EJN fens EUROPEAN JOURNAL OF NEUROSCIENCE

European Journal of Neuroscience, Vol. 33, pp. 2091–2100, 2011 doi:10.1111/j.1460-9568.2011.07697.x

A perceptual discrimination task abnormally facilitates reflexive saccades in Parkinson's disease

Saskia van Stockum,[1,2] Michael R. MacAskill,[1,2] Daniel Myall[1] and Tim J. Anderson[1,2,3]
[1]Van der Veer Institute for Parkinson's & Brain Research, 66 Stewart Street, Christchurch, New Zealand
[2]Department of Medicine, University of Otago, Christchurch, New Zealand
[3]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

Keywords: human, Parkinson's disease, saccades, visual attention

Abstract

Numerous studies have shown that Parkinson's disease (PD) affects the ability to generate voluntary saccades and the ability to suppress reflexive saccades. The effects of PD on the generation of reflexive saccades, however, are not clear. Some studies report impairments, but there are also reports of abnormal facilitation or hyper-reflexivity of the saccade system in PD. Meanwhile, it has been reported that the concurrent performance of a perceptual discrimination task facilitates saccade initiation and reduces saccade latencies in healthy subjects [A. Montagnini & L. Chelazzi (2005) *Vis. Res.*, 45, 3391–3401; L. Trottier & J. Pratt (2005) *Vis. Res.*, 45, 1349–1354]. To investigate the circumstances under which the saccade system may appear hyper-reflexive in PD, we compared reflexive saccades with and without a concurrent perceptual discrimination task in 20 PD patients and 20 controls. Without the discrimination task, the PD group produced reflexive saccades at normal latencies. The discrimination task reduced saccade latencies more in the PD group than in the control group, resulting in abnormally short mean reflexive saccade latencies in the PD group. The discrimination task increased saccade gain in both groups, but saccades in the PD group remained hypometric as compared with saccades in the control group. We conclude that the attentional demands of this paradigm revealed a hypersensitivity to visual inputs in the PD group.

Introduction

In Parkinson's disease (PD), the function of the saccadic system is affected by dopamine depletion in the basal ganglia. Impairments in PD have been consistently detected in tasks that require the generation of voluntary saccades, such as delayed, memory-guided or anti-saccade tasks. These tasks require, in addition to the execution of voluntary saccades, the inhibition of reflexive saccades. PD patients' impairments in these tasks include hypometria (the eyes initially land short of the target, and some catch-up steps are required to foveate the intended location) (Lueck *et al.*, 1992; Shaunak *et al.*, 1999; Armstrong *et al.*, 2002; Le Heron *et al.*, 2005), prolonged latencies, and failure to suppress unwanted reflexive saccades towards a visual stimulus (Briand *et al.*, 1999; Armstrong *et al.*, 2002; Chan *et al.*, 2005; Amador *et al.*, 2006; Gurvich *et al.*, 2007). In contrast, reports on the performance of reflexive saccade tasks in PD are inconsistent [see Chambers & Prescott (2010) for a review]. Reflexive saccades are often thought to be normal in PD, but there are also reports of prolonged latency (Chen *et al.*, 1999) and of abnormal facilitation of the reflexive saccadic system (or hyper-reflexivity; Briand *et al.*, 2001; Armstrong *et al.*, 2002; Kingstone *et al.*, 2002; Chan *et al.*, 2005; van Stockum *et al.*, 2008).

The tasks most often used to investigate voluntary saccades involve, in addition to the programming of a voluntary saccade, the suppression of a reflexive saccade. That is, subjects must shift attention to a visual stimulus, without making a saccade to that stimulus. In these paradigms, top-down saccade selection competes with bottom-up visual input. Performance of these tasks will be impaired if top-down control of the saccade system is impaired, but also if bottom-up processes are abnormally active.

Current models of PD propose that progressive degeneration of dopaminergic inputs into the striatum causes overactivity of inhibitory outputs from the basal ganglia via the substantia nigra pars reticulata (SNr) to the superior colliculus and via the thalamus to the cortex (Mink, 1996; Hikosaka *et al.*, 2000). The basal ganglia are crucially involved in the selection of voluntary saccades and in the suppression of unwanted saccades (Hikosaka *et al.*, 2000). Excessive inhibitory output from the basal ganglia in the saccade system in PD is thought to affect the ability to generate voluntary saccades and the ability to suppress unwanted reflexive saccades (Chan *et al.*, 2005; Gurvich *et al.*, 2007; Hood *et al.*, 2007; Cameron *et al.*, 2010). In general, impairments of the saccade system in PD have been interpreted as evidence of a failure of top-down control, owing to disruption of fronto-striatal circuitry. However, it is not clear why hyper-reflexivity is observed only in some studies, and whether hyper-reflexivity (when

Correspondence: S. van Stockum, [1]Van der Veer Institute for Parkinson's & Brain Research, as above.
E-mail: saskia.vanstockum@vanderveer.org.nz

Received 30 November 2010, revised 15 February 2011, accepted 16 March 2011

it does occur) should be attributed to a deficit of top-down control in PD, or to overactivity of bottom-up processes.

To further investigate the circumstances under which the reflexive saccade system may be abnormally facilitated in PD, we adapted an experimental paradigm in which saccades are performed together with a perceptual discrimination task (Deubel, 2008). The instruction to make a perceptual discrimination at the saccade target has been found to facilitate saccade initiation and reduce saccade latencies in healthy subjects (Montagnini & Chelazzi, 2005; Trottier & Pratt, 2005). The combination of a discrimination task with a saccade task allows the investigation of top-down and bottom-up influences in the saccade system, without competition between top-down saccade control and bottom-up visual inputs. Instead of evoking competition, the demands of the discrimination task enhance the performance of the saccade task by promoting a shift of attention to the saccade target. The use of this task also enabled us to investigate the relationship between saccadic and visuospatial attention deficits in PD. Comparison with the study using the original version of this paradigm (Deubel, 2008) will not be appropriate, because that study did not use reflexive saccades, and the saccade task was not performed without the discrimination task.

Materials and methods

Participants

Two groups were recruited: 20 PD patients (eight females) and 20 control subjects (eight females). The groups were matched for mean age and years of education. The mean age in the PD group was 65.0 years, ranging from 50 to 77 years [Hoehn and Yahr (H&Y) score 1–3]. In the control group, the mean age was 65.5 years, ranging from 56 to 76 years. Only subjects who scored 25 or more on the Montreal Cognitive Assessment (Nasreddine *et al.*, 2005) 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 subjects in the PD group were tested 'on' medication. This project received ethical approval from the Upper South A Regional Ethics Committee. All participants gave informed consent. See Table 1 for details of the subjects in the PD group.

