

Saccadic adaptation in neurological disorders

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Abstract: The role of saccadic adaptive processes in recovery from the effects of various neurological disorders, such as myasthenia gravis, extraocular muscle palsies, and age-related macular degeneration, is reviewed. Studies of clinical populations (e.g. cerebellar disease, mild closed head injury, and opsoclonus) in which intrasaccadic displacement of visual targets has been used to stimulate adaptation are also reviewed. Our own data from such a study of 12 subjects with Parkinson's disease are presented, showing that visually guided adaptation is preserved in PD while memory-guided adaptation is impaired. This supports a model in which different brain regions subserve adaptation in different tasks.

Keywords: Saccadic adaptation; Motor learning; Parkinson's disease; Neurological disorder

The need for adaptive tuning of motor output

The ability to make accurate movements is vital for successful functioning. For movements of a duration greater than one reaction time, sensory feedback can be used to monitor the trajectory in-flight and to make any necessary corrections while the movement is ongoing. Movements which are rapid enough to be completed in less than one reaction time cannot be corrected in-flight, and are known as ballistic or open-loop movements because they cannot be controlled during their execution using closed-loop perceptual feedback. To accurately perform ballistic movements, the brain must maintain a precise

model of the efferent commands required to achieve a movement of a given amplitude. As this 'gain' of efference to amplitude will change over time, due to factors such as illness or aging, there must be a compensatory adaptive mechanism by which the brain can amend its gain model over time.

Adaptive control of ocular velocity

Adaptive processes are necessary throughout the nervous system to ensure that appropriate actions are taken in response to perceptual information. Even relatively simple systems such as the vestibular system must be capable of adaptive changes in order to maintain their accuracy:

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"A fairly common example of the brain repairing itself is the recovery from a sudden peripheral vestibular lesion. Spontaneous nystagmus and dizziness result. These symptoms diminish over the next two to three weeks and, in a few months, not a trace of the disorder

remains. . . Some part of the brain must sense it if our responses are no longer appropriate to the stimuli. . . It not only detects dysmetria but sets about at once to correct it. . . Such a process is adaptive because it restores proper function; it is plastic because the changes in behavior are semipermanent and it is a primitive form of learning by the brain." (Robinson, 1975, p. 413)

Such adaptation does not occur solely in response to lesions of the nervous system. The simple act of putting on strong glasses can necessitate a similar correction (Robinson, 1975). The human VOR is so adaptable that in response to prolonged wearing of lateral reversing prisms, even its sign can be changed, resulting in compensatory eye movements in the *same* direction as head movements (Gonshor and Melvill Jones, 1976).

Adaptive control of the ocular position signal

A saccade to a given position requires a 'pulse' of innervation to drive the eyes to the target and an ongoing 'step' of innervation to maintain them there. If the size of the pulse and step are not matched, then the eyes will drift at the end of the saccade until they reach the position dictated by the step signal. A pulse-step mismatch can be simulated by making the visual field drift slowly at the end of a saccade, mimicking the effects of post-saccadic drift (Optican and Miles, 1985). Kapoula et al. (1989) found that their human subjects adapted to this stimulation (after 10,000–20,000 saccades) by developing a zero-latency post-saccadic drift in the same direction as the pattern motion. This presumably indicated that the step signal, indicating intended eye position following a saccade, can be adapted separately from the pulse signal, indicating the amplitude of the saccade.

Generally, however, the pulse and step signals are in agreement (Kommerell et al., 1976), and most studies of adaptation in the saccadic system assume that the phasic and tonic components of the neural saccade signal will change in concert with each other. It is this adaptation of overall saccade amplitude that is the concern of the remainder of this paper. Adaptive control of other eye movements (pursuit, vergence, and torsion) has been discussed recently by Takagi et al. (2001).

Adaptive control of saccade amplitude in central and peripheral disorders

In many motor tasks, we can choose to perform either fast or slow movements. The velocities of saccades, however, are not under conscious control (Bahill et al., 1975), and because they are too brief to be modified in-flight, saccades are always open-loop (unless slowed grossly by disease; Zee et al., 1976; MacAskill et al., 2000). There is, therefore, a unique requirement for the saccadic system to rely completely on open-loop learning processes to maintain its accuracy.

There a number of neurological illnesses which reveal the action of adaptive processes attempting to maintain saccadic metricity. Myasthenia gravis, for example, is an autoimmune disease which attacks the acetylcholine receptor, leading to failed neuromuscular transmission and subsequent muscle weakness. Ocular manifestations of myasthenia gravis include ptosis, diplopia, and hypometria of large saccades (Leigh and Zee, 1999). That adaptive processes can at least partially counteract extraocular muscle weakness is shown by administration of edrophonium, which temporarily improves neuromuscular transmission. Following edrophonium, saccades often become hypermetric, as "the central nervous system has adaptively increased the size of the saccadic pulse in an attempt to overcome the myasthenic weakness. . . If the brain had been standing idly by, edrophonium would merely have caused refixations to become orthometric" (Leigh and Zee, p. 378).

A similar adaptation process was observed in a person subject to the sudden onset of a medial rectus palsy secondary to a partial third nerve palsy (Abel et al., 1978). Saccades made by the affected eye were initially hypometric but recovered to normal size over several days during which the patient was forced to use the affected eye while the good eye was patched. Similar results were found by Optican et al. (1985) in four patients with ocular muscle weakness. As the weak eye returned to normal accuracy, the patched, normal, eye became correspondingly overactive, indicating the presence of a central signal to both eyes (an effect also demonstrated by Kommerell et al., 1976). Optican et al. showed that this overactivity also occurred in pursuit movements: when the weak eye became able to follow a target moving at 15°/s, the patched eye reached speeds of up to 50°/s.

