OCULAR MOTOR DEFICITS IN PARKINSON’S DISEASE

II. CONTROL OF THE SACCADIC AND SMOOTH PURSUIT SYSTEMS

by OWEN B. WHITE, JEAN A. SAINT-CYR, R. DAVID TOMLINSON and JAMES A. SHARPE

(From the Neuro-ophthalmology Unit, Division of Neurology, the Playfair Neuroscience Unit, Toronto Western Hospital, and the Departments of Medicine, Ophthalmology and Anatomy, University of Toronto, Canada)

SUMMARY

We quantified the horizontal pursuit and saccadic function of 14 parkinsonian patients and 10 normal subjects matched for age. Eight patients had mild, and 6 advanced disease. Ocular motor deficits were more marked in patients with advanced disease. Saccadic reaction times and postsaccadic refractory periods were prolonged. Peak saccadic velocities were significantly reduced. Slow saccades may be caused by inappropriate coactivation of opposing ocular muscles. Multiple step, hypometric saccades were abnormally frequent. Correct final eye position towards a brief target flash was attained without visual feedback. Brief corrective intervals occurred after hypometric saccades. They are attributed to internal (nonvisual) efference copy feedback of eye position errors. Frequent square wave jerks were also a feature of Parkinson’s disease.

Smooth pursuit gain was lowered in all patients while tracking sinusoidal targets at frequencies from 0.25 to 1 Hz. Pursuit gain was uniformly reduced at all target velocities at each frequency. This decrease in gain indicates that dysfunction of the gain element, rather than abnormal drop acceleration saturation is responsible for impaired smooth pursuit.

The results indicate that Parkinson’s disease damages structures involved in the regulation of the saccadic and pursuit systems. We infer that nigrostriatal pathways, known to be damaged in Parkinson’s disease, control the latency, velocity and amplitude of saccades, and the gain element of smooth pursuit.

INTRODUCTION

Parkinson’s disease is a syndrome of disordered motor performance attributed to abnormal dopaminergic systems in the basal ganglia. Studies of limb motor function have demonstrated prolonged latencies and bradykinesia (Evarts et al., 1981), inappropriate coactivation of agonist-antagonist muscle pairs and abnormalities of stretch and shortening responses, impaired predictive capacity and abnormalities of long-loop reflexes (Evarts et al., 1979). These deficits are translated into the clinical features by which we recognize parkinsonism of any aetiology: tremor, rigidity, akinesia and bradykinesia.

Reprint requests to Dr J. A. Sharpe, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario M5T 2S8, Canada.
Ocular motor functions lend themselves to quantification of motor performance, relative to limb movement, because of the accessibility of eye movements for recording and the ease with which single movements can be accurately repeated. The balanced agonist-antagonist muscle pairings, low inertia of the globe and the relatively constant viscoelastic properties of the orbit permit analysis of neural control mechanisms. Despite these attributes, few studies have quantified the function of the saccadic or smooth pursuit systems in parkinsonism. In a qualitative oculographic study Corin et al. (1972) observed 'cog-wheel' pursuit, hypometric saccades, gaze impersistence, subnormal optokinetic reflexes, impaired vergence and defective vertical eye movements. Shibasaki et al. (1979) and Teräväinen and Calne (1980) recorded an increased frequency of saccades during pursuit but they did not measure smooth pursuit. Shibasaki et al. (1979) described reduced saccadic velocities but did not correlate velocity with amplitude. Quantitative study of saccades has found increased latency of self-placed refixations and hypometric saccades (DeJong and Melvill Jones, 1971; Melvill Jones and DeJong, 1971; Teräväinen and Calne, 1980). The relationship between saccadic velocity and amplitude was reported to be normal.

We report a quantitative study of the saccadic and pursuit systems. We examined horizontal saccadic latency, accuracy and velocity to predictable and unpredictable target motion. Smooth pursuit gain, the ratio of smooth eye movement velocity to target velocity, was measured during horizontal tracking of sinusoidal and constant velocity targets.

METHODS AND SUBJECTS

Descriptions of the subjects and equipment used were detailed in the companion paper (White et al., 1983). Briefly, we examined 14 parkinsonian patients and 10 control subjects matched for age and sex. Eye movements were recorded by photoelectric infrared oculography and data were stored on magnetic tape. After data were digitized off-line at 200 samples/s for computer analysis, the full system bandwidth was 0 to 100 Hz. Calibrations were performed before and after each paradigm. Subjects were seated with the head stabilized by chin, frontal, parietal and occipital supports.

