

Visual exploration in Parkinson's disease and Parkinson's disease dementia

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Parkinson's disease, typically thought of as a movement disorder, is increasingly recognized as causing cognitive impairment and dementia. Eye movement abnormalities are also described, including impairment of rapid eye movements (saccades) and the fixations interspersed between them. Such movements are under the influence of cortical and subcortical networks commonly targeted by the neurodegeneration seen in Parkinson's disease and, as such, may provide a marker for cognitive decline. This study examined the error rates and visual exploration strategies of subjects with Parkinson's disease, with and without cognitive impairment, whilst performing a battery of visuo-cognitive tasks. Error rates were significantly higher in those Parkinson's disease groups with either mild cognitive impairment ($P = 0.001$) or dementia ($P < 0.001$), than in cognitively normal subjects with Parkinson's disease. When compared with cognitively normal subjects with Parkinson's disease, exploration strategy, as measured by a number of eye tracking variables, was least efficient in the dementia group but was also affected in those subjects with Parkinson's disease with mild cognitive impairment. When compared with control subjects and cognitively normal subjects with Parkinson's disease, saccade amplitudes were significantly reduced in the groups with mild cognitive impairment or dementia. Fixation duration was longer in all Parkinson's disease groups compared with healthy control subjects but was longest for cognitively impaired Parkinson's disease groups. The strongest predictor of average fixation duration was disease severity. Analysing only data from the most complex task, with the highest error rates, both cognitive impairment and disease severity contributed to a predictive model for fixation duration [$F(2,76) = 12.52$, $P \leq 0.001$], but medication dose did not ($r = 0.18$, $n = 78$, $P = 0.098$, not significant). This study highlights the potential use of exploration strategy measures as a marker of cognitive decline in Parkinson's disease and reveals the efficiency by which fixations and saccades are deployed in the build-up to a cognitive response, rather than merely focusing on the outcome itself. The prolongation of fixation duration, present to a small but significant degree even in cognitively normal subjects with Parkinson's disease, suggests a disease-specific impact on the networks directing visual exploration, although the study also highlights the multi-factorial nature of changes in exploration and the significant impact of cognitive decline on efficiency of visual search.

Keywords: Parkinson's disease; Parkinson's disease dementia; visual exploration; saccade; fixation

Abbreviations: AEMSS = age- and education-adjusted Mayo's Older Americans Normative Studies subscale score; DRS-2 = Mattis dementia rating scale; LED = levodopa equivalent dose; MCI = mild cognitive impairment; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

To make sense of the visual environment, humans must direct the fovea rapidly and accurately to appropriate parts of a given scene. The rapid eye movements used to achieve this are known as saccades and are interspersed with foveal fixations in a goal-directed fashion (Henderson and Hollingworth, 1999). Spatially accurate saccade generation is under the influence of frontal (Pierrot-Deseilligny *et al.*, 1995; Muri *et al.*, 1996), supplementary and parietal eye fields (Pierrot-Deseilligny *et al.*, 1991; Muri *et al.*, 1996), as well as regions of the prefrontal and posterior parietal cortex (Pierrot-Deseilligny *et al.*, 1995, 2005). These cortical areas project, via the superior colliculus, thalamus and basal ganglia, to lower brainstem structures concerned with saccadic eye movements (Hikosaka *et al.*, 2000).

'Runs' of fixations and saccades are used to deliver visual information, via the dorsal and ventral processing streams, to the higher visual centres involved in visuo-perceptual and visuospatial processing (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992). Neurodegeneration in Parkinson's disease targets these regions (Beyer *et al.*, 2007; Pereira *et al.*, 2009), as well as fronto-parietal attentional and executive networks, leading to impairments in visuospatial, visuo-perceptual and executive function, as well as attention and memory (Cormack *et al.*, 2004; Mosimann *et al.*, 2004b; Muslimovic *et al.*, 2005; Williams-Gray *et al.*, 2007). The co-localization of visual, cognitive and oculomotor functions provides an opportunity to use saccadic characteristics to examine the cortical impact of Parkinson's disease and Parkinson's disease dementia (Perneckzy *et al.*, 2011).

Patients with Parkinson's disease display a number of eye movement abnormalities; deficient smooth pursuit, restricted vergence and reduced range of eye movements have all been described (Corin *et al.*, 1972; White *et al.*, 1983; Rascol *et al.*, 1989; Repka *et al.*, 1996; Bares *et al.*, 2003). Evidence for disease-specific disruption of saccadic programming and execution in Parkinson's disease is contradictory. Whereas some studies have demonstrated increases in saccadic latency, reductions in amplitude and increased error rates (Kennard and Lueck, 1989; Rascol *et al.*, 1989; Briand *et al.*, 1999; MacAskill *et al.*, 2002; Hood *et al.*, 2007; van Stockum *et al.*, 2008), others have not replicated these findings (Lueck *et al.*, 1990; Vidailhet *et al.*, 1994; Briand *et al.*, 1999, 2001; Vidailhet *et al.*, 1999; Mosimann *et al.*, 2005).

The properties of the stimulus used, medication effects and the cognitive heterogeneity of study cohorts are important determinants of saccadic metrics and may help explain some of the inconsistencies in the reported literature (Hodgson *et al.*, 1999; Mosimann *et al.*, 2005; Michell *et al.*, 2006; Hood *et al.*, 2007; Chambers and Prescott, 2010). For example, patients with neurodegenerative disorders characterized by cognitive impairment (Alzheimer's disease, Parkinson's disease dementia and dementia

with Lewy bodies) show longer fixation durations, increased saccadic latency and more saccadic errors than control subjects (Lueck *et al.*, 2000; Ogrocki *et al.*, 2000; Mosimann *et al.*, 2005), suggesting cortical neurodegeneration can impair oculomotor function.

In addition to examining the absolute metrics of saccades and fixations, the overall strategy used when interacting with complex visual information can also be studied. For example, patients with Alzheimer's disease demonstrate impairments in text and clock reading, with less focused visual exploration strategies correlating with task error rates and dementia severity (Lueck *et al.*, 2000; Mosimann *et al.*, 2004a). Facial emotion recognition is also impaired in Alzheimer's disease, with fewer fixations on salient facial regions and greater time spent in 'off face' areas (Ogrocki *et al.*, 2000). Parkinson's disease also appears to alter gaze strategy. Using a modified Tower of London task, Hodgson *et al.* (2002) demonstrated less efficient distribution of fixations and saccades and increased error rates in subjects with Parkinson's disease compared with control subjects. In addition to increased fixation duration whilst visually scanning commonly used visuo-cognitive tasks (cube, overlapping figures, Rey-Osterrieth complex figure), cognitively normal subjects with Parkinson's disease made fewer saccades, and of smaller amplitude, than control subjects. The area of visual scanning was also smaller, with all these measures influenced by the degree of image complexity (Matsumoto *et al.*, 2011). To date, there is no information available on the impact of differing degrees of cognitive impairment on visual exploration behaviour in Parkinson's disease.

The aim of this study was to examine the impact of Parkinson's disease and Parkinson's disease dementia on basic oculomotor metrics and eye tracking strategies. We hypothesized that, with impaired cognition, exploration strategies would become less efficient. We also hypothesized that basic oculomotor metrics, such as fixation duration and saccade amplitude, would differ between control subjects and subjects with Parkinson's disease, but that the differences would be greatest in those with cognitive impairment.

Materials and methods

Subjects

The study was approved by the National Health Service (NHS) Local Research Ethics Committee, and all participants gave written informed consent. Participants with Parkinson's disease and Parkinson's disease dementia aged >49 years were consecutively recruited from the Newcastle upon Tyne NHS Foundation Trust Movement Disorder service. To supplement the number of patients with Parkinson's disease dementia in the study, additional subjects were approached from Parkinson's disease nurse-specialist clinics. The healthy control cohort comprised spouses/partners of study participants and was

supplemented from a research database held at the Institute for Ageing and Health, Newcastle University, UK. Total recruitment figures were as follows: Parkinson's disease $n = 64$; Parkinson's disease dementia $n = 26$; control $n = 32$. All participants fulfilled UK Brain Bank Criteria for a diagnosis of Parkinson's disease (Hughes *et al.*, 1992). All Parkinson's disease dementia participants met Movement Disorder Society consensus criteria for dementia associated with Parkinson's disease (Emre *et al.*, 2007).

