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The influence of motor and cognitive impairment upon visually-guided saccades in Parkinson's disease

Michael R. MacAskill [a,b,*], Charlotte F. Graham [a,b], Toni L. Pitcher [a,b], Daniel J. Myall [a], Leslie Livingston [a,b], Saskia van Stockum [a,b], John C. Dalrymple-Alford [a,b,c], Tim J. Anderson [a,b,d]

[a] New Zealand Brain Research Institute, Christchurch, New Zealand
[b] Department of Medicine, University of Otago, Christchurch, New Zealand
[c] Department of Psychology, University of Canterbury, Christchurch, New Zealand
[d] Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

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ABSTRACT

Studies of saccades in Parkinson's disease (PD) have seldom examined the influence of cognitive status, ranging from normal cognition, through mild cognitive impairment, to dementia. In a large and heterogeneous sample, we examined how motor and cognitive impairment was reflected in the performance of reflexive, visually-guided saccades. We examined 163 people with PD and 47 similar-aged controls. Ninety three of the PD group had normal cognition (PDN), 48 had mild cognitive impairment (PD-MCI), and 22 had dementia (PDD). Pseudo-random targets (amplitudes of 5, 10, 15 and 20 deg and inter-stimulus-intervals ranging from 550 to 1800 ms) were shown in 108 mixed randomised trials, incorporating gap, step, and overlap onset conditions. Analyses were conducted using multi-level regression modeling. Participants were first assessed by continuous measures (Unified PD Rating Scale motor score and the Montreal Cognitive Assessment). Prolonged latency was significantly related to both motor and cognitive impairment, with the cognitive effect being compounded by increasing age. Decreased saccade amplitude, meanwhile, was primarily related to motor impairment. When assessed by discrete cognitive categories, all of the PD groups showed reduced saccadic amplitude relative to controls. Saccadic latencies, meanwhile, were abnormally prolonged only in the PD-MCI and PDD groups (the control and PDN groups were similar to each other). Latency in the overlap task was particularly sensitive to increasing motor and cognitive impairment. We conclude that reflexive saccades in PD are subtly decreased in amplitude even early in the disease process. Prolonged saccade latency, meanwhile, tends to occur later in the disease process, in the presence of more substantial motor and cognitive impairment, and greater age. The progressive impairment of reflexive saccades, and the differential onset of amplitude and latency impairments, may make them a useful objective tool for assessing disease status.

1. Introduction

Fast gaze-shifting eye movements (saccades) have been studied extensively in Parkinson's disease (PD). The decreased amplitude of saccades mirrors the hypokinesia of other motor systems, which is the hallmark of the disease (MacAskill, Anderson, & Jones, 2002). As with other motor deficits, saccadic impairments in PD are task-dependent. Simple reflexive saccades in response to a suddenly appearing target have often been reported as unaffected (for example, Crevits, Vandierendonck, Stuyven, Verschaete, & Wildenbeest, 2004; Tanyeri, Lueck, & Kennard, 1989). In contrast, impairments are pronounced when higher-level voluntary control is involved, such as when the movement is guided by memory, by a learned rhythmic pattern, or when it must be sent in the opposite direction (an 'anti-saccade') to a visual target (Kimmig, Haußmann, Mergner, & Lücking, 2002; Le Heron, MacAskill, & Anderson, 2005; O'Sullivan et al., 1997; van Stockum, MacAskill, Anderson, & Dalrymple-Alford, 2008).

Despite the resulting emphasis on voluntary saccades in PD, the assessment of reflexive saccades has been revisited recently (Chambers & Prescott, 2010; Terao et al., 2011). Chambers and Prescott's meta-analysis showed that across 47 conflicting studies, there was overall evidence of slightly prolonged reflexive saccade latency in PD. The difference was most consistent in the 'step' task,

* Corresponding author at: University of Otago, New Zealand Brain Research Institute, Department of Medicine, 66 Stewart St, Christchurch 8011, New Zealand. Tel.: +64 3 378 6072; fax: +64 3 378 6080.
E-mail address: michael.macaskill@nzbri.org (M.R. MacAskill).

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in which a peripheral target appears at the same moment as the currently-fixated target disappears. The difference was not significant when the two events were separated temporally (the 'gap' task) or when the onset of the peripheral target preceded the offset of the fixation point (the 'overlap' task). They attributed much of the variation across studies to methodological issues, such as target eccentricity, patient age, and to certain types of eye tracking and display technologies. Meta-analyses are valuable but limited by inconsistencies in methodology and data reporting across component studies. For example, Chambers and Prescott could not meaningfully assess the effect of disease severity as, when reported, these measures were generally collapsed across the entire sample (with a mean of only 14 patients and 12 controls in each study).

A recent investigation by Terao et al. (2011) addressed this, with their large sample of 66 patients and 87 controls allowing for a meaningful consideration of the effect of (motor) disease severity. They showed that impairment of memory-guided saccades generally occurred early in the disease and increased progressively with Hoehn and Yahr disease stage. Reflexive saccades, however, did not show uniform deterioration. Reflexive saccade amplitude was reduced in the early stage of motor impairment but did not continue to decrease thereafter. Reflexive latency, meanwhile, was unaffected at Hoehn and Yahr Stage 1, became prolonged significantly at Stage 2, and did not deteriorate thereafter. By contrast, Mosimann et al. (2005) reported that both latency and gain of reflexive saccades was significantly worse in a group with Parkinson's disease dementia (PDD) compared to PD without dementia. It is increasingly recognised that cognitive deterioration is a common and important aspect of PD, with up to 80% eventually developing dementia (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). Given the tight linkage between oculomotor control and attentional, memory and visuoperceptual processes, one might expect progressive saccadic impairment to accompany neuropsychological deterioration. The lack of progressive impairment of reflexive saccades seen by Terao et al. therefore might reflect their exclusion of patients with significant cognitive impairment (Mini Mental Status Exam score <25). Studies other than Mosimann's have excluded PD participants with evidence of dementia, but many are likely to have included a proportion with mild cognitive impairment (PD-MCI). Patients with PD-MCI have measurable deficits in one or more cognitive domains including memory, attention, executive functioning, and visuospatial perception (Dalrymple-Alford et al., 2011; Goldman, Weis, Stebbins, Bernard, & Goetz, 2012), but unlike patients with PDD, they remain able to perform adequately in activities of daily living. Agreed criteria for the diagnosis of PD-MCI are only now being adopted (Litvan et al., 2012). Therefore, a portion of the unexplained variation across studies noted by Chambers and Prescott (2010) might be accounted for by the recruitment of differing numbers of participants with undetected PD-MCI.

In summary, Terao et al. (2011) demonstrated the influence of the degree of motor impairment upon reflexive saccade performance in Parkinson's, but excluded patients with substantial cognitive impairment. Mosimann et al. (2005) examined the influence of the extremes of cognitive status (patients who were unimpaired compare to those with dementia) but did not assess the role of motor status. We hypothesised that the two factors (cognitive and motor impairment) might independently influence aspects of saccadic performance. If so, then measurement of saccades might be an objective biomarker which is differentially sensitive to both facets of the disease.