Adaptive changes observed in the normal eye varied as a function of eye position and movement direction, consistent with the way in which the effects of ocular muscle weakness also vary with orbital position and with whether the muscle acts as an agonist or antagonist. The adaptation process cannot, therefore, arise from a simple global parametric change in innervation.

The purpose of a saccade is to direct the fovea to the intended point of fixation, and thus adaptation of saccade size may be required in response to sensory as well as motor pathology. An example is age-related macular degeneration, which is the leading cause of blindness among the elderly in Europe and North America (Cheraskin, 1992). The scotoma formed in central vision usually causes people to adopt a consistent extrafoveal preferred retinal location (PRL) to fixate objects (Whittaker and Cummings, 1988; White and Bedell, 1990). Although each person consistently uses a single PRL, its location depends upon the shape and size of their scotoma (Timberlake et al., 1986). There is a tendency to form a PRL in the lower visual field (i.e. retinally superior to the fovea), perhaps because most important information for primates is gained from the lower visual field (Bertera and Timberlake, 1988; Heinen and Skavenski, 1992). Following changes in preferred fixation locus, saccades should also adapt so as to direct the PRL rather than the fovea to the target. In order to control for the inherent variability among human subjects with naturally occurring maculopathy, Heinen and Skavenski (1992) examined saccades and fixation in monkeys following precisely administered bilateral foveal lesions induced by laser photocoagulation. They found that adaptation in the fixation system occurred almost overnight, while adaptation of saccades was slower and incomplete. The different time constants suggested that their mechanisms were also different, and different from mechanisms underlying saccadic adaptation in other situations.

Fortunately, another technique exists so that scotomata can be induced experimentally in a non-invasive fashion. Bertera and Timberlake (1988) used an eyetracker to project an artificial, retinally stabilised 'scotoma' upon the fovea of healthy human subjects. They found that a PRL developed, visually below the scotoma, within a few minutes in all

subjects. Unfortunately this work has not been reported in full, but the technique is of particular value as adaptation findings in monkeys do not always generalise to humans, an observation to which we shall return shortly. Hence Heinen and Skavenski's claim that the saccadic adaptation seen in response to macular degeneration is different to other forms of saccadic adaptation remains to be confirmed by further human studies.

A number of neurological conditions, sensory and motor, stimulate the adaptive repair mechanism of the saccadic system. In the case of myasthenia gravis, this adaptive capacity may not always be sufficient to compensate for the degree of impairment. Other disorders, such as Parkinson's disease and cerebellar disease, also result in enduring saccadic dysmetria (see Fig. 1). It is not clear whether this is again due to impairments that are too large to be completely compensated for by adaptation, or if the adaptive process itself is impaired, or even if stable dysmetria may be independent of standard adaptive processes (Harris, 1995; Mezey, 2000). To resolve these issues in such chronic disorders, it is necessary to measure the responses of these patients using an experimental technique designed to stimulate observable short-term adaptation.

The laboratory-induced model of saccadic adaptation

McLaughlin (1967) pioneered a visual manipulation which stimulates the adaptive modification of saccade size. As subjects made a saccade to a target, the target was shifted back slightly in the opposite direction. Such intrasaccadic movements are not perceived consciously (Dodge, 1900), provided that they are not too large (Bridgeman et al., 1975; McConkie and Currie, 1996; MacAskill et al., 1999). Despite the imperceptibility of the second movement, the motor system responds appropriately, executing a corrective saccade to bring the fovea to the new target location. Over a number of trials, saccadic amplitude alters, reducing or even eliminating the need for a corrective saccade. If the intrasaccadic step is of a consistent size and direction, then the eyes are eventually directed toward the final target position rather than to where the target was when the saccade was initiated. Adaptation is stimulated

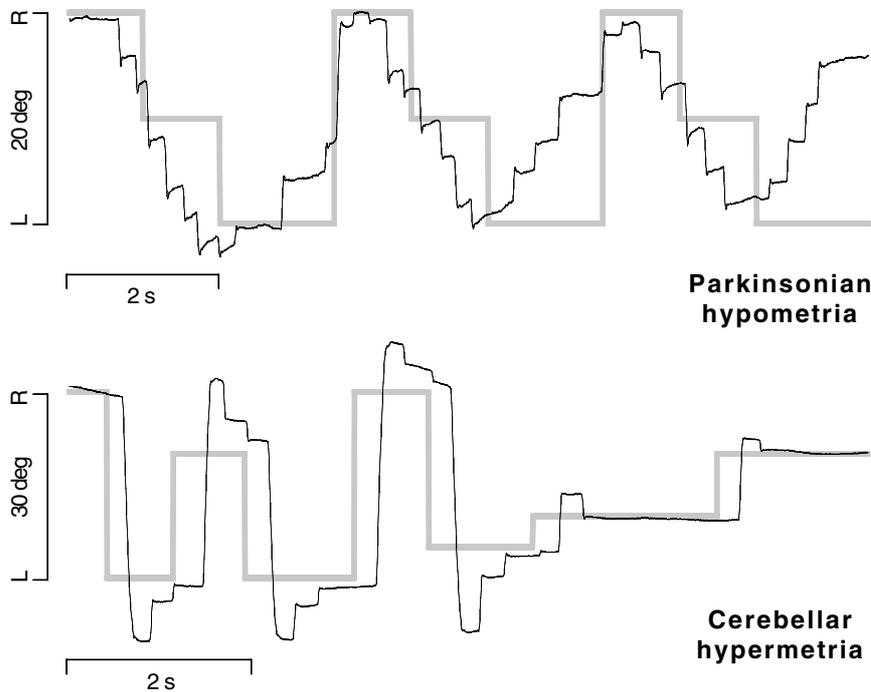


Fig. 1. Example saccades made by people with enduring saccadic dysmetria in response to moving targets (grey lines). (Top) Grossly hypometric saccades made by a middle-aged man with PD while following a repetitive three-step target sequence (due to the target predictability, all initial saccades precede their corresponding target steps). (Bottom) Hypermetric saccades made by a teenage girl some years after resection of a cerebellar tumour while following a randomly stepping target.

by visual error at the end of a saccade rather than by the occurrence of corrective saccades, and results in changed motor output rather than a perceptual remapping (Wallman and Fuchs, 1998).

