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

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Movement in Parkinson's disease (PD) is fragmented, and the patients depend on visual information in their behavior. This suggests that the patients may have deficits in internally monitoring their own movements. Internal monitoring of movements is assumed to rely on corollary discharge signals that enable the brain to predict the sensory consequences of actions. 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. In line with previous reports, the patients had difficulties in fixating the second target when the eye movement was performed without visual guidance. Furthermore, the patients had difficulties in taking into account the error in the first saccade when making a saccade towards the second target, especially when eye movements were made towards the side with dominant motor symptoms. Across PD patients, the impairments in saccadic eye movements correlated with the integrity of the dopaminergic system as measured with [123I]FP-CIT SPECT: Patients with lower striatal (caudate, anterior putamen and posterior putamen) dopamine transporter binding made larger errors in saccades. This effect was strongest when patients made memory-guided saccades towards the second target. Our results provide tentative evidence that the motor deficits in PD may be partly due to deficits in internal monitoring of movements.

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7 **signals?**

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45   discharge signals that enable the brain to predict the sensory consequences of actions. We
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48   movements. The participants performed a double-saccade task where, in order to accurately
49   fixate a second target, the participant must correct for the displacement caused by the first
50   saccade. In line with previous reports, the patients had difficulties in fixating the second target
51   when the eye movement was performed without visual guidance. Furthermore, the patients had
52   difficulties in taking into account the error in the first saccade when making a saccade towards
53   the second target, especially when eye movements were made towards the side with dominant
54   motor symptoms. Across PD patients, the impairments in saccadic eye movements correlated
55   with the integrity of the dopaminergic system as measured with [^{123}I]FP-CIT SPECT: Patients
56   with lower striatal (caudate, anterior putamen and posterior putamen) dopamine transporter
57   binding made larger errors in saccades. This effect was strongest when patients made memory-
58   guided saccades towards the second target. Our results provide tentative evidence that the motor
59   deficits in PD may be partly due to deficits in internal monitoring of movements.

1. Introduction

60

61 Parkinson's disease (PD) leads to hypometric and fragmented eye movements. These deficits in

62 are most prominent when the eye movements cannot be guided by external visual information

63 (Terao, et al., 2011; Rieger, et al., 2008; Hodgson, et al., 1999; Kimmig, et al., 2002; Blekher, et

64 al., 2009). In general, patients with PD are known to depend on visual feedback in controlling

65 their movements more than healthy individuals (Klockgether, et al., 1995; Jobst, et al., 1997;

66 Glicksterin & Stein, 1991). This suggests that PD patients may have deficits in monitoring their

67 own movements, a process assumed to depend on corollary discharge (CD) signals that relay a

68 copy of the motor command to sensory areas (Wurtz, 2008). The present study aimed to examine

69 if PD patients show deficits in monitoring the eye movements they have performed. A secondary

70 objective was to assess if the impairments in saccadic eye movements correlates with the

71 integrity of the dopaminergic system as measured with dopamine transporter imaging in human

72 PD patients.

73 Saccadic eye movements are triggered by neurons in the superior colliculus (SC). Saccade-

74 related activity in SC is assumed to be triggered by activation of the caudate nucleus, which

75 releases the SC from tonic inhibition exerted by the substantia nigra pars reticulata (Hikosaka, et

76 al., 2000). The basal ganglia are thus assumed to play the role of a gatekeeper, securing that the

77 driving input from cortical areas that guide the voluntary initiation of eye movements do not lead

78 to a chaotic cascade of saccades (Hikosaka, et al., 2000). Put differently, the BG is in a position

79 to select the appropriate action given incoming sensory information and task demands (Shires, et

80 al., 2010).

81 One of the defining features of PD is the degeneration of dopaminergic neurons in the

82 substantia nigra pars compacta (Kordower, et al., 2013), which leads to excessive inhibition in

83   the basal ganglia and the thalamus, and results in decreased motor output (Albin, et al., 1989;

84   DeLong & Wichmann, 2007; Calabresi, et al., 2014). In PD patients this results in hypometric

85   saccadic eye movements, and this defect becomes more pronounced in conditions where the

86   saccades are memory-guided (as opposed to visually-guided), when compared to healthy controls

87   (Kimmig, et al., 2002; Blekher, et al., 2009; Crawford, et al., 1989; Terao, et al., 2011). That

88   specifically memory-guided saccades are impaired in PD is consistent with the observation that

89   the dopamine system supports the accurate maintenance of memory traces by modulating neural

90   activity in prefrontal cortex (Floresco & Phillips, 2001; Landau, et al., 2009). During the

91   execution of voluntary saccades, PD patients display lack of activation especially in frontal

92   cortical areas (Rieger, et al., 2008). Striatum and prefrontal cortex could also mediate action

93   monitoring as activity in these areas have been observed to correlate with information about

94   recent actions and goals (Tsujimoto & Postle, 2012; Genovesio & Ferraina, 2014; Kim, et al.,

95   2013).

96   Direct evidence concerning the effects of dopamine on saccadic eye movements is scarce

97   in human subjects. Hotson et al. (1986) showed that saccades become infrequent and hypometric

98   in MPTP-induced parkinsonism. Similar observations have been in monkeys (Brooks, et al.,

99   1986; Schultz, et al., 1989; Kato, et al., 1995). Impairments in memory-guided saccades have

100   been observed also in humans with caudate lesions (Matsumura, et al., 1996). The present study

101   examined whether the deficits in making memory-guided saccades correlates with dopaminergic

102   deficiency in human PD patients. We also hypothesized that the saccadic deficits in PD may

103   reflect an impairment in predicting and monitoring the outcomes of motor programs.

104   To trigger spatially accurate saccades, and to stitch together a stable visual percept from

105   the samples provided by individual eye fixations, the brain must predict the sensory

106   consequences of the eye movements (Wurtz, 2008). In order to examine how well PD patients

107   can internally monitor the eye movements they make, we employed a *double-saccade task* which

108   requires the participants to take into account the displacement caused by a first saccade to

109   accurately perform a second saccade (Figure 1) (Wurtz, 2008; Ostendorf, et al., 2010; Thakkar,

110   et al., 2015). Corollary discharge (CD) signals that relay a copy of the motor command to

111   sensory areas via medial thalamus are crucial for this spatial remapping (Sommer & Wurtz,

112   2008; Wurtz, 2008). The dopaminergic deficit in PD results in abnormal functioning of the

113   structures that are assumed to relay the CD to cortex (DeLong & Wichmann, 2007; Albin, et al.,

114   1989; Pifl, et al., 2012).

115

116   --- Figure 1 here ---

117

118   The CD signal can be seen as a part of a more general mechanism that integrates bottom-

119   up sensory information and contextual information. This is clearly formalized in the predictive

120   coding framework which assumes that the brain is constantly attempting to predict (model)

121   incoming sensory information based on previous experiences (Hohwy, 2013; Clark, 2016). The

122   CD signal conveys a prediction about the sensory consequences of a movement. According to

123   this framework, during (eye) movements the brain compares its current model of the world

124   (predictions) against incoming sensory information (Friston, et al., 2012). Saccades (or any other

125   actions) that are guided by external sensory stimuli are predictions which aim to minimize the

126   discrepancy between the brain's model of the world (predictions), and incoming sensory

127   information (prediction error) (Friston, et al., 2010). Voluntarily triggered saccades are

128   predictions about the sensory consequences of those movements (Friston, et al., 2010). Friston et

129 al. (2012) have hypothesized, and using dopamine depletion simulations provided evidence, that

130 the dopaminergic system mediates sensorimotor integration by adjusting the how much the brain

131 relies on the predictions. Specifically, they have proposed that the dopaminergic deficiency in

132 PD causes the patients to rely more on their internal predictions (i.e. their model of the world)

133 than bottom-up sensory information (prediction errors such as proprioceptive feedback or visual

134 input) (Friston, et al., 2012).

135   Defects in CD have been observed in neurological patients with thalamic lesions

136 (Bellebaum, et al., 2005; Ostendorf, et al., 2010). Using the double-saccade task, Thakkar et al.

137 (2015) observed that in schizophrenia patients the errors in the angle of the second saccade

138 suggested reduced CD relative to motor signals (although this effect was only observed for one

139 of the two possible saccade target arrangements). As schizophrenia has been associated with

140 hyperactive striatal dopamine neurotransmission (Howes & Kapur, 2009), this raises the question

141 whether PD patients – who characteristically have nigrostriatal dopaminergic defects (Kordower,

142 et al., 2013) – display a reverse effect (i.e. amplified CD relative to motor commands). Previous

143 studies have not tested whether the integrity of the dopaminergic system correlates with

144 performance in the double-saccade task. While dopamine is not *per se* assumed to relay the CD

145 information, it is assumed to contribute to internal monitoring of movements by mediating the

146 integration of bottom-up sensory information and contextual information such as previously

147 performed movements (e.g. CD) (Friston, et al., 2012). The two possible outcomes of CD

148 deficits (reduced vs. amplified CD relative to the motor signals) are displayed in Figure 1B. As

149 shown in Figure 1C, CD also allows for taking into account variation in the endpoint of the first

150 saccade on a trial-to-trial basis to produce accurate saccades to the second target (Joiner, et al.,

151 2010; Munuera, et al., 2009). Deficits in the trial-by-trial monitoring of saccades could produce

152   the fragmented, multi-step saccade pattern which is characteristic of PD patients (Kimmig, et al.,

153   2002).

154   Deficits in sensorimotor integration could lead to problems in visual stability and

155   contribute to the motor symptoms of PD as the patient's internal model of the world does not

156   accurately reflect the state of the world (Friston, et al., 2012). Abnormal CD could also

157   contribute to visual symptoms observed in PD (Weil, et al., 2016), such as hallucinations

158   (Diederich, et al., 2014; Thakkar, et al., 2017). Hence, the present study included a short

159   questionnaire that probed for possible deficits in the experienced visual stability in PD. We also

160   measured visual detection threshold of the participants during fixation and saccades because CD-

161   type "extraretinal" signals have been hypothesized to underlie the suppression of visual

162   sensitivity during saccades (i.e. saccadic suppression) (Ross, et al., 2001).

