Neuropsychologia 48 (2010) 1948–1957

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Executive impairment in Parkinson's disease: Response automaticity and task switching

Ian G.M. Cameron[a,b], Masayuki Watanabe[a,b], Giovanna Pari[a,c], Douglas P. Munoz[a,b,c,d,e,*]

[a] Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada
[b] CIHR Group in Sensory-Motor Integration, Queen's University, Kingston, Ontario, Canada
[c] Department of Medicine, Queen's University, Kingston, Ontario, Canada
[d] Department of Physiology, Queen's University, Kingston, Ontario, Canada
[e] Department of Psychology, Queen's University, Kingston, Ontario, Canada

ARTICLE INFO

Article history:
Received 2 November 2009
Received in revised form 17 February 2010
Accepted 12 March 2010
Available online 19 March 2010

Keywords:
Saccade
Antisaccade
Oculomotor
Basal ganglia
Executive function

ABSTRACT

Patients with Parkinson's disease (PD) show slowed movement initiation and can have deficits in executive function, leading to impairments in controlling involuntary behavior. This results in difficulties performing an *antisaccade*, which requires one to suppress an automatic eye movement (a *prosaccade*) to a visual stimulus, and execute a voluntary eye movement in the opposite direction. Antisaccade deficits are similar to those seen in *task switching*, whereby one is required to change a response after performing a different behavior. Both antisaccade (Hood et al., 2007) and task switching (Cools, Barker, Sahakian, & Robbins, 2001) deficits in PD have been attributed to fronto-basal ganglia (BG) dysfunction. Previously, we demonstrated with functional magnetic resonance imaging that BG circuitry is important to both task switching and voluntary saccade generation, as greater caudate activation was seen when healthy young adults first prepared a prosaccade, but then switched to an antisaccade (Cameron, Coe, et al., 2009). Therefore, we hypothesized that PD patients would have difficulty switching from one saccade response to the other, with particular impairment in switching from a pro to an antisaccade. Here, we not only confirmed this prediction, but also showed that PD patients performed better than controls in switching from an anti to a prosaccade. This suggests that task switching deficits in PD are particularly pronounced when more automatic behavior needs to be overridden with alternative behavior. We suggest that this occurs primarily at the level of establishing the appropriate *task set*, which is an internalized rule that governs how to respond.

1. Introduction

Parkinson's disease (PD) involves the degeneration of dopamine producing cells in the substantia nigra pars compacta that input to the striatum (Betchen & Kaplitt, 2003). The consequence of this is altered neuronal firing in the two principal pathways of the basal ganglia (BG): the *direct* and *indirect*, which leads to a net increase in inhibitory output from the BG on thalamo-cortical circuits, and on the superior colliculus (Dagher & Nagano-Saito, 2007; Hikosaka, Takikawa, & Kawagoe, 2000; Mink, 1996; Schultz, 2001). This results in the hallmark motor symptoms of bradykinesia (slowed movement execution) and akinesia (impaired movement initiation), and is thought to contribute to executive dysfunction often observed in PD which resembles that following frontal lobe damage (Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen, 2004). Accordingly, tasks that require both an initiation of a motor response as well as executive control over behavior unearth deficits in behavioral control in PD. In the *antisaccade* task, PD patients fail to suppress an automatic *prosaccade* to a visual stimulus more frequently than normal healthy adults, resulting in erroneous eye movements in the direction of the stimulus (Amador, Hood, Schiess, Izor, & Sereno, 2006; Briand, Strallow, Hening, Poizner, & Sereno, 1999; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Hood et al., 2007). PD patients are also slower to initiate an antisaccade. The antisaccade task is one of the simplest models of behavioral control, and deficits in PD suggest that deficient dopaminergic (DA) input to the BG disrupts the suppression and focusing mechanisms (Mink, 1996) of the BG on cortical (e.g., frontal eye fields, dorsolateral prefrontal cortex) signals critical to generating a voluntary saccade, and suppressing an automatic saccade (Munoz & Everling, 2004). Importantly, these antisaccade deficits highlight an asymmetric impairment in PD, in which an *unimpaired* automatic response interferes with the execution of an alternative, voluntary, response. Some evidence exists that this impairment might occur

* Corresponding author at: Centre for Neuroscience Studies, Botterell Hall, Room 234, 18 Stuart Street, Queen's University, Kingston, Ontario, Canada K7L 3N6. Tel.: +1 613 533 2111; fax: +1 613 533 6840.
E-mail address: doug_munoz@biomed.queensu.ca (D.P. Munoz).

0028-3932/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2010.03.015

Table 1
Clinical information for PD patients.

Patients	Gender	Age (yrs)	MMSE	UPDRS				Medication	Yrs since initial diagnosis
				Part II (ADL)	Part III (motor)	Part V (Hoehn and Yahr)	Part VI (Schwab and England)		
1	m	68	30	3	10	1.0	100	R	0.50
2	m	67	29	13	32	2.0	90	R	7.00
3	m	35	29	11	23	2.0	90	A, E, L, L-CR	3.00
4	f	60	30	5	30	2.5	90	D, L, R	3.25
5	m	45	30	5	19	2.5	90	L, R	1.50
6	m	67	29	8	26	2.0	90	L, P	6.00
7	m	61	30	13	33	2.0	80	L, P	7.50
8	m	69	29	9	18	2.5	90	L, P, S	11.00
9	f	73	30	6	27	2.5	90	L, L-CR, R	9.50
10	m	55	27	10	23	2.5	90	L	6.25
11	f	59	30	11	26	3.0	90	P	1.00
12	f	64	30	8	22	2.0	90	P	2.50
13[a]	m	72	28					L, R	6.00
14[a]	m	47	26	11	26	2.5	80	A, L, L-CR, R	10.25
Mean (n = 14)	10m; 4f	60.1	29.1						
Mean (n = 12)	8m; 4f	60.3	29.4	8.5	24.1	2.2	90.0		4.92
Controls mean (n = 12)	5m; 7f	59.9	29.8						

A, anticholinergic (trihexyphenidyl); ADL, Activities of Daily Living; D, domperidone; E, entacapone; L, levodopa/carbidopa; L-CR, controlled release levodopa/carbidopa; MMSE, Mini Mental State Examination; P, pramipexole dihydrochloride; R, ropinirole HCl; S, amantadine; UPDRS, Unified Parkinson's Disease Rating Scale (UPDRS for subject 13 was not available); Yrs, years.

[a] Subjects removed for failure to perform task switching design.

at a more cognitive stage, during which an antisaccade *task set* (a rule about how to respond) is established prior to response programming (Rivaud-Pechoux, Vidailhet, Brandel, & Gaymard, 2007). However, most previous studies have focused on the failure to suppress an automatic prosaccade to a peripheral stimulus, and on the slower programming of the voluntary antisaccade away from the stimulus in PD. More work is needed to understand how the easier prosaccade task set might compete with the more difficult antisaccade task set, setting-up a person with PD for an incorrect or impeded response before a response is programmed.

To explore this, we now draw on studies of *task switching* that have been more optimally designed to explore the interaction between competing task sets. Task switching experiments have also shown that PD patients have deficits in behavioral flexibility that can be explained, at least partially, by fronto-BG dysfunction. Deficits include slowed reaction times when the appropriate response changes across trials (Cools, Barker, Sahakian, & Robbins, 2001, 2003), perseveration errors in the Wisconsin Card Sorting Task (Lees & Smith, 1983; Milner, 1963) related to the inability to change task set, and impairments in working memory resulting in deficits manipulating rule representations (Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen, 2004). Importantly, it has been demonstrated with functional magnetic resonance imaging (fMRI) that fronto-BG circuitry is important to task switching (Cools, Ivry, & D'Esposito, 2006) and that differences in cortical as well as BG activation are seen when comparing PD patients and control subjects performing switching tasks (Monchi et al., 2004; Monchi, Petrides, Mejia-Constain, & Strafella, 2007). However, unlike the antisaccade task, studies in task switching typically rely on participants to switch between stimulus–response mappings learned in a given experiment, and do not contrast highly automatic behavior to alternative, more difficult behavior to perform. An exception to this is a study by Woodward, Bub, and Hunter (2002), who showed in a Stroop paradigm that patients with PD had greater reaction time 'costs' than controls when they first performed the more automatic word reading response, but then subsequently performed the more difficult color naming response. Thus, deficits in task switching in PD may relate to how 'easily' one can switch between two behaviors that differ in automaticity.