Apparatus and stimuli

Eye movements were recorded monocularly with 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 the subject, who sat with the 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 control subjects (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°); targets (0.62° wide × 1° high) were white (R255 G255 B255). Targets appeared at the four corners of an imaginary square, each 5.4° 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 recalibration procedure covering the display area was conducted. 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 with PsychoPy, an open-source experimental-control software package (Peirce, 2007, 2008).

Saccade and perceptual discrimination tasks

The paradigm, adapted from Deubel (2008), is one in which saccades can be performed, with or without a concurrent perceptual discrimination task. In our study, the onset of a figure 8 was used as the cue

Table 1. Details of the subjects in the PD group

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

F, female; M, male; MoCA, Montreal Cognitive Assessment. The MoCA is a general cognitive screening test. The MDS-UPDRS Part III is a scale assessing the motor signs of PD. The H&Y score reflects disease severity in PD.

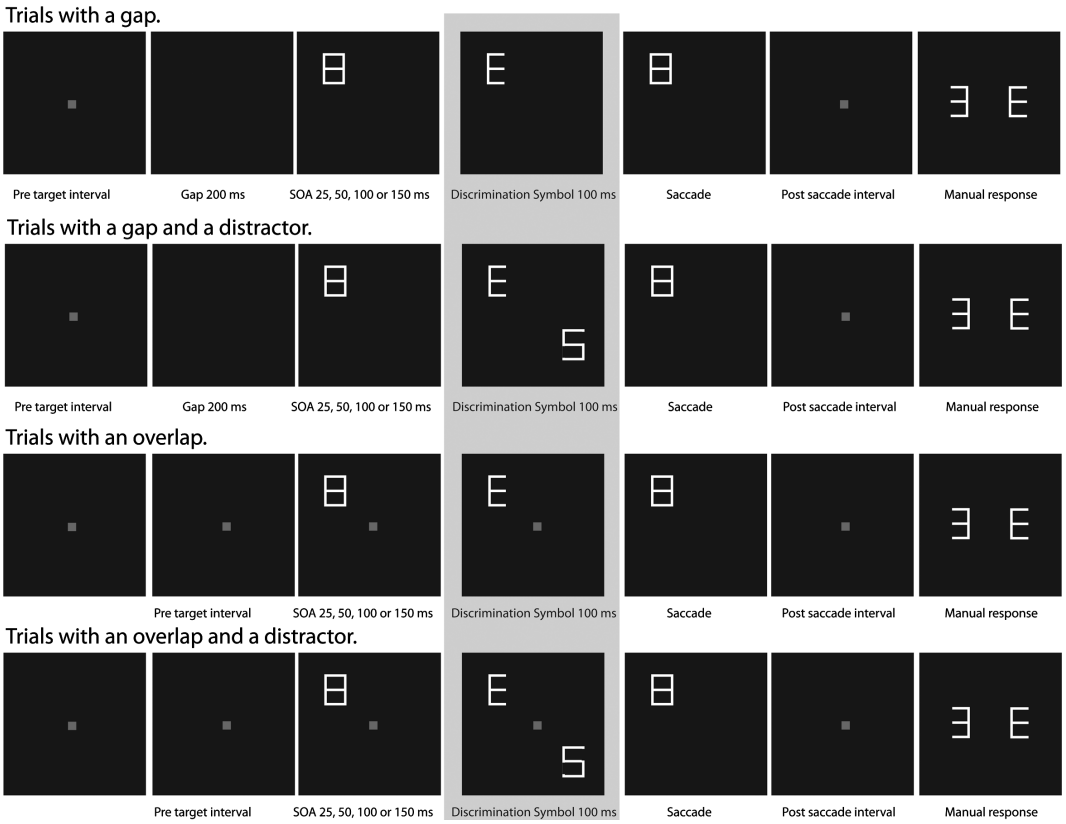

FIG. 1. Schematic illustration of the stimulus display, showing the sequence of events during each trial. Two gap conditions (with a gap and with an overlap) and two trial types (with and without a distractor) were used. In gap trials, the fixation point disappeared 200 ms before target onset, and in overlap trials, the fixation point remained visible until the discrimination symbol at the target location disappeared. In distractor trials, a Figure 2 or 5 appeared at a location diagonally opposite the target location, simultaneously with the appearance of the discrimination symbol at the target location (see the shaded column in the centre). The sequence of events was identical for the saccade task without and the saccade task with the perceptual discrimination task; only the instructions to the subjects differed.

for a reflexive saccade. The perceptual discrimination task required subjects to report the identity of a symbol, which appeared briefly at the target location shortly after target onset. Subjects first performed the saccade task without the perceptual discrimination task. In this condition, the instruction was: 'Move your eyes as quickly as possible to the target'. Subsequently, subjects performed the saccade task with the perceptual discrimination task. In this condition, the instruction was: 'Move your eyes as quickly as possible to the target, and report after each trial whether an E or 3 was displayed'. After making a saccade, subjects responded with a manual button press to indicate whether they had seen an E (right button) or a 3 (left button). Instructions stressed the importance of making a saccade on each trial. Also, it was made clear that it was important to guess an answer even if the subject was not sure which symbol had been displayed, and to push a button at random after trials where the subject thought no symbol had appeared.

Stimulus sequence

Each trial started with a variable fixation interval. Targets consisted of figure 8s, which changed briefly (for 100 ms) into either E or 3 at 25, 50, 100 or 150 ms after target onset [the stimulus onset asynchrony (SOA)]. In gap trials, the fixation point disappeared 200 ms before target onset, and in overlap trials, the fixation point remained until the end of the display of the discrimination symbol. In distractor trials, a

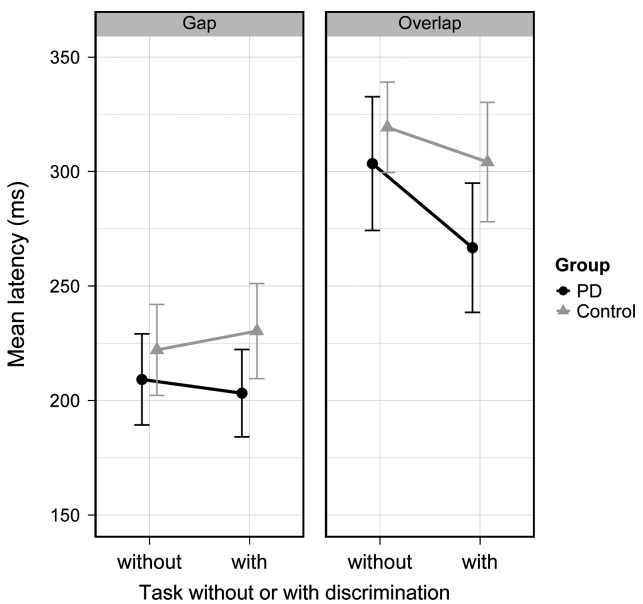

FIG. 2. Mean latencies are shown for saccades, made by each group, with and without a concurrent discrimination task. Gap trials are shown on the left, and overlap trials on the right. The error bars represent 95% confidence intervals. The concurrent performance of the perceptual task reduced saccade latencies more in the PD group than in the control group.