163

164   **2. Methods**

165   *2.1. Participants*

166   Eight female (M_{age} = 60, range: 45–72 years) and six male (M_{age} = 62, range: 44–74 years)

167   PD patients (13 right-handed and one ambidextrous) and seven female (M_{age} = 60, range: 60–74

168   years) and seven male (M_{age} = 67, range: 44–78 years) right-handed neurologically healthy

169   control participants took part in the experiment. PD patients were diagnosed using the UK Brain

170   Bank criteria, all diagnoses were supported by marked striatal defects in dopamine transporter

171   SPECT and none of the patients presented features suggestive of atypical parkinsonism. All

172   participants had normal or corrected-to-normal vision. Three control participants had to be

173   excluded from the analysis due to technical problems during testing. In most cases the control

174   participants were the spouses of the PD patients. The duration of motor symptoms in PD patients

175   was on average 24 months (range: 3–72 months), and the Hoehn-Yahr stages of the patients were

176   as follows: Six patients at stage I, seven patients at stage II, and one patient at stage III. The

177   patients had a mean motor MDS-UPDRS score of 37 (range 11–95, SD = 20). In eight patients

178   the motor symptoms were primarily on the left side, in four patients in the right side, and two

179   patients had nearly symmetrical motor symptoms. None of the patients had depression (mean

180   BDI = 3.8, range 1-12, SD = 2.8), and none showed signs of abnormal cognitive abilities as

181   measured by the Mini-Mental State Examination (mean 27.6, range 26-30). Only PD patients

182   completed the BDI and MMSE examination (during SPECT imaging, see below).

183   Eleven patients underwent a voluntary break in medication before the experiment and did

184   not take medication on the morning of the test session. One patient did not have any medication,

185   and two participants did not go through a break in medication. Because the majority of the

186   patients were on 12-hour medication break, these patients can be considered an OFF phase. A

187   voluntary break in medication was encouraged because we assumed that PD medication may

188   counteract the possible deficits in CD. Three patients were on levodopa, nine patients were

189   treated with MAO-B inhibitors and/or dopamine agonists and medication was unknown for one

190   patient.

191   The experiment was approved by the Ethics committee of the hospital district of South-

192   West Finland (ETMK 18/1801/2016), and a written informed consent was obtained prior the

193   study. The study was conducted according to the principles of the Declaration of Helsinki.

194

195   *2.2. Tasks, stimuli and procedure*

196   The present study included three parts. First, the participants responded to a short

197   questionnaire about their subjective experience of visual stability. Second, the participants

198   completed the double-saccade task. Third, the strength of saccadic suppression in the participants

199   was evaluated by measuring visual thresholds during saccades and fixation.

200   In the questionnaire the participants were asked if they had perceived motion, experienced

201   vertigo, or had feelings that the world has "changed position" during saccadic or smooth pursuit

202   eye movements. Smooth pursuit eye movements were included in the questionnaire as control

203   questions, and we hypothesized that possible impairments in visual stability would selectively

204   affect saccades. Participants were also asked if they had trouble estimating the positions of

205   objects, had visual hallucinations, or had experienced any other visual symptoms. Answers were

206   given on a four step scale (0 = never … 3 = often).

207   In the double saccade task the two targets are typically presented so briefly that when the

208   participant initiates the first saccade, both visual targets have disappeared from the screen. Thus

209   the participant must use of CD to take into account the spatial change produced by the first

210   saccade in order to correctly fixate the second target (Hallett & Lightstone, 1976; Sommer &

211   Wurtz, 2008; Thakkar, et al., 2015). Pilot experiments for the present study showed that the

212   traditional double saccade task was too challenging for the elderly participants (the participants

213   had trouble perceiving and making saccades to the locations of the briefly presented stimuli). In

214   order to make the task easier, we modified the task so that each target stimulus is presented for a

215   longer duration, but the participants were instructed to initiate the saccades only after both

216   targets had disappeared from the screen (Memory condition; Figure 1B). While this means that

217   short-term visuospatial memory may contribute to performance more in our modified version

218   than in the traditional form of the task (which taxes the sensory memory more), the key idea

219   behind the double saccade task remains unchanged. In the Baseline condition (Fig. 1A), which

220   was physically identical to the experimental condition, the participants were not required to wait

221   until the targets have disappeared and could initiate their eye movements voluntarily.

222   For the double saccade task, round white (45 cd/m^2) target stimuli with the dimension of

223   0.6° were presented on a black (3 cd/m^2) background (i.e. Weber contrast = 46.6). The double

224   saccade task began with a nine point calibration of the eye-tracker (i.e. whole screen was

225   calibrated). After calibration, each trial began with a white fixation point presented at the center

226   of the screen. This fixation point was also used as a (eye-tracking) drift-correction point in the

227   beginning of each trial. After the participants correctly fixated the center of the screen for 1.2-1.5

228   sec, the two target stimuli were presented. The first stimulus was always presented in one of the

229   four quadrants of the screen (e.g. upper right quadrant as in Fig. 1A) for 500 msec ~16 degrees

230   from the fixation point. Right after the first target, a second target was presented for 130 msec on

231   the horizontal meridian at the same side of the screen as the first target. The exact horizontal

232   position of the second target varied from trial to trial (there were four equally likely positions,

233   separated by a minimum of ~2.4 degrees). Each participant performed the baseline and memory

234   conditions once. Thirty trials were collected for Memory condition and thirty trials for Baseline

235   condition (order counterbalanced). Before the experimental runs, each participant performed at

236   least 10 practice trials without eye-tracking.

237   Visual 81% thresholds were measured by presenting a horizontally oriented, low-

238   frequency, luminance modulated Gabor grating (diameter ~12°, 0.33 cycles per degree, phase

239   varied randomly on each trial) in the upper or lower visual field (center of the Gabor was 7

240   degrees from the center of the screen) for one screen refresh (11.8 msec). The stimuli were

241   presented on mid-grey background. Participants' task was to report whether the Gabor stimulus

242   was presented in the upper or lower visual field using the up and down arrow keys. The detection

243 threshold was determined by adaptively varying the Michelson contrast of the Gabor using a

244 Bayesian staircase method QUEST (Watson & Pelli, 1983). This procedure is similar to

245 previously reported means of measuring saccadic suppression (Burr, et al., 1994). Each

246 participant performed three different conditions (in separate blocks, order counterbalanced)

247 during which visual thresholds were measured: fixation, saccade, and right after saccade. When

248 the thresholds were measured during fixations, the participants kept fixating to a fixation dot,

249 presented in the middle of the screen. In the 'saccade condition', the visual threshold was

250 determined for Gabor stimuli presented while participants performed ~19 degree saccades from a

251 fixation point on the left side of the screen to a black dot at the center of the screen. In the 'after

252 saccade' condition the Gabor stimulus was presented ~100 msec after the saccade had ended.

253 Participants always initiated the saccades voluntarily after a brief period of fixation during which

254 the eye-tracker was drift corrected. To enable accurate tracking of horizontal eye-position, the

255 eye-tracker was calibrated by three calibration points presented on the horizontal meridian (left

256 side, right side and center of the screen).

257   In both tasks (double saccade and visual threshold) the stimuli were presented using

258 Psychtoolbox (Brainard, 1997) running on Matlab 2014b. Eye movements were recorded using

259 EyeLink 1000 eye-tracker (SR Research) that was operated using the EyeLink Toolbox

260 (Cornelissen, et al., 2002). The eye movement registration was done monocularly, typically for

261 the right eye, using 1000 Hz sampling frequency. The stimuli were presented on a 19″ CRT

262 screen with a screen resolution of 1024 × 768 pixels and 85Hz refresh rate. Participants were

263 seated 70 cm from the screen and a head rest was used to stabilize the head.

264

265   *2.3. SPECT imaging*

266    To image dopamine transporter (DAT) binding, all PD patients underwent brain [123I]FP-

267 CIT ([123I]N- ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane) SPECT. The

268 interval between the scanning and behavioural testing (e.g. double saccade task) was 8-29

269 months. Dopamine transporter (DAT) binding a relatively stable parameter which has been

270 reported to decrease on average 1-5% per year (Kaasinen, et al., 2015; Pirker, et al., 2002; Pirker,

271 et al., 2003). All of the reported results were also replicated when the models included a

272 covariate denoting the delay between scanning and behavioral testing. Prior to scanning,

273 thyroidal update of the ligand was blocked by administering oral potassium perchlorate (250 mg)

274 60 minutes before the injection of [123I]FP-CIT. An 185 MBq bolus of [123I]FP-CIT was

275 administered and scanning performed 3 hours after the injection. Imaging was performed as

276 described earlier (Kaasinen, et al., 2014). The images were reconstructed and analysed using

277 BRASS (Hermes Medical Solutions AB, Stockholm, Sweden). Specific binding ratios (SBRs)

278 for the caudate nucleus and the putamen were quantified using occipital cortex as the reference

279 region $SBR_{ROI} = (ROI - OCC) / OCC$, where ROI refers to the uptake in the region of interest

280 and OCC in the occipital cortex. Although occipital cortex may contain minute concentrations of

281 DAT, it has been shown to be a valid reference region in [123I]FP-CIT imaging (Joutsa, et al.,

282 2015). Mean striatal values (caudate, anterior putamen and posterior putamen) in the left and

283 right hemisphere were used for correlation analyses. In statistical analysis of the relationship

284 between DAT binding and behavioural performance, the analyses always included a factor that

285 indicated whether saccades were made ipsilaterally or contralaterally with respect to the

286 hemisphere with lower binding.

287

288   *2.4. Data analysis*

289   Group level differences and effects of within-subject experimental manipulations on

290   average saccade performance were analyzed using linear mixed-effects models using the lme4

291   package (Bates, et al., 2014) in R statistical software (R Development Core Team , 2014). The

292   analysis is performed on a single-trial basis rather than on aggregated means, which means that

293   the mixed-effects models take into account within-participant variation in addition to group-level

294   effects (Baayen, et al., 2008). Participants were included in the model as random variables, that

295   is, each individual participant's data was fitted with individual intercepts and slopes (concerning

296   the Baseline/Memory condition). The fixed-effect predictors included in the models are

297   described in the Results section. The models were pruned by removing fixed-effects predictors

298   that did not significantly ($t < |2|$) contribute to the model. The visual detection thresholds

299   (saccadic suppression) were analyzed using linear mixed effects models with separate intercepts

300   for each subject. As there is no standardized way to calculate the degrees of freedom and the

301   corresponding p values in mixed-effects models (Baayen, et al., 2008), we do not report p values.

