Journal of Clinical Neuroscience 19 (2012) 1119–1124

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

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

Clinical Study

Impairment of voluntary saccades and facilitation of reflexive saccades do not co-occur in Parkinson's disease

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ARTICLE INFO

Article history:
Received 20 April 2010
Accepted 23 October 2011

Keywords:
Neuropathology
Parkinson's disease
Saccades

ABSTRACT

Reflexive saccades (fast eye movements) and voluntary saccades activate overlapping parts of the oculomotor system. It is assumed that striatal dopamine depletion in Parkinson's disease (PD) only affects the voluntary saccadic system and that the often-reported facilitation of the reflexive saccadic system in PD is secondary to impairment of the voluntary saccadic system. If this assumption is correct, facilitation of reflexive saccades should co-occur with impaired performance of voluntary saccades in patients with PD. We measured reflexive and voluntary saccades in a group of patients with PD (both "on" and "off" medication) and a matching group of control subjects. Interestingly, performance measures showed strong positive correlations across reflexive and voluntary saccades in the PD group. Our results suggest that facilitation of reflexive saccades does not co-occur with impairment of voluntary saccades and that PD may affect the parts of the oculomotor system which are common to reflexive and voluntary saccade generation.

1. Introduction

Saccades are fast eye movements, which align retinal images of objects or locations of interest in the visual field with the fovea. A distinction is usually made between reflexive (exogenous) and voluntary (endogenous) saccadic tasks, depending on the type of cue used to elicit the eye movements. Reflexive saccades are made in response to a sudden peripheral stimulus onset, but voluntary saccades require some additional cognitive processing. Latency distributions of reflexive saccades are often bimodal and it is customary to further classify reflexive saccades into express and regular reflexive saccades reflecting the two peaks in the distribution. Express saccades are initiated at latencies between 80 ms and 140 ms and regular reflexive saccades at latencies over 140 ms from target onset.[1] The minimum latency for voluntary saccades is about 200 ms, depending on the time required to process the cue in voluntary saccadic tasks.[2] Patients with PD generally perform reflexive saccades normally or faster than control groups.[3–9] Impairments are found when people with PD perform voluntary saccades, such as memory-guided (looking towards a location stored in memory) or antisaccades (looking away from a peripheral stimulus). Characteristic deficits include hypometria (that is, the primary eye movement falls abnormally short of the target), prolonged latencies and increased error rates (unintended reflexive saccades) compared to controls.[4,7–15] These observations are consistent with models of eye movement control such as the "tonic inhibition model", where the voluntary saccadic system is responsible for inhibitory control over reflexive components of the saccadic system.[16] Such models predict that impairment of the voluntary saccadic system is associated with disinhibition or facilitation of the reflexive saccadic system.[3,7,11,16,17] Facilitation of the reflexive saccadic system may be an adaptive response to impairment of the voluntary saccadic system in PD.[7] That is, people with PD may compensate for the slow initiation of voluntary saccades by reducing saccadic response inhibition. In either case, whether a functional or an adaptive account is correct, facilitation of reflexive saccades in PD should be associated with impairment of voluntary saccades. However, it is not yet known if facilitation of reflexive saccades actually co-occurs with impairment of voluntary saccades in people with PD. So far, this question has not been addressed directly because the tasks most often used to identify impairment of the voluntary saccadic system in PD (that is, memory-guided and antisaccade tasks, require not only the execution of a voluntary saccade but also the suppression of a reflexive glance at a visual stimulus. These tasks involve competitive interactions between the voluntary and the reflexive systems,[18,19] meaning that performance will be impaired unless both systems are unaffected. To investigate the effect of PD on reflexive and voluntary saccades separately, we used two tasks specifically designed to avoid conflicting requirements of suppression and generation of saccades. A traditional reflexive task with a gap (where target onset

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http://dx.doi.org/10.1016/j.jocn.2011.10.014

occurs 200 ms after fixation point offset) was used to elicit reflexive saccades and promote the production of express saccades.[1] A task with a central arrow cue was used to elicit voluntary saccades without the requirement to suppress reflexive saccades.[2] We hypothesised that if facilitation of the reflexive saccadic system in PD is associated with impairment of the voluntary saccadic system, performance measures should be negatively correlated across the two tasks in the group with PD. Some studies have suggested that L-dopa may affect saccadic latencies[17,20] so that the group with PD was tested both "on" and "off" L-dopa.

