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A perceptual discrimination task results in greater facilitation of voluntary saccades in Parkinson's disease patients

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Abstract

Many studies have shown that Parkinson's disease (PD) affects not only the ability to generate voluntary saccades but also the ability to suppress reflexive saccades (hyper-reflexivity). To further investigate these apparently contradictory effects of PD on the saccade system we adapted a well-known dual-task paradigm (Deubel, 2008) to measure saccades with and without a peripheral discrimination task. Previously we reported that the concurrent performance of a perceptual discrimination task abnormally reduced the latencies of reflexive saccades in PD. Here we report the effects of the concurrent discrimination task on the generation of voluntary saccades in a PD and a control group. As expected, when saccades were performed without the discrimination task the PD group made voluntary saccades with longer latencies and smaller gain than the control group. The concurrent performance of the perceptual discrimination task facilitated the initiation of voluntary saccades in both groups, but, surprisingly, this facilitatory effect was stronger in the PD group than in the control group. In addition, in the PD group voluntary saccades were abnormally facilitated by the peripheral symbol-changes that occur during saccade planning in this paradigm. The results of this study may help to clarify apparently contradictory oculomotor abnormalities observed in PD.

Introduction

Saccades are fast eye movements, which align the fovea with objects and areas of interest. The saccade system is controlled by a range of visual, cognitive, attentional and oculomotor signals which are processed by the basal ganglia (Hikosaka *et al.*, 2000). In Parkinson's disease (PD), the saccade system is thought to be affected by over-activity of inhibitory outputs from the basal ganglia to the superior colliculus (SC) due to striatal dopamine depletion (Albin *et al.*, 1995; Mink, 1996; Hikosaka *et al.*, 2000). Many studies have shown that PD patients have difficulty performing voluntary saccade tasks such as antisaccade, memory-guided or delayed saccade tasks (Lueck *et al.*, 1990; Briand *et al.*, 1999; Chan *et al.*, 2005; Amador *et al.*, 2006; Hood *et al.*, 2007). These tasks are termed voluntary to distinguish them from reflexive (or purely visually guided) saccade tasks. In reflexive tasks the sudden onset of a visual stimulus automatically determines the saccade target, but in voluntary saccade tasks some cognitive operation is required to select the saccade target (Walker *et al.*, 2000). In the voluntary saccade tasks that are traditionally used to detect impairments in PD, participants must shift attention to a visual stimulus without making a saccade to that stimulus, and either initiate a saccade in the opposite direction (antisaccades) or wait for a further cue (delayed or memory-guided saccades). In these tasks, people with PD make more unintended saccades to the visual stimulus (hyper-reflexivity), and they make the correct voluntary saccades at longer latencies and with smaller gain values (hypometria) than control subjects (Briand *et al.*, 1999; Mosimann *et al.*, 2005).

In contrast to the consensus regarding the performance of voluntary saccade tasks, there is no agreement regarding the initiation of reflexive or visually guided saccades in PD, at least in the absence of cognitive impairment. Some studies have detected impairments (Rascol *et al.*, 1989; Chen *et al.*, 1999), but others report that reflexive saccades are intact (Kimmig *et al.*, 2002; Mosimann *et al.*, 2005) or even abnormally facilitated in PD (Briand *et al.*, 2001; Kingstone *et al.*, 2002; Chan *et al.*, 2005; van Stockum *et al.*, 2008, 2011b); for a review see Chambers & Prescott (2010). To reconcile these apparently contradictory deficits – impaired saccade initiation and impaired saccade suppression or hyper-reflexivity – it has been suggested that PD may affect visually guided and voluntary saccades differentially and that abnormal basal ganglia output in PD might delay the initiation of voluntary saccades, while abnormally releasing reflexive processes in the saccade system from inhibition (Chan *et al.*, 2005; Amador *et al.*, 2006; Hood *et al.*, 2007). However, it has been noted that this type of disinhibition (or hyper-reflexivity) is inconsistent with over-activity of inhibitory output

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from the basal ganglia to the saccade system (Shaikh *et al.*, 2011; Terao *et al.*, 2011). Also, there is some evidence that disinhibition of reflexive saccades does not necessarily co-occur with impairment of voluntary saccades in PD (van Stockum *et al.*, 2012).

The efficient operation of the saccade system depends on the ability to exert voluntary control (an endogenous process) over the automatic response to sensory events (an exogenous process). The antisaccade and memory-guided saccade tasks, which have traditionally been used to investigate saccade initiation in PD, involve competition between contradictory processes: subjects must simultaneously suppress and generate an eye movement. This makes it difficult to establish the origin of impairments in these tasks. To clarify the effect of PD in the saccade system, we elected to use a saccade task that allows the separate measurement of endogenous and exogenous processes in the saccade system and that does not require suppression of saccades. We adapted a well-known task (Deubel, 2008), in which saccades can be performed with or without a concurrent perceptual discrimination task. Participants are instructed to make a voluntary saccade to a peripheral target location, which is indicated by a central arrow cue. Shortly after the onset of the arrow cue, before the saccade is initiated, symbols can appear briefly at the target location and at distractor locations. After each saccade, observers are asked to report the identity of the symbol that appeared at the target location. It has been shown that the concurrent performance of a discrimination task can facilitate saccade initiation (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005). The brief, pre-saccadic, peripheral symbol-changes can also modulate saccade latencies in this paradigm (Deubel, 2008; van Stockum *et al.*, 2011a). The effect of the discrimination task can be attributed to endogenous processes, because it is due solely to the task instructions and the observer's intention. The effect of the peripheral symbol-changes can be attributed to exogenous processes, because it is due solely to a change in visual input. When a group of PD patients and a control group performed reflexive (visually guided) saccades in a variant of this paradigm, the discrimination task reduced saccade latencies more in the PD group than in the control group (van Stockum *et al.*, 2011b). This observation is consistent with reports of hyper-reflexivity in PD (Chan *et al.*, 2005; van Stockum *et al.*, 2008; van Koningsbruggen *et al.*, 2009; Cameron *et al.*, 2012). Moreover, the discrimination task facilitated saccade initiation in the PD group especially in trials with an overlap, where the ongoing presence of the central fixation point (the overlap) had a smaller inhibitory effect in the PD group than in the control group. We suggested therefore that the discrimination task reveals a source of abnormal endogenous saccadic facilitation in PD, which may affect the saccade system globally (van Stockum *et al.*, 2011b). Such a global effect of PD in the saccade system is inconsistent with models that assume that PD affects visually guided and voluntary saccades differentially. To assess whether there is indeed evidence for global endogenous saccadic facilitation in PD, we used the same dual task paradigm to measure voluntary saccade production with and without a perceptual discrimination task.