302   However, the statistical significance of an effect can be checked from the confidence intervals

303   (CI): whenever the value zero is included in the CI, the effect is not considered statistically

304   significant. Another reason to not report p values is to draw the reader's attention to the size of

305   the effect (Cumming, 2012). Error bars in all the figures are 95% CIs calculated from 1000

306   bootstrap samples.

307   In the double-saccade task, separate models were built for horizontal and vertical errors

308   (relative to the target location). Random variation between participants concerning the intercept

309   and the effect of the condition was included in the models. Only trials where the first saccade

310   was directed towards the first target and where the participants made a following saccade

311   towards the second target were included in the analysis (5.8% of trials were excluded). For each

312 participant, the fixations closest to the first and second target locations were included in the

313 analysis. The participants typically returned their gaze to the center of the screen in one large

314 amplitude saccade after they had made the saccade towards the second target location. Before the

315 analysis of fixation accuracy, the data was transposed to correspond to the case where the first

316 target was at the upper right corner of the screen and the second target directly below it. These

317 preprocessing steps were performed in Matlab 2014b.

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

319

320   **3.   Results**

321   *3.1.   Visual symptoms (questionnaire)*

322   PD patients reported experiencing somewhat more general confusion about locations of

323 objects, and experiencing spatial shifts during saccades compared to healthy controls, but this

324 difference was not statistically significant (Mann-Whitney test; Table 1). Two patients (and none

325 of the control participants) reported general confusion about object locations or reported noticing

326 spatial shifts during saccades.

327

328   --- Table1 here ---

329

330   *3.2.   Saccadic suppression*

331   Visual thresholds did not differ between the control group and the PD group during

332 fixation (t = -.13), saccade (t = .15), or after saccade (t = -.91). These factors were hence

333 removed from the linear model used to analyze visual threshold. The pruned model showed that

334 both groups displayed clear saccadic suppression as visual thresholds increased during saccades

335   (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

336   = 3.21) when compared to thresholds during fixation (see Figure 2). This indicates that the

337   patients' visual sensitivity was similar to the control group during fixation, saccades, and right

338   after saccades.

339

340   --- Figure 2 here ---

341

342   3.3.   Double-saccade task

343   3.3.1.   Horizontal and vertical errors

344   Figure 3 shows the participants' accuracy in fixating the first and second targets. Note that

345   for the saccades towards the first target negative values indicate hypometric saccades, whereas

346   for the

347

348   --- Figure 3 here ---

349

350   second target positive (vertical) values are a sign of hypometric saccades. Visual inspection of

351   the data suggests that the performance of the two groups (PD vs. control) did not significantly

352   differ from each other in the Baseline condition. However, in the Memory condition the PD

353   patients' saccades to the first target were hypometric, and the saccades to the second target were

354   biased towards the fixation when compared to the control participants. The data were analyzed

355   using linear mixed-effects models that included the predictors group (Control vs. PD), condition

356   (Baseline vs. Memory), target (T1 vs. T2), and their interactions. Horizontal and vertical errors

357   were modelled separately. The results of the regression models are presented in Table 2

358   (horizontal error) and Table 3 (vertical error).

359   As shown on Figure 3, fixations to the first target were somewhat hypometric, whereas

360   fixations to the second target tended to overshoot the target slightly (as shown by the intercepts

361   of the regression models). In both groups, fixations to the second target were vertically more

362   accurate than fixations to the first target (Target: t = 5.11). When compared to the baseline

363   condition (i.e. visually-guided saccades), memory-guided saccades were horizontally more

364   accurate in both groups (Condition: t = 2.07). However, the PD patients' saccades to the first

365   target were vertically more hypometric in the Memory condition (PD x Condition: t = -3.16).

366   Moreover, whereas the fixations to the second target were biased horizontally outward in the

367   memory condition in control participants (Target x Condition: t = 2.19), similar effect was not

368   observed in the PD patients (PD x Target x Condition: t = -2.19). In other words, consistent with

369   amplified CD relative to motor commands, when making memory guided-saccades, the PD

370   patients' fixations towards the second target were biased towards the center of the screen when

371   compared to control participants. This effect could simply reflect the fact that the patients'

372   saccades towards the first target were hypometric. For this reason, we also examined trial-by-

373   trial variation in how well changes in the endpoint of the first saccade are taken into account

374   when making the second saccade (see section: Compensation in angle and amplitude following

375   the first saccade). Concerning errors in the vertical direction, the results showed that whereas

376   control participants tended to overshoot the second target in the memory condition (Target x

377   Condition: t = -3.53), such effect was not observed in patients (PD x Target x Condition: t = 5.3).

378

379   --- Table 2 here ---

380

381   --- Table 3 here ---

382   As motor symptoms in PD are often asymmetric [see (Choi, et al., 2011), for an example

383   concerning eye movements], we analyzed if the accuracy of fixations was modulated by whether

384   the targets were presented ipsi- or contralaterally with respect to the predominant motor

385   symptoms. This analysis was restricted to PD patients who showed asymmetric symptoms

386   (N=12). The model included factors condition (Baseline vs. Memory), target (T1 vs. T2), a

387   laterality factor (indicating whether the targets were presented ipsi- or contralaterally with

388   respect to primary motor symptoms), and their interactions. The data are presented in Figure 4.

389   The analysis showed that horizontal errors increased (biased towards to the center of the screen)

390   when saccades were made towards the side with primary motor symptoms (main effect of target

391   laterality: β = -11.18, CI = [-18.30, -4.06], t = -3.07), and that this effect was stronger in the

392   Memory condition (laterality x condition: β = -14.77, CI = [-25.82, -3.72], t = -2.61). Target

393   laterality (with respect to primary motor symptoms) did not modulate vertical errors.

394

395   --- Figure 4 here ---

396

397   *Modulation by DAT binding.* Finally, we wanted to see if the accuracy of fixations

398   correlated with striatal dopamine transporter (DAT) binding in PD patients. This analysis

399   focused on mean striatal DAT binding (caudate, anterior putamen and posterior putamen). In

400   addition to the condition (Baseline vs. Memory), the model included predictors condition, target,

401   the overall DAT binding in the more affected hemisphere (i.e. the one with lower binding), the

402   motor MDS-UPDRS score of the patient, and the interactions of these predictors. We observed

403   that DAT binding modulated vertical errors ($\beta = 25.40$, CI $= [3.74, 46.89]$, t $= 2.40$): the larger

404   the DAT binding, the more accurate were the fixations. This result is visualized in Figure 5A.

405   Note that Fig. 5A displays fixations to both targets because the model suggested that Target did

406   not modulate the correlation. No effects for DAT binding were observed for horizontal errors.

407   We hypothesized that the effect may be better detected if we analyze the amplitudes of the

408   saccades (not the accuracy of fixations). The results showed that DAT binding weakly (not

409   statistically significantly) correlated with saccade amplitudes (main effect of DAT binding: $\beta =$

410   27.69, CI $= [-1.75, 57.16]$, t $= 1.8$), and a stronger effect was observed in the Memory condition

411   for saccades to the second target (DAT x Condition x Target: $\beta = 42.38$, CI $= [14.96, 69.80]$, t $=$

412   3.02). These effects are visualized in Figure 5B (saccades to first target) and Figure 5C (saccades

413   to second target).

414

415   --- Figure 5 here ---

416

417   Importantly, all correlations with DAT binding were also observed when the MDS-UPDRS

418   motor score of the participant was included in the model. This suggests that the observed

419   correlations represent true correlation with the integrity of the dopaminergic system, and not just

420   the severity of the PD.

421

422   *3.3.2.   Compensation in angle and amplitude following the first saccade*

423   As explained in Fig. 1C we also examined how well the participants took into account the

424   trial-by-trial variability in the first saccade when executing the second saccade. In the regression

425   models, the predictor variables were the centered optimal angle/amplitude of the saccade (see

426   Fig. 1C), group, condition, and all interaction between these three variables. Models were pruned

427   by removing non-significant regressors.

428   As shown in Figure 6A-B, the trial-to-trial variability in the *angle* of the second saccade

429   was strongly predicted by the optimal angle required to perfectly fixate the second target ($\beta =$

430   0.71, CI = [0.67, 0.76], t = 29.62). In other words, the participants clearly had information about

431   the error in the endpoint of the first saccade which they could use to correctly aim to the second

432   target. In the Memory condition, the angle of the second saccade was smaller than in the

433   Baseline condition. That is, participants' saccades (in both groups) were biased towards the

434   center of the screen (i.e. the initial fixation point; $\beta = -4.69$, CI = [-7.75, -1.67], t = -3.09).

435   Furthermore, in the Memory condition, the larger the optimal angle, the larger was the bias

436   towards the center of the screen (interaction: $\beta = -0.13$, CI = [-0.20, -0.02], t = -4.32). PD

437   patients were not statistically significantly different from control participants (t ≤ |1|).

438

439   --- Figure 6 here ---

440

441   Also the *amplitude* of second saccade strongly correlated with the optimal amplitude ($\beta =$

442   0.87, CI = [0.78, 0.96], t = 19.46). Moreover, although the amplitudes of the second saccades did

443   not differ between groups (t = 0.04), there was an interaction between group and optimal

444   amplitude: Patients' second saccades become more hypometric as the optimal amplitude required

445   to reach the target increased (Fig. 6C-D, blue line: $\beta = -0.15$, CI = [-0.27, -0.04], t = 2.61). In

446   other words, the patients had trouble making long saccades.