Diagnostic procedures

Disease severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part II and part III, part III reflecting the degree of motor impairment (Fahn and Elton, 1987). Medications were expressed as levodopa equivalent doses (LED) (Tomlinson *et al.*, 2010). Cognition was assessed using the Folstein Mini-Mental State Examination (Folstein *et al.*, 1975) and the Mattis Dementia Rating Scale (DRS-2) (Brown *et al.*, 1999). The DRS-2 consists of five subscales, providing information on attention, initiation/perseveration, construction, conceptualization and memory. The scores of the five subscales contribute to a total DRS-2 score, and normative data allow adjustment for age and education [age- and education-adjusted Mayo's Older Americans Normative Studies subscale score (AEMSS)]. The construction subscale score of the DRS-2 may be insensitive to subtle changes of visuoconstructional impairment in Parkinson's disease; therefore, clock drawing, scored using the Shulman method (Shulman, 2000), was included as part of the cognitive assessment.

To address the potential impact of cognitive heterogeneity on the eye-tracking measures, we defined two non-demented Parkinson's disease sub-groups: cognitively normal and those with mild cognitive impairment (MCI). In the absence of published criteria for MCI in Parkinson's disease at the start of this study (Litvan *et al.*, 2012), we used both a global cognitive score (AEMSS) and domain subscale scores (attention, initiation/perseveration, construction, conceptualization, memory, Clock Drawing Test) to define MCI. An AEMSS score ≥ -1.5 standard deviations (SD) below the control group mean, or ≥ 2 domain subscale scores ≥ -1.5 SD below control group mean values, was taken as evidence of MCI. This approach split the Parkinson's disease group into 37 subjects with normal cognition (Parkinson's disease-cognitively normal subjects) (58%) and 27 with mild cognitive impairment (Parkinson's disease-MCI subjects) (42%).

Assessment of visual exploration

Participants explored a range of visual stimuli, including an angle matching task, a clock task (regular and inverted clocks), a shape position task and an overlapping figures task, as part of an eye tracking battery (Fig. 1).

Overlapping figures, first described by Poppelreuter (1917) and Ghent (1956) and formalized by De Renzi *et al.* (1969), have been used in previous studies of Parkinson's disease dementia and dementia with Lewy bodies (De Renzi *et al.*, 1969; Mori *et al.*, 2000; Mosimann *et al.*, 2004b) to provide information on impairment of object-form perception. In our experiment, participants were required to study a central composite image and choose which one of four individual comparators presented underneath appeared centrally.

Clock reading is an over-learned perceptual task that is impaired both in Alzheimer's disease, dementia with Lewy bodies and patients with parietal lobe lesions (Schmidtke and Olbrich, 2007). Visual exploration of clock faces is impaired in Alzheimer's disease, with patients making fewer fixations at the ends of the clock hands and taking longer to explore the clock face (Mosimann *et al.*, 2004a). Although

clock drawing is frequently impaired in Parkinson's disease dementia (Cahn-Weiner *et al.*, 2003), clock reading has not been studied in Parkinson's disease and Parkinson's disease dementia. For this reason, we included a clock task, requiring participants to perform both clock reading and clock matching. An inverted clock task was also included in the test battery, introducing a greater spatial component to the clock task, by requiring participants to mentally rotate the comparators by 180° before giving their response (Amick *et al.*, 2006).

Impairment in the judgement of line orientation is impaired in Parkinson's disease and Parkinson's disease dementia (Montse *et al.*, 2001; Mosimann *et al.*, 2004b). Owing to the screen layout constraints, we modified Benton's original task, requiring participants to match a centrally presented angle to one of four comparator angles beneath. Finally, we included a shape position in the battery. This task incorporated elements of the position discrimination task of Warrington and James (1988) and the spatial location task of MacQuarrie (1953), previously found to be impaired in Parkinson's disease dementia and dementia with Lewy bodies (Mori *et al.*, 2000; Mosimann *et al.*, 2004b).

Stimuli were presented on a 20-inch TFT computer monitor, and eye movements were recorded with an EyeLink 1000 remote eye tracker (EyeLink®, SR Research Ltd). Participants were positioned 80 cm from the stimulus monitor, wore normal refractive correction and were able to resolve the stimuli presented during a practice block, in the training phase of the experiment. Viewing was binocular, but recordings were made from one or other eye. A chin rest and forehead bar maintained the participant's head position and distance from the computer monitor. Measurements of eye movements were conducted in a dimly lit room, and online viewing of data collection was undertaken behind a blackout curtain.

The eye tracker was calibrated for each participant before each experiment. Calibration consisted of having the participant fixate on nine calibration points (three points each across the top, middle and bottom of the screen), one at a time. Stimuli were presented in blocks: angle-clock-inverted clock; shape position; overlapping figure, in a pseudorandom fashion. Each block began with a previously viewed practice image, followed by 16 trial images, presented in one of six randomized orders. A total of 80 images were viewed by each participant, and the battery took 10–15 min to complete. Participants were encouraged to take a break if required. Screen layout was identical for each stimulus, with a central stimulus and four comparators arrayed beneath. All comparators appeared equally for each category, to ensure no bias emerged for any particular choice option. Participants gave a verbal response ('1', '2', '3' or '4'), at which point the investigator (N.A.) activated a key press, and the stimulus moved on to a central fixation point, before the next stimulus presentation.

The EyeLink 1000 system incorporates a unique on-line parsing system that analyses eye position data into meaningful events and states (saccades, fixations and blinks). The average duration of fixations (ms) and saccade amplitudes (degrees) were analysed. Interest areas, such as the central stimulus, four comparator stimuli and correct/incorrect interest areas were defined for each visual stimulus (Fig. 2). Analysis of the distribution of fixations in correct and incorrect interest areas, the first interest areas explored and the number of times a given interest area is revisited during exploration (run count) reveals the strategy used by participants to solve the visual task presented to them. We chose three measures to define the efficiency of the visual exploration strategy: time to first fixation in the correct interest area, run count into the central stimulus and run count ratio.

The run count ratio is generated from the mean run count into the three incorrect interest areas, divided by the run count into the correct interest area. Low run count ratios reflect a strategy where the correct interest areas are explored in preference to incorrect regions. High run

