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Don't look now or look away: Two sources of saccadic disinhibition in Parkinson's disease?

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ABSTRACT

Recent studies found evidence of impaired inhibition of saccades (fast eye movements) in non-demented people with PD. It has been suggested that impaired eye movement control reflects a general deficit of automatic response inhibition associated with impaired cognitive function in Parkinson's disease (PD). This study investigated the nature and source of saccadic disinhibition in PD. Eighteen non-demented PD patients and 18 control subjects completed prosaccade ('look towards'), delayed ('wait for cue') and antisaccade tasks ('look away') and a number of neuropsychological tests. There was evidence of saccadic disinhibition and cognitive impairment in the PD group. In the eye movement tasks the PD group made more express saccades (very fast reflexive responses) in the prosaccade task with a gap, more timing errors in the delayed response task and more directional errors in the antisaccade task than the control group. On average, neuropsychological test scores for the PD group were lower than for the control group. Subjects in the PD group who made a large number of directional errors in the antisaccade task did not necessarily also make a large number of timing errors in the delayed response task. Timing error rates, but not directional error rates, were negatively associated with neuropsychological test scores. Higher directional error rates in the antisaccade tasks were associated with higher proportions of express saccades in prosaccade tasks. This pattern of results suggests that there is more than one source of saccadic disinhibition in PD. We conclude that evidence of saccadic disinhibition may not necessarily reflect a general deficit of automatic response inhibition and cognitive impairment in PD.

1. Introduction

Parkinson's disease (PD) is associated with nigrostriatal and mesocorticolimbic dopamine depletion, which produces not only characteristic motor symptoms but also cognitive and oculomotor impairments. Investigations of oculomotor function often use the recording of saccades (fast eye movements), and make a distinction between reflexive (exogenous) saccades and voluntary (endogenous) saccades. The generation of reflexive saccades is usually found to be normal or faster than normal in PD (Armstrong, Chan, Riopelle, & Munoz, 2002; Briand, Strallow, Hening, Poizner, & Sereno, 1999; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Ventre, Zee, Papageorgiou, & Reich, 1992). In contrast, studies using voluntary saccadic tasks (e.g. delayed response, memory guided or antisaccade tasks) have found evidence of prolonged latencies, hypometria and impaired voluntary suppression of unwanted saccades in PD (Amador, Hood, Schiess, Izor, & Sereno, 2006; Armstrong et al., 2002; Briand et al., 1999; Crawford, Henderson, & Kennard, 1989; Crevits, Versijpt, Hanse, & De Ridder, 2000; Chan et al., 2005; Grande et al., 2006; Hood et al., 2006; Le Heron, MacAskill, & Anderson, 2005; Lueck, Tanyeri, Crawford, Henderson, & Kennard, 1990; O'Sullivan et al., 1997; Shaunak et al., 1999; Ventre et al., 1992). This pattern of results is consistent with the tonic inhibition model of eye movement control, in which dysfunction of the voluntary eye movement system results in impaired execution of voluntary saccades as well as saccadic disinhibition (Amador et al., 2006; Chan et al., 2005; Hood et al., 2006; Sereno & Holzman, 1995, 1996). The inhibitory function of the voluntary saccadic system involves prefrontal processing and saccadic disinhibition in PD is thought to be associated with disruption of fronto-striatal circuitry (Amador et al., 2006; Briand et al., 1999; Chan et al., 2005). This argument is strengthened by studies of eye movement control in clinical populations with known prefrontal dysfunction, where deficits of response inhibition are found also (Munoz, Armstrong, Hampton, & Moore, 2003; Nieman et al., 2000; Reuter

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& Kathmann, 2004). Furthermore, it has been suggested that oculomotor deficits in PD reflect a general deficit of automatic response suppression, extending to non-motor domains including cognitive function (Amador et al., 2006; Chan et al., 2005).

The tonic inhibition model of eye movement control predicts that people with PD who are impaired at generating voluntary saccades also have a decreased ability to suppress unwanted saccades (Amador et al., 2006). However, in their investigation of these issues, Amador et al. (2006) reported a negative correlation between latencies and error rates in antisaccade tasks. Also, if saccadic disinhibition in PD is evidence of fronto-striatal dysfunction, saccadic disinhibition would be expected to be associated with impaired cognitive function. So far, however, eye movement studies in PD have not included a detailed assessment of cognitive abilities of the subjects. The aim of the present study was to investigate the source of saccadic disinhibition in PD by exploring correlations between different measures of oculomotor function and correlations between measures of oculomotor function and measures of cognitive ability.