447   As with previous analyses, we examined whether the laterality of the motor symptoms

448   correlated with the angles/amplitudes of the second saccades. As shown in Figure 7, when the

449   targets were presented at the same side as the motor symptoms the compensation in saccade

450   angle was worse than when the targets were presented on the side with less motor symptoms –

451   the second saccades become biased towards the center of the screen, consistent with amplified

452   CD (β = -0.11, CI = [-0.19, -0.033], t = -2.78). In other words, although the PD group did not in

453   general as a group differ from healthy controls in compensating for variability in the endpoint of

454   the first saccade, such an effect was observed when the laterality of the symptoms was

455   considered. In other words, this means that since in some patients the symptoms are

456   predominantly on the right side, and in other patients on the left side, the deficit is only observed

457   when the laterality of the symptoms is taken into account.

458   Target side relative to motor symptoms did not modulate the precision of compensation

459   for saccade *amplitudes*.

460

461   --- Figure 7 here ---

462

463   *Modulation by DAT binding.* We also examined whether the success of compensating for

464   variability in the endpoint of the first fixation correlated with dopamine transporter binding in

465   PD patients. As previously, the model included condition, target laterality (with respect to the

466   more affected hemisphere), the amount of DAT binding, the optimal angle to perfectly fixate the

467   second target, and the motor MDS-UPDRS score of the participant (and the interactions between

468   these regressors).

469   As previously stated the actual *angles* of the saccades were strongly predicted by the

470   optimal angle required to reach the second target (β = 0.74, CI = [0.67, 0.81], t = 20.3). As

471   shown in Figure 8A (blue dashed line) patients with lower DAT transporter binding values were

472   more inefficient in taking into account for the trial-to-trial variability in the endpoint of the first

473   saccade and their saccades become more biased towards the center of the screen, consistent with

474   stronger reliance on CD than bottom-up visual information (Ideal angle × DAT: $\beta = 0.17$, CI =

475   [0.070, 0.28], t = 3.2). Furthermore, the modulation of the angle of the second saccade by DAT

476   was not explained by the severity of PD as the motor MDS-UPDRS score revealed similar

477   modulatory effect (Ideal angle × UPDRS: $\beta = 0.0030$, CI = [0.00081, 0.0053], t = 2.6). Note that

478   although the β coefficient of the Ideal angle × UPDRS interaction (0.0030) is much smaller than

479   the β coefficient of the Ideal angle × DAT interaction (0.17), the relative size of this effect is in

480   fact very similar (due to the fact that the range of motor MDS-UPDRS scores is much higher

481   than DAT values). The modulatory effect by motor MDS-UPDRS is visualized in Figure 8A as

482   the red dotted line which overlaps the blue dashed line that depicts modulation by DAT. In

483   addition to the above mentioned two-way interactions, a Ideal angle × motor MDS-UPDRS ×

484   DAT interaction was observed ($\beta = 0.014$, CI = [0.004, 0.025], t = 2.8). This three-way

485   interaction indicates that the modulation by DAT binding was stronger in participants with more

486   severe PD (i.e. higher UPDRS scores).

487

488   --- Figure 8 here ---

489

490   Next, we examined whether DAT binding was associated with the ability to modulate the

491   *amplitude* of the second saccade to compensate for trial-to-trial variability in the first saccade.

492   Although patients were in general successful in making a second saccade whose amplitude

493   closely resembled the ideal amplitude required to perfectly fixate the second target ($\beta = 0.73$, CI

494   = [0.65, 0.81], t = 17.7), patients with lower DAT binding made more hypometric saccades (β =

495   53.94, CI = [19.23, 88.65], t = 3.0), as shown in Figure 7B. UPDRS score did not statistically

496   significantly modulate saccade amplitudes in general (main effect of UPDRS: t = -0.3).

497   However, patients with higher motor MDS-UPDRS scores were more inefficient in making a

498   close-to-ideal amplitude saccade to the second target (Ideal amplitude × motor MDS-UPDRS: β

499   = -0.010, CI = [-0.015, -0.0050], t = -3.7). Surprisingly, this effect was only observed when the

500   targets were presented ipsilaterally with respect to the hemisphere with lower DAT binding

501   (Contralateral × Ideal amplitude × motor MDS-UPDRS: β = 0.012, CI = [0.0048, 0,020], t =

502   3.1).

503

504   **4. Discussion**

505   We examined how well early PD patients can update their spatial representations during eye

506   movements, and whether this ability correlates with the integrity of the dopaminergic system.

507   The participants were asked to make either visually-guided or memory-guided eye movements to

508   two targets presented in succession. First, the observed results replicate the previous finding that

509   PD patients have difficulties in making memory-guided saccades when compared to control

510   participants (Kimmig, et al., 2002; Blekher, et al., 2009; Crawford, et al., 1989; Terao, et al.,

511   2011). Second, we observed that the deficits in saccadic eye movements correlated with striatal

512   (caudate, anterior putamen and posterior putamen) dopamine transporter (DAT) binding. Third,

513   our results suggest that in addition to general impairments in making saccadic eye movements,

514   the patients have deficits in internally monitoring their eye movements: The angle of the saccade

515   towards the second target was biased in a manner that suggests that the patients overestimated

516   the length of their first saccade. That is, the errors in the angle of the second saccade cannot be

517   explained by simply assuming that PD produces hypometric movement. We suggest that these

518 errors reflect an impairment in monitoring their own movements. As discussed below, the which

519 exact mechanisms explains this deficit, remains open.

520

521   *4.1.   Internal monitoring of movements*

522   When examining the accuracy of fixations, PD patients' fixations towards the second target

523 were on average biased towards the center of the screen. This effect is consistent with the

524 hypothesis that PD patients' CD signals indicate that a sufficiently large eye movement was

525 made, when in reality the eye movement was hypometric. However, the effect could reflect the

526 fact that the patients' saccades towards the first target were hypometric. On the other hand, one

527 could argue that the result shows that the patients did not notice that their first saccade was

528 hypometric, and hence were not able to correct for the saccadic hypometria when performing the

529 second saccade. To tease apart the monitoring of eye movements from saccadic hypometria, we

530 also examined whether the patients' ability to correct for the variation in the endpoint of the first

531 saccade was impaired when compared to the control participants. The results showed that in

532 addition to being hypometric, the angle of the second saccade was biased in a manner consistent

533 with amplified CD relative to the actual movement in PD patients. The effect was only observed

534 when the patients made saccades towards the side with predominant motor symptoms. The bias

535 in the angle of the second saccade (in PD patients) cannot be explained simply by saccadic

536 hypometria. However, the effect was observed both during visually-guided and memory-guided

537 saccades (Fig. 8A), which is at odds with our hypothesis that deficits in CD are only observed in

538 the Memory condition. The result may indicate that the deficit is not in the CD, but instead

539 reflects some more general impairment in encoding or updating spatial representations after eye

540 movements.

541   The observed findings are consistent with the mechanism proposed by Friston et al. (2012):

542   dopaminergic deficiency leads to reduced precision in bottom-up sensory information (prediction

543   errors, such as visual input or procrioceptive input from extraocular muscles), which causes the

544   brain to rely more on top-down information (i.e. predictions such as motor programs and

545   commands). This means that the hypokinetic movements (predictions) begin to dominate action,

546   because feedback concerning the performed, hypometric movements (prediction errors) is not

547   sufficiently assimilated into the current model of the world. This could lead to the fragmented,

548   multi-step movement patterns observed in PD (Berardelli, et al., 2001; Kimmig, et al., 2002),

549   especially in situations where visual information is not available to guide behavior (Glicksterin

550   & Stein, 1991; Klockgether, et al., 1995; Jobst, et al., 1997). Such mechanism could also result in

551   an impaired ability to take into account visual information (prediction errors) when performing

552   actions: Due to the reduced precision in incoming visual information (i.e. location of the second

553   target), the movements towards the target will be predominated by the internal model of the

554   patient.

555   Previous research has shown that deficits in CD are associated with *reduced* CD relative to

556   motor signals (Sommer & Wurtz, 2002; Thakkar, et al., 2015), that is, converse to what we

557   observed here. However, there is no reason to assume that deficits in CD always results in

558   reduction of the CD signal (although this is obviously the case when an area that conveys the CD

559   signal is lesioned; Sommer & Wurtz, 2008). The present findings are consistent with the finding

560   that schizophrenic patients (who in contrast to PD patients have hyperactive striatal dopamine

561   neurotransmission (Howes & Kapur, 2009)) reveal the reverse pattern of results when

562   performing the double-saccade task: in contrast to the present results, schizophrenic patients

563   seem to underestimate the size of the first saccade in the double-saccade task (Thakkar, et al.,

564   2015). This conclusion rests on the assumption that the dopaminergic system contributes to the

565   monitoring of movements. Future studies should aim to directly compare these two groups of

566   patients in the same study.

567

568   *4.2.   Contributions of the dopaminergic system to saccades*

569   The integrity of the striatal dopaminergic system was observed to correlate with the accuracy of

570   saccadic eye movements. The smaller the DAT binding, the more hypometric were the patients'

571   saccades (Fig. 5B), as previously reported (Hotson, et al., 1986; Brooks, et al., 1986; Schultz, et

572   al., 1989; Kato, et al., 1995). Second, our results suggest that in addition to correlating with

573   saccadic hypometria, the integrity of the dopaminergic system may also correlate with the ability

574   to monitor one's own eye movements. This conclusion is based on the finding that the angle of

575   the second saccade was more optimal in patients with higher DAT binding (Fig. 8A), and that

576   DAT binding more strongly correlated with amplitudes of saccades to the second target in the

577   Memory condition (Fig. 5). These findings may, however, also reflect dopaminergic

578   contributions to maintaining information in memory (Landau, et al., 2009; Costa, et al., 2003).

579   Altogether the observed correlation between DAT binding and saccadic metrics (hypometria and

580   the angle of the second saccade) are consistent with the proposal that the dopaminergic system

581   contributes to taking into account previous movements and contextual information when making

582   sequential movements (Friston, et al., 2012).