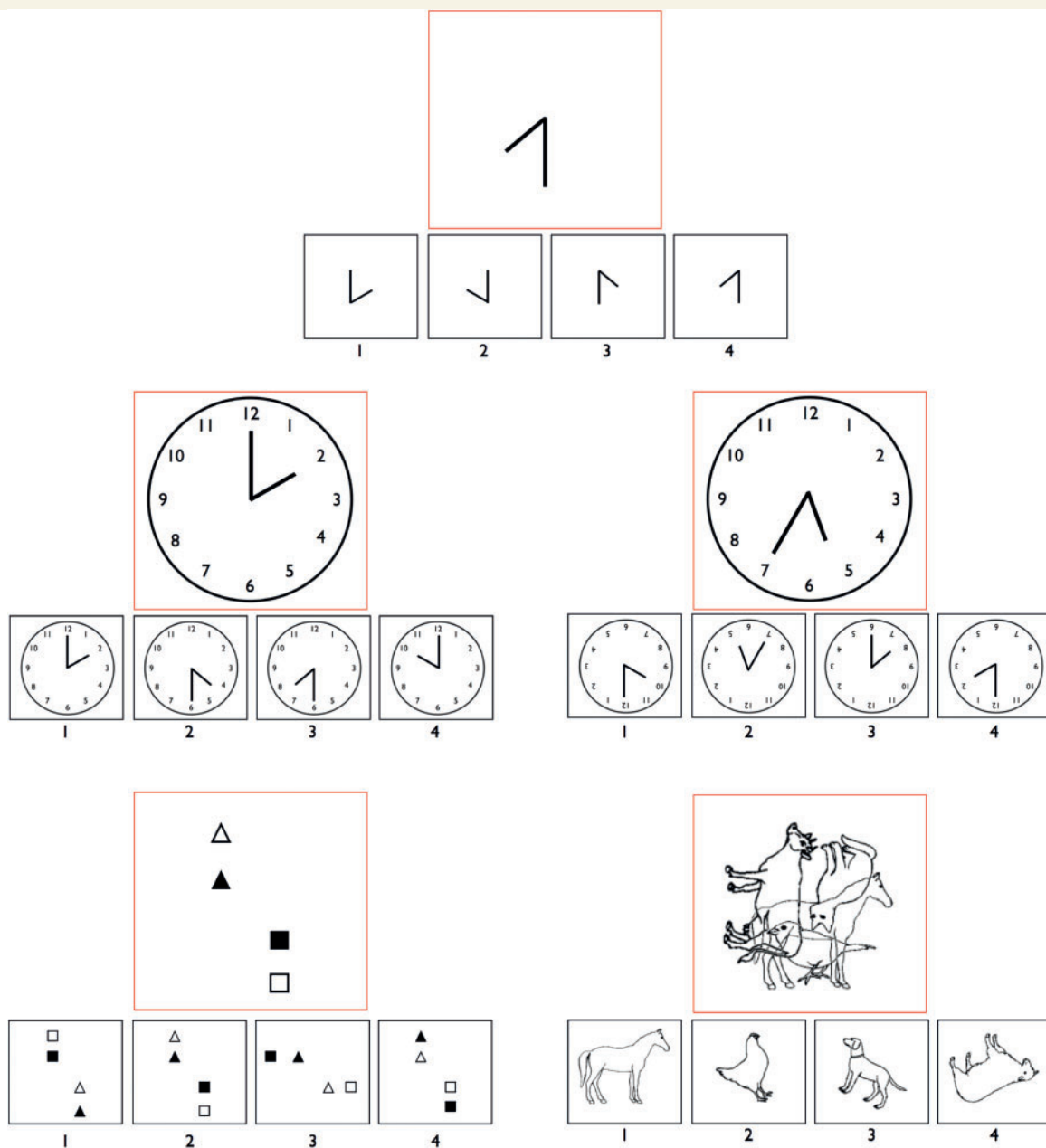


Figure 1 Tests used in the eye-tracking battery. Note the standardized screen layout, with a central stimulus and four comparator stimuli underneath. Tasks within the battery included an angle matching task, clock and inverted clock matching task, shape position task and overlapping figures task.

count ratios suggest either a less efficient strategy, where incorrect interest areas are revisited repeatedly, or a cautious approach, aimed at minimizing errors. Time to first fixation in the correct interest area was chosen, as this measure has previously been demonstrated to provide information on efficiency of visual exploration during clock reading in patients with Alzheimer's disease (Mosimann *et al.*, 2004a). Run count and run count ratio are novel approaches to quantifying gaze distribution, although gaze distribution itself has previously been shown to be impaired in Parkinson's disease during a 'one touch' Tower of London task (Hodgson *et al.*, 2002).

Not all subjects contributed to the final eye tracking data set, for a variety of reasons outlined in the flow chart (Fig. 3). Reasons for data loss included withdrawal from the study, inability to tolerate the test or failure

of the eye-tracking equipment. The recruitment figures for this part of the study were therefore as follows: control subjects $n = 29$, cognitively normal Parkinson's disease subjects $n = 35$, Parkinson's disease-MCI subjects $n = 22$ and Parkinson's disease dementia $n = 22$. In addition, a proportion of participants completed only part of the eye-tracking battery, due to poor comprehension, fatigue, drowsiness and so forth. As expected, the group most affected by data loss was the Parkinson's disease dementia cohort. When comparison was made between the demographic features of those subjects with Parkinson's disease dementia completing every task in the battery ($n = 16$) and those failing to do so ($n = 10$), there were no differences in age (Wilcoxon rank sum; $z = 0.40$, $P = 0.692$, not significant), education (Wilcoxon rank sum; $z = 0.08$, $P = 0.934$, ns), UPDRS III (Wilcoxon rank sum; $z = 0.77$, $P = 0.444$, not

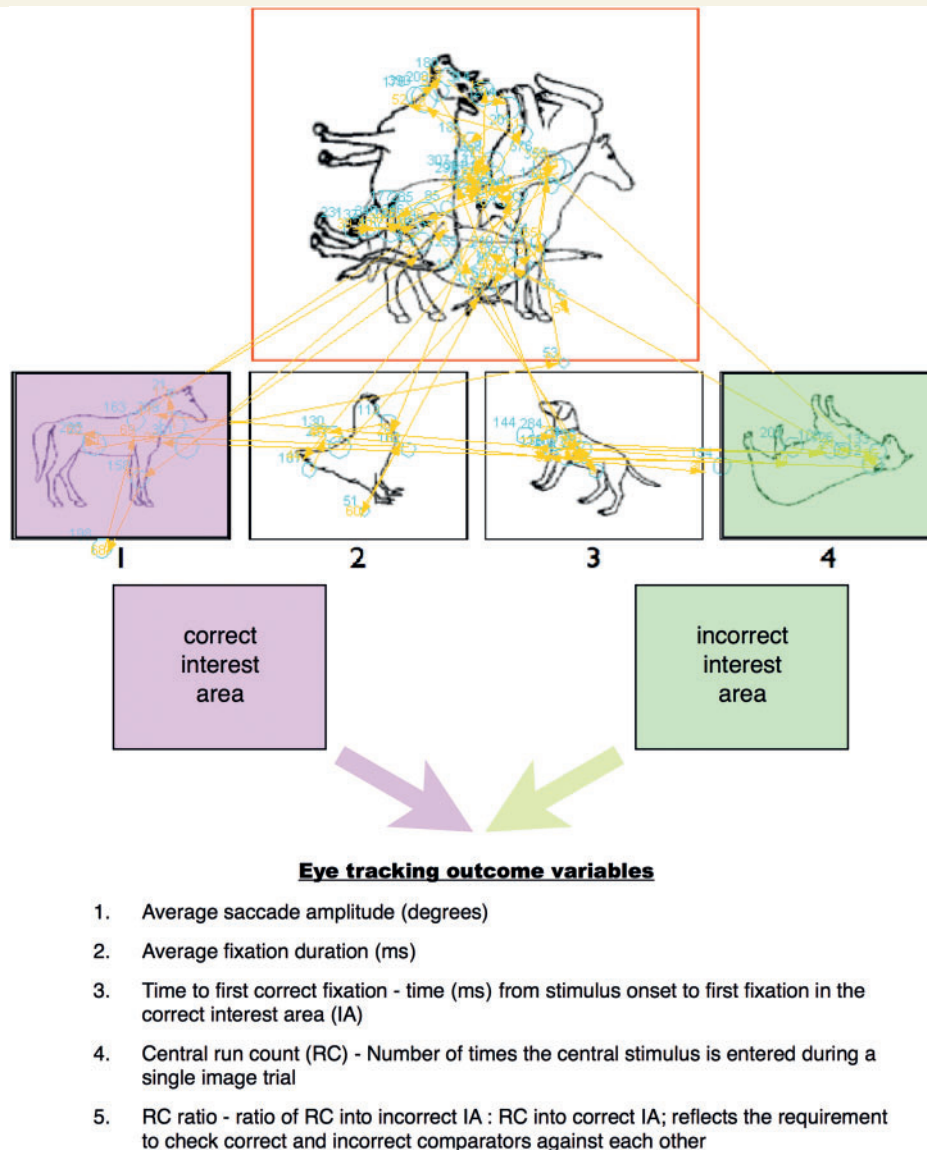


Figure 2 Example of fixation/saccade map for a single study participant. Blue circles represent each fixation, with the size of each circle reflecting the individual fixation duration. Yellow arrows represent each saccade. Interest area analysis provides insight into the visual exploration strategy used for each image viewed. IA = interest area; RC = run count.

significant) or global cognition (AEMSS: Wilcoxon rank sum; $z = 0.64$, $P = 0.507$, not significant). Subjects failing to complete the eye tracking battery did, however, have a significantly longer dementia duration (Parkinson's disease duration: Wilcoxon rank sum; $z = 2.27$, $P = 0.023$; dementia duration: Wilcoxon rank sum; $z = 2.68$, $P = 0.007$).

