

Adaptive modification of saccade amplitude in Parkinson's disease

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Summary

The accuracy of saccades (fast eye movements) is maintained over time and is an adaptive ability usually ascribed to the cerebellum. Adaptation might occur elsewhere in certain tasks, such as in the prefrontal cortex for memory-guided saccades. We hypothesized that adaptation of memory-guided saccades would be impaired in Parkinson's disease, as basal ganglia dysfunction can disrupt the operation of the prefrontal cortex, while adaptation of visually guided saccades would be preserved. Adaptation was induced by consistently yet imperceptibly displacing targets as saccades were made toward them, causing artificial saccadic inaccuracy. Twelve Parkinson's disease subjects (OFF medication) and 12 age-matched controls performed 245 visually- and memory-guided horizontal saccades in separate sessions. An infrared eye tracker detected the saccade, during which the target was displaced by 12.5% of the size of the initial jump, either in the same (centri-

fugal) or the opposite (centripetal) direction. Parkinson's disease subjects made smaller visually guided saccades than did controls [$F(1,20) = 9.10$, $P < 0.01$], yet both groups modified saccade size appropriately. Parkinson's disease memory-guided saccades were also smaller than those of controls [$F(1,19) = 5.93$, $P < 0.05$]. While controls decreased (by 8.6%) or increased (by 4.1%) the size of these saccades appropriately, Parkinson's disease subjects decreased saccade size in response to both centripetal adaptation (by an excessive 18.3%) and centrifugal adaptation (by 3.5%). Parkinson's disease subjects were less able to modify saccadic size appropriately when the movement size was specified in motor memory: a predilection for excessive hypometria was invoked, regardless of adaptation direction. This indicates that, in certain tasks, saccadic adaptation involves structures other than the cerebellum.

Keywords: Parkinson's disease; eye movements; saccades; saccadic adaptation; basal ganglia

Abbreviation: DLPFC = dorsolateral prefrontal cortex

Introduction

Parkinson's disease and saccade control

Parkinson's disease is a progressive motor disorder characterized by resting tremor, rigidity and slow movements of decreased amplitude. The face can become expressionless, the voice quiet, the gait slow and shuffling. Symptoms occur following degeneration of dopaminergic neurones in the substantia nigra pars compacta. This leads to decreased dopamine levels in the striatum and, subsequently, increased firing from the inhibitory basal ganglia output nuclei, including the substantia nigra pars reticulata (Hikosaka *et al.*, 2000). The GABAergic substantia nigra pars reticulata maintains tonic inhibition of the superior colliculus, which is involved in the triggering of saccades in many behavioural situations (Hikosaka and Wurtz, 1983). Basal ganglia

dysfunction should, therefore, cause impairments of saccade execution—although such impairments would not be global as the (monkey) oculomotor basal ganglia circuit has been shown to change its discharge only selectively. Substantia nigra pars reticulata neurones decrease firing rate markedly in response to memory-guided saccades, but only minimally prior to reflexive, visually guided, saccades (Evarts *et al.*, 1984).

There are conflicting results on the nature and extent of the effect of Parkinson's disease on oculomotor control. This may not be surprising given the heterogeneity of the presentation of the disease. In most reports, reflexive saccades in Parkinson's disease were of normal metricity (Gibson and Kennard, 1987; Crawford *et al.*, 1989; Lueck *et al.*, 1990,

1992a, 1992b; Ventre *et al.*, 1992; Vidailhet *et al.*, 1994; Hodgson *et al.*, 1999). These studies generally involved patients with relatively mild disease. However, hypometria of reflexive saccades has been observed—generally when more severely affected patients were examined (Shibasaki *et al.*, 1979; White *et al.*, 1983; Rascol *et al.*, 1989; Nakamura *et al.*, 1991; Rottach *et al.*, 1996). In studies of moderately affected patients, there is a tendency towards hypometricity (Vidailhet *et al.*, 1994). With few exceptions (Shibasaki *et al.*, 1979; Bronstein and Kennard, 1985), the latency of reflexive saccades is normal in Parkinson's disease. Impairment of memory-guided saccades, meanwhile, has been a more consistent finding in the literature (for hypometria, see Lueck *et al.*, 1990, 1992a; for hypometria and multi-stepping, see Hodgson *et al.*, 1999; for hypometria, multi-stepping and increased gain variability, see Crawford *et al.*, 1989). It appears that the execution of saccades is impaired in Parkinson's disease and that it is particularly characterized by hypometria of primary volitional saccades. Hypometria of reflexive saccades has been observed but is a less consistent finding across studies.

Adaptation of saccade amplitude

Saccades are usually described as ballistic or open-loop movements. Due to their short duration, visual feedback cannot be used to alter the characteristics of saccades in-flight. [The inability of control subjects to respond in a closed loop way to the intrasaccadic stimulus shifts used in this study was demonstrated quantitatively by MacAskill *et al.* (2000).] As the size of a saccade is programmed before its initiation, the gain of the eye movement command signal must be adaptable over time in order to take account of aging processes while maintaining the accuracy of the system. Such adaptation has been observed in humans following the sudden onset of an oculomotor paresis, where saccades made by the affected eye were initially hypometric but recovered to normal size over a period of several days (Abel *et al.*, 1978; Optican *et al.*, 1985). Similar adaptive changes have also been observed in monkeys following surgically induced extraocular muscle weakening (Optican and Robinson, 1980).

McLaughlin (1967) developed a technique for inducing adaptation of saccades in a non-invasive fashion. 'Dysmetria' was artificially induced in human eye movements by shifting a visual target intrasaccadically in the direction opposite to that of the saccade. The phenomenon of saccadic suppression of displacement (Bridgeman *et al.*, 1975) can render such intrasaccadic target shifts invisible. Despite the imperceptibility of the second shift, a compensation for the apparent overshoot occurred over a number of trials so that the eyes eventually began to land short of the initial target position and closer to the final, centripetally displaced, target position. The artificial dysmetria seemed to invoke an adaptive process similar to that observed in the lesion studies mentioned above, but over a period of minutes rather than days. Their differing rates of adaptation might suggest that adaptation in

response to visual manipulation is not a good model of adaptation in response to muscular weakening (Optican and Robinson, 1980), yet Scudder and colleagues (Scudder *et al.*, 1998) showed convincingly that the same adaptive process does appear to be elicited in both situations.