583

584   *4.3.   Limitations of the present study*

585   The present study has important limitations. First, the sample size of our study was small

586   and possible confounding effects of medication cannot be ruled out. However, because out of 14

587   patients only two chose to take their morning medication, we consider unlikely that acute

588   medication effects were involved in the described effect. The present study's power to detect

589   correlations between DAT binding and saccade performance is very limited, and the small

590   sample size may also lead to inflated correlations (Yarkoni, 2009). Second, although our results

591   suggest that the patients' internal monitoring mechanisms signaled a larger movement than was

592   actually performed, the size of this result is relatively small (e.g. compared to the size of saccadic

593   hypometria for saccades towards the first target). This could in part be explained by the fact that

594   the patients learned the locations of the targets and could use e.g. the monitor's frame to guide

595   their eye movements. Similarly, a better approach would have been to employ novel,

596   unpredictable target locations on every trial (Hodgson, et al., 1999). The present study employed

597   a modified version of the double-saccade task. In the classical version (Hallett & Lightstone,

598   1976; Sommer & Wurtz, 2002; Thakkar, et al., 2015) the visual targets are presented so briefly

599   that they are removed from the screen before the eye movements begin; hence the saccades

600   cannot be guided by sensory information. Because the classical double-saccade task-set up

601   proved too demanding for elderly subjects, we used a modified task where the targets were

602   presented for a longer duration. Third, we cannot rule out the possibility that the observed spatial

603   bias in the Memory condition in PD patients results from impaired spatial memory, rather than

604   deficits in internal monitoring of movements, although impaired spatial memory does not in

605   itself imply that saccades are biased towards the center of the screen. Fourth, it is possible that

606   the observed correlations between fixation errors and dopamine reflect e.g. *combining* motor

607   commands to sequences (not integrating information about what type of movement was made).

608   This interpretation may in part explain correlations between the *amplitude* of the second saccade

609   and DAT binding, but it cannot explain why the *angle* of the second saccade is spatially biased

610   towards the initial fixation. Finally, the present conclusions are restricted by the correlative

611   nature of our study. Causal evidence could be acquired by experimentally manipulating

612   dopaminergic activity in healthy humans.

613

614   *4.4.   Conclusion*

615   Our results provide preliminary evidence that the patients may have impairments in

616   incorporating information about previously made movements and incoming visual information

617   into their current model of the world. The observed disturbances in eye movements, together

618   with the shown associations with DAT binding suggest that, as the disease progresses, and the

619   dopaminergic deficit deepens, relevant clinical motor and visual symptoms associated with

620   impaired internal monitoring of movements may emerge. The PD patients in the present study

621   were at early stages of PD, did not report visual symptoms, and the visual sensitivity of the

622   patients was similar to the control group. Advanced PD patients have many visual symptoms

623   (Weil, et al., 2016) and impaired internal monitoring of movements could lead to deficits in

624   experienced visual stability in later stages of PD.

625

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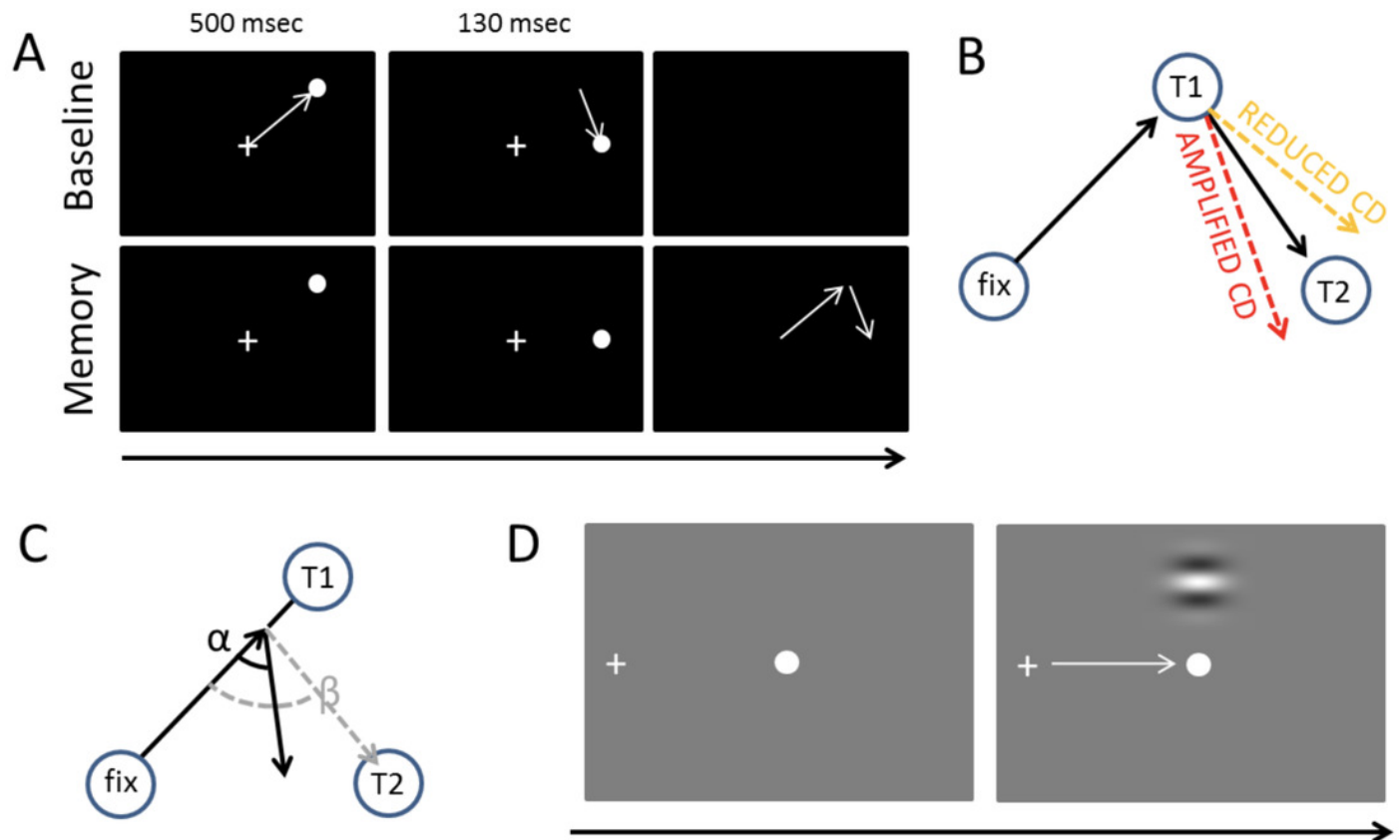
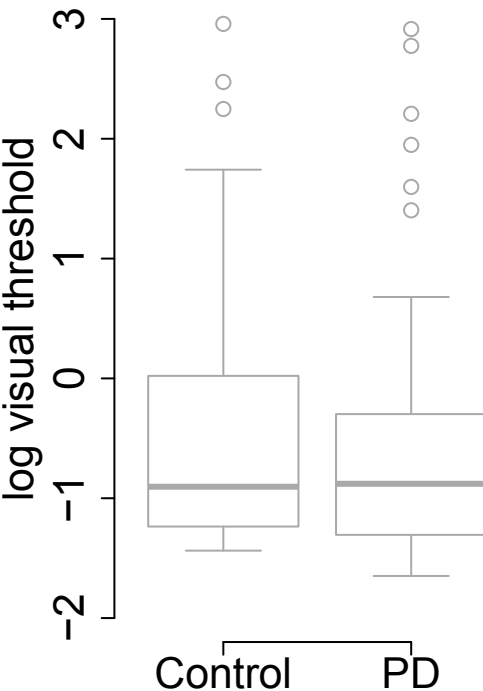
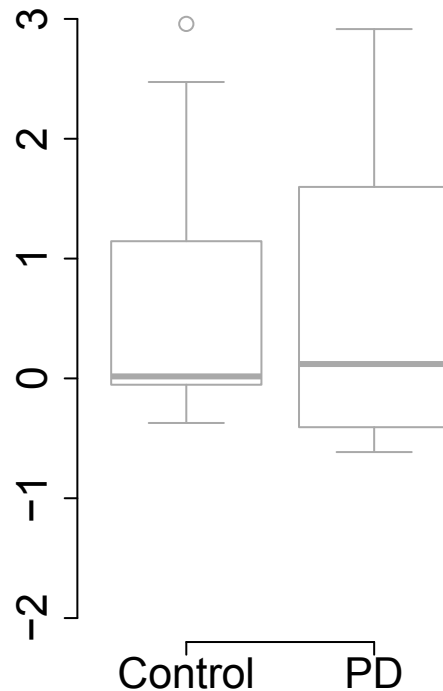
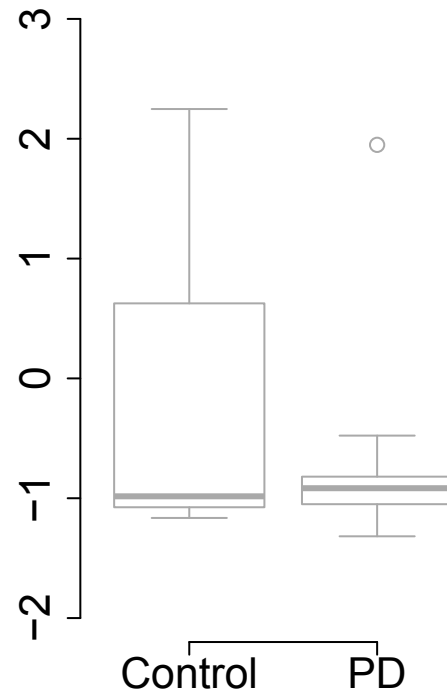
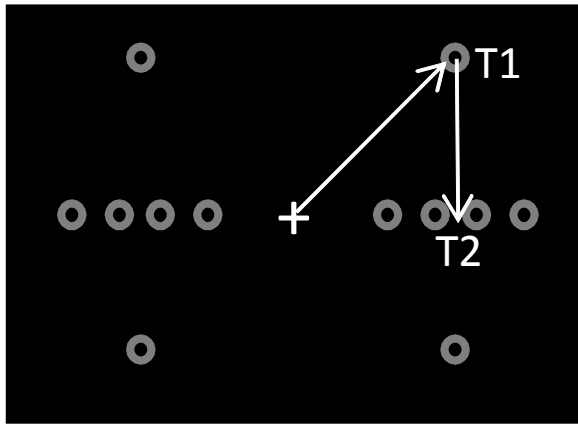
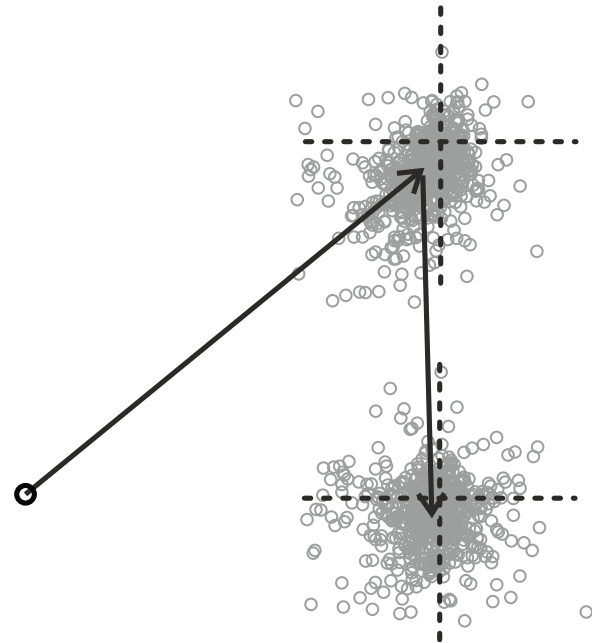
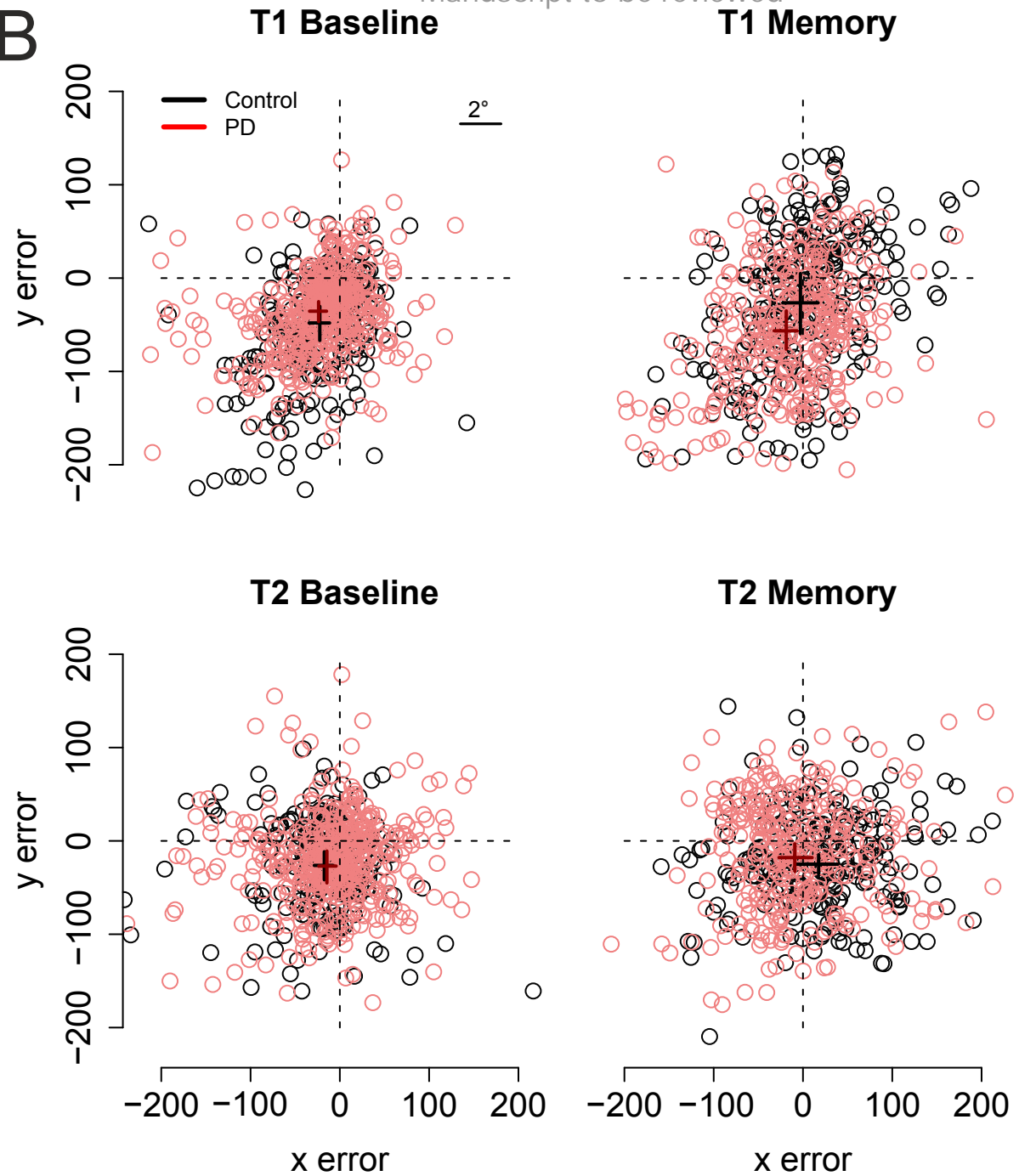
783