2. Methods

2.1. Participants

Eleven participants (seven males, four females) with mild to moderate PD (Hoehn and Yahr stages 1–3) taking L-dopa medication, with a mean disease duration of 7.5 years (±3.1 standard deviation [SD]) and 11 control subjects (seven males, four females) were recruited. The PD and the control groups were matched for age, mean 68.1 years (±8.0 SD) and 67.1 years (±5.7 SD) respectively, and for years of education (mean: 12.4 and 13.4 years, respectively). All participants had normal or corrected-to-normal visual acuity (better than 6/12 in the best eye). All participants gave their informed consent.

2.2. Design

All participants performed the reflexive and voluntary saccadic tasks. Each subject performed both tasks in two separate sessions. Five PD patients were tested "off" medication in the first and "on" medication in the second session and the remainder were tested in the opposite order. Control subjects also were assigned to two subgroups, and their testing sessions were labeled "sham on" and "sham off" in a counterbalanced order. At the time of testing in the "off" condition, subjects in the PD group had not taken any PD-related medication for at least 12 h. The average interval between the two sessions was four days.

2.3. Apparatus and stimuli

Eye movements were recorded monocularly using a video-based iView X Hi-Speed system (SMI, Berlin, Germany) at a sampling rate of 240 Hz. Stimuli were displayed on a 21-inch cathode ray tube screen with a 100 Hz refresh rate and a resolution of 800 × 600 pixels. The screen was positioned 500 mm in front of subjects, who sat with head supported by the chin and forehead rest of the iView tracking column. Stimuli were presented on a grey background (R128 B128 G128). The fixation point in both tasks was a red square (R255 B0 G0), targets were green squares (R0 B0 G255) and the central cue in the voluntary saccade task was a light blue arrow (R0 B255 G255). All stimuli subtended 0.8 × 0.8° of visual angle.

2.4. Tasks

Both the reflexive and the voluntary task were designed to elicit horizontal eye movements of 12° to the left or to the right of the central fixation point. The difference between the two tasks was in the cue for the saccades: the onset of a peripheral target in the reflexive task or the appearance of a central arrow in the voluntary task. In the reflexive task, the central fixation point disappeared after a variable (800–1700 ms) fixation interval. After a gap of 200 ms, a green target appeared randomly 12° to the left or to the right of the centre. In the voluntary task, two green targets remained visible throughout the trial at 12 to the left and the right of the central fixation point. The fixation point changed from a red square into either a left or a right pointing arrow after a variable (800–1700 ms) fixation interval (Fig. 1). In both tasks, the central fixation point reappeared after 2000 ms and the next trial started. Participants were instructed to look "as quickly and accurately as possible" at the target following the appearance of the cue and to return their gaze to the central fixation point for the start of the next trial. A set consisted of a sequence of 50 trials (25 to the left and 25 to the right, presented in random order, fixed across subjects). In each session, participants performed three or four sets of each task, alternating between the reflexive and voluntary task.

2.5. Measurements and analysis

Latencies were measured from the appearance of the cue (that is, the peripheral onset in the reflexive task and the change of the fixation point into an arrow in the voluntary task). Saccades with latencies shorter than 80 ms (9% of the total number of observations) and directional errors (3% of the remaining observations) were removed from the analysis. Gain was defined as the ratio of

