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Neuropsychologia 43 (2005) 784–796

NEUROPSYCHOLOGIA

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Deficits in saccadic eye-movement control in Parkinson's disease

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Received 10 November 2003; received in revised form 13 May 2004; accepted 17 June 2004

Abstract

In contrast to their slowed limb movements, individuals with Parkinson's disease (PD) produce rapid automatic eye movements to sensory stimuli and show an impaired ability to generate voluntary eye movements in cognitive tasks. Eighteen PD patients and 18 matched control volunteers were instructed to look either toward (pro-saccade) or away from (anti-saccade) a peripheral stimulus as soon as it appeared (immediate, gap and overlap conditions) or after a variable delay; or, they made sequential saccades to remembered targets after a variable delay. We found that PD patients made more express saccades (correct saccades in the latency range of 90–140 ms) in the immediate pro-saccade task, more direction errors (automatic pro-saccades) in the immediate anti-saccade task, and were less able to inhibit saccades during the delay period in all delay tasks. PD patients also made more directional and end-point errors in the memory-guided sequential task. Their inability to plan eye movements to remembered target locations suggests that PD patients have a deficit in spatial working memory which, along with their deficit in automatic saccade suppression, is consistent with a disorder of the prefrontal-basal ganglia circuit. Impairment of this pathway may release the automatic saccade system from top-down inhibition and produce deficits in volitional saccade control. Parallel findings across various motor, cognitive and oculomotor tasks suggest a common mechanism underlying a general deficit in automatic response suppression.

Keywords: Basal ganglia; Anti-saccades; Frontal cortex; Pro-saccades; Gap effect; Express saccades

1. Introduction

The motor impairments of Parkinson's disease (PD), including muscle rigidity and slowness of movement (Lezak, 1995), result from degeneration of dopaminergic neurons in the substantia nigra pars compacta (Bergman & Deuschl, 2002; Leenders & Oertel, 2001). In addition to their slowed movements, individuals with PD are often impaired in their ability to suppress automatic behavioral responses (Henik, Singh, Beckley, & Rafal, 1993; Hayes, Davidson, Keele, & Rafal, 1998; Owen et al., 1993).

One set of simple behavioral tasks that may provide insight into the neural control of response suppression uses saccadic eye movements to investigate and quantify motor impairments in PD (Jones & De Jong, 1971; Shibasaki, Tsuji, & Kuroiwa, 1979; White, Saint-Cyr, Tomlinson, & Sharpe, 1983). Saccades can be measured easily and precisely; and, there is considerable understanding of the neural circuitry controlling the planning and execution of saccadic eye movements (Leigh & Zee, 1999; Munoz, Dorris, Paré, & Everling, 2000; Scudder, Kaneko, & Fuchs, 2002; Wurtz & Goldberg, 1989). Two types of responses are of interest for this study: visually triggered and volitionally guided saccades. Visually triggered saccades (sometimes called reflexive or automatic saccades) are inititated by the sudden appearance of a visual

Abbreviations: CV, coefficient of variation; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; FP, fixation point; LED, light-emitting diode; MPTP, methyl phenyl tetrahydropyridine; PD, Parkinson's disease; REX, real-time data-acquisition system; SRT, saccadic reaction time

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doi:10.1016/j.neuropsychologia.2004.06.026

stimulus and are mediated by the superior colliculus, with important inputs from the visual and posterior parietal cortices (Guitton, Buchtel, & Douglas, 1985; Hanes & Wurtz, 2001; Schiller, Sandell, & Maunsell, 1987). Volitionally guided saccades, generated by internal goals, sometimes in the absence of any overt triggering stimulus, rely upon circuitry that includes higher brain centers such as the frontal cortex and the basal ganglia (Dias & Segraves, 1999; Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Hikosaka & Wurtz, 1989; Hikosaka, Takikawa, & Kawagoe, 2000). Volitionally guided saccades can be elicited by asking participants to look from a central point to the direction opposite the eccentric stimulus (the anti-saccade task; Munoz & Everling, 2004). For success in the anti-saccade task, participants must first inhibit a visually guided saccade towards the eccentric stimulus and instead prepare a volitional saccade to an area of the visual field without visual stimuli.

The study of saccadic inhibition provides a powerful, yet simple evaluation of control over volitional and automatic-reflexive processes (Everling & Fischer, 1998; Leigh, Newman, Folstein, Lasker, & Jensen, 1983; LeVasseur, Flanagan, Riopelle, & Munoz, 2001; McDowell, Brenner, Myles-Worsley, Coon, Byerley, Clementz, 2001; Munoz & Everling, 2004; Munoz, Armstrong, Hampton, & Moore, 2003; Ross, Harris, Olincy, & Radant, 2000). The aim of this study is to use pro- and anti-saccade tasks with immediate and delayed responses to quantify the control of automatic and volitional responses in individuals with PD. In addition, our battery of oculomotor tasks included a delayed memory-guided sequential task as a test of spatial working memory. The delayed memory-guided sequential task requires participants to suppress any eye movements during the delay period while remembering the spatial location of three targets that are flashed briefly, and then to plan the direction of movement before initiating any saccades. We measured the ability of PD patients to use spatial working memory correctly to plan eye movements to the remembered locations of the sequential targets.

2. Methods

2.1. Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Eighteen mild to moderate PD patients (Hoehn–Yahr stages I–III; Hoehn & Yahr, 1967) were compared with 18 age-matched normal controls. The PD participants met clinical criteria for diagnosis and were referred by a neurologist (G.P. or R.J.R.). The PD group (11 of 18 were men) had a mean age of 67 years (range: 38–81 years). All PD patients were medicated and were not asked to interrupt their medication on the days of recording. Twelve patients were receiving dopamine precursor treatment (carbidopa/levodopa), nine were taking dopamine agonists (ropinirole, bromocriptine, pergolide, domperidone, or pramipexole), six were taking amantadine, four were taking a monoamine oxidase inhibitor (selegeline), and two were on anticholinergic medication (ethopropazine or trihexyphenidyl). All control participants (5 of 18 were men; mean age 65.7 years, ranging from 35 to 83 years) had no known neurological, psychiatric, or visual disorders. Participants wore corrective lenses if needed throughout the experiments. Participants were informed of the nature of the study and provided written consent to participate in the study in accordance with the Declaration of Helsinki.

2.2. Experimental paradigms

Participants were run in three separate experimental sessions. In the first session, participants performed one block of the *immediate* pro- and two blocks of the *immediate* anti-saccade task. Each block consisted of 120 trials. In a second session, participants performed the *delayed pro-/anti-saccade* task in three blocks (160 trials each). Each block contained randomly interleaved pro- and anti-saccade trials. In a third session, they performed two blocks (96 trials each) of the *delayed memory-guided sequential* task. Participants were given breaks between blocks of trials. Two PD patients did not complete the *delayed pro-/anti-saccade* task.