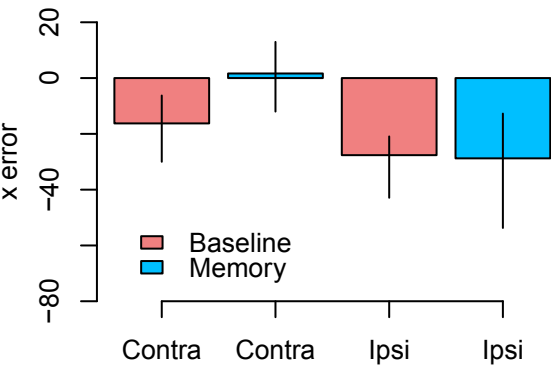
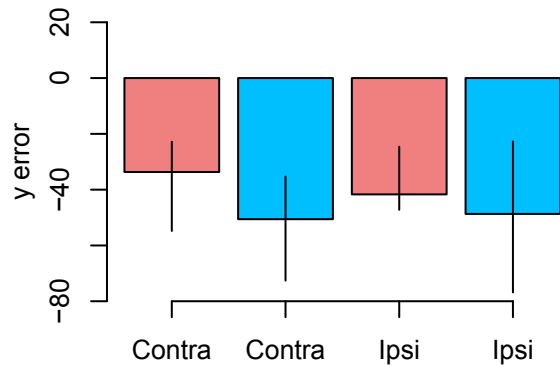
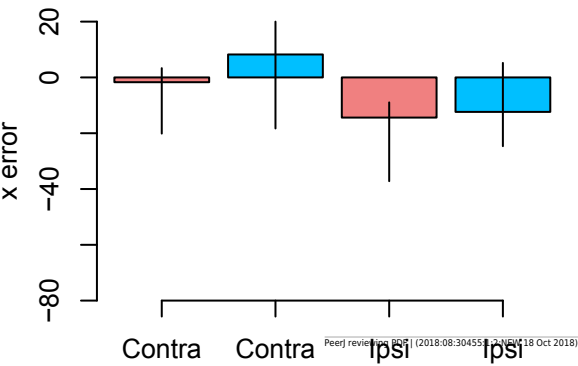
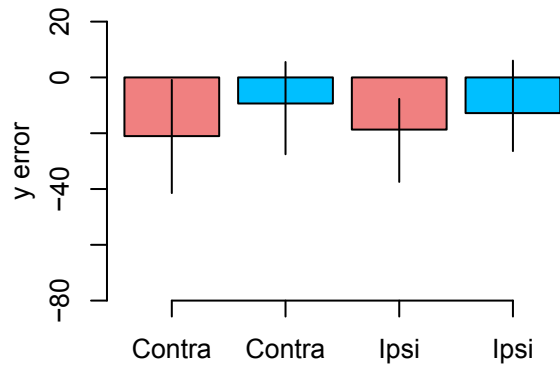
Figure 1