Methods

Participants

The PD and control subjects that comprised the groups in the earlier report (van Stockum *et al.*, 2011b) [20 PD patients (eight females) and 20 control participants (eight females)] performed the voluntary saccade tasks. The groups were matched for mean age and years of education. Mean age in the PD group was 65.0 years, ranging from 50 to 77. In the control group the mean age was 65.5 years, ranging from 56 to 76. Hoehn & Yahr scores in the PD group ranged from 1 to 3. To exclude subjects with dementia, only participants who scored 25 or more on the Montreal Cognitive Assessment (Nasreddine *et al.*, 2005; Dalrymple-Alford *et al.*, 2010) were included. The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess motor impairment in the PD group (Goetz *et al.*, 2008). The participants in the PD group were tested 'on' medication; see Table 1 for demographic details of the PD group. This project received ethical approval from the Upper South A Regional Ethics Committee of the

TABLE 1. Details of the participants in the PD group

H&Y	Age (years)	Sex	Years of education	Years with PD	MoCA	MDS-UPDRS Part III	Medications
1	59	M	12	2	30	22	Ropinirole, domperidone
1	60	M	12	2	30	18	Selegeline, Sinemet
1	63	M	15	2	29	22	Moclobemide, Sinemet
1	68	F	14	3	27	15	None
1	68	F	9	3	27	36	Amantadine
1	72	F	15	9	25	25	Sinemet, fluoxetine
1.5	65	F	10	5	30	33	Ropinirole, amantadine
2	54	M	16	3	30	25	Ropinirole, amantadine
2	62	M	16	2	26	30	Amantadine
2	63	F	8	3	29	22	Selegiline, Madopar, Sinemet
2	65	M	10	1	28	31	Ropinirole, amitryptiline, amantadine
2	65	M	12	4	25	22	Ropinirole, Sinemet, amantadine
2	67	M	10	2	27	40	Sinemet, benztropine, amantadine
2	70	F	11	14	27	17	Madopar, pergolide, amantadine
2	70	M	18	7	30	44	Madopar, entacapone, amantadine
2	74	M	10	2	30	38	Sinemet
2.5	58	M	14	13	30	54	Selegiline, Sinemet, lisuride, amantadine
2.5	70	F	15	9	26	55	Sinemet, ropinirole, amantadine
2.5	77	M	18	4	27	70	Madopar
3	50	F	14	4	26	29	Amantadine

The Montreal Cognitive Assessment (MoCA) is a general cognitive screening test (Dalrymple-Alford *et al.*, 2010). The MDS-UPDRS Part III is a scale assessing the motor signs of PD. The Hoehn and Yahr (H&Y) score reflects disease severity in PD.

New Zealand Ministry of Health and participants gave informed consent.

The tasks

The paradigm was adapted from Deubel (2008), with saccades performed with and without a concurrent two-alternative forced choice (2AFC) perceptual discrimination task (van Stockum *et al.*, 2011b). Four potential saccade targets were displayed throughout each trial and the onset of a central arrow cue indicated which of the four was the saccade target. This procedure ensured that the task elicited voluntary saccades (the saccade target was not exogenously determined by the appearance of a peripheral visual stimulus), without the need to suppress a reflexive saccade. The 2AFC discrimination task required participants to report the identity of a symbol (E or 3), which appeared for 100 ms at the target location shortly (the stimulus onset asynchrony or SOA) after the onset of the arrow cue. The SOA and the duration of the discrimination symbol were such that the discrimination symbol generally disappeared before saccade onset and therefore the E or 3 was not foveated directly. Exactly the same trials were presented (albeit in a different order) for the saccade task 'without discrimination' and the saccade task 'with discrimination'. Only the instructions to the participants differed: in the task 'without discrimination', participants were instructed simply to 'look at the target indicated by the arrow as quickly and accurately as possible' and to ignore any flickers they might notice in the display, as they were irrelevant to the task. In the task 'with discrimination', participants were instructed to 'look at the target indicated by the arrow as quickly and accurately as possible' and to 'pay attention to the symbol-changes at the target location' because, after each trial, they would be asked to choose which symbol had been displayed (E or 3).

Stimulus sequence

The stimulus display is illustrated in Fig. 1. Four potential targets (consisting of figure 8 symbols) were displayed throughout each trial. Participants controlled the start of each trial by pushing a button when they were ready with their gaze upon the central fixation point. After a variable fixation interval (1000–1400 ms) the central fixation point turned into an arrow to indicate which of the four figure 8s would be the saccade target. At 25, 75, 150 or 250 ms after the onset of the arrow (the SOA), the figure 8 at the target location could change briefly (for 100 ms) into either E or 3, while the figure 8s at non-target locations could change into 5 or 2. Four trial types were used to allow the separate assessment of the effects