Saccadic System

Targets for saccadic eye movements were light-emitting diodes (LED) arrayed on a stimulus arc, radius 114 cm, with the subject seated at the origin in order to eliminate changes in vergence (Sharpe et al., 1979). Target position was controlled by a microprocessor. All paradigms were performed in darkness. Frequent verbal encouragement ensured alertness while saccades were made under each of four conditions. (1) Predictable target steps. The target was stepped from 10 deg left to 10 deg right at predictable intervals greater than 2 s. All saccadic responses to at least 50 target steps were analysed in each subject. (2) Unpredictable amplitude target steps. The target was stepped 5, 10, 15, 20 or 40 deg left or right at predictable intervals (3 s), in pseudorandom directions and amplitudes. Large target steps always crossed the centre so that angular displacement never exceeded 20 deg from midposition, the limits of the linear range of the infrared system. Saccadic responses to target steps (n > 150) were quantified for each subject. (3) Unpredictable amplitude target flash. The target was stepped in
unpredictable directions and amplitudes as in condition 2, except that when the original target was extinguished, the new target was illuminated for only 40 ms and then extinguished for 2 s (fig. 1e). The LED was then reilluminated and became the fixation target. Since normal saccadic latency is approximately 200 ms, the brief target flash ensured that subjects made saccades without visual feedback. As in condition 2, saccadic data from at least 150 target steps were analysed for each subject.

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Unpredictable time target steps. The target stepped from 10 deg left to 10 deg right at pseudorandom intervals ranging from 300 to 2000 ms. This paradigm made the time of target shift unpredictable, but amplitude and direction remained predictable. We recorded for 4 min in each subject. Fixation time was designated as the period from the instant of fixation of the target until the target stepped again. Fixation time was measured to differentiate between prolonged latencies to target steps and a prolonged refractory period after refixation, before another saccade could be generated. Refractory delay and initiation delay could both be construed as saccadic akinesia, but quite separate mechanisms may be responsible.

Fixation stability was observed in all patients and quantified in 8 patients while fixating a stationary LED target for 3 min. The frequency of square wave jerks was recorded.

Smooth Pursuit System

Subjects were instructed to follow a laser target (0.25 deg at the retina) projected from the rear on to a screen 170 cm from their nasion. Target movement was achieved by reflecting the laser beam on to a galvanometer mounted mirror and was controlled by a microprocessor. Target motion was 20 deg peak-to-peak. Ambient lighting was maintained at a low level.

1. Predictable ramps. The target moved in predictable directions and velocities. Fixed intervals between each ramp also made timing predictable. Ramp velocities were 10, 20 and 40 deg/s. We analysed responses to 80 ramps at each velocity for each subject.

2. Predictable sinusoids. The target moved sinusoidally at constant frequencies of 0.25, 0.5 or 1.0 Hz. Peak-to-peak amplitude was 20 deg. Peak velocity was 16, 31 and 63 deg/s, yielding peak target accelerations of 25, 99 and 395 deg/s/s, respectively. The sinusoidal motion elicited a large range of target velocities with low acceleration demands relative to ramp targets. We analysed all responses to 25 target cycles at each frequency for each subject.

Data Analysis

Digitized eye position data were displayed on a graphics terminal simultaneously with a differentiated velocity trace. For target steps, cursors placed on the target channel defined the time, direction and amplitude of target motion. Cursors on the eye position channel delineated the onset and termination of each saccade. The peak velocity was measured from the eye position trace between 2 cursors, 10 ms apart, at the segment corresponding to the peak of the differentiated signal.

For pursuit paradigms, the target movement was marked and the cursors were placed on the eye position channel at the onset and completion of all smooth eye movement segments. A computer program divided sinusoidal target motion into segments of approximately uniform velocity, and selected time-locked smooth eye movement segments; pursuit gain was then computed for a range of velocities at each target frequency.

Statistical analyses of all data were performed using the nonparametric Mann-Whitney U test.

RESULTS

Patients were divided into two groups, mild and advanced, on the basis of severity of rigidity and bradykinesia, and the duration of disease, as described in the companion article (White et al., 1983).

Saccadic System

1. Predictable target steps and 2, unpredictable amplitude target steps. Protocols 1 and 2, in which target timing was always predictable, are considered together since
Latencies and saccade metrics did not differ significantly for any individual subject between the two conditions. Normal subjects and patients often made eye movements before target steps, whether or not the amplitude and direction of target step were predictable. These anticipatory movements towards the expected goal were of two types: either saccades, or smooth eye movements which had velocities less than 1 deg/s. When the direction and amplitude of target step were unpredictable (condition 2), subjects frequently made errors in the direction of their anticipatory movements but persisted in attempts to predict. Anticipatory movements, having negative latencies, were excluded from latency data. Patients with advanced disease had significantly longer mean saccadic latencies than normals ($P < 0.001$; Table 1; fig. 2A). There was a wide intrasubject range of saccadic latencies even for mildly affected patients (SD ± 80 ms) compared to normal subjects (SD ± 40 ms).