We previously created a paradigm in which participants were prompted to plan one response (pro or antisaccade) but then switch it, unexpectedly, to the alternative on a subset of trials (Cameron, Watanabe, & Munoz, 2007). Importantly, the switching difficulty was asymmetric, meaning that subjects could be switching to a response that was either more automatic (prosaccade), or less automatic (antisaccade), to perform. Moreover, the time in a given trial in which the switch occurred varied with respect to peripheral stimulus onset, such that if the switch in instruction occurred in advance of stimulus onset, it would constitute a change of task set alone. Using a version of this paradigm, we also showed with fMRI that activation in the caudate nucleus (CN), the BG input nucleus in the oculomotor system, correlated to switching difficulty (Cameron, Coe, Watanabe, Stroman, & Munoz, 2009). A greater increase in CN activation occurred when subjects first planned a prosaccade, but then had to switch to an antisaccade, than when subjects first planned an antisaccade, but then had to switch to a prosaccade. This demonstrated that activation of the CN correlated with switching from a more automatic to a more difficult behavior. Based on previous findings from the antisaccade and task switching literature, we hypothesize that PD patients in a similar task will show greater difficulties (increased reaction time and error rates) on antisaccade trials compared to control subjects, greater difficulties in switching task, and greatest difficulties in switching from a pro to an antisaccade. We are also interested in determining if deficits exist when only task set is changed.

The results show that PD patients had an underlying bias towards the more automatic prosaccade response that interacted with their task switching behavior: patients were overall superior at prosaccade performance, but impaired at antisaccade performance. Thus, with respect to task switching, patients showed poorer performance in switching from a pro to an antisaccade in comparison to the controls, but showed superior performance in switching from an anti to a prosaccade. Interestingly, their poorer performance in switching from a pro to an antisaccade occurred only when a change in task set was required. Therefore, we suggest that enhanced biases towards more automatic or habitual behavior exist prior to programming a response in PD, and this can explain some of the deficits observed in both antisaccade and task switching experiments.

2. Methods

2.1. Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board and adhered to the Declaration of Helsinki. 26 individuals (14 PD, 12 age-matched control participants) with normal or corrected-to-normal vision were recruited. All participants were permitted to wear corrective lenses if required, and all participants provided written informed consent and were compensated for their participation ($10/h). PD patients (mean age = 60.1, 10 males) were recruited from GP's movement disorder clinic at the Kingston General Hospital, and age-matched controls (mean age = 59.9, 5 males) were recruited from the Kingston community. PD patients were considered early/moderate stage based on a mean Hoehn and Yahr score of 2.2. Clinical data and participant demographics are shown in Table 1.

PD patients were medicated and were not asked to interrupt their medication on the days of recording, due to the difficulty of the task (expected to produce a large percentage of error trials), and the fact that antisaccade deficits have been shown to occur in PD even while taking dopaminergic medications (Briand et al., 1999; Cameron, Pari, Alahyane, Coe, Stroman, & Munoz, 2009; Chan et al., 2005; Hood et al., 2007). Medication information for each patient is given in Table 1. All control participants reported no history of neurological, psychiatric or visual disorders (other than refractive error), and did not differ as a population in terms of age and years of education. Finally, all participants underwent an evaluation of mental status, using the Mini Mental State Examination (MMSE) by IC. A score of 26 or lower was used as exclusion criteria.

2.2. Design and procedure

Horizontal eye position was monitored online with DC-electrooculography (EOG). To minimize DC drift the skin was cleaned with rubbing alcohol and participants wore the electrodes for approximately 5-10 min before the experiment began. Additional DC drift was corrected manually during the experiment. Stimulus presentation and monitoring of eye position were done using REX Version 5.4, sampling at 1000 Hz (Hays, Richmond, & Optican, 1982). Prior to data collection the EOG signal was calibrated by having subjects look between targets that were located at 10° left, 10° right and center position. Data analyses were conducted with custom software developed in MATLAB 7.4 (The Mathworks, Natick, MA).

Participants were seated 1 m from a tangent visual screen and an array of LED stimuli was positioned just in front of the screen. A head rest was used to minimize any change in head position. All of the experiments were conducted in the dark however the screen was diffusely illuminated for 600 ms between trials to prevent dark adaptation.

2.3. Blocked design

Participants first performed a prosaccade task that required them to initiate a saccade to a peripheral stimulus (target) that appeared 10° to the left or right of a central fixation point (FP) that marked the onset of the trial (Fig. 1). The FP was a light emitting diode (LED), colored red (8.0 cd/m^2) or green (3.0 cd/m^2), because subjects would subsequently perform an antisaccade task with the opposite fixation color (described below), and fixation color was counterbalanced across subjects. In the end, 5/12 controls and 7/14 PD patients received the red fixation instruction for the prosaccade task. The target appeared 900 ms after participants fixated the fixation point, and was the same color as the central fixation point. Participants were required to look to the target as soon as it appeared and to hold their gaze on the target for 160 ms before the target disappeared and the screen was illuminated for 600 ms to end the trial. Participants were required to complete 100 correct trials (defined by direction and by reaction time of <1000 ms from target onset).

Next, the participants performed a block of 100 correct antisaccade trials. The parameters of the antisaccade block were identical to those in the prosaccade block, however the participants were required to refrain from eliciting a saccade to the target, and instead, to make a saccade to the mirror location. The target remained the same color as in the prosaccade block but the FP was now the opposite color to instruct an antisaccade.

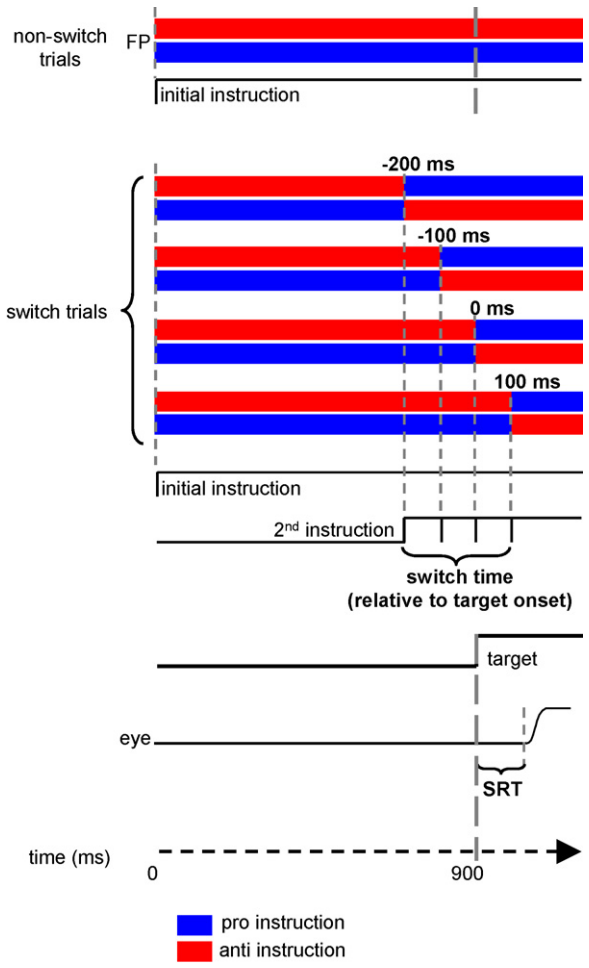

Fig. 1. Experimental parameters. In both the blocked and task switching design, a green or red fixation point (FP) was presented, instructing subjects to prepare a pro or antisaccade (illustrated in the figure as blue = pro instruction, red = anti-instruction). In the blocked design the peripheral stimulus (target) appeared 900 ms after fixation was acquired, and subjects executed a saccade upon its presentation. Saccade reaction time (SRT) was calculated relative to target onset. The blocked design consisted of 100% non-switch trials. In the task-switching design, 66% of the trials were non-switch, as on 33% of the trials, the initial instruction switched at −200, −100, 0 or +100 ms relative to the onset of the target.