To investigate the source of saccadic disinhibition it is necessary to assess both reflexive and voluntary saccades (Kingstone et al., 2002). The neural systems responsible for reflexive and voluntary saccades are thought to operate at least partly in parallel (Massen, 2004) before converging in the superior colliculus, where saccades are triggered (Hikosaka, Takikawa, & Kawagoe, 2000). The reflexive saccadic system is investigated with prosaccade tasks in which the subject is instructed to look, as quickly and accurately as possible, at an unpredictable peripheral target onset. The voluntary saccadic system can be investigated with antisaccade or delayed response tasks. In the antisaccade task, the subject is instructed to suppress a reflexive saccade towards an unpredictable peripheral stimulus onset and to make a saccade in the opposite direction ('look away') as quickly as possible after stimulus onset. In delayed response tasks, the subject is instructed to suppress a reflexive saccade towards an unpredictable peripheral target onset and delay a saccade ('don't look now') until a further cue occurs. Eye movements towards the stimulus in the antisaccade task and eye movements initiated prematurely in the delayed response task are categorised as direction and timing errors respectively.

Response latencies and error rates are important indicators of the integrity of the saccadic system. Response latencies are modulated by temporal characteristics of the stimulus presentation and by task requirements. Saccadic latencies are shortest when a temporal gap of 200 ms is inserted between fixation point offset and target onset. This 'gap effect' is a combination of exogenous and endogenous effects. Fixation point offset automatically disinhibits saccade related neurons in the superior colliculus and it warns the subject of the upcoming target appearance (Kingstone & Klein, 1993; Spantekow, Krappmann, Everling, & Flohr, 1999). In reflexive saccadic tasks the gap effect promotes the generation of express saccades, which are very fast reflexive responses with latencies in the range 90–140 ms (Chan et al., 2005; Fischer, Gezeck, & Hartnegg, 2000; Munoz & Fecteau, 2002). Response latencies in the antisaccade task are, on average, longer than response latencies in reflexive saccade tasks. This 'anti-effect' represents the time needed to attend covertly to the peripheral stimulus (without making a reflexive saccade), and select the spatial parameters for the correct antisaccade (Everling & Fischer, 1998; Munoz & Fecteau, 2002). Proportions of directional errors (incorrect reflexive saccades) in antisaccade tasks and timing errors (premature responses in the correct direction) in delayed response tasks provide measures of saccadic disinhibition. In addition, abnormally high proportions of express saccades also can be considered a result of saccadic disinhibition (Matsue et al., 1994).

The present study used prosaccade, delayed response and antisaccade tasks to assess the integrity of the reflexive and voluntary saccade systems and to obtain different measures of saccadic disinhibition in people with PD and a control group. A range of standard neuropsychological tests was used to obtain measures of memory and attentional functions for each participant.

2. Methods

2.1. Subjects

Approval for this study was obtained from the Upper South A Regional Ethics Committee of the New Zealand Ministry of Health. Participants gave informed consent. Eye movement and neuropsychological data were obtained from 18 mild to moderate (Hoehn and Yahr stages 1–3), non-demented (Mini Mental State Exam score $\geq$ 27) and non-depressed (Beck's Depression Inventory score < 14) PD patients and 18 control subjects. The diagnosis of subjects in the PD group was confirmed by a movement disorder neurologist (TJA). Each group contained 12 males and 6 females. The PD and control groups were matched in age (mean age 65.7 (±S.D. 8.6) vs 66.3 (±S.D. 6.2) respectively) and years of education (mean number of years 5.9 (±S.D. 2.1) vs 7.2 (±S.D. 2.7) respectively). PD patients (except one) were medicated at the time of testing. Disease duration, age, sex and medication for each subject in the PD group are shown in Table 1. Participants had normal or corrected-to-normal visual acuity.

2.2. Experimental paradigm

Participants completed six eye movement tasks and ten neuropsychological tests in one morning session of 2.5–3.5 h duration.

2.3. Apparatus

Eye movements were recorded using a video-based iView X Hi-Speed (SMI, Berlin) system at a sampling rate of 240 Hz. Stimuli were displayed on a 21 in. CRT screen at 100 Hz, with a resolution of 640 × 480 pixels. The computer screen was positioned 500 mm in front of the subject, who sat with head supported by the chin and forehead rest of the iView tracking column. Customised software was used to display targets and analyse recorded eye movement traces off-line.