Adaptation in response to intrasaccadic target steps occurs rapidly (within several hundred saccades for humans and within fifteen hundred for monkeys; Fuchs et al., 1996). 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). Scudder et al. (1998), however, showed that the two phenomena do access the same adaptive process. As adaptation occurs independently for different saccade amplitudes (Deubel, 1987; Frens and van Opstal, 1994; Albano, 1996), Scudder et al. reasoned that adaptation to eye muscle weakening should take longer as all saccade amplitudes are affected and need to be adjusted, in a variety of behavioural circumstances. The laboratory-induced technique merely appears to produce adapta-

tion faster, as subjects are exposed only to the limited subset of saccade amplitudes and tasks decided upon by the investigator (see also Miller et al., 1981). Scudder et al. validated their hypothesis in monkeys which either underwent surgical weakening of the extraocular muscles or experienced McLaughlin's illusory dysmetria. The number of visual targets was equated in each paradigm and the rates of adaptation were indeed found to be equal. The non-parametric nature of saccadic adaptation was further confirmed by varying the size of the intrasaccadic displacement as a function of orbital position, mimicking the way in which the effects of a weakened muscle are not constant in different gaze positions. Once more the groups performed similarly, again indicating that adaptation in response to visual manipulation relies upon the same neural processes as that in response to weakness of the extraocular muscles.

Although the high speed of laboratory-induced saccadic adaptation should not generate suspicion that subjects are employing a conscious strategy

rather than a natural adaptive capacity, when exceptionally fast adaptive changes occur (for example, within several trials in Erkelens and Hulleman, 1993), it seems likely that subjects are aware of the intrasaccadic displacements. Generally, however, saccadic adaptation does not seem to be a conscious process. In an experiment where the target was displaced intrasaccadically when it appeared as a green cross but not when it appeared as a red circle, Deubel (1995a) showed that even for subjects made aware of this distinction, all saccades were adapted, regardless of the target to which they were directed. Fuchs et al. (1996) studied the adaptation of saccadic gain in seven macaques. They argued that the adaptation seen was evidence of a “real neuronal reorganisation” (p. 2523) and not a cognitive strategy, as (1) the adaptation had a gradual time course (800–1200 saccades), (2) readaptation to normal gain had a similar time course to the initial adaptation (see also Straube et al., 1997), and (3) adaptation persisted after 20 h in a darkened room.

The primate model of human saccadic adaptation

It should be noted, however, that observations in monkeys can differ from human findings. The time course for human adaptation is considerably shorter (Deubel, 1995a; Fuchs et al., 1996), perhaps due to stronger cortical involvement in saccade generation in humans than in macaques (Frens and van Opstal, 1997). It has also been argued that the difference is due to monkeys being exposed to a greater number of targets (Desmurget et al., 2000), which, as we have seen, can slow the adaptation process.

Other differences between adaptation in humans and monkeys are that recalibration in humans can take longer than the initial adaptation (Deubel, 1995a), and that adaptation of saccades in monkeys transfers to head movements (Phillips et al., 1997) whereas in humans it does not (Krölller et al., 1996). Most significant, however, are the differences in gain transfer between saccade types. Following adaptation of saccades in one behavioural task, the alteration in saccade size in another task can be measured. Fuchs et al. (1996) demonstrated substantial adaptation transfer between reflexive and memory-guided saccades in monkeys (never less than 69%). In humans little or no transfer occurs: only 2.4% of

the change in size of reflexive saccades transferred to memory-guided saccades, with only 17% transfer in the opposite direction (Deubel, 1999). Fuchs et al. were “forced to conclude that humans and monkeys simply employ different mechanisms of adaptation to solve apparently identical problems of saccadic gain control” (p. 2534).

On the basis of saccade dynamics, Frens and van Opstal (1994) speculated that different neural pathways underlie adaptation in humans and monkeys. Adapted saccades in the rhesus monkey can have decreased peak velocities relative to same-sized normal saccades (Fitzgibbon et al., 1985; Frens and van Opstal, 1997; Straube et al., 1997), while Frens and van Opstal’s (1994) data showed that saccade dynamics are not altered in humans. There is conflicting evidence on this point, however, as two other studies (Abrams et al., 1992; Straube and Deubel, 1995) have shown that human saccade dynamics are altered by the adaptation process.

In summary, although there is debate on some findings, the non-human primate model of saccadic adaptation currently has significant limitations in approximating human processes. There is, therefore, a value in examining adaptation in human populations with neurological disorders, as lesion studies in non-human primates may not generalise to humans. We will discuss human clinical studies after first discussing some of the brain regions thought to be important in the adaptive control of saccades.