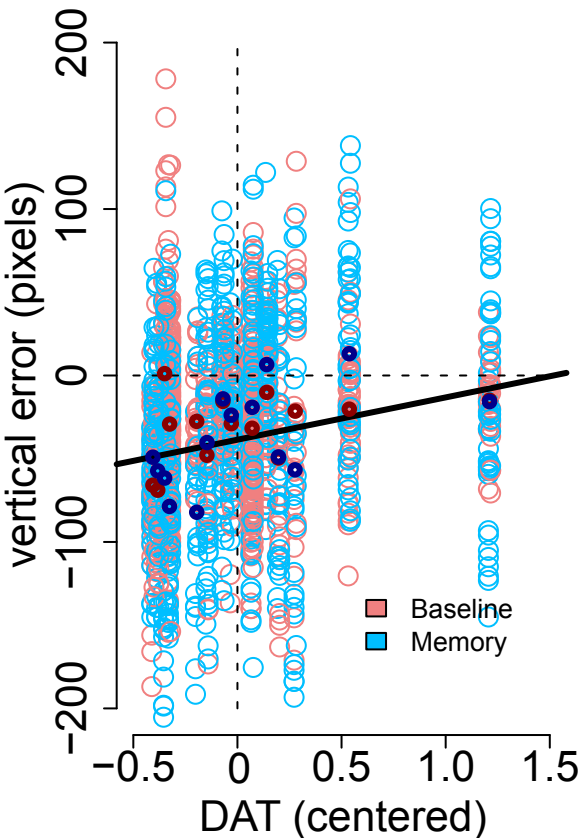
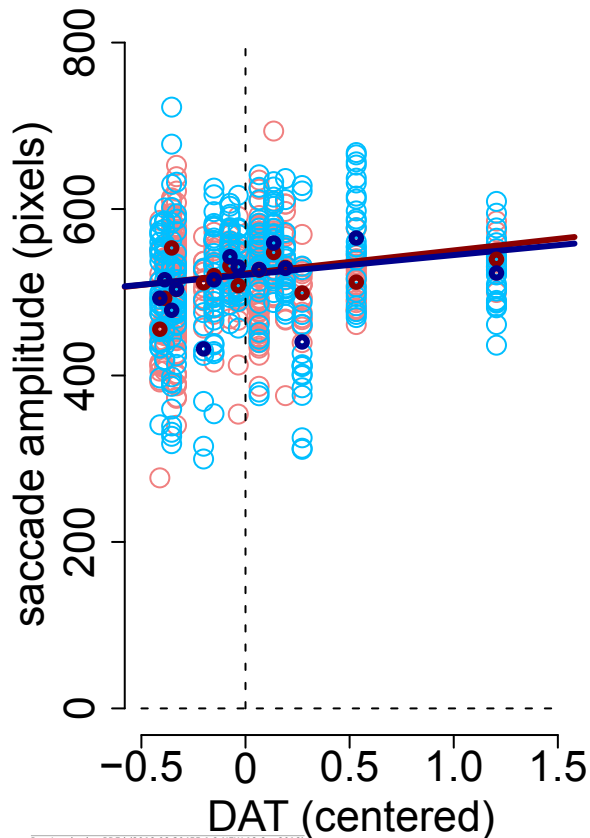
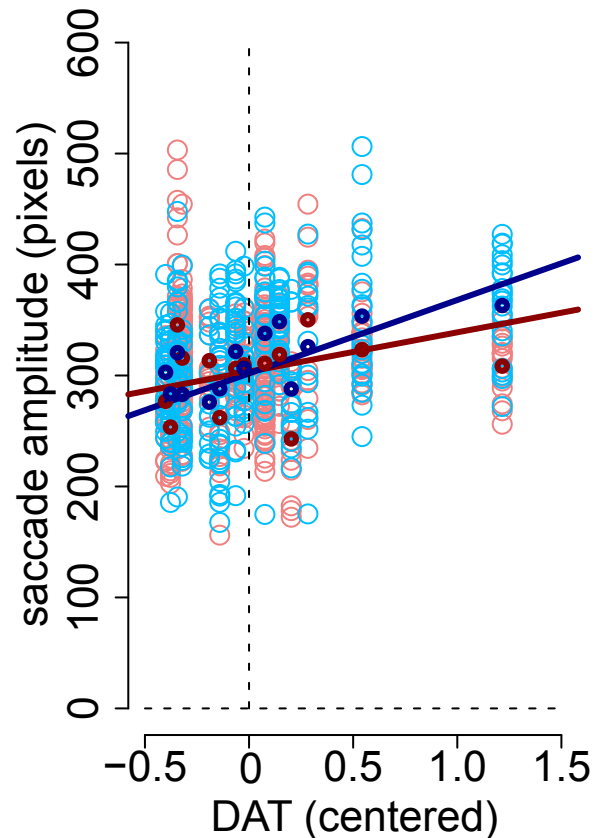
Tasks and measures.

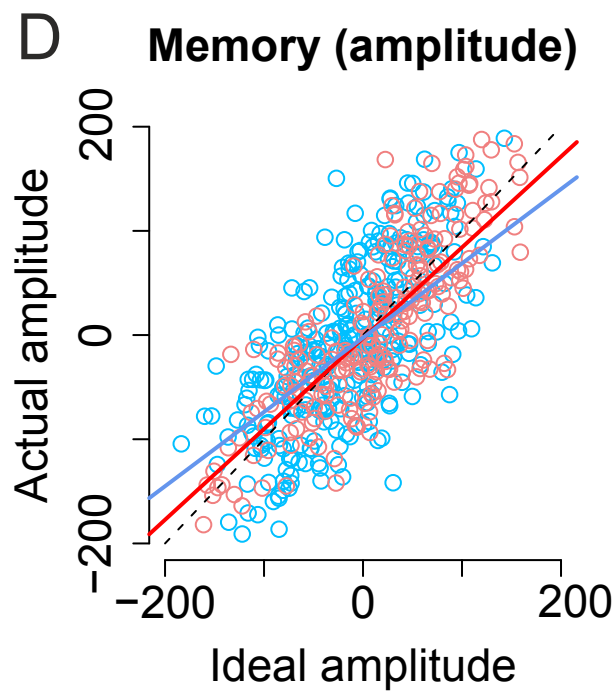
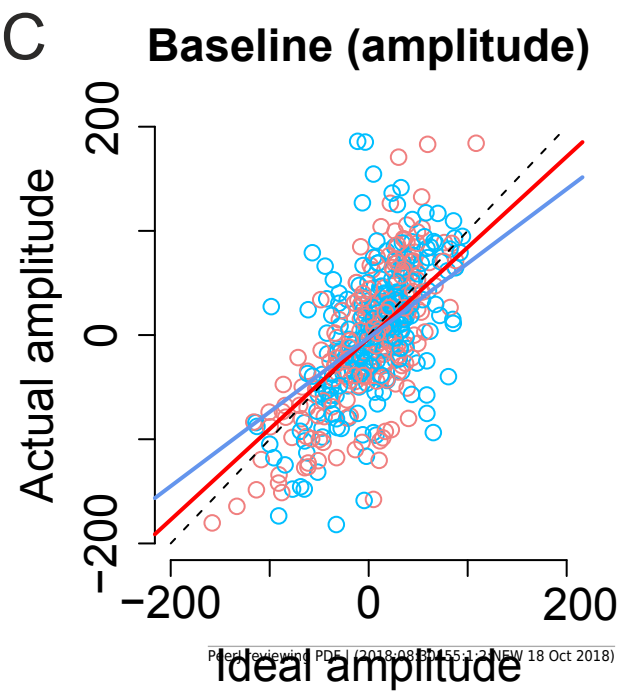
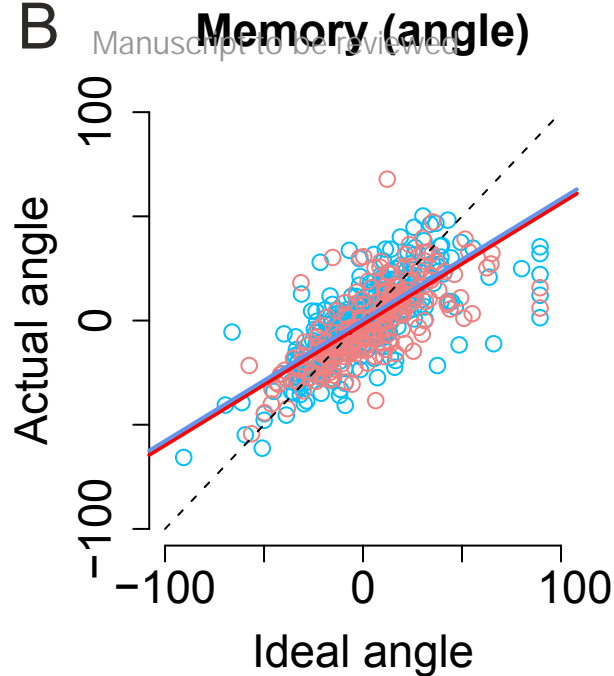
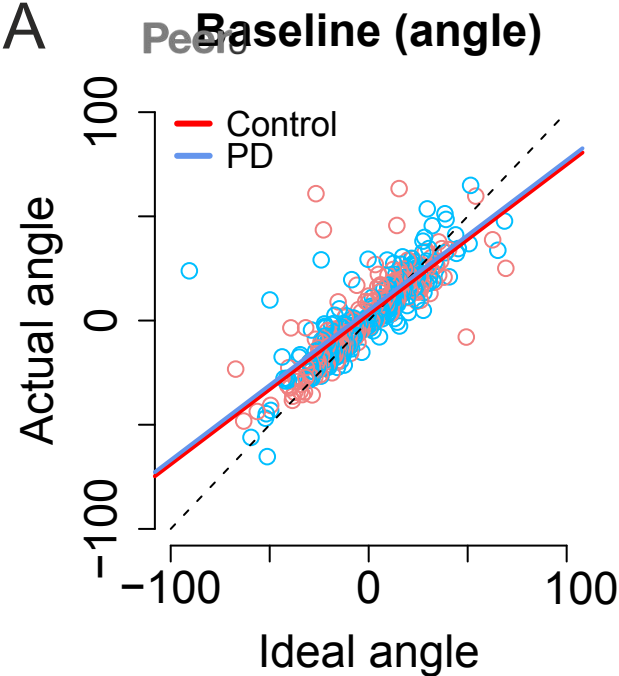
A) The double-saccade task. In the baseline condition the participants made two sequential visually-guided saccades (white arrows) to targets. In the Memory condition, the participants made saccades to memorized target locations. B) Hypothesis concerning the CD. If CD is diminished relative to the strength 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). C) 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 is hypometric. 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). D) Visual detection thresholds were measured (2-alternative forced-choice task) by presenting a Gabor patch in the top or bottom half of the screen during fixation, saccade, or right after saccade. An adaptive staircase method was used to adjust the contrast of the patch to find the 81% detection threshold.

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.The bold horizontal line depicts the median and the box is the interquartile range. The ends of the whiskers are 1.5 times the interquartile range from the box. Circles are outliers.

Fixation maps.

A) 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. B) Fixation maps for the first target (T1, upper panels) and second target (T2, lower panels), separately for Baseline condition (left) and Memory condition (right). The black and red dots denote individual fixations of control participants and PD patients, respectively. The black and red crosses show the respective group averages; the lengths of the lines are 95% confidence intervals of the mean. Unit of error is pixels (22 pixels is ~1^0, see inset).

Amount of error as a function of laterality in the PD group.

Observed data, not model results. 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 ~1⁰).

Correlation between DAT binding and saccades.

A) Vertical accuracy of fixations was modulated by DAT binding. The plot shows fixations to both the first and the second targets. B) The amplitudes of saccades to the first target did not statistically significantly correlate with DAT binding in either condition. C) The amplitudes of the saccades towards the second target correlated with DAT binding in the Memory condition. DAT binding variable has been centered (i.e. zero represented the mean). The lighter dots represent the observed data (all observations), and the bold dots represent the participant-wise averages of these data. Lines represent the observed correlation with DAT binding from the mixed-effects models. Red color denotes the baseline condition (visually-guided saccades) and blue color the memory-guided saccade condition.

Second saccade angles (A-B) and amplitudes (C-D) as a function of ideal angle/amplitude.