2.4. Oculomotor tasks

Prosaccade and antisaccade tasks were performed. Prosaccade and antisaccade tasks used identical stimulus presentations; only the instructions to the subject differed between the tasks. In the prosaccade trials the instruction was to 'look towards' a peripheral target and in the antisaccade trials the instruction was to 'look away' from the peripheral stimulus to a mirror location. Prosaccade and antisaccade tasks were presented in three different fixation conditions, making a total of six eye movement tasks. The three fixation conditions were: (1) *with a gap* (200 ms blank

Table 1
Disease duration, sex, age and medication details for each participant in the PD group

Duration of PD	Sex	Age	Medications
9	F	73	Madopar*, selegiline, atenolol
20	M	65	Sinemet**, lisuride
4	F	72	Sinemet, clonazepam
3	M	76	rotigotine
10	M	60	Sinemet, selegiline, benztropine, pergolide, amantadine, cilazapril, domperidone
20	M	65	Sinemet, selegiline, orphenadrine, pergolide, amantadine, omeprazole
4	F	64	Sinemet, selegiline, orphenadrine
5	F	66	Sinemet, pergolide
16	M	46	Sinemet, madopar, lisuride
3	M	73	Sinemet, selegiline, pergolide, propanolol, domperidone
10	M	70	Sinemet, lisuride, entacapone, clonazepam
2	M	75	–
10	M	56	Sinemet, selegiline, pergolide, propanolol
3	M	71	Sinemet, selegiline, orphenadrine, pergolide
16	M	65	Sinemet, selegiline, metoprolol, simvastatin
10	F	66	Madopar, pergolide, omeprazole
9	M	56	Sinemet, lisuride, orphenadrine, propanolol
5	F	63	Sinemet, pergolide, orphenadrine

* Madopar: levodopa and benserazide.
** Sinemet: levodopa and carbidopa.

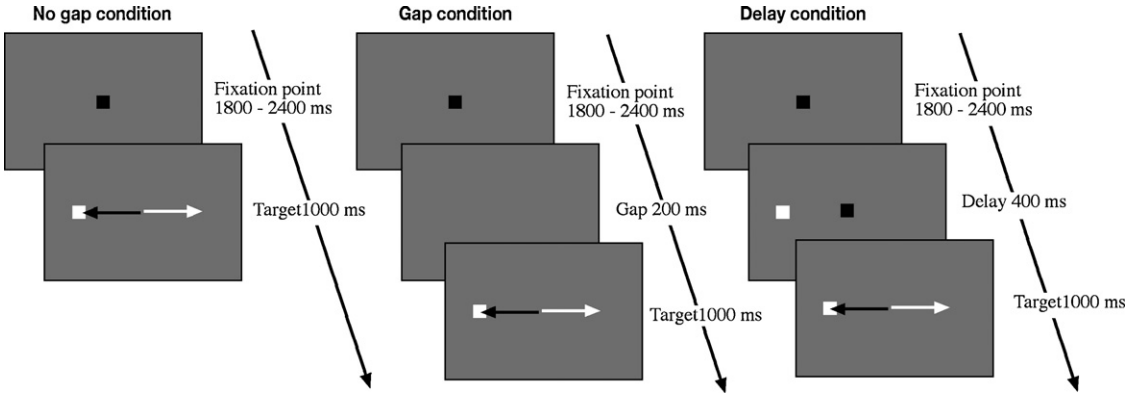

Fig. 1. Sequence of stimulus presentation during the oculomotor tasks. Stimuli were presented in three conditions: without a gap, with a 200 ms gap (a blank screen) between fixation point offset and stimulus onset, or with a 400 ms delay, during which both fixation point and stimulus were visible. The prosaccade and antisaccade tasks used identical stimulus presentations. The black and white arrows indicate correct responses in prosaccade and antisaccade trials respectively. In the delay condition the subject was instructed to delay a response until fixation point offset.

screen between fixation point offset and stimulus onset); (2) *without a gap* (stimulus onset coincided with fixation point offset) or (3) *with a delay* (a period of 400 ms during which both fixation point and stimulus were visible). In the tasks with a gap and without a gap the subject was instructed to make a saccade as quickly and as accurately as possible, as soon as the stimulus appeared. In the tasks with a delay the subject was instructed to withhold a saccade until fixation point offset. A schematic representation of the stimulus presentation conditions is shown in Fig. 1.

The six eye movement tasks were presented in blocks of 24 trials each. A trial consisted of the display of a central fixation point followed by a peripheral stimulus. Stimuli could be located at 8°, 10.5° and 13° to the left or the right of the central fixation point. The duration of the display of the central fixation point before target onset was 1800, 2000, 2200 or 2400 ms. Locations of the stimuli and durations of the display of the fixation point were pseudo-randomised. Each peripheral stimulus location was used four times in one block of trials. Peripheral stimuli were always displayed for 1000 ms. The fixation point was red (R254 G0 B0), peripheral stimuli were green (R0 G254 B0) and the background was grey (R143 G155 B164). The size of the fixation point and the peripheral stimuli was 10 × 10 pixels, subtending 0.75°.