The cerebellum and adaptation

There is a great deal of evidence from the experimental literature which implicates the cerebellum in the adaptive control of saccades. Optican and Robinson (1980) studied adaptation following surgical weakening of the lateral recti of rhesus monkeys, some of which also underwent partial or total cerebellectomies. Total ablation abolished adaptation. 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). The flocculus, meanwhile, was said to be responsible for adapting the step of innervation (i.e. compensating for post-saccadic drift). Takagi et al. (1998) also showed that lesions of the dorsal cerebellar vermis in mon-

keys resulted in an inability to adapt the size of the saccadic pulse, resulting in pulse-size dysmetria. Optican et al. (1986) confirmed that floccular lesions abolished adaptive control of post-saccadic ocular drift in primates, resulting in enduring pulse-step mismatch dysmetria.

Desmurget et al. (1998, 2000) conducted PET studies of healthy human subjects performing reflexive saccades with intrasaccadic steps. 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 rCBF increase in the medioposterior cerebellar cortex, more marked on the side ipsilateral to the direction of the adapted saccades. No significant activation occurred in the deep cerebellar nuclei, the frontal eye field or the superior colliculus. Impressively, there was a correlation between increased activation and the amount of adaptation.

Straube and Deubel (1995) claimed that the dynamics of human saccades are altered when they undergo adaptation, which implicates the cerebellum in the adaptive process as its caudal fastigial nucleus (cFN) has a role in the acceleration and deceleration of visually guided saccades (as described by Robinson, 1995). Although Desmurget et al.'s (1998) data did not show the direct involvement of the cFN in adaptation, it is possible that cerebellar disease could impair adaptation by disrupting the input to the cFN from vermal oculomotor cells.

It seems indisputable that the cerebellum is involved in the adaptation of saccades in some way. It should be noted, however, that almost all experimental work on adaptation has examined only reflexive visually guided saccades. It may be that the cerebellum is less involved in adapting the size of saccades made in other situations.

Saccadic adaptation in neurologically impaired humans

Saccadic adaptation probably exists to counteract gradual changes in muscle efficiency as a result of aging, and possibly also to aid in the initial acquisition of accurate saccades in infancy (the saccades of young babies are grossly hypometric, Aslin and Salapatek, 1975). As we have seen, this latent adap-

tive capacity can also aid in counteracting the effects of neurological illness, although this is unlikely to be the teleological reason for its existence. Studying saccadic adaptation in clinical populations is of value because of the insight it yields both into the underlying disorder and into the adaptation process itself. A number of such studies are reviewed below.

Cerebellar disease

Given the importance of the cerebellum as revealed by experimental studies, investigations of saccadic adaptation in people with cerebellar disorders have been surprisingly limited until very recently.

Waespe and Baumgartner (1992) examined adaptation of visually guided reflexive saccades in two patients with cerebellar cortical atrophy and an enduring saccadic hypermetria. They did not exhibit any adaptive changes in saccade gain following 160–200 centripetal double-step reflexive trials.

Straube et al. (1995) examined a human subject with a midline cerebellar tumour and showed that this bilateral deep cerebellar nuclei lesion had differential effects upon externally and internally triggered saccades: hypermetria was greater for reflexive saccades to suddenly appearing targets than it was for 'scanning' saccades to continuously visible targets. It appears that damage to the cerebellum impaired the maintenance of the metricity of the reflexive saccades only.

The most comprehensive study of saccadic adaptation in people with cerebellar disease was conducted recently by Straube et al. (2001). They examined nine patients with cerebellar degeneration, five with cerebellar infarcts, and two with congenital malformations. The degeneration group showed no significant adaptation of reflexive saccades, although individual performance within this group was highly variable. Both the infarct and congenital groups exhibited a significant adaptive gain change although the magnitude of this change was still significantly less than that of the control group. Primary saccade accuracy in cerebellar conditions is extremely variable from trial to trial, and it is possible that it is this variability, rather than the cerebellar damage itself, which impairs the adaptive process. Straube et al. found, however, that there was no correlation between the variability of saccade gain at baseline

and the subsequent degree of adaptive gain change. It was concluded that cerebellar lesions impair the adaptation of saccades, although there is large variation between subjects due to differing lesion extent and location.

Extracerebellar lesions disrupting cerebellar pathways

Waespe and Baumgartner (1992) also examined 13 patients with ischaemia in the lateral medulla or the cerebellar territory of the posterior inferior cerebellar artery (although the former had a lesion outside the cerebellum, it interrupted olivo-cerebellar pathways). Unlike their two patients with cerebellar atrophy, some adaptation occurred but was less than that achieved by controls. The lesions were unilateral and a lateralised effect was seen in some subjects: adaptation was decreased only for ipsilaterally directed saccades. Many of the patients showed an enduring dysmetria of saccades at baseline, which was also lateralised (ipsilaterally directed saccades hypermetric, contralateral saccades hypometric).

Although the cerebellum is clearly important for maintaining adaptive control of visually guided saccades, it is likely that cortical areas may also be involved in adaptation, particularly in other, more volitional, saccade types (Deubel, 1995b, 1999). Gaymard et al. (2001) reasoned that this would require cerebellar communication with cortical oculomotor areas via the thalamus and in particular the ventrolateral thalamic nuclei. They examined four patients with focal lesions of the thalamus, two with cerebellar signs and two without (presumably involving non-cerebellar areas of the thalamus). All subjects underwent a gain-shortening paradigm of reflexive visually guided saccades. The non-cerebellar subjects reduced gain normally. The cerebellar subjects reduced the gain of their saccades but in an atypical fashion: saccades made in a direction ipsilateral to the lesion decreased in gain significantly less than did control saccades, while those in the contralateral direction showed a significantly *larger* decrease in gain than did control saccades. Once again implicating the ipsilateral cerebellum in adaptive saccade control, this study was also notable for demonstrating the importance of cerebello-thalamo-cortical communication.

