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RESEARCH ARTICLE

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Memory-guided saccades in Parkinson's disease: long delays can improve performance

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Abstract A recent study in control subjects suggested the existence of separate pathways for oculomotor spatial working memory tasks depending on whether the delay before movement execution is either short or long (>20 s). The long delay pathway might bypass brain areas commonly affected by Parkinson's disease (PD). This study aimed to assess spatial working memory in Parkinson's disease using short (3 s) and long (30 s) delays in a memory-guided saccade task. Fifteen mild-moderately affected PD subjects off-medication, and 15 age and sex-matched controls were tested (PD mean age 65.3; control 65.9). Subjects were tested in a darkened room using a horizontal LED bar to generate eye movements which were recorded using an infrared limbus tracker. Percentage error in amplitude of the primary saccade was analysed by repeated measures ANOVA. There was a significant interaction between the groups and their response to the short and long delay periods ($P<0.02$). PD subjects were more strongly impaired in the short delay than the long delay trials when compared with controls. Analysis of the percentage error in amplitude of the final eye position showed the same pattern but only in female subjects. This study provides the first evidence that the proposed parallel spatial memory pathway utilised in longer delay periods is relatively unimpaired in PD. In a broader sense, our results suggest there might be other alternative pathways to overcome deficits in functions impaired by PD.

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Introduction

A useful technique with which to study spatial working memory is the measurement of saccades (fast eye movements) to remembered targets. A memory-guided saccade requires a subject to remain fixated on a stimulus while a peripheral target is displayed briefly and then, after a delay period, to execute a saccade to the location of the no-longer-visible target. To perform a memory-guided saccade a subject must maintain an accurate internal representation of the target location during the delay period and then generate a saccade to the remembered position in the absence of a visual target. Memory-guided saccade studies indicate that spatial working memory particularly involves frontal (dorsolateral prefrontal cortex, DLPFC) and parietal (posterior parietal cortex, PPC) areas, often in close synchrony (O'Sullivan et al. 1995; Sweeney et al. 1996; Chafee and Goldman-Rakic 1998, 2000; Tsujimoto and Sawaguchi 2004).

The neural pathways involved in saccadic spatial working memory have been well-studied (for a review see Pierrot-Deseilligny et al. 2002). According to one prominent model proposed by Pierrot-Deseilligny and colleagues, the following areas are said to be involved in particular:

1. PPC, which controls the initial stage of visuospatial integration, approximately 300 ms following target display, allowing subjects to locate the target in relation to their own body (Müri et al. 1996);
2. DLPFC, which is important for early memorisation, up to about 15–20 s (Müri et al. 1996, 2000); and
3. the parahippocampal cortex (PHC) within the medial temporal lobe (MTL), which is important for memorisation at durations ranging from 20 s to several minutes (Ploner et al. 1998, 2000).

There are extensive reciprocal connections between the PPC and the DLPFC (Chafee and Goldman-Rakic 2000). For short delay memory-guided saccades (i.e. a few seconds), the DLPFC employs connections via the rostral caudate nucleus to the frontal eye fields (FEF), from where the memory-guided saccade is triggered (Selemon and Goldman-Rakic 1988; Yeterian and Pandya 1991). For longer delays (i.e. greater than 20 s), the DLPFC utilises connections to the MTL (Selemon and Goldman-Rakic 1988). This network (i.e. PPC to DLPFC to PHC) has been termed the "serial" information pathway (Nyffeler et al. 2002).

Recent research, however (Nyffeler et al. 2002, 2004), involving transcranial magnetic stimulation (TMS) of the DLPFC in healthy subjects has led to the proposal of an alternative "parallel" pathway, whereby the PPC connects directly to the MTL, bypassing the DLPFC. This connection has been shown anatomically by Ding et al. (2000) and by Lavenex et al. (2002). Nyffeler et al. (2004) measured the accuracy of MGS at short (3 s) and long (30 s) delays, with and without bilateral TMS. They found that disruption of the DLPFC by TMS significantly increased the mean percentage error in amplitude of the memory-guided saccade for short and long delays. They also found that short delay memory-guided saccades were significantly more impaired by TMS than were the long delay memory-guided saccades. These studies suggest a dual model for spatial working memory, with both serial and parallel pathways, each operating over different time-scales.