2.2.1. Immediate and delayed pro- and anti-saccade tasks

In the *immediate* and *delayed* pro-/anti-saccade tasks (Fig. 1), participants were seated in complete darkness facing the center of a translucent screen located 100 cm away. A red light-emitting diode (LED; 2.0 cd/m^2) was back-projected onto the center of the screen and served as a central fixation point (FP). The delayed task also used a green LED (2.0 cd/m^2) as a central FP that alternated randomly with the central red FP (see below). Red target LEDs (5.0 cd/m^2) were positioned 20° to the right and left of the central FP. The screen was diffusely illuminated between trials to decrease dark adaptation.

In the *immediate* pro-saccade task (Fig. 1A), participants were instructed to look to an eccentric target as soon as it appeared. Each trial began with a 250 ms period of complete darkness. The FP then appeared and after 1000 ms, one of two events took place. In the gap condition (Fig. 1C), the FP disappeared and, following a gap interval of 200 ms of darkness, the eccentric target appeared. During the overlap condition (Fig. 1D) the FP remained visible when the eccentric target appeared and throughout the remainder of the trial. Participants were instructed to look to the eccentric target as soon as it appeared. The target appeared randomly either 20° to the left or right and remained visible for 1000 ms, after which all LEDs disappeared and the background illumination reappeared signifying the completion of the trial. Target location (left or right) and fixation condition (gap or overlap) were randomly interleaved throughout each block of trials.

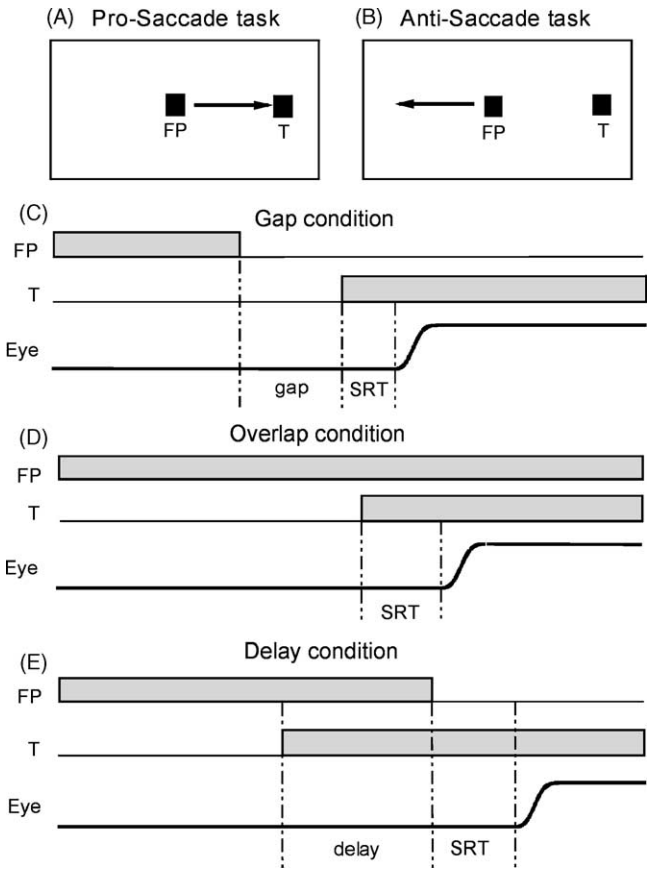

Fig. 1. Pro- and anti-saccade paradigms. In the immediate pro-saccade task (A); participants were instructed to look from the central fixation point (FP) toward the eccentric target stimulus (T) after its appearance. In the immediate anti-saccade task (B); participants were instructed to look away from the target towards its mirror location. In both tasks, the state of fixation was manipulated by interleaving the gap (C); and overlap (D) conditions randomly. In the gap condition, the FP was extinguished 200 ms before the onset of the target. In the overlap condition, the FP remained on when the target appeared. In the delayed pro-/anti-saccade task (E); the target appeared while the FP was still illuminated and participants were instructed to refrain from initiating a saccade until the FP disappeared. The delay period was varied randomly from 200 to 1000 ms and pro- and anti-saccade trials were interleaved randomly.

The *immediate* anti-saccade task (Fig. 1B) used the same visual presentations as in the pro-saccade task, except that participants were instructed that, after the appearance of the eccentric target, they were to generate a saccade away from it to its mirror location. Target location and fixation condition were randomly interleaved within blocks.

In the *delay* task (Fig. 1E) pro- and anti-saccade trials were randomly interleaved in each block. Stimulus presentation was identical to the *immediate* tasks with the following exceptions: the FP was either red or green and it disappeared after the appearance of the eccentric target with a variable delay (200, 400, 600, 800 or 1000 ms). Participants were instructed to wait until the FP disappeared before making an eye movement and then to look toward the eccentric target (pro-saccade) if the FP was red and away from the target (anti-saccade) if the FP was green. Target direction (20° left or right), color of FP (red or green), and delay interval (200, 400, 600, 800, 1000 ms) were all varied randomly within a block of trials. Participants did not receive any practice trials prior to recording but were asked to repeat the instructions to ensure that they were understood.

2.2.2. Delayed memory-guided sequential task

Each participant was seated upright in a chair 60 cm from a computer screen on which a white circular FP (0.2 cd/m^2) was centered on a black background and green circular targets (0.2 cd/m^2) appeared. Head movements were restricted by the use of a chin rest. Visual presentations were generated on a ViewSonic 17PS monitor with a S3 VGA card with resolution of 640 × 480 pixels and a frame rate of 120 Hz.

Participants were instructed to fixate the central FP while three eccentric targets flashed sequentially in three of the four quadrants of the visual field (Fig. 2). Targets appeared for 100 ms each and there was no interstimulus delay interval between target presentations. Targets flashed randomly within each quadrant at one of 25 preset locations. These locations were centred at 8° of visual angle from the FP and evenly spaced within a 5 × 5 grid that ranged from 5° of visual angle at the location nearest FP to 11° at the location farthest from FP. Participants were required to move their eyes to the remembered locations of the targets in the correct sequence of appearance following the disappearance of the FP, which occurred at variable delays (0, 600, 1200, or 1800 ms) following the disappearance of the final target. The sequence and location of the targets varied randomly between trials, and the targets appeared with equal probability in each location and in each quadrant. Participants received 20 practice trials with corrective feedback before eye-movement recording began.

