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Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies

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Summary

Neurodegeneration in Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) affect cortical and subcortical networks involved in saccade generation. We therefore expected impairments in saccade performance in both disorders. In order to improve the pathophysiological understanding and to investigate the usefulness of saccades for differential diagnosis, saccades were tested in age- and education-matched patients with PDD (n = 20) and DLB (n = 20), Alzheimer's disease (n = 22) and Parkinson's disease (n = 24), and controls (n = 24). Reflexive (gap, overlap) and complex saccades (prediction, decision and antisaccade) were tested with electrooculography. PDD and DLB patients had similar impairment in all tasks ($P > 0.05$, not significant). Compared with controls, they were impaired in both reflexive saccade execution (gap and overlap latencies, $P < 0.0001$; gains, $P < 0.004$) and complex saccade performance (target prediction, $P < 0.0001$; error decisions, $P < 0.003$; error antisaccades: $P < 0.0001$). Patients with Alzheimer's disease were only impaired in complex saccade performance (Alzheimer's disease versus controls, target prediction $P < 0.001$, error decisions $P < 0.0001$, error antisaccades $P < 0.0001$), but not reflexive saccade execution (for all, $P > 0.05$). Patients with Parkinson's disease had, compared with controls, similar complex saccade performance (for all, $P > 0.05$) and only minimal impairment in reflexive tasks, i.e. hypometric gain in the gap task (P = 0.04). Impaired saccade execution in reflexive tasks allowed discrimination between DLB versus Alzheimer's disease (sensitivity $\geqslant$60%, specificity $\geqslant$77%) and between PDD versus Parkinson's disease (sensitivity $\geqslant$60%, specificity $\geqslant$88%) when $\pm$1.5 standard deviations was used for group discrimination. We conclude that impairments in reflexive saccades may be helpful for differential diagnosis and are minimal when either cortical (Alzheimer's disease) or nigrostriatal neurodegeneration (Parkinson's disease) exists solely; however, they become prominent with combined cortical and subcortical neurodegeneration in PDD and DLB. The similarities in saccade performance in PDD and DLB underline the overlap between these conditions and underscore differences from Alzheimer's disease and Parkinson's disease.

Keywords: Parkinson's disease dementia; dementia with Lewy bodies; Alzheimer's disease; saccades

Abbreviations: ANOVA = analysis of variance; CS = central stimulus; DLB = dementia with Lewy bodies; PDD = Parkinson's disease dementia

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Introduction

Patients with Parkinson's disease are at increased risk of developing dementia compared with elderly controls (Aarsland *et al*., 2003). The symptoms of Parkinson's disease dementia (PDD) may show considerable overlap with those of dementia with Lewy bodies (DLB), apart from a longer duration of extrapyramidal motor features (Noe *et al*., 2004).

Clinical studies comparing PDD and DLB have found similar fluctuation of attention (Ballard *et al*., 2002), over-representation of the postural instability-gait type of parkinsonism (Burn *et al*., 2003), similar visuoperceptual impairment (e.g. Simard *et al*., 2003; Mosimann *et al*., 2004*b*) and response to cholinergic therapy (McKeith *et al*., 2000*a*; Emre *et al*., 2004). PDD and DLB have, in contrast to Alzheimer's disease, more profound cortical cholinergic loss (Perry *et al*., 1994; Tiraboschi *et al*., 2002; Bohnen *et al*., 2003) and reduced dopamine in the basal ganglia (Piggott *et al*., 1999; Suzuki *et al*., 2002). Lewy body disorders are associated with abundant striatal pathology (Duda *et al*., 2002) and DLB with reduced putamen volumes (Cousins *et al*., 2003).

Saccades are humans' fastest eye movements, used to shift the fovea towards visual targets. Since saccade control requires interplay of cortical and subcortical areas (Hikosaka *et al*., 2000; Pierrot-Deseilligny *et al*., 2003*b*) and pathology in PDD and DLB is found in the cortex and the basal ganglia, we expected impaired saccade performance in both disorders. However, we are not aware of any published reports which have quantified saccade performance in these disorders. The cortex mediates saccadic triggering and inhibition (Hikosaka *et al*., 2000; Pierrot-Deseilligny *et al*., 2003*b*), and the basal ganglia allow saccade initiation by removing tonic inhibition to the superior colliculus (Hikosaka *et al*., 2000). Neural networks involved in saccade generation are task-dependent. Reflexive saccades are mainly cue-driven, and complex saccades follow an internal goal or intention (Leigh and Kennard, 2004). We used a combination of reflexive (gap and overlap) and complex saccade tasks (prediction, decision and antisaccade) to test the different aspects of saccade performance and the different networks involved.

Studies assessing saccades in Parkinson's disease and Alzheimer's disease have so far revealed contradictory results (Pirozzolo and Hansch, 1981; Briand *et al*., 1999; Abel *et al*., 2002). Given the clinical and pathological overlap of PDD and DLB, we expected them to show changes in saccade performance, which were similar to each other, but different from Alzheimer's disease and Parkinson's disease. We aimed to determine differences between DLB versus PDD and Alzheimer's disease versus DLB and Parkinson's disease versus PDD because these differential diagnoses are clinically particularly challenging.