Mild closed head injury

Heitger et al. (2001), in the largest study to date involving saccadic adaptation, examined 30 people with mild closed head injury (CHI) and 30 matched controls. Neuropsychological tests revealed impairments of explicit cognitive learning in the CHI group. The CHI subjects also showed deficits on a range of anti-saccade and memory-guided saccade measures, and produced a smaller number of self-paced saccades in a given time period. All of those impairments are consistent with the primarily frontal lobe damage caused by mild CHI. The extent and rate of reflexive saccade adaptation, however, did not differ between the groups. That saccadic adaptation following CHI is normal is consistent with studies that have shown deficits on other, frontal-reliant, cognitive learning tasks whereas implicit learning was preserved (McDowall and Martin, 1996; Shum et al., 1996).

Interestingly, approximately a third of both the control and CHI subjects did not show an exponential decrease in saccade gain during the adaptation phase but instead exhibited a linear decrease. Straube et al. (2001) reported a similar phenomenon in an unspecified number of their subjects. It appears that the classic exponential learning 'curve' of saccadic adaptation (Straube et al., 1997) is not a universal feature, in humans at least. We speculate that this may be due to the large inter-trial variability in gain frequently seen in subjects, which acts to mask the shape of any underlying function. Additionally, breaking the long adaptation phase into several discrete blocks of trials can introduce discontinuities into the data due to the small amount of 'unlearning' which can occur in these brief periods (unpublished observations).

Post-opsoclonus syndrome

Mezey (2000) studied adaptation of reflexive saccades in seven children with a history of opsoclonus. Opsoclonus consists of high frequency saccadic oscillations with vertical, horizontal and torsional components, and is consequently also known as saccomania or dancing eye syndrome (Leigh and Zee, 1999). The opsoclonus had resolved in Mezey's seven subjects although five had ongoing

neurological deficits, including two with abnormal saccadic hypermetria and two with hypometria. Six of the seven children showed a saccadic gain decrease within the normal range, including the two with pre-existing hypermetria. The only one to not adapt saccade size was a child with a gross pre-existing hypometria (mean baseline gain = 0.63). Mezey concluded that, as three of the four subjects with pre-existing baseline dysmetria had a preserved ability to alter saccadic gain, the absolute baseline gain level may be at least partially independent of the mechanism to change that level. It has been proposed that the saccadic system operates to minimise the flight time taken to reach a target (Harris, 1995). Consequently, the saccadic system will tend to undershoot targets rather than overshoot. For subjects with a large variability in saccade amplitude, the theory predicts that their mean gain will tend to be more hypometric than normal. Such a strategy ensures that the majority of their corrective saccades are in the same direction as the primary saccade, hence minimising total flight time. Therefore the presence of abnormally hypometric saccades does not necessarily imply the impairment of adaptive control mechanisms: abnormally sized primary saccades may in fact indicate a preserved capacity to optimise saccadic gain in response to high variability of gain. This has important implications for the study reported below, in which we examined subjects with Parkinson's disease who had a pre-existing saccadic hypometria.

Saccadic adaptation in Parkinson's disease

As was mentioned in the discussion of Gaymard et al.'s (2001) thalamic lesion study, cortical regions may play a significant role in adjusting the accuracy of saccadic movements. The preponderance of evidence indicating the importance of the cerebellum may be due to most experiments measuring adaptation only in response to reflexive, visually guided saccades, in which the cerebellum is particularly involved. Exceptions have been Deubel (1995b, 1999) and Erkelens and Hulleman (1993), who found that reflexive saccades and other, more volitional, saccade tasks appear to be adapted somewhat independently. That is, adapting the size of saccades in one behavioural task does not necessarily transfer to the

size of saccades performed immediately afterward in another context. Deubel (1999) factorially assessed the degree of transfer of adaptation between reflexive, scanning, overlap, and memory-guided saccades, leading to a multiple-locus model in which at least three brain regions are involved in controlling the accuracy of saccades. As might be expected, reflexive visual saccades were said to be adapted by the cerebellum, but the adaptation of more volitional saccades was said to involve the frontal cortex (in the region of the dorsolateral prefrontal cortex for memory-guided saccades and the region of the frontal eye fields for scanning and overlap saccades).

In this context, we decided it would be pertinent to measure the adaptation of reflexive and memory-guided saccades in Parkinson's disease (PD). PD is a disorder of basal ganglia function (see Lang and Lozano, 1998a,b for a broad introduction), particularly characterised by motor slowing, rigidity, tremor, and hypometria. Oculomotor deficits have been thoroughly investigated and although results are often in conflict due to the variability of symptom severity in different samples, memory-guided saccades are usually impaired (Hodgson et al., 1999). Simple reflexive saccades tend to be impaired only in more severely affected subjects (MacAskill et al., 2002).

PD is particularly relevant to the study of saccadic adaptation as:

(1) The basal ganglia are involved in extensive feedback loops with cortical, and especially frontal cortical, areas (Alexander et al., 1990). Hence it might be expected that disordered basal ganglia operation might impair the proposed adaptation pathways (Deubel, 1999) between frontal cortical adaptation zones and brainstem and superior colliculus oculomotor centres. Such an impairment should be more evident in memory-guided rather than reflexive saccades as the latter should rely more upon the cerebellum for adaptation.

(2) People with PD show an enduring saccadic hypometria, particularly of memory-guided saccades (Crawford et al., 1989; Lueck et al., 1990). We therefore wished to assess any asymmetry in the degree of gain-increasing and gain-decreasing adaptation.

(3) There is evidence that the basal ganglia themselves may be important in feedback and error correction in a variety of domains (Brainard and Doupe, 2000; Lawrence, 2000).