Figures 2 or 5 appeared at the location diagonally opposite the target location for 100 ms, simultaneously with the discrimination symbol onset (Fig. 1). Target locations, gap conditions, trials with and without distractor and the two discrimination symbols were balanced across trial blocks. During each block of trials, three of the four target locations (top right, bottom left, top left, or bottom right) were used at each SOA (25, 50, 100 or 150 ms), in each trial type (with or without distractor) and in each gap condition (gap or overlap). Four different trial blocks were used to balance the target locations used at each SOA. On half of these trials, the discrimination symbol was 3, and on the other half it was E. Interspersed in each block of trials were eight trials with target onsets, but without symbol changes. Each block consisted of 56 trials. For the analysis, the data from all trials were pooled across the four SOAs. The effects of SOA are not relevant to the present report and are not reported here.

Procedure

All subjects attended two testing sessions, 1 week apart. Vision was tested at the start of each session, and corrected to normal with spectacles if necessary. Subjects controlled the timing of the trials by pushing a button to start each new trial only when they were ready, and looking at the central fixation point. Practice trials were presented, allowing subjects to become familiar with the push buttons and the task requirements before the start of the actual test. In the first session, two blocks of trials were performed 'without discrimination', and subjects were told to concentrate on moving their eyes as quickly as possible to the targets. It was explained that they might see something flicker in the display on some trials, but that this was irrelevant to the task. Next, two blocks of trials were performed 'with discrimination'. Now, subjects were asked to pay attention to the symbol changes at the target location, because after each trial they would be asked to identify which symbol (3 or e) was shown. After each of these saccade trials, a prompt appeared on the monitor, asking the subject to report which symbol had appeared. In the second session, two more blocks of trials 'with discrimination' were performed. Each block of trials was presented in a different randomized order.

Measurement and analysis

Latency and gain of the primary saccade (the first saccade following the appearance of the target) were measured off-line. Latency was calculated from the onset of the target. Gain was defined as the absolute amplitude of the saccade divided by the target vector (which was always 5.4°). The eye position trace was searched to find the first instance where the eye velocity reached 80°/s after cue onset. The beginning and end of a primary saccade were determined by searching backwards and forwards in time from this point for the nearest velocity minimum. Trials without evidence of a saccade (because of blinks or no response), with saccades at latencies shorter than 80 ms or longer than 600 ms, or with a gain of less than 0.3 or more than 1.3, were excluded. Trials with saccades initiated at latencies longer than 80 ms, but with directional errors (the primary saccade was not directed at the cued target location), were analysed separately. The proportion of excluded trials did not differ between the control group and the PD group, leaving 83 and 81% of trials for analysis from each group respectively. The proportion of correct discriminations was calculated from the total number of remaining trials with symbol onsets in the blocks of trials with the perceptual discrimination task. Mean latencies and gain of saccades made in the trials with the discrimination task did not differ between the first and the second session in either group, so the results from the two sessions were pooled. Effects of the discrimination task on saccade latency and gain were analysed with linear mixed-effects models. The function *lme* from the R package *nlme* was used to fit the models (Pinheiro, Bates, DebRoy, Sarkar, & Team, 2009). For piecewise linear regression, *bentcableAR* was used (Chiu, 2010).

Results

Latencies

Latencies were analysed with a linear mixed-effects model, with Group as a between-subjects factor (control or PD), and Task (with or without discrimination task), Gap (gap or overlap) and Trial type (with or without distractor) as within-subjects factors. Effects are shown as mean values followed by 95% confidence intervals.

The Gap manipulation had a significant effect on saccade latencies: the overlap condition lengthened mean saccade latency by 97 ms (84, 111) as compared with trials with a gap ($t_{39} = 14.59$, $P < 0.001$). There was also a main effect of Trial type: distractors lengthened mean saccade latency by 29 ms (34, 24) ($t_{159} = 12.25$, $P < 0.001$). Overall, there was a significant interaction between Gap and Task ($F_{1,\ 77} = 10.35$, $P < 0.01$): in trials with a gap, the discrimination task did not affect saccade latencies, but in trials with an overlap, the discrimination task shortened latencies by 29 ms (−47, −11) ($t_{77} = -3.22$, $P < 0.01$). Overall, there was also a significant interaction between Group and Task ($F_{1,\ 77} = 4.56$, $P < 0.05$): the discrimination task reduced latencies more in the PD group than in the control group. No other interactions were significant. Figure 2 shows the effects on saccade latency pooled across trials with and without distractors. The mean latencies of reflexive saccades, in gap and overlap trials, with and without the concurrent discrimination task are shown for each group in Table 2.

Production of express saccades

Proportions of express saccades were compared with a mixed-effects binomial model with Group (control or PD), Task (saccades with or

TABLE 2. Mean saccade latency (ms; 95% confidence interval) in gap and overlap trials, pooled across trials with and trials without a distractor, in which saccades were made with and without the perceptual discrimination task

	Gap trials		Overlap trials	
	Without discrimination	With discrimination	Without discrimination	With discrimination
Control	223 (201, 246)	231 (209, 253)	323 (301, 346)	307 (285, 329)
PD	212 (189, 235)	203 (181, 226)	310 (287, 332)	267 (245, 290)*

*Difference between the groups, $P < 0.05$.

without discrimination task), Gap (gap or overlap) and Trial type (with or without distractor) as factors. There was an effect of Group: the PD group made more express saccades than the control group (14% vs. 5%, $z = 2.16$, $P = 0.03$). There was an effect of Gap: in overlap trials, the proportion of express saccades was smaller than in gap trials ($z = -10.29$, $P < 0.001$). There was also an interaction between Group and Gap. The overlap decreased the production of express saccades more in the control group (from 10 to 1%) than in the PD group (from 21 to 7%; $z = 2.72$, $P < 0.01$). The discrimination task or the distractors did not affect the production of express saccades in either group. Table 3 shows the proportions of express saccades for each group, in trials with and without a distractor, in gap and overlap trials, with and without the discrimination task.