Methods

Subjects

All subjects were recruited from the Newcastle Lewy body disease study (Burn *et al*., 2003). The National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al*., 1984) criteria were used to diagnose Alzheimer's disease and the Consensus guidelines to diagnose DLB (McKeith *et al*., 1996, 1999). Parkinson's disease was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria (Gibb and Lees, 1988). PDD patients had Parkinson's disease for more than 12 months, before then developing dementia (McKeith *et al*., 1996). Subjects with other cerebral pathology (e.g. strokes or significant white matter changes) were excluded by cerebral CT or MRI. Diagnosis was determined independently by three experienced clinicians using a method with established accuracy as determined by autopsy confirmation (McKeith *et al*., 2000*b*). The control group consisted of elderly volunteers recruited from relatives and friends of patients. To be eligible for the study, patients were required to have an informant/caregiver. All subjects with a known history of macular degeneration or coexisting medical illness that could interfere with cognitive or visual testing were excluded. Of 122 subjects intending to take part, 12 subjects were excluded for the following reasons: three had poor sitting stability, five did not understand simple instructions for calibrations and four had a history of glaucoma or macular degeneration, leaving 110 patients to be studied. Characteristics of the sample are summarized in Table 1. The only anti-parkinsonian medications allowed were levodopa preparations, and patients were tested on medication. All patients with Parkinson's disease and PDD and 40% of the DLB patients were on levodopa. Patients stabilized on cholinesterase inhibitors were eligible provided no dose change had been made during the preceding 3 months. The percentage of demented patients on long-term cholinesterase inhibitor treatment did not differ between groups (PDD 60%, DLB 65%, Alzheimer's disease 73%; χ^2 test, $P > 0.05$, not significant). The local research ethics committee granted ethical approval and all patients and their caregivers gave written informed consent.

Testing procedure

Global cognitive impairment was assessed with the Cambridge Cognitive Examination (Roth *et al*., 1986). The Bristol Activities of Daily Living Scale (Bucks *et al*., 1996), the Neuropsychiatric Inventory (Cummings *et al*., 1994) and the One Day Fluctuation Assessment Scale (Walker *et al*., 2000) were used to assess functional impairment, neuropsychiatric symptoms and fluctuation. The severity of extrapyramidal motor features was assessed with the Unified Parkinson's Disease Rating Scale motor subsection (Fahn and Elton, 1987). Neuro-ophthalmological screening included inspection of the eyes, pupil reactions, light reflex (penlight), measurement of best near and far vision (Landolt broken rings, test distance 40 cm and 5 m), ocular movements (range, vergence, smooth pursuit, saccades) and estimation of the visual field by confrontation testing. The ocular fundus was assessed by direct ophthalmoscopy and colour vision was tested with the 14 plate Ishihara test (Ishihara, 1997).

Saccade measurement

Eye movements were measured with direct current electro-oculography in a dedicated testing room at the Institute for Ageing and Health in Newcastle upon Tyne, UK. Silver/silver–chloride electrodes were placed at the outer canthi of each eye. To minimize signal drift, electrodes were attached 30 min before the experiment, and during this time subjects became dark-adapted for at least 10 min.

Prior to each task, the signal was calibrated for horizontal angles of 0, 8, 12, 16 and 24° on the right and left (Hess *et al*., 1986). The signal was amplified and filtered (bandwidth 0–100 Hz) and the data sampled at a frequency of 1000 Hz with a data acquisition card. The digital signal was analysed off-line using a graphical interface and analysis program, written by one of the authors (J.F.) in Matlab

Table 1 *Demographical and clinical characteristics of the groups*

	Controls	Parkinson's disease	PDD	DLB	Alzheimer's disease	Between-group comparison
n	24	24	20	20	22	NS
Age (years)	75.3 ± 5.8	76.9 ± 5.4	75.3 ± 6.6	77.6 ± 6.9	78.1 ± 6.8	NS†
Education (years)	13.0 ± 3.0	13.0 ± 0.0	13.0 ± 0.0	13.0 ± 0.0	13.0 ± 0.0	NS*
Estimated dementia duration (years)	NA	NA	3.9 ± 2.1	3.2 ± 2.1	5.4 ± 1.7	$P = 0.002^{\dagger 1}$
MMSE (max. 30)	28.1 ± 1.3	27.3 ± 1.9	20.5 ± 4.0	18.0 ± 4.9	17.9 ± 4.7	$P < 0.0001^{\dagger 2}$
CAMCOG (max. 105)	96.5 ± 5.1	90.1 ± 7.4	69.0 ± 14.0	61.9 ± 15.9	62.8 ± 14.6	$P < 0.0001^{\dagger 2}$
Estimated duration of EPMS (years)	NA	5.0 ± 5.0	6.5 ± 5.5	2.5 ± 3.3	NA	$P = 0.04^{*1}$
UPDRS motor score (max. 108)	1.6 ± 1.9	30.0 ± 11.1	35.7 ± 12.2	29.2 ± 17.3	6.9 ± 6.5	$P < 0.0001^{\dagger 3}$
NPI (max. 144)	0.0 ± 0.0	4.0 ± 4.0	16.0 ± 20.3	14.5 ± 21.5	5.0 ± 14.0	$P < 0.0001^{*2}$
Fluctuation (max. 21)	0.0 ± 0.0	0.0 ± 3.0	6.0 ± 8.8	3.5 ± 4.0	0.0 ± 4.0	$P < 0.0001^{*3}$
Bristol-ADL (max. 60)	0.0 ± 0.0	3.3 ± 5.7	17.4 ± 10.1	21.7 ± 11.2	13.6 ± 10.1	$P < 0.0001^{\dagger 4}$