2.3. Recording and analysis of eye movements

2.3.1. Immediate and delayed pro- and anti-saccade tasks

Bi-temporal direct current electrooculography was used to record horizontal eye position (for details, see Munoz, Broughton, Goldring, & Armstrong, 1998). A computer running a real-time data-acquisition system (REX version 5.4; Hays, Richmond, & Optician, 1982) controlled the experimental paradigms, visual displays, and horizontal eye position at a rate of 500 Hz. Digitized data were stored on a hard disk and off-line analysis was carried out on a Sun Ultra 60 workstation.

Eye velocity beyond 30°/s marked the onset and termination of saccades. The first saccade after the target appearance was scored as correct if it was in the correct direction and occurred after the disappearance of the FP in the delay tasks. Otherwise, a saccade was labeled a direction error if it was in the incorrect direction and a timing error if it occurred before the disappearance of the FP in the delay tasks. Saccades with both direction and timing errors were given both labels and stored as a separate error group.

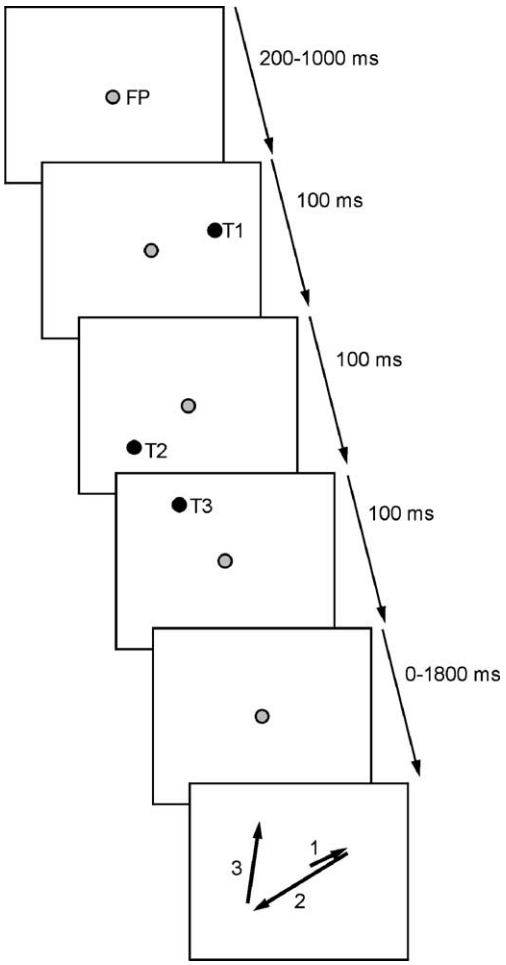

Fig. 2. Delayed memory-guided sequential task. Participants were instructed to maintain fixation at the central FP until its disappearance. A sequence of three target stimuli (T1, T2, T3) was presented for 100 ms each in three out of the four quadrants of the visual field. The location and sequence of the three targets were varied randomly. After the final target disappeared, the FP remained illuminated for a variable amount of time (0, 600, 1200, and 1800 ms). Once the FP was extinguished, participants were instructed saccade to the remembered location of each of the targets in the correct order of their appearance.

In the *immediate* tasks, saccadic reaction time (SRT) was measured as the time from target appearance to the onset of the first saccade. In the *delay* tasks, SRT was measured as the time from FP disappearance to the initiation of the first saccade. Only SRTs between 90 and 1000 ms were analyzed (see Munoz, Broughton, Goldring, & Armstrong, 1998).

For the *immediate* tasks, we computed the following values for each condition (gap, overlap) and target location (right, left): the mean SRT for correct trials, the coefficient of variation of SRT for correct trials [(CV = standard deviation/mean) × 100], the percentage of express saccades (latency: 90–140 ms; for review, see Fischer & Weber, 1993; Paré & Munoz, 1996), and the percentage of direction errors. The gap effect (overlap SRT–gap SRT; Fischer & Weber, 1992; Kalesnykas & Hallett, 1987; Munoz, Broughton, Goldring, & Armstrong, 1998; Saslow, 1967) was also computed. In the *delay* tasks, we computed the mean SRT for correct trials and the percentage of timing errors and direction errors. Values for left and right target positions were not significantly different; therefore, data were collapsed across direction. For correct pro-saccades with amplitudes between 18° and 21°, the mean peak velocity and duration were also calculated. This narrow window of amplitudes was used to control for well-known main sequence effects of amplitude on velocity and duration (Leigh and Zee, 1999).

Normally distributed data were analyzed with repeated-measures analysis of variance (ANOVA) with the factors pathology (PD versus control) and fixation condition (gap versus overlap) for the *immediate* task, and pathology and delay interval for the *delay* task. Non-normal data were analyzed using non-parametric Wilcoxon signed ranks tests to compare results from PD patients with age-matched controls.

2.3.2. Delayed memory-guided sequential task

In the delayed memory-guided sequential task (Fig. 2), eye movements were measured with a head-mounted camera (see Cabel, Armstrong, Reingold, Munoz, 2000 for details). The EyeLink system (S.R. Research Ltd., Toronto, Canada), a video-based infrared eye-tracker, tracked the movement of the participant's pupil, extracting measures of vertical and horizontal eye position and pupil size at a sampling rate of 250 Hz. Only the left eye position was digitized. The Eyelink system detected saccades when peak velocities were greater than 30°/s, acceleration was greater than 9500°/s^2, and there was minimum motion greater than 0.15°. A separate camera also monitored the location of the head so as to compensate for small head movements. The accuracy of subjects' movements to each target was measured by calculating the distance between each target and the closest eye fixation. Eye-movement sequences that were not executed in the same order as target sequences were classified as sequence errors. Eye movements that occurred before the offset of the FP were classified as timing errors. Normal data were analyzed using two-tailed paired Student's *t*-tests and non-normal data were analyzed using non-parametric Wilcoxon signed ranks tests. A Bonferroni correction was made for multiple comparisons, which adjusted the level of significance to $p \leq .02$.