2.4. Task switching design

The basic experimental setup remained the same as the blocked design, with each trial beginning with the onset of the red or green FP corresponding to the same instructions as in the blocked design. However, on 33% of the trials, the initial fixation color switched to the opposite color at 4 variable 'switch times' relative to target appearance: −200, −100, 0 and +100 ms (Fig. 1). When this occurred, subjects were required to switch task, and these trials are referred to as 'switch trials'.

We chose the 4 switch times to investigate how behavior would differ if subjects had more or less time to switch task. Greater percentage direction errors and increased saccade reaction time (SRT) on switch trials relative to non-switch trials are referred to as 'switch costs' and it was expected that switch costs should be greater when participants had less time to switch (Cameron et al., 2007). Importantly, two of the switch times occurred before target onset (−200 and −100 ms) meaning that if PD patients have difficulty in establishing a new *task set* (a rule about which action to perform) (Sakai, 2008), switch costs might be greater than controls, and a deficit at these switch times would suggest impairments in executive function primarily. In contrast, the 0 and +100 ms switch times involved a change in task concurrent with, or after, the target had appeared, meaning that a pro or antisaccade response to the target may have already been in preparation (Cameron et al., 2007). Thus, greater switch costs in PD at these times would suggest a deficit in overriding one prepared response with another.

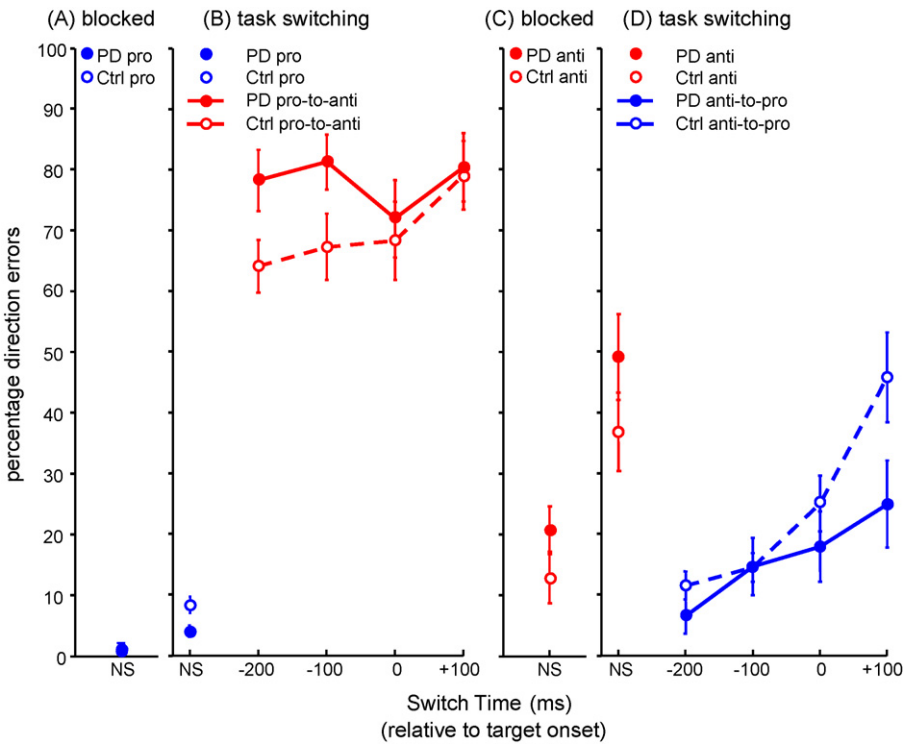

Fig. 2. Percentage direction errors. (A) Blocked design, prosaccade trials (pro). Solid data points represent the PD patients (PD), and hollow data points represent the controls (Ctrl). 'NS' signifies that trials were non-switch. (B) Task switching design, non-switch prosaccade trials (pro) and pro-to-antisaccade switch trials (pro-to-anti). (C) Blocked design, antisaccade trials (anti). (D) Task switching design, non-switch antisaccade trials (anti) and anti-to-prosaccade switch trials (anti-to-pro). Error bars represent standard error of the mean.

Participants were asked to perform 4–5 blocks of 100 correct trials. However, no subject was required to perform more than 200 trials (correct or error) per block, and no subject was required to perform more than 1000 trials in total. In the end, 11/12 control participants achieved 400 correct trials in the task switching design with one achieving 250. For PD patients, 8/14 achieved 400 correct trials, 2 achieved 300 correct trials, and 2 achieved 150 correct trials. The remaining 2 PD participants (numbers 13 and 14 in Table 1) could not perform the task (executed close to 100% errors on all switch trials), and were excluded from further analysis, yielding the comparison of 12 PD participants (mean age = 60.3 years, 8 male, see Table 1) to 12 age-matched controls.

2.5. Analysis

Failure to fixate the first fixation point within 5000 ms, failure to maintain fixation, failure to initiate a saccade within 1000 ms, and failure to fixate the saccade target for at least 160 ms were removed from analysis. SRT was defined as the time from when the target appeared to when the first saccade away from fixation exceeded 30°/s. Saccades with reaction times <90 ms were also excluded, representing anticipatory errors as defined by a previous study in the same laboratory that showed that prosaccades of human subjects less than this value were initiated with only 50% accuracy (Munoz, Broughton, Goldring, & Armstrong, 1998).

The errors of primary interest in the current study were those in which participants executed the wrong saccade to the target based on the current instruction (a prosaccade on anti instruction or vice versa). These errors were labelled as 'direction errors', and the percentage of direction errors was calculated by dividing the errors by the total number of valid trials (correct trials + direction error trials) for the pro or antisaccade condition. Errors that qualified as failures to initiate a saccade were also analyzed by dividing these errors by the total number of all trials.

Reaction times and percentage direction errors on non-switch and switch trials were analyzed first with omnibus 3-way repeated measures ANOVAs in SPSS Statistics version 17.0, with a between-subject factor of 'Group' (2 levels: PD and Control), a within-subject factor of 'Switch Time' (5 levels: non-switch, −200, −100, 0, +100), and a within-subject factor of 'Initial Task' (2 levels: pro and anti). To test our a priori hypothesis, subsequent 2-way repeated measures ANOVAs were conducted between (i) non-switch prosaccade trials and pro-to-antisaccade switch trials, and (ii) non-switch antisaccade and anti-to-prosaccade switch trials, to contrast trials that that began with the identical initial instruction, and thus, with an identical initial task set. The significance level for all tests was set at $P < 0.05$, and the Greenhouse-Geisser (ε) correction was used if the sphericity of variances was violated.

To specifically understand differences in task switching between PD patients and controls, 'switch costs' in SRT and percentage direction errors were calculated by comparing non-switch trials to switch trials of an identical initial task (e.g., non-switch pro trials, and pro-to-anti switch trials). Switch costs were presumed to reflect the requirements of the brain to override one behavior with the alternative. For direction errors, switch costs at each switch time were calculated by subtracting the mean of non-switch trials from the mean of switch trials for a given switch time for each participant. A positive value indicated a switch cost. For SRT switch costs, we used a normalized index:

$$\text{switch cost index} = \frac{\text{MEANswitch} - \text{MEANnon-switch}}{|\text{MEANswitch} - \text{MEANnon-switch}| + \sqrt{(\text{SDswitch})^2 + (\text{SDnon-switch})^2}}$$

which incorporated variability in reaction times in addition to mean reaction times (Prince, Pointon, Cumming, & Parker, 2002). We did not assume that variability in reaction times would be the same across patients and controls, and across non-switch and switch trials. If the difference of the means was large and the variance was small, this index was close to ±1 depending on which mean was larger; if the variance was large, the switch cost indices were smaller. For switch costs, a 2×4 ANOVA was conducted, with a between-subjects factor of Group (PD and Control) and a within-subjects factor of Switch Cost with 4 levels (−200, −100, 0, +100). Post hoc t-tests (independent, two-tailed) were conducted at individual switch times to compare PD patients with controls for a given response where stated.