The frontal eye field and the superior colliculus have been proposed as candidate areas for control of saccadic adaptation (Frens and van Opstal, 1994), although further investigations discounted the superior colliculus and favoured the cerebellum (Frens and van Opstal, 1997). Optican and Robinson (1980) showed that total cerebellar ablation abolished all adaptive repair of the saccadic system in rhesus monkeys with surgically weakened lateral rectus muscles. Partial ablation revealed that the midline cerebellum (vermis, paravermis and fastigial nuclei) was important in adaptive control of saccadic dysmetria (i.e. the pulse of saccadic innervation), while the flocculus was said to be responsible for adapting the step of innervation (i.e. compensating for post-saccadic drift). These findings have subsequently been confirmed by Optican *et al.* (1986) and Takagi *et al.* (1998). Waespe and Baumgartner (1992) examined saccadic adaptation in two human patients with cerebellar cortical atrophy, who both exhibited a pre-existing hypermetria of saccades. The patients did not exhibit any adaptive changes in saccade gain following 160–200 centripetal trials of the McLaughlin procedure. Recently, Straube *et al.* (2001) also examined visually guided saccade adaptation in people with cerebellar pathology (nine with cerebellar degeneration, five with infarcts and two with congenital malformations). The congenital and infarct groups showed a significant change in saccade amplitude, although this change was also significantly smaller than that achieved by the control group. The performance of the patients with cerebellar degeneration was highly variable but, as a group, they did not exhibit a significant amount of adaptation.

Perhaps the most persuasive evidence implicating the cerebellum comes from recent functional imaging studies of healthy human subjects who performed reflexive saccades to a target that stepped intrasaccadically (Desmurget *et al.*, 1998, 2000). These steps were either of a consistent size and direction leading to adaptation, or of random size and direction, forming a non-adaptation control condition. In the adaptation condition, they found a focal region of regional cerebral blood flow increase in the medioposterior cerebellar cortex which, although medial, was more marked in the cortex ipsilateral to the direction of the adapted saccades. No other areas showed significant activation. Impressively, there was a significant positive correlation between the amount of adaptation shown by a given subject and the degree of increase in regional cerebral blood flow.

It seems indisputable that the cerebellum is involved in the adaptation of saccades in at least some circumstances. It should be noted, however, that most studies of adaptation have examined only reflexive, visually guided saccades. It may be that the cerebellum is not involved in adapting the size of saccades made in other situations. For example, Straube *et al.* (1995) examined a human subject with a

midline cerebellar tumour. They found that this bilateral deep cerebellar nuclei lesion had differential effects on externally and internally triggered saccades. Hypermetria was greater for reflexive saccades to suddenly appearing targets than it was for scanning saccades towards a number of continuously visible targets, implying that the cerebellum was important in maintaining the metricity of the reflexive saccades alone. Kanayama *et al.* (1994) also reported findings from a single patient with a cerebellar angioma in the dorsal vermis and fastigial nuclei area. Reflexive, visual-remembered, vestibular-remembered and cervical-remembered primary saccades were all hypermetric. In the last two conditions only, however, primary saccades were often followed by a post-saccadic centripetal drift rather than by corrective saccades. Kanayama *et al.* (1994) proposed that the cerebellar role in matching the pulse and step of oculomotor innervation may be different for saccades elicited in response to different sources of perceptual information.

The concept that there may be multiple independent systems for the adaptation of saccades in different behavioural tasks was proposed by Deubel (1995a, 1995b, 1999). He noted that immediately following appreciable saccadic gain reductions during an experimental session, subjects' spontaneous eye movements outside the lab were normometric (Deubel, 1999). This suggested that 'ecological' scanning saccades are to some extent neurally independent of the reflexive saccades generally elicited within laboratory settings. This was confirmed experimentally by inducing adaptation in each of three saccadic paradigms and then measuring the extent to which that adaptation transferred to other types of saccades. Adaptive changes transferred only minimally from reflexive or memory-guided saccades to the other saccade types. Adaptation did, however, transfer partially from scanning to reflexive saccades, and more completely from scanning to memory-guided and overlap saccades. These results produced a model wherein there are at least three sites of adaptation (Deubel, 1999). Firstly, the cerebellum can adapt the amplitude of reflexive and express (i.e. very short latency) saccades by modulating the collicular signal to the paramedian pontine reticular formation. More intentional saccades (e.g. scanning saccades made in natural tasks) are generated mainly via a direct projection from the frontal eye field to the paramedian pontine reticular formation, meaning that they are largely independent of any cerebellar adaptive control. Rather, Deubel proposed that they were adapted by the frontal eye field itself. Lastly, memory-guided saccades are likely to be adapted at the dorsolateral prefrontal cortex (DLPFC). This area is not involved in the generation of other saccade types, explaining why memory-guided adaptation does not transfer to saccades made in other tasks.

Adaptation of saccades in Parkinson's disease

As yet, no imaging study has been performed in order to identify directly the location of any centres of adaptive

control which may be involved in non-reflexive saccade tasks. An indirect method of examining the role of non-cerebellar structures in saccadic adaptation is to measure adaptation of different saccade types in people with Parkinson's disease. In general motor activity, the basal ganglia may have a role in adapting to novel situations and adapting motor performance to changed circumstances (Marsden and Obeso, 1994). As Deubel (1999) proposed that the adaptation of memory-guided saccades occurs at the output of DLPFC, it would be of relevance to examine the effect of basal ganglia dysfunction on saccadic adaptation in light of the feedback loops between frontal areas and the basal ganglia (Hikosaka *et al.*, 2000). Due to this extensive feedback, adaptation could become disrupted by impaired basal ganglia function. Therefore, an adaptive deficit in Parkinson's disease would not necessarily imply that the basal ganglia themselves have a role in the normal adaptive process. Simply by being downstream of the actual site of adaptation, impaired basal ganglia functioning could serve to disrupt the adaptive process.