We therefore present a study of reflexive saccades in Parkinson's disease using the largest patient sample to date, covering a wide range of severity in both motor and cognitive impairment. For the first time in a saccadic study, each patient underwent comprehensive neuropsychological testing and was then categorised using established criteria (Dalrymple-Alford et al., 2011; Litvan et al., 2012) as being either in the normal range or as having PD-MCI or PDD. We hypothesised that reflexive saccade amplitude would be subtly reduced even early in the course of the disease and should deteriorate further with increasing motor impairment. Reflexive latency, meanwhile, should be relatively normal in patients with intact cognition but become progressively prolonged in those with cognitive impairment. Such findings would suggest that these two reflexive saccade parameters might be faithful markers of PD motor and cognitive status, respectively, and therefore potential biomarkers for tracking disease progression and patients' response to putative neuro-protective or neuro-restorative therapies.

2. Material and methods

2.1. Subjects

A convenience sample of 163 PD participants was recruited from the Movement Disorders Clinic at the New Zealand Brain Research Institute, Christchurch, New Zealand. A movement disorders specialist (TJA) confirmed that subjects met the UK Parkinson's Disease Society's criteria for idiopathic PD (Hughes, Daniel, Kilford, & Lees, 1992). Forty seven healthy control subjects were recruited, matched for mean age and years of education. Exclusion criteria were previous history of other neurological, psychological or medical conditions, including atypical Parkinson's disease; moderate or severe head injury, stroke, major depression or learning disability; a history of cranial neurosurgery; major heart disease; diabetes requiring insulin; medication other than PD treatment known to have a significant effect on the CNS; alcohol abuse; and corrected visual acuity worse than 6/12 in the best eye. The study was approved by the Upper South A Ethics Committee of the New Zealand Ministry of Health. All subjects gave written consent and caregivers provided additional consent for participants with cognitive impairment.

PD patients were classified as having normal cognition (PDN, $n=93$), mild cognitive impairment (PD-MCI, $n=48$) and dementia (PDD, $n=22$) (Table 1). Our classifications were consistent with the Movement Disorders Society Task Force

Table 1
Clinical and demographic characteristics of the sub-groups.

	Controls $n=47$	**PDN** $n=93$	**PD-MCI** $n=48$	**PDD** $n=22$
Age	67.2 (9.9)	64.9 (8.6)	69.3 (8.0)	72.8 (7.0)
Sex ratio (M:F)	32:15	62:31	30:18	18:4
Years of education	13.7 (2.9)	13.0 (2.9)	12.6 (2.8)	12.8 (3.0)
WTAR (Premorbid IQ)	112 (9.5)	112 (8.0)	108 (9.9)	108 (11.1)
MMSE	29.0 (1.0)	28.9 (1.1)	27.3 (2.0)	23.9 (3.0)
MoCA	27.2 (1.9)	26.5 (2.2)	23.5 (2.6)	17.2 (4.1)
PD duration		4.8 (4.1)	6.9 (4.5)	12.2 (8.2)
UPDRS III		23.9 (13.5)	29.8 (14.3)	48.5 (20.3)
Hoehn & Yahr		1.9 [1–4]	2.4 [1–4]	3.3 [2–4]

Values in round brackets = SD, square brackets = ranges. PDN = PD with normal cognition, PD-MCI = PD with mild cognitive impairment, PDD = PD with dementia.

criteria (Emre et al., 2007; Litvan et al., 2012). Those classified as PD-MCI were those who performed adequately on functional assessment of activities of daily living (and hence were not PDD) but were impaired on neuropsychological testing. The neuropsychological criterion for PD-MCI was scoring at least 1.5 standard deviations below the mean (using standardised normative comparisons) on two or more measures within at least one of four cognitive domains (executive function; learning and episodic memory; attention and working memory; and visuoperception) (Dalrymple-Alford et al., 2011). The MMSE and Montreal Cognitive Assessment (MoCA, Dalrymple-Alford et al., 2010; Nasreddine et al., 2005) provided brief global measures of cognition. We use the MoCA here as our continuous measure of overall cognition. A summary measure of the full neuropsychological assessment (the mean standardised *z*-score of all the component tests) provided similar results. For ease of comparison to future studies (which may not wish to use the full suite of tests required to classify patients as having PD-MCI or PDD) we therefore report the simple and cost-effective MoCA score. The Unified Parkinson's Disease Rating Scale (UPDRS: part III motor score, Fahn & Elton, 1987) was used to assess motor function for PD participants. The PD sample showed a wide range of impairment in both motor and cognitive function (Table 1 and Fig. 4).

2.2. Apparatus

Eye movements were recorded with a video-based iView X Hi-Speed (SMI, Berlin), an infrared pupil and corneal reflection tracking system which acquired samples monocularly at 1250 Hz. One PC controlled the eye tracking system while another presented the stimuli using custom software and the open source presentation program PsychoPy (Peirce, 2008). The subject was seated, with their head resting on the height-adjustable chin rest of the eye tracker. A high-speed DLP projector (with a resolution of 800 × 600 pixels and a refresh rate of 100 Hz) projected stimuli on the wall, 1605 mm in front of the subject's eyes, on an image area 1092 mm wide by 829 mm high. Red fixation and target stimuli were 12 × 12 pixel squares, subtending 0.75 deg against a white background. The iView X system was calibrated prior to each recording session, using a 13 point grid covering the area in which targets were presented.

2.3. Procedures

The target was first presented at the centre of the screen. It then jumped pseudo-randomly, at inter-stimulus intervals ranging from 550 to 1800 ms, moving horizontally by 5, 10, 15 or 20 deg left or right. The new target position served as the fixation point for the next trial. In the 'step' condition, the offset of the fixation target and the onset of the subsequent target were simultaneous. In the 'gap' condition, there was a 200 ms gap between the two events, and in the 'overlap' condition, the offset of the fixation target occurred 200 ms after the next target appeared (see Fig. 1). These three onset conditions were interleaved randomly in a single block of 108 trials (block duration 121 s). Participants were instructed simply to look at the red square as quickly and accurately as possible, and were not told of the differing onset conditions.

2.4. Saccade measures

Three primary measures of saccadic performance – latency, gain and peak velocity – were measured on each trial. Saccade latency was defined as the difference in time between the target onset and the initiation of the primary saccade towards it. Latencies were subsequently classified as either anticipatory (initiated less than 70 ms after target onset), express (fast responses, initiated 70–130 ms after target onset) or reactive (made more than 130 ms after target onset, Roll, Wierzbicka, & Wolf, 1996). Anticipatory saccades were excluded from subsequent analysis. The proportion of express saccades was calculated as the number of express saccades divided by the total number of reactive and express saccades, from the 'gap' trials only (express saccades seldom occur in step or overlap conditions). Gain was measured as the amplitude of the primary saccade divided by target amplitude. Peak velocity was calculated as the maximum velocity (deg/s) occurring within the duration of each primary saccade.