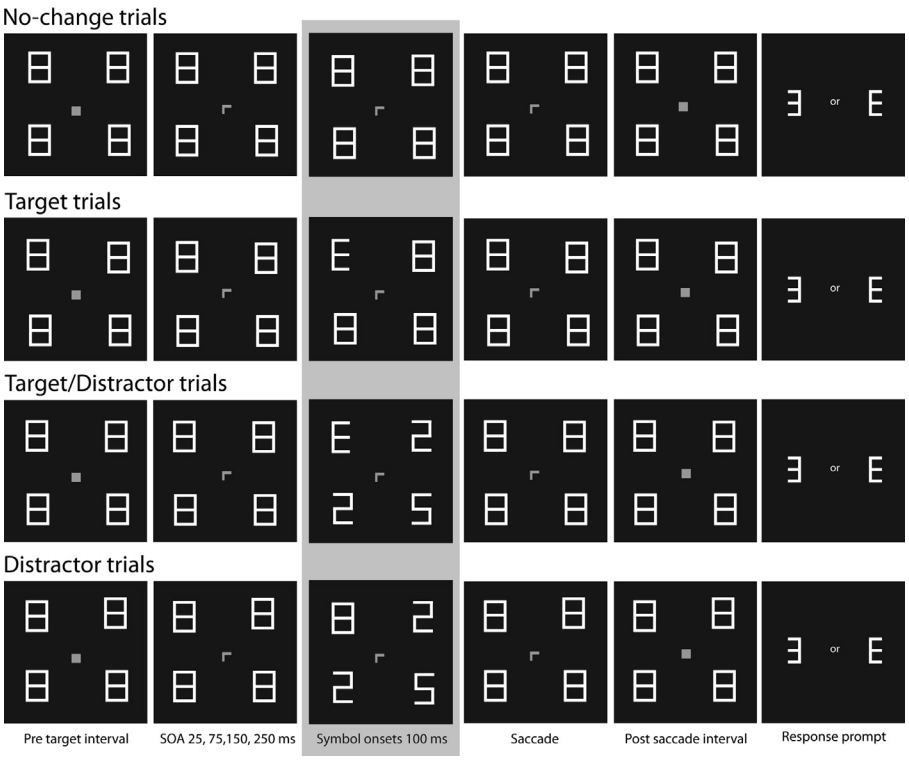

FIG. 1. Schematic illustration of the stimulus display in voluntary saccade trials. The rows show the four different trial types. *Top row*: No-change trials: all symbols remained unchanged. *Second row*: Target trials: only the symbol at the target location changed into a discrimination symbol. *Third row*: Target/Distractor trials: all symbols changed simultaneously. *Fourth row*: Distractor trials, the symbol at the target location did not change, but the three symbols at the non-target locations changed into 2s and 5s. The columns show the six different stages of the stimulus presentation. The four trial types differed only during the display of the discrimination symbol (the shaded third column). *First column*: Each trial started with the display of a central fixation square for a variable pre-trial interval (1000–1400 ms). *Second column*: the fixation square changed into an arrow indicating the saccade target. *Third column*: top row (No-change trials): the stimulus display remained unchanged after the onset of the arrow. Second row (Target trials): after an SOA of 25, 75, 150 or 250 ms a discrimination symbol (E or 3) appeared for 100 ms at the cued target location. Third row (Target/Distractor trials): after an SOA of 25, 75, 150 or 250 ms a discrimination symbol (E or 3) appeared for 100 ms at the cued target location, and the figure 8s at non-target locations changed into 2 or 5. Fourth row (Distractor trials): the figure 8 at the target location remained unchanged and the figure 8s at non-target locations changed into 2 or 5. *Fourth column*: all symbols changed back to figure 8s and remained for 1500 ms. *Fifth column*: the arrow changed back to the central fixation square and remained for 1000 ms. *Sixth column*: the participant was prompted to indicate, with a right or left manual button press, which symbol (E or 3) was seen during the trial.

of symbol-changes at target and at peripheral non-target locations: (1) 'No-change' trials, where all four figure 8s remained unchanged throughout the trial; (2) 'Target' trials, where only the figure 8 at the target location changed into E or 3, while the three figure 8s at the non-target locations remained unchanged; (3) 'Distractor' trials, where only the three figure 8s at the non-target locations changed into 5 and 2 and the figure 8 at the target location remained unchanged; and (4) 'Target/Distractor' trials where all four figure 8s changed at the SOA: at the target location into E or 3 and at the non-target locations into 5 and 2. The task was presented in blocks of 52 trials and each block was presented in a different randomized order. Interspersed in each block were four No-change trials. The remaining 48 trials consisted of four trials of each trial type (Target, Target/Distractor or Distractor trials), at each of the four SOAs. On half of the trials in which the target symbols changed into discrimination symbols (i.e. Target and Target/Distractor trials), the figure 8 turned into E, on the other half into 3.

Apparatus and stimuli

Eye movements were recorded monocularly using a video-based iView X Hi-Speed system (SMI, Berlin, Germany) at a sampling rate of 1250 Hz. This system uses a combination of corneal reflection and pupil tracking with a typical spatial accuracy of 0.25–0.5° and a tracking resolution of < 0.01°. Stimuli were displayed on a 21-inch CRT screen with a 100-Hz refresh rate on a display area of 400 × 300 mm, at a resolution of 800 × 600 pixels. The computer screen was positioned 600 mm in front of participants, who sat with head supported by the chin and forehead rest of the iView tracking column. As PD patients may have lower contrast sensitivity and a smaller 'useful field of view' than controls (Uc *et al.*, 2005), high-contrast stimuli and small target amplitude were used to minimize any potential differences in perceptual ability between the groups. Stimuli were presented on a dark grey background (R50 G50 B50). The fixation point was a red (R255 G0 B0) square (0.67 × 0.67°); the directional cue was a red (R255 G0 B0) arrow (0.67 × 0.67°); targets were white (R255 G255 B255) figure 8s (0.62 × 1°); discrimination symbols were white (R255 G255 B255) Es or 3s (0.62 × 1°); distractors were white (R255 G255 B255) 2s or 5s (0.62 × 1°). Targets were located at the four corners of an imaginary square, each 5.4° diagonally from the central fixation point. Each block of trials started with a check of the calibration quality and, if required, a two-dimensional 13-point re-calibration procedure covering the display area. At the beginning and end of each recording, a sequence of reflexive saccades was recorded to provide data for *post hoc* assessment and adjustment of the calibration if required. Stimuli were presented using PsychoPy, an open-source experimental control software package (Peirce, 2007, 2008).