There is, nevertheless, reason to believe that the basal ganglia may be important in adaptation processes in their own right. There is a clear parallel with the enduring saccadic hypometria characteristic of Parkinson's disease and the enduring hypermetria resulting from cerebellar dysfunction. This indicates that both the basal ganglia and the cerebellum are important in adaptively maintaining the accuracy of movements over time. The participation of the basal ganglia in motor-perceptual learning was demonstrated by Brainard and Doupe's (2000) study of the plasticity of birdsong. Birdsong, like human speech, deteriorates following deafness as both forms of communication rely upon continual auditory feedback to maintain their quality and accuracy. A number of zebra finches were deafened by bilateral cochlear removal, while some birds also received a stereotactic lesion to the basal ganglia-forebrain pathway. Birds with cochlear lesions alone showed a deterioration in tonal and temporal characteristics of their song over a period of weeks to months. Birds with both lesions demonstrated no deterioration: their song characteristics changed no more than did control birds with intact hearing. Changes in song were not merely delayed but did not occur for the entire period of follow-up (up to a year). In effect, the deleterious changes that normally follow deafness were prevented by a second insult to the nervous system. Brainard and Doupe concluded that damage to basal ganglia circuits had 'little effect on previously learned behaviour while conspicuously disrupting the capacity to adaptively modify that behaviour' (Brainard and Doupe, 2000, p. 762).

There are significant differences between humans and other primates on tests of saccadic adaptation (Fuchs *et al.*, 1996) and we should therefore place results from song plasticity in finches in their proper perspective. There is, however, evidence from studies of asymptomatic gene carriers of Huntington's disease that the basal ganglia may have a general role in humans in monitoring and correcting

Table 1 Individual and mean characteristics of the Parkinson's disease participants

Sex	Age	H+Y	UPDRS	Duration	Medication
M	70	1.5	23	1 year	benztropine
M	58	2	37	5 years	carbidopa/levodopa, pergolide
M	59	2	37	2.5 years	benztropine, pergolide, amantadine
M	68	2	37	4 years	pergolide
F	64	2.5	34	2 years	carbidopa/levodopa, pergolide
F	61	2.5	38	5 years	benztropine
M	72	2.5	44	8 months	none
F	49	2.5	48	7 years	selegiline, amantadine
M	56	2.5	58	6.5 years	selegiline, bromocriptine, carbidopa/levodopa
M	44	2.5	66	1.5 years	benztropine, selegiline
M	69	3	69	5 years	pergolide
M	63	4	87	10 years	carbidopa/levodopa, benserazide/levodopa
Mean	61	2.5	48.2	4.2 years	

H+Y = Hoehn and Yahr; UPDRS = Unified Parkinson's Disease Rating Scale.

errors in output—a role which may extend across the motor, cognitive and emotional domains (Lawrence, 2000). Marsden and Obeso (1994) proposed that it:

'...may be that the crucial contribution of the basal ganglia to the distributed system controlling movement is to alter routine automatic motor behaviour in response to new novel needs. Loss of their output to premotor regions might not grossly impair routine movement; the remainder of the distributed system could cope adequately in ordinary circumstances. However, loss of this basal ganglia connection might impair motor flexibility and adaptation. One purpose of this paper is to encourage others to seek abnormalities in these subtle areas of motor behaviour in animals or humans with basal ganglia disease.' (p. 878)

This experiment addresses that call by examining adaptation of saccade amplitude in response to artificial dysmetria in people with Parkinson's disease. In particular, we wished to assess the difference in the adaptive response between saccades made to a visual target and those made to a location specified in memory. Because of the tendency to hypometria of saccades in Parkinson's disease, we also wished to examine the extent of saccadic adaptation in both amplitude-increasing and amplitude-decreasing conditions.

Methods

Experimental design

The between-subject variables were group (Parkinson's disease or control) and adaptation direction (centrifugal or centripetal). The within-subject variable was saccade type (reflexive and memory-guided), which was balanced for order (first or second session) across subjects. Three subjects were assigned to each of the eight resulting combinations of factors to yield $n = 24$ (12 Parkinson's disease subjects and 12 controls).

Subjects

Subject consent was obtained according to the Helsinki Declaration. The conduct of the study was approved by the Canterbury Ethics Committee of the New Zealand Ministry of Health.

Parkinson's disease

Fifteen participants with Parkinson's disease were recruited to obtain the 12 required: eye movement recordings of acceptable quality could not be obtained from three participants. In one case, bifocal spectacles attenuated the infrared signal to a level at which the eye movement recorder could not be calibrated accurately. The other two participants could not maintain steady and accurate gaze control throughout the course of a session, due to fatigue in one case and poor vision in the other. Of the 12 subjects from whom useable recordings were obtained, one produced data from only one session, as recording difficulties due to his spectacles resulted in an unacceptable quality of data from the first session (memory-guided centrifugal).

Testing session start times ranged from 7:30 a.m. to 11:00 a.m. All subjects had refrained from taking any anti-parkinsonian medication from at least the evening before testing (a minimum of 12 h OFF medication). A minimum of 6 days separated the first and second session to minimize any transfer of adaptation between tests. 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 using the Mini Mental State Exam (MMSE). The mean MMSE score was 28.6 out of 30 (range 25–30) (<24 is considered outside the normal range; Fuller, 1993). All had visual acuity (with or without correction) no worse than 6/12. Subject characteristics are given in Table 1.

Controls

The control characteristics were similar to those of the Parkinson's disease group. Mean age was 63 years (range 44–73 years), mean MMSE = 28.9 (27–30). All had visual acuity (with or without correction) no worse than 6/12. One subject was excluded due to the poor quality of the eye movement recording and a replacement was recruited. Seven subjects were male and five were female.

Apparatus

Eye movements were recorded using a Skalar IRIS infrared limbus tracker (Delft, The Netherlands) (Reulen *et al.*, 1988) at 200 Hz. A computer-generated stimulus (a red square target subtending 0.75° on a homogeneous background) was projected on to a large screen using a video 1.70 m in front of the seated subject, whose head was restrained by use of a bite bar.

One 486 personal computer (PC Direct, Christchurch, New Zealand) controlled the screen display while another stored the eye movement data, detected saccades in real time and transferred this information back to the first computer for control of the saccade-contingent display changes.

Procedures

Calibration

Calibration was performed prior to each trial block, with the subject alternately fixating three point targets at 15° left, at centre and at 15° right. Signal gain and offset and sensor positions were adjusted in an iterative process until the eye position signal corresponded to the three target values (the IRIS is linear within this range).

Sessions

Each subject performed reflexive (visually guided) or memory-guided saccade tests on different sessions, separated by a week. The order of test types was balanced across subjects.