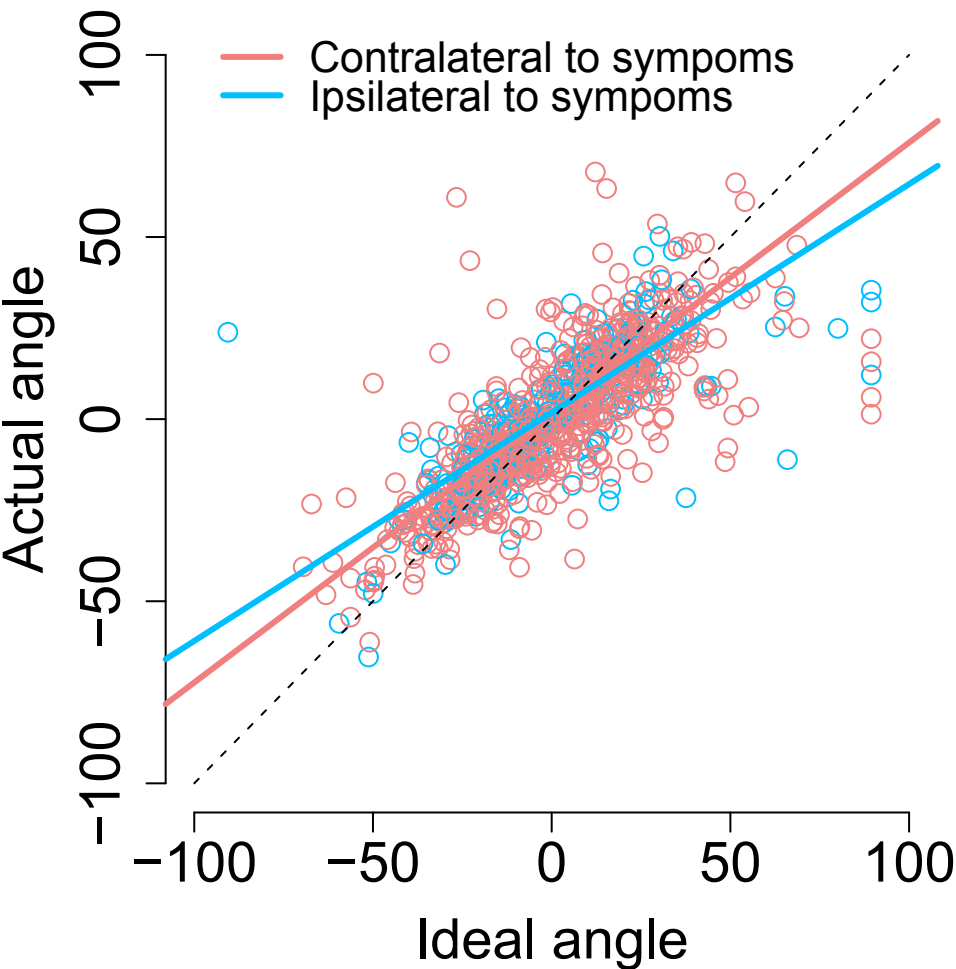
Left panels show the baseline condition, and the right panel the Memory condition. Red color denotes the healthy control participants, and the blue color the patient group. Dots show the observed data (individual saccades) and lines the results of the fitted linear mixed-effects models. Note that angle/amplitude variables are centered, i.e. negative values show that angle/amplitude was smaller than average. Unit is pixels (22 pixels is ~1^0).

The angle of the second saccade as a function of ideal angle.

The solid lines show the results of the model. Compensation for variation in the endpoint of the first fixation is worse for targets that are at the predominant side of motor symptoms. Compensation for variation in the endpoint of the first fixation is worse for targets that are at the predominant side of motor symptoms.

PD group (angle)

Actual angle

Ideal angle

Contralateral to sympoms
Ipsilateral to sympoms

Modulation of compensation in the amplitude of the second saccade.

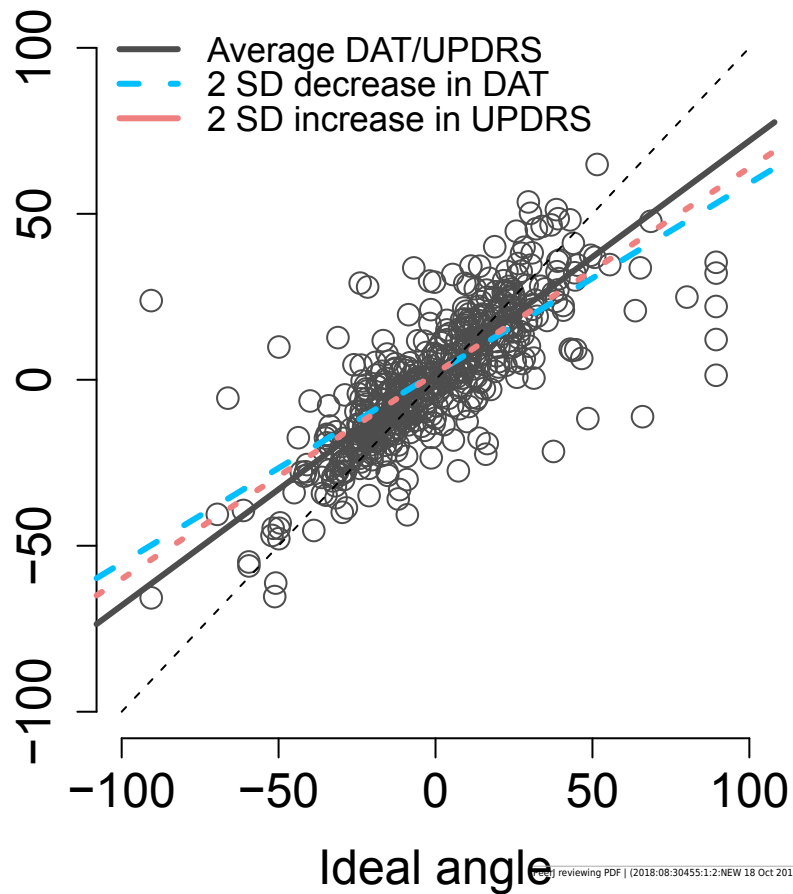
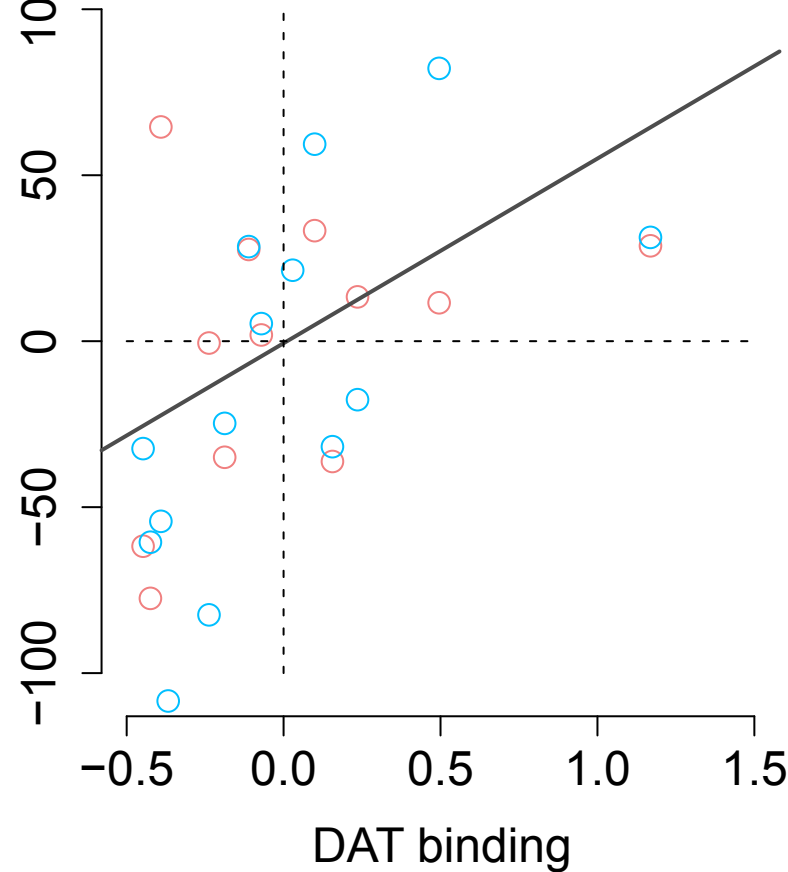
A) Compensation for variation in the endpoint of the first fixation is modulated by DAT binding (blue dashed line) and MDS-UPDRS (red dotted line). The visualized effects represent 2 SD decrease (DAT) or increase (MDS-UPDRS) relative to the patient group average, which is plotted as a grey solid line. The circles represent the observed data. B) Correlation between the amplitude of the second saccade (centered) and DAT binding (centered). 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).

Visual symptoms (mean and SD)

Table 1. Visual symptoms (mean and SD)

Predictor		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

Results of the linear mixed-effects model. Dependet variable: horizontal errors

Table 2. Results of the linear mixed-effects model. Dependet variable: horizontal errors

Predictor	Estimate	95% CI	t value
Intercept	-22.99	[-34.39, -11.55]	-3.92
PD	-2.50	[-17.69, 12.56]	-0.32
Target (= T2)	5.09	[-4.34, 14.47]	1.05
Condition (= memory)	20.85	[1.25, 39.35]	2.07
PD x Target	8.29	[-3.36, 19.92]	1.39
PD x Condition	-12.95	[-38.40, 12.30]	-0.99
Target x Condition	14.85	[1.57, 28.08]	2.19
PD x Target x Condition	-18.96	[-35.89-.2.00]	-2.19

Results of the linear mixed-effects model. Dependet variable: vertical errors

Table 3. Results of the linear mixed-effects model. Dependet variable: vertical errors

Predictor	Estimate	95% CI	t value
Intercept	-49.48	[-64.09, -34.83]	-6.59
PD	11.48	[-8.00, 30.90]	1.15
Target (= T2)	23.74	[14.70, 32.93]	5.11
Condition (= memory)	23.94	[5.04, 42.87]	2.46
PD x Target	-8.72	[-20.03, -2.52]	-1.51
PD x Condition	-40.86	[-66.08, -15.71]	-3.16
Target x Condition	-23.18	[-36.04, -10.37]	-3.53
PD x Target x Condition	44.45	[28.06, 60.87]	5.3