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**Fig. 2.** A, histogram of saccade latencies for patients with advanced disease (crosshatched columns) and normal subjects (open columns). B, graph of saccade mean peak velocity vs amplitude for advanced patients (A) and normal subjects (O). Error bars indicate 1 SD. C, histogram of frequency of saccades of varying amplitudes in response to predictably timed target steps of 20 deg; mild patients (crosshatched columns); normal subjects (open columns). D, histogram of saccadic amplitude for patients having advanced disease (crosshatched columns) shows more frequent saccadic hypometria. Negative amplitude indicates leftward saccades, positive rightward.
The peak velocity-amplitude relationship of 4, 10 and 18 deg saccades, made by patients and normals, were compared. We obtained these velocities from conditions 1 and 2, using over 15 saccades at each amplitude for each subject (Table 1). Patients demonstrated far more variability than normals. Mean saccadic velocities were significantly slowed at all amplitudes for advanced patients (P < 0.01; Table 1; fig. 2B), but velocities were within the normal range (normal mean ± 2 SD). Patients also generated many more saccades terminated by slow glissadic movements than did normal subjects. In patients, initial responses, after target steps, were frequently slow movements, continuous with the saccade, which were not by their timing anticipatory (fig. 1B). Such slow acceleration was not a feature of saccades in normal subjects.

| TABLE I. SACCADIC LATENCIES AND VELOCITIES FOR PREDICTABLY TIMED TARGET STEPS |
|---------------------------------|-------|-------|-------|
|                                 | Normals | Mild | Advanced |
| Latency (ms)                    | 220 ±40 | 270 ±80 | 360 ±90** |
| Mean peak velocity (deg/s)      |         |       |         |
| Saccade amplitude               |         |       |         |
| 4 deg                           | 176 ±15 | 157 ±36* | 130 ±34*** |
| 10 deg                          | 314 ±43 | 288 ±49*** | 246 ±56** |
| 18 deg                          | 396 ±54 | 387 ±66 | 296 ±55*** |
| * P < 0.05, ** P < 0.01, *** P < 0.001. |

Saccadic inaccuracy was frequent in patients. They made multiple hypometric steps to refixate the target (fig. 1c). Hypometria was measured by computer histogram plots of the frequency of saccades of all amplitudes in response to a target step of constant amplitude (fig. 2c, d). Normal subjects made primary saccades close to or equal to the amplitude of the target step of 20 deg. Patients made initial hypometric saccades unrelated in amplitude to the size of the target step. They were followed by a corrective saccade, beginning at a mean interval of 150 ms (range 10 to 1000 ms) after the completion of the primary saccade (fig. 1c). Mean correction time was not significantly different from normal subjects but the range was greater. Hypometric saccadic segments had the same reduced peak velocity-amplitude relationship as the patients' normometric saccades.

3. Unpredictable amplitude target flash. This paradigm examined saccadic accuracy without visual feedback. Nine patients, 4 with advanced disease and 3 normal subjects, were examined. Accuracy of saccades to a flashed target did not differ from accuracy to a continuous target in patients or normals. Patients generated multiple hypometric saccades but attained the position of the target flash prior to its reillumination like normal subjects (fig. 1E). Latencies, saccadic velocities
and corrective times were comparable to those obtained with constantly lighted targets.

4. **Unpredictable time target steps.** Variation of the timing of target steps prolonged the latency for saccades (see Tables 1 and 2). Fixation times were grouped in bins and correlated with latency (Table 2). Normal subjects demonstrated only

![Table 2](https://example.com/table2.png)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Fixation time (ms)</th>
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<tbody>
<tr>
<td></td>
<td>&lt;200</td>
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<tr>
<td>Normals</td>
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<tr>
<td>L</td>
<td>390</td>
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<tr>
<td>C</td>
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<tr>
<td>Advanced patients</td>
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<td>Y</td>
<td>670*</td>
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* P < 0.05, ** P < 0.01. Latencies are the mean of the mean values for each subject.

mild lengthening of latency for refixations performed after periods of fixation less than 300 ms. Although mildly affected patients had prolonged latencies, these did not differ significantly from normal. Advanced patients showed significantly prolonged latencies (Table 2). After brief fixation periods the increase in saccadic delay was twice that of normal subjects. In other words, the time required to initiate a saccade increased as the time available for target sampling (fixation time) decreased.