Primary saccade gain

Saccade gain was compared with a linear mixed-effects model, with Group as a between-subjects factor (control or PD), and Task (with or without discrimination task), Gap (gap or overlap) and Trial type (with or without distractor) as within-subjects factors. Effects are shown as mean values followed by 95% confidence intervals. There were main effects of Group, Gap, Trial type and Task on the gain of saccades. The mean gain of saccades in the PD group was 0.10 (−0.15, −0.05) smaller than in the control group ($t_{38} = -4.33$, $P < 0.001$). In overlap trials, saccades were 0.03 (0.01, 0.05) larger than in gap trials ($t_{39} = 3.17$, $P < 0.01$). Distractors decreased mean saccade gain by 0.02 (−0.01, −0.03) ($t_{159} = -4.29$, $P < 0.001$). The discrimination task increased saccade gain by 0.02 (0.001, 0.04) ($t_{77} = 2.06$, $P < 0.05$). There were no significant interactions. Figure 3 shows the effects on saccade gain pooled across trials with and without distractors. Mean gain values of reflexive saccades, in gap and overlap trials, with and without the concurrent discrimination task, are shown for each group in Table 4.

Directional errors

All trials with saccades initiated at latencies between 80 and 600 ms were included in the following analysis. For each subject, the proportion of trials with directional errors (saccades that were not directed at the target location) was calculated. Proportions of directional errors were compared with a mixed-effects binomial model, with Group (control or PD), Gap (gap or overlap), Task (saccades with or without discrimination task) and Trial type (with or without distractor) as factors. There were main effects of Gap, Task, and Trial type. More errors were made in trials with a gap than in trials with an overlap ($z = 4.48$, $P < 0.001$). More errors were made in trials with the discrimination task than in trials without the discrimination task ($z = -2.08$, $P < 0.05$). More errors were made in trials with a distractor than in trials without a distractor ($z = -14.18$, $P < 0.001$). There were no significant interactions. Only 3% of directional errors in trials with distractors were not directed at the distractor location. Table 5 shows the proportions of directional errors for each group in each condition.

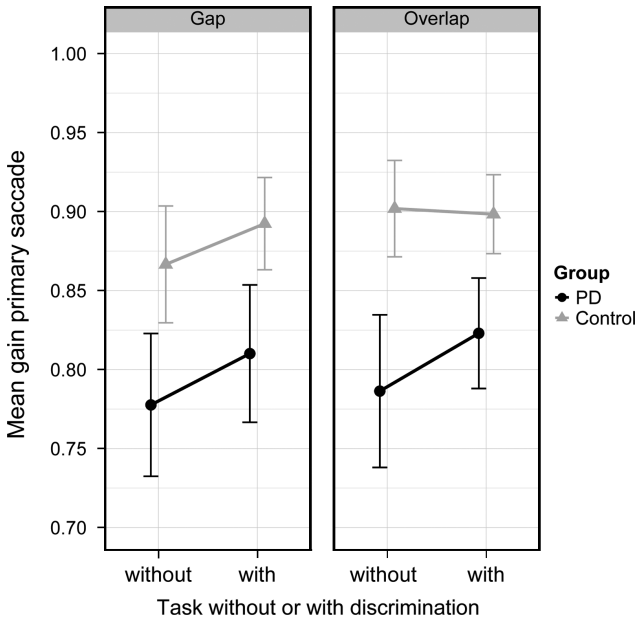

FIG. 3. Mean gain values are shown for primary saccades, made by each group, with and without a concurrent discrimination task. Gap trials are shown on the left, and overlap trials on the right. The error bars represent 95% confidence intervals. The concurrent performance of the perceptual discrimination task resulted in increased saccade gain in the PD group, but saccades remained hypometric as compared with the control group.

Perceptual discrimination task

Proportions of correct judgements were compared with a mixed-effects binomial model, with Group (control or PD), Gap (gap or overlap) and Trial type (with or without distractor) as factors. There was a main effect of Group. The control group made more correct judgements than the PD group (79% vs. 68%, $z = -3.00$, $P < 0.01$). There was also a main effect of Trial type: fewer correct judgements were made in trials with a distractor than in trials without a distractor ($z = -2.31$, $P = 0.02$). There were no significant interactions. Table 6 shows the proportion of correct discrimination judgements in each group.

TABLE 3. Proportion of express saccades (%) in the tasks with and without the concurrent discrimination task in trials with and in trials without a distractor in each group

	Without distractor				With distractor			
	Without discrimination		With discrimination		Without discrimination		With discrimination	
	Gap	Overlap	Gap	Overlap	Gap	Overlap	Gap	Overlap
Control	9	1	9	2	12	1	9	1
PD	20	7*	21*	9*	24	5	21	8*

*Difference between the groups, $P < 0.05$.

The proportion of trials in which the saccade was initiated before, during or after the display of the discrimination symbol was calculated for each group. These proportions did not differ between the groups. Table 7 shows these proportions, together with the proportion of correctly identified discrimination symbols in each category.

Association between saccade production and discrimination performance

In the control group, the performance of the discrimination task was associated with mean saccade latency: subjects who had longer mean saccade latencies made more correct discrimination judgements ($r = 0.52$, $P < 0.01$). In the PD group, the performance of the discrimination task was associated with mean saccade gain: subjects who had larger mean gain values made more correct discrimination judgements ($r = 0.57$, $P < 0.01$); see Fig. 4.

Association between saccade latency and gain

In both groups, longer latencies resulted in saccades with higher gain values, but only when saccades were initiated at relatively short latencies. A piece-wise linear model showed that, on average, gain increased linearly with latency, until, by a latency of 176 ms, gain remained constant (Fig. 5). Two separate mixed-effects models were used to test effects on the gain of short-latency (below 176 ms) saccades and of long-latency (over 176 ms) saccades. For saccades with latencies below 176 ms, there were main effects of Latency, Group, and Task. Overall, for saccades initiated at latencies below 176 ms, gain increased from the intercept at 0.57 by 0.03 (0.02, 0.04) per 10 ms of increase in latency ($t_{1641} = 7.49$, $P < 0.001$). The PD group made saccades at latencies below 176 ms that were 0.06 (0.13, 0.005) smaller than in the control group ($t_{38} = 2.33$, $P = 0.03$). Overall, the concurrent performance of the perceptual discrimination task increased saccade gain by 0.04 (0.01, 0.07) ($t_{64} = 2.51$, $P = 0.01$). No interactions were significant.