2.5. Analysis of eye movement data

As the main interest of the present study was the cognitive aspect of eye movement control, latencies, proportions of express saccades, directional and timing errors were chosen as parameters of interest. Eye movement responses were assessed individually. To exclude anticipatory or random eye movements saccades were only included if the latency was between 90 and 900 ms, peak horizontal velocity exceeded 150°/s and the gain (amplitude of the primary saccade divided by target amplitude) of the primary eye movement response was more than 0.3. Saccadic latencies in the conditions with and without a gap were measured from stimulus onset. The proportion of express saccades (responses with latencies between 90 and 140 ms) was calculated for each participant as a percentage of the total number of responses in the prosaccade tasks, with and without a gap. In the delayed prosaccade task, responses initiated more than 90 ms after stimulus onset, but before fixation point offset (400 ms after stimulus onset) were categorised as timing errors. In the antisaccade tasks, responses with latencies longer than 90 ms in the direction of the stimulus were categorised as directional errors, which were further categorised as corrected (if followed by a saccade away from the stimulus) or uncorrected errors. In the antisaccade task with a delay, responses in the correct direction (i.e. away from the stimulus), but initiated before fixation point offset were categorised as timing errors. In the delayed response tasks, if a premature saccade occurred, but the eyes returned to the fixation point during the delay, the response was categorised as a corrected timing error. These trials (fewer than 3%) were not included in the analysis.

Latencies of correct responses and proportions of express saccades were analysed with analysis of variance (ANOVA) for repeated measures with group (PD or Control) as between group factor and task (prosaccade or antisaccade) and fixation condition (with gap or without gap) as within group factors. Latencies in the tasks with a delay were not included in the analysis because latencies of delayed saccades cannot be directly compared to latencies of saccades made in response to unpredictable stimulus onsets. Proportions of errors in the antisaccade and the delayed prosaccade tasks were analysed with ANOVA with group (PD or Control) and error type (directional or timing errors) as factors. Correlations of measures of eye movement performance and neuropsychological test scores of subjects in the PD group were analysed with Spearman Rank Order tests.

2.6. Neuropsychological testing

In addition to the Mini Mental State Exam and the Beck's Depression Inventory, eight standardised neuropsychological tests were administered. The aim of the neuropsychological testing in this study was to obtain for each subject an assessment of cognitive functions such as attention, memory and working memory function using neuropsychological measures sensitive to cognitive deficits in PD (Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Bosboom, Stoffers, & Wolters, 2004; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Mahieux et al., 1998; McKinlay, Dalrymple-Alford, Anderson, Fink, & Hudson, 2004; Woods & Troster, 2003; Woods et al., 2005). Cognitive impairment in PD is often characterised by a degree of executive dysfunction. Executive function refers to the ability to deploy attention and working memory resources in an efficient and goal-directed manner. The Wechsler Memory Scale (WMS-III) Digits Backwards (preceded by Digits Forward) and the Digit Ordering Test (DOT-A) (Werheid et al., 2002) were used as measures of working memory function. Delis Kaplan Executive Function System – (FAS) Letter Fluency (D-KEFS) (Delis, Kaplan, & Kramer, 2001) and the Action Fluency Test (AFT) (Piatt, Fields, Paolo, & Troster, 2004) provided measures of verbal fluency. Performance in these tests is considered to rely heavily on executive function. The acquisition and long delay recall measures of the short version of the California Verbal Learning Test (CVLT-Short Form) (Elwood, 1995) were used to assess memory. The acquisition part of this test contains an executive function component in addition to the memory component. The incomplete letters test of the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991) and the Benton Judgement of Line Orientation-Form H (JLO) (Benton, Hamsher, Varney, & Spreen O, 1994) were used to assess visuospatial perception. Problem solving skills were assessed with the Matrix Reasoning Test from the Wechsler Abbreviated Scale of Intelligence (WASI). This test involves complex cognitive processing, including visuospatial perception, attention, working memory and reasoning skills. Raw scores in each test were adjusted for age and sex according to guidelines provided in test manuals. For ease of comparison across tests, scores were converted to *z*-scores, based on normative data provided by the test manuals. These *z*-scores were converted to *T*-scores (mean of 50 and a standard deviation of 10). For each participant the mean *T*-scores for working memory, verbal fluency, memory, visuospatial perception, and problem solving were used to summarise cognitive ability.

