PAPER

Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease

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Background: The integrity of frontal systems responsible for voluntary control and their interaction with subcortical regions involved in reflexive responses were studied in patients with Parkinson's disease (PD). Previous studies have shown that patients with PD have impaired executive function, including deficits in attention, motor planning and decision making.

Methods: Executive function was measured through eye movements: reflexive (stimulus driven) prosaccades and voluntary (internally guided) antisaccades. Patients with advanced idiopathic PD, off and on their optimal levodopa therapy, were tested on a prosaccade and an antisaccade task and compared with matched controls.

Results: Levodopa significantly increased response time for reflexive prosaccades and reduced error rate for voluntary antisaccades.

Conclusions: Consistent with our proposed model, patients with PD in the medicated state are better able to plan and execute voluntary eye movements. These findings suggest levodopa improves function of the voluntary frontostriatal system, which is deficient in PD.

Parkinson's disease (PD) is identified by a series of motor abnormalities caused by dopaminergic disruption in the basal ganglia. Also, the basal ganglia have many diverse connections with several brain regions, including frontal cortical areas responsible for executive function and other cognitive processes. Therefore, patients with PD can develop a wide range of cognitive difficulties (eg, dementia, psychosis, depression), and imaging shows that patients with PD tend to have decreased activity in the prefrontal cortex.^{1–2} The cardinal medicinal treatment of PD, levodopa/carbidopa, helps replenish the lack of dopamine and reduces tremor, rigidity and other common *motor* symptoms, but what effect does levodopa have on *cognition*? Recent work has shown that levodopa has both deleterious and beneficial effects on cognition in patients with PD.^{3–7} Some researchers conclude that dopaminergic medication may improve certain types of neuropsychological performance and hinder others because the brain regions involved are differentially affected by dopamine.³ A reasonable hypothesis is that brain regions have an optimal dopamine level, and shifts from the norm can impair some tasks/measures while benefiting others. Therefore, the present study measured the effect of levodopa on two saccade tasks with dissociable neural substrates.

The analysis of saccades is increasingly used for studying cognition and memory.⁸ Saccade circuitry is clearly understood, and saccades possess dynamic properties that are easily measured non-invasively.^{9–10} It is clear from recent imaging studies that the physiological substrates for saccades (overt orienting) and spatial attention (covert orienting) overlap in many brain regions.¹¹ Moreover, recent work has shown a similar pattern of dysfunction across overt and covert orienting in various clinical populations, suggesting saccades may be a useful tool to evaluate higher cognitive functions.^{12–13}

Our Tonic Inhibition Model of orienting proposes that there is a voluntary system (prefrontal cortex and basal ganglia) exerting tonic inhibition on a reflexive system (superior colliculus and brainstem); the voluntary system modulates reflexive saccades and attention.¹⁴ Typical paradigms that test this model are the prosaccade (reflexively look at the stimulus)

and the antisaccade (inhibit the reflexive response and voluntarily look *away* from the stimulus). In the Tonic Inhibition Model, a deficit in the voluntary system would predict both impaired performance in voluntary saccades and decreased inhibition of reflexive saccades (eg, more direction errors in an antisaccade task and/or shorter latencies for reflexive saccades). Such a baseline pattern has been found in pathologies that involve frontal dysfunction, such as schizophrenia, PD, autism and attention deficit hyperactivity disorder.^{8–15–20}

Saccades have rarely been used to test the effects of levodopa in PD. Therefore, we tested patients with PD in a moderately advanced stage of the disease on a voluntary antisaccade (AS) task and a reflexive prosaccade (PS) task to measure the effects of levodopa on executive function. Furthermore, each task contained both gap and overlap trials to maximise task sensitivity.¹² The present study had two main hypotheses: (1) levodopa would improve performance on the AS task because of improved frontal lobe function; and (2) levodopa would enhance the tonic inhibition of the reflexive system, consequently slowing performance on the reflexive PS task. Finally, a control group was included to evaluate the ability of levodopa to normalise voluntary and reflexive performance.