Method

Subjects

Nine men and three women with idiopathic PD were tested off-medication. Symptom severity was mild to moderate as assessed by Hoehn and Yahr staging and the Unified Parkinson's Disease Rating Scale. Mean age was 61 (range 44–72). A control group of seven male and five female subjects was recruited, with a mean age of 63 (range 44–73).

Apparatus

Eye movements were recorded using a Skalar IRIS infrared limbus tracker (Reulen et al., 1988) at 200 Hz. A computer-generated stimulus (a red square target subtending 0.75° on a homogeneous background) was video front-projected (refresh rate 70 Hz) on to a large screen 1.70 m in front of the seated subject, whose head was restrained by use of a bite bar or chin rest.

Procedures

Sessions

Each subject performed both the reflexive (visually guided) and memory-guided saccade tests in differ-

ent sessions, separated by a week. Session order was balanced across subjects.

Reflexive test

Representative recordings illustrating the three phases (baseline, adaptation, and test) in the reflexive condition are shown in Fig. 2.

Baseline phase. Subjects followed a target which made steps of 12, 14, 16, 18, 20, 22, or 24 degrees left or right from its previous position. This phase consisted of 1 test of 49 trials, lasting approximately 80 s.

Adaptation phase. As for the baseline phase but as soon as the saccade to the new target position was detected (by a real-time eye velocity threshold of $30^\circ/s$), the target was displaced by a fixed proportion (12.5%) of the distance between the current and previous target positions. This displacement was either in the same direction as the initial displacement (centrifugal) or in the opposite direction (centripetal), this direction being constant for a given subject. After a random delay (1000–2000 ms), sufficient to allow the subject to re-fixate on the new target position, the cycle repeated. This phase consisted of 245 trials, split into 5 consecutive tests of 49 trials each.

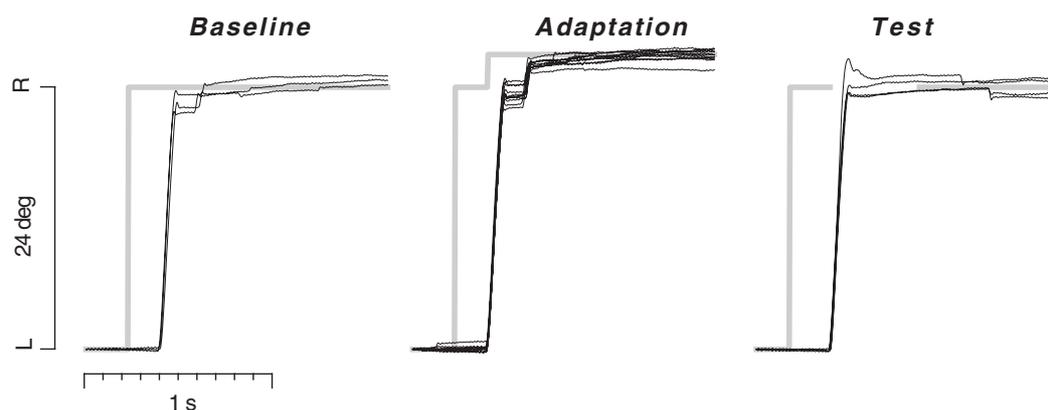


Fig. 2. Recordings of all 24° rightward saccades made by one control subject during each phase (baseline, centrifugal adaptation, and test) in the reflexive condition. Grey lines indicate representative target displacements. In the baseline phase, the primary saccades undershot the target location, requiring corrective saccades to achieve foveation. The adaptation phase increased the apparent hypometria of primary saccades because of the intrasaccadic centrifugal target displacement. The resulting adaptation yielded test-phase primary saccades that were normometric or even hypermetric (the increased corrective saccade latency in this phase was due to the presence of the 500 ms period in which the target was blanked).

Test phase. As for 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 place. This lack of visual information immediately following the primary saccade slows the recalibration to normal saccadic gain considerably (Deubel, 1999).

Memory-guided test

Baseline phase. After a fixation stimulus had been displayed for 1250 ms, a peripheral target flashed briefly (400 ms duration at 12, 14, 16, 18, 20, 22, or 24 degrees to the left or right of the fixation target). The subject remained fixated on the original target. After a variable period (500–1500 ms) the fixation target disappeared, with a simultaneous tone. The subject then executed a saccade to the remembered location of the peripheral target. 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 target for the next cycle. This phase consisted of 1 test of 35 trials lasting approximately 100 s.

Adaptation phase. As in the baseline phase, detection of a saccade caused the peripheral target to be re-displayed. However, the new target position was at a location displaced by 12.5% from its original flashed eccentricity, either in a centrifugal or centripetal direction (constant for a given subject). This phase consisted of 245 trials, split into 7 consecutive tests of 35 trials each.

Test phase. As for the baseline condition but with a delay of 500 ms following saccade initiation before the peripheral target reappeared, again to slow the recalibration to normal saccadic gain.

Results

Comparison of baseline saccade gain

Saccade gain was defined as the amplitude of the primary saccade divided by the stimulus amplitude, generally known as primary saccade gain. The gains of primary saccades in the baseline phase were compared by a mixed-design ANOVA. Con-

trols made larger primary saccades than did PD subjects ($F(1,21) = 5.09$, $p < 0.04$), and, overall, reflexive saccades were larger than memory-guided ones ($F(1,21) = 12.84$, $p < 0.002$). There was no significant interaction effect; that is, both groups exhibited a similar magnitude difference in gain between the saccade types.

Adaptation of saccades

A mixed-design ANOVA was conducted separately for each saccade type to analyse differences in saccade gain between the baseline and test phases. The between-group variables were Group (PD vs control) and Direction (centripetal vs centrifugal) while the within-group variable was Phase (baseline vs test). The mean gain values are shown in Fig. 3.