Procedure

All participants attended two testing sessions. At the first session, after a 6-m visual acuity test with the Snellen wall chart (each subject was required to have visual acuity of no worse than 6/12 corrected in their best eye), each participant's vision was checked whilst they were seated in front of the computer screen with the chin supported by the chinrest of the recording column. At a viewing distance of 600 mm, some participants' own corrective lenses were not suitable. A range of corrective lenses of various strengths was then tried until the best possible acuity at 600 mm was achieved. Vision was then tested again with an array of symbols at the size and contrast actually used in the experiments. The actual test and recording started after calibration of the eye movement recording system.

At the first session, subjects first performed two blocks of the saccade task 'without discrimination', and then two blocks of the saccade task 'with discrimination'. The saccade task 'without discrimination' was always performed at the start of the first session, while participants were not yet aware of the potential relevance of the symbol-changes. Another two blocks of the task 'with discrimination' were performed at the second session, 1 week after the first session. In the task 'with discrimination', each trial was followed by a visual prompt asking the participant whether E or 3 had appeared. Participants responded E or 3 with a right or left manual button press, respectively. Participants were explicitly told to guess if unsure of the answer. They were also told that on some trials there would be no discrimination symbol, and to push one of the two buttons at random when they thought no discrimination symbol had appeared. In No-change and Distractor trials there was no discrimination symbol, but subjects were not told about the different symbol-change conditions or the likelihood of a discrimination symbol occurring.

Practice trials allowed participants to become familiar with the push buttons and the task requirements before the start of each test. Instructions and practice trials were repeated until the participant and the experimenter were confident the task requirements were understood.

Analysis and measurement

Trials were excluded when the saccade was masked by a blink; when no saccade was made; when saccades were made at latencies shorter than 80 ms (i.e. anticipations), or longer than 700 ms; or when saccades had a primary gain of less than 0.3 or more than 1.3. The proportion of excluded trials was similar in the control and the PD groups (both 20%). Trials with saccades initiated at latencies longer than 80 ms, but with directional errors (i.e. the primary saccade was not directed at the cued target location), were analysed separately. The proportion of correct discriminations in the saccade tasks 'with discrimination' was calculated from the total number of valid trials without directional errors. Effects of the discrimination task and the symbol-changes on saccade latency and gain were analysed with multi-level models. These have the advantage that all observations contribute to the model, and the data are not reduced to mean values per condition for each participant, as occurs in traditional ANOVA. The function *lme* from the R package *nlme* (Pinheiro *et al.*, 2009) was used to fit the models. Latency and gain values of voluntary saccades were analysed with a linear multi-level model. Proportions of errors and discrimination judgments were compared with multi-level binomial models. Associations between variables were assessed with Pearson's product-moment correlations. In the text, predicted group means are shown followed by 95% CI in parentheses.

Results

Sessions 1 and 2

The saccade task without discrimination was performed only in the first session. The saccade task with discrimination was performed in both the first and the second session. There was no significant practice effect and the mean latencies and gain in the discrimination trials were similar in the two sessions in both groups, so the results from the two sessions were pooled (see Table 2).

TABLE 2. Mean latency [95% CI] and gain values of voluntary saccades performed in the trials with the discrimination task

	Latency		Gain	
	Session 1	Session 2	Session 1	Session 2
Controls	367 ms [345, 388]	366 ms [351, 381]	0.90 [0.88, 0.93]	0.90 [0.87, 0.94]
PD	399 ms [368, 431]	391 ms [369, 413]	0.83 [0.78, 0.86]	0.84 [0.81, 0.88]

Trials with symbol-changes

Saccades were performed in trials without peripheral symbol-changes (in the No-change trials) and in trials with peripheral symbol-changes (in the Target, Distractor and Target/Distractor trials). Within each group, the mean latency and gain values in the three trial types with symbol-changes were similar (see Table 3). Therefore, the results from these three trial types were pooled for comparison with the No-change trials: the model included Group (Control or PD), Trial type (trials with or without peripheral symbol-change) and Task (with or without discrimination task) as predictors. The factor Trial type was nested inside the factor Task, which was nested within Subject. Due to the collapsing of the data across SOAs there were more trials with symbol-changes than trials without symbol-changes. However, when means were calculated for each subject the standard error in the No-change trials did not differ from the standard error in the trials with symbol-changes (between 10 and 14 ms). Also, the statistical model does not use the mean values for each subject but takes all valid observations into account.

Saccade latencies

In the control group, the mean latency of voluntary saccades in No-discrimination/No-change trials was 391 ms [364, 417], the intercept of the model. In this baseline condition, the PD group made saccades at latencies that were 71 ms [32, 110] longer than in the control group ($t_{38} = 3.69$, $P < 0.001$). In the control group in No-discrimination trials, the peripheral symbol-changes did not significantly affect saccade latencies: there was a small latency increase of 10 ms [−13, 33] ($t_{38} = 0.85$, $P = 0.40$). In contrast, in the PD group in No-discrimination trials, the symbol-changes reduced latencies by 26 ms [2, 49] ($t_{38} = –2.23$, $P = 0.03$) compared with No-change trials. The discrimination task reduced latencies in the control group, by 33 ms [9, 58] ($t_{76} = –2.70$, $P = 0.01$). In the PD group, the effect of the discrimination task on latencies was significantly larger, with latencies reduced by an additional 37 ms [2, 71] over and above the 33 ms reduction in the control group ($t_{76} = –2.09$, $P = 0.04$). In discrimination trials, the symbol-changes no longer abnormally affected saccade latencies in the PD group. Figure 2 shows the uncorrected mean group latencies [95% CI] calculated from each participant's mean latency in each of the four trial types, No-discrimination/No-change, No-discrimination/Change, Discrimination/No-change and Discrimination/Change trials.