For the blocked design, paired t-tests were used to compare SRTs within subjects for pro and antisaccades, and independent t-tests were used to compare across groups, $P < 0.05$, corrected for multiple comparisons (Bonferroni). Mann–Whitney U-tests (Z) were used for direction errors due to the fact that very few errors on prosaccade trials were made, meaning that the distribution of prosaccade error rates was non-parametric around a floor value of zero (Kolmogorov–Smirnov test, $P < 0.05$). Finally, Pearson's r values were used for correlation analyses.

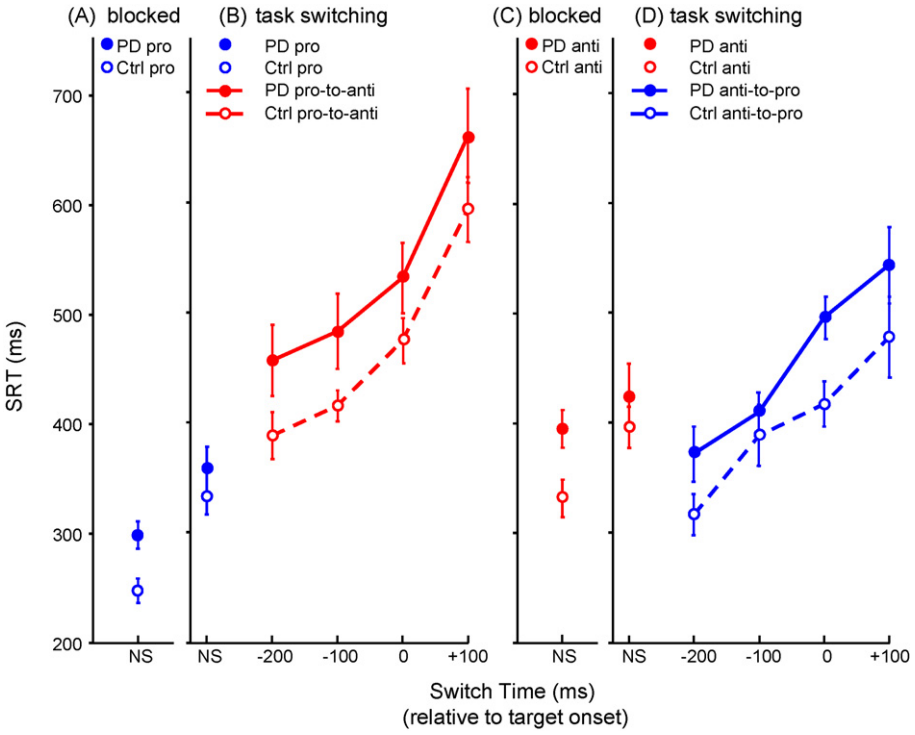

Fig. 3. Saccade reaction time (SRT). (A) Blocked design, prosaccade trials. (B) Task switching design, non-switch prosaccade trials and pro-to-antisaccade switch trials. (C) Blocked design, antisaccade trials. (D) Task switching design, non-switch antisaccade trials and anti-to-prosaccade switch trials.

3. Results

3.1. Blocked design

Both PD patients and controls made more errors on antisaccade trials than on prosaccade trials, PD: $Z = 3.06$, $P < 0.01$, control: $Z = 2.67$, $P < 0.01$ (compare Fig. 2A and C). There was a greater percentage of direction errors on antisaccade trials for PD (21%) compared to controls (13%) (Fig. 2C), however this did not reach significance, $Z = 1.65$, $P = 0.10$. Both PD and control participants had greater SRTs for antisaccade trials relative to prosaccade trials, PD: $t(11) = 5.65$, $P < 0.01$, control: $t(11) = 4.79$, $P < 0.01$ (compare Fig. 3A and C). Finally, PD patients were slower to respond than control participants for both prosaccade trials (299 ms vs. 247 ms), $t(22) = 3.04$, $P < 0.01$, and antisaccade trials (395 ms vs. 331 ms), $t(22) = 2.64$, $P < 0.05$. These results show that PD patients were significantly slower to respond overall, and exhibited behavior that fits with previous findings (Briand et al., 1999; Chan et al., 2005; Hood et al., 2007).

3.2. Task switching design

Changing from the blocked design to the task switching design increased the percentage direction errors significantly for both non-switch pro (Fig. 2B) and antisaccade (Fig. 2D) trials, for both PD patients and control subjects, $Z > 1.96$, $P < 0.05$. SRT on non-switch pro and antisaccade trials also increased significantly for controls $t(11) > 6.11$, $P < 0.01$, and on non-switch prosaccades for PD patients, $t(11) = 3.13$, $P = 0.01$ (Fig. 3B and D). PD patients did not have a significantly greater SRT on non-switch antisaccade trials relative to the blocked design, $t(11) = 1.80$, $P = 0.17$.

A test of normality (K–S) revealed that >75% of the direction errors at each switch time were normally distributed. Therefore, the ANOVA as described in Section 2 was used because we were most interested in interactions between 'Group' and 'Switch Time', highlighting the differences between the two groups (Figs. 2B,D and 3B,D). However, the Mann–Whitney *U*-test was used for post hoc tests at each switch time for percentage direction errors. The Group × Switch Time × Initial Task ANOVA revealed no significant interaction for direction errors $F(4,19) = 1.87$, $P = 0.16$, or for SRT, $F(4,19) = 0.57$, $P = 0.69$. There was, however, a main effect of Group for SRT, $F(1,22) = 4.54$, $P < 0.05$. Two-way ANOVA's were subsequently conducted to determine the influence of switching from an initially planned behavior to the alternative, as described above.

3.2.1. Pro and pro-to-antisaccade trials

For direction errors, there was a significant Group × Switch Time interaction, $F(4,19) = 4.49$, $P < 0.01$, and there was a main effect of Switch Time, $F(2.74, 60.59) = 143.28$, $P < 0.01$. There was no main effect of Group $F(1,22) = 1.18$, $P = 0.29$. As shown in Fig. 2B, this demonstrates that PD patients did not make greater errors overall in comparison to control subjects, however, the interaction shows that PD patients made fewer errors on non-switch prosaccade trials (4% vs. 8%), but greater errors on pro-to-antisaccade switch trials (average 78% vs. 70% across the switch times). Post hoc Mann–Whitney *U*-tests confirmed that PD patients made significantly fewer non-switch prosaccade errors than controls, $Z = 2.37$, $P < 0.05$, and greater pro-to-antisaccade errors at the −200 ms switch time, $Z = 2.31$, $P < 0.05$. At the −100 ms switch time, the difference approached significance, $Z = 1.73$, $P = 0.08$. Percentage direction errors did not differ between groups at the 0 and +100 ms switch times, $P > 0.67$.

For SRT, there was not a significant Group × Switch Time interaction, $F(4,19) = 0.61$, $P = 0.66$. However, there was a main effect of Switch Time, $F(4,88) = 55.6$, $P < 0.01$, and there was a main effect of Group, $F(1,22) = 4.35$, $P < 0.05$, illustrating that PD patients were slower to respond overall, but showed a similar switching behavior to the controls (Fig. 3B).

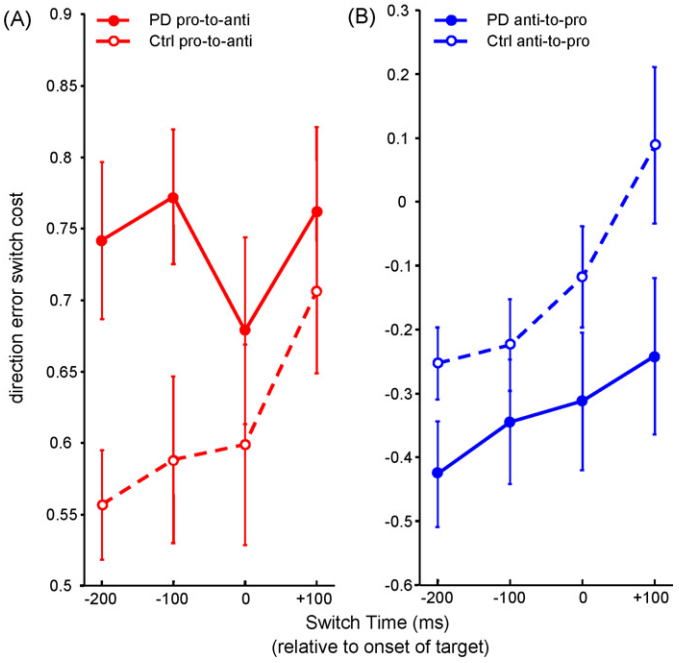

Fig. 4. Direction error switch costs across each switch time. (A) Switching from a pro to an antisaccade (pro-to-anti). Solid data points represent the PD patients, and hollow data points represent the controls. (B) Switching from an anti to a prosaccade (anti-to-pro). Positive values on the *Y*-axis indicate a switch cost, and negative values indicate a switch benefit. Error bars represent standard error of the mean.

