CI =
481 [19.23, 88.65], t = 3.0), as shown in Figure 7B. UPDRS score did not statistically significantly modulate
482 saccade amplitudes in general (main effect of UPDRS: t = -0.3). However, patients with higher motor
483 MDS-UPDRS scores were more inefficient in making a close-to-ideal amplitude saccade to the second
484 target (Ideal amplitude × motor MDS-UPDRS: *β* = -0.010, CI = [-0.015, -0,0050], t = -3.7). Surprisingly,
485 this effect was only observed when the targets were presented ipsilaterally with respect to the
486 hemisphere with lower DAT binding (Contralateral × Ideal amplitude × motor MDS-UPDRS: *β* = 0.012,
487 CI = [0.0048, 0,020], t = 3.1).
488

489 **Discussion**

490 We examined how well early PD patients can update their spatial representations during eye
491 movements, and whether this ability correlates with the integrity of the dopaminergic system. The
492 participants were asked to make eye movements to two targets presented in succession. When
493 compared to age-matched control participants, the patients' second saccades were biased towards
494 the center of the screen. Similar effects were observed when examining how well the participants
495 took into account trial-by-trial variation in the endpoint of the first saccade. In patients, the observed
496 effects were most prominent when the patients made saccades towards the side with primary motor
497 symptoms. The spatial error in the second saccade correlated with the integrity of the dopaminergic
498 system in the PD group.

499 The present results suggest that the brain systems that internally monitor eye movements are
500 impaired in PD patients, and that this impairment correlates with dopaminergic deficiency. Crucially,
501 correlations between dopamine transporter binding and saccade performance were observed only for
502 fixations to the *second* target, implying that the dopaminergic system contributes specifically to
503 spatial remapping and not to performing saccades in general. This suggests that the dopaminergic
504 system may contribute to taking into account previous movements and contextual information when
505 making sequential saccades. This could be caused by a mismatch between the motor output
506 commands and the CD signal (previous saccade was shorter than suggested by CD), or a more general
507 impairment in integrating bottom-up sensory information with top-down contextual information
508 (Friston, et al., 2012). The present results do not imply that the dopamine system per se carries the
509 CD, but that dopamine modulates the functioning of the network of brain regions that mediate
510 visuomotor integration. According to Friston's theory, dopaminergic deficiency leads to reduced

511 precision in bottom-up sensory information (prediction errors), which causes the brain to rely more
512 on top-down contextual information (i.e. predictions such as CD signals) than bottom-up visual
513 information (Friston, et al., 2012). This essentially means that the CD signals start to dominate
514 sensorimotor integration, and hence motor performance, over motor commands, which is in line with
515 what we observed.

516 Previous research has shown that deficits in CD are associated with *reduced* CD relative to
517 motor signals, that is, converse to what we observed here (Sommer & Wurtz, 2002; Thakkar, et al.,
518 2015). However, there is no reason to assume that abnormal CD always results in reduction of the CD
519 signal (although this is obviously the case when an area that conveys the CD signal is lesioned;
520 (Sommer & Wurtz, 2008)). The present findings are consistent with the finding that schizophrenia
521 patients reveal the reverse pattern of results when performing the double-saccade task: in contrast to
522 the present results, schizophrenia patients underestimate the size of the first saccade (Thakkar, et al.,
523 2015).

524 The present study employed a modified version of the double-saccade task. In the classical
525 version (Hallett & Lightstone, 1976; Sommer & Wurtz, 2002; Thakkar, et al., 2015) the visual targets
526 are presented so briefly that they are removed from the screen before the eye movements begin;
527 hence the saccades cannot be guided by sensory information. Because the classical double-saccade
528 task-set up proved too demanding for elderly subjects, we used a modified task where the targets
529 were presented for a longer duration. We expected that the PD patients would show deficits
530 especially in the Memory condition, where the saccades to the two target locations are performed
531 solely based on memory. However, the present results show that PD patients are impaired in their
532 second saccade also when the first saccade could be directed based on visual information, suggesting

533 that the impairement is associated with integrating incoming sensory information and top-down
534 contextual information (Friston, et al., 2012). Because previous studies using the double-saccade task
535 have focused on the condition where the saccades are directed without visual information, it is
536 difficult to estimate whether this also applies to previous studies.

537 Previous studies have emphasized the role of kinesthetic feedback in PD (Jobst, et al., 1997;
538 Klockgether, et al., 1995), and it could be argued that the errors in fixating the second target are due
539 to impaired kinesthetic feedback from the extra-ocular muscles, instead of impaired CD. While our
540 interpretation of the results suggests that the dopaminergic system mediates visuomotor integration,
541 we cannot completely rule out the explanation that the present results reflect purely deficits motor
542 behavior as opposed to visuomotor integration. One could argue that the observed correlations
543 between fixation errors and dopamine partially reflect e.g. combining motor commands to sequences.
544 This interpretation may in part explain correlations between the *amplitude* of the second saccade and
545 DAT binding, but it cannot explain why the *angle* of the second saccade is spatially biased towards the
546 initial fixation. We also wish to note that the present conclusions are restricted by the correlative
547 nature of our study; more conclusive evidence could be acquired by experimentally manipulating
548 dopaminergic activity in healthy humans.

549 PD patients are known to undershoot targets when performing eye movements (Terao, et al.,
550 2011; Crawford, et al., 1989). In the present study the main difference between the two groups in
551 making the first saccade was that the PD patients' performance deteriorated in the Memory
552 condition, which is consistent with previous reports (Le Heron, et al., 2005; Terao, et al., 2011;
553 Crawford, et al., 1989). Our results also replicate the finding that deficits in saccades are typically
554 worse on the side with larger primary motor symptoms (Choi, et al., 2011). Importantly, the deficits in

spatial remapping were also dependent on the laterality of the primary motor symptoms: the hypothesized deficits in the trial-to-trial variability in the angle of the second saccade were only observed when the laterality of motor symptoms was taken into account (see Fig. 6). This is consistent with the observation that thalamic lesions (that interfere with the CD) produce lateralized defects (e.g. (Sommer & Wurtz, 2006)).

The PD patients in the present study were at the early stages of PD, generally did not report visual symptoms, and the visual sensitivity of the patients was similar to the control group. It is important to note that with the double-saccade task we were able to detect subclinical deteriorating visual functions that the patients were unaware of. These disturbances, together with the shown associations with DAT binding suggest that, as the disease progresses, and the dopaminergic deficit deepens, relevant clinical CD-associated motor and visual symptoms will emerge. Advanced PD patients have many visual symptoms (Weil, et al., 2016) and abnormal CD may lead to deficits in experienced visual stability in PD. More generally, the present study suggests that motor deficits in PD are partly produced by difficulties in internal monitoring of movements. Studies with patients with more progressed PD and other dopaminergic diseases are required to confirm these findings.

Acknowledgements

HR was funded by Turku Institute of Advanced Studies and Academy of Finland (grant #308533), and received a grant from the Finnish Cultural Foundation. HO was funded by the Finnish Cultural Foundation. JJ was funded by the Academy of Finland (grant # 295580), the Finnish Medical Foundation and the Orion Research Foundation, and has received travel grants from Orion and

Abbvie, and a research grant from Lundbeck. VK was funded by the Turku University Hospital (ERVA-funds).

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