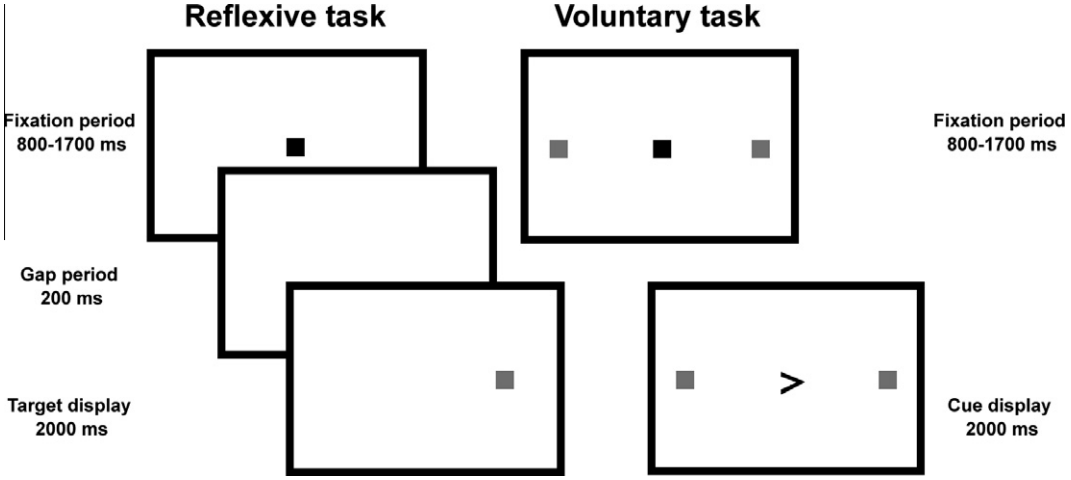

Fig. 1. Schematic illustration of stimulus presentation. In the reflexive saccadic task, saccades are executed in response to the onset of a peripheral target, 200 ms after the disappearance of the fixation point. In the voluntary saccadic task, both targets are displayed continuously and saccades are executed to the appropriate one in response to the central fixation point changing into a left-pointing or right-pointing arrow.

Table 1
Latencies and gain measurements for reflexive and voluntary saccades for each group (control or patients with Parkinson's disease) and testing condition

Group	Reflexive saccades		Voluntary saccades	
	Latency (ms)	Gain	Latency (ms)	Gain
Control group				
SHAM ON	172 ± 44	0.92 ± 0.06	362 ± 37	0.94 ± 0.07
SHAM OFF	169 ± 33	0.93 ± 0.03	371 ± 42	0.95 ± 0.07
PD group				
ON	158 ± 20	0.88 ± 0.07	415 ± 83	0.86 ± 0.10
OFF	165 ± 31	0.88 ± 0.07	417 ± 90	0.85 ± 0.08

The PD group was tested "on" and "off" L-dopa medication. The control group was also tested in two separate testing sessions (labeled "sham on" and "sham off").

the amplitude of the first saccade (i.e. the primary response) following the appearance of the cue to the target amplitude (12°). Latencies and gain were analysed with mixed-design analysis of variance (ANOVA) with session (1 or 2), medication condition ("off" or "on" L-dopa) and task (reflexive or voluntary) or saccade type (express, regular reflexive or voluntary) as within subject factors, and group (PD or control) and subgroup ("off"-first or "on"-first) as between subject factors. Pearson coefficients were calculated to assess associations of performance measures across reflexive and voluntary saccades.

3. Results

3.1. L-dopa

ANOVA of mean latencies and gain over the two sessions showed no effect of L-dopa condition in the PD group. The following analyses were therefore performed on all saccade measurements obtained for each subject, collapsed across the "on" and "off" sessions. Latency and gain measurements for each testing condition are shown in Table 1.

3.2. Latencies

Latencies of express saccades fall by definition within a narrow range. Therefore, latencies of express and regular reflexive saccades were combined to calculate the mean latency in the reflexive task for each subject. Overall, reflexive saccades were initiated at significantly shorter latencies than voluntary saccades (166 ms compared to 391 ms), $F_{(1,20)} = 255.22$, $p < 0.001$. There was a significant interaction between group and task, $F_{(1,20)} = 4.36$, $p = 0.049$ (eta-squared = 0.08, F = 0.29, indicating a medium effect size[21]). *Post-hoc* Fisher least significant difference (LSD) contrasts showed that the mean reflexive saccade latency in the PD group (161 ms, ±17 SD) did not differ significantly from the control group's (171 ms, ±38 SD), but the mean voluntary saccade latency in the PD group (416 ms, ±85 SD) was significantly longer than in the control group (367 ms, ±36 SD), $p = 0.048$ (Fig. 2A). The proportion of express saccades did not differ between the PD (mean 43%, ±18 SD) and control groups (mean 41%, ±22 SD).