Reflexive test

Baseline phase. (i) The stimulus appeared between -15° and $+15^\circ$, and remained on for a variable length of time (1000–2000 ms). (ii) The stimulus disappeared and immediately reappeared at a different location (12, 14, 16, 18, 20, 22 or 24° left or right of the previous position) with a simultaneous tone. The subject made a saccade to the new location, which served as the starting point for the next trial.

The baseline phase consisted of one block of 49 trials lasting approximately 80 s.

Adaptation phase (see Fig. 1). As for the baseline phase, but as soon as the saccade to the new target was detected (when

the instantaneous velocity of the eye exceeded $30^\circ/\text{s}$), the target was displaced by a fixed proportion (12.5%) of the size of the initial target shift. This displacement was either in the same direction as the initial shift (centrifugal) or in the opposite direction (centripetal). This direction was constant for a given subject. After a random delay (1000–2000 ms) sufficient to allow the subject to re-fixate on the new stimulus position, the cycle repeated.

The adaptation phase consisted of five consecutive blocks of 49 trials each, separated by a short break that included instrument calibration checking.

Testing phase. The test phase was the same as the baseline phase except that when a subject's saccade towards a new target position was detected, the target was extinguished for 500 ms and then reappeared at the same point. This lack of visual information immediately following the primary saccade considerably slows the recalibration to normal saccadic gain (Deubel, 1999).

Memory-guided test

Baseline phase. (i) The stimulus appeared between -15° and $+15^\circ$. (ii) After 1250 ms, and while the fixation stimulus remained visible, a peripheral target flashed briefly (100 ms duration at 12, 14, 16, 18, 20, 22 or 24° to the left or right of the first stimulus). The subject remained fixated on the first stimulus. (iii) After a variable period of time (500–1500 ms), the first stimulus disappeared with a simultaneous tone. The subject then executed a saccade to the remembered location of the peripheral target. (iv) Immediately the saccade was detected, the peripheral target reappeared and the subject made a corrective saccade to it (if required). This target then served as the fixation stimulus for the next cycle.

The baseline phase consisted of one block of 35 trials lasting ~100 s.

Adaptation phase. (i) See Fig. 1. As in the baseline phase, detection of saccade initiation caused the peripheral target to be displayed. However, the new target position was at a location displaced by 12.5% from its original flashed eccentricity, either in the same direction as the initial displacement (centrifugal) or in the opposite direction (centripetal). This direction was constant for a given subject. (ii) The displaced target position served as the new fixation stimulus for the next trial.

The adaptation phase consisted of seven consecutive blocks of 35 trials each, separated by a short break which included instrument calibration checking.

Testing phase. The test procedure was as for the baseline condition, but with a delay of 500 ms following saccade initiation before the peripheral target reappeared. Once more, this lack of lack of visual information immediately following the primary saccade was intended to slow the recalibration to normal saccadic gain.