2.5. Analysis

Data were analysed within the statistical environment R (R Development Core Team, 2012) using its *lm* function for classical regression models and the *lme* function from the *nlme* package for multi-level models (Pinheiro, Bates, Debroy & Sarkar, 2011). Multi-level modeling was adopted because simple ANCOVA failed when applied to this repeated-measures data. Multi-level models, meanwhile, are robust to correlations with subjects and allow the effects of covariates to be estimated separately within sub-groups (Gelman & Hill, 2007; Gueorguieva & Krystal, 2004). The variables age, years of education, premorbid IQ were centred on their mean values across the subjects. This allows model intercepts to be interpreted as corresponding to the value of, say, an average-aged and educated subject in the control group. UPDRS scores were not transformed, and Control subjects were assigned a UPDRS score of zero. For consistency with the UPDRS, however, MoCA scores were transformed by subtracting them from 30, such that an "ideal" score on either measure was zero. We denote the transformed score as $MoCA_{dev}$, as it reflects the deviation from the maximum score of 30. This process allowed model intercepts (where all predictors have a value of zero) to have a meaningful value, corresponding to that of a person of average age (67), with no measured cognitive or motor impairment. In figures, however, for clarity we plot the untransformed MoCA score.

The *nls* non-linear curve-fitting function was used to create velocity main sequences, with a curve generated individually for each subject for both their abducting and their adducting saccades. The function estimated was peak velocity $= Vmax \times (1 - \exp(-1 \times \text{saccade amplitude}/c))$. *Vmax* is the coefficient of interest and represents the maximum peak saccadic velocity, the asymptotic value for a given individual at which the main sequence relationship saturates despite increasing saccadic amplitude (Collewijn, Erkelens, & Steinman, 1988). Initial estimates of 500 deg/s for *Vmax* and 5.0 deg for *c* were supplied for the first iteration. All figures were created in DataGraph (Visual Data Tools Inc, see MacAskill (2012).

3. Results

3.1. Gain and latency

The influence of cognitive and motor impairment was assessed simultaneously using $MoCA_{dev}$ and UPDRS scores for each individual. Latency was found to be related significantly to UPDRS, to $MoCA_{dev}$, and to an interaction between $MoCA_{dev}$ and age. That is, latency was prolonged with increasing motor and cognitive impairment, and the effects of cognitive decline were compounded by increasing age. Latency was also strongly influenced by the gap/step/overlap manipulation. The full model, along with confidence intervals for the parameter estimates, is given in Table 2. For ease of interpretation, the model can be distilled

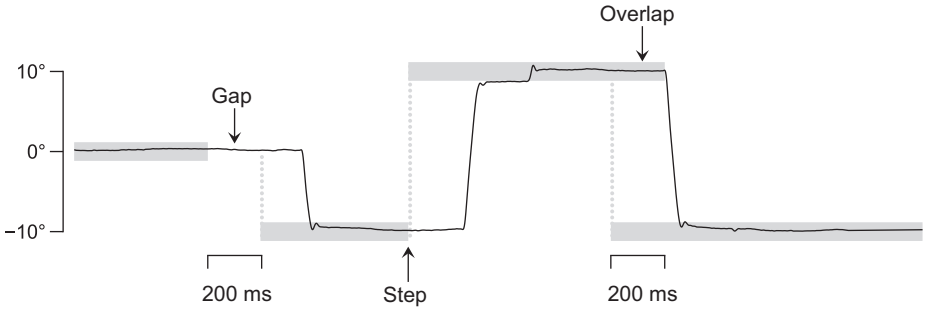

Fig. 1. Representative extract of an eye movement recording, showing three consecutive trials in the gap, step, and overlap conditions, respectively. The *y* axis indicates the horizontal position of the eye (black trace) and stimuli (grey bars). The centre of the screen is at 0 deg, with positive values indicating right of centre and negative values, left of centre. The *x* axis represents time, running from left to right. Dotted lines indicate the time of onset of each new target. Relative to the disappearance of the previous stimulus, this could occur either 200 ms afterwards (creating a temporal 'gap' between them), at the same time (making a simple 'step' from one position to the next), or 200 ms beforehand (resulting in a temporal 'overlap' of the stimuli). In each condition, the latency was measured as the time between the onset of the new target (dotted line) and the initiation of the primary saccade toward it.

Table 2
Fixed effects: Latency ~ (Task × $MoCA_{dev}$) + (Task × $UPDRS_{partIII}$) + (Age − 67 × $MoCA_{dev}$). Random effects: a random effect at the level of subject, and task within subject.

	Parameter	95%CI	SE	df	*t*	*p*
Intercept (Step task)	195 ms*	[186, 205]	4.7	13,126	41.6	< 0.0001
Gap effect	−64 ms	[−71, −56]	3.9	400	−16.2	< 0.0001
Overlap effect	20 ms	[13, 27]	3.6	400	5.6	< 0.0001
$MoCA_{dev}$	2.3 ms per point	[0.6, 4.1]	0.9	201	2.6	0.01
UPDRS	0.8 ms per point	[0.4, 1.1]	0.2	201	4.6	< 0.0001
Age − 67	−0.02 ms per year	[−0.9, 0.8]	0.4	201	−0.06	0.95
Gap:$MoCA_{dev}$	0.3 ms per point	[−1.1, 1.7]	0.7	400	0.4	0.68
Overlap:$MoCA_{dev}$	2.3 ms per point	[0.9, 3.7]	0.7	400	3.3	0.001
Age:$MoCA_{dev}$	0.2 ms per year per point	[0.06, 0.35]	0.07	201	2.8	0.005
Gap:UPDRS	−0.2 ms per point	[−0.5, 0.05]	0.14	400	−1.6	0.11
Overlap:UPDRS	0.4 ms per point	[0.1, 0.6]	0.13	400	2.7	0.007

* The intercept value (195 ms) is the predicted latency in the step task of a person of average age (67 years), with UPDRS and $MoCA_{dev}$ scores of zero.