When the gain of saccades with latencies longer than 176 ms was analysed, the main effect of Group remained: the mean gain value of these longer-latency saccades in the PD group was 0.06 (0.10, 0.01) smaller than in the control group ($t_{38} = -3.77$, $P < 0.001$). In contrast to the gain of short-latency saccades, the gain of saccades with latencies longer than 176 ms basically remained constant, and increased by only 0.0007 (0.0005, 0.0013) per 10 ms of latency. Overall, gain was only marginally increased by the perceptual

TABLE 4. Mean saccade gain (95% confidence interval) in gap and overlap trials, pooled across trials with and trials without a distractor, in which saccades were made with and without the perceptual discrimination task

	Gap trials		Overlap trials	
	Without discrimination	With discrimination	Without discrimination	With discrimination
Control	0.86 (0.83, 0.90)	0.89 (0.86, 0.92)	0.90 (0.87, 0.94)	0.90 (0.86, 0.93)
PD	0.77 (0.73, 0.81)*	0.81 (0.77, 0.84)*	0.79 (0.76, 0.83)*	0.81 (0.78, 0.85)*

*Difference between the groups, $P < 0.01$.

TABLE 5. Proportion of directional errors (%) in the task with and without the concurrent discrimination task in trials with and in trials without a distractor in each group

	Without distractor				With distractor			
	Without discrimination		With discrimination		Without discrimination		With discrimination	
	Gap	Overlap	Gap	Overlap	Gap	Overlap	Gap	Overlap
Control	0	0	1	1	12	5	15	7
PD	0	0	1	1	11	7	14	12*

*Difference between the groups, $P < 0.05$.

TABLE 6. Proportion of correct judgements (%; 95% confidence interval) in trials with and trials without a distractor in each group

	Gap trials		Overlap trials	
	Without distractor	With distractor	Without distractor	With distractor
Control	82 (74, 89)	76 (69, 84)	83 (77, 89)	75 (66, 84)
PD	72 (67, 78)*	64 (57, 71)*	69 (64, 74)**	67 (59, 76)

*Difference between the groups, $P < 0.05$. **Difference between the groups, $P < 0.01$.

TABLE 7. Proportions of trials with saccade initiation before, during or after discrimination symbol onset and the proportion of correct perceptual discriminations in each category

	Saccade before symbol onset	Saccade during symbol onset	Saccade after symbol onset
Control	2% (86% correct)	12% (79% correct)	86% (78% correct)
PD	5% (83% correct)	16% (67% correct)	79% (69% correct)

discrimination task ($t_{78} = 1.91$, $P = 0.06$). This effect was mainly attributable to a significant Group × Task interaction. The discrimination task increased the gain of saccades 0.03 (0.002, 0.05) more in the PD group than in the control group ($t_{77} = 2.00$, $P < 0.05$). No other interactions were significant.

Short-latency and long-latency saccades

Without the perceptual task, subjects in the PD group made, on average, 30% of all saccades at latencies below 176 ms. This proportion was 36% when saccades were made with the discrimination task. The control group made only 20% of all saccades at latencies below 176 ms, and the perceptual task did not change this proportion. The proportions of short-latency saccades differed between the groups in the trials with the discrimination task ($t_{35} = -2.62$, $P = 0.01$). Figure 5 shows the association of saccade latency and gain for each group in two-dimensional density plots.

Discussion

The effect of a perceptual discrimination task on the production of reflexive saccades was assessed in a group of people with PD and a control group. The discrimination task reduced saccade latencies more in the PD group than in the control group, resulting in abnormally short mean reflexive saccade latencies in the PD group (Figs 2 and 5). The discrimination task increased saccade gain in both groups, but saccades in the PD group were still abnormally hypometric as compared with the control group (Fig. 3). Also, the performance of the perceptual discrimination task was impaired in the PD group as compared with the control group.

The latency of reflexive saccades in PD

The initiation of reflexive saccades at abnormally short latencies (or hyper-reflexivity) in the PD group is consistent with previous reports of abnormal facilitation of the reflexive saccade system in PD (Briand *et al.*, 2001; Armstrong *et al.*, 2002; Kingstone *et al.*, 2002; Chan *et al.*, 2005; van Stockum *et al.*, 2008). In our paradigm, the reduction of saccade latencies in the PD group resulted from top-down facilitation of the saccade system, in response to the attentional demands of the discrimination task. The mean latency of reflexive saccades was abnormally reduced in the PD group, especially in trials with an overlap. This observation is consistent with the result of a recent comprehensive meta-analysis of investigations of reflexive saccade latency in PD (Chambers & Prescott, 2010). This meta-analysis concluded that overall latencies of reflexive saccades are prolonged in PD, except in overlap paradigms and for targets at eccentricities of 5° and smaller (Chambers & Prescott, 2010). Chambers and Prescott's hypothesis regarding the underlying neural cause of this phenomenon involves altered retinal inputs into the superior colliculus resulting from dopamine depletion in PD. This interpretation, however, does not explain the abnormal reduction of saccade latencies caused by task demands in the PD group in our study. The association of short saccade latencies with smaller gain values of reflexive saccades was the same in both groups.

The gain of reflexive saccades in PD

Despite the reduction in latencies, members of the PD group were able to increase the mean gain of their reflexive saccades in the discrimination task. However, overall reflexive saccades remained hypometric in our PD group as compared with the control group. Many investigations have found that, in contrast to the gain of voluntary saccades, gain values of reflexive saccades are normal in PD (Crawford *et al.*, 1989; Lueck *et al.*, 1992; Vidailhet *et al.*, 1994; Shaunak *et al.*, 1999). However, our results are consistent with some

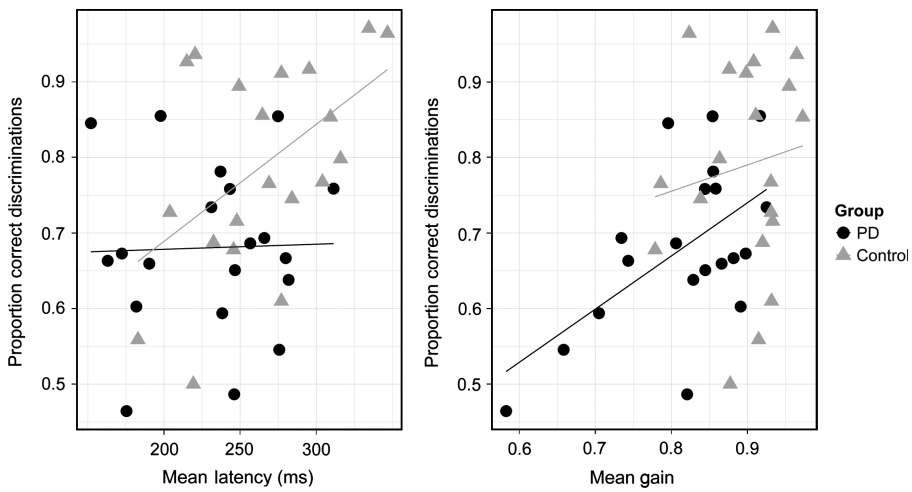

FIG. 4. The scatterplot on the left shows the mean saccade latency on the *x*-axis and the proportion of correct discriminations for each subject on the *y*-axis. The scatterplot on the right shows the mean saccade gain on the *x*-axis and the proportion of correct discriminations for each subject on the *y*-axis. In the control group, better performance in the discrimination task was associated with longer mean latencies. In the PD group, better performance in the discrimination task was associated with larger mean saccade gain values.