3. Results

3.1. Latencies

Mean latencies for each group in the prosaccade and antisaccade tasks, with and without a gap, are shown as a function of fixation condition in Table 2. Latencies of correct responses were analysed with ANOVA for repeated measures with group (PD or Control) as between subjects factor, and task (prosaccade or antisaccade) and fixation condition (with or without gap) as within subject factors. As expected, a significant main effect of task was found, with mean latencies of prosaccades shorter (182 ms) than latencies of correct antisaccades (314 ms), $F(1,34) = 172.81$, $p < 0.001$. The effect of fixation condition on latencies (the gap effect) was

Table 2
Mean (±S.E.) latency of correct responses and proportion of express saccades in the prosaccade tasks with a gap (200 ms between fixation point offset and target onset) or without a gap for the Parkinson's (PD) and control groups

	Prosaccades		Antisaccades	
	Latency (ms)	Express saccades (%)	Latency (ms)	Direction errors (%)
With a gap				
PD	156 ± 7	49 ± 5*	311 ± 16*	40 ± 5
Control	165 ± 7	34 ± 5	262 ± 15	26 ± 5
Without a gap				
PD	210 ± 10	8 ± 2	357 ± 22	42 ± 6*
Control	196 ± 10	6 ± 2	325 ± 20	25 ± 6

* PD-Control: $p < 0.05$.

also significant, $F(1,34) = 95.99$, $p < 0.001$, with latencies in the tasks with a gap shorter (224 ms) than latencies in the tasks without a gap (272 ms). Average latencies in the prosaccade tasks did not differ between the PD and the control groups (183 ms vs 181 ms). The mean latency for correct antisaccades was longer in the PD group (334 ms) than in the control group (294 ms), but the interaction of group and task did not reach significance, $F(1,34) = 3.68$, $p = 0.064$. The ANOVA showed a significant interaction of group, task and fixation condition, $F(1,34) = 4.24$, $p = 0.05$. The PD group showed a larger gap effect in the prosaccade task compared to the control group (54 ms vs 31 ms), but a smaller gap effect in the antisaccade task (46 ms vs 63 ms).

3.2. Express saccades in the prosaccade tasks

Express saccade production was examined only in the prosaccade tasks with and without a gap, because in the antisaccade tasks most express saccades (99% in this study) were also directional errors, and in delayed response tasks express saccades are errors by definition. The proportions of express saccades generated by each subject were analysed with ANOVA with group (PD or Control) and fixation condition (gap or no gap) as factors.

The proportions of express saccades in the prosaccade tasks for each group are shown as a function of fixation condition in Table 2. The ANOVA showed that the production of express saccades was modulated significantly by fixation condition in both groups. The proportion of express saccades was much larger in the prosaccade tasks with a gap than without a gap (41% vs 7%), $F(1,34) = 85.7$, $p < 0.001$. Overall, the PD group made more express saccades than the control group (29% vs 20%), $F(1,34) = 4.17$, $p = 0.05$. This effect was due to the difference between the proportions of express saccades of the PD group (49%) and the control group (34%) in the prosaccade task with a gap.

3.3. Errors in the antisaccade and delayed response tasks

For each subject, the proportion of direction errors in the antisaccade tasks and the proportion of timing errors in the delayed response tasks were calculated. Uncorrected direction errors (less than 1%) were pooled with corrected direction errors. Proportions of errors were analysed with ANOVA with group (PD or Control) and error type (direction or timing) as factors. Overall, the PD group made more errors than the control group, 31% vs 20%, $F(1,34) = 4.45$, $p < 0.05$. No effect of error type or interaction effect was found. The mean proportions of directional and timing errors in the antisaccade and delayed response tasks for each group are shown in Tables 2 and 3.

In the delayed prosaccade task the PD group made significantly more timing errors than the control group (42% and 20% respectively, $F(1,34) = 8.34$, $p < 0.01$). In this task, all saccades initiated before fixation point offset, which occurs 400 ms after target onset, are timing errors. Fig. 2 shows the pooled cumulative distribution of latencies of correct and incorrect responses in the delayed prosaccade task for each group. The production of correct responses in the control group is illustrated by a steep increase in responses initiated around 175 ms after fixation point offset. In comparison, the PD group generated many premature responses (timing errors) during the delay period after target onset.

Table 3
Delayed response tasks: mean (±S.E.) proportion of errors (%) in the prosaccade and antisaccade tasks with a delay (400 ms) for the Parkinson's (PD) and control groups

	Direction errors (%)	Timing errors (%)
Prosaccade task		
PD	–	42 ± 6*
Control	–	20 ± 6
Antisaccade task		
PD	22 ± 5	14 ± 4
Control	14 ± 5	16 ± 4

* PD-Control: $p < 0.05$.