Statistics

Data were analysed using the JMP 8 statistical package (SAS Institute Inc.). The distribution of data was examined for normality (Shapiro–Wilk test). Means and standard deviations were calculated. Normally distributed data were analysed with parametric tests (independent sample t -tests, ANOVA) and non-normally distributed data with non-parametric tests (Wilcoxon rank sums, Kruskal–Wallis). Pearson chi-square test was used for comparison of frequencies, and Fisher's exact test used when expected frequency in either group was < 5 . All reported P -values are two-tailed for parametric tests. Wilcoxon rank

sum test results are presented using normal approximation, and a P -value of < 0.05 was considered significant.

Planned group comparisons for the eye-tracking analysis were as follows: (i) control versus cognitively normal Parkinson's disease subjects; (ii) cognitively normal Parkinson's disease subjects versus Parkinson's disease-MCI subjects; (iii) cognitively normal Parkinson's disease subjects versus Parkinson's disease dementia subjects; and (iv) Parkinson's disease-MCI subjects versus Parkinson's disease dementia subjects. The relationship between global cognition (AEMSS), disease severity (UPDRS III), LED and average fixation duration was investigated using Pearson product-moment correlation coefficient and stepwise linear regression (standard least squares approach with backward elimination). The same analysis was performed using just the fixation duration for the overlapping figures task to explore the association between task complexity, cognition, motor status and fixation duration. This was selected as the dependent variable because the overlapping figures task had the highest error rates and greatest task complexity.

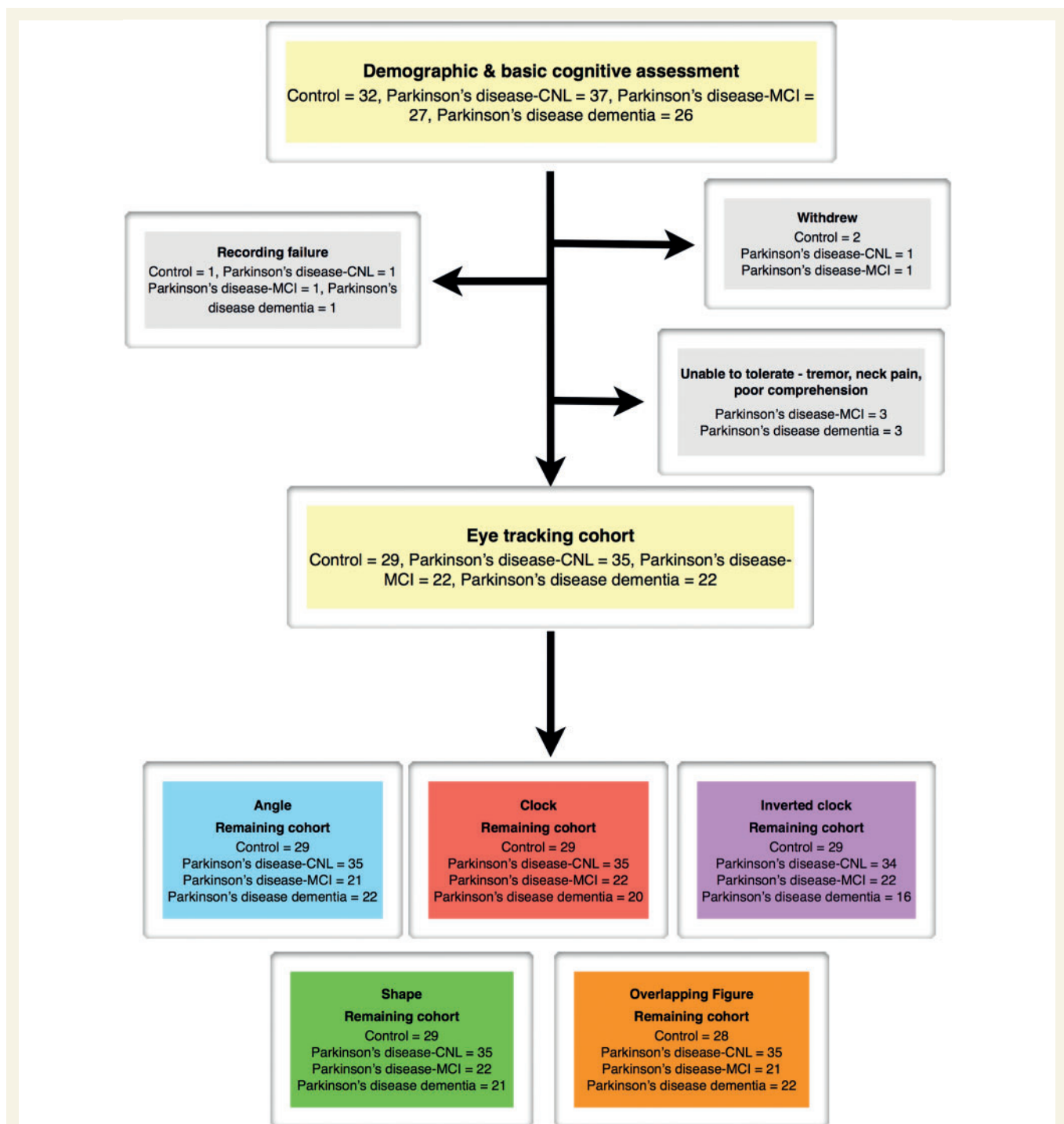


Figure 3 Flow chart for the eye-tracking study. Note the smaller number taking part in the eye tracking experiment owing to withdrawal, recording failure or problems tolerating the procedure. In addition, several of the eye-tracking cohorts failed to complete all five tasks in the battery. CNL = cognitively normal.

Results

Demographic characteristics

Demographic and cognitive features are shown in Table 1. All four groups were well matched for age and education. Estimated

dementia duration was 1.7 years (range 0–3 years, where 0 represents a new diagnosis of dementia at study entry). Cognitively normal Parkinson's disease subjects and control subjects were well matched for global and subscale cognition. Parkinson's disease-MCI subjects scored lower than cognitively normal Parkinson's disease subjects and control subjects on all cognitive

Table 1 Demographics and cognitive features of the eye tracking study group

	Control subjects n = 29	Parkinson's disease-CNL subjects n = 35	Parkinson's disease-MCI subjects n = 22	Parkinson's disease dementia subjects n = 22	P-value
Age (years)	72.3 (7.8)	69.4 (9.0)	70.8 (7.1)	72.3 (6.0)	0.409 ^a (ns)
Education (years)	11.6 (2.7)	12.3 (3.1)	12.0 (3.4)	11.2 (3.0)	0.361 ^b (ns)
Gender (% male)	48	60	77	86	0.451 ^{c,d} (ns), 0.025 ^e (ns), 0.042 ^f , 0.698 ^g (ns)
Parkinson's disease duration (years)	n/a	7.6 (5.6)	8.8 (5.4)	11.6 (6.1)	0.426 ^{e,h} (ns), 0.015 ^f , 0.118 ^g (ns)
Estimated dementia duration (years)	n/a	n/a	n/a	1.7 (0.9)	
UPDRS II	n/a	11.9 (6.4)	14.9 (5.4)	28.8 (5.8)	0.099 ^{e,i} (ns), <0.001 ^{f,g}
UPDRS III	n/a	21.3 (10.5)	25.6 (8.8)	35.4 (14.7)	0.187 ^{e,i} (ns), 0.001 ^f , 0.023 ^g
LED	n/a	579 (406)	774 (479)	917 (450)	0.105 ^{e,h} (ns), 0.005 ^f , 0.312 ^g (ns)
Global cognition					
Mini-Mental State Examination	29.6 (0.8)	29.5 (0.7)	28.3 (1.6)	24.5 (2.7)	0.219 ^{d,i} (ns), 0.003 ^e <0.001 ^{f,g}
AEMSS (DRS)	12.8 (2.9)	12.4 (2.1)	7.6 (2.5)	3.9 (1.7)	0.487 ^{d,i} (ns), <0.001 ^{e,f,g}
Cognitive subscale scores (DRS)					
Attention	12.2 (1.3)	12.1 (1.2)	10.9 (1.9)	9.9 (2.6)	0.813 ^{d,i} (ns), 0.012 ^e , <0.001 ^f , 0.231 ^g (ns)
Initiation/perseveration construction	11.0 (1.4)	11.0 (1.3)	6.8 (2.5)	4.1 (2.0)	0.785 ^{d,i} (ns), <0.001 ^{e,f,g}
Clock Drawing Test (Shulman)	10.0 (0.0)	10.0 (0.0)	9.7 (0.9)	8.7 (2.3)	n/a ^{d,i} , 0.072 ^e , 0.001 ^f , 0.097 ^g (ns)
Conceptualization	4.9 (0.3)	4.7 (0.4)	4.2 (0.9)	2.9 (1.5)	0.050 ^{d,i} (ns), 0.020 ^e , <0.001 ^f , 0.001 ^g
Memory	11.5 (1.5)	10.9 (1.6)	9.2 (2.8)	8.1 (3.2)	0.149 ^{d,i} (ns), 0.021 ^e , <0.001 ^f , 0.267 ^g (ns)
	10.0 (3.2)	10.6 (1.9)	8.1 (3.1)	4.6 (2.5)	0.734 ^{d,i} (ns), 0.002 ^e , <0.001 ^{f,g}