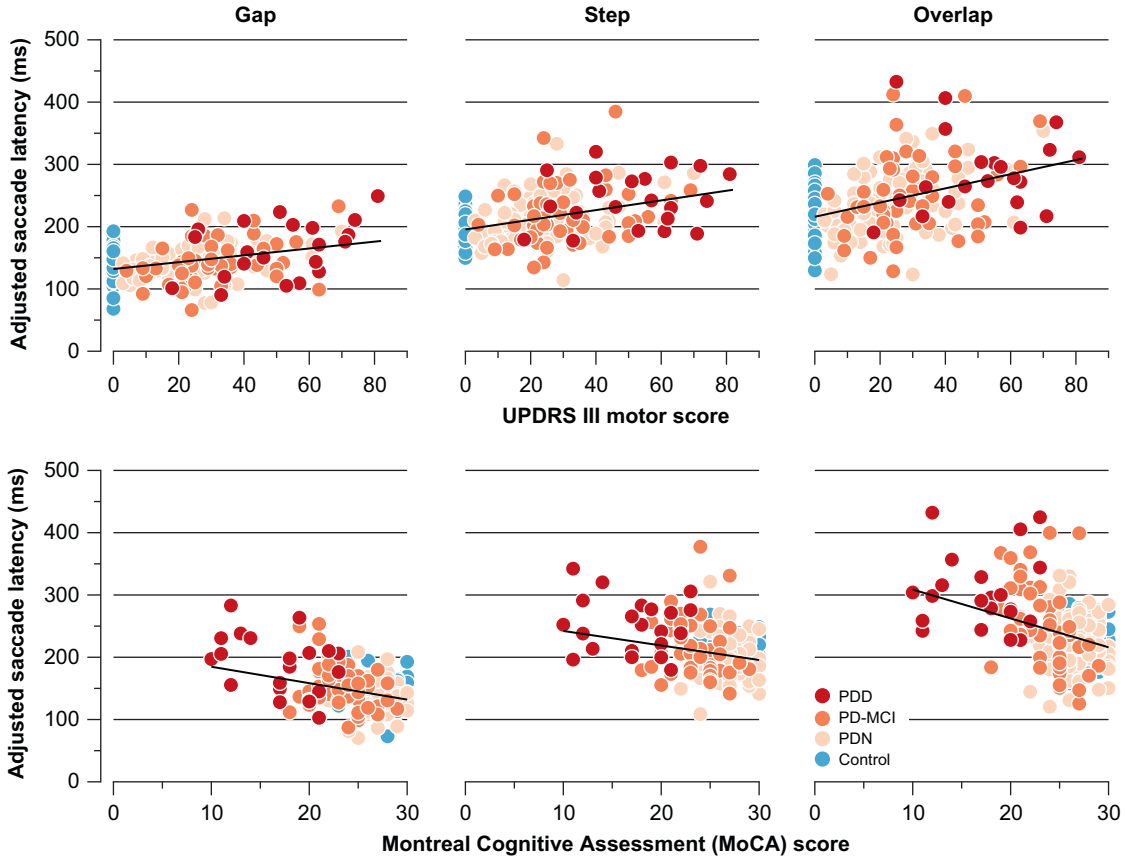

Fig. 2. The influence of cognitive and motor status on saccadic latency. The data and fitted lines correspond to the model in Table 2. *Top row*: Latency as a function of UPDRS motor score in the gap, step, and overlap onset conditions (controls were assigned a UPDRS score of zero). Each latency value has been corrected for that individual's MoCA score and age, and the fitted lines represent only the independent contribution due to motor impairment. The relationship between latency and UPDRS was similar in the gap (+0.6 ms per UPDRS point) and step tasks (+0.8 ms per point) but was significantly stronger in the overlap condition (+1.2 ms per point), see Table 2. *Bottom row*: Latency as a function of MoCA. Each latency value was corrected for that individual's UPDRS score, and the model fits represent only the contribution due to cognitive impairment. The relationship between latency and MoCA was similar in the gap (−2.6 ms per MoCA point) and step tasks (−2.3 ms per point) but was significantly stronger in the overlap condition (−4.6 ms per point).

down to the following equations, which allow us to predict latency in the gap, step or overlap condition for a given individual as a function of their age, $MoCA_{dev}$, and UPDRS part III motor scores:

$$Latency_{step} = 195\ ms + [0.8 \times UPDRS] + [2.3 \times MoCA_{dev}] + [0.2 \times MoCA_{dev} \times (Age - 67)].$$

$$Latency_{gap} = 132\ ms + [0.6 \times UPDRS] + [2.6 \times MoCA_{dev}] + [0.2 \times MoCA_{dev} \times (Age - 67)].$$

$$Latency_{overlap} = 216\ ms + [1.1 \times UPDRS] + [4.6 \times MoCA_{dev}] + [0.2 \times MoCA_{dev} \times (Age - 67)].$$

For example, for a control subject with a MoCA score of 30, regardless of age, the additional terms become zero and the predicted latency in the step task is the intercept value, 195 ms. Meanwhile, for a 70 year old with PD and a UPDRS of 40 and MoCA of 23, the predicted latency in the step task would be 247 ms. Note that latencies in the overlap condition were more sensitive to the influence of motor (1.1 ms per UPDRS point) and cognitive impairment (4.6 ms per $MoCA_{dev}$ point) than were latencies in the gap and step tasks. The relationship between latency and UPDRS and MoCA scores is depicted in both Fig. 2 and Fig. 4.

Table 3
Fixed effects: Primary gain ~ (Task × $MoCA_{dev}$) + (Task × $UPDRS_{partIII}$). Random effects: a random effect at the level of subject, and task within subject.

	Parameter	95%CI	SE	df	*t*	*p*
Intercept (Step task)	0.96*	[0.94, 0.98]	0.009	13,126	106.2	< 0.0001
Gap effect	−0.03	[−0.05, −0.02]	0.008	400	−4.1	0.0001
Overlap effect	−0.03	[−0.05, −0.02]	0.007	400	−4.2	< 0.0001
$MoCA_{dev}$	−0.003 per point	[−0.006, 0.0004]	0.002	203	−1.7	0.09
UPDRS	−0.0017 per point	[−0.002, −0.001]	0.0003	203	−5.0	< 0.0001
Gap:$MoCA_{dev}$	−0.0027 per point	[−0.006, 0.0002]	0.001	400	−1.8	0.07
Overlap:$MoCA_{dev}$	0.0014 per point	[−0.001, 0.004]	0.001	400	1.08	0.31
Gap: UPDRS	0.0005 per point	[0.000, 0.001]	0.0003	400	1.7	0.08
Overlap: UPDRS	−0.0001 per point	[−0.0001, 0.0004]	0.0003	400	−0.4	0.69

* The intercept value (0.962) is the predicted saccadic gain in the step task of a person of average age (67 years), with UPDRS and $MoCA_{dev}$ scores of zero.