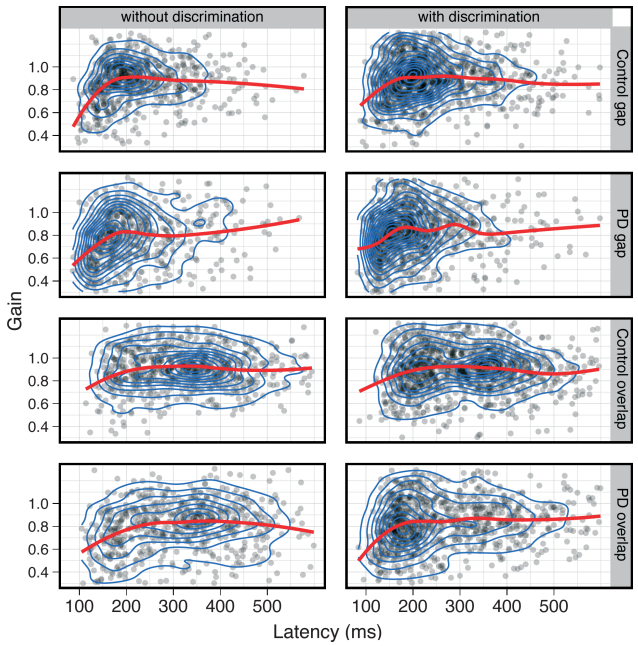

FIG. 5. These two-dimensional density plots illustrate the effect of the discrimination task on saccade latencies and gain in the PD and control groups. Each dot represents one saccade, with the latency shown on the *x*-axis and the gain on the *y*-axis. The plots in the column on the left represent saccade trials without the discrimination task. The plots in the column on the right represent saccade trials with the discrimination task. The top two rows show trials with an overlap, and the bottom two rows show trials with a gap. The red lines show the association between gain and latency. The blue contour lines show areas of equal frequency. Where the lines are close together, the frequency changes rapidly, and where the lines are further apart, the frequency changes more slowly. For saccades with latencies below 176 ms, gain increased with increasing latencies, but at latencies longer than 176 ms, saccades did not further increase in gain. The discrimination task promoted the production of saccades at latencies below 176 ms in the PD group, especially in the overlap trials. In contrast, in the overlap trials, the control group produced a bimodal latency distribution, with a larger proportion of responses at latencies over 176 ms than the PD group.

previous reports of hypometric reflexive saccades in PD (White *et al.*, 1983; Rascol *et al.*, 1989; Nakamura *et al.*, 1991; Rottach *et al.*, 1996; Armstrong *et al.*, 2002). Saccadic hypometria in PD has been attributed to striatal dopamine depletion and excessive inhibition in the saccade system, but there is no strong evidence that levodopa therapy improves saccade gain in PD (Nachev & Kennard, 2005).

Top-down effects

In tasks where visual input competes with top-down attentional selection, people with PD often have difficulty in ignoring irrelevant visual stimuli (Deijen *et al.*, 2006; Machado *et al.*, 2009). In our paradigm, the distractor onsets, which occurred on a proportion of trials, may have induced top-down inhibition, as subjects tried to avoid distraction by the irrelevant onsets. However, the distractors affected the performance of the two tasks equally in both groups, and there was no evidence that subjects in the PD group were more susceptible to the appearance of the distractors than subjects in the control group. Top-down inhibition, induced by the distractor onsets, would have competed with the task's instructions, because the correct performance of the task depended on subjects responding as quickly as possible to the target onset. Instead, the instructions in this paradigm may have induced subjects to prepare for the onset of the target and the discrimination symbol by increasing the size of the 'attentional window' from the fixation area to encompass the potential target locations. The top-down strategy, to disengage attention from the fixation area before target onset, revealed abnormal facilitation of the saccade system in the PD group. The finding that this facilitation was most obvious in the overlap condition suggests that it may be associated with a reduction of fixation-related inhibition in the saccade system. In turn, reduced fixation-related inhibition may render the oculomotor system hypersensitive to visual inputs in PD. This interpretation is also consistent with reports of increased bottom-up distractibility without impaired top-down distractor inhibition in PD and aged subjects (Langley *et al.*, 1998; Troche *et al.*, 2006). It could be proposed, consistent with the traditional assumption that saccade deficits in PD reflect a failure of top-down control mechanisms, that subjects in the PD group were not able to use fixation-related inhibition to control the initiation of saccades in the discrimination task. However, subjects in the control group did not increase their latencies in the discrimination task, but they reduced their saccade latencies in overlap trials, and this effect was enhanced in the PD group.

Association of saccade latency, gain, and perceptual discrimination

In the PD group, the perceptual discrimination task facilitated the initiation of saccades more than in the control group, but the performance of the discrimination task was worse than in the control group. In both groups, the gain of saccades initiated at latencies shorter than 176 ms depended strongly on latency: shorter saccade latency was associated with smaller saccade gain. In the control group, better performance in the discrimination task was associated with longer mean latency, but in the PD group, better performance in the discrimination task was associated with larger mean gain values. Together, these results are consistent with previous studies showing that longer saccade latencies allow better pre-saccadic visual processing of the target stimulus and ensure better spatial accuracy of the eye movement (Findlay, 1982; Findlay & Walker, 1999). If saccades are triggered at very short latencies, not only the processing of visual information at the target location but also the gain of the saccade may be reduced (Ottes *et al.*, 1985; Coeffe & O'Regan, 1987). This suggests that, in PD, hypometria of saccades may be associated with impaired processing of visual information at the saccade target location. In the PD group, the build-up of neural activity in the oculomotor system during saccade latency may have been insufficient to produce spatially accurate saccades or to allow efficient perceptual discrimination.