Two-group comparisons included the comparisons of controls versus Parkinson's disease, Parkinson's disease versus PDD, DLB versus PDD, DLB versus Alzheimer's disease and Alzheimer's disease versus controls. Significant differences are reported: *median and interquartile range and Kruskal–Wallis and Mann–Whitney *U* tests: ^{*1}PDD versus DLB, $P = 0.014$; ^{*2}Parkinson's disease versus controls, $P < 0.0001$; Parkinson's disease versus PDD, $P < 0.0001$; Alzheimer's disease versus controls, $P < 0.0001$; ^{*3}Parkinson's disease versus PDD, $P < 0.0001$. †Mean and SD ANOVA with *post hoc* Games–Howell test: $^{\dagger 1}$DLB versus Alzheimer's disease, $P = 0.002$; $^{\dagger 2}$Parkinson's disease versus PDD, $P < 0.0001$; Alzheimer's disease versus controls, $P < 0.0001$; $^{\dagger 3}$Parkinson's disease versus controls, $P < 0.0001$; DLB versus Alzheimer's disease, $P < 0.0001$; $^{\dagger 4}$Parkinson's disease versus PDD, $P < 0.0001$; DLB versus Alzheimer's disease, $P = 0.034$; Alzheimer's disease versus controls, $P < 0.0001$. CAMCOG = Cambridge Cognitive Examination Scale; EPMS = extrapyramidal motor symptoms; MMSE = Mini-Mental State Examination; UPDRS-III = Unified Parkinson disease rating scale, motor score; NPI = Neuropsychiatric Inventory; Fluctuation = One Day Fluctuation Assessment Scale; Bristol-ADL = Bristol Activities of Daily Living scale.

(MathWorks, Natick, MA, USA). The calibration was used to control for signal linearity and to calculate digital equivalent for a 1° angle. The start and end of each saccade was determined manually for each target presentation. The analysis was done by the same person (U.P.M.).

Subjects were positioned 80 cm in front of a screen with red/green light-emitting diodes, with their head positioned comfortably on a chin–forehead rest. A green stimulus was used for the central stimulus (CS) and the targets, and a red stimulus indicated a non-target. Tasks were presented in a random order. Thirty saccades were tested in blocks of 10 or 15 saccades per task. The task instruction was read by the experimenter and was followed by a training block containing 10 targets prior to each task. During the training, the patients received verbal feedback from the experimenter. Before starting data acquisition, patients were asked whether they understood the instructions. On the rare occasions when patients did not understand the instruction, the training was repeated. To avoid distraction and talking, no verbal feedback was given during the subsequent acquisition of data. Patients determined the resting period between the blocks, and the overall duration of the experiment was in the range of 30–45 min. All tasks are summarized in Fig. 1.

Gap task

The aim of the gap task was to test reflexive saccades. In this task, the CS was presented for 1700–2900 ms then disappeared 200 ms (gap) before target onset (Saslow, 1967). All targets were presented for 1500 ms at 16° to the right or left of the CS (direction randomized). The instruction to the subject was to look at all green stimuli as precisely and fast as possible. Two blocks of 15 targets were presented. Saccade latency in milliseconds and gain [i.e. saccade amplitude (degrees)/target amplitude (degrees)] of correct saccades were determined.

Overlap task

In the overlap task the CS remained continuously visible during target presentation, i.e. overlap of CS and target. The aim was to test reflexive saccades and fixation disengagement. The instruction, target presentation and the interval between CS and target presentations were similar to those in the gap task. Two blocks of 15 targets were tested. Outcome variables were latency (ms), gain of correct saccades and the gap effect. The gap effect is the difference between latencies in the overlap and gap tasks, i.e. the difference between internal and external fixation disengagement (Reuter-Lorenz *et al*., 1991).

Prediction task

In the prediction task, target direction (left, CS, right, CS, left etc.), amplitude (16°) and duration of CS and target presentation (1000 ms) were entirely predictable. The aim was to assess how often subjects were able to predict the subsequent target position. Since more than 80 ms is required to perceive a visual stimulus, a target was considered to be predicted when saccade latency was less than 80 ms (Pierrot-Deseilligny *et al*., 2003*a*). Two blocks with 15 targets were tested. The percentage of predicted saccades was the primary outcome variable. Saccade latency and accuracy were also determined.

Decision task

This task aimed to assess the subject's ability to make a spatial judgement and decision (Lévy-Schoen, 1969). Two green targets were presented simultaneously at different angles on either side of the CS (Fig. 1). The subjects were instructed to look at the target nearest to the CS. Whenever they saw a red light, the instruction was to go back to CS. The following pairs of targets were presented: 16° and 12°;16° and 8°;12° and 8°. The nearer target appeared on the left