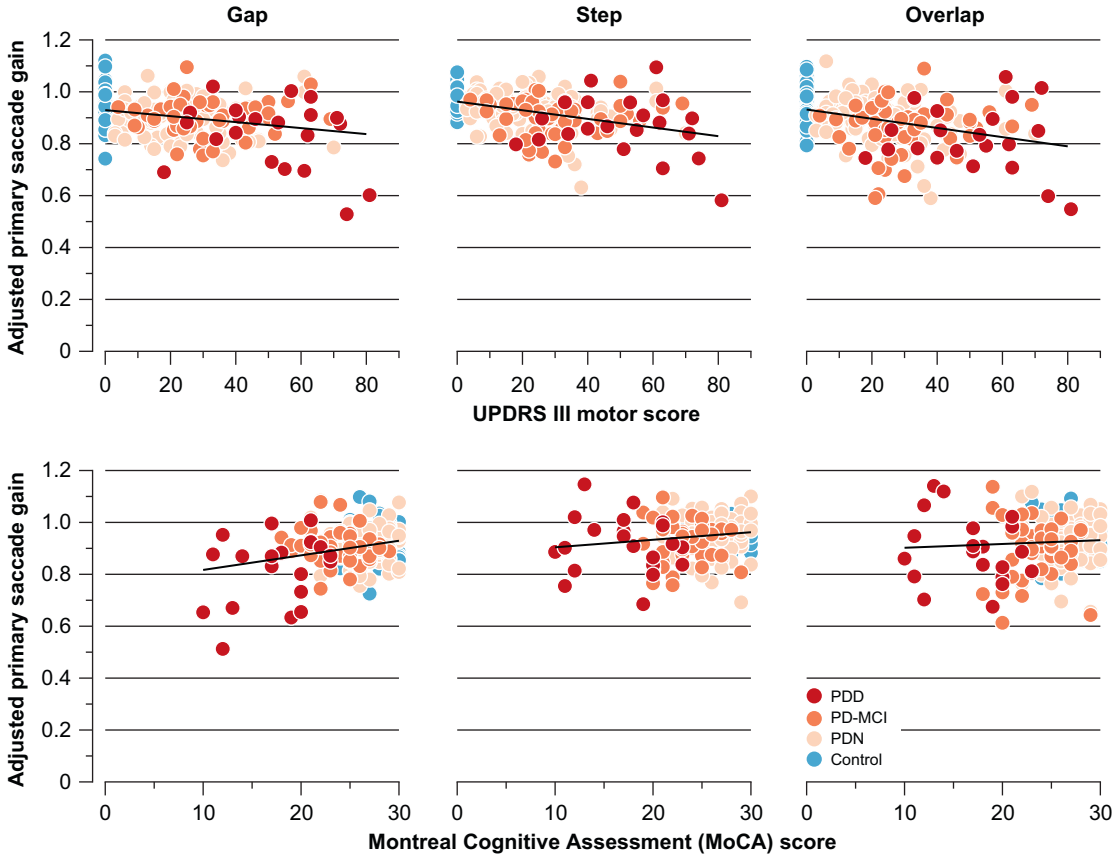

Fig. 3. The influence of cognitive and motor status on primary saccade gain. The data and fitted lines correspond to the model in Table 3. *Top row*: Gain as a function of UPDRS motor score in the gap, step, and overlap onset conditions (controls were assigned a UPDRS score of zero). Each gain value has been corrected for that individual's MoCA score, and the model fits represent only the independent contribution due to motor impairment. *Bottom row*: Gain as a function of MoCA. Each gain value was corrected for that individual's UPDRS score, and the model fits represent only the contribution due to cognitive impairment.

A model was constructed similarly for primary saccade gain, with only motor impairment found to be a significant predictor. The full model is given in Table 3. In the simplified predictive equations for each task given below, we still include a contribution due to the cognitive factor although it did not reach statistical significance. Table 3, Fig. 3, and Fig. 4 suggest that it may be reasonable to posit a weak influence upon saccade gain by cognitive status, particularly in the gap task:

$$Gain_{step} = 0.96 - [0.002 \times UPDRS] - [0.003 \times MoCA_{dev}].$$
$$Gain_{gap} = 0.93 - [0.001 \times UPDRS] - [0.006 \times MoCA_{dev}].$$
$$Gain_{overlap} = 0.93 - [0.002 \times UPDRS] - [0.001 \times MoCA_{dev}].$$

The proportion of express saccades was calculated only from the gap trials, as these rapid-onset saccades (latency between 70 and 130 ms) occur infrequently in step or overlap conditions. A classical regression was used to compare individual proportions of express saccade across groups. Controls made a mean of 40% (95% CI [33, 46]) of saccades at express latencies, not significantly different from the PDN (44%) and PD-MCI (35%) groups. The PDD group, however, had a significantly lower express saccade rate of 25% (95% CI [16, 34]).

To assess the relevance of these findings to clinical cognitive status, we then conducted an analysis with the subjects classified into their discrete groups (Control, PDN, PD-MCI, and PDD) rather than having cognition defined by the continuous MoCA measure. The mean latency for each group and task is shown in Fig. 5A. Latencies from each trial for all subjects were analysed in a multilevel model with task (gap, step, or overlap), group (Control, PDN, PD-MCI, PDD), age, sex, years of education, and premorbid IQ as

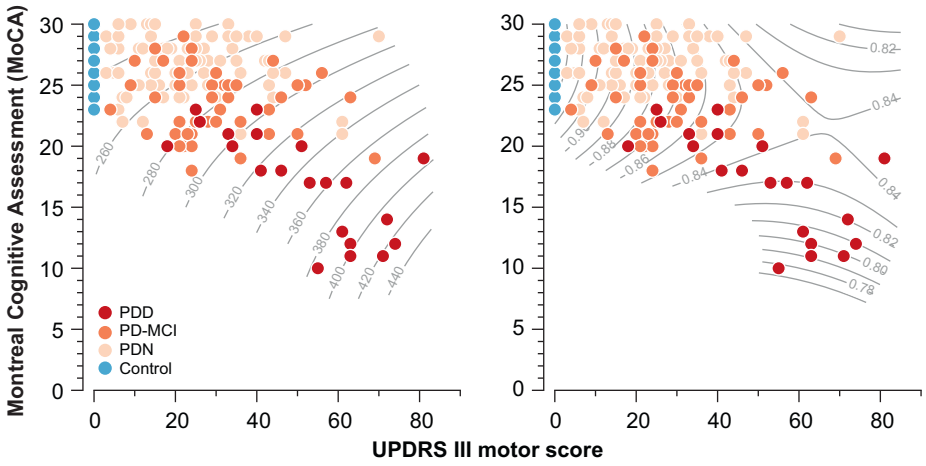

Fig. 4. There was a wide range of cognitive (*y* axis) and motor impairment (*x* axis) in the participants (each represented as a circle). *Left panel*: The contour lines represent saccade latency in the overlap task (ms) as a function of the two clinical measures. The oblique orientation of the contours indicates that latency prolongation was associated with increasing impairment on both measures. That is, with minimal impairment (top left corner of the graph), individuals tended to have a latency less than 240 ms, while latency exceeded 420 ms in the lower right corner, where patients were impaired on both clinical measures. *Right panel*: The data points are identical but the contour lines now represent primary saccadic gain. The initially rightward-marching contours indicate that reduced gain was associated primarily with increasing motor severity for the majority of patients. Only for the most clinically-impaired did cognitive status exert more of an effect. (PDN = PD with normal cognition, PD-MCI = PD with mild cognitive impairment, PDD = Parkinson's dementia).