METHODS

Participants

Patients with PD recruited from the University of Texas Movement Disorders Clinic had been diagnosed with PD based on the CAPIT Diagnostic Criteria for PD, responded to levodopa and had reached a steady dosing schedule before testing (table 1). Patients with atypical parkinsonism or dementia were excluded. Both the control and PD groups were required to have a Mini Mental State Examination (a general screening for severe dementia) score of at least 26/30, normal or corrected-to-normal vision and no history of substance abuse exceeding 5 years. The controls were recruited from the community via pre-approved advertisements. Each participant gave informed

Abbreviations: AS, antisaccade; PD, Parkinson's disease; PS, prosaccade

Table 1 Participant demographics and clinical measures

Group	Sex	Age (y)	Education (y)	Mean MMSE	Disease duration (y)	H&Y	S&E	UPDRS (motor)		Medications
						Off	Off	Off/On	% Change	
Patients										
1	M	61	15	27	14	4.0	40	76/70	7.9	L, E, R
2	M	75	16	27	20	3.5	80	32/29	9.4	L, E, P
3	M	61	4	29.5	15	3.0	70	49/37	24.5	L, P
4	F	56	12	30	14	4.0	80	48/16	66.7	A, L, E, P
5	F	65	9	26.5	7	5.0	30	73/34	53.4	A, L, Pe
6	M	48	6	30	10	5.0	20	84/14	83.3	L, P
7	F	70	22	28	12	3.5	70	35/14	60.0	L, P
8	F	64	8	29.5	21	4.0	70	69/16	76.8	L, E, R
9	M	50	8	28	8	4.0	50	63/34	46.0	L, P
10	F	49	6	27	15	4.0	50	63/32	49.2	A, L, P
11	M	58	12	27.5	25	3.5	60	54/41	24.1	L, P
12	M	64	13	26	4	2.5	70	54/41	24.1	L, P
13	M	52	14	26	16	3.0	80	29/25	13.8	L
14	M	66	17	27	25	2.5	80	54/35	35.2	L, E, R
Mean		59.93	11.57	27.89	14.71	3.6	61.54	56/31**	41.0	
Controls (n = 14)	8 M; 6 F	57.79†	14.21†							

A, amantadine HCl; E, entacapone; H&Y, Hoehn and Yahr Scale; L, carbidopa/levodopa; MMSE, Mini Mental State Examination; P, pramipexole dihydrochloride; Pe, pergolide; R, ropinirole HCl; S&E, Schwab and England Scale; UPDRS, Unified Parkinson Disease's Rating Scale (**Bold % Change** = clinically significant improvement (>20%)).

†Mean values for the control group.

**p<0.01 PD-On is better than PD-Off.

consent before enrolment, and the study was approved by the Committee for the Protection of Human Subjects at our institution in accordance with the Declaration of Helsinki.

The final groups comprised 14 patients with PD and 14 controls; there were no statistically significant differences between the groups in terms of sex, age or education (table 1).

Procedure

Each participant was tested on one day; controls were tested once and patients were tested twice. Previous work in our laboratory shows that retest on these tasks does not affect performance.²¹ The PD group was first tested in the off state (at least 12 h after the last levodopa dose²²) and then in the on state (when patient and neurologist agreed the medication was in full effect²³; 0.5–2 h after the dose). Because many patients came from long distances, it proved difficult to bring them back in a timely fashion for a second testing session, so medication states were not randomised.

Behavioural testing took 30–45 min for each session, and patients with PD had a break between sessions to take their medication. Also, a neurologist conducted a battery of clinical

measures, including the Hoehn and Yahr Rating Scale, Schwab and England Activities of Daily Living Scale and the Unified Parkinson's Disease Rating Scale version 3.0 to evaluate disease severity, functional capacity and disease state, respectively. Table 1 shows the individual scores.

Apparatus and tasks

Eye movements were recorded using an ISCAN RK-426 system with an infrared-sensitive camera, which has a spatial resolution of 0.5° visual angle and a temporal resolution of 6 ms. The participant placed his/her head on a chin rest, and the apparatus was calibrated for each participant. The display was black with a grey fixation point in the centre, and the targets were presented at 7° eccentricity. Variable fixation intervals (400 or 800 ms) before target onset helped prevent anticipations.