Values expressed as means (\pm SD) (unless otherwise stated).

a ANOVA test.

b Kruskal-Wallis test.

c Pearson χ^2 \pm Fisher's exact test where groups frequency <5.

d Control subjects versus Parkinson's disease-CNL subjects.

e Cognitively normal Parkinson's disease subjects versus Parkinson's disease-MCI subjects.

f Cognitively normal Parkinson's disease subjects versus Parkinson's disease dementia subjects.

g Parkinson's disease-MCI subjects versus Parkinson's disease dementia subjects.

h *t*-test.

i Wilcoxon rank sum test.

CNL = cognitively normal; ns = non-significant.

subscale scores of the DRS-2, apart from the construction scale previously noted to discriminate poorly between cognitively normal and cognitively impaired individuals.

Eye-tracking battery performance

Task performance

Error rates, expressed as a percentage of the total trials, illustrate the types of visual task found most challenging by the study subjects (Table 2). For all groups, fewest errors were made on the clock task, followed by the angle, shape, inverted clock and overlapping figures tasks. There was no difference between control subjects and cognitively normal Parkinson's disease subjects in the total number of errors made on the battery, or in error rate percentages on the individual task types. There were, however, significant differences in performance between the three Parkinson's disease groups. Compared with the cognitively normal Parkinson's disease group, error rate percentages on angle and overlapping figures tasks were significantly higher in the Parkinson's disease-MCI group, and there was a trend towards significance for the inverted clock task. Comparison of error rates between cognitively normal Parkinson's disease and Parkinson's disease dementia groups reached significance for all five tasks. Parkinson's disease-MCI subjects made significantly fewer errors than those with Parkinson's disease dementia, with the exception

of performance on the inverted clock task, where Parkinson's disease-MCI performance closely resembled that of the dementia group.

Saccade amplitude

Saccade amplitude was largest for the control group, with a general trend towards progressively lower saccadic amplitudes across the three disease groups (cognitively normal Parkinson's disease > Parkinson's disease-MCI > Parkinson's disease dementia) (Table 3). There was a significant difference in amplitudes between cognitively normal subjects with Parkinson's disease and those with both MCI and dementia. Comparisons between Parkinson's disease-MCI and Parkinson's disease dementia groups did not reach significance. Of note, although cognitively normal Parkinson's disease subjects had reduced saccadic amplitudes compared with control subjects, this comparison also failed to reach significance ($P = 0.178$, not significant).

Fixation duration

The average duration of fixations was shorter in control subjects than cognitively normal Parkinson's disease subjects (Table 3). A similar pattern was seen when comparing cognitively normal Parkinson's disease subjects with Parkinson's disease-MCI subjects. The trend to prolonged fixation duration was replicated when comparing Parkinson's disease-MCI subjects with subjects with

Table 2 Perception errors across the study groups

Error rate (%)	Control subjects n = 29	Parkinson's disease-CNL subjects n = 35	Parkinson's disease-MCI subjects n = 22	Parkinson's disease dementia subjects n = 22	P-value
Total	2.8 (2.9)	2.3 (2.0)	6.9 (6.1)	14.5 (12.0)	0.838 ^{a,b} (ns), 0.001 ^c , <0.001 ^d , 0.015 ^e
Angle	1.7 (2.8)	1.6 (3.1)	4.9 (6.0)	13.1 (10.0)	0.727 ^{a,b} (ns), 0.012 ^c , <0.001 ^d , 0.002 ^e
Clock	0.2 (1.1)	0.5 (2.3)	1.4 (3.2)	5.3 (7.4)	0.672 ^{a,b} (ns), 0.324 ^c (ns), <0.001 ^d , 0.006 ^e
Inverted clock	3.8 (6.3)	3.4 (5.3)	12.2 (19.8)	19.5 (26.0)	0.747 ^{a,b} (ns), 0.079 ^c (ns), 0.002 ^d , 0.277 ^e (ns)
Shape	2.7 (6.3)	3.6 (5.3)	3.5 (3.7)	16.4 (16.9)	0.265 ^{a,b} (ns), 0.602 ^c (ns), 0.002 ^d , 0.010 ^e
Overlap	5.0 (6.1)	3.3 (4.4)	10.9 (11.8)	20.2 (16.9)	0.275 ^{a,b} (ns), 0.003 ^c , <0.001 ^d , 0.037 ^e

Values expressed as means (\pm SD).

a Statistical tests: Wilcoxon rank sum test.

b Control subjects versus cognitively normal Parkinson's disease subjects.

c Cognitively normal Parkinson's disease subjects versus Parkinson's disease-MCI subjects.

d Cognitively normal Parkinson's disease subjects versus Parkinson's disease dementia subjects.

e PD-Parkinson's disease versus Parkinson's disease dementia.

CNL = cognitively normal; ns = non-significant.

Table 3 Exploration strategy by study group

	Control subjects n = 29	Parkinson's disease-CNL subjects n = 35	Parkinson's disease-MCI subjects n = 22	Parkinson's disease dementia subjects n = 22	P-value
Saccade amplitude (degrees)					
Total	6.20 (0.54)	5.94 (0.52)	5.54 (0.79)	5.28 (0.69)	0.178 ^{a,b} (ns), 0.027 ^c , <0.001 ^d , 0.174 ^e (ns)
Fixation duration (ms)					
Total	185 (22)	203 (29)	222 (32)	241 (41)	0.022 ^{a,b} , 0.029 ^c , <0.001 ^d , 0.052 ^e (ns)
Time to first fixation in correct interest area (ms)					
Total	1749 (271)	1920 (335)	2299 (674)	2811 (775)	0.187 ^{a,b} (ns), 0.008 ^c , <0.001 ^d , 0.003 ^e
Run count (central)					
Total	3.02 (0.40)	2.86 (0.36)	3.15 (0.44)	3.48 (0.64)	0.313 ^{a,b} (ns), 0.020 ^c , <0.001 ^d , 0.026 ^e
Run count ratio					
Total	0.46 (0.08)	0.45 (0.07)	0.51 (0.07)	0.57 (0.11)	0.752 ^{a,b} (ns), 0.010 ^c , <0.001 ^d , 0.036 ^e

Values expressed as means (\pm SD).

a Statistical tests: *t*-test.

b Control subjects versus cognitively normal Parkinson's disease subjects.

c Cognitively normal Parkinson's disease subjects versus Parkinson's disease-MCI subjects.

d Cognitively normal Parkinson's disease subjects versus Parkinson's disease dementia subjects.

e Parkinson's disease-MCI subjects versus Parkinson's disease dementia subjects.

CNL = cognitively normal; ns = non-significant.

Parkinson's disease dementia, although the comparison just failed to reach significance ($P = 0.052$). The comparison between cognitively normal Parkinson's disease subjects and those with dementia was the most striking, with fixations in the Parkinson's disease dementia group lasting ~ 40 ms longer than the cognitively normal Parkinson's disease group.