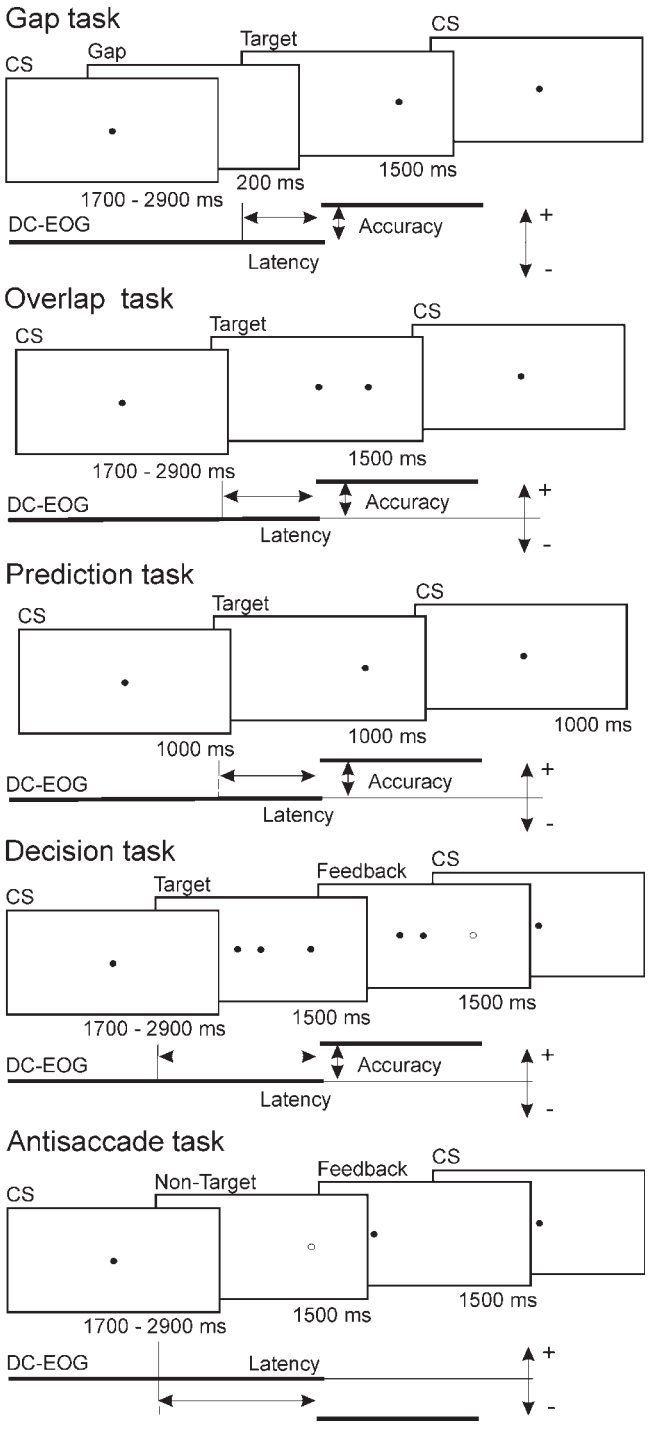

Fig. 1 Schematic representation of the sequence of stimulus appearance and direct current electro-oculography signal. A positive signal indicates a rightward saccade and a negative signal a leftward saccade. Horizontal saccades were tested using two reflexive saccade tasks (gap and overlap) and three complex tasks (prediction, decision and antisaccade tasks). A detailed task description is given in the Methods section.

or right at random. The CS was presented for 1700–2900 ms and then the two targets were presented for 1500 ms. Thereafter, the further changed to red, thus indicating an erroneous decision (visual feedback for 1500 ms). The mean percentage of direction errors (looking at the further target) was the primary outcome variable. Mean saccade latency and error correction rate were also calculated. A direction error was only considered to be corrected if it was corrected within the 1500 ms of target presentation, i.e. before the red feedback appeared. Three blocks containing 10 targets were tested.

Antisaccade task

The antisaccade task assessed subjects' ability to suppress looking at a non-target and to direct a saccade in the opposite direction (Hallett, 1978). The task was adapted for cognitively impaired patients: non-targets were presented in red (at 16° for 1500 ms) and visual feedback was given by a green stimulus on the side opposite to the non-target (at 16° for 1500 ms) after its disappearance (Fig. 1). Subjects were instructed to look opposite to the red stimulus and to follow all green stimuli. CS was presented for 1700–2900 ms and the direction of the non-targets was unpredictable. Three blocks of 10 trials were tested. Saccade latency and the percentage of errors (misdirected saccades towards the non-target) were calculated. Consistent with the decision task, a direction error was considered to be corrected if it was corrected within 1500 ms, i.e. before the feedback stimulus appeared.

To receive general feedback about the tolerability of eye movement testing, we asked participants at the end of the testing alternative choice (yes/no) questions to find out whether they experienced testing as (i) boring, (ii) tiring or (iii) painful, whether they would (iv) like to do it again or (v) recommend it to a friend.

Data analysis and statistics

Anticipated saccades were defined as saccades with latencies below 80 ms (Fischer *et al*., 1993) and delayed saccades as those triggered after target disappearance. They were both excluded. Direction errors were saccades directed opposite to a target or towards non-targets and ignored targets were targets which triggered no saccade at all. The distribution of data was tested for normality (Shapiro–Wilk test) within each group. If data were normally distributed, the mean, standard deviation or 95% confidence interval were calculated and parametric tests (independent sample *t*-test, ANOVA with *post hoc* Games–Howell test) were applied for within- and between-group comparisons. If data deviated significantly from normality, the median and interquartile range were presented and non-parametric tests (Kruskal–Wallis and Mann–Whitney) were used. The χ^2 test was used for the comparison of frequencies and Fisher's exact test when the expected frequency of a symptom in either group was <5. The sensitivity and specificity of delayed latency and/or hypometric amplitudes in gap and overlap tasks were calculated using both ± 1.5 and ± 2 standard deviations of mean latency and gain for group discrimination of Alzheimer's disease versus DLB or Parkinson's disease and versus PDD. Positive predictive values were calculated as the proportions of patients with delayed latencies and/or hypometric saccades who were correctly allocated to the PDD and DLB groups; the negative predictive values were the proportions of patients with normal latency and accuracy who were correctly allocated to the Parkinson's disease and Alzheimer's disease groups. The likelihood ratio was the probability that delayed latencies and/or hypometric saccades were found in PDD or DLB rather than Alzheimer's disease or Parkinson's disease. All reported *P*-values were two-tailed and a *P*-value of less than 0.05 was considered statistically significant.