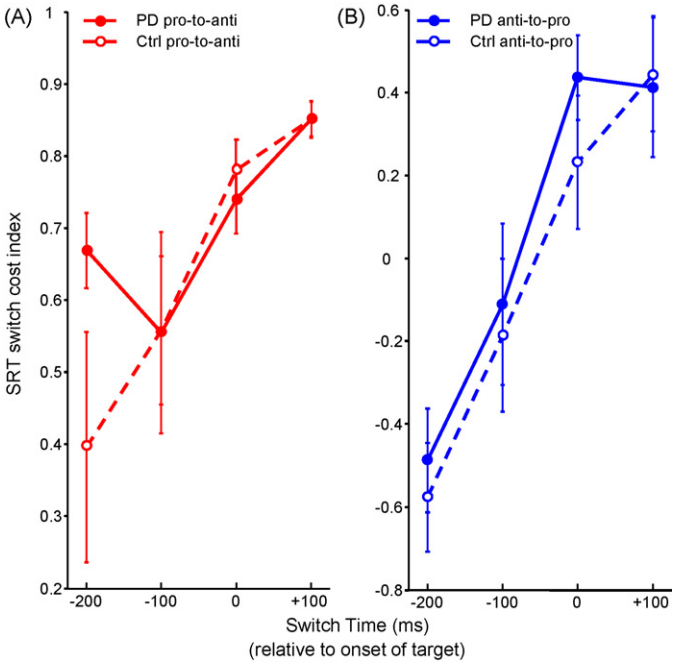

Fig. 5. SRT switch costs. (A) Switching from a pro to an antisaccade. (B) Switching from an anti to a prosaccade.

Fig. 4A shows that both groups produced switch costs in error rates for pro-to-antisaccade trials (*Y* axis > 0), with the switch costs being greater (close to significance) across the switch times in PD patients, $F(3,20) = 2.42$, $P = 0.096$. The main effect of Group was also close to significance, $F(1,22) = 3.27$, $P = 0.08$. Importantly, the early switch times had significant differences between the groups, $t(22) > 2.40$, $P < 0.05$, whereas the latter two did not, $t(22) < 0.831$. There was no difference in SRT switch costs between the two groups $F(3,20) = 1.46$, $P = 0.26$, nor was there a main effect of Group, $F(1,22) = 0.52$, $P = 0.48$ and at −200 ms, switch costs were not significantly greater for PD patients, $t(22) = 1.64$, $P = 0.11$ (Fig. 5A).

To summarize, PD patients showed greater direction error switch costs and greater errors on pro-to-antisaccade switch trials at the −200 and −100 switch times compared to the controls. PD patients also had fewer errors on non-switch prosaccade trials, but were slower to respond overall and did not show greater SRT switch costs.

3.2.2. Anti and anti-to-prosaccade trials

There was no significant Group × Switch Time interaction for percentage direction errors, $F(4,19) = 2.13$, $P = 0.12$, but as above, there was a main effect of Switch Time, $F(1.43, 31.40) = 16.39$, $P < 0.01$. There was no main effect of Group $F(1,22) = 0.90$, $P = 0.35$. As seen in Fig. 2D, PD patients made greater errors relative to controls on non-switch antisaccade trials (49% vs. 37%), but fewer errors than controls on anti-to-prosaccade trials overall, and also showed less of a change in error rates across the switch times than did the controls. PD patients showed significantly fewer anti-to-prosaccade errors at the −200 ms, $Z = 2.04$, $P < 0.05$, and at the +100 ms switch time, $Z = 1.99$, $P < 0.05$, relative to controls.

For SRT, there was no significant Group × Switch Time interaction, $F(4,19) = 1.05$, $P = 0.41$. However, there was a main effect of Switch Time, $F(2.15,47.38) = 19.06$, $P < 0.01$. The main effect of Group approached significance, $F(1,22) = 3.59$, $P = 0.07$. As with pro and pro-to-antisaccade switch trials, this suggests that PD patients were slower to respond overall (Fig. 3D).

Analysis of switch costs showed that PD patients had enhanced switch *benefits* in direction errors relative to control subjects, $F(3,20) = 2.94$, $P = 0.06$ (Fig. 4B), approaching significance, $t(22) = 1.9$, $P = 0.07$, at the +100 ms switch time. The main effect of Group did not reach significance however, $F(1,22) = 2.53$, $P = 0.13$. For SRT, there was no difference in SRT switch costs between the two groups, $F(3,20) = 0.42$, $P = 0.74$, and the main effect of Group was not significant, $F(1,22) = 0.26$, $P = 0.62$ (Fig. 5B).

In summary, an opposite pattern of behavior emerged for switching from an anti to a prosaccade than for switching from a pro to an antisaccade with respect to percentage direction errors (Fig. 2B and D): PD patients showed a performance deficit on the non-switch trials (antisaccade), but a performance advantage on the switch trials (anti-to-prosaccade) relative to the control subjects.

3.3. Correlation with disease severity and medication

For each patient, their UPDRS motor score (Table 1) was correlated against SRT and direction errors in the blocked and task switching designs. Data was collapsed across the 4 switch times. All correlations, except for SRT on anti-to-prosaccade switch trials, were in the positive direction (i.e., greater SRT and greater percentage direction errors corresponded to a greater UPDRS score) however no correlation had an *r* value greater than 0.48, indicating that there was no correlation between UPDRS motor score and performance. Years from initial diagnosis (Table 1) were also correlated to SRT and direction errors in the same way, and all correlations were also in the positive direction, with significant correlations resulting for non-switch anti SRT, $r(10) = 0.80$, $P < 0.01$, in the task switching design, and for pro-to-antisaccade SRT in the task switching design, $r(10) = 0.60$, $P < 0.05$.

On average, control subjects failed to initiate a saccade on 2.4% of all trials, whereas PD patients failed to initiate a saccade on 12.2% of all trials. There was no correlation between the percentage of these errors and with the UPDRS motor score, $r(10) = 0.21$.

Correlations to medication regimen were not conducted due to the heterogeneous medications across subjects, however the

switch costs of the 4 patients who were not taking L-DOPA (patients 1, 2, 11 and 12 in Table 1) were compared to the remaining 8 who were. Note that these 4 patients were also on average less advanced in terms of years with diagnosed PD. There was a significant Group × Switch Time interaction for the anti-to-prosaccade direction error switch costs, $F(3,8) = 4.17$, $P < 0.05$, and a main effect of Group, $F(1,10) = 5.14$ $P < 0.05$, such that the 4 non-L-DOPA patients had a reduced prosaccade switch benefit, that reached significance at the −100, 0 and +100 ms switch times (all Ps < 0.05). This effect arose not from significant differences in non-switch antisaccade error rates ($P = 0.17$), but from significantly greater anti-to-prosaccade error rates at these 3 switch times in the non-L-DOPA participants (all Ps < 0.05). These 4 patients also had reduced pro-to-antisaccade SRT switch costs at +100 ms, $t(10) = 3.98$, $P < 0.01$. No other comparisons were significant.