Neurophysiology of the saccadic system in PD

From neurophysiology studies in monkeys, we know that saccades are triggered when saccade neurons in the superior colliculus and the frontal eye fields reach a threshold level of activity (Everling *et al.*, 1998). The basal ganglia are preferentially involved in the initiation of voluntary saccades and in the prevention of unwanted saccades (Hikosaka *et al.*, 2000). Basal ganglia output contributes to the control of the saccade system by exerting a constant tonic inhibition via the SNr. When a saccade is to be made, a striatal signal selectively releases this neural inhibition in the saccade system via the direct pathway that connects the striatum directly with the SNr. Striatal dopamine depletion interferes with this function, and results in excessive inhibition (impaired release of inhibition) in the saccade system. During fixation, when saccades must be suppressed, the inhibitory output from the basal ganglia is enhanced via the indirect

pathway that connects the striatum with the SNr via the external capsule of the globus pallidus and the subthalamic nucleus, and neural activity in the saccade system is further suppressed (Hikosaka *et al.*, 2000). Together, these mechanisms allow the saccade system to select appropriate saccades before any unwanted saccades are triggered. In PD, abnormally slow generation of voluntary saccades and abnormally fast triggering of reflexive saccades may reflect pathological changes in the direct and the indirect pathways, respectively. PD and/or its treatment may affect the ability to suppress neural activity in the saccade system during fixation, which is normally associated with enhanced output from the SNr via the indirect pathway. This interpretation is consistent with reports of impaired control of fixation in PD (Fielding *et al.*, 2006; Pinnock *et al.*, 2010).

Conclusion

We attribute the observed reduction of saccade latencies and the increase in saccade gain in the PD group to a top-down effect in response to the demands of the discrimination task. This effect revealed a source of abnormal facilitation of the saccadic system in the PD group. In the PD group, saccade latencies were abnormally short, and proportions of express saccades and direction errors were increased, when saccades were made in conjunction with the discrimination task, especially in overlap trials. The triggering of saccades at abnormally short latencies, especially in overlap trials, may reflect impairment of fixation-related inhibition in the saccade system in PD, which would result in an enhanced oculomotor response to visual inputs. In our paradigm, this enhanced response to visual inputs promoted the initiation of saccades at short latencies, but it did not benefit the performance of the discrimination task in the PD group. Diminished fixation-related inhibition may be a direct result of pathology or a compensatory mechanism in PD. A potentially enhanced response to visual inputs is consistent with converging evidence that, in PD, the allocation of visual attention may be abnormally dominated by salient visual inputs. This phenomenon has been observed in various paradigms, for instance in a set shifting task (Cools *et al.*, 2010), a pro-anti-saccade switching task (Cameron *et al.*, 2010), a manual response task (Deijen *et al.*, 2006), a cueing task (Seiss & Praamstra, 2006), and a saccade task with distractors (Machado *et al.*, 2009). This type of facilitation may adversely affect the performance of saccade tasks where visual input competes with top-down saccade selection, such as an anti-saccade task, whereas it may enhance the performance of saccade tasks such as the paradigm used in this study, where visual input reinforces top-down saccade selection.

Acknowledgements

The authors would like to thank the reviewers for commenting on earlier versions of the manuscript. S.v.S. was supported by a New Zealand TEC Scholarship.

Abbreviations

H&Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; SNr, substantia nigra pars reticulata; SOA, stimulus onset asynchrony.

References

Amador, S.C., Hood, A.J., Schiess, M.C., Izor, R. & Sereno, A.B. (2006) Dissociating cognitive deficits involved in voluntary eye movement dysfunctions in Parkinson's disease patients. *Neuropsychologia*, **44**, 1475–1482.

Armstrong, I.T., Chan, F., Riopelle, R.J. & Munoz, D.P. (2002) Control of saccades in Parkinson's disease. *Brain Cognit.*, **49**, 198–201.

Briand, K.A., Strallow, D., Hening, W., Poizner, H. & Sereno, A.B. (1999) Control of voluntary and reflexive saccades in Parkinson's disease. *Exp. Brain Res.*, **129**, 38–48.

Briand, K.A., Hening, W., Poizner, H. & Sereno, A.B. (2001) Automatic orienting of visuospatial attention in Parkinson's disease. *Neuropsychologia*, **39**, 1240–1249.

Cameron, I.G., Watanabe, M., Pari, G. & Munoz, D.P. (2010) Executive impairment in Parkinson's disease: response automaticity and task switching. *Neuropsychologia*, **48**, 1948–1957.

Chambers, J.M. & Prescott, T.J. (2010) Response times for visually guided saccades in persons with Parkinson's disease: a meta-analytic review. *Neuropsychologia*, **48**, 887–899.

Chan, F., Armstrong, I.T., Pari, G., Riopelle, R.J. & Munoz, D.P. (2005) Deficits in saccadic eye-movement control in Parkinson's disease. *Neuropsychologia*, **43**, 784–796.

Chen, Y.F., Chen, T. & Tsai, T.T. (1999) Analysis of volition latency on antisaccadic eye movements. *Med. Eng. Phys.*, **21**, 555–562.

Chiu, G. (2010) *CSIRO Mathematics, Informatics and Statistics bentcableAR: Bent-Cable Regression for Independent Data or Autoregressive Time Series, R package version 0.2.3*. Available online at http://cran.r-project.org/web/packages/bentcableAR.

Coeffe, C. & O'Regan, J.K. (1987) Reducing the influence of non-target stimuli on saccade accuracy: predictability and latency effects. *Vis. Res.*, **27**, 227–240.

Cools, R., Rogers, R., Barker, R.A. & Robbins, T.W. (2010) Top-down attentional control in Parkinson's disease: salient considerations. *J. Cogn. Neurosci.*, **22**, 848–859.

Crawford, T., Henderson, L. & Kennard, C. (1989) Abnormalities of nonvisually-guided eye movements in Parkinson's disease. *Brain*, **112**(Pt 6), 1573–1586.

Deijen, J.B., Stoffers, D., Berendse, H.W., Wolters, E. & Theeuwes, J. (2006) Abnormal susceptibility to distracters hinders perception in early stage Parkinson's disease: a controlled study. *BMC Neurol.*, **6**, 43.

Deubel, H. (2008) The time course of presaccadic attention shifts. *Psychol. Res.*, **72**, 630–640.

Everling, S., Pare, M., Dorris, M.C. & Munoz, D.P. (1998) Comparison of the discharge characteristics of brain stem omnipause neurons and superior colliculus fixation neurons in monkey: implications for control of fixation and saccade behavior. *J. Neurophysiol.*, **79**, 511–528.