Results

Demographics

Demographic data, summarized in Table 1, show that the groups were well matched for age and education. Global cognitive impairment (Cambridge Cognitive Examination and Mini-Mental State Examination scores) was similar between the demented groups and between Parkinson's disease and controls. Dementia duration was longer in Alzheimer's disease than in DLB, and PDD patients had a longer duration of parkinsonism than DLB patients. The duration of parkinsonism was not different between Parkinson's disease and PDD patients and the Unified Parkinson's Disease Rating Scale motor score was similar in Parkinson's disease, PDD and DLB. The Neuropsychiatric Inventory and fluctuation scores were higher in PDD than in Alzheimer's disease group and the DLB group was more impaired in activities of daily living (Bristol–ADL) than the Alzheimer's disease group. Neuro-ophthalmological assessment did not reveal impairments that could interfere with eye movement testing and best visual acuity did not differ between the groups (controls near, 0.58, far, 0.66; Parkinson's disease near, 0.61, far, 0.68; DLB near, 0.60, far, 0.59; PDD near, 0.57, far, 0.64; Alzheimer's disease near, 0.54, far, 0.49) (ANOVA for near and far, $P > 0.05$, not significant).

Eye movements

Reflexive gap and overlap tasks

Saccade latency and gain for correct saccades are summarized in Fig. 2. The gap and overlap tasks revealed significant group differences in latency (ANOVA for both, $P < 0.0001$) and first saccade gain (ANOVA for both, $P < 0.0001$); the final eye position, however, was similar in all groups (ANOVA for both, $P > 0.05$, not significant). Saccade latency and gain did not differ between the PDD and DLB groups (*post hoc* Games–Howell test for all comparisons, $P > 0.05$, not significant). Compared with controls, subjects with PDD were impaired in gap and overlap saccade execution (gap and overlap latencies, $P < 0.0001$ and gains, $P < 0.004$) and the same was found in DLB (gap and overlap latencies, $P < 0.0001$ and gains, $P < 0.001$). The only difference found when Parkinson's disease was compared with controls was a lower gain of the first saccade in the gap task (*post hoc* Games–Howell test, $P = 0.033$). The comparison of Alzheimer's disease and controls did not reveal any significant differences. Patients with PDD had significantly longer latencies than patients with Parkinson's disease in reflexive saccades (*post hoc* Games–Howell test for gap, $P = 0.002$; for overlap, $P = 0.003$) and latencies of DLB patients were longer than those of Alzheimer's disease patients (*post hoc* Games–Howell test for gap, $P = 0.016$; for overlap, $P = 0.001$). The gain of the first saccade was lower in DLB compared with Alzheimer's disease (*post hoc* Games–Howell test, $P = 0.007$). Gap effect (mean ± SD) was not different between the five groups (controls: 94 ± 41 ms; Parkinson's disease: 106 ± 52; PDD: 167 ± 107; DLB: 140 ± 167 ms; Alzheimer's disease: 110 ± 90 ms) (ANOVA, $P = 0.04$, *post hoc* Games–Howell test: not significant).

Table 2 summarizes group discrimination of gap and overlap saccades. Overall, optimal sensitivity was achieved using ± 1.5 SD for the group discriminations. Delayed latency and/or hypometric amplitude was 4.8–5.4 times more likely to occur in PDD than in Parkinson's disease and 2.8–4.3 times more likely in DLB than in Alzheimer's disease.

Complex saccades

Prediction task. Target prediction was rare in both PDD and DLB groups (Table 3). Patients with PDD predicted fewer targets than Parkinson's disease, and DLB fewer than patients with Alzheimer's disease. In Parkinson's disease saccade latency of non-predicted saccades was similar to controls. Latency was longer in PDD than in patients with Parkinson's disease and also in DLB patients compared with Alzheimer's disease. Mean gain of the first saccade was similar in DLB (0.78 ± 0.15) and PDD (0.84 ± 0.16) (*post hoc* Games–Howell test, $P > 0.05$, not significant) but hypometric compared with Alzheimer's disease (0.95 ± 0.10) (*post hoc* Games–Howell test: DLB versus AD, $P = 0.001$). No significant difference was found between the gain of patients with Parkinson's disease (0.93 ± 0.12) and controls (0.99 ± 0.09) (*post hoc* Games–Howell test for both, $P > 0.05$, not significant). The final eye position was not different (gain of controls, 1.0 ± 0.05; Parkinson's disease, 1.0 ± 0.08; PDD, 1.02 ± 0.06; DLB, 1.0 ± 0.06; Alzheimer's disease, 1.0 ± 0.07) (ANOVA, $P > 0.05$, not significant).

Decision task. Patients with Alzheimer's disease made significantly more errors than controls, and PDD patients made fewer errors than DLB patients (Table 3). Saccade latency for correct decisions was longer in PDD and DLB compared with controls, but was not different within the demented groups. Median error correction rate of patients with Alzheimer's disease (74 ± 47%) was lower than in controls (100 ± 13%) (Mann–Whitney test, $P = 0.001$) but tended to be higher than in DLB patients (27 ± 72%) (Mann–Whitney test, $P > 0.05$, not significant). A similar trend was observed when the percentages of corrected errors of Parkinson's disease (89 ± 38%) and PDD (40 ± 78%) were compared (Mann–Whitney test, $P > 0.05$, not significant).