Reflexive saccades

There was a main effect of Group ($F(1,20) = 9.10$, $p < 0.01$), with control saccades larger overall than PD saccades. There was also a main effect for 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 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. That is, subjects adapted the size of their saccades in the same direction as that of the intrasaccadic step. There was no interaction between Group and any of the other variables, indicating that there was no difference in the extent of adaptation between the PD and control groups.

Memory-guided saccades

There was again a main effect of Group, with control saccades having a larger gain overall than PD saccades ($F(1,19) = 5.93$, $p < 0.03$). A main effect for Direction was not present: as Fig. 3 indicates, due to the PD performance, there was not a consistent relationship between the direction of adaptation and the resulting change in saccade gain. 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

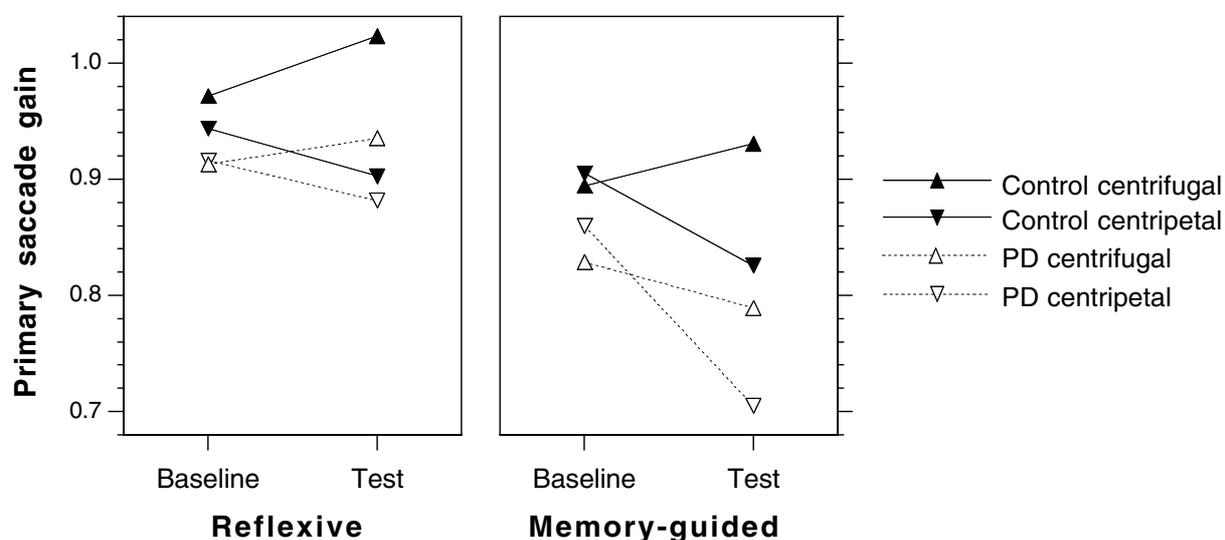


Fig. 3. Primary saccade gain for PD subjects (unfilled symbols) and controls (filled symbols) in the baseline and test phases for each adaptation direction (upward-pointing triangles, centrifugal; downward, centripetal). PD subjects produced smaller reflexive saccades overall, yet adaptation led to appropriate changes in saccade gain for both PD and control subjects (left panel). Adaptation of memory-guided saccades, however (right panel), resulted in appropriate gain changes only for control subjects, while PD subjects showed decreased gain following both centripetal and centrifugal adaptation.

baseline phase, again due to the PD subjects performance. Finally, there was an interaction between Phase and Direction ($F(1, 19) = 6.98$, $p < 0.02$). That is, collapsed across Group, there was negligible change in gain following centrifugal adaptation, but a substantial gain reduction following centripetal adaptation.

Awareness of intrasaccadic manipulation

Following the baseline test, subjects were instructed to continue performing the saccadic task in the same way, but were told that the procedure would be changed in some way and were asked to report any awareness they had of any such change.

A number of subjects reported erroneous or irrelevant changes (e.g. that the beeps changed in tone or that the inter-trial intervals altered). Nine (three PD and six controls) claimed that the target reappeared in a different position during the test phase in at least one session. As there was no target displacement during the test phase this was also an erroneous report. Nine other subjects (seven PD and two controls) did not report any awareness of intrasaccadic displacements in either session. Three

subjects (one PD and two controls) noticed, occasionally to frequently, that their eyes did not land at the target position during the adaptation phase of at least one session. They attributed this to the inaccuracy of their own eye movements, however, rather than to target manipulation. Another PD subject (undergoing centripetal adaptation of memory-guided saccades) reported the impression that his eyes were undershooting the target. This subject exhibited a substantial hypometria in this condition and continually undershot the final target position even though the centripetal target movement should have resulted in saccadic overshooting. That is, in this case the subject was accurately reporting the dysmetria of his own eye movements and not the oppositely directed target displacement, which remained unperceived.

Six subjects (two PD and four controls) did notice intrasaccadic target displacements during at least one of the adaptation phases (one of these was also one of the subjects who reported displacements during the test phase). Their reports of the frequency of the intrasaccadic shifts are given in Table 1.

TABLE 1
Reports of the frequency of the intrasaccadic shifts^a

Group	ISS	Reflexive session	Memory-guided session
PD	+	occasional but attributed to self	2/3 of trials
PD	-	2 trials in first block	NIL
Control	+	NIL	1/3 to 1/2 of trials
Control	-	1 trial in fourth block	up to 2/3 but attributed to self
Control	+	3-4 trials per block	2/3 of trials
Control	+	'quite often' but attributed to self	'frequent'

Six subjects reported that they saw the target make a double step or reappear at a different location during one of the adaptation phases. Their descriptions of how often this occurred are given. Three subjects noticed their eyes landing in the wrong location but attributed this to their own inaccuracy rather than to target displacement. 'ISS' indicates the direction of the intrasaccadic step (+ for centrifugal, - for centripetal).