3.3. Gain of primary saccades

For each subject, the mean gain of express, regular reflexive and voluntary saccades was calculated. Overall, the PD group made smaller primary saccades than the control group (0.87, ±0.8 SD compared with 0.93, ±0.6 SD), $F_{(1,20)} = 4.71$, $p = 0.042$ (eta-squared = 0.21, F = 0.52, indicating a large effect size[21]). There was a significant interaction between group and saccade type, $F_{(2,40)} = 4.45$, $p = 0.02$ (Fig. 2B). *Post-hoc* Fisher LSD contrasts showed that in the PD group, saccades were significantly hypometric compared to the control group only in the voluntary task ($p = 0.05$). In the PD group there was no significant difference between the gain of express, regular reflexive and voluntary saccades, but in the control group, express saccades were significantly smaller than regular reflexive and than voluntary saccades ($p < 0.001$).

3.4. Correlations between tasks

Mean latencies of reflexive saccades were positively correlated with mean latencies of voluntary saccades for individuals in the PD group ($r = 0.71$, $p = 0.01$, $N = 11$), but not in the control group ($r = 0.27$, $p = 0.42$, $N = 11$) (Fig. 3). Latencies of voluntary saccades were not associated with the gain of voluntary saccades in either group (Fig. 3B). Mean gain of express saccades was correlated with the gain of voluntary saccades in the PD group ($r = 0.83$, $p < 0.01$, Fig. 3C), but not in the control group ($r = 0.16$, $p = 0.63$, Fig. 3C). In the PD and the control groups the mean gain of regular reflexive saccades was correlated with mean gain of voluntary saccades ($r = 0.81$, $p = 0.002$ and $r = 0.72$, $p = 0.012$ respectively, Fig. 3D).

4. Discussion

4.1. General discussion

The suggestion that facilitation of the reflexive saccadic system is associated with impairment of the voluntary saccadic system in

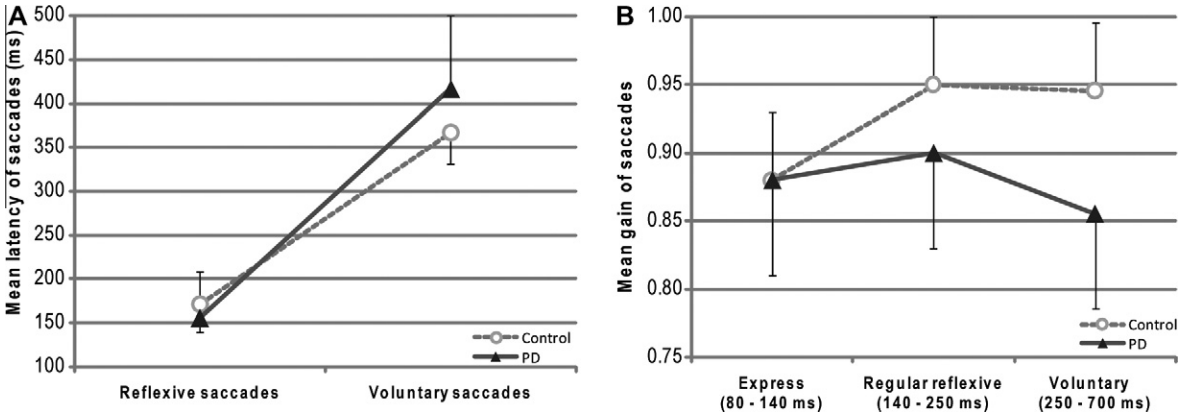

Fig. 2. Graphs representing: (A) mean latencies in the voluntary saccadic task were significantly longer in the Parkinson's disease (PD) group compared to the control group; (B) the gain of regular reflexive and voluntary saccades was significantly larger than the gain of express saccades in the control group but not in the PD group. Error bars indicate standard deviations.