Saccade gain

The mean primary gain of voluntary saccades in No-change trials without the discrimination task in the control group was 0.85 [0.82, 0.89], the intercept of the model. In this baseline condition, the PD group's primary gain was 0.06 [0.01, 0.11] smaller ($t_{38} = –2.42$, $P = 0.02$). The discrimination task increased gain values in both groups: in the control group the discrimination task increased gain by 0.05 [0.02, 0.08] ($t_{38} = 3.10$, $P = 0.01$) and in the PD group by 0.04 [0.01, 0.08] ($t_{38} = 2.51$, $P = 0.02$). Gain values were not affected by peripheral symbol-changes.

Direction errors

In Distractor and Target/Distractor trials the peripheral symbol changes could potentially interfere with saccade plans as they occurred away from the target location. To assess the effect of the peripheral symbol changes on the production of direction errors (saccades that were not directed at the cued target location) these trials with a symbol-change at a non-target location were pooled into a condition labelled 'with distractors'. In Target and No-change trials, the symbol-changes were not expected to interfere with saccade plans as they occurred at the target location or not at all. Therefore, No-change and Target trials were combined into a condition labelled 'without distractors'.

There was a significant interaction between the effects of the discrimination task and the distractors ($z = −2.82$, $P = 0.005$). In both groups, in trials without the discrimination task, distractors did not greatly affect the production of directional errors (3.5–4%), but in trials with the discrimination task, distractors increased the production of directional errors from 6 to 12%. In trials with the discrimination task and distractors, the proportion of direction errors depended on the timing of the symbol-change relative to the onset of the central arrow cue (the SOA) ($z = 2.62$, $P = 0.01$). In both groups, the proportion of errors declined in trials with longer SOA compared with trials with shorter SOA. Figure 3 shows the proportion of direction errors at each SOA for each group in trials with and without distractors, in each task.

Association between the effect of the discrimination task and the effect of the symbol-changes on saccade latency

For each participant, the magnitude of the effect of the discrimination task on saccade latency was calculated by subtracting their

TABLE 3. Mean latencies and gain [95% CI] of voluntary saccades performed in the No-change trials and in the three trial types with peripheral symbol-changes, with and without the discrimination task

Task	Without discrimination				With discrimination			
Trial type	No change	Target	Target/Distractor	Distractor	No change	Target	Target/Distractor	Distractor
Latency								
Controls	389 (363, 416)	398 [376, 421]	406 [382, 429]	398 [376, 420]	357 (336, 379)	361 [342, 380]	373 [355, 391]	377 [358, 397]
PD	464 (436, 491)	433 [406, 461]	436 [410, 462]	438 [413, 463]	394 (364, 423)	383 [356, 411]	399 [369, 428]	403 [374, 432]
Gain								
Controls	0.82 [0.76, 0.88]	0.86 [0.81, 0.90]	0.86 [0.82, 0.91]	0.85 [0.81, 0.88]	0.91 [0.87, 0.95]	0.91 [0.88, 0.93]	0.91 [0.88, 0.93]	0.89 [0.86, 0.92]
PD	0.76 [0.68, 0.83]	0.79 [0.74, 0.84]	0.80 [0.76, 0.84]	0.79 [0.73, 0.84]	0.83 [0.77, 0.89]	0.84 [0.79, 0.89]	0.84 [0.81, 0.88]	0.82 [0.78, 0.86]

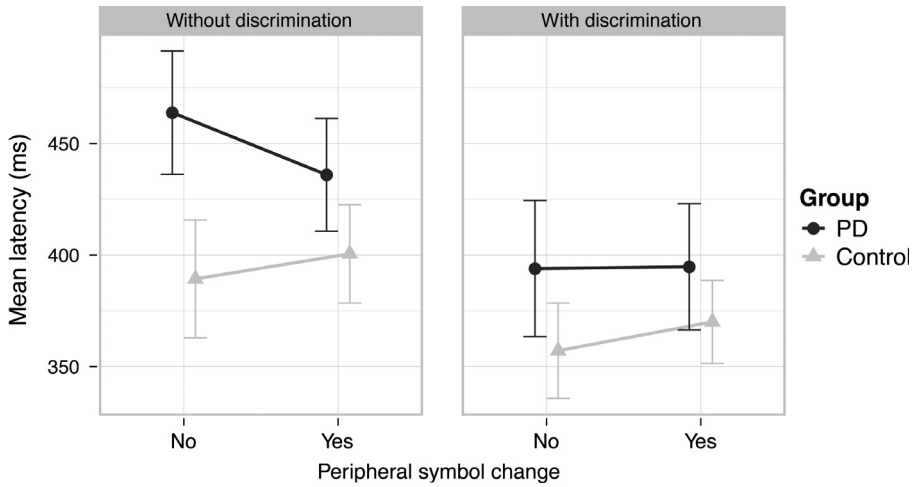

FIG. 2. Mean latencies for each group are shown for trials without the discrimination task (on the left) and for trials with the discrimination task (on the right). Two effects reduced saccade latencies more in the PD group than in the control group. First, in the trials without the discrimination task, compared with No-change trials, the peripheral symbol-changes (in Target, Target/Distractor and Distractor trials) reduced latencies in the PD group, but not in the control group. Secondly, the discrimination task reduced latencies more in the PD group than in the control group.

mean saccade latency in No-change trials without the discrimination task, from their mean saccade latency in No-change trials with the discrimination task. Also, for each participant the magnitude of the effect of the peripheral symbol-changes on saccade latency in the trials with the discrimination task was calculated by subtracting their mean saccade latency in No-change trials from their mean saccade latency in trials with symbol-changes.