3. Results

3.1. Immediate pro- and anti-saccade task

Fig. 3 illustrates the distribution of reaction times for correct (values above 0 on ordinate) pro- and anti-saccades and direction errors (values below 0 on ordinate) for PD (dashed lines) and age-matched controls (solid lines) in the immediate pro- and anti-saccade tasks with gap and overlap conditions. There are several important points to make. First, in the immediate pro-saccade task, PD patients tend to elicit more short-latency responses than control subjects. Second, among PD patients, the reaction times of correct anti-saccades are

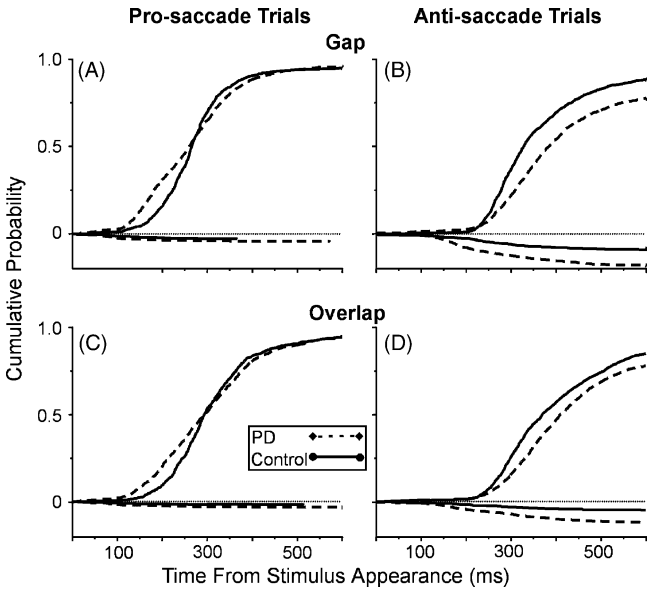

Fig. 3. Cumulative distribution of saccadic reaction times for correct responses (positive values on ordinate) and direction errors (negative values on ordinate) for pro-saccade (A, C) and anti-saccade (B, D) trials in the gap (A, B) and overlap (C, D) conditions. Solid traces, control data; dashed traces, PD data.

Table 1
Mean values (±S.E.) for saccadic reaction time (SRT), coefficient of variation in SRT (CV), and the percentage of express saccades for the Parkinson's (PD) and control groups as a function of fixation condition (gap or overlap) in the immediate pro-saccade task

	SRT (ms)	CV	Express saccades (%)
Gap condition			
PD	267 ± 14	31 ± 2*	19 ± 2
Control	276 ± 15	24 ± 2	3 ± 1
Overlap condition			
PD	312 ± 17	34 ± 2*	5 ± 1*
Control	320 ± 17	29 ± 2	1 ± 0

* PD–control: $p < .05$.

markedly slower than control subjects. Third, PD patients make more direction errors on anti-saccade trials. These observations are summarized in Tables 1 and 2. Table 1 shows the mean SRT, intra-subject variance in SRT expressed as the CV, and percentage of express saccades for correct responses in the *immediate* pro-saccade task as a function of pathology (PD versus control) and fixation condition (gap versus overlap). Table 2 displays the mean SRT, CV, and percentage of direction errors in the *immediate* anti-saccade task. There are several notable findings comparing PD patients to controls with respect to mean SRT. First, PD patients showed a gap effect (overlap SRT–gap SRT) that was equivalent to controls; that is, the overlap condition slowed reaction time for both groups. Second, PD patients showed a greater anti effect (anti-saccade SRT–pro-saccade SRT). Third, responses of PD subjects were more variable. Fourth, PD patients made more express saccades in the pro-saccade task. These findings are confirmed by the statistics.

Table 2
Mean values (±S.E.) for saccadic reaction time (SRT), coefficient of variation in SRT (CV), and percentage of direction errors (saccades toward target) for the Parkinson's (PD) and control groups as a function of fixation condition (gap or overlap) in the immediate anti-saccade task

	SRT (ms)	CV	Direction errors (%)
Gap condition			
PD	390 ± 18*	26 ± 1*	19 ± 3*
Control	340 ± 19	22 ± 1	19 ± 2
Overlap condition			
PD	433 ± 19*	29 ± 1*	14 ± 3*
Control	395 ± 23	25 ± 2	4 ± 1

* PD–control: $p < .05$.

Both the PD patients and the control group produced a gap effect that was similar in magnitude, $F(1, 17) = 135.75$, $p < .001$. The anti effect was driven by longer mean SRT in the anti-saccade task for the PD patient group as shown by a three-factor ANOVA (pathology × task × fixation condition) which revealed a significant interaction between pathology and experimental task, $F(1, 17) = 8.45$, $p = .01$. PD patients had longer mean SRT than control participants but only in the anti-saccade task, $F(1, 17) = 4.23$, $p = .05$; mean SRT for the PD group did not differ from the control group in the pro-saccade task, $F(1, 17) < 1$, ns. Longer anti-saccade mean SRT and equivalent pro-saccade mean SRT yielded a larger anti effect for PD patients.

The PD patient group showed increased intra-subject variability, CV, compared to the control group. A three-factor ANOVA (pathology × task × fixation condition) revealed PD participants to be more variable in responding than controls, $F(1, 17) = 8.47$, $p = .01$.

PD patients made more express saccades (latency 90–140 ms) in the immediate pro-saccade task. The PD–control difference approached significance, $Z = -1.70$, $p < .09$ in the gap condition and was significant in the overlap condition, $Z = -2.29$, $p < .05$ (Table 1). Earlier work (Munoz, Broughton, Goldring, & Armstrong, 1998) showed that older participants (>40 years) with no known pathology make very few express saccades. In contrast, the PD patient group in the current study (mean age = 67 years) made significantly more express saccades than the control group. More express saccades, especially in the overlap condition, suggest that PD patients are less subject to the inhibitory effects of fixation and are suggestive of pathophysiology (Biscaldi, Fischer, & Stuhr, 1996).

The lack of response inhibition is shown again in the anti-saccade performance of PD patients: they made significantly more direction errors in the anti-saccade task than control participants, $F(1, 17) = 9.12$, $p < .01$. Both groups made fewer direction errors on overlap trials than on gap trials, $F(1, 17) = 15.15$, $p = .001$ (Table 2).

The metrics of correct pro-saccades in the *immediate* task were computed (see Section 2) and are shown in Table 3, including the mean amplitude, duration and peak velocity of the primary saccade. There were no significant differences in velocity, $F(1, 17) = 3.63$, $p > .7$ or duration, $F(1, 17) = 3.29$,

Table 3
Saccade metrics from the immediate pro-saccade task

	Duration (ms)	Peak velocity (°/s)	Amplitude (°)	Number of saccades
Gap condition				
PD	81 ± 4	375 ± 12	18 ± 0.3*	1.3 ± 0.5*
Control	90 ± 2	350 ± 8	20 ± 0.1	1.1 ± 0.3
Overlap condition				
PD	82 ± 4	371 ± 10	18 ± 0.3*	1.3 ± 0.5*
Control	89 ± 2	346 ± 8	20 ± 0.1	1.1 ± 0.2

Mean values (±S.E.) for duration, peak velocity, amplitude and number of saccades executed for the Parkinson's (PD) and control groups in the immediate pro-saccade task as a function of fixation condition (gap or overlap).
* PD–control: $p < .05$.