There was a significant negative correlation between AEMSS and average fixation duration ($r = -0.31$, $n = 68$, $P = 0.011$), a strong positive correlation between UPDRS III and fixation duration ($r = 0.50$, $n = 68$, $P < 0.001$) and a significant negative correlation between AEMSS and UPDRS III ($r = -0.37$, $n = 68$, $P = 0.001$). There was a weak, and non-significant, correlation between fixation duration and LED ($r = 0.17$, $n = 68$, $P = 0.164$,

not significant). Multiple regression was used to assess the contribution that global cognition (AEMSS) and motor severity (UPDRS III) made to duration of fixation. A model containing both measures was significant [$F(2,68) = 12.50$, $P \leq 0.001$], predicting 28% of the variance in fixation duration. As suggested by the correlation analysis, UPDRS III positively correlated with fixation duration ($\beta = 0.45$, $P \leq 0.001$) and contributed most to the model, whereas AEMSS negatively correlated with fixation duration and made a weaker, non-significant contribution to the overall predictive value of the model ($\beta = -0.16$, $P = 0.150$, not significant). In contrast, re-running the model for the overlapping figures task yielded a slightly stronger model [$F(2,76) = 12.52$, $P \leq 0.001$], predicting 34% of the variance in fixation duration. UPDRS III

remained the strongest contributor ($\beta = 0.44$, $P \leq 0.001$), and AEMSS made a weaker, but significant, contribution to the overall predictive value of the model ($\beta = -0.27$, $P = 0.013$).

Exploration strategy by diagnostic group

In general, control subjects were first to fixate the correct interest areas, with cognitively normal Parkinson's disease, Parkinson's disease-MCI and Parkinson's disease dementia subjects taking progressively longer (Table 3). Although there was no significant difference in total time to first correct fixation between cognitively normal Parkinson's disease and control subjects, comparisons between the three Parkinson's disease groups were significant. The most striking difference in the Parkinson's disease group comparison was between cognitively normal subjects and those with dementia. Cognitively normal Parkinson's disease central run count strategy matched that of control subjects. The total central run count strategy was significantly different between cognitively normal Parkinson's disease, Parkinson's disease-MCI and Parkinson's disease dementia subjects. As with time to first correct fixation, the strategic performance of subjects with Parkinson's disease dementia was most impaired. The total run count ratio was similar for control and cognitively normal Parkinson's disease groups. In line with the other strategic measures, total run count ratio increased significantly across the three Parkinson's disease groups.

Discussion

To the best of our knowledge, this is the first study to report on visual cognition and visual exploration strategy in Parkinson's disease with predefined and differing levels of cognitive impairment. We have demonstrated significant differences in visual exploration strategies between cognitive sub-groups of Parkinson's disease and shown the potential of visual exploration analysis in providing non-verbal and objective measures of cognitive dysfunction in Parkinson's disease.

Our results highlight the cognitive heterogeneity present in a cross-sectional cohort of patients with Parkinson's disease and Parkinson's disease dementia. This is particularly true of non-demented Parkinson's disease cohorts, where a significant proportion of subjects are likely to have cognitive impairment (Foltnie *et al.*, 2004). In particular, non-demented patients with Parkinson's disease are reported to have impairments in executive function, memory, visuospatial and visuoperceptual abilities (Mosimann *et al.*, 2004b; Muslimovic *et al.*, 2005; Uc *et al.*, 2005; Williams-Gray *et al.*, 2007). In the absence of published criteria at the start of the study, we relied on global and subscale cognitive scores to identify those subjects with Parkinson's disease who, although not fulfilling diagnostic criteria for Parkinson's disease dementia, clearly did not score in the normal range—a group we defined as 'MCI'. Although we did not perform the detailed neuropsychological assessments used in some previous studies of Parkinson's disease-MCI subjects (Janvin *et al.*, 2006; Caviness *et al.*, 2007; Petersen *et al.*, 2009), analyses suggest that our approach did generate a group with a cognitive phenotype very different from the cognitively normal Parkinson's disease group.

The percentage of defined as Parkinson's disease-MCI was also comparable with previous studies (Litvan *et al.*, 2011), suggesting that our approach has external validity.

With respect to performance on the eye-tracking battery, we found very similar low error rates for both control and cognitively normal Parkinson's disease groups, and no evidence to suggest a specific visuospatial or visuoperceptual deficit in subjects with Parkinson's disease with normal cognition. This contrasts with the performance of subjects with Parkinson's disease-MCI, who demonstrated significant differences in memory, attentional and frontal-executive abilities, as well as higher error rates on visuospatial and visuoperceptual tasks. The extent of these deficits was intermediate between the cognitively normal Parkinson's disease group, who performed as control subjects, and the Parkinson's disease dementia group, with the highest error rates. Interestingly, clock reading and matching was not markedly impaired in the Parkinson's disease dementia group (5% error rate), perhaps reflecting the over-learned nature of the task.

In line with our first hypothesis, exploration strategy, as defined by time to first correct fixation, central run count and run count ratio, was identical for control subjects and cognitively normal subjects with Parkinson's disease. Subjects in the cognitively normal Parkinson's disease, Parkinson's disease-MCI and Parkinson's disease dementia groups differed in all exploration efficiency strategy measures. As expected, the most striking differences were between the cognitively normal Parkinson's disease subjects and those with dementia. This clear separation of groups based on novel measures of exploration strategy provides, for the first time, a measure not only of the outcome of a cognitive task (correct versus incorrect) but also of how efficiently fixations and saccades are deployed in the build-up to a cognitive response.

In keeping with our second hypothesis, we noted small, but significant, differences in fixation duration across the study cohort. Despite being well matched for error rates, subjects in the cognitively normal Parkinson's disease group made consistently longer fixations than control subjects, in the magnitude of 18 ms. This prolongation of fixation duration was most marked in subjects with Parkinson's disease with dementia; those with MCI represented an intermediate group.

Although saccade amplitudes were lower in the cognitively normal Parkinson's disease group than control subjects, the comparison did not reach significance. Rather, it was those subjects with Parkinson's disease with MCI or dementia that demonstrated significant reductions in saccade amplitude. This is in contrast to a recent study of visual scanning in Parkinson's disease, where differences in fixation duration between patients with Parkinson's disease and control subjects were of much greater magnitude than in our study, ~40–150 ms (depending on task complexity), and Parkinson's disease saccadic amplitudes were significantly lower (Matsumoto *et al.*, 2011).

These differences may be explained, in part, by the differing nature of the tasks; in our study, subjects matched comparator images against a central stimulus—a standardized screen layout across all five tasks; Matsumoto *et al.* (2011) required subjects to memorize a variety of visual images of varying complexity. Intuitively, one would predict that the latter task would generate

longer fixations than those seen in our study. With respect to saccade amplitude in control subjects and cognitively normal Parkinson's disease subjects, it may be that the observed trend in our study would have reached significance had a greater number of iterations been performed. Given the more striking differences in saccade amplitude observed in those subjects with Parkinson's disease with MCI and dementia, it is possible that unrecognized cognitive heterogeneity in previous study cohorts might have influenced saccadic measures.

One potential explanation for the prolonged fixation duration is a Parkinson's disease-specific oculomotor deficit, resulting from disruption of subcortical and cortical saccadic eye movement control, leading to a delay between the intention to make a voluntary saccade and its actual initiation. An alternative explanation would be that impairment of visual cognition, executive function or attention, too subtle to be picked up by cognitive screening, is influencing the characteristics of the fixations, even in cognitively normal subjects with Parkinson's disease. Such impairment, requiring subjects to spend longer in each location to extract adequate visual information, could result in small changes in fixation duration without necessarily causing higher error rates on the visual battery itself.

Parkinson's disease severity, reflected by UPDRS III score, was the most important predictor of fixation duration in our regression model, both for average fixation duration across all five tasks and when the model was applied only to the overlapping figures task—the most demanding of the conditions and the one with the highest error rates. In addition, global cognition, as assessed by the AEMSS score, made a significant contribution to the predictive model when task complexity was greatest. In contrast, total LED did not contribute to either model.

As cognition declines and motor impairment worsens, fixation duration becomes significantly longer. The longer fixation duration is therefore a potential reflection not just of subcortical oculomotor deficits but may also serve to highlight the involvement of fronto-parietal eye fields and/or dorsal and ventral streams in the neurodegenerative process in Parkinson's disease. In support of this argument, Pernecky *et al.* (2011) demonstrated negative correlations between frontal executive function, grey matter volume in the frontal and parietal eye fields and the latency of visually evoked saccades.