For participants in the PD group, but not in the control group, the two effects were negatively associated with each other ($r = -0.54$ [-0.79, -0.12], $P = 0.01$). Figure 4 shows that in the PD group, larger latency reductions due to the discrimination task were associated with smaller latency reductions, or even small latency increases due to the symbol-changes.

Discrimination judgments

Correct discrimination judgments were made in 71% (control group) and in 70% (PD group) of all valid trials. In the PD group, but not in the control group, worse performance of the discrimination task was associated with smaller primary saccade gain ($r = 0.64$ [0.27, 0.84], $P = 0.003$; see Fig. 5). The performance of the discrimination task was not associated with saccade latencies in either group.

Discussion

As expected, the PD group made voluntary saccades at longer latencies than the control group in a baseline condition. However, this voluntary saccade paradigm revealed two sources of abnormal saccadic facilitation in the PD group. First, when saccades were performed without the discrimination task the peripheral symbol-changes, which occurred during saccade planning, reduced latencies in the PD group but not in the control group. Secondly, when saccades were performed with the discrimination task, the latency reduction was greater in the PD group than in the control group (Fig. 2). The discrimination task increased the saccadic gain in both groups, but saccades in the PD group remained abnormally hypometric in comparison with the control group.

Saccade latencies in PD

When we scan the visual field, detailed visual processing occurs during fixation. During these periods, fixation neurons are active and saccade neurons in the SC are inhibited, preventing eye movements and maintaining fixation until the initiation of the next saccade. The end of a period of fixation is marked by the release of attention from the location that is currently fixated, followed by a shift of attention to the location that will be fixated next (Deubel, 2008).

The finding that the PD group initiated voluntary saccades at abnormally long latencies in the baseline condition is consistent with many previous reports (Kennard & Lueck, 1989; Kitagawa *et al.*, 1994; Amador *et al.*, 2006). It is also consistent with the premise that saccade initiation in PD is impaired due to over-activity of inhibitory outputs from the basal ganglia via the substantia nigra pars reticulata (SNr) projection to the SC (Albin *et al.*, 1995; Mink, 1996; Hikosaka *et al.*, 2000). The tonic inhibitory output to the SC must be selectively released to allow burst firing of saccade-triggering cells (Hikosaka & Wurtz, 1985). Nigral dopaminergic innervation of the striatum is crucially involved in generating the signal that suppresses the tonic inhibitory output from the SNr to the SC when a saccade is to be made (Hikosaka *et al.*, 2000; Nakamura & Hikosaka, 2006). Thus, in PD, degeneration of nigral dopamine cells may result in over-activity of the inhibitory output from the SNr, thereby affecting the build-up of neural activity in the SC and delaying the triggering of saccades.

The effect of the symbol-changes

In the PD group, latencies were abnormally reduced by (pre-saccadic) peripheral symbol changes when voluntary saccades were performed without the discrimination task. This observation is consistent with other studies showing that exogenous stimuli can facilitate endogenous saccades (Shepherd *et al.*, 1986). We suggest that peripheral visual events (i.e. the symbol changes in this paradigm) might accelerate saccade initiation in PD by boosting the build-up of neural activity in saccade neurons. This exogenous boost might reduce the delay in the build-up of neural activity in the SC in PD.

The effect of the discrimination task

The PD group exhibited an abnormally large latency reduction when voluntary saccades were made in conjunction with the discrimination task. We suggest that the intention to perform the

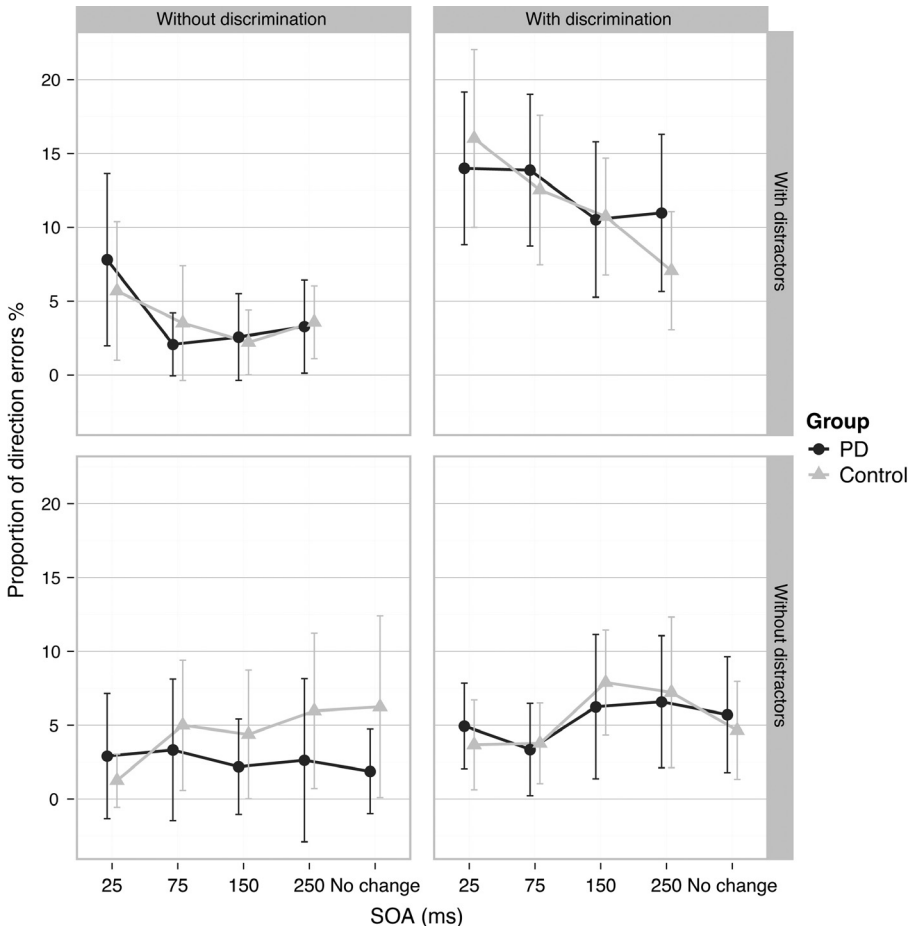

FIG. 3. The proportion of trials with direction errors from the total number of trials with distractors (i.e. in Target/Distractor and Distractor trials) is shown as a function of SOA for trials without the discrimination task in the panel on the left and for trials with the discrimination task in the panel on the right. The percentage of direction errors in No-change trials is shown on the right of each panel for comparison with the trials with distractors. The error bars indicate 95% CI. The discrimination task increased the proportion of errors in trials with distractors, but not in trials without distractors (No-change trials). The frequency of errors and the effect of SOA on the production of errors did not differ between the groups.