3.4. Neuropsychological test scores

Five mean scores and the component scores in each cognitive area for the PD and the control groups are shown in Table 4. All scores were adjusted according to normative data and converted to *T*-scores, which are distributed around a mean of 50 with a standard deviation of 10. This means that scores of 35 (one and a half standard deviation below the mean of 50) and above can be considered normal or better than normal for a specific age group. All subjects

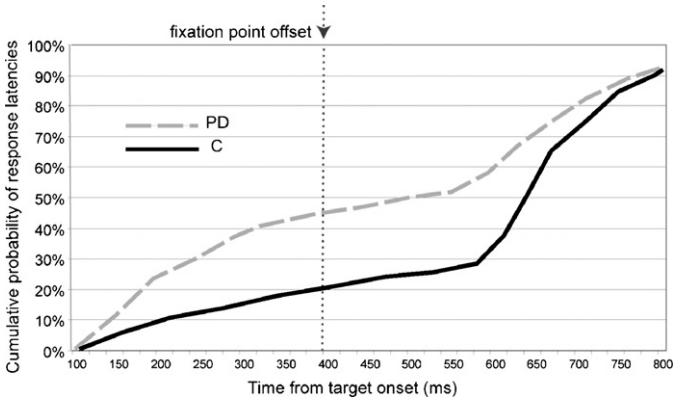

Fig. 2. Cumulative distribution of response latencies in the delayed prosaccade task in the PD and the control groups. Target onset occurs at 0 ms and fixation point offset occurs at 400 ms. Saccades initiated before 400 ms are timing errors. In the control group a steep rise indicates the generation of many correct responses 175 ms after fixation point offset, whereas the PD group exhibits continuous responding throughout the delay period.

Table 4
Mean test scores (±S.D.) for all neuropsychological tests for the Parkinson's (PD) and control groups, adjusted for age and sex according to test guidelines and converted to *T*-scores (mean = 50 and S.D. = 10)

Cognitive test	PD	Control
Working memory	41.3 ± 11.4*	48.6 ± 8
Digit Ordering Test	43.94	50.56
Digits Backwards	38.69*	46.64
Verbal fluency	53.8 ± 10.1	59.2 ± 6.2
Action fluency	52.79	56.36
Letter fluency	54.81	62.04
Memory	53.4 ± 8.5*	61.6 ± 7.5
CVLT acquisition	53.73*	62.89
CVLT long delay	53.06*	60.31
Visuo-perception	55.2 ± 4.5*	57.1 ± 3.5
VOSP incomplete letters	55.60	54.70
Line orientation judgement	54.74*	59.52
Problem solving	57.1 ± 9.1*	65.0 ± 4.8
WASI matrix reasoning	57.13*	65.00

* PD-Control: $p < 0.05$.

in the control group scored at or above the expected level for their age group. On average the cognitive scores of the subjects in the PD group were within the range expected for their age and gender, but the individual scores within the PD group ranged from well above to below the expected average level. The average over eight tests was lower in the PD group (mean 52.13 ± S.D. 6.80) than in the control group (mean 58.42 ± S.D. 3.78), $F(1,34) = 11.62$, $p < 0.01$. In four cognitive areas the scores differed significantly ($p < 0.05$) between the two groups. The difference between the groups on the verbal fluency component did not reach statistical significance, at $p = 0.062$.

3.5. Associations between measures of eye movement control in the PD group

Four measures were calculated to characterise oculomotor function for each subject in the PD group: (1) proportion of express saccades in the prosaccade tasks, (2) proportion of timing errors in the delayed response tasks (prosaccade and antisaccade tasks), (3) latency for correct antisaccades and (4) proportion of direction errors in the antisaccade tasks. Potential associations between these four oculomotor measures were explored with Spearman Rank Order Tests. To correct for multiple comparisons, a *p*-value of 0.01 was chosen as the cut-off for statistical significance. In the PD group, higher proportions of direction errors in the antisaccade tasks were associated with higher proportions of express saccades in the prosaccade tasks, $r = 0.64$, $p < 0.01$. Subjects in the PD group who generated a high proportion of direction errors did not also make a high proportion of timing errors, $r = 0.08$. Latencies of correct antisaccades were not associated with any other eye movement measure. This means that those subjects in the PD group, who were slow to produce correct antisaccades, did not necessarily make a large number of errors in the antisaccade or in the delayed response tasks. A full set of correlations between measures of eye movement control for the PD group is shown in Table 5.

Table 5
Spearman Rank Order correlations between four measures of eye movement control in the Parkinson's disease group

	Express saccades	Timing errors	Antisaccade latency	Direction errors
Express saccades	–			
Timing errors	0.38	–		
Antisaccade latency	0.04	0.02	–	–
Direction errors	0.64*	0.08	0.30	

* Correlations significant at $p < 0.01$.

3.6. Associations of oculomotor and neuropsychological measures in the PD group

Associations between measures of oculomotor function and cognitive function in the PD group were explored with Spearman Rank Order Tests. Proportions of express saccades or direction errors were not significantly associated with neuropsychological test scores. Proportions of timing errors in the delayed response tasks were negatively associated with memory and visuo-perception scores, $r = -0.73$ and $r = -0.58$ respectively. Longer latencies for correct antisaccades were associated with lower working memory scores, $r = -0.59$. The full set of correlations of eye movement measures and neuropsychological test scores for the PD group is shown in Table 6.