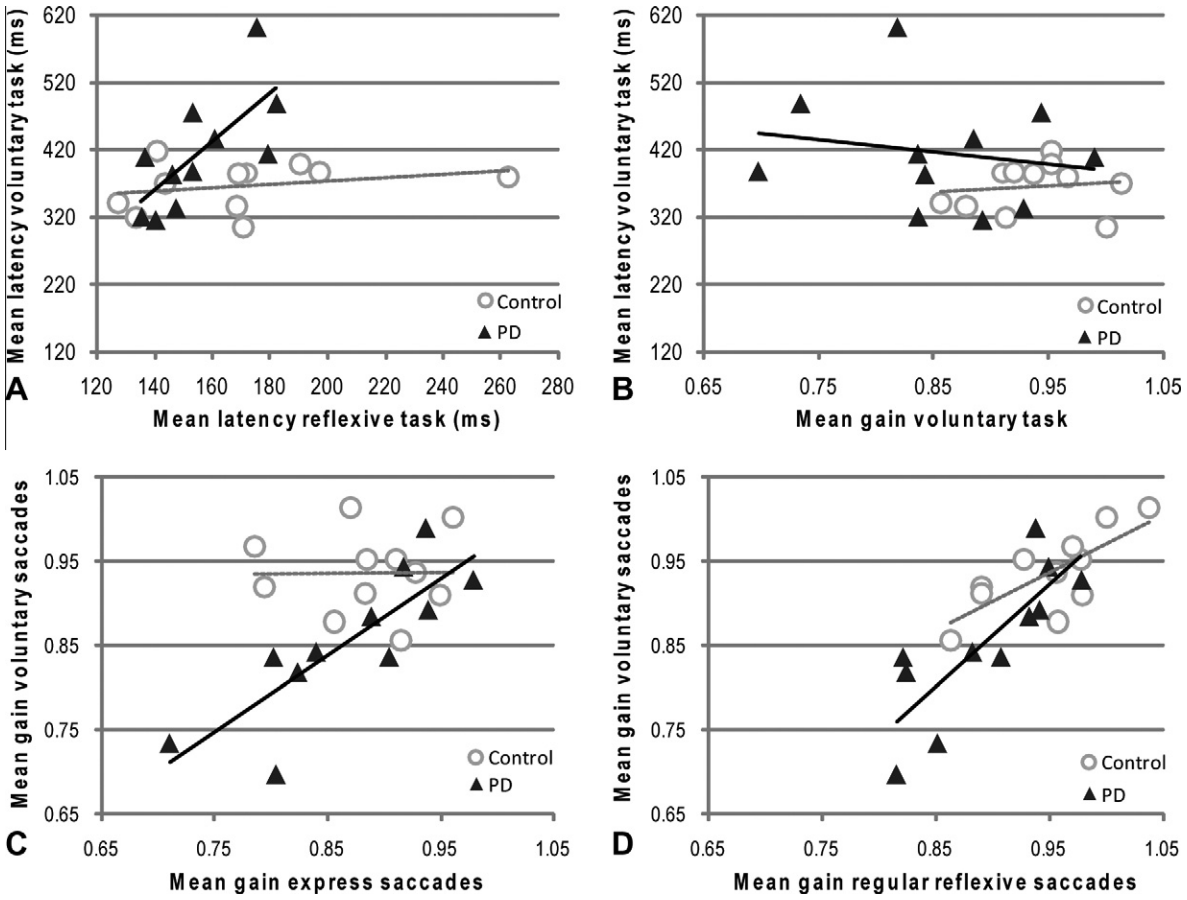

Fig. 3. Graphs representing: (A) mean latencies of saccades across tasks in the PD group were positively correlated in the PD group, but not in the control group; (B) hypometria was not associated with prolonged latencies of voluntary saccades in the PD or the control group; (C) mean gain of voluntary saccades was positively correlated with mean gain of express saccades in the PD group, but not in the control group; and (D) mean gain of regular reflexive saccades was positively correlated with mean gain of voluntary saccades in both groups. (Triangles = group with PD; circles = control group).