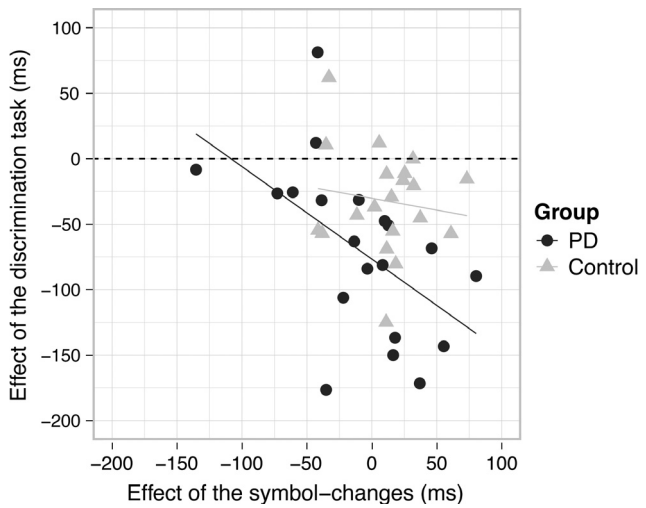

FIG. 4. For each participant the effect of the symbol-changes in trials with the discrimination task is shown on the *x*-axis and the effect of the discrimination task in No-change trials is shown on the *y*-axis. On each axis negative values indicate a latency reduction. In the PD group, larger latency reductions due to the discrimination task (negative values on the *y*-axis) were associated with latency increases due to the peripheral symbol-changes (positive values on the *x*-axis).

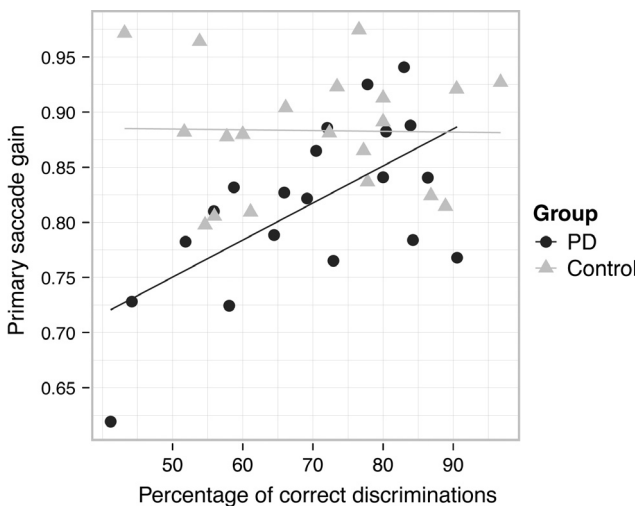

FIG. 5. For each participant the percentage of correct discriminations is shown on the *x*-axis and the mean saccade gain is shown on the *y*-axis. In the PD group worse performance of the discrimination task was associated with smaller saccade gain.

discrimination task promotes the release and shift of attention away from the central fixation point, in preparation for the impending appearance of the discrimination symbol at the peripheral saccade target location. This effect supports and facilitates saccade planning and can thereby reduce saccade latencies (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005).

Previously, we reported that the concurrent performance of a discrimination task abnormally reduced latencies of visually guided (or reflexive) saccades in the same PD group (van Stockum *et al.*, 2011b). Especially in overlap trials, the continued presence of the fixation point apparently did not exert the same inhibitory effect in the PD group as in the control group. We proposed that the abnormal endogenous facilitation of visually guided saccades observed in PD may be associated with a decrease in the inhibition of saccade cells during fixation. The results from the present study – voluntary saccades, cued by a central arrow, were also abnormally facilitated by the discrimination task in the PD group – are consistent with that interpretation. In this task, attention remains focused on the central fixation point while participants wait for the onset of the arrow cue, but shortly after the arrow appears attention should be released from the fixation area in preparation for the onset of the discrimination symbol at the cued location. For participants in the PD group, this endogenously promoted release of attention appeared to greatly facilitate the triggering of saccades (voluntary as well as reflexive saccades). The abnormal magnitude of the facilitatory effect of the discrimination task in the PD patients was not simply due to their longer latencies at baseline: baseline latencies were not associated with the magnitude of the latency reduction in the discrimination task in either group. Facilitation and impaired attentional control has been observed also in an animal model of dopamine depletion in PD, where attentional deficits in MPTP-treated monkeys were reversed when attention was enhanced by spatial cueing (Decamp & Schneider, 2004; Decamp *et al.*, 2004).

Abnormal facilitation of saccades in PD has previously been observed mainly as an increase in unintended reflexive saccades in anti-saccade or memory-guided saccade tasks, and has been interpreted as evidence of impaired voluntary control (Chan *et al.*, 2005; Amador *et al.*, 2006; Terao *et al.*, 2011). However, some studies also report a decrease in latencies or an increase in the production of express saccades in PD in saccade tasks, which do not require the voluntary suppression of reflexive saccades (Kingstone *et al.*, 2002; Chan *et al.*, 2005; Gurvich *et al.*, 2007; van Stockum *et al.*, 2008). Chan *et al.* (2005) acknowledged the possibility that, rather than a 'frontal' deficit, hyper-reflexivity might reflect an adaptive mechanism in PD. Our results are consistent with this proposal. The reduction in saccade latencies promoted by the attentional demands of the discrimination task might reflect a decrease in the lateral inhibition exerted by saccade neurons during fixation, which compensates for the delay in the build-up of saccade-triggering neural activity in the SC in PD. Interestingly, when PD subjects endogenously shortened their saccade latencies in response to the demands of the discrimination task the peripheral symbol-changes did not further reduce latencies.