Discussion

Adaptation of visually and memory-guided saccades in PD

Despite a pre-existing saccadic hypometria, PD subjects showed a normal capacity to adaptively increase or decrease the size of their saccades in response to intrasaccadic target displacements when following a simple stepping visual target (see Fig. 3). As in Mezey's (2000) study of opsoclonus, a pre-existing and enduring saccadic dysmetria does not necessarily indicate an impairment of the ability to adaptively modify saccade accuracy. That is, our PD subjects were not impaired at adaptation per se but showed an adaptive deficit that was specific to memory-guided saccades: increased hypometria regardless of the intended direction of adaptation. This adaptive impairment is different to that observed in cerebellar disorders, in which adaptation tends to be either absent or reduced (Waespe and Baumgartner, 1992; Straube et al., 2001). It is similar to the findings of an excessive gain decrease in saccades ipsilateral to lesions of cerebellar thalamic nuclei (Gaymard et al., 2001). In three patients with hemi-Parkinson's disease, Carl and Wurtz (1985) found ipsilaterally directed reflexive saccades to be normal or slowed symmetrically, while ipsilateral memory-guided saccades were slowed or had abnormal trajectories. Our patients, however, were generally affected bilaterally. When categorised as to whether their motor symptoms were predominantly left-sided, right-sided, or equal, no differences were seen.

Our data indicate that the basal ganglia do not have a generalised role in saccadic adaptation. This supports Deubel's (1999) multiple locus model, with basal ganglia impairment possibly impairing the communication from frontal cortical adaptation regions to subcortical oculomotor centres in memory-guided saccades.

Awareness of intrasaccadic displacements

The rate of detection of target double-steps during the reflexive adaptation phase was acceptably low for a study of adaptation. Undoubtedly, if the subjects had been told what the target manipulation was, and were asked to detect it trial by trial in a psychophysical study, they would have been more sensitive.

Few subjects detected that the target reappeared at a new location during the memory-guided adaptation phase. Of concern, however, was their impression that this happened on a large proportion of trials (1/2 to 2/3). For this subset of the subjects, it could be said that the observed adaptation of memory-guided saccades may have been affected at least partially by conscious strategies. Frens and van Opstal (1994) found that the three of their ten subjects who did not exhibit reflexive adaptation were also the only subjects to notice the target shift throughout the adaptation phase. No consistent effects on adaptation were noted in our results and, hence, all subjects were retained in the analysis. Perhaps of note, however, is that the only PD subject who increased rather than decreased the size of his memory-guided saccades following centrifugal adaptation was

also the only one to have noticed the target shift.

Saccadic suppression of displacement (SSD, Bridgeman et al., 1975) decreases the probability of detecting a target displacement during a saccade. Preliminary experimentation to establish appropriate thresholds for intrasaccadic displacements in our laboratory (MacAskill et al., 1999) examined detection solely in the reflexive saccade task, and we are not aware of any other study that has investigated SSD thresholds in other saccade types. It might be expected that target shifts would be more detectable in memory-guided saccades than in reflexive saccades, as the memory-guided task effectively includes a period of target blanking. That is, the target appears peripherally, is extinguished for a period, and is then re-illuminated during the saccade toward it. Such a period of blanking can make target displacements more detectable (Deubel and Schneider, 1994; Deubel et al., 1996, 1998). Although only a small number of subjects appeared to perceive the target manipulation during memory-guided saccades, those subjects were quite sensitive to it. This indicates that further studies should be conducted on the detectability of intrasaccadic manipulations during various non-reflexive saccade types. When examining the transfer of adaptation between saccades of different types (Deubel, 1987; Erkelens and Hulleman, 1993; Deubel, 1995b, 1999), it is important to know that similar (that is, unconscious) adaptation processes are being examined.

A sizeable proportion of our subjects (9 of 24) reported that the target was displaced during the test phase of either saccade type, when in fact the target was not displaced at all. This verifies that subjects are capable of spontaneously reporting an impression of unusual target displacement, although in these cases it was erroneous. This illusion of target displacement may have been due to the 500 ms period of target blanking following each saccade. This was introduced to slow re-calibration to baseline gain levels (Deubel, 1999). Deubel et al. (1998) also showed, however, that blanking a target can lead to an impression of displacement even when no displacement occurs. This effect, perhaps in concert with the adaptation-induced inaccuracy of saccade landing position with respect to the target when it reappeared, may have caused the subjects' erroneous perception of displacement.

Conclusion

The oculomotor system, for all its complexity, has been described as a 'cartoon' of motor control (Robinson, 1986), as it is relatively simple and well-understood compared to other motor systems. Studying the adaptation of saccades is relatively easy due to the way in which the oculomotor system can be visually deceived in order to produce compensatory motor learning and the way in which this learning can be assessed in a quantitative and accurate manner. This adaptive system provides at least a caricature of more general motor adaptation processes. In some neurological conditions and in some behavioural tasks, saccades can be made more accurate despite a pre-existing dysmetria. This provides hope that analogous training techniques could also be developed to correct the disturbances of limb and posture control experienced in such disorders.

Abbreviations

cFN	caudal fastigial nucleus
CHI	closed head injury
ISS	intrasaccadic step
PD	Parkinson's disease
PET	positron emission tomography
PRL	preferred retinal location
rCBF	regional cerebral blood flow
SSD	saccadic suppression of displacement
VOR	vestibuloocular reflex

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