Each task contained 96 trials that balanced left and right targets and overlap and gap trials. During overlap trials, the fixation point remained visible for the entire trial. During gap trials, the fixation point was removed 183 ms before target onset (fig 1). The task sessions were counterbalanced such that half of the participants performed the PS task first, and each PD

Figure 1 Paradigms. Schematic representation of the stimulus sequences used in the two tasks (prosaccade and antisaccade) with two fixation trial types (overlap and gap). Total fixation time was 400 or 800 ms; in the gap trials, the fixation point was removed 183 ms before target presentation.

Table 2 Group means for tasks and dependent measures

	PD patients		Controls	
	Off	On		
Error rate (%)				
Prosaccade: overlap	2.8	2.0	0.2	Within subject MSE = 10.38 Between subject MSE = 53.20
Prosaccade: gap	1.9	2.0	1.7	
Antisaccade: overlap	34.8	25.4	11.0	
Antisaccade: gap	49.9	42.1	21.0	
Response time (ms)				
Prosaccade: overlap	314	357	287	Within subject MSE = 778.96 Between subject MSE = 1718.79
Prosaccade: gap	274	300	234	
Antisaccade: overlap	579	571	426	
Antisaccade: gap	497	529	364	
Gain (%)				
Prosaccade: overlap	89	87	97	Within subject MSE = 77.11 Between subject MSE = 60.94
Prosaccade: gap	88	88	96	
Antisaccade: overlap	79	73	109	
Antisaccade: gap	80	72	105	

MSE, mean square error.

patient retained his/her same order for both sessions. There was no statistical difference between counterbalance orders.

In the PS task, the fixation point was presented at the beginning of the trial. The participant was required to maintain fixation and make a speeded saccade towards the target when it appeared. The AS task was identical to the PS task in stimulus presentation; however, the participant had to make a saccade to the visual field opposite the target. The AS required considerably more cognitive load than the PS because the participant was required to (1) inhibit the reflexive draw to look at the stimulus and (2) generate a voluntary saccade away from the stimulus to blank space (fig 1).

Dependent measures and analyses

Error rate is the proportion of incorrect trials. A saccade was correct if the eye position fell within 4.4° of the correct spatial

location. When an error occurred, visual feedback ("wrong location") was displayed for 500 ms.

Response time is the latency to initiate a saccade (above 120°/s) after target onset. If no eye movement was made within 1000 ms, visual feedback ("too slow") was presented, and that trial was aborted and randomly presented again. Only response times for correct saccades were included in the analyses.

Gain (amplitude) is the ratio of saccade size (distance to the first saccade endpoint) to distance of the target from the fixation point. Gain below and above 100% reflects an under-shot and overshoot target, respectively.

Only trials with latencies between 100 ms and 900 ms were included for analysis. This removed anticipations and akinetic responses (only 8% of the data). Secondly, we checked group data for outliers (in a pairwise fashion) and instead of complete removal, we replaced any (only 1.6%; within random variation) with the group mean for our analyses. Statistical tests were considered significant at $\alpha = 0.05$. Group means are listed in table 2.

PD medication effects analyses

We used a three way, within subject repeated measures analysis of variance (ANOVA) with task (PS, AS), fixation procedure (overlap, gap) and medication state (off, on) for patients with PD to measure within subject medication effects. To test specific hypotheses comparing off and on medication results, we ran planned two tailed *t* tests using the mean square error (table 2) of the three way interaction from this within subject ANOVA.

Control versus PD analyses

To analyse the baseline PD deficit and the normalising properties of levodopa, we used a three way, between subject repeated measures ANOVA using task (PS, AS) and fixation procedure (overlap, gap) as within subject factors and condition (PD-off, PD-on, control) as the between subject factor. To test specific hypotheses comparing the conditions, we ran planned two tailed *t* tests using the MSE (see table 2) of the three way interaction from the between subject ANOVA.

RESULTS

Clinical measures

The seemingly variable Unified Parkinson Disease's Rating Scale motor scores did not contain outliers, and these scores improved significantly with medication (table 1).

Figure 2 Error rate group means. (A, B) Parkinson's disease (PD)-off medication and PD-on medication were equal. Both PD conditions were as accurate as controls on prosaccade overlap and gap. (C, D) PD-on made fewer errors than PD-off. Both PD conditions made more errors than controls on antisaccade overlap and gap. *** $p < 0.001$. Values are mean (SEM).