Together, the results from our investigations of reflexive and voluntary saccades suggest that PD might affect the saccade system globally. Besides impaired initiation of saccades there may be a reduction in fixation-related neural inhibition, which may go unnoticed in standard saccade tasks, where it can be masked by a delay in saccade initiation.

Saccade gain in PD

The discrimination task increased the gain of saccades in both groups, but saccades remained hypometric in the PD group compared with the controls. Some models of saccade generation make a distinction between the 'when' and the 'where' systems of saccade control, in which saccade latencies and gain are determined by different neural processes (Findlay & Walker, 1999). The 'when' system, which determines saccade latency, reflects directly the build-up of activity in saccade neurons in the intermediate layer of the SC. The 'where' system, which determines saccade gain, reflects patterns of neural activity across multiple brainstem structures during saccade execution. It is therefore not surprising that the discrimination task abnormally affected only saccade latency in the PD group. The release of attention promoted by the demands of the discrimination task may directly change only the excitability of saccade-triggering neurons in the SC. The association of smaller mean saccade gain with worse performance of the discrimination task in the PD group is consistent with the suggestion that the amount of pre-saccadic visual processing at the saccade target location determines the spatial accuracy of saccades (Findlay, 1982; Findlay & Walker, 1999). Thus, in PD saccadic hypometria may be associated with a deficit in pre-saccadic visual processing.

Directional errors

PD patients often have difficulty ignoring distracting visual stimuli in tasks where endogenous attentional selection competes with visual inputs (Deijen *et al.*, 2006; Machado *et al.*, 2009). Although our paradigm induced two types of abnormal saccadic facilitation in our PD group – one endogenous and another exogenous – the number of directional errors generated in the PD group did not differ from the control group. The performance of the discrimination task induced both groups to make more directional errors, but only in trials with symbol-changes at non-target locations. We propose that a premature release of attention from fixation, induced by the intention to perform the discrimination task, allowed the peripheral symbol-changes to trigger a number of inappropriate saccades in both groups. The frequency of these directional errors depended on the timing of the symbol-change (the SOA): fewer errors were made in trials with longer SOAs. This suggests that the triggering of a directional error was less likely if the symbol-change occurred at a time when the saccade target selection process was further advanced. The similarity of the slopes of this effect in the PD and the control group suggests that the time course of the target selection process is normal in PD at least in this paradigm.

The saccade system in PD

Others have recently proposed neurophysiological explanations for the apparently contradictory changes in the saccade system observed in PD (hyper-reflexivity, together with impaired saccade initiation). Chambers & Prescott (2010) proposed that in PD fixation-related inhibition in the SC might decay abnormally quickly and Terao *et al.* (2011) proposed that pathological oscillatory firing patterns in the subthalamic nucleus or in basal ganglia-cortical loops might cause abnormal fluctuations in activity levels in the SC (Brown, 2006). These fluctuations could render inhibition in the saccade system 'leaky' and account for periodic disinhibition of the saccade system. Our suggestion of abnormal facilitation of saccade triggering due to a reduction in fixation-related neural inhibition in the saccade system is consistent with both proposals. It is not clear where the observed facilitation may originate. While pathological SNr outputs directly affect neuronal activity levels in the SC, abnormal facilitation may originate in other components of the saccade system beyond the basal

ganglia and SC, such as the frontal and supplementary eye fields, which play a role in the control of eye movements and fixation.

Compensatory or pathological facilitation?

We suggest that for some PD patients, the attentional demands of the discrimination task put the saccade system in an abnormal state of high alert. This effect may result from nigrostriatal degeneration and dopamine depletion, it may reflect a compensatory mechanism that occurs secondary to pathology in PD, or it could be a medication-induced effect. The observation that other PD patients were less susceptible to this endogenous facilitation could reflect a difference in disease progression or a difference in disease type. In PD, fronto-striatal activity is expected to decrease over the course of the disease. As long as frontal processes are intact, the SC might be abnormally susceptible to facilitation when attentional demands are high, to compensate for or to mask the effects of dopamine depletion in the saccade system. With the progression of the disease, the ability to compensate might be impaired or lost, and the inhibitory effects of PD in the saccade system might be revealed. In this context, it may also be relevant that D1 and D2 antagonists in the caudate had opposite effects on top-down modulation of saccade latencies in monkeys (Nakamura & Hikosaka, 2006). Another related possibility is that the combination of impaired saccade triggering and abnormal saccadic facilitation in PD is associated with an imbalance between dopaminergic and cholinergic neural systems (Calabresi *et al.*, 2006).

Conclusion

Our results indicate that saccade initiation is impaired globally in PD but that two facilitatory effects can alleviate or mask this deficit. Saccade initiation in PD can be abnormally facilitated when attentional demands are high and saccade latencies can also be abnormally reduced by peripheral visual events. Together, these two effects illustrate the complementary functions of endogenous and exogenous processes in the saccade system: when saccade initiation is facilitated endogenously, it is not likely that visual events can further reduce latencies. These results may also clarify inconsistent findings regarding saccade initiation in PD. In reflexive saccade tasks, the sudden appearance of a peripheral saccade target may alleviate problems with saccade initiation and normalize mean latencies of visually guided saccades in PD. Other saccade tasks may have high attentional demands and require a covert shift of attention to the location of a visual stimulus, revealing saccadic facilitation and apparent hyper-reflexivity.

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Abbreviations

PD, Parkinson's disease; SC, superior colliculus; SNr, substantia nigra pars reticulata; SOA, stimulus onset asynchrony.

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