PD is based on studies comparing the performance of groups of PD patients with the performance of control groups. Our results are consistent with previous reports, but indicate that impairment of voluntary saccades does not co-occur with facilitation of reflexive saccades in people with PD. Instead of the expected negative relationships, positive correlations between performance measures across reflexive and voluntary saccadic tasks emerged in the PD group. First, subjects in the PD group who made voluntary saccades at relatively long latencies did not make reflexive saccades at shorter-than-average latencies nor did they make many express saccades. Conversely, subjects in the PD group who made reflexive saccades at relatively short latencies (including many express saccades) were not impaired in the voluntary task, but performed the voluntary saccadic task as well as subjects in the control group. The finding that, in the PD group, saccadic latencies were positively correlated across reflexive and voluntary tasks, suggests that PD affects saccadic latencies irrespective of the type of saccade.

Second, subjects in the PD group who made hypometric saccades in the voluntary task also made relatively small saccades in the reflexive task, at regular as well as express latencies. In the control group, regular reflexive and voluntary saccades were significantly larger than express saccades. In contrast, in the PD group there was no significant difference between the amplitude of express, regular reflexive and voluntary saccades. Smaller gain of express saccades compared to the gain of regular reflexive saccades has been reported previously in healthy subjects.[1] This difference has been attributed to the beneficial effect of longer visual processing time for regular reflexive saccades.[22] This effect was not apparent in the PD group. The finding that, for PD patients, saccadic gain was significantly correlated across express, regular reflexive and voluntary saccades, suggests that PD affects not only latencies but also the amplitude of saccades irrespective of the type of saccade.

Third, PD patients who made hypometric saccades did not necessarily make these saccades at abnormal latencies. Overall, hypometria may therefore be a better indicator of the effect of PD on the saccadic system than saccadic latencies, at least in mildly affected patients.

It can be argued that the visual input in the voluntary saccade task used in this study differed from the input in the reflexive saccade task and that this difference may have contributed to the impairment in the PD group. Therefore, as further evidence for our finding that PD affects saccadic parameters across reflexive and voluntary tasks, we re-analysed data from a previous study (van Stockum et al. 2008) in which we measured reflexive saccades and antisaccades (voluntary saccades where the subject is instructed to look away from a peripheral stimulus). In this study the visual input at the time of saccade initiation was identical in both the reflexive and the voluntary saccade task. In the PD group and the control group, mean latencies of reflexive saccades with a gap were positively correlated with latencies for correct antisaccades ($r = 0.54$, $p = 0.04$, and $r = 0.65$, $p = 0.006$ respectively, Fig. 4). Together these results indicate that facilitation of reflexive saccades and impairment of voluntary saccades do not co-occur in people with PD. The strong positive correlations between performance measures across tasks suggest that the effect of PD on the

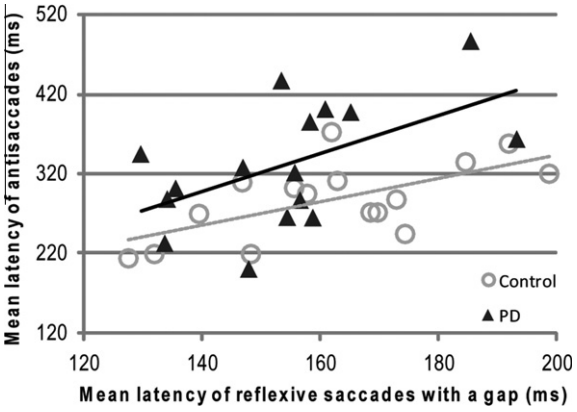

Fig. 4. Graph representing a new analysis of data from a previous study.[8] Mean latencies of antisaccades were positively correlated with mean latencies of reflexive saccades in a gap task in a PD and a control group.

saccadic system may be best understood in terms of processes common to the generation of both reflexive and voluntary saccades.