4. Discussion

Oculomotor deficits associated with PD include impaired initiation of voluntary saccades and saccadic disinhibition. In the search for a unitary model of impaired eye movement control in PD, researchers have attributed these deficits to a single source: impairment of the voluntary saccadic system. The tonic inhibition model (Amador et al., 2006) suggests that dysfunction of the voluntary saccadic system results in impaired performance of voluntary saccades as well as disinhibition of reflexive saccades. It has been suggested also that saccadic disinhibition in PD reflects a general deficit in automatic response suppression, extending to the cognitive domain, consistent with disruption of fronto-striatal circuitry (Chan et al., 2005). We hypothesised that if this unitary model is correct, different oculomotor deficits should be associated with each other and with measures of cognitive ability in PD. To investigate these issues the present study explored the pattern of associations between different measures of eye movement control and between measures of eye movement control and measures of cognitive ability in PD.

Differences were found between the performance of a group of people with PD and a control group on a range of oculomotor tasks and neuropsychological tests. Our PD group made, on average, more express saccades in prosaccade tasks, more errors in delayed response and antisaccade tasks and they were slower to initiate

Table 6
Spearman Rank Order correlations of test scores in five cognitive areas and four eye movement measures for the Parkinson's disease group

	Visuospatial perception	Memory	Verbal fluency	Problem solving	Working Memory
Express saccades	−0.38	−0.15	−0.16	−0.20	−0.23
Timing errors	−0.58*	−0.73*	−0.30	−0.31	−0.41
Antisaccade latency	−0.19	−0.06	−0.31	−0.01	−0.59*
Direction errors	−0.48	−0.17	−0.14	0.10	−0.31

* Correlations significant at $p < 0.01$.

correct antisaccades than the control group. Results from this study confirmed reports of normal prosaccades in PD (Armstrong et al., 2002; Briand et al., 1999; Chan et al., 2005; Ventre et al., 1992), more express saccades (Chan et al., 2005) and saccadic disinhibition in PD (Armstrong et al., 2002; Briand, Hening, Poizner, & Sereno, 2001; Chan et al., 2005; Crevits et al., 2000). Previous studies using the antisaccade task in PD have yielded inconsistent results (e.g. compare Vidailhet et al. (1994) and Mosimann et al. (2005) to Crevits et al. (2000), Chan et al. (2005) and Amador et al. (2006)). Methodological differences, including stimulus presentation and disease severity of the PD groups, make it difficult to compare results across studies. Overall, the PD group in the present study was not impaired in the antisaccade task, but they made more direction errors in the antisaccade task without a gap and initiated correct antisaccades at longer latencies in the antisaccade task with a gap compared to the control group.

A unitary model of eye movement deficits in PD predicts that saccadic disinhibition, impaired voluntary eye movements and cognitive deficits will be associated with each other (Amador et al., 2006; Chan et al., 2005). To test this prediction, correlations between oculomotor measures in the PD group were explored. Measures of saccadic disinhibition were not all associated with each other. Subjects who produced a large number of direction errors in the antisaccade task did not also generate a large number of timing errors in the delayed response tasks. In contrast, there was a clear association between the production of express saccades in the prosaccade tasks and the production of direction errors in the antisaccade tasks, while the production of express saccades was only weakly associated with the production of timing errors in the delayed response tasks. Further, prolonged antisaccade latencies in the PD group were only weakly associated with the production of direction errors in the antisaccade task and not at all with the production of timing errors in the delayed response tasks.

Next, associations between measures of oculomotor function and measures of cognitive ability were explored in the PD group. Two measures of saccadic disinhibition, i.e. proportions of direction errors in the antisaccade tasks and express saccades in the prosaccade tasks, were not significantly associated with any neuropsychological test scores. In contrast, the third measure of saccadic disinhibition (timing errors in the delayed response tasks) was associated with lower memory and visuo-perception scores in the PD group. Finally, relatively long latencies for correct antisaccades were associated with low scores in the working memory test. This pattern of associations argues against the usefulness of a unitary model of eye movement impairment in PD. Instead, these correlations suggest that there may be more than one source of saccadic disinhibition in PD.

The error rate in the antisaccade task was better predicted by subjects' tendency to produce express saccades in the prosaccade tasks than by any of the other oculomotor or cognitive measures. This result is consistent with previous reports that in the antisaccade task, the ability to deploy attention to a stimulus onset without triggering a reflexive saccade may be compromised in subjects who make large numbers of express saccades (Biscaldi, Fischer, & Stuhr, 1996). There is no indication that the production of express saccades in reflexive saccadic tasks is associated with cognitive impairment. Thus, direction errors in the antisaccade task may not necessarily reflect a general deficit of response inhibition or general cognitive impairment in PD. The production of express saccades is thought to be mainly due to an automatic increase in excitability of saccade neurons in the superior colliculus after fixation point offset (Munoz, Dorris, Pare, & Everling, 2000). The activity of saccade neurons in the superior colliculus depends on the modulation of endogenous (voluntary) and exogenous (sensory) excitatory cortical signals (including inputs from frontal and supplementary eye fields) by inhibitory basal ganglia outputs (Hikosaka et al., 2000). In PD, a potentially enhanced effect of fixation point offset may be due to impaired inhibitory basal ganglia outputs or it may involve additional changes in cortical parts of the oculomotor system.