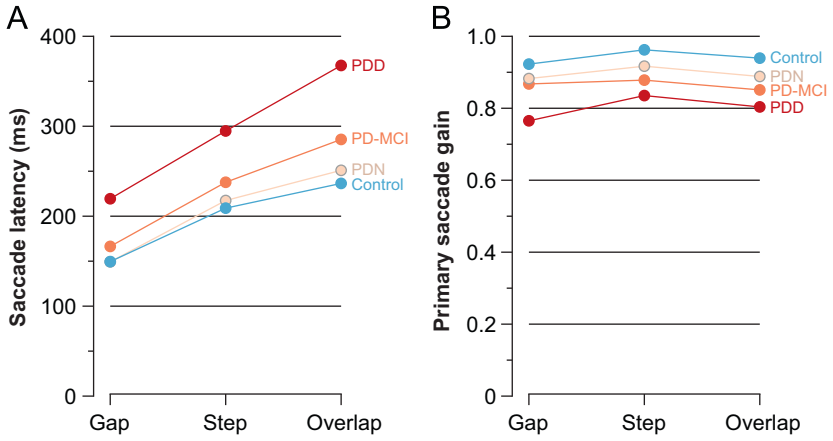

Fig. 5. (A) Mean saccade latency by task (gap, step, overlap) for each group (PDD = PD with dementia, PD-MCI = PD with mild cognitive impairment, PDN = PD with normal cognition). There were no significant difference between the Control and PDN groups across the three tasks but the PD-MCI and PDD groups had significantly prolonged latencies. For all groups, the gap manipulation shortened latencies while the overlap prolonged them, but the overlap effect was significantly more pronounced in the cognitively impaired groups. (B) Mean primary saccade gain by task and group. All PD groups produced saccades that were significantly shorter than those of the Control group. Saccades in the gap and overlap conditions were slightly but significantly smaller than in the step task.

predictors. Sex, education, and premorbid IQ were not significant predictors and were dropped from the model. UPDRS was omitted although it was significant. It tended to remove group differences, and unlike when considered with a continuous motor measure, the independent contribution due to each factor was not apparent.

The reference level (i.e., the intercept of the model) was 208 ms, 95% CI [196, 219], corresponding to the mean latency of a control subject of mean overall age (67 years) in the step task. There was no significant increase in latency between Controls and PDN in the step task (+11 ms, 95% CI [−3, 26]), while mean latency was considerably longer in the PD-MCI (+25 ms, [9, 42]) and PDD groups (+73 ms, [48, 98]). In the Controls, there was a substantial latency decrease in the gap task (−60 ms [−69, −51]) and an increase in the overlap task (+29 ms [21, 38]). The Task by Group interactions indicated a trend for both of the task effects to be amplified in the PD groups, but this was significant only for the cognitively impaired groups in the overlap task. That is, in the gap task there were non-significant latency decreases of −8 ms [−19, 3] in PDN, −9 ms [−23, 4] in PD-MCI, and −18 ms [−36, 1] in PDD, additional to the −60 ms decrease in the controls. In the overlap task, the increase in latency in PDN was not significantly larger than the 29 ms seen in the controls (an additional 5 ms [−6, 15] prolongation). The overlap effect was, however, significantly larger in PD-MCI (by an additional 17 ms [5, 29]) and PDD (additional 44 ms [27, 62]).

Age did not have a significant effect on latency in the Controls (0 ms per year, [−1, 1]) or PDN group (1 ms per year, [−0, 2]. Age was however associated with prolonged latency in PD-MCI (by 2 ms per year [1, 3]) and PDD (3 ms per year, [+0, 5]). Further analysis showed that the age effect within the PD-MCI and PDD groups was not related to duration of disease. The lack of association with age in the Control and PDN groups was not due to their lower mean age, as each of those groups actually had a wider range of ages than the older PD-MCI and PDD groups, which would have allowed an effect to be seen if it was present.

Mean primary saccade gain by group and task is shown in Fig. 5B. Gain values from each trial for all subjects were analysed

in a multi-level model with Task, Group, age, sex, years of education, and premorbid IQ as predictors. Only task and group were useful predictors. The pattern was different to the latency results, in that all of the PD groups showed significant reductions in saccadic gain relative to controls in the step task. Control mean step gain was 0.96 [0.94, 0.98]. Gain was significantly smaller by −0.05 [−0.07, −0.02] in PDN, −0.08 [−0.11, −0.05] in PD-MCI, and −0.13 [−0.17, −0.09] in PDD. The gap (−0.04 [−0.06, −0.03]) and overlap (−0.02 [−0.04, −0.01]) manipulations each resulted in decreased gain relative to the step task but there was little evidence of these effects being greater or lesser in the PD groups.

3.2. Target position and amplitude

Fixation position and target amplitude can have effects upon saccadic latency and accuracy. In Fig. 6, we examine whether there are any differential influences of Parkinson's upon these effects, as suggested by Chambers and Prescott (2010). For simplicity, only data from the step task are shown, as similar results were seen in the gap and overlap conditions.

The position of the stimulus at the end of a trial served as the fixation position for the following one (that is, the target did not return to a central position each time). Although the timing and amplitude of the target jumps was pseudo-randomised, this arrangement inevitably leads to a predictable bias in target direction. That is, the direction of the upcoming target is unpredictable when fixating at a central position, but as the fixation position approaches, for example, the left boundary of the stimulus area, the next target becomes increasingly likely to appear to the right. Subjects can utilise this partially predictive information, and hence latency is not uniform across fixation positions (Fig. 6A). That is, latencies are longest when the current fixation is near the centre of the screen because the direction of the upcoming target is less predictable than when fixation is near the screen edge. Although the PD-MCI and PDD groups had prolonged latencies overall, they too showed an ability to benefit from this predictive information. There was no effect of fixation position upon saccadic gain (Fig. 6C).

Fig. 6B shows the influence of stimulus amplitude. That is, regardless of starting position, what effect does the size of the target jump have upon latency? There was no evidence for a differential effect of PD. Within each group, latency was reasonably constant for all amplitudes of leftward movements. For rightward movements, in all groups latency was shortened at the smallest (5 deg) amplitude, and prolonged but constant at the larger amplitudes. Although the amplitude of saccades was smaller overall in the PD groups, they showed the same range effect as controls, with larger target jumps eliciting a greater degree of hypometria (Fig. 6D).