Functional imaging studies (e.g. Kaasinen et al. 2001; Kikuchi et al. 2001) have shown disrupted activity of the DLPFC in Parkinson's disease (PD). Perhaps as a result of this disruption, memory-guided saccades are abnormal in PD, while simple visually-guided saccades are usually normal (see MacAskill et al. 2002 for a review). The cardinal impairment is that the first memory-guided saccade toward a target (the primary saccade) is less accurate in PD, generally falling short of the target compared with control subjects' saccades (Crawford et al. 1989; Lueck et al. 1990, 1992; Hodgson et al. 1999; MacAskill et al. 2002). The longest memory delay period assessed, however, was only 5 s (in Shaunak et al. 1999). The operation of the proposed parallel spatial memory pathway has therefore not been assessed in PD previously.

In this experiment, people with PD performed memory-guided saccades with either short (3 s) or long (30 s) delay periods. It was expected that PD patients would be less accurate than controls under the short delay condition, as has been found previously. If there is a parallel pathway operating over longer delays, however, it might bypass areas which cause impairments in PD in short-delay memory tasks. If so, the performance of the PD and the control groups should converge in the long delay task. This would provide further evidence in favour of the dual pathway model and also indicate the possibility of strategies to compensate for the impairment of memory-guided tasks in PD.

Method

Subjects

Subject consent was obtained according to the declaration of Helsinki and the study was approved by the Canterbury Ethics Committee of the New Zealand Ministry of Health. Fifteen subjects (8 male, 7 female) with mild to moderate PD were tested after refraining from taking any antiparkinsonian medication for a minimum of twelve hours. The severity of parkinsonian symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr scale (H&Y). Dementia was screened for with the Mini Mental State Exam (MMSE). The mean MMSE score was 29.5/30 (range 27–30) (<26 is considered outside the normal range; Bodis-Wollner 2003). Mean age was 65.3 years (range 52–76), mean UPDRS motor score was 18.8 (range 9–24), and UPDRS total score was 30.7 (range 14–41). Mean H&Y was 2.5 (range 2–3). Mean duration of symptoms was 6.5 years (range 2–15) and mean treatment duration was 4.2 years (range 0–10 years). Control subjects were matched for age (within 5 years) and sex. The mean age was 65.9 years, range 52–78; mean MMSE was 29.5, range 28–30. All participants had no history of neurological disorder other than PD, were not taking any psychoactive drugs other than antiparkinsonian treatment, and had Snellen visual acuity (with or without correction) no worse than 6/12.

Apparatus

Eye movements were recorded using a Skalar IRIS infrared limbus tracker (Reulen et al. 1988). Eye position signals were low-pass filtered at 100 Hz, sampled and digitized at 200 Hz, displayed on the operator's computer screen, and recorded on disk for off-line analysis. Subjects were seated in a darkened room with head movements restrained either by a bite-bar or, if the subject had dentures, by a chin rest. Eye-movement stimuli were light-emitting diodes (LED) placed at 5 deg intervals along a horizontal curvilinear bar 1.5 m in front of the subject. Calibration was performed prior to each trial block, with the subject alternately fixating three point targets at 15 deg left, at centre, and at 15 deg right. Signal gain and offset and sensor position were adjusted in an iterative process until the eye-position signal corresponded to the three target values (the IRIS is linear within this range). The tests were generated and recorded by a 486 PC running the EMMA (Eye Movement Measurement and Analysis) program (Muir et al. 2003).

Procedure

The experiment was conducted in six blocks of ten trials with each block lasting 2.5 min. A block contained three long delay and seven short delay trials (the extra short delay trials were included to ensure that sufficient fixation

points were available to confirm the calibration accuracy). The blocks were balanced for left- and right-wards saccades and for stimulus amplitudes and every block included every possible position at least once. Three different orders for the blocks were used, with subjects balanced across these orders.

Subjects were tested in one morning session lasting 45 to 90 min. Following the initial calibration, the task was explained and sufficient practice was given to ensure that it could be performed. Testing was carried out in complete darkness and lights were switched on between blocks to limit dark adaptation. The trial procedure is shown in Fig. 1. At the beginning of each trial the subject maintained gaze on the fixation stimulus. After 2 s and while the fixation stimulus remained visible, a peripheral target (5, 10 or 15 deg left or right of the fixation point) was presented for 400 ms, while the subject maintained fixation. Following extinction of the peripheral target there was a delay period of either 3 or 30 s. At the end of the delay period, the fixation stimulus was extinguished and a tone sounded. This cued the subject to perform a saccade as rapidly as possible to where they remembered the target flash occurring. One second after the tone the peripheral target was re-illuminated and became the fixation point for the next trial.