$p > .08$ of the primary saccade between participants with PD and control participants. However, mean amplitude of the first correct saccade was smaller among PD patients, $F(1, 17) = 12.28$, $p < .01$ and they generated more saccades to reach the final target position, $F(1, 17) = 11.48$, $p < .01$, consistent with previous findings with PD patients (Kimmig, Haussmann, Mergner, & Lucking, 2002; Rottach, Riley, DiScenna, Zivotofsky, & Leigh, 1996; Shibasaki, Tsuji, & Kuroiwa, 1979; Teravainen & Calne, 1980; White, Saint-Cyr, Tomlinson, & Sharpe, 1983) and with MPTP-induced parkinsonism in humans and monkeys (Brooks, Fuchs, & Finocchio, 1986; Hotson, Langston, Langston, 1986; Kori, Miyashita, Kato, Hikosaka, Usui, & Matsumura, 1995).

3.2. Delayed pro-/anti-saccade task

Several aspects of performance among PD patients were impaired in the *delayed* pro-/anti-saccade task (Table 4). Although there was a trend toward increased SRT in the PD group, mean SRT for correct trials in the *delayed* tasks did not differ significantly between the groups (pro-saccades, $Z = -1.19$, $p > .2$; anti-saccades, $Z = -0.93$, $p > .3$). However, PD patients made more errors than control participants during both pro-saccade ($Z = -2.28$, $p < .05$) and anti-saccade trials ($Z = -2.43$, $p < .05$). Among saccades made in the correct direction, PD patients produced more timing errors than control participants during *delayed* pro-saccade trials, $Z = -2.12$, $p < .05$, but this deficit did not reach significance during *delayed* anti-saccade trials, $Z = -1.66$, $p > .09$. Among correctly delayed saccades, PD patients made more direction errors than controls during anti-saccade trials, $Z = -2.51$, $p < .05$ but not during pro-saccade trials, $Z = -0.78$, $p > .44$. PD patients made more errors that combined incorrect direction and timing than control participants in both tasks (pro-saccades, $Z = -2.44$, $p < .05$; anti-saccades, $Z = -2.48$, $p < .05$).

Table 4
Mean values (±S.E.) for saccadic reaction time (SRT), the percentage of correct trials, the percentage of timing errors, the percentage of direction errors, and the percentage of timing and direction errors for the Parkinson's (PD) and control groups in the delayed pro-/anti-saccade task as a function of task condition (pro-saccade or anti-saccade)

	SRT (ms)	Correct trials (%)	Timing errors (%)	Direction errors (%)	Timing and direction errors (%)
Pro-saccade task					
PD	366 ± 21	53 ± 7*	41 ± 7*	2 ± 1	4 ± 1*
Control	352 ± 17	78 ± 5	19 ± 5	2 ± 0.4	0.8 ± 0.2
Anti-saccade task					
PD	400 ± 19	53 ± 7*	27 ± 4	8 ± 2*	12 ± 3*
Control	377 ± 20	81 ± 5	15 ± 4	3 ± 1	2 ± 1

* PD–control: $p < .05$.

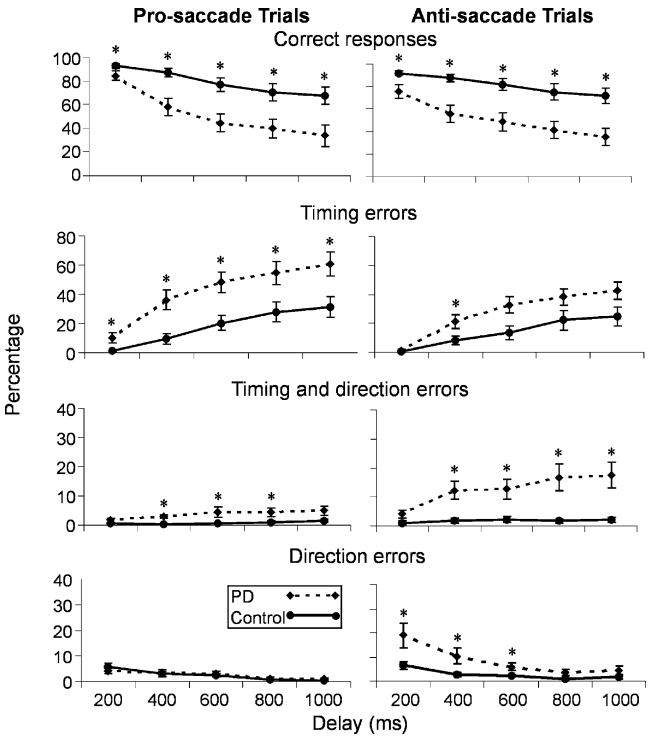

Fig. 4. Percentage (±S.E.) of trial types in the delayed pro-/anti-saccade task as a function of delay interval: *$p < .05$.

To examine the influence of the delay interval, each response type (correct, timing error, direction error, timing and direction error) was also calculated as a function of delay interval (Fig. 4). Both PD and control participants displayed a progressive decline in the percentage of correct trials as the delay interval increased from 200 to 1000 ms. Although, the difference in correct trials between PD and control participants increased from the 200 ms delay to 400 ms, the PD-to-control difference was more or less constant for delay intervals from 400 to 1000 ms. This same pattern of performance held for timing errors and combined timing and direction errors: at the short delay of 200 ms, PD patients were relatively similar to controls, but PD performance declined and stayed lower than controls for all delays over 200 ms. In contrast, while almost no direction errors occurred on pro-saccade trials for either group, patients with PD made more direction errors on anti-saccade trials but only for the relatively short delays between 200 and 600 ms.

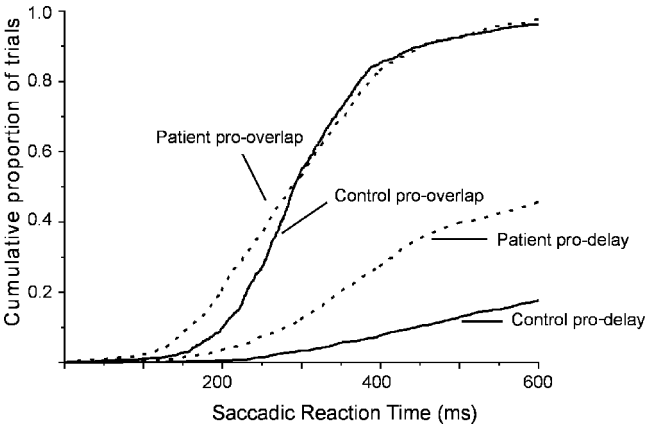

Fig. 5. Cumulative distributions of SRT from target appearance for immediate pro-overlap trials (correct responses) and delayed pro-saccade trials (timing errors) with a delay of 600 ms or greater.