3.3. Peak velocity

Peak velocity is a function of saccadic amplitude. Because saccades in the PD groups were hypometric relative to controls, a simple comparison of mean peak velocities would likely reveal an

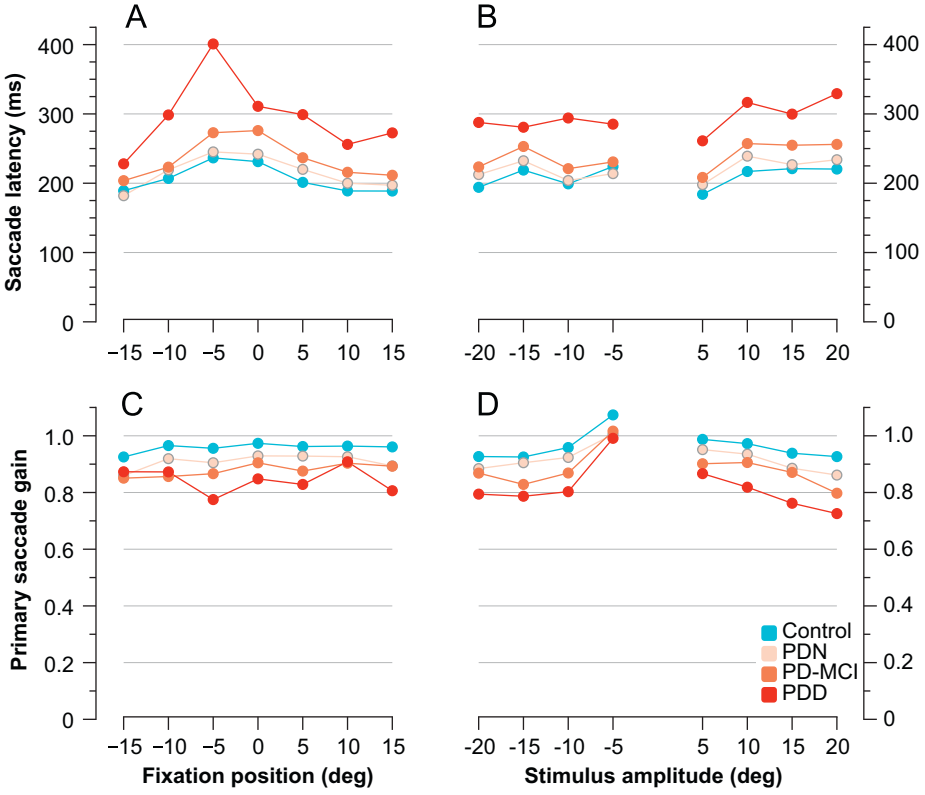

Fig. 6. Effects of the current fixation position (left column) and the upcoming target amplitude (right column) upon latency (upper panels) and gain (lower panels). These effects appeared to be consistent across all groups. For simplicity, only data from step trials are shown, but effects were similar in the gap and overlap conditions. (A) There was a strong relationship between fixation position and latency to the upcoming target (0 deg=the centre of the screen, −15 deg=left boundary, +15 deg=right boundary). At the centre of the screen, the direction of the next stimulus is unpredictable, but as the fixation position approaches either boundary, it becomes increasingly likely that the next target will jump in the opposite direction. Hence latencies are shorter near the screen boundaries. The PD-MCI and PDD groups had longer latencies overall, but were still able to make use of this predictive information. (B) Latency shown as a function of the size of the stimulus jump. Leftward displacements (negative amplitudes) showed no relationship with latency, while for rightward displacements, 5 deg jumps tended to have shorter latencies than larger stimulus movements. (C) The size of saccades did not vary as a function of the starting position. (D) There was, however, clear evidence of a range effect, with larger target jumps leading to greater hypometria for all groups.

artefactual decrease. Accordingly, we calculated main sequence curves for each individual as a measure of maximum performance. By convention we recorded the left eye, but due to technical reasons, utilised the right eye in three of the controls and in 16 PD subjects. As each saccade's direction was classified as either abducting or adducting, all subjects' data could be included regardless of which eye was recorded. Fits were rejected in one of the directions for six of the PD subjects, as they either failed to converge or yielded values of *Vmax* greater than 1000 deg/s. Such improbably large values of *Vmax* were generated when a main sequence showed only a linear relationship over the range of amplitudes in its valid trials, and thus a meaningful saturation value could not be calculated.

The estimated maximum peak velocity (*Vmax*) for abducting saccades in the control group was 540 deg/s, 95%CI [507, 574], with adducting saccades slightly but significantly slower, by −18 deg/s, 95%CI [−29, −7]. Maximum peak saccadic velocity was not significantly different in the PD groups relative to the controls (PDN, 0 deg/s; PD-MCI, −10 deg/s; PDD, −15 deg/s). Age did not have a significant influence (within the restricted range of this elderly sample).

4. Discussion

The performance of simple, visually-guided, saccades has often been regarded as preserved in Parkinson's disease, in contrast to the marked deficits of saccades made in more cognitively-demanding tasks. Only one previous study has explicitly examined saccades and cognitive impairment in Parkinson's. Mosimann et al. (2005) recruited a group of non-dementia PD, as well as groups with PDD, Lewy body dementia (DLB), and Alzheimer's dementia (AD). They found that the gain of reflexive saccades was reduced in all of the Parkinsonian groups (i.e., PD, PDD, and DLB) but that prolonged latency occurred only in the groups with dementia, which is consistent with our findings. Mosimann et al. posited that the combination of striatonigral/dopaminergic and cortical/cholinergic pathology, as in PDD and DLB, leads to greater impairment of reflexive saccades than when either of these pathologies are present in isolation, as in PD and AD. In this study, however, we have extended the findings of both Mosimann et al. and Terao et al. (2011) by simultaneously examining the influence of both motor impairment and cognitive status, including the first explicit examination of PD with mild cognitive impairment. The hypothesis that saccadic gain is primarily related to motor status was confirmed, with only a small and non-significant contribution due to cognitive status. Latency meanwhile, was influenced by *both* motor and cognitive impairment, with the effect of the latter being compounded by increasing age.

4.1. Saccade latency

The previous literature on reflexive saccade latency in PD is extensive but conflicting. Various studies have found that latency is either normal, prolonged, or shortened. Chambers and Prescott's (2010) meta-analysis concluded that is significantly prolonged in PD, but only in the step task. We, however, found that while there was little difference between controls and cognitively normal PD patients, latencies were prolonged across all three tasks when cognitive impairment was present. In fact, with our more heterogeneous sample, the overlap task was significantly more sensitive to the influence of both motor and cognitive impairment (Table 2 and Fig. 2) than was the step task.

The meta-analytic model proposed by Chambers and Prescott was hampered by not being able to include measures of disease severity or cognitive impairment, due to the group-level and inconsistent reporting in the studies involved. Their model accounted for 52% of the variance in latency across the studies, but in the absence of the important motor and cognitive factors, the meaningful influence of the model's significant predictors is doubtful. For example, we are not convinced that the particular eye tracking technology used in a study could interact with the effects of Parkinson's to produce up to a 41 ms difference in latency (comparable to the duration of a typical saccade). The model also attributes some of the variability across studies to an effect of target eccentricity, in which the initiation of large saccades is slowed in PD whereas small ones may be hastened. Our data (Fig. 6B) provide no evidence for a substantial differential effect of PD with target amplitude. Although the smallest rightward saccades were initiated sooner than others, this was the case for both the control and PD groups. We tested Chambers and Prescott's predictive model, applying it only to our PDN group in order to be most compatible with the studies they surveyed. Using values of 2.3 years for difference in mean age, 12.5 deg for mean stimulus eccentricity, −1 for tracking equipment (video), and +1 for display equipment (interpreted as 'CRT'), the model predicted that our PDN group should have a reaction time 46 ms faster than controls, when they were actually not significantly different (11 ms slower, 95% CI=3 ms faster to 26 ms slower).