Antisaccade task. No difference was found when errors were compared within the demented groups (Table 3). PDD patients made more errors in the antisaccade task than patients with Parkinson's disease and patients with Alzheimer's disease made more errors than controls. DLB patients corrected fewer errors (71 ± 32%) than patients with Alzheimer's disease (95 ± 12%) (Mann–Whitney test, $P = 0.005$) and PDD patients (59 ± 47%) fewer than patients with Parkinson's disease (100 ± 0%) (Mann–Whitney test, $P < 0.0001$). Error correction rates of controls (100 ± 22%) and Alzheimer's disease patients (95 ± 12%) were similar. Saccade latency of correct antisaccades was longer in PDD

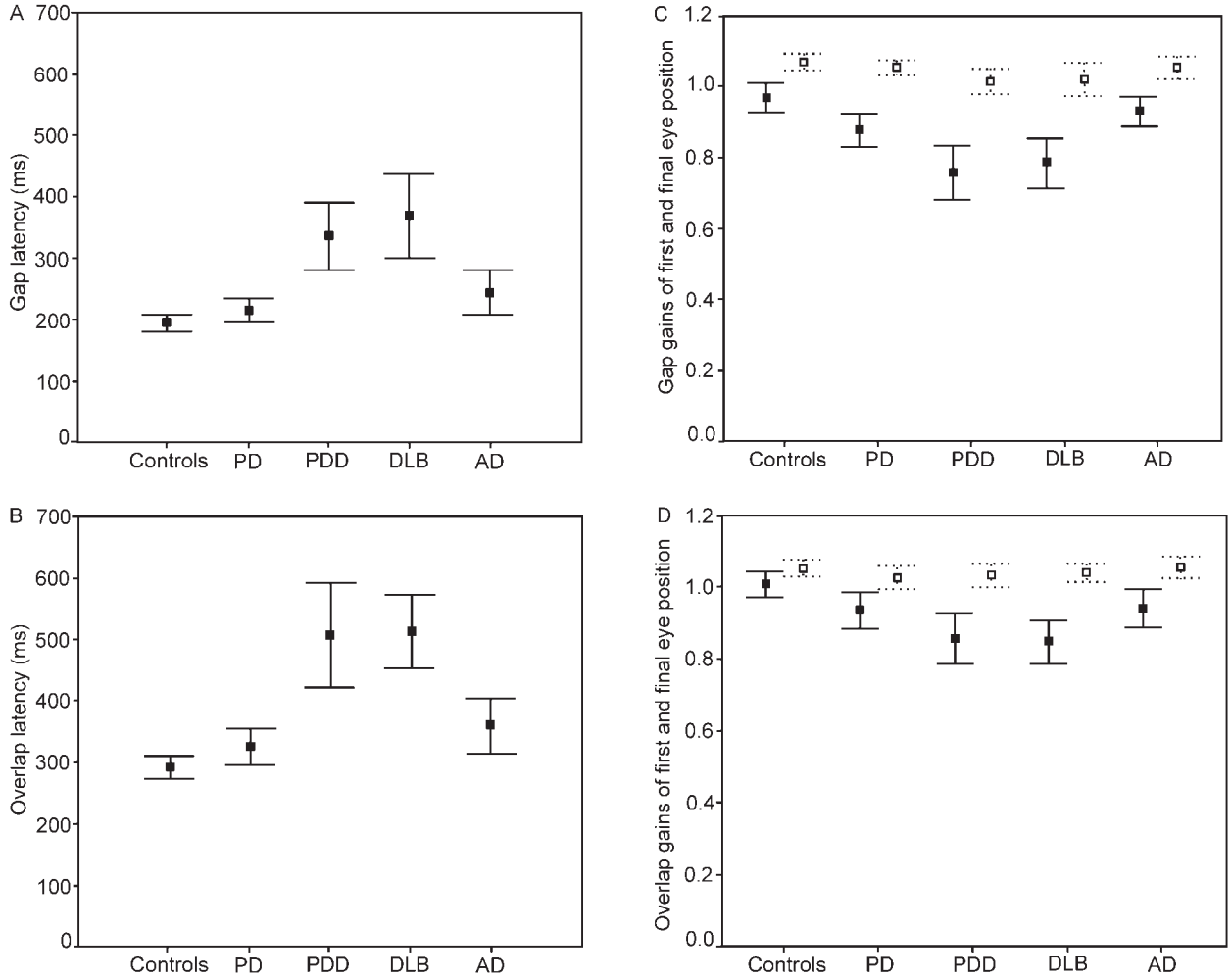

Fig. 2 Latency and accuracy in reflexive gap and overlap tasks. Error bars show mean and 95% confidence interval. (**A** and **B**) Gap and overlap saccade latency (ms). In both tasks latency was longest in patients with DLB and PDD. No significant difference was found when controls were compared with patients with Alzheimer's disease or Parkinson's disease. (**B** and **C**) Accuracy of the first saccades (bold symbols) and final eye position (open symbols), expressed as gain (saccade amplitude/target amplitude). First saccade gain was hypometric in DLB and PDD; however, the final eye positions of the five groups were similar.

Table 2 *Group discrimination using ±1.5 (A) and ±2 (B) standard deviations of saccade latencies and gains for group discrimination*

Discrimination of	Sensitivity		Specificity		PPV		NPV		LR	
	A	B	A	B	A	B	A	B	A	B
Gap task										
PDD and Parkinson's disease	0.65	0.65	0.88	1.0	0.81	1.0	0.75	0.77	5.4	*
DLB and Alzheimer's disease	0.60	0.40	0.86	1.0	0.80	1.0	0.70	0.65	4.3	*
Overlap task										
PDD and Parkinson's disease	0.60	0.55	0.88	0.92	0.80	0.85	0.72	0.71	4.8	6.6
DLB and Alzheimer's disease	0.65	0.40	0.77	1.0	0.72	1.0	0.71	0.65	2.8	*

*Could not be computed since specificity was 1.0 [LR = sensitivity/(1 – specificity)]. PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio.

compared with Parkinson's disease, and was longer in patients with Alzheimer's disease compared with controls, but not different between DLB and Alzheimer's disease.