Response inhibition can be examined directly by contrasting the cumulative SRT distribution for correct pro-saccade trials (*immediate*, overlap) with the cumulative SRT distribution of timing errors in the *delayed* pro-saccade task (*delay* ≥600 ms; Fig. 5). Note that the stimulus display was identical in the two conditions and only the instructions were different. In both, there was a visible, central FP and an eccentric target, however, in the *immediate* overlap condition, participants were instructed to move their eyes to the eccentric target immediately while in the *delay* condition, participants were instructed to withhold their eye movement until the FP disappeared. The difference between the immediate and delayed curves in Fig. 5 represents the ability of participants to inhibit an automatic response. If no timing errors were made, the latter (*delay*) curve would be flat, indicating that all saccades were executed after at least 600 ms following target appearance. If participants were completely unable to delay a saccade, the latter curve should be indistinguishable from the *immediate*-task curve. Although PD patients generated more timing errors than control participants, they successfully delayed saccadic eye movements on many trials, consequently, the cumulative distribution for timing errors was neither flat nor did it match the immediate overlap distribution. However, the area between the curves was clearly smaller for PD participants than for control participants (Wilcoxon $Z = 25.74$, $p < .001$) indicating once again that participants with PD were less able to inhibit a response to the eccentric target.

3.3. Delayed memory-guided sequential task

Fig. 6 shows a sample trial of the delayed memory-guided sequential task for a participant with PD and a control participant that highlights some consistent findings. The PD patient was less accurate in reaching the remembered target locations (Fig. 6A), undershooting the locations of the remembered targets, and also moving in the incorrect sequence by looking toward the location of target 3 before target 2. The control participant performed the task accurately, moving his eyes to

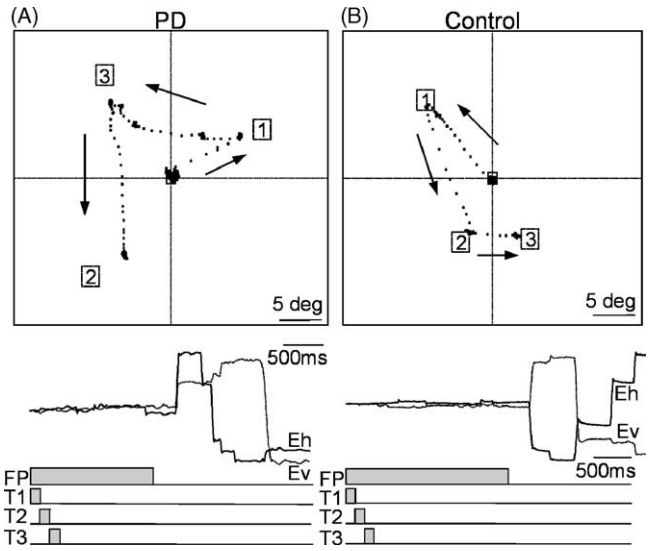

Fig. 6. Sample eye tracings of a trial from a PD patient (A) and control participant (B) in the delayed memory-guided sequential task. Participants were required to move their eyes to the remembered locations of the three target flashes in the remembered order of appearance. Horizontal (Eh) and vertical (Ev) eye tracings are shown. The PD patient undershot the remembered target locations and moved his eyes in the sequence of targets incorrectly. The control participant was accurate in reaching the remembered target locations and moved his eyes toward the correct sequence of targets.

the correct remembered locations of the targets in the correct sequence only after the disappearance of the FP (Fig. 6B). All trials were analyzed for timing and spatial errors.

Consistent with the other delay tasks, PD patients had greater difficulty delaying eye movements until the disappearance of the central FP, $t(17) = -2.90$, $p = .01$ (Fig. 7A). For correctly delayed trials, we computed displacement error (distance between each target and the closest eye fixation) for PD and control subjects. PD displacement error was greater

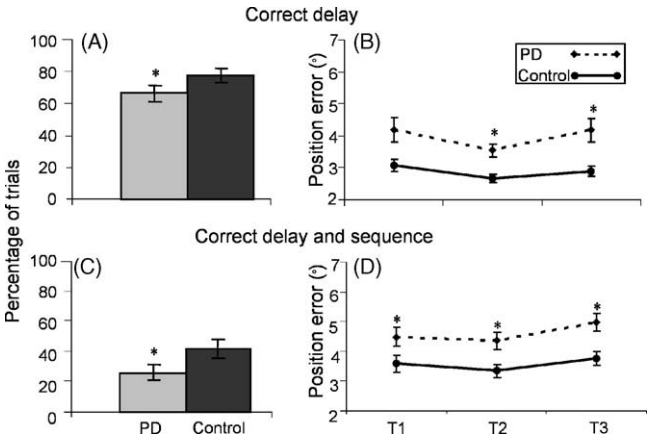

Fig. 7. The mean percentage (±S.E.) of trials in which PD patients and control participants were able to correctly hold gaze at the central FP until its offset (A) and also generate the correct sequence of saccades to the remembered target locations (C). The magnitude of displacement error between each target (T1, T2, T3) and the closest eye fixation (±S.E.) of PD and control participants for correct delay trials (B) and correct delay and sequence trials (D): $^{*}p < .02$.

than controls' towards target 2, $t(17) = 3.60$, $p < .01$ and target 3, $t(17) = 3.92$, $p = .001$ but not towards target 1, although the same robust trend was present, $t(17) = 2.41$, $p > .02$ (Bonferroni corrected; Fig. 7B). Fig. 7C illustrates the percentage of trials in which the participants were able to correctly maintain their eyes at the central FP until its disappearance, and move their eyes toward the remembered location of the three targets in the correct sequence. PD patients had fewer of these successes compared to control participants, $t(17) = -2.81$, $p < .05$, and they had greater displacement error towards all of the targets, $p < .01$ (see Fig. 7D). These results demonstrate that PD patients are impaired in their ability to inhibit a response and to move accurately to a sequence of remembered targets.

4. Discussion

We have shown that specific characteristics of saccadic eye movements are impaired in PD. We stress five important observations. First, PD patients made more express saccades in the immediate pro-saccade task. Second, they generated more direction errors in the immediate anti-saccade task. Third, PD patients were less able to inhibit saccades during the delay period in all delay tasks. Fourth, PD patients had longer reaction times in the anti-saccade task. Fifth, PD patients were impaired in their ability to move their eyes to remembered targets in the correct sequence. The first three observations reveal that participants with PD have deficits in their ability to inhibit automatic saccades; the fourth observation demonstrates that volitional saccades took longer to generate for the patient group; and the fifth observation shows deficits in spatial working memory processes in PD patients. These deficits are discussed in relation to previous studies and we speculate on the possible neural circuitry for the lack of inhibition of eye-movement responses in PD.