3.4. Supplementary analysis of task switching

We focused the above analysis on the switch costs related to changing an initially planned behavior in comparison to maintaining the initially planned behavior. As such, these switch costs are akin to the switch costs reported in our previous fMRI study of caudate nucleus activation in task switching (Cameron, Coe, et al., 2009), and to the fMRI activation patterns also reported in a card sorting task, in which trials where PD patients had to maintain a given behavior were subtracted from trials in which PD patients had to change behavior (Monchi et al., 2004). However, an alternative method to measure switch costs is to compare trials that share identical responses (e.g., non-switch anti trials and pro-to-anti switch trials), to measure the time required for, and ability of, executive processes to reconfigure to the appropriate task set. If PD patients have a deficit in this reconfiguration processes, they would be expected to produce enhanced switch costs. However, if there is an underlying bias towards one behavior (e.g., prosaccades), this might not reveal switch costs because the identical saccade response is compared.

Under this analysis, no significant differences in task switching behavior were found between the groups, except for an interaction that approached significance between Group and Switch Time for direction error *reconfiguration* costs derived from comparing non-switch prosaccade to anti-to-prosaccade switch trials, $F(3,20) = 2.94$, $P = 0.06$. This interaction arose from the fact that PD patients showed reduced reconfiguration costs at the later switch times (but that were not individually significantly different from the controls, $P > 0.11$). A main effect of Group for SRT reconfiguration costs approached significance, $F(1,22) = 3.13$, $P = 0.09$, indicating that PD patients showed a trend for increased SRT reconfiguration costs overall for anti-to-prosaccade trials. The full results of this analysis are described in Supplementary Content, including Supplementary Figs. 1 and 2 that illustrate reconfiguration costs for direction errors and SRT, respectively.

3.5. Summary

The results taken together demonstrate a strong prosaccade bias in PD patients; they made fewer errors when executing a prosaccade, or switching to a prosaccade, but they were significantly impaired at executing an antisaccade in comparison to controls. Patients were slower at responding overall. There was no correlation of UPDRS motor score to saccade behavior, however the 4 patients not taking L-DOPA showed a reduced prosaccade advantage compared to the 8 who were. Correlations involving years since diagnosis showed that the patients with fewer years with PD executed antisaccades faster than patients with more years with PD.

4. Discussion

We hypothesized that if PD patients had an underlying deficit in task switching, they would have shown increased switch costs in both SRT and the occurrence of direction errors. However, PD patients only showed greater direction error switch costs when switching from the more automatic prosaccade to the less automatic antisaccade. In fact, PD patients showed an advantage over the controls in terms of fewer errors when switching *towards* the more automatic prosaccade. Additional analysis showed that because *reconfiguration* costs were not greater in PD than in control subjects, there was not a generalized impairment in task switching in PD; rather, deficits arose depending on the relative automaticity between two tasks. Together the findings point to a task set bias towards the more automatic behavior, which underlies their difficulty in generating alternative, voluntary behavior.

Previous studies have shown deficits in antisaccade performance in PD (Chan et al., 2005; Hood et al., 2007), and have attributed these deficits to greater difficulty in suppressing the automatic prosaccade. However these studies were unable to make predictions about a prosaccade *advantage* in PD, because percentage direction errors on pro trials are typically few in blocked designs (e.g., Fig. 2A). In the current study, a prosaccade advantage in PD was seen as consistently fewer direction errors on trials where a prosaccade was required (Fig. 2A, B and D), in particular at the +100 ms switch time on anti-to-pro trials where this effect was most pronounced. Reconfiguration costs occurred in both groups at this switch time, but less so in PD (see Supplementary Content). Reconfiguration costs are expected given that the alternative antisaccade task was initially instructed, and these trials were compared to the simplest trials: non-switch prosaccades. However, only the PD patients showed a *switch benefit* in terms of correct performance at this time (Fig. 2D and B), suggesting that even if an antisaccade response could be prepared based on the target being present, PD patients were still advantaged by switching to a prosaccade. As SRT switch costs did still occur, this might suggest a speed-accuracy trade-off in PD, perhaps as compensation for their known antisaccade difficulty; however, being slower to respond may have contributed to their advantage in switching to the more automatic response (explained in the following section). In contrast to the prosaccade advantage observed, a significant antisaccade impairment in PD occurred on trials where an antisaccade was required (Fig. 2B, C and D), except on those trials that involved switching from a pro to an antisaccade *after* target onset. This suggests that biases towards a more automatic task set are present in PD, and these biases can interfere with the setting of the appropriate task set prior to programming a response.

Task set can be thought of as the configuration of neural signals related to rule representation and preparatory processes that govern how one should respond to a stimulus (Sakai, 2008; Wallis, Anderson, & Miller, 2001). Because no information existed about the direction of the saccade response on trials with negative switch times, the behavioral deficits observed in PD at these switch times must have occurred at the level of establishing an antisaccade task set. Results from a recent study by Rivaud-Pechoux et al. (2007), suggested that simultaneous activation of both pro and antisaccade task sets in an interleaved design might contribute to the greater error costs for antisaccades in PD in comparison to a standard blocked design. However, because there were also prosaccade costs associated with performing the interleaved design by Rivaud-Pechoux et al. (2007) (as well as in the current study, Fig. 2A and B), we cannot conclude that the antisaccade error costs are associated with interference from the prosaccade task set by comparing blocked to interleaved designs. In contrast, differential switch costs and switch benefits highlight the asymmetric interference that one task set has over the other in producing, or reducing, error rates

when the task switches mid-trial. Taken together, our results suggest that a stronger bias towards the more automatic prosaccade task set in PD made it more difficult for PD patients to override automatic behavior with an alternative behavior.

4.1. Neurological substrate underlying behavior

Our results are consistent with models of BG dysfunction in PD that posit that deficits in behavioral control are the result of increased inhibitory output from the BG on downstream motor structures (i.e., the superior colliculus) and on thalamo-cortical circuits (Alexander, DeLong, & Strick, 1986; Betchen & Kaplitt, 2003; Mink, 1996; Nambu, 2005). We hypothesize that impairment in establishing the antisaccade task set in PD is the result of changes in neural signalling in the frontal cortex due to increased BG inhibition on the excitatory cortical afferents from the thalamus. Voluntary saccade control is mediated by frontal cortical regions which include the dorsolateral prefrontal cortex (DLPFC), supplementary eye fields (SEF) and frontal eye fields (FEF) that input to the SC and brain stem (Munoz, 2002; Pierrot-Deseilligny, Milea, & Muri, 2004). Preliminary results from our laboratory show that there is a generalized hypo-activation in the DLPFC, SEF, and FEF as PD patients prepare and execute antisaccades (Cameron, Pari, et al., 2009), which fits with findings of hypo-activation in executive and attention networks of the frontal cortex in PD (Dagher & Nagano-Saito, 2007). If the frontal cortex is under-activated in PD, the establishment of the more voluntary antisaccade task set may be impaired and the automatic prosaccade task set predominates. The FEF, SEF, and in particular, the DLPFC, are critical to presetting the saccade network for an antisaccade and overriding automatic prosaccades (Condy, Wattiez, Rivaud-Pechoux, Tremblay, & Gaymard, 2007; Guitton, Buchtel, & Douglas, 1985; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Sereno, 1996), and correlates of antisaccade task set in the FEF (Everling & Munoz, 2000; Munoz & Everling, 2004) and DLPFC (Connolly, Goodale, Menon, & Munoz, 2002; DeSouza, Menon, & Everling, 2003; Everling & Desouza, 2005; Johnston & Everling, 2006) have been identified with monkey neurophysiology and fMRI. Recent evidence also shows that inactivation of the principal sulcus (anatomical location of DLPFC in monkeys) increased errors on antisaccade trials, but decreased errors on prosaccade trials, when animals were instructed to establish and maintain a pro or antisaccade task set prior to target appearance (Koval, Lomber, & Everling, 2009). Similarly, it has been shown in humans that a single pulse from transcranial magnetic stimulation (TMS) over the DLPFC increased antisaccade errors when applied at −100 ms with respect to target onset, but not at 0 or +100 ms (Nyffeler et al., 2007). Taken together, studies do show that disruption of DLPFC processing during task set establishment biases the subject towards prosaccade behavior. Importantly, the DLPFC has also been shown to be involved in shifting attention and task set (Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Rogers et al., 1998; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000), and has been implicated in other forms of executive dysfunction in PD (Monchi et al., 2004; Monchi, Petrides, Mejia-Constain, & Strafella, 2007; Owen, Doyon, Dagher, Sadikot, & Evans, 1998), in particular those involving planning, strategy and manipulation of items in working memory (Owen, 2004).