Data on the metrics of fixations and saccades during 'naturalistic' scene viewing in Parkinson's disease are conflicting. There are reports of prolonged fixations during reading and scanning of visuocognitive tasks (Gottlob *et al.*, 2004; Matsumoto *et al.*, 2011), but in a study of visual exploration duration the Tower of London task, Hodgson *et al.* (2002) showed that, despite strategic differences between subjects with Parkinson's disease and control subjects, fixation durations were identical. Fixation duration during facial emotion viewing is influenced by executive function in Parkinson's disease (Clark *et al.*, 2010), and the impact of cognitive impairment on fixation characteristics is therefore an important factor in interpreting our results. It has been argued that saccadic measurements (latency, amplitude, velocity) may act as a surrogate neurophysiological biomarker for disease progression in clinical trials of Parkinson's disease, although the interaction between medication effects, and the influence of

both cortical and subcortical structures, makes such an approach potentially challenging (Barker and Michell, 2009).

There are limitations to our study in terms of recruitment and sample size. We effectively excluded patients aged <50 years, to allow adequate age matching of the study groups. However, as the average age of the Parkinson's disease population in clinic and community-based studies is 70–72 years (Lo *et al.*, 2009; Newman *et al.*, 2009), we feel our results are likely to have considerable external validity. We employed consecutive recruitment for the Parkinson's disease group to minimize potential bias, but the dementia cohort was a convenience sample. Our sample sizes were relatively small compared with other studies of cognition in Parkinson's disease, and withdrawals from the study, technical issues and an inability to complete the protocol resulted in a degree of data loss, most evident in the Parkinson's disease dementia group. However, this is one of the largest eye-tracking studies of Parkinson's disease to date, the first to include patients with dementia, and the first to explore the influence of differing degrees of cognitive impairment on visual exploration.

Concerns over deteriorating performance and drop-outs associated with a longer assessment battery dictated that we use a relatively small number of images within each task category. Refinement of the battery to those tasks most likely to discriminate cognitive sub-groups would allow a greater number of iterations to be run. A much more detailed cognitive assessment battery would be required to better define the interaction between attention, executive function, working memory and the perceptual and spatial abilities required to efficiently dissect out these 'visual' tasks. Further studies are warranted, perhaps incorporating assessment of reflexive and voluntary saccades, in addition to more naturalistic scene/object viewing, to provide a more complete picture of the influence of Parkinson's disease on eye movement control.

Using eye tracking to measure visual search strategies during task performance, combined with more basic measures of oculomotor control such as average fixation duration and saccade latency, provides an alternative means of assessing and quantifying cognitive impairment in Parkinson's disease and may even act as a surrogate biomarker for those at risk of cognitive impairment. If replicated in longitudinal studies, visual exploration measures and saccadic metrics may ultimately provide a new way of monitoring response to novel disease-modifying agents and cognitive enhancers, as and when they become available.

The functional implications of disordered visual exploration are unknown, but, given that cortical saccade programming and integration of visuospatial input with motoric output are performed in contiguous cortical regions, disruption of efficient visual exploration strategies may contribute to motor complications such as visually induced gait freezing, difficulty turning and falls. Turning, for example, involves a complex integration of eye and head movements, in conjunction with trunk rotation and stepping (Hollands *et al.*, 2004), and the risk of falling in older adults is associated with delays between horizontal saccade initiation and the beginning of foot lift (Greany *et al.*, 2008). Additionally, freezing of gait is often precipitated by turning and can lead to lateral falls and injury (Spildooren *et al.*, 2010). Subtle perturbations in the turning sequence can be demonstrated in early Parkinson's disease; eye movements contribute more to gaze shift than in

healthy control subjects (Anastasopoulos *et al.*, 2011), and, at least in a static environment, saccade performance is predictive of 'on the spot' turn performance (Lohnes and Earhart, 2011). Under more complex, naturalistic conditions such as walking and turning under cognitive distraction, subjects with Parkinson's disease make fewer, early 'preparatory' saccades before turning, with these measures associated with poorer cognition (Galna *et al.*, 2012).

Given that the most striking changes in saccade amplitude, fixation duration and exploration efficiency are seen in those subjects with cognitive impairment, and that postural instability and falls are strongly associated with cognitive decline (Yarnall *et al.*, 2011), our results suggest that oculomotor characteristics have the potential to predict those at risk of motor complications. A longitudinal study, combining detailed 'static' assessments of visual exploration, with a more 'dynamic' approach, using portable eye tracking devices during walking, would allow this hypothesis to be tested. A better understanding of the distribution of gaze during navigation may, ultimately, facilitate the tailoring of visual cueing strategies to help overcome freezing when turning.

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References

- Amick MM, Schendan HE, Ganis G, Cronin-Golomb A. Frontostriatal circuits are necessary for visuomotor transformation: mental rotation in Parkinson's disease. *Neuropsychologia* 2006; 44: 339–49.
- Anastasopoulos D, Ziavra N, Savvidou E, Bain P, Bronstein AM. Altered eye-to-foot coordination in standing parkinsonian patients during large gaze and whole-body reorientations. *Mov Disord* 2011; 26: 2201–11.
- Bares M, Brazdil M, Kanovsky P, Jurák P, Daniel P, Kukleta M, *et al.* The effect of apomorphine administration on smooth pursuit ocular movements in early Parkinsonian patients. *Parkinsonism Relat Disord* 2003; 9: 139–44.
- Barker RA, Michell AW. "The eyes have it". Saccadometry and Parkinson's disease. *Exp Neurol* 2009; 219: 382–4.
- Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. *Neurology* 2007; 69: 747–54.
- Briand KA, Hening W, Poizner H, Sereno AB. Automatic orienting of visuospatial attention in Parkinson's disease. *Neuropsychologia* 2001; 39: 1240–9.
- Briand KA, Strallow D, Hening W, Poizner H, Sereno AB. Control of voluntary and reflexive saccades in Parkinson's disease. *Exp Brain Res* 1999; 129: 38–48.
- Brown GG, Rahill AA, Gorell JM, McDonald C, Brown SJ, Sillanpaa M, *et al.* Validity of the Dementia Rating Scale in assessing cognitive function in Parkinson's disease. *J Geriatr Psychiatry Neurol* 1999; 12: 180–8.
- Cahn-Weiner DA, Williams K, Grace J, Tremont G, Westervelt H, Stern RA. Discrimination of dementia with lewy bodies from Alzheimer disease and Parkinson disease using the clock drawing test. *Cogn Behav Neurol* 2003; 16: 85–92.
- Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, *et al.* Defining mild cognitive impairment in Parkinson's disease. *Mov Disord* 2007; 22: 1272–7.
- Chambers JM, Prescott TJ. Response times for visually guided saccades in persons with Parkinson's disease: a meta-analytic review. *Neuropsychologia* 2010; 48: 887–99.
- Clark US, Neargarder S, Cronin-Golomb A. Visual exploration of emotional facial expressions in Parkinson's disease. *Neuropsychologia* 2010; 48: 1901–13.
- Corin MS, Elizan TS, Bender MB. Oculomotor function in patients with Parkinson's disease. *J Neurol Sci* 1972; 15: 251–65.
- Cormack F, Aarsland D, Ballard C, Tovee MJ. Pentagon drawing and neuropsychological performance in Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease and Parkinson's disease with dementia. *Int J Geriatr Psychiatry* 2004; 19: 371–7.
- De Renzi E, Scotti G, Spinnler H. Perceptual and associative disorders of visual recognition. Relationship to the side of the cerebral lesion. *Neurology* 1969; 19: 634–42.
- Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, *et al.* Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 2007; 22: 1689–707; quiz 1837.
- Fahn S, Elton RL. Members of the Unified Parkinson's Disease Rating Scale Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. *Recent developments in Parkinson's disease*. New York: Macmillan; 1987. p. 153–63.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
- Foltnie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain* 2004; 127: 550–60.
- Galna B, Lord S, Daud D, Archibald N, Burn D, Rochester L. Visual sampling during walking in people with Parkinson's disease and the influence of environment and dual-task. *Brain Res* 2012; 1473: 35–43.
- Ghent L. Perception of overlapping and embedded figures by children of different ages. *Am J Psychol* 1956; 69: 575–87.
- Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci* 1992; 15: 20–25.
- Gottlob I, Proudlock FA, Shekhar H, Rajabally Y. Reading in Parkinson's disease. *Invest Ophthalmol Visual Sci* 2004; 45: 2517.
- Greany JF, Di Fabio RP. Saccade to stepping delays in elders at high risk for falling. *Aging Clin Exp Res* 2008; 20: 428–33.
- Henderson JM, Hollingworth A. High-level scene perception. *Annu Rev Psychol* 1999; 50: 243–71.
- Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol Rev* 2000; 80: 953–78.
- Hodgson TL, Ditttrich WH, Henderson L, Kennard C. Eye movements and spatial working memory in Parkinson's disease. *Neuropsychologia* 1999; 37: 927–38.
- Hodgson TL, Tiesman B, Owen AM, Kennard C. Abnormal gaze strategies during problem solving in Parkinson's disease. *Neuropsychologia* 2002; 40: 411–22.
- Hollands MA, Ziavra NV, Bronstein AM. A new paradigm to investigate the roles of head and eye movements in the coordination of whole-body movements. *Exp Brain Res* 2004; 154: 261–6.
- Hood AJ, Amador SC, Cain AE, Briand KA, Al-Refai AH, Schiess MC, *et al.* Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007; 78: 565–70.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; 55: 181–4.

- Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord* 2006; 21: 1343–9.
- Kennard C, Lueck CJ. Oculomotor abnormalities in diseases of the basal ganglia. *Rev Neurol (Paris)* 1989; 145: 587–95.
- Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Mov Disord* 2011; 26: 1814–24.
- Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012; 27: 349–56.
- Lo RY, Tanner CM, Albers KB, Leimpeter AD, Fross RD, Bernstein AL, et al. Clinical features in early Parkinson disease and survival. *Arch Neurol* 2009; 66: 1353–8.
- Lohnes C, Earhart G. Saccadic eye movements are related to turning performance in Parkinson disease. *J Parkinsons Dis* 2011; 1: 109–18.
- Lueck CJ, Tanyeri S, Crawford TJ, Henderson L, Kennard C. Antisaccades and remembered saccades in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1990; 53: 284–8.
- Lueck KL, Mendez MF, Perryman KM. Eye movement abnormalities during reading in patients with Alzheimer disease. *Neuropsychiatry Neuropsychol Behav Neurol* 2000; 13: 77–82.
- MacAskill MR, Anderson TJ, Jones RD. Adaptive modification of saccade amplitude in Parkinson's disease. *Brain* 2002; 125: 1570–82.
- MacQuarrie TW. MacQuarrie's test for mechanical ability. Monterey, CA: California Test Bureau; 1953.
- Matsumoto H, Terao Y, Furubayashi T, Yugeta A, Fukuda H, Emoto M, et al. Small saccades restrict visual scanning area in Parkinson's disease. *Mov Disord* 2011; 26: 1619–26.
- Michell AW, Xu Z, Fritz D, Lewis SJ, Foltynie T, Williams-Gray CH, et al. Saccadic latency distributions in Parkinson's disease and the effects of L-dopa. *Exp Brain Res* 2006; 174: 7–18.
- Montse A, Pere V, Carme J, Francesc V, Eduardo T. Visuospatial deficits in Parkinson's disease assessed by judgment of line orientation test: error analyses and practice effects. *J Clin Exp Neuropsychol* 2001; 23: 592–8.
- Mori E, Shimomura T, Fujimori M, Hirono N, Imamura T, Hashimoto M, et al. Visuo-perceptual impairment in dementia with Lewy bodies. *Arch Neurol* 2000; 57: 489–93.
- Mosimann UP, Felblinger J, Ballinari P, Hess CW, Muri RM. Visual exploration behaviour during clock reading in Alzheimer's disease. *Brain* 2004a; 127: 431–8.
- Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology* 2004b; 63: 2091–6.
- Mosimann UP, Muri RM, Burn DJ, Felblinger J, O'Brien JT, McKeith IG. Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies. *Brain* 2005; 128: 1267–76.
- Muri RM, Vermersch AI, Rivaud S, Gaymard B, Pierrot-Deseilligny C. Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. *J Neurophysiol* 1996; 76: 2102–6.
- Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005; 65: 1239–45.
- Newman EJ, Breen K, Patterson J, Hadley DM, Grosset KA, Grosset DG. Accuracy of Parkinson's disease diagnosis in 610 general practice patients in the West of Scotland. *Mov Disord* 2009; 24: 2379–85.
- Ogrocki PK, Hills AC, Strauss ME. Visual exploration of facial emotion by healthy older adults and patients with Alzheimer disease. *Neuropsychiatry Neuropsychol Behav Neurol* 2000; 13: 271–8.
- Pereira JB, Junque C, Marti M-J, Ramirez-Ruiz B, Bargallo N, Tolosa E. Neuroanatomical substrate of visuospatial and visuoperceptual impairment in Parkinson's disease. *Mov Disord* 2009; 24: 1193–9.
- Pernecky R, Ghosh BC, Hughes L, Carpenter RH, Barker RA, Rowe JB. Saccadic latency in Parkinson's disease correlates with executive function and brain atrophy, but not motor severity. *Neurobiol Dis* 2011; 43: 79–85.
- Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. *Arch Neurol* 2009; 66: 1447–55.
- Pierrot-Deseilligny C, Muri R, Nyffeler T, Milea D. The role of the human dorsolateral prefrontal cortex in ocular motor behavior. *Ann N Y Acad Sci* 2005; 1039: 239–51.
- Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of memory-guided saccades in man. *Exp Brain Res* 1991; 83: 607–17.
- Pierrot-Deseilligny C, Rivaud S, Gaymard B, Muri R, Vermersch AI. Cortical control of saccades. *Ann Neurol* 1995; 37: 557–67.
- Poppelreuter W. Die psychischen Schädigungen durch Kopfschuss im Kriege 1914-1916: die Herabsetzung der körperlichen Leistungsfähigkeit und des Arbeitswillens durch Hirnverletzung im Vergleich zu Normalen und Psychogenen. Leipzig: Voss; 1917.
- Rascol O, Clanet M, Montastruc JL, Simonetta M, Soulier-Esteve MJ, Doyon B, et al. Abnormal ocular movements in Parkinson's disease. evidence for involvement of dopaminergic systems. *Brain* 1989; 112: 1193–4.
- Repka MX, Claro MC, Loupe DN, Reich SG. Ocular motility in Parkinson's disease. *J Pediatr Ophthalmol Strabismus* 1996; 33: 144–7.
- Schmidtke K, Olbrich S. The Clock Reading Test: validation of an instrument for the diagnosis of dementia and disorders of visuo-spatial cognition. *Int Psychogeriatr* 2007; 19: 307–21.
- Shulman KI. Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry* 2000; 15: 548–61.
- Spildooren J, Vercruyse S, Desloovere K, Vandenberghe W, Kerckhofs E, Nieuwboer A. Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning. *Mov Disord* 2010; 25: 2563–70.
- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010; 25: 2649–53.
- Uc EY, Rizzo M, Anderson SW, Qian S, Rodnitzky RL, Dawson JD. Visual dysfunction in Parkinson disease without dementia. *Neurology* 2005; 65: 1907–13.
- Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DG, Goodale MA, Mansfield RJQ, editors. *Analysis of visual behaviour*. Cambridge: MIT Press; 1982. p. 549–86.
- van Stockum S, MacAskill M, Anderson T, Dalrymple-Alford J. Don't look now or look away: two sources of saccadic disinhibition in Parkinson's disease? *Neuropsychologia* 2008; 46: 3108–15.
- Vidailhet M, Rivaud S, Gouider-Khouja N, Pillon B, Bonnet AM, Gaymard B, et al. Eye movements in parkinsonian syndromes. *Ann Neurol* 1994; 35: 420–6.
- Vidailhet M, Rivaud S, Gouider-Khouja N, Pillon B, Gaymard B, Agid Y, et al. Saccades and antisaccades in parkinsonian syndromes. *Adv Neurol* 1999; 80: 377–82.
- Warrington EK, James M. Visual apperceptive agnosia: a clinico-anatomical study of three cases. *Cortex* 1988; 24: 13–32.
- White OB, Saint-Cyr JA, Tomlinson RD, Sharpe JA. Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain* 1983; 106: 571–87.
- Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain* 2007; 130: 1787–98.
- Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease. *Mov Disord* 2011; 26: 2496–503.