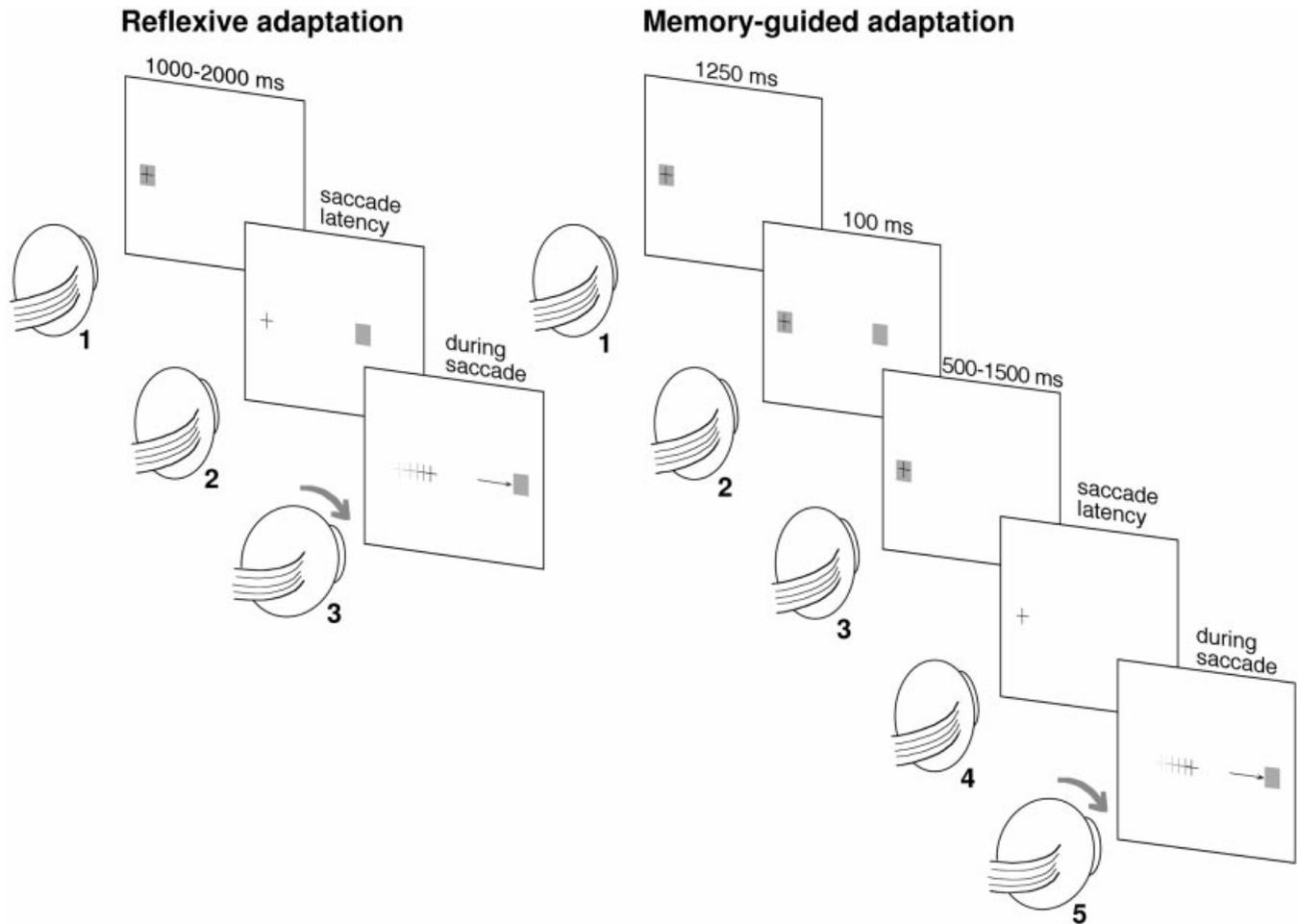


Fig. 1 The procedure during the adaptation phases of the experiment. In each frame, the stimulus is represented by a grey square and the current eye position by a cross. *Reflexive adaptation*: (1) The subject fixates the stimulus. (2) The stimulus is extinguished and simultaneously reappears elsewhere. The subject prepares a saccade to the new stimulus position. (3) While the eyes are saccading to the new location, the stimulus is displaced, in this case centrifugally. This final stimulus location serves as the start point for the next trial. *Memory-guided adaptation*: (1) The subject fixates the stimulus. (2) A peripheral target is flashed briefly while the subject maintains fixation on the first stimulus. (3) The subject maintains fixation for a further variable period. (4) The stimulus is extinguished. The subject prepares a saccade to the remembered location of the flashed target. (5) While the eyes are saccading, the peripheral target reappears, but is displaced centrifugally from its earlier appearance. This final target location serves as the start point (i.e. fixation stimulus) for the next trial.

Measuring saccadic gain

Representative eye movement traces from the three phases of the reflexive condition of the experiment (baseline, adaptation and test) are shown in Fig. 2. The data are from a control subject undergoing centrifugal adaptation (for clarity, only 24° amplitude rightward saccades are shown). These eye movement traces represent the raw data of the experiment from which were measured the saccade gain, latency and other saccade characteristics.

Gain is defined as the ratio of an output (e.g. saccade size) to an input (e.g. stimulus amplitude). In the case of saccades, gain can be quantified in a number of ways (described by Hodgson *et al.*, 1999). We utilized the amplitude of the primary saccade divided by the stimulus amplitude; this is generally known as 'primary saccade gain'. Often memory-

guided saccades are also described using 'final eye position gain', which is the ratio of the distance between the initial and final eye positions and the stimulus amplitude, when the peripheral stimulus has not yet reappeared. In our baseline and adaptation memory tasks, however, the peripheral target reappeared during the saccade and was then continuously visible during the post-saccade fixation. This made the measurement of final eye position gain inappropriate in this study.

Results

Comparison of baseline saccade characteristics

The gain of primary saccades in the baseline phase was compared with a mixed-design ANOVA (analysis of vari-

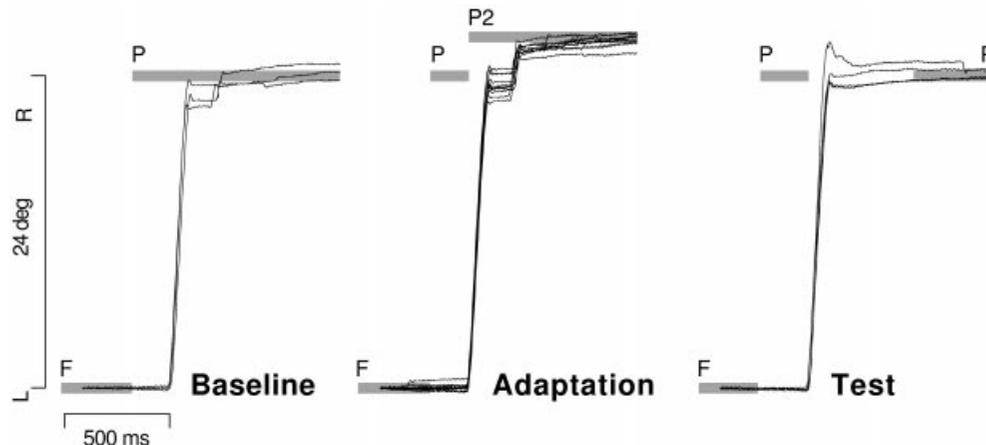


Fig. 2 Eye position recordings of all 24° rightward saccades made by one control subject during the baseline, centrifugal adaptation and test phases of the reflexive condition. Grey lines indicate representative stimulus positions in each phase. (*Baseline phase*) The subject made saccades from the fixation stimulus (F) to a new peripheral target (P). In this case, the primary saccades generally undershot the target, requiring corrective saccades to achieve foveation. (*Adaptation phase*) The subject again made saccades from F to P but, during each saccade, the stimulus was displaced further (to P2). The apparent hypometria of primary saccades was initially increased due to the intrasaccadic centrifugal displacement of the target. (*Test phase*) The resulting adaptation yielded primary saccades that were normometric or even hypermetric with regard to the amplitude of the target shift.

ance). The between-groups variable was Group (Parkinson's disease versus control) and the within-group variable was Saccade Type (reflexive versus memory-guided). Subjects were collapsed across the centrifugal/centripetal conditions as the same baseline test was performed in each condition. Mean gain values are shown in Fig. 3A. There was a significant main effect for Group, with controls having larger saccades than Parkinson's disease subjects [$F(1,21) = 5.09, P < 0.04$]. There was also a significant main effect for Saccade Type, with reflexive saccades being larger than memory-guided ones [$F(1,21) = 12.84, P < 0.002$]. There was no significant interaction effect; i.e. both groups exhibited a similar magnitude difference in gain between the saccade types.

A second mixed-design ANOVA was carried out to compare the saccade latency of both groups in the baseline condition. The variables were again Group and Saccade Type. Mean latencies are shown in Fig. 3B. There was a significant main effect for Saccade Type, with reflexive saccade latencies being shorter than memory-guided ones [$F(1,21) = 68.47, P < 0.0001$]. There was no significant effect of Group or a significant interaction. Although not significant, the pattern of Parkinson's disease subjects having prolonged reflexive latencies yet faster memory-guided latencies is the same as that reported by Crawford *et al.* (1989), which was also non-significant).

Adaptation of saccades

A mixed-design ANOVA was conducted separately for each saccade type in order to analyse differences in saccade gain between the baseline and test phases for each group and adaptation direction. The between-group variables were

Group (Parkinson's disease versus control) and Direction (centripetal versus centrifugal). The within-group variable was Phase (baseline versus test). The mean gain values for both saccade types are shown in Fig. 4.