The slower SRT in PD in the current study can be also predicted by a model of increased BG inhibition. Saccade neurons in the SC are under tonic inhibition from the substantia nigra pars reticulata (SNr), and there is a pause in this inhibition prior to saccade initiation (Basso & Wurtz, 2002; Hikosaka & Wurtz, 1983; Hikosaka et al., 2000). If the pausing of SNr neurons in the BG's direct pathway is impeded in PD, or if saccade related activity in the SC must overcome increased inhibition (due to an enhanced indirect pathway) (Nambu, 2004, 2005), then both pro and antisaccades should be slower to elicit. Thus, increased SRT in the current study in PD can be explained by increased BG inhibition on the SC, which is consistent with results from another laboratory (Hood et al., 2007). Based on these simple models, suppression of SC saccade neurons via the indirect pathway through the BG should assist in the prevention of short latency prosaccades, and should predict decreased errors on antisaccade trials in PD. However, because it takes longer to respond in PD means that there is more time available for the visual signal from the stimulus (target) to trigger a prosaccade error at longer latencies. We observed that the mean SRTs of erroneous prosaccades in PD patients were greater than 300 ms across all 4 switch times, showing that PD patients were not executing a high percentage of short-latency errors on antisaccade trials. Thus, it is possible that the enhanced prosaccade bias in PD could be explained by the failure of the frontal cortex to establish, or maintain antisaccade task set, and also by the fact that the target stimulus is continually providing inputs to SC saccade neurons from areas (e.g., visual cortex) independent of the BG impairment. This might also contribute to their advantage in switching to the prosaccade at the +100 ms switch time.

In summary, we suggest that the ability to establish the antisaccade task set takes place in neural networks in the frontal cortex involving the DLPFC that receive positive feedback signals via BG thalamo-cortical channels (Alexander et al., 1986). These signals may be weaker in PD, resulting in reduced activation of the antisaccade task set, and consequently, reduced inhibition against eliciting a prosaccade. Our findings are similar to those reached by other tests of behavioral control. For example, in the Stroop task (Stroop, 1935), the tendency to perform the more automatic response (word reading) interferes with the required task of reading font color, and the more automatic word reading response impedes the reading of color, and is often executed erroneously (MacLeod, 1991). Indeed, it has been observed that PD patients show response time deficits in the Stroop task, specifically when having to *switch* to the less automatic color naming response after performing the word reading task (Woodward et al., 2002). Similarly, it has been shown that monkeys given chemical lesions to the substantia nigra (pars compacta) by 1-methyl-4-phenyl-1,2,3,6-terahydropyridine (MPTP) displayed perseverative errors in switching from 'go' to 'no-go' behavior, indicative of fronto-BG dysfunction in executive control (Slovin et al., 1999).

4.2. Limitations and future directions

A methodological limitation in our study is that patients were taking dopaminergic (DA) medications, and heterogeneous medication regimens. However, their scores of motor function on the UPDRS, and their antisaccade deficits that mirror previous studies of patients in either an 'on' or 'off' medication state (Cameron, Pari, et al., 2009; Chan et al., 2005; Hood et al., 2007), suggest that the DA therapy was not sufficient in bringing the patients' performance up to the level of the controls. Moreover, withholding DA medication 12–18 h prior to testing (as is typical practice in many experiments) may contain residual effects of DA, especially with the agonists taken by a subset of patients (Cools, 2006). Interestingly, an association with medication was observed. Our comparison of the 4 patients who were not taking L-DOPA showed that these 4 patients had a significantly reduced prosaccade advantage making them appear more like the controls than the remaining 8. Thus, there may be a medication effect due to L-DOPA, however these results are more likely due to the fact that these patients were less advanced in PD, as L-DOPA was not prescribed to patients in the earlier stages of the disease. Nevertheless, we are planning future studies whereby patients will participate in an on–off medication design of the current experiment in conjunction with fMRI. It is important to consider the effects of medication because executive

dysfunction in PD may depend on levels of dopamine in the frontal cortex itself, either due to pathology or adverse effects from therapy (Cools, 2006; Owen, 2004). In addition, patients with PD may over-activate motor areas in fMRI studies of simple motor responses (Dagher & Nagano-Saito, 2007), perhaps related to compensation for increased BG inhibition (Mallol et al., 2007). Thus, fMRI may be able to identify a correlate of hyper-activation in PD related to their prosaccade advantage.

5. Conclusions

We employed a saccade switching paradigm to identify an underlying bias in PD towards a more automatic prosaccade response that influenced their ability to switch task. Specifically, PD patients performed with impairment or superiority relative to controls, depending on the switch direction. Our results suggest that an underlying deficit in setting a task set towards a non-habitual and voluntary motor task can explain behavioral deficits in PD when a required voluntary behavior competes with an automatic behavior. We suggest that for PD patients to improve performance in daily activities, assistance from externally triggered behavior can be utilized where available (a well known phenomenon) (Martin, 1967; Oliveira, Gurd, Nixon, Marshall, & Passingham, 1997). Conversely however, performance on non-automatic tasks can be ameliorated if steps in concentration or improving attention are taken to avoid the detrimental interference from habitual tasks that are more automatic in nature (Cunnington, Iansek, & Bradshaw, 1999; Morris, Iansek, Matyas, & Summers, 1996).

Acknowledgements

We thank members of the Munoz lab for comments on earlier versions of the manuscript, and the participants for their time. This research was supported by the Canadian Institutes of Health Research grant number MOP-97741 to DPM and GP, and the Canada Research Chair Program to DPM. IGMC is the recipient of a Frederick Banting and Charles Best Canada Graduate Scholarship.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2010.03.015.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Reviews Neuroscience*, *9*, 357–381.

Amador, S. C., Hood, A. J., Schiess, M. C., Izor, R., & Sereno, A. B. (2006). Dissociating cognitive deficits involved in voluntary eye movement dysfunctions in Parkinson's disease patients. *Neuropsychologia*, *44*(8), 1475–1482.

Basso, M. A., & Wurtz, R. H. (2002). Neuronal activity in substantia nigra pars reticulata during target selection. *Journal of Neuroscience*, *22*(5), 1883–1894.

Betchen, S. A., & Kaplitt, M. (2003). Future and current surgical therapies in Parkinson's disease. *Current Opinion in Neurology*, *16*(4), 487–493.

Briand, K. A., Strallow, D., Hening, W., Poizner, H., & Sereno, A. B. (1999). Control of voluntary and reflexive saccades in Parkinson's disease. *Experimental Brain Research*, *129*(1), 38–48.

Cameron, I. G., Coe, B., Watanabe, M., Stroman, P. W., & Munoz, D. P. (2009). Role of the basal ganglia in switching a planned response. *European Journal of Neuroscience*, *29*(12), 2413–2425.

Cameron, I. G., Pari, G., Alahyane, N., Coe, B. C., Stroman, P. W., & Munoz, D. P. (2009). Deficits in anti-saccade performance in Parkinson's disease: A rapid event-related fMRI study. *In Abstracts of the Organization for Human Brain Mapping*, 151.

Cameron, I. G., Watanabe, M., & Munoz, D. P. (2007). Contrasting instruction change with response change in task switching. *Experimental Brain Research*, *182*(2), 233–248.

Chan, F., Armstrong, I. T., Pari, G., Riopelle, R. J., & Munoz, D. P. (2005). Deficits in saccadic eye-movement control in Parkinson's disease. *Neuropsychologia*, *43*(5), 784–796.

Condy, C., Wattiez, N., Rivaud-Pechoux, S., Tremblay, L., & Gaymard, B. (2007). Antisaccade deficit after inactivation of the principal sulcus in monkeys. *Cerebral Cortex*, *17*(1), 221–229.

Connolly, J. D., Goodale, M. A., Menon, R. S., & Munoz, D. P. (2002). Human fMRI evidence for the neural correlates of preparatory set. *Nature Neuroscience*, *5*(12), 1345–1352.

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neuroscience Biobehavioral Reviews*, *30*(1), 1–23.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*(11), 1431–1441.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*, *124*(12), 2503–2512.