Our data indicate that the latency of reflexive saccades is similar to control values in cognitively-unimpaired PD. This does not, however, imply that the task is of no value in investigating the early stage of the disease. In a recent study we showed that, although latency in a PDN group was normal in a simple reflexive protocol, adding a simultaneous perceptual task revealed an abnormal degree of facilitation in PDN (van Stockum, MacAskill, Myall, & Anderson, 2011). Thus the concept of saccadic hyperexcitability, at least in the early stages of the disease, certainly remains tenable, but may require specific attentional demands in order to be elicited reliably. With more advanced disease (motor and cognitive) and increased age, latencies certainly become prolonged in PD. The overlap task was particularly sensitive in this respect. Perhaps related to these increased reaction times may be a reduced ''excitability'', reflected in the significantly reduced proportion of express saccades made by the PDD group in the gap task.

4.2. Saccade size

Our study is consistent with others which have shown that the amplitude of reflexive saccades is decreased even in early PD, but to a relatively subtle degree that could often go undetected in small samples (Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Mosimann et al., 2005; Terao et al., 2011; van Stockum et al., 2011). Terao et al. reported that most of the impairment in visually-guided saccades occurred early in the disease course and did not worsen at later stages. By contrast, we found that deterioration was correlated with increasing disease severity, whether assessed by categorical cognitive status (Fig. 5) or by continuous measures of cognitive or motor impairment (Figs. 2 and 4). This difference may very well be due to the exclusion of subjects with substantial cognitive impairment from the Terao et al. study, as those were the subjects in our study who had the greatest saccadic impairments.

The reduced amplitude of saccades in PD may be due to excessive inhibition of the superior colliculus (SC), by output from the basal ganglia via the substantia nigra pars reticulata (SNpr) (Hikosaka & Wurtz, 1983). According to Terao et al., as the predominantly frontal eye field signal for voluntary saccades reaches the SC via fronto-striatal pathways, they (voluntary saccades) receive a 'double hit' from basal ganglia dysfunction.

That is, the effect of the abnormal tonic suppression from SNpr may be amplified by the effect of the disrupted frontostriatal triggering signal. Reflexive saccades, however, have a cortical-level signal which engages a direct pathway to SC from parietal eye fields (PEF), bypassing the basal ganglia, and hence are less disrupted by their malfunctioning. The excessive basal ganglia inhibition of PD is still evident in reflexive saccades, as shown by the subtle decrease in amplitude which is seen even in mild disease. Moreover, further amplitude reduction is associated primarily with increasing motor impairment. We propose an extension to Terao et al.'s account, and contend that a related argument could be made for why the prolongation of latency occurs later in the disease course for reflexive saccades than in more voluntary tasks. As the initiation signal for reflexive saccades from PEF avoids the basal ganglia, reaction times should be more affected later in the course of the disease. This is when more cortical-level pathology occurs, affecting the PEF itself and causing increasingly widespread cognitive impairments (Braak, Rub, & Del Tredici, 2006). This is consistent with our data, in which prolonged latency was strongly driven by both cognitive and motor impairment. The finding that latencies of visually-guided saccades in the overlap condition were particularly sensitive to disease burden may reflect the more voluntary nature of this task. In the overlap condition, in contrast to the gap or step conditions, the decision to release attention from the fixation stimulus to allow the visually-guided saccade to be triggered may, at least partially, be under voluntary control and involve more basal ganglia output. Saccadic gain, however, meanwhile was more strongly associated with motor impairment. This is consistent with an account in which the main influence of the basal ganglia on reflexive saccades is on movement amplitude rather than onset time. By contrast, in voluntary saccades, as noted by Terao et al., basal ganglia impairment affects both aspects.

PD patients with advanced disease or with cognitive impairment have traditionally been excluded from eye movement studies (including our own previous work). This has been justified on the basis of measuring only the effects of 'pure' basal ganglia disorder, prior to the more widespread and cortical involvement which occurs later in the disease process. This may be justified when PD is being used simply as a model to test theories of basal ganglia involvement in oculomotor control. If, however, the disorder itself is the topic of investigation, then patients with cortical-level pathology and cognitive impairment should be included, as these effects are inherent parts of the disease process.

4.3. Peak velocity

A reduction of the peak velocity of visually-guided saccades in PD has been reported in response to stimuli of certain amplitudes (Shibasaki, Tsuji, & Kuroiwa, 1979; White, Saint-Cyr, Tomlinson, & Sharpe, 1983). As saccades in Parkinson's are usually hypometric, however, the lower velocity may simply be secondary to the decreased amplitude of the primary saccade. Hence, to assess saccadic velocity in PD with validity, one must measure the 'main sequence' relationship between peak velocity and the actual amplitudes of saccades, rather than the amplitudes of the stimuli. Other studies that have adopted this approach (Gitchel, Wetzel, & Baron, 2012; Lueck, Tanyeri, Crawford, & Henderson, 1990; Rottach, Riley, DiScenna, Zivotofsky, & Leigh, 1996; Tanyeri et al., 1989) have also found horizontal visually-guided saccades in PD to be no slower than control saccades, once the primary deficit of decreased amplitude is considered. We did not assess vertical saccades, but they are also likely to be of normal velocity in idiopathic PD (Gitchel et al., 2012; Tanyeri et al., 1989).

4.4. Conclusion

There are currently no reliable biomarkers that faithfully signal the underlying neurodegeneration or track PD status and progression (O'Keeffe, Michell, & Barker, 2009). There is a particular need to find a marker that correlates closely not only with motor status but also with cognitive status. Such a biomarker should ideally reflect, or even predict, decline from normal cognition to PD-MCI, and from PD-MCI to PDD. An advantage of the reflexive saccade task is that it allows the probing of cognitive-level processes via the gap/step/overlap manipulation yet it does not require complicated, or even differing, instructions (the subject is simply told to look at the target quickly and accurately). Memory-guided and antisaccade tasks, while perhaps more strongly influenced by PD (Amador, Hood, Schiess, Izor, & Sereno, 2006; Terao et al., 2011), in our experience often become difficult to comprehend or to perform for aged and cognitively-impaired participants. These tasks are also more likely to be influenced by day-to-day variations in alertness and motivation than the relatively simple reflexive task. There remains however, a substantial variation in reflexive saccade measures across subjects with similar clinical status (for example, Figs. 2 and 3). A useful biomarker would have to demonstrate, within individuals, sufficient stability over time to faithfully reflect changes in clinical status. We are currently following-up some of the subjects in this study over a 2-year period to assess whether reflexive saccade measures can provide that.

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