For reflexive saccades, there was a main effect of Group [$F(1,20) = 9.10, P < 0.01$], with control reflexive saccades larger overall than Parkinson's disease reflexive saccades. There was also a main effect of Direction [$F(1,20) = 9.48, P < 0.01$]: averaged across the baseline and test, saccades in the centrifugal condition were larger than those in the centripetal condition. Lastly, there was an interaction effect between Direction and Phase [$F(1,20) = 24.61, P < 0.0001$]: saccades increased in size between baseline and test in the centrifugal condition, and decreased in size in the centripetal condition. This interaction effect verified that our reflexive adaptation procedures were effective, as subjects adapted the size of their saccades in the same direction as that of the intrasaccadic target shift. There was no interaction between Group and any of the other variables, indicating that there was no significant difference in the extent of adaptation between the Parkinson's disease and control groups (i.e. the corresponding Parkinson's disease and control lines in the reflexive graph of Fig. 4 are nearly parallel).

For memory-guided saccades, there was again a main effect of Group, with control saccades having a larger gain than Parkinson's disease saccades [$F(1,19) = 5.93, P < 0.03$]. A main effect for Direction was not present—as Fig. 4 indicates, there was not a consistent relationship between the direction of adaptation and the resulting change in saccade gain, as Parkinson's disease subjects undergoing centrifugal adaptation inappropriately decreased the size of their saccades. In reflexive adaptation, there was no effect of

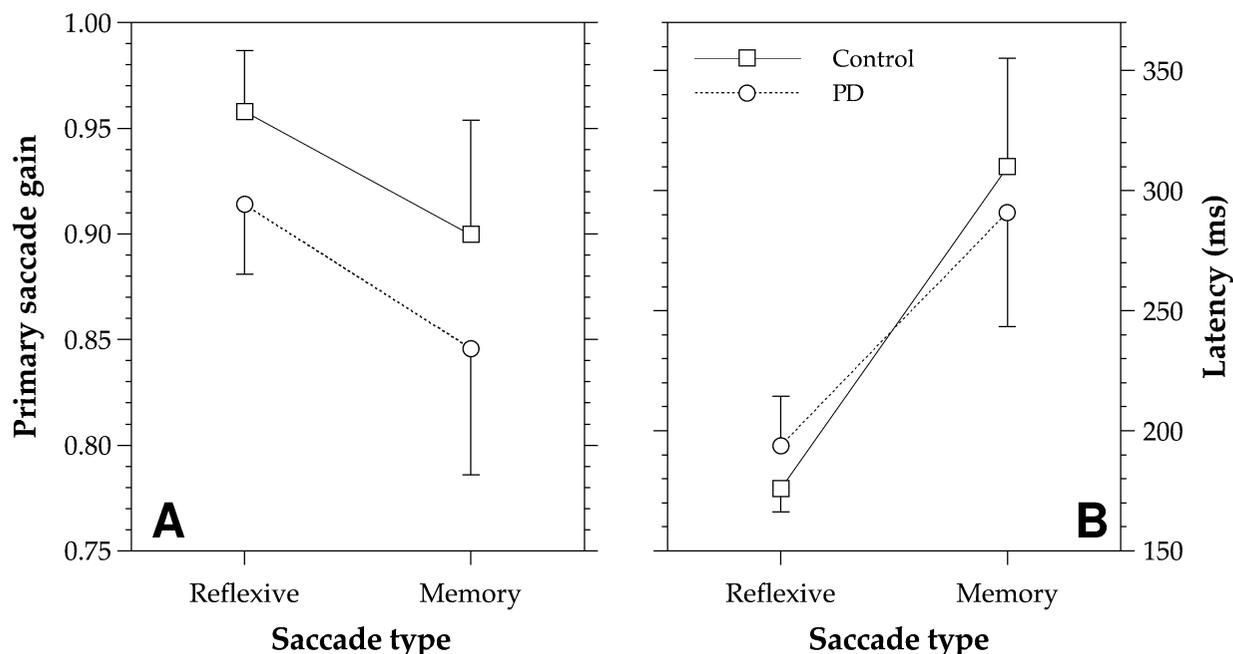


Fig. 3 Mean gains (A) and latencies (B) of baseline saccades of Parkinson's disease subjects (circles) and controls (squares) in the reflexive and memory-guided tasks. Error bars represent 95% confidence intervals. There was a main effect of both subject group and saccade type on gain, while latency was significantly affected by saccade type only.

Phase, as the increased and decreased gains in the respective test phases cancelled out, leaving the mean gain similar to the mean of the baseline conditions. In the memory-guided condition, however, there was a main effect of Phase [$F(1,19) = 7.33, P < 0.02$]; saccades were smaller overall in the test phase than in the baseline phase, again due to the Parkinson's disease subjects performance. Finally, there was an interaction between Phase and Direction [$F(1,19) = 6.98, P < 0.02$]; i.e. collapsed across Group, there was negligible change in gain following centrifugal adaptation, but a substantial gain reduction following centripetal adaptation. Although the control subjects did exhibit a smaller degree of gain change in the centrifugal compared with the centripetal condition, the interaction was largely due to the influence of the Parkinson's disease group.

The intrasaccadic target shift was a constant 12.5% of the stimulus amplitude. To assess how much saccade gain altered in response to this, a relative change in gain was calculated. This was defined as the difference between the gains in the test and baseline phases, divided by the baseline gain. Mean values of this percentage change are given in Table 2.

For both groups, the largest gain change occurred in the centripetal memory-guided adaptation. For the Parkinson's disease subjects, the gain change actually exceeded the size of the adaptation stimulus (12.5%). As previously mentioned, under memory-guided centrifugal adaptation, Parkinson's disease subjects decreased rather than increased the size of their saccades.

Discussion

Parkinson's disease and saccadic adaptation

Although Parkinson's disease subjects had smaller amplitude reflexive saccades overall, their pattern of reflexive adaptation was similar to that of control subjects (Fig. 4). In memory-guided saccades, however, the Parkinson's disease group exhibited a strikingly different pattern of change, characterized by inappropriately increased hypometria regardless of the intended direction of adaptation, i.e. with centrifugal adaptation their memory-guided saccades became more hypometric than at baseline. Centripetal training resulted in double the size of adaptation shown by the control group and, in fact, exceeded the size of the adaptation stimulus by 47%. This is the first report to show that a group of subjects could 'adapt' to an extent that actually exceeded the displacement of the target stimulus. In previous studies employing centripetal reflexive adaptation (Semmlow *et al.*, 1989; Frens and van Opstal, 1994; de Graaf *et al.*, 1995; Deubel, 1999), the degree of adaptation ranged from 40–75% of the size of the target manipulation, while memory-guided saccades adapted by ~75–90% (Deubel, 1999).