Cools, R., Ivry, R. B., & D'Esposito, M. (2006). The human striatum is necessary for responding to changes in stimulus relevance. *Journal of Cognitive Neuroscience*, *18*(12), 1973–1983.

Cunnington, R., Iansek, R., & Bradshaw, J. L. (1999). Movement-related potentials in Parkinson's disease: External cues and attentional strategies. *Movement Disorders*, *14*(1), 63–68.

Dagher, A., & Nagano-Saito, A. (2007). Functional and anatomical magnetic resonance imaging in Parkinson's disease. *Molecular Imaging in Biology*, *9*(4), 234–242.

DeSouza, J. F., Menon, R. S., & Everling, S. (2003). Preparatory set associated with prosaccades and anti-saccades in humans investigated with event-related FMRI. *Journal of Neurophysiology*, *89*(2), 1016–1023.

Everling, S., & Desouza, J. F. (2005). Rule-dependent activity for prosaccades and antisaccades in the primate prefrontal cortex. *Journal of Cognitive Neuroscience*, *17*(9), 1483–1496.

Everling, S., & Munoz, D. P. (2000). Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *Journal of Neuroscience*, *20*(1), 387–400.

Guitton, D., Buchtel, H. A., & Douglas, R. M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research*, *58*(3), 455–472.

Hays, A. V., Richmond, B. J., & Optican, L. M. (1982). A UNIX-based multiple process system for real-time data acquisition and control. *WESCON Conference Proceedings*, *2*, 1–10.

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiological Reviews*, *80*(3), 953–978.

Hikosaka, O., & Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. *Journal of Neurophysiology*, *49*(5), 1285–1301.

Hood, A. J., Amador, S. C., Cain, A. E., Briand, K. A., Al-Refai, A. H., Schiess, M. C., et al. (2007). Levodopa slows prosaccades and improves antisaccades: An eye movement study in Parkinson's disease. *Journal of Neurology Neurosurgery & Psychiatry*, *78*(6), 565–570.

Johnston, K., & Everling, S. (2006). Monkey dorsolateral prefrontal cortex sends task-selective signals directly to the superior colliculus. *Journal of Neuroscience*, *26*(48), 12471–12478.

Koval, M. J., Lomber, S. G., & Everling, S. (2009). Bilateral principal sulcus inactivation impairs maintenance of task set. In *Abstracts of the Society for Neuroscience Annual Meeting* , 851.19

Lees, A. J., & Smith, E. (1983). Cognitive deficits in the early stages of Parkinson's disease. *Brain*, *106*(2), 257–270.

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *Journal of Neuroscience*, *23*(15), 6351–6356.

Lewis, S. J., Slabosz, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2005). Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. *Neuropsychologia*, *43*(6), 823–832.

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: An integrative review. *Psychological Bulletin*, *109*(2), 163–203.

Mallol, R., Barros-Loscertales, A., Lopez, M., Belloch, V., Parcet, M. A., & Avila, C. (2007). Compensatory cortical mechanisms in Parkinson's disease evidenced with fMRI during the performance of pre-learned sequential movements. *Brain Research*, *1147*, 265–271.

Martin, J. P. (1967). *The basal ganglia and posture*. London: Pitman Medical.

Milner, B. (1963). Effects of different brain lesions on card sorting. *Archives of Neurology*, *9*, 90–100.

Mink, J. W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, *50*(4), 381–425.

Monchi, O., Petrides, M., Doyon, J., Postuma, R. B., Worsley, K., & Dagher, A. (2004). Neural bases of set-shifting deficits in Parkinson's disease. *Journal of Neuroscience*, *24*(3), 702–710.

Monchi, O., Petrides, M., Mejia-Constain, B., & Strafella, A. P. (2007). Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. *Brain*, *130*(1), 233–244.

Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin card sorting revisited: Distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *Journal of Neuroscience*, *21*(19), 7733–7741.

Morris, M. E., Iansek, R., Matyas, T. A., & Summers, J. J. (1996). Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain*, *119*(2), 551–568.

Munoz, D. P. (2002). Commentary: Saccadic eye movements: Overview of neural circuitry. *Progress in Brain Research*, *140*, 89–96.
Munoz, D. P., Broughton, J. R., Goldring, J. E., & Armstrong, I. T. (1998). Age-related performance of human subjects on saccadic eye movement tasks. *Experimental Brain Research*, *121*(4), 391–400.
Munoz, D. P., & Everling, S. (2004). Look away: The anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience*, *5*(3), 218–228.
Nambu, A. (2005). A new approach to understand the pathophysiology of Parkinson's disease. *Journal of Neurology*, *252*(Suppl 4), IV1–IV4.
Nambu, A. (2004). A new dynamic model of the cortico-basal ganglia loop. *Progress in Brain Research*, *143*, 461–466.
Nyffeler, T., Muri, R. M., Bucher-Ottiger, Y., Pierrot-Deseilligny, C., Gaymard, B., & Rivaud-Pechoux, S. (2007). Inhibitory control of the human dorsolateral prefrontal cortex during the anti-saccade paradigm—A transcranial magnetic stimulation study. *European Journal of Neuroscience*, *26*(5), 1381–1385.
Oliveira, R. M., Gurd, J. M., Nixon, P., Marshall, J. C., & Passingham, R. E. (1997). Micrographia in Parkinson's disease: The effect of providing external cues. *Journal of Neurology, Neurosurgery & Psychiatry*, *63*(4), 429–433.
Owen, A. M. (2004). Cognitive dysfunction in Parkinson's disease: The role of frontostriatal circuitry. *Neuroscientist*, *10*(6), 525–537.
Owen, A. M., Doyon, J., Dagher, A., Sadikot, A., & Evans, A. C. (1998). Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. *Brain*, *121*(5), 949–965.
Pierrot-Deseilligny, C., Milea, D., & Muri, R. M. (2004). Eye movement control by the cerebral cortex. *Current Opinion in Neurology*, *17*(1), 17–25.
Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., & Agid, Y. (1991). Cortical control of reflexive visually-guided saccades. *Brain*, *114*(3), 1473–1485.
Prince, S. J., Pointon, A. D., Cumming, B. G., & Parker, A. J. (2002). Quantitative analysis of the responses of V1 neurons to horizontal disparity in dynamic random-dot stereograms. *Journal of Neurophysiology*, *87*(1), 191–208.
Rivaud-Pechoux, S., Vidailhet, M., Brandel, J. P., & Gaymard, B. (2007). Mixing pro- and antisaccades in patients with Parkinsonian syndromes. *Brain*, *130*(1), 256–264.
Rogers, R. D., Andrews, T. C., Grasby, P. M., Brooks, D. J., & Robbins, T. W. (2000). Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. *Journal of Cognitive Neuroscience*, *12*(1), 142–162.
Rogers, R. D., Sahakian, B. J., Hodges, J. R., Polkey, C. E., Kennard, C., & Robbins, T. W. (1998). Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain*, *121*(5), 815–842.
Sakai, K. (2008). Task set and prefrontal cortex. *Annual Reviews Neuroscience*, *31*, 219–245.
Schultz, W. (2001). Reward signaling by dopamine neurons. *Neuroscientist*, *7*(4), 293–302.
Sereno, A. B. (1996). Parsing cognitive processes: Psychopathological and neurophysiological constraints. In S. W. Matthysse, D. L. Levy, J. Kagan, & F. M. Benes (Eds.), *Psychopathology* (pp. 407–432). New York: Cambridge University Press.
Slovin, H., Abeles, M., Vaadia, E., Haalman, I., Prut, Y., & Bergman, H. (1999). Frontal cognitive impairments and saccadic deficits in low-dose MPTP-treated monkeys. *Journal of Neurophysiology*, *81*(2), 858–874.
Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*, 643–662.
Wallis, J. D., Anderson, K. C., & Miller, E. K. (2001). Single neurons in prefrontal cortex encode abstract rules. *Nature*, *411*(6840), 953–956.
Woodward, T. S., Bub, D. N., & Hunter, M. A. (2002). Task switching deficits associated with Parkinson's disease reflect depleted attentional resources. *Neuropsychologia*, *40*(12), 1948–1955.