Different mechanisms are involved in the suppression of reflexive responses in antisaccade and delayed response tasks. In the antisaccade tasks with and without a gap, fixation point offset interferes directly with the requirement to suppress a reflexive saccade. In the delayed response tasks, response suppression is not affected by fixation point offset and suppression of premature reflexive saccades relies on the ability to maintain fixation during the delay period. We speculate that the impaired performance in the delayed response task observed in the PD group may be associated with a general deficit in maintaining the focus of attention which may affect aspects of cognitive function in some people with PD. Besides response suppression, the antisaccade task tests the programming and execution of voluntary saccades. Those subjects in the PD group who were slow to produce correct antisaccades had relatively low scores in the working memory task. This correlation is consistent with the notion that specification of correct antisaccades involves manipulation of spatial information to calculate the amplitude and direction of the correct response. The Digits Backwards and Digits Ordering Tests, which were used to assess working memory function, similarly require manipulation of information in working memory.

4.1. Support from oculomotor studies in other clinical populations

The use of the antisaccade task for the assessment of disturbed higher cognitive functioning in various clinical populations is well established (Heitger et al., 2004; Reuter & Kathmann, 2004; Sereno & Holzman, 1995). However, the patients' basic performance needs to be intact for the task to be useful (Reuter & Kathmann, 2004). The increased production of express saccades associated with PD suggests caution when using the antisaccade task in this population. A recent imaging study of patients with frontal lesions showed that higher percentages of errors on an antisaccade task were associated with reduced volume of the right frontal eye fields, while longer latencies of correct antisaccades were associated with reduced volumes of pre-supplementary motor area and supplementary eye fields (Boxer et al., 2006). This is consistent with our finding that increased proportions of errors and longer latencies in the antisaccade task are not associated with each other in the PD group. The relationship between saccadic disinhibition and cognition has also been addressed in schizophrenia (Broerse, Holthausen, van den Bosch, & den Boer, 2001). Contrary to expectation, the Wisconsin Card Sorting Test and Stroop tests (used to assess prefrontal function) were not consistently associated with saccadic disinhibition in schizophrenia. In this study, deficits in a delayed response task were found to be associated with CVLT-derived memory scores (Broerse et al., 2001). These results are consistent with the evidence from our study.

4.2. Effect of dopaminergic medication on action control and cognition in PD

In our study all but one of the subjects in the PD group were medicated at the time of testing. Human and animal studies show that both dopamine depletion and its replenishment may impair working memory function (Castner & Goldman-Rakic, 2004; Williams & Castner, 2006). Eye movement studies have found deficits in the antisaccade task in PD, whether subjects were tested 'on' or 'off' medication (Amador et al., 2006; Chan et al., 2005). Recently both positive and negative effects of dopaminergic medication on cognitive functions have been reported in PD. The direction of the effect

was found to depend on task conditions and baseline dopamine levels (Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001, 2003; Cools, Altamirano, & D'Esposito, 2006; Frank & O'Reilly, 2006; Woods et al., 2005). Frank and O'Reilly (2006) propose a model of striatal dopamine function explaining how dopamine dynamically modulates Go and No-Go signals in the basal ganglia. In this model these complementary functions not only control actions, but also extend to the updating of working memory representations in prefrontal areas. In PD, dopaminergic treatments can enhance Go learning and impair No-Go learning, depending on baseline levels of dopamine function (Cools et al., 2001; Frank, 2005). Our speculation that the delayed response task (No-Go) and the antisaccade task (Go) may reveal independent sources of saccadic disinhibition in PD is consistent with this model.

5. Conclusion

This study compared measures of oculomotor control and cognitive abilities of a group of people with PD and a control group. Increased production of express saccades, and higher error rates in antisaccade and delayed response tasks confirmed reports of saccadic disinhibition in the PD group. On average, the PD group scored lower in the neuropsychological tests than the control group. The pattern of associations between oculomotor measures and between oculomotor measures and neuropsychological test scores supports the suggestion that there may be more than one source of saccadic disinhibition in PD. High proportions of errors in antisaccade tasks ('look away'), accompanied by a tendency to produce many express saccades, may reflect a different type of saccadic disinhibition than high proportions of errors in the delayed response task ('don't look now').

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