4.2. PD and the saccadic system

The interpretation of results is simplified compared to studies using antisaccade or memory-guided saccadic tasks, as our simple arrow-cued voluntary saccadic task involves only minimal cognitive processing and does not require response suppression via prefrontal cortical areas or frontostriatal circuitry.[23] Both reflexive and voluntary saccades appear to be affected by PD, suggesting that changes in oculomotor behavior may be related to disordered neural activity in subcortical structures which are common to the initiation of both reflexive and voluntary saccades.

A crucial structure in the saccadic system, where cortical and subcortical pathways converge, is the superior colliculus, a midbrain centre, which is directly responsible for the triggering of saccades in the brainstem reticular formation.[24] Neurons in the superior colliculus represent the visual field in terms of saccadic target locations. When neural activity in a spatially specific area of the superior colliculus reaches a threshold level, a saccade to the selected location is triggered. Dopamine transmission in the basal ganglia indirectly modulates neural activity patterns in the superior colliculus. In the pre-clinical stages of PD, brainstem structures may be affected before basal ganglia outputs are disrupted by nigrostriatal dopamine depletion.[25] Abnormal facilitation of saccades may reflect a pathological reduction of inhibitory control of saccade-triggering neurons. This effect may be apparent only in tasks such as a reflexive task with a gap, where target selection is automatic and immediate and latencies directly reflect the time required to trigger a saccade.[26,27] However, pathological impairment of fronto-striatal circuitry may delay saccade selection and initiation. This impairment may become apparent only in voluntary saccadic tasks, where response selection constitutes a large proportion of the saccadic latency. Therefore, when a group of PD patients is assessed, some subjects may show evidence of facilitation of reflexive saccades, while others may show evidence of impairment of voluntary saccades. Comparing the performance of a PD group as a whole with a control group may have led some researchers to the interpretation that PD affects the reflexive and the voluntary saccadic system in opposite ways and that facilitation of reflexive saccades may be associated with impairment of the voluntary saccadic system in PD.[7,11,17] While the results of our study are not inconsistent with this interpretation, we base our conclusion (that facilitation of reflexive saccades does not co-occur with impairment of voluntary saccades in PD patients) on the positive correlations of saccadic performance measures for individuals in the PD group across the two saccadic tasks.

Finally, our results also suggest that saccades may be hypometric in PD even when latencies are normal. From studies in non-human primates we know that saccadic latencies reflect the time-course of the neural response in the superior colliculus, but the amplitude of primary saccades is determined in oculomotor nuclei further down in the reticular formation in the brainstem.[28–30] We suggest that the dissociation of the effects of PD on saccadic latencies and saccadic gain may reflect differences in the spread of pathology in the midbrain and the brainstem.[31]

4.3. Limitations of the study

The small number of subjects recruited for this study may limit the generalisation of the results. Also, some of the subjects in the PD group made voluntary saccades where a (albeit very simple) cognitive manipulation is required, at much longer latencies than the control group. Disease progress in PD may be associated with impairment of cognitive functions and even dementia. Even though all PD subjects in this study were non-demented at the time of testing, the group may have been cognitively heterogeneous. To confirm our interpretation, future studies should recruit more subjects and include neuropsychological measures to investigate whether changes in oculomotor behaviour may be associated with a decline in cognitive ability.

5. Conclusion

Saccades of individuals with mild to moderate PD were assessed with a reflexive and a voluntary saccadic task. Spatial and temporal parameters of reflexive and voluntary saccades co-varied, suggesting that PD affects parts of the oculomotor system common to the generation of reflexive and voluntary saccades and that facilitation of reflexive saccades does not co-occur with impairment of voluntary saccades in patients with PD. The notion that PD has opposite effects on the reflexive and the voluntary saccadic system may have arisen from examining PD patients as a group.

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