Could the impairment of adaptation be attributed to the pre-existing impairment of saccade gain seen at baseline level? We consider this unlikely for several reasons. Firstly, reflexive saccades were also hypometric relative to controls at baseline, yet the adaptation of reflexive saccades was not impaired. Secondly, there is evidence that the size of corrective saccades made to foveate the final target position is not important in driving the adaptation process; the crucial

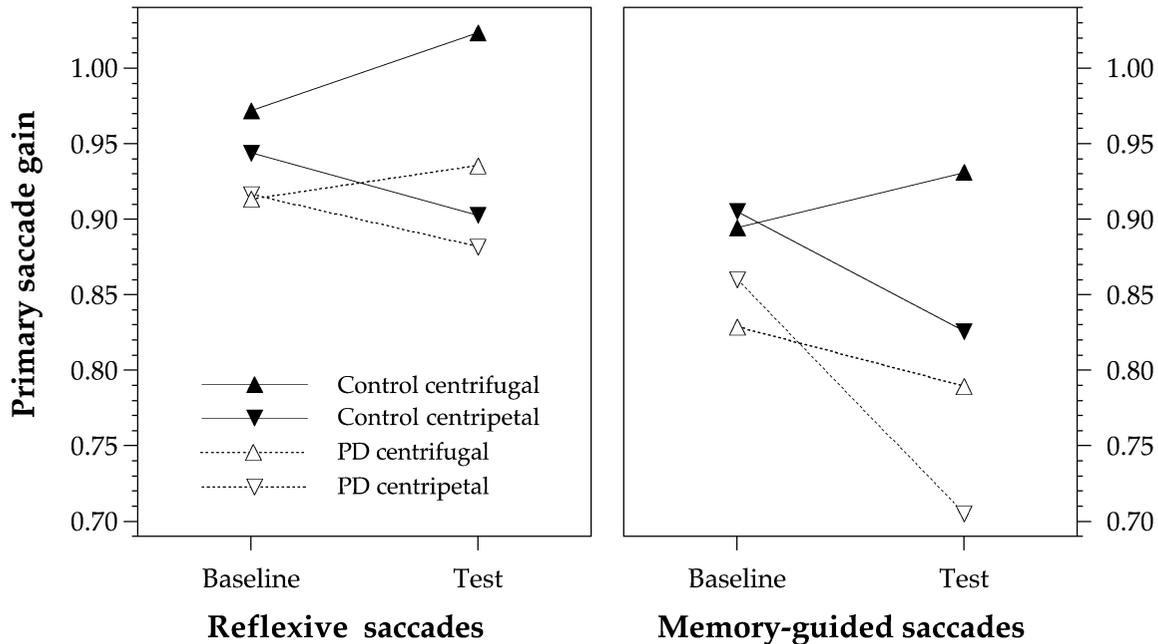


Fig. 4 Gain of primary saccades for Parkinson's disease subjects (unfilled symbols) and for controls (filled symbols) in the baseline and test phases for each adaptation direction (upward-pointing triangles = centrifugal, downward = centripetal). Although Parkinson's disease subjects produced smaller saccades overall when performing reflexive saccades (left panel), adaptation resulted in appropriate changes in saccade gain for both Parkinson's disease and control subjects. However, adaptation of memory-guided saccades (right panel) resulted in directionally appropriate gain changes only for control subjects, while Parkinson's disease subjects showed decreased saccade gain following both centripetal and centrifugal adaptation.

element appears to be the shift in location of the target itself (Wallman and Fuchs, 1998; Bahcall and Kowler, 2000).

The observed impairment of adaptation might have been due to some other deficit in the execution of memory-guided saccades. Such saccades require both a motor output and a spatial memory signal for the location of the target. Is the error in metricity due to an error in this memory signal or is it purely a motor phenomenon? If memory-guided saccades in Parkinson's disease are driven by an erroneous memory signal, this could imply that any observed deficits in motor adaptation were an epiphenomenon of the spatial memory impairment. The low baseline gains of both reflexive and memory-guided saccades in this study indicate that the error in Parkinson's disease saccades was due to the motor response rather than to the memory of the target location. Additional evidence comes from studies using the standard memory-guided paradigm, in which the peripheral target is not re-illuminated immediately the primary saccade is executed, but only some time later. This allows the subject an opportunity to make corrective saccades to a final eye position, which in the absence of a visual target, are informed solely by the memory of the target location. Although memory-guided saccades in Parkinson's disease are hypometric compared with those of controls (often exhibiting a multi-stepping pattern), their final eye position is as accurate as that of controls (Hodgson *et al.*, 1999; Shaunak *et al.*, 1999). This led Hodgson *et al.* (1999) to conclude that, in Parkinson's disease, the memory for target location is correct

and that the impairment of single memory-guided saccades is confined to the motor response.

Could the observed patterns of adaptation be explained by fatigue effects specific to the Parkinson's disease subjects? That is, the long duration and repetitive nature of the task could have led to a decrease in saccade size purely due to fatiguing. As evidence against this, Parkinson's disease subjects in the reflexive task were able to either increase or decrease their saccade size as appropriate. The memory-guided task was more demanding, however, and comprised nine consecutive trial blocks compared with the seven in the reflexive task. By examining the time course of adaptation in the centripetal memory-guided condition, we found that much of the extreme decrease in saccade gain by the Parkinson's disease subjects occurred within the first adaptation block and remained at a low level for the rest of the adaptation phase. This is not compatible with a fatigue process.

Finally, it is possible that the adaptation process increased the complexity of the memory-guided task sufficiently to cause impaired performance of the Parkinson's disease subjects. Nakamura *et al.* (1994) showed that memory-guided saccades that relied upon vestibular information were more impaired in Parkinson's disease than saccades utilising purely visual information. They attributed this to the decreased ability of Parkinson's disease subjects to perform motor tasks when guided by non-visual information. However, it may be that memory-guided performance becomes more degraded in

Table 2 Changes in the gain of saccades between baseline and test phases as a percentage of the baseline size

	Control		Parkinson's disease	
	Centripetal	Centrifugal	Centripetal	Centrifugal
Reflexive	-4.3	5.4	-3.5	2.4
Memory-guided	-8.6	4.1	-18.3	-3.5

Negative values indicate that the saccades became smaller in the test phase.