Error rate

PD medication effects

Within subject ANOVA

There was a significant main effect of medication state, and a significant interaction of medication state $\times$ task such that patients with PD made fewer errors when on medication (vs off) on the AS task (with no effect for the PS).

Planned *t* tests

For the PS task, there were no significant effects of medication on error rate (fig 2A, B). However, for the AS task, patients were significantly improved (fewer errors) when on medication (fig 2C, D).

Control versus PD

Between subject ANOVA

There were significant main effects of both task and fixation procedure, indicating that all participants made more errors on the AS task (vs the PS) and gap trials (vs overlap), respectively. There was also a significant interaction of task $\times$ fixation procedure such that participants had the most errors on the AS gap trials. Furthermore, there was a significant interaction of task $\times$ condition, with controls having fewer errors than PD-on, and PD-on having fewer errors than PD-off on the AS task (with no group differences for the PS).

Planned *t* tests

Patients with PD (off and on medication) were statistically unimpaired on the PS task (fig 2A, B). In contrast, patients with PD (off and on medication) made significantly more errors than controls on the AS task (fig 2C, D).

Error rate summary

Patients with PD were impaired (more errors than controls) only on the AS task, and levodopa medication improved (but did not normalise) their performance.

Figure 3 Response time group means. (A, B) Parkinson's disease (PD)-off medication was slower than controls on prosaccade gap. PD-on medication was slower than PD-off and controls on prosaccade overlap and gap. (C, D) PD-on was slower than PD-off on antisaccade gap. Both PD conditions were slower than controls on antisaccade overlap and gap. * $p < 0.05$; *** $p < 0.001$. Values are mean (SEM).

Response time

PD medication effects

Within subject ANOVA

There was a significant interaction of task $\times$ fixation procedure $\times$ medication state, indicating that levodopa slowed response time of patients with PD on each task type except AS overlap.

Planned *t* tests

For the PS task, patients were significantly slower to respond when on medication (vs off) (fig 3A, B). For the AS task, medication slowed patient response time for only the gap trials (no effect for AS overlap) (fig 3C, D).

Control versus PD

Between subject ANOVA

There were significant main effects for both task and fixation procedure, indicating that all participants were slower to respond on the AS task (vs the PS) and overlap trials (vs gap), respectively. There was also a significant interaction of task $\times$ condition, indicating that there was a larger response time difference between the control and PD groups on the AS task (vs the PS).

Planned *t* tests

Compared with controls, patients with PD off medication were normal for the PS overlap, but the patients became significantly slower on medication (fig 3A). However, patients with PD (in both medication states) were significantly slower than controls on PS gap, AS overlap and AS gap (fig 3B–D).

Response time summary

Compared with controls, patients with PD off levodopa were slower to respond (except on PS overlap), and levodopa slowed them further (except on AS overlap).

Figure 4 Gain group means. (A, B) Parkinson's disease (PD)-off medication and PD-on medication were equal. Both PD conditions made smaller amplitude saccades than controls on prosaccade overlap and gap. (C, D) PD-on had smaller gain than PD-off on antisaccade gap. Both PD conditions made smaller amplitude saccades than controls on antisaccade overlap and gap. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Values are mean (SEM).

Gain

PD medication effects

Within subject ANOVA

There were no significant main effects or interactions.

Planned t tests

There was only a significant medication effect for AS gap (fig 4D) such that levodopa shortened saccade amplitude on this task type.

Control versus PD

Between subject ANOVA

There was a significant main effect of task such that all participants were more accurate on the PS task (vs the AS). In addition, there was a significant interaction of task $\times$ condition, indicating there was a larger difference in gain between the control groups and the PD groups on the AS task (vs the PS).

Planned t tests

Patients with PD (off and on medication) had significantly lower gain than controls on all tasks (fig 4).

Gain summary

Patients with PD had abnormally short saccades that undershot the target, and levodopa reduced gain amplitude further on the AS gap trials.

Correlations

We did not find any significant correlations between behavioural and clinical variables for the patients with PD.