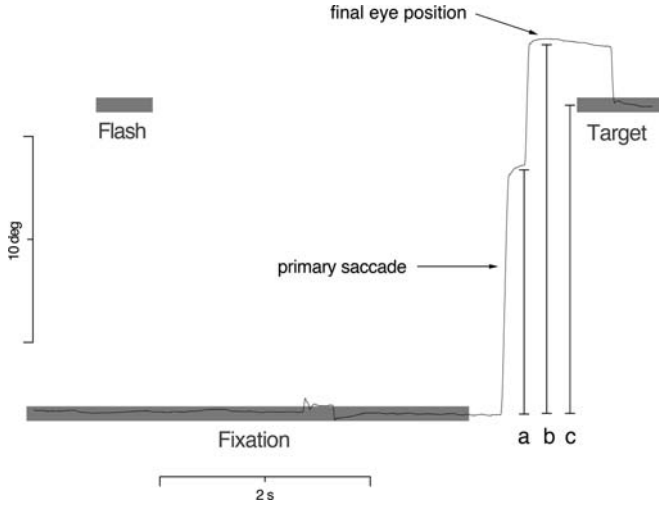

Fig. 1 This recording of one short delay memory-guided saccade trial illustrates the trial procedure and the measurement of the main dependent variables. While the subject maintains gaze on the fixation stimulus, the stimulus for the upcoming saccade is flashed briefly. The fixation stimulus is extinguished at the end of the delay period, cueing the subject to make a primary memory-guided saccade to the remembered target location. The primary saccade may be followed by other saccades until the final eye position is reached. The memory target then re-appears and the subject makes a corrective saccade to fixate the target if required. The cycle then repeats. The percentage error in amplitude (PEA) of the primary saccade was defined as the absolute value of $(c-a)/c\times100\%$. The PEA of the final eye position was defined as the absolute value of $(c-b)/c\times100\%$. The gain of the primary saccade was defined as a/c and the gain of the final eye position as b/c

Data analysis

The primary measure was saccade accuracy, defined as the percentage of error in amplitude (PEA, Nyffeler et al. 2004):

$$\frac{|\text{target amplitude} - \text{saccade amplitude}|}{\text{target amplitude}} \times 100\%$$

Saccade amplitude was measured with respect to both the end point of the primary saccade and to the final eye position. The final eye position was defined as the fixation position reached following the primary saccade plus any corrective saccades, prior to the target reappearing (Fig. 1). The PEA measure is preferred here to other measures of saccade accuracy, such as gain, as it reflects the variability of error which is characteristic of changes in memory-guided saccade accuracy (Pierrot-Deseilligny et al. 2002).

A secondary measure was the proportion of trials in which a subject executed an inappropriate saccade. These were defined as reflexive saccades to the peripheral target flash or as anticipatory saccades toward the memorised target during the delay period, during which fixation should have been maintained. (Trials were excluded from the other analyses if the subject made an inappropriate saccade or if they blinked either during the flash or at the tone.) Other secondary measures were the latency, velocity, and gain of the primary saccade; and the gain of the final eye position. The definitions of gain and PEA are depicted graphically in Fig. 1.

Results

A repeated measures ANOVA was carried out for each of the dependent variables below, with Group (PD vs control) and Sex (male vs female) as between-group variables and with Delay (short vs long) as a within-group variable. The alpha level was set at 0.05.

PEA of primary saccade

There was an interaction (Fig. 2) between Group and Delay on the PEA of the primary saccade, $F_{(1,26)}=6.26$, $P=0.02$. That is, PD primary saccade PEA was worse than that of controls in the short-delay condition but converged toward the control level in the long delay condition. Planned comparisons confirmed a significant difference between PD and control PEA in the short delay, $F_{(1,26)}=9.07$, $P=0.006$, whereas there was no significant difference in the long delay, $F_{(1,26)}=0.39$, $P=0.54$. There was also a main effect of Delay ($F_{(1,26)}=35.38$, $P=0.000003$), with PEA being worse in the long delay condition overall.