Parkinson's disease subjects when any further complexity is added to the task [Nakamura *et al.* (1991) used vestibular information while our study imposed an adaptive learning task]. A similar interpretation could be applied to the finding that people with Parkinson's disease are worse at executing a sequence of memory-guided saccades than they are at executing individual ones (Hodgson *et al.*, 1999). The deleterious effect of added complexity upon memory tasks in Parkinson's disease is a possible explanation for our own results. By its very nature, however, saccadic adaptation is an unconscious process and should not impose any additional cognitive load upon subjects. Even at an unconscious level, the adaptive learning process is distributed across many trials. In contrast, each experimental trial was appreciably more complex or difficult to perform in the complex tasks of the aforementioned studies than in their simpler tasks.

It seems likely, therefore, that we have demonstrated a genuine deficit of the adaptive modification of memory-guided saccade size in Parkinson's disease. This is consistent with the concept that the basal ganglia are involved in error correction in various domains (Brainard and Doupe, 2000; Lawrence, 2000; Smith and Shadmehr, 2000). As far as we are aware, the only other study of Parkinson's disease subjects to have systematically manipulated the gain between motor output and the perceptual feedback from that output was that by Fucetola and Smith (1997). Their subjects drew on a digitising tablet, producing visual output on a computer monitor that was either larger or smaller than the size of the movements made on the tablet. Over time, subjects adapted the size of their movements to compensate for the distorted feedback. The amount of learning by Parkinson's disease subjects was, however, less than that of controls. When Fucetola and Smith's baseline and final data are compared, the results appear very similar to the visually guided condition of our experiment (Fig. 4), i.e. Parkinson's disease subjects could adapt appropriately to distorted feedback although not to the same extent as could controls.

Our Parkinson's disease subjects exhibited excessive hypometria following the adaptation of memory-guided saccades. A tendency to increased hypometria in Parkinson's disease following changes in task demands has also been observed in other motor activities such as walking (Morris *et al.*, 1994) and repeated opposition of the thumb and forefinger (Oliveira *et al.*, 1998). There is growing evidence that people with Parkinson's disease have difficulty in allocating their cognitive processing capacity when con-

fronted with competing tasks, leading to impaired motor performance in a dual-task situation (Dalrymple-Alford *et al.*, 1994). Morris *et al.* (1994) and Oliveira *et al.* (1998) showed that this impairment may often be expressed as increased hypometria. In our study, however, the excessive hypometria that was observed did not result from the increased complexity and hence increased attentional load of the memory-guided task. The baseline Parkinson's disease memory-guided saccades were hypometric by the same amount as the simpler reflexive saccades. Rather, it was the adaptation process that led to the excessive hypometria of the memory-guided saccades. This is consistent with the basal ganglia being involved in an adaptive error correction system, which in the human oculomotor system at least, is invoked in internally generated (for example, memory-guided) rather than visually guided activity. When damaged, as in a disease process such as Parkinson's disease, the system is unable to accurately carry out this adaptive error correction and defaults to a strategy of decreasing the size of movement regardless of the size of the motor error signal.

Multiple locus model of saccadic adaptation

Only one other study has demonstrated an impairment of saccadic adaptation in people with lesions outside the cerebellum. Gaymard *et al.* (2001) studied centripetal reflexive adaptation in four patients with focal lesions of the thalamus. Two of these showed cerebellar signs, presumably due to involvement of ventrolateral thalamic nuclei to which the cerebellum projects. Although outside the cerebellum itself, such lesions disrupt the communication between cerebellum and cerebral cortex. Adaptation was disrupted only in the two patients with cerebellar syndrome. Saccades made in a direction ipsilateral to the lesion showed a smaller amplitude decrease than in controls, but saccades in the contralateral direction showed a larger decrease than in controls. In both this study and that of Gaymard *et al.* (2001), deficits in adaptation were more complicated than in humans or animals with purely cerebellar damage, in which the degree of adaptive change is usually decreased and certainly never increased relative to controls (e.g. Straube *et al.*, 2001).

The specificity of adaptation impairment in Parkinson's disease to memory-guided saccades supports the operation of multiple loci for saccadic adaptation as proposed by Deubel

(1999). The basal ganglia could either disrupt the output of the proposed adaptation pathway leading from DLPFC, or 'misinform' it by providing it with an erroneous error signal input. For example, the postparietal cortex is involved in the pathway controlling memory-guided saccades (Pierrot-Deseilligny *et al.*, 1995), and is closely linked to the DLPFC via basal ganglia-thalamo-cortical loops (Hikosaka *et al.*, 2000). Within the postparietal cortex are the parietal eye fields—better known as area LIP (lateral intraparietal) in monkeys. In area LIP are neurones that encode the position of a saccade target in retinocentric coordinates, shifting their receptive field to the saccade target area prior to the onset of the saccade. Furthermore:

'When an eye movement brings the spatial location of a recently flashed stimulus into the receptive field of an LIP neurone, the neurone responds to the memory trace of that stimulus ... Remapping of the memory trace maintains the alignment between the current image on the retina and the stored representation in cortex' (Colby *et al.*, 1995, p. 470)

Areas in the postparietal cortex seem to be well suited to play a role in determining the error in a given saccadic movement. The basal ganglia could conduct such an error signal to the frontal cortical areas responsible for spatial memory (DLPFC) and for the long-term correction of saccadic error.

This conception is speculative. Due to the complex relationships of the basal ganglia with many cortical areas, it is difficult to determine what their role might be in memory-guided adaptive modification. To date functional imaging studies have been conducted only on reflexive adaptation. We hope that functional imaging studies will eventually be conducted on adaptation in different saccadic paradigms. This should resolve any ambiguity in the localization of the area or areas which subserve the adaptive modification of non-reflexive saccades.

In the absence of functional imaging observations, lesion studies and the examination of the transfer of adaptation between saccade types are the best tools available. Support for the multiple locus model has come from one other clinical case, the previously mentioned patient with a cerebellar tumour who exhibited hypermetric visually guided reflexive saccades despite having accurate scanning saccades (Straube *et al.*, 1995). It would be useful to apply our experimental design in patients with such cerebellar lesions. We postulate that results opposite to those of the present study would be obtained: preserved memory-guided adaptation but impaired reflexive adaptation. Deubel (1995*b*) briefly mentions preliminary results that support such a claim.

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