Additional analysis

We performed a sign test to investigate whether the primary medication effects reported in this paper—increased response time for prosaccades and decreased error rate for antisaccades in the on state—truly predicted each patient's behaviour. Ten patients showed this pattern of results and four did not; when compared, the result was highly significant ($\chi^2 = 13.71$, $p < 0.001$). Thus, for most patients with PD, levodopa slowed prosaccades and reduced antisaccade errors concurrently.

DISCUSSION

Summary

We examined the effects of levodopa on cognition (specifically, executive function) by measuring eye movements in patients with PD. Briefly, at off-levodopa baseline, the PD group was significantly impaired (high error rate) on the voluntary task and normal or slow on the reflexive task. After taking levodopa, voluntary performance improved (decreased error rate), and reflexive performance slowed further. This concurrent change in error rate and response time could be evidence of levodopa strengthening voluntary cognitive processes. Additionally, patients undershot the targets (low gain) on both voluntary and reflexive tasks, and levodopa did not improve this deficit.

Levodopa improves voluntary saccades

To our knowledge, this is the first study to report voluntary antisaccade improvement in PD with levodopa, and it is consistent with a previous study of improved voluntary memory saccades in PD.²⁴ The Tonic Inhibition Model suggests the improvement in voluntary performance (executive function) we report could be due to improved generation of a voluntary response and/or improved voluntary inhibition of inappropriate reflexive responses.¹⁴ Some researchers suggest these two processes can be anatomically dissociated, and levodopa could primarily affect only one of these processes.^{3 8 10} Thus, a decrease in antisaccade errors with medication might be a

direct measure of improvement in response generation. However, based on the fact that we saw only reduced errors (without benefit for latency or gain), one might conclude, instead, that levodopa is likely strengthening inhibition of reflexive behaviours.

Levodopa slows reflexive saccades

When given levodopa, the normal or slow reflexive prosaccade response time of our patients increased significantly. There is only one other report of slowed reflexive saccades with medication in PD, but those patients had early stage disease.²⁵ Some previous PD studies reported patients with hyper-reflexive (faster than controls) baseline orienting.^{12 15 26} Hence, in those studies, a levodopa slowing effect might have been beneficial for patients' reflexive responding.

Influence of dopamine agonists?

The slowed reflexive baseline performance found in our study (which contrasts with some previous findings) may be related to current medication practices. Specifically, dopamine agonists are becoming a more popular and common treatment in the US. Dopamine agonists achieve peak plasma levels rapidly (1–4 h) with complete clearance taking 2–5 days.²⁷ Therefore, it is possible that residual dopamine agonists are responsible for the slowed reflexive baseline responding in our PD group, as all but one PD patient were taking a dopamine agonist.^{12 15} One previous study suggested that addition of an agonist did not further alter the effect of levodopa on an antisaccade task.²⁸ Therefore, even if our patients had a novel baseline performance due to residual agonists, the medication effects we report are likely attributable to levodopa alone.

Levodopa and prefrontal cortex

Decreased voluntary eye movement control has been reported in several pathologies involving prefrontal cortex dysfunction (eg, schizophrenia, autism, attention deficit hyperactivity disorder, PD^{8 15–20}). In our study, we found evidence for improved prefrontal executive function shown by both improved voluntary antisaccades and slowed reflexive saccades after dopamine supplementation (via levodopa). Therefore, our results may have ramifications for other patient populations with executive dysfunction who are treated with dopamine antagonists (eg, schizophrenia).

Gap and overlap conditions

Our previous work has shown that the fixation procedure can affect reflexive prosaccade performance in PD.¹² Here, we found only voluntary antisaccade fixation procedures had different medication effects. Specifically, on the antisaccade gap task, we observed error rate improvement with levodopa but worse (slower) response time. Although it is possible that levodopa independently and oppositely affected error rate (voluntary inhibition) and response time (voluntary generation) on the antisaccade gap trials, we cannot rule out a simple speed accuracy trade-off. The antisaccade task with overlap trials had no such trade-off; levodopa unambiguously improved performance on antisaccade overlap trials. Future studies are needed to better understand these differences in medication effects across fixation conditions.

CONCLUSION

We have demonstrated for the first time in patients with advanced Parkinson's disease that levodopa can improve voluntary cognitive performance while concurrently slowing reflexive performance. Our results suggest that levodopa may have significant impact on neural substrates of executive function involved in planning and executing voluntary behaviours.

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