4.1. Automatic response inhibition in PD

In the current study, the sudden appearance of an eccentric stimulus acted to facilitate movements toward the target in PD, resulting in an increased percentage of express saccades in the *immediate* pro-saccade task, an increased percentage of direction errors in the *immediate* anti-saccade task, and increased occurrence of timing errors in the *delay* tasks. Previous oculomotor studies of PD patients employed the gap condition only (Briand, Strallow, Hening, Poizner, & Sereno, 1999; Crevits & De Ridder, 1997; Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Lueck, Tanyeri, Crawford, Henderson, & Kennard, 1990; Kitagawa, Fukushima, & Tashiro, 1994; Roll, Wierzbicka, & Wolf, 1996), which is known to facilitate the initiation of automatic saccades (Fischer & Weber, 1993; Munoz & Corneil, 1995; Saslow, 1967). Performance in the overlap condition was not investigated in patients with PD. Because fixation activity in the brain is increased during fixation of a visible stimulus (as in the overlap condition; Dorris & Munoz, 1995; Everling, Pare, Dorris, & Munoz, 1998a; Everling, Dorris, Klein, & Munoz, 1999), fewer direction errors and increased SRT are expected in such trials. In the present study, PD patients nonetheless made a greater number of express saccades and direction errors in the overlap condition, consistent with an abnormality in saccadic suppression. Increased occurrence of express saccades in overlap trials indicate potential pathophysiology in the system controlling fixation (Biscaldi, Fischer, & Stuhr, 1996; Cavegn & Biscaldi, 1996) or saccadic inhibition (Muri et al., 1999).

Previous investigations on motor and cognitive control in PD have identified similar deficits to what we have described. Cognitive processes, such as attention control, are also impaired in PD (Brown and Marsden, 1990). Individuals with PD were faster than controls on a reflexive visual-orienting task (Briand, Hening, Poizner, & Sereno, 2001) and showed impairment in suppression of visuomotor activation (Praamstra and Plat, 2001). In the Stroop task, participants are presented with color or neutral words in various colors and asked to ignore the word and name its color. Individuals with PD demonstrate greater difficulty in inhibiting the reflexive response to read the word (Henik, Singh, Beckley, & Rafal, 1993). These parallel findings across various cognitive and oculomotor tasks suggest a common mechanism underlying a general deficit in automatic response suppression.

It has long been known that the slow, hypokinetic movements of PD can be improved through the provision of external cues (Cunnington, Iansek, Bradshaw, & Phillips, 1995; Jahanshahi, Jenkins, Brown, Marsden, Passingham, & Brooks, 1995; Morris, Iansek, Matyas, & Summers, 1996). For example, stride length can be increased with external visual cues (Morris, Iansesk, Matyas, & Summers, 1994) and reaching movement speeds can be improved during visually cued conditions (Majsak, Kaminski, Gentile, & Flanagan, 1998); thus, automatic motor actions (i.e., movements to an external visual cue) appear to be spared in PD, unlike movements which are volitional. Even more intriguing is the observation that long-latency reflexes are also altered in PD. Tatton and colleagues (Tatton & Lee, 1975; Tatton, Eastman, Bedingham, Verrier, & Bruce, 1984) demonstrated that long-loop reflexes, which are presumed to include transcortical pathways, are exaggerated in PD (see also Mortimer & Webster, 1979; Rothwell, Obeso, Traub, & Marsden, 1983). These exaggerated "M2" responses in PD have been attributed to reduced inhibition onto cortical motor output neurons. Thus, it appears that PD patients are hyper excitable to sensory stimuli and reflexive or automatic responses to external stimuli are enhanced or exaggerated.

Sereno and Holzman (1995, 1996) proposed a model of schizophrenia to account for reflexive and voluntary control of attention that may also be valid for eye-movement control in PD. Sereno and Holzman's model argues that eye movements are controlled by two different attentional systems, one controlling reflexive or automatic saccades and the other controlling voluntary saccades. Normally, the voluntary eye-

movement system tonically inhibits the reflexive system. If the voluntary system is not performing properly, there will be deficits in voluntary eye-movement control and less inhibition on the reflexive system. Our results support this hypothesis.

4.2. Spatial working memory in PD

The delayed memory-guided sequential task examined both spatial working memory and response suppression. PD participants made less accurate eye movements toward remembered locations, they had greater difficulty in moving their eyes towards the targets in the correct sequence, and their final eye position was hypometric to the targets relative to controls, replicating results obtained by Hodgson, Dittrich, Henderson, and Kennard (1999). Hodgson et al. (1999) used only four target locations left and right of fixation, hence, it was unclear from their study whether participants were recalling the spatial locations of the target flashes, or simply memorizing potential target locations. Because we used many more potential locations (a target appeared in any of 25 locations in each of the four quadrants of the visual field; i.e., 100 possible locations), memorization across trials was much less likely to account for our results and we conclude that the PD group performance reflects a deficit in working memory for motor plans.

Hodgson et al. (1999) demonstrated that deficits in spatial working memory in PD patients are not simply due to difficulties in coordinating movement sequences, as individuals with PD show normal eye position gain when sequences were over-learned. Although the spatial memory representation of target location in memory-guided saccades to a single target appears normal (Crawford, Henderson, & Kennard, 1989), PD patients execute hypometric saccades when required to fixate a sequence of locations (Vermersch et al., 1994). Other studies show that PD patients make increased errors in tasks requiring spatial working memory (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Postle, Jonides, Smith, Corkin, & Growdon, 1997).

5. Neural pathways

The mechanisms by which the voluntary system exerts inhibitory control over the reflexive or automatic system including how target locations are memorized for future actions are hallmarks of frontal lobe function. Hallet (1978) hypothesized that, in the anti-saccade task, the inhibition of reflexive saccades requires frontal processes to send a stop signal to the superior colliculus. If the stop signal is delayed beyond a critical point, a reflexive or automatic response ensues. The signals that the superior colliculus receives from frontal areas may normally provide an effective cancellation signal, while dysfunction in executive function and working memory processes may impede such signals in PD, leading to abnormal control of inhibitory operations. Suppression of automatic saccades may rely heavily on working memory processes (Roberts, Hager, & Heron, 1994; Stuyven, Van der, Vandierendonck, Claeys, & Crevits, 2000). As such, it is probable that operations shared by both working memory and stop signal generation are included in the voluntary saccade system and work in concert to regulate the expression of automatic responses.