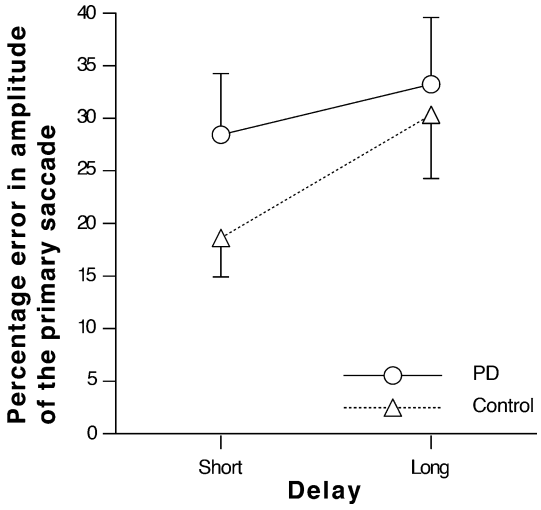

Fig. 2 Percentage error in amplitude of the primary saccade for PD (*circles*) and control subjects (*triangles*) at short and long delays. *Error bars* indicate 95% confidence intervals of the mean. There was an interaction between Group and Delay: the percentage error of the PD subjects was significantly worse than that of the controls in the short delay but not in the long delay

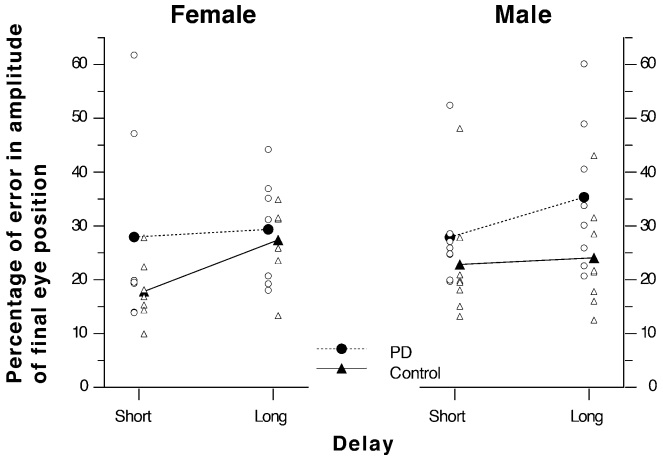

Fig. 3 Percentage error in amplitude of the final eye position for PD (*circles*) and control subjects (*triangles*) at short and long delays. *Filled symbols* indicate group means whereas *unfilled symbols* indicate values for individual subjects. There was an interaction between Group, Sex, and Delay: female subjects showed the same differential response between PD and controls as shown in Fig. 2, whereas males showed a different pattern

PEA of final eye position

There was an interaction (Fig. 3) between Group, Delay, and Sex on the PEA of final eye position, $F_{(1,26)}$=4.44, P=0.04. Female subjects showed the same differential pattern of impairment between PD and controls as seen for the PEA of the primary saccade: worse performance in PD in the short delay but similar performance in the long delay. Males, however, showed a different pattern, with performance of the PD and control groups diverging from the short to long delay rather than converging. Planned comparisons showed that the only significant difference between the groups at each delay was that of male PD subjects being worse than their male controls in the long delay condition, $F_{(1,26)}$=4.48, P=0.04. The only other significant effect was that of Delay, $F_{(1,26)}$=8.33, P=0.008, with PEA being worse in the long delay condition overall.

There were no significant differences in age as a function of either Group or of Sex. There was no significant difference in the mean UPDRS motor score between male (19.1) and female (18.4) PD subjects.

Secondary measures

The mean percentage of trials in which subjects made an inappropriate saccade was higher in the PD group than in the controls (19.4% vs 9.8%, one-tailed t-test, $t_{(28)}$=1.82, P=0.04).

Other measures of saccade performance are given in Table 1. There was an effect of Group on saccade latency, with mean latency in the PD group being longer than that in the control group (398 ms vs 312 ms, $F_{(1,26)}$=5.76, P=0.02). There were no effects of Group, Sex, or Delay on the remaining measures.

Discussion

Consistent with Nyffeler et al. (2002, 2004), we measured the percentage error in amplitude (PEA) of the primary saccade in a memory-guided saccade task. Nyffeler et al. found that when TMS was applied to the DLPFC, PEA was increased markedly in the short delay task but was not increased as much in the long delay task. We found similar results: subjects with PD had a significantly worse PEA than controls in the short delay condition but were not significantly worse in the long delay (Fig. 2). This differential pattern of performance indicates that the effect of PD on this task is similar to that due to pure DLPFC disruption.