Fielding, J., Georgiou-Karistianis, N. & White, O. (2006) The role of the basal ganglia in the control of automatic visuospatial attention. *J. Int. Neuropsychol. Soc.*, **12**, 657–667.

Findlay, J.M. (1982) Global visual processing for saccadic eye movements. *Vis. Res.*, **22**, 1033–1045.

Findlay, J.M. & Walker, R. (1999) A model of saccade generation based on parallel processing and competitive inhibition. *Behav. Brain Sci.*, **22**, 661–674; discussion 674–721.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Schrag, A., Teresi, J.A., van Hilten, J.J. & LaPelle, N. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov. Disord.*, **23**, 2129–2170.

Gurvich, C., Georgiou-Karistianis, N., Fitzgerald, P.B., Millist, L. & White, O.B. (2007) Inhibitory control and spatial working memory in Parkinson's disease. *Mov. Disord.*, **22**, 1444–1450.

Hikosaka, O., Takikawa, Y. & Kawagoe, R. (2000) Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol. Rev.*, **80**, 953–978.

Hood, A.J., Amador, S.C., Cain, A.E., Briand, K.A., Al-Refai, A.H., Schiess, M.C. & Sereno, A.B. (2007) Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **78**, 565–570.

Kingstone, A., Klein, R., Morein-Zamir, S., Hunt, A., Fisk, J. & Maxner, C. (2002) Orienting attention in aging and Parkinson's disease: distinguishing modes of control. *J. Clin. Exp. Neuropsychol.*, **24**, 951–967.

Langley, L.K., Overmier, J.B., Knopman, D.S. & Prod'Homme, M.M. (1998) Inhibition and habituation: preserved mechanisms of attentional selection in aging and Alzheimer's disease. *Neuropsychology*, **12**, 353–366.

Le Heron, C.J., MacAskill, M.R. & Anderson, T.J. (2005) Memory-guided saccades in Parkinson's disease: long delays can improve performance. *Exp. Brain Res.*, **161**, 293–298.

Lueck, C.J., Crawford, T.J., Henderson, L., Van Gisbergen, J.A., Duysens, J. & Kennard, C. (1992) Saccadic eye movements in Parkinson's disease: II.

Remembered saccades – towards a unified hypothesis? *Q. J. Exp. Psychol. A Hum. Exp. Psychol.*, **45**, 211–233.
Machado, L., Devine, A. & Wyatt, N. (2009) Distractibility with advancing age and Parkinson's disease. *Neuropsychologia*, **47**, 1756–1764.
Mink, J.W. (1996) The basal ganglia: focused selection and inhibition of competing motor progammes. *Prog. Neurobiol.*, **50**, 381–425.
Montagnini, A. & Chelazzi, L. (2005) The urgency to look: prompt saccades to the benefit of perception. *Vis. Res.*, **45**, 3391–3401.
Nachev, P. & Kennard, C. (2005). Oculomotor dysfunction. In Pfeiffer, R.F. & Bodis-Wollner, I. (Eds.), *Parkinson's Disease and Nonmotor Dysfunction*. Humana Press, Totowa, NJ, pp. 271–280.
Nakamura, T., Kanayama, R., Sano, R., Ohki, M., Kimura, Y., Aoyagi, M. & Koike, Y. (1991) Quantitative analysis of ocular movements in Parkinson's disease. *Acta Otolaryngol. Suppl.*, **481**, 559–562.
Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L. & Chertkow, H. (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.*, **53**, 695–699.
Ottes, F.P., Van Gisbergen, J.A. & Eggermont, J.J. (1985) Latency dependence of colour-based target vs nontarget discrimination by the saccadic system. *Vis. Res.*, **25**, 849–862.
Peirce, J.W. (2007) PsychoPy – psychophysics software in Python. *J. Neurosci. Methods*, **162**, 8–13.
Peirce, J.W. (2008) Generating stimuli for neuroscience using PsychoPy. *Front. Neuroinformatics*, **2**, 10.
Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D. & Team. (2009) *nlme: Linear and Nonlinear Mixed Effects Models, R package version 3.1-96*. Available online at: http://cran.r-project.org/web/packages/nlme.
Pinnock, R.A., McGivern, R.C., Forbes, R. & Gibson, J.M. (2010). An exploration of ocular fixation in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. *J. Neurol.*, **257**, 533–539.
Rascol, O., Clanet, M., Montastruc, J.L., Simonetta, M., Soulier-Esteve, M.J., Doyon, B. & Rascol, A. (1989) Abnormal ocular movements in Parkinson's disease. Evidence for involvement of dopaminergic systems. *Brain*, **112**(Pt 5), 1193–1214.
Rottach, K.G., Riley, D.E., DiScenna, A.O., Zivotofsky, A.Z. & Leigh, R.J. (1996) Dynamic properties of horizontal and vertical eye movements in parkinsonian syndromes. *Ann. Neurol.*, **39**, 368–377.
Seiss, E. & Praamstra, P. (2006) Time-course of masked response priming and inhibition in Parkinson's disease. *Neuropsychologia*, **44**, 869–875.
Shaunak, S., O'Sullivan, E., Blunt, S., Lawden, M., Crawford, T., Henderson, L. & Kennard, C. (1999) Remembered saccades with variable delay in Parkinson's disease. *Mov. Disord.*, **14**, 80–86.
van Stockum, S., MacAskill, M., Anderson, T. & Dalrymple-Alford, J. (2008) Don't look now or look away: two sources of saccadic disinhibition in Parkinson's disease? *Neuropsychologia*, **46**, 3108–3115.
Troche, S.J., Trenkwalder, C., Morelli-Canelo, M., Gibbons, H. & Rammsayer, T.H. (2006) Unimpaired negative but enhanced positive priming in Parkinson's disease: evidence from an identity and a location priming task. *Neuropsychologia*, **44**, 1811–1821.
Trottier, L. & Pratt, J. (2005) Visual processing of targets can reduce saccadic latencies. *Vis. Res.*, **45**, 1349–1354.
Uc, E.Y., Rizzo, M., Anderson, S.W., Qian, S., Rodnitzky, R.L. & Dawson, J.D. (2005) Visual dysfunction in Parkinson disease without dementia. *Neurology*, **65**, 1907–1913.
Vidailhet, M., Rivaud, S., Gouider-Khouja, N., Pillon, B., Bonnet, A.M., Gaymard, B., Agid, Y. & Pierrot-Deseilligny, C. (1994) Eye movements in parkinsonian syndromes. *Ann. Neurol.*, **35**, 420–426.
White, O.B., Saint-Cyr, J.A., Tomlinson, R.D. & Sharpe, J.A. (1983) Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain*, **106**, 571–587.