Delayed saccades (1%) and anticipated saccades (4%) were excluded from analysis and were not predominant in one group. Ignored targets were observed in PDD (18%) and DLB patients (17%) but rarely in Alzheimer's disease patients (2%) (Mann–Whitney test DLB versus Alzheimer's disease $P = 0.002$). Patients with Parkinson's disease and controls did not ignore any targets. Most ignored targets

Table 3 *Predicted saccades, direction errors and correct saccade latency in complex saccade tasks*

	Controls	Parkinson's disease	PDD	DLB	Alzheimer's disease	Between-group comparison
Prediction task						
Predicted (%)	53 ± 35	43 ± 39	7 ± 18	8 ± 21	23 ± 32	$P < 0.0001^{*1}$
Latency (ms)	235 ± 62	259 ± 59	346 ± 65	401 ± 109	304 ± 81	$P = 0.0001^{\dagger 1}$
Decision task						
Errors (%)	13 ± 17	17 ± 19	27 ± 15	40 ± 24	40 ± 34	$P < 0.0001^{*2}$
Latency (ms)	437 ± 90	505 ± 133	583 ± 142	554 ± 125	500 ± 130	$P = 0.002^{\dagger 2}$
Antisaccade task						
Errors (%)	25 ± 38	21 ± 35	64 ± 35	63 ± 26	80 ± 42	$P < 0.0001^{*3}$
Latency (ms)	431 ± 195	520 ± 147	660 ± 207	740 ± 184	596 ± 202	$P < 0.0001^{\dagger 3}$

†Mean and SD and ANOVA with *post hoc* Games–Howell test; *median and interquartile range and Kruskal–Wallis and Mann–Whitney *U* tests. Two-group comparison included the comparisons of controls versus Parkinson's disease, Parkinson's disease versus PDD, DLB versus PDD, DLB versus Alzheimer's disease and Alzheimer's disease versus controls. Significant differences are reported: *[1]Parkinson's disease versus PDD, $P < 0.0001$; DLB versus Alzheimer's disease, $P = 0.034$; Alzheimer's disease versus controls, $P = 0.001$; *[2]Alzheimer's disease versus controls, $P < 0.0001$; *[3]Parkinson's disease versus PDD, $P < 0.0001$; Alzheimer's disease versus controls, $P < 0.0001$; †[1]Parkinson's disease versus PDD, $P < 0.0001$; DLB versus Alzheimer's disease, $P = 0.022$; Alzheimer's disease versus controls, $P = 0.019$; †[2]PDD and DLB were different from controls ($P < 0.01$), otherwise no differences; †[3]DLB versus controls, $P < 0.0001$; PDD versus controls, $P = 0.008$.

Table 4 *Synopsis of changes in saccade performance*

	Parkinson's disease versus controls	Alzheimer's disease versus controls	Parkinson's disease versus PDD	DLB versus Alzheimer's disease	DLB versus PDD
Saccade execution	↔[1]	↔	↓↓↓	↓↓↓	↔
Target prediction	↔	↓↓↓	↓↓↓	↓	↔
Saccade suppression	↔	↓↓↓	↓↓↓	↔	↔
Spatial decision	↔	↓↓↓	↔	↔	↔

Non-demented controls: Parkinson's disease and controls; demented groups: PDD, DLB, Alzheimer's disease. The comparison PDD versus Alzheimer's disease is not included, since clinically less relevant. ↔ = No significant difference; ↓ = impairment ($P < 0.05$); ↓↓ = impairment ($P < 0.01$); ↓↓↓ = impairment ($P < 0.001$); [1]Except gap saccade accuracy.

were found in the overlap (PDD 22%; DLB 32%) and decisions tasks (PDD 15%; DLB 11%).

Patients on or off treatment with cholinesterase inhibitors or levodopa did not perform differently in saccade latency, gain, direction errors or ignored targets (independent sample *t*-test and Mann–Whitney test, respectively; all $P > 0.05$, not significant). None of the patients found saccadic eye movement testing painful, 92% would agree for another assessment or recommend it to a family member or friend, 5% (mainly controls) considered testing to be boring and 5% (mainly PDD patients) expressed that the assessment was tiring.

Discussion

We assessed reflexive (gap and overlap tasks) and complex saccades (prediction, decision and antisaccades) in four different neurodegenerative disorders and found similar saccadic eye movement changes in DLB and PDD, quite different from those seen in Alzheimer's and Parkinson's disease. PDD and DLB patients showed impaired saccade execution compared with Parkinson's disease and controls. Complex saccade performance, i.e. target prediction, spatial decision-making and saccade suppression, was impaired in all demented patients groups (Alzheimer's disease, DLB and PDD) compared with Parkinson's disease and controls. PDD patients corrected fewer direction errors in complex tasks than patients with Parkinson's disease and DLB less than patients with Alzheimer's disease. A synopsis of the changes in saccade performance can be found in Table 4.

Knowledge about the networks controlling saccadic eye movements may be helpful to determine the pattern of brain pathology involved. Models of cortical and subcortical saccade control (Hikosaka *et al*., 2000; Pierrot-Deseilligny *et al*., 2003*b*; Leigh and Kennard, 2004) suggest that reflexive saccades are triggered by the parietal eye field and complex saccades by the frontal eye field, both having excitatory connections with the superior colliculus and striatum, and receiving feedback from the basal ganglia via thalamocortical tracts. Hikosaka and colleagues (Hikosaka *et al*., 2000) suggested the presence of tonic inhibition of the superior colliculus by the basal ganglia output nuclei, globus pallidus pars interna and substantia nigra pars reticulata which may be removed by phasic inhibitory signals from the striatum. Removal of inhibition of superior colliculus is a precondition for the triggering of a saccade.