First, these findings provide further evidence in support of DLPFC malfunction in PD. (The subjects with PD had a higher rate of inappropriate saccades than controls and it

Table 1 Mean (standard deviation) of primary saccade gain, final eye position gain, latency, and velocity for control and PD subjects in the short and long delay conditions

	PD		Control	
	Short	Long	Short	Long
Primary saccade gain	0.89 (0.22)	0.86 (0.24)	0.96 (0.12)	0.92 (0.22)
FEP gain	1.05 (0.23)	1.03 (0.26)	1.07 (0.13)	1.01 (0.14)
Latency (ms)	382 (114)	419 (169)	308 (30)	313 (43)
Velocity (deg s^{-1})	269 (54)	271 (63)	301 (58)	285 (81)

has also been shown that the DLPFC is involved in saccade inhibition; Pierrot-Deseilligny et al. 2003.) Second, they also support the model of two parallel pathways in spatial working memory tasks, operating over different time scales. Third, they indicate that people with PD are able to utilise the second, long delay pathway to achieve normal levels of performance. This indicates that spatial working memory deficits in PD are not global and can be most problematic in tasks requiring memory durations of only a few seconds.

An alternative to the dual pathway model could also explain our findings. In subjects with PD, there might have been rapid degradation in a putative internal spatial target position signal following target offset. For control subjects, this process of decay in the memory trace may simply have taken longer. An analogous argument could also be applied to the TMS studies of Nyffeler et al. (2004). Further experiments would be required to decide between the alternative explanations.

Nyffeler et al. (2004) did find that long delay memory-guided saccade accuracy was impaired by TMS although not to the same extent as were short delay memory-guided saccades. This might be because of the PHC still relying on the DLPFC for some input (that is, both pathways contribute to the PHC). We found that impairment due to PD did not affect long-delay memory-guided saccade accuracy significantly. This might be because of the gradual neuro-degeneration in PD. In contrast to the instantaneous impairment due to TMS, the long time course of PD might enable the parallel pathway to adaptively compensate for the deterioration in the serial pathway, preserving the accuracy of long delay memory-guided saccades.

Unlike Nyffeler et al., we also measured the PEA of the final eye position, as the size of the primary saccade is not a direct measure of spatial memory per se. That is, a subject may know precisely where a target is yet be unable to foveate it on the first attempt because of problems with motor processes rather than with memory. Several corrective saccades might be required to reach a stable final eye position, which should then correspond to the subject's actual memory for the spatial location of the target. In PD, abnormality in the accuracy of the primary memory-guided saccade has been found consistently. Final eye position, meanwhile, can often be normal (Hodgson et al. 1999), leading to suggestions that it is not the spatial memory signal itself that is disrupted in PD, but its transformation into a motor command (Hodgson et al. 1999; Ketcham et al. 2003). The pattern of response seen in the PEA of the primary saccade would not, therefore, necessarily also be seen in the PEA of final eye position. The female subjects, however, did show the pattern of converging performance between the groups in the long delay condition (Fig. 3). The male subjects, meanwhile, actually showed a divergence in performance (note that both the control and the PD males acted differently from their corresponding female groups). It should be noted that there were no differences in mean age or UPDRS scores between males and females in the study.

The sex of subjects is seldom included explicitly as an independent variable in the oculomotor literature. This, however, probably reflects a shortcoming in the standard of practice within the field rather than the lack of any sex differences. In a range of non-oculomotor spatial working memory tasks, females show superior performance to males, attributed to differences in the development and operation of the prefrontal cortex between the sexes (Duff and Hampson 2001). It is important, therefore, to consider sex as a factor in all studies investigating spatial working memory. The significance of this factor is amplified when studying elderly subjects and those with Parkinson's disease, because the sex of a subject interacts with both of those processes. Coffey et al. (1998), for example, showed that there are sex differences in the degree of brain atrophy due to aging. Males had greater relative decreases than females in a number of regional cerebral volumes, including parietal areas. In PD, meanwhile, a PET study by Kaasinen et al. (2001) showed that fluorodopa uptake was reduced in PD subjects in the basal ganglia but elevated in medial frontal and in dorsolateral prefrontal cortex. In the right DLPFC, however, there was also an interaction between sex and diagnosis: in subjects with PD, women had higher fluorodopa uptake than men, while there was no difference between control men and women.

Our results are consistent with a specific deficit in the accuracy of primary memory-guided saccades in Parkinson's disease due to malfunctioning of the DLPFC. This deficit is reduced after long delay periods, when regions other than the DLPFC make a greater contribution to spatial working memory. The accuracy of final eye position in a memory-guided task, meanwhile, is influenced not only by Parkinson's disease and the delay duration but also by sex.

This study provides the first evidence that the so-called parallel pathway for spatial working memory is unimpaired in PD. In a broader sense, it suggests there may be alternative pathways which compensate for functions that are impaired by PD. The challenge is to identify such alternative pathways and also to determine if they can be exploited therapeutically.

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