Areas of frontal cortex involved in the generation of oculomotor responses include the frontal eye field (FEF), the supplementary eye field, and the dorsolateral prefrontal cortex (DLPFC; Pierrot-Deseilligny, Rivaud, Gaymard, Muri, & Vermersch, 1995; Pierrot-Deseilligny, Ploner, Muri, Gaymard, & Rivaud-Pechoux, 2002); these areas all receive input integrated through the basal ganglia (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2002). The DLPFC has been especially implicated in both the inhibition of automatic saccades and in spatial working memory. Patients with lesions of the DLPFC make more reflexive timing errors (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Ploner et al., 1999) and direction errors (Guitton, Buchtel, & Douglas, 1985; Walker, Husain, Hodgson, Harrison, & Kennard, 1998) in saccadic tasks. Functional imaging studies have observed DLPFC activation during voluntary saccade tasks (Sweeney et al., 1996; Doricchi et al., 1997). One role of the DLPFC in the generation of voluntary saccades is thought to be the mediation of the suppression of automatic saccades by direct and also indirect cortical projections to the FEF and the midbrain superior colliculus (see Munoz & Everling, 2004 for review). Everling and colleagues (Everling & Munoz, 2000; Everling, Dorris, & Munoz, 1998b; Everling, Dorris, Klein, & Munoz, 1999) showed that the successful suppression of automatic visually triggered saccades in an anti-saccade task depends on the reduction of pretarget neural excitability of saccade neurons in the superior colliculus and FEF which is likely influenced by prestimulus processing in the DLPFC.

The DLPFC has also been shown to have a special role in spatial working memory (Funahashi, Bruce, & Goldman-Rakic, 1991; Funahashi, Bruce, & Goldman-Rakic, 1993b; Goldman-Rakic, 1987; Kessels, Postma, Wijnalda, & de Haan, 2000; Pierrot-Deseilligny, Ploner, Muri, Gaymard, Rivaud-Pechoux, 2002; Yeterian & Pandya, 1991). Lesions of the prefrontal cortex in monkey interfere with working memory tasks (Bachevalier & Mishkin, 1986) and activation of DLPFC has been demonstrated on tasks requiring spatial working memory (Baker et al., 1996; McCarthy et al., 1994, 1996). Funahashi, Chafee and Goldman-Rakic (1993a) showed that a subset of neurons in the DLPFC is involved in both coding of the spatial location of a visual stimulus and in the suppression of a response to the target in a delayed anti-saccade task.

Results from the current study demonstrate a deficit in saccadic inhibition and spatial working memory in PD patients, a pattern that is consistent with DLPFC impairment. The DLPFC is known to be involved in one of several discrete frontal-basal ganglia circuits that act to “funnel” inte-

grated inputs to cortex (Alexander, DeLong, & Strick, 1986). Regions of DLPFC receive significant input from substantia nigra pars reticulata via the thalamus (Middleton & Strick, 2002). Thus, loss of dopaminergic input to the striatum in PD will lead to the disruption of this prefrontal-basal ganglia circuitry resulting in impairment in both automatic response suppression and working memory processes involved in the generation of voluntary saccades. Support for DLPFC impairment has been demonstrated through working memory deficits in PD (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Hodgson, Dittrich, Henderson, & Kennard, 1999) and imaging studies that reveal changes in DLPFC blood flow in PD patients (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Kikuchi et al., 2001). Furthermore, transcranial magnetic stimulation applied over the DLPFC results in facilitation of express saccades (Muri et al., 1999), consistent with results of the current study. It remains to be determined whether the "frontal" deficits we have described in PD patients performing oculomotor tasks are the result of striatal pathophysiology alone or whether this includes additional pathology of frontal cortex directly.

6. Adaptive mechanisms?

PD patients had shorter SRT, more express saccades, more impulsive saccades toward a target; and, they did not wait for the signal to go before making a saccade to a target. Neurological deficits may elicit these behaviors directly (see above), but an alternative explanation could be that patients with PD adapt their behavior over the course of their illness to cope with disabilities. PD patients are slow to initiate voluntary, goal-directed movements. For example, correct anti-saccades have abnormally long SRTs (see Fig. 3 and Table 2). As a consequence, patients with PD may alter (reduce) baseline response inhibition in an effort to initiate movements more rapidly. For most physical movements, such a mechanism would not be apparent because voluntary movements continue to be initiated more slowly in PD patients. However, eye movements to visual targets can take advantage of direct sensory-to-motor mapping in structures like the superior colliculus (Munoz, Dorris, Paré, & Everling, 2000). Hence visually triggered eye movements made by PD patients can be initiated more easily if saccadic suppression signals are attenuated. There is some merit to this explanation. LeVasseur, Flanagan, Riopelle, and Munoz (2001) also described a paradoxical effect in patients with Tourette's Syndrome performing oculomotor tasks. In their study, Tourette's patients had longer reaction times, fewer express saccades, and no increase in the occurrence of direction errors in the immediate anti-saccade task despite their well-known deficit in inhibitory control. Patients with Tourette's syndrome lack adequate control over isolated response behaviors, and, possibly adapt to this reality by imposing more inhibition to reduce inappropriate behavioral responses. Thus, performance of Tourette's patients on oculomotor tasks could also be consistent with an adaptive mechanism that served to increase baseline response inhibition. From our results, we cannot rule out the possibility that an adaptive mechanism could account for the hyper excitability of PD patients in response to sensory stimuli.

7. Conclusions

We described performance of PD patients in a battery of saccadic eye-movement tasks. PD patients executed more express saccades in the pro-saccade task, had increased direction errors in the anti-saccade task, and had greater difficulty inhibiting eye movements in the delayed oculomotor tasks. Additionally, they were impaired in their ability to accurately localize remembered targets. These results are consistent with PD impairment in saccadic inhibition and working memory, thus consistent with a disorder of the prefrontal-basal ganglia circuit. We have implied that the PD participants had otherwise intact frontal lobes without showing this to be true through physical (i.e., MRI) or functional (i.e., neuropsychological) tests. Hence, we can merely suggest that our results are consistent with an impairment of frontal-basal ganglia circuits that releases the automatic saccade system from inhibition and produces deficits in the system controlling voluntary saccade generation. Additional research may confirm this dysfunction. The development of adaptive mechanisms may have contributed to these behavioral abnormalities.

Acknowledgements

We gratefully acknowledge the assistance of K. Moore. A. Bell, I. Cameron, M. Dale, J. Fecteau, J. Gore, A. Lablans, R. Levy, and R. Marino who commented on an earlier version of the manuscript. This work was supported by the Canadian Institutes for Health Research and the Canada Research Chair Program.

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