Such widespread and complex networks involving extended cortical and subcortical structures and their connections are vulnerable to multiple disruptions and it would be difficult

to postulate a single locus as the reason for saccadic eye movement changes in PDD and DLB. Similar gap effects (a measure to compare external and internal fixation disengagement) did not suggest an isolated fixation disengagement deficit in PDD and DLB. The combination of impaired saccade execution and impairments in volitional saccade control suggests disrupted processing within subcortical structures, e.g. impaired removal of tonic inhibition of the superior colliculus, or between cortex and subcortex, e.g. disruption of excitatory connections from the frontal eye field to the superior colliculus or inhibitory connections of the dorsolateral prefrontal cortex to the superior colliculus. The α-synuclein positive pathology in the striatum (Duda *et al*., 2002) and the reduced putamen volumes (Cousins *et al*., 2003) in PDD and DLB may reflect anatomical changes for such disruptions. Combined dopaminergic (Piggott *et al*., 1999; Walker *et al*., 1999; O'Brien *et al*., 2004) and cholinergic (Perry *et al*., 1994; Tiraboschi *et al*., 2002) deficits in PDD and DLB, which exceed those of Alzheimer's and Parkinson's diseases, are likely to additionally contribute to impaired saccade execution, since the lack of these transmitters can both be associated with impaired saccade triggering and inaccurate amplitudes in healthy controls (Oliva *et al*., 1993; Kato *et al*., 1995).

Our results suggest that nigrostriatal dopaminergic loss in Parkinson's disease without dementia is associated with minimal hypometria in reflexive gap tasks, when compared with age-matched controls. This is consistent with previous studies, where changes in reflexive saccades were minimal in Parkinson's disease (Crawford *et al*., 1989*b*; Vidailhet *et al*., 1994; Roll *et al*., 1996; Rottach *et al*., 1996; Briand *et al*., 1999). The lack of impaired complex saccades (normal saccade suppression, prediction and decisions) is consistent with some (Crawford *et al*., 1989*a*; Lueck *et al*., 1990; Fukushima *et al*., 1994; Vidailhet *et al*., 1999) but not all (Bronstein and Kennard, 1985; Kitagawa *et al*., 1994; Crevits and De Ridder, 1997; Briand *et al*., 1999) previous reports. These inconsistencies between studies may be explained by the inclusion of some patients with Parkinson's disease and cognitive impairment or by the assessment of PD patients in the off condition (Vidailhet *et al*., 1994).

Complex saccade performance was impaired whenever dementia was present. Since the prefrontal cortex is involved in the triggering of predictive saccades (Pierrot-Deseilligny *et al*., 2003*a*) and the suppression of erroneous antisaccades (Guitton *et al*., 1985; Pierrot-Deseilligny *et al*., 2003*a*) and the posterior parietal cortex may be needed for spatial decisions (Tootell *et al*., 1998), impaired performance in complex tasks may reflect the profound cortical neurodegenerative changes commonly found in these areas in Alzheimer's disease (Mirra *et al*., 1991) and PDD and DLB (McKeith *et al*., 1996). In Alzheimer's disease, reflexive saccade control was normal, but complex saccade performance was impaired relative to controls; more errors in the antisaccade task have been found in previous studies (Fletcher and Sharpe, 1986; Currie *et al*., 1991; Abel *et al*., 2002; Shafiq-Antonacci *et al*., 2003). Small sample sizes and diagnostic heterogeneity probably explain contradictory reports as to whether reflexive saccade execution is impaired in Alzheimer's disease (Pirozzolo and Hansch, 1981; Fletcher and Sharpe, 1986; Moser *et al*., 1998; Abel *et al*., 2002; Shafiq-Antonacci *et al*., 2003; Mosimann *et al*., 2004*a*).

Taken together, our results suggest that impairments in reflexive saccade execution were minimal when either cortical (e.g. Alzheimer's disease) or nigrostriatal neurodegeneration (e.g. Parkinson's disease) was present solely, but became prominent in PDD and DLB when cortical and subcortical neurodegeneration coexisted (Emre, 2003; McKeith *et al*., 2004). Cortical neurodegeneration was associated with impaired complex saccade performance, such as saccade suppression, target prediction and spatial decisions, supporting the assumption that the contribution of the cortex in the generation of complex saccades is higher (Pierrot-Deseilligny *et al*., 2003*b*). The results also underpin the importance of using different tasks and testing numerous saccades (here 150 per subject) in a standardized environment to quantify saccade performance in dementia. During confrontation testing we were not able to detect impaired saccade execution in PDD and DLB patients. Such clinical testing, however, involves the assessment of very few saccades (e.g. four to six) and does not allow reliable quantification of subtle impairments in saccade execution. This may explain why eye movement disturbances in PDD and DLB have not been reported previously. Reflexive saccades assessed by electro-oculography may be useful to assist clinical differential diagnosis; this would allow separation of Parkinson's disease versus PDD or Alzheimer's disease versus DLB in about 80% of PDD and DLB patients respectively.

Saccade testing may provide a well-tolerated clinical method contributing to the differential diagnosis of these common neurodegenerative disorders. Instructions for reflexive tasks are simple. Correct final eye position in reflexive saccade tasks, high error correction rate in antisaccades and less than 50% errors in decision tasks suggest that subjects understood the task instructions, and high compliance and positive feedback from patients indicate that eye movement testing was well tolerated. Optimal group separation in this study was better than that reported for absence of medial temporal lobe atrophy on MRI for the distinction Alzheimer's disease versus DLB (Barber *et al*., 1999), but poorer than the sensitivity and specificity found when dopaminergic functional imaging was used for making the same distinction (O'Brien *et al*., 2004). Our findings highlight differences in saccadic eye movement control between different neurodegenerative disorders.

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