Square wave jerks, consisting of horizontal saccades followed after an interval by saccadic return to the fixation position, occurred far more frequently in patients with Parkinson's disease (mean frequency 52/min ± 29, range 5-82) than in normal subjects (Herishanu and Sharpe, 1981). Abnormally frequent square wave jerks were observed both during fixation and low velocity pursuit.

**Smooth Pursuit System**

1. **Predictable ramps.** All but one patient (Case 14, White et al., 1983) showed significant reduction in smooth eye velocities while pursuing ramps at both 10 and 20 deg/s (Table 3). Neither patients nor normals pursued the repeated single ramps successfully at 40 deg/s. Patients, like normals, generated anticipatory smooth eye movements before target movement (fig. 3). These anticipatory movements frequently attained velocities up to 10 deg/s. Saccadic intrusions, in both directions, were frequent, but patients with advanced disease adopted a stratagem of saccadic pursuit, even at the lowest target velocities (fig. 3). This smooth pursuit eye movement deficit is illustrated by histograms of cumulative time spent in smooth
TABLE 3. SMOOTH PURSUIT OF PREDICTABLE SINGLE RAMPS

<table>
<thead>
<tr>
<th>Target velocity</th>
<th>Normals</th>
<th>Mild</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 deg/s</td>
<td>8.99 ± 0.72</td>
<td>8.49 ± 0.59*</td>
<td>7.29 ± 1.97*</td>
</tr>
<tr>
<td>20 deg/s</td>
<td>15.82 ± 2.02</td>
<td>13.22 ± 1.89***</td>
<td>10.33 ± 3.49***</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01, *** P < 0.001.

Pursuit expressed as a percentage of the total time that the target moved across the screen at each velocity (fig. 4). Patients demonstrated greater variability and spent more time at lower pursuit gain than normals, a deficit more evident in advanced disease (fig. 4; Table 3).

Fig. 3. Examples of digitized smooth pursuit movements made by patients with advanced disease and normal subjects. A, single repeated ramps. B, sinusoidal target. Right is upward, left downward.
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2. Predictable sinusoids. Normal subjects pursued targets at 0.25 and 0.5 Hz with gain close to unity; at 1.0 Hz, gain declined to 0.55 (Table 4; fig. 5). Pursuit gain, the ratio of smooth eye movement velocity to target velocity, was independent of target velocity at each target frequency (for example, 0 to 63 deg/s at 1.0 Hz; fig. 6). The relationship between target velocity and smooth eye movement velocity indicated that pursuit gain decreased with increasing target frequency not with increasing target velocity. Patients had significantly lower pursuit gains at each frequency than controls (Table 4; fig. 5). All but Case 14 substituted saccadic tracking for defective smooth pursuit at even the lowest frequency.

Smooth pursuit depends on visual feedback; it is a closed-loop negative feedback system (fig. 7). Closed-loop pursuit gain was measured as the ratio of eye velocity to target velocity for each target segment, then averaged to obtain mean pursuit gains for each target frequency over the range of target velocities. We estimated pursuit

<table>
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<tr>
<th>TABLE 4. SMOOTH PURSUIT OF SINUSOIDAL TARGETS</th>
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<tr>
<td>Closed-loop pursuit gain</td>
</tr>
<tr>
<td>Patients</td>
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<tr>
<td>Frequency (Hz)</td>
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<tr>
<td>Normals</td>
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<td>---------</td>
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<tr>
<td>0.25</td>
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<td>0.5</td>
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<td>1.0</td>
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| Open-loop pursuit gain                       |
| Patients                                      |
|---------|------|----------|
| 0.25    | 11.5 | 5.25     | 2.33     |
| 0.5     | 9.0  | 2.8      | 1.2      |
| 1.0     | 1.2  | 0.95     | 0.54     |

No significance was obtained at 1.0 Hz for mildly impaired patients but 2 patients from this group and 3 more severely impaired patients were unable to follow at this frequency. *P < 0.05, **P < 0.01, ***P < 0.001.
Fig. 5. Graph of smooth pursuit gain vs target frequency for sinusoidal targets. Patients with advanced disease (▲). Patients with mild disease (▲). Normal subjects (○). Error bars indicate ± 1 SD.

Fig. 6. Graph of smooth pursuit gain vs target velocity for a sinusoidal target at 0.5 Hz. Patients with advanced disease (▲). Patients with mild disease (▲). Normal subjects (○).
system performance by calculating the open-loop gain \( k \) from the closed-loop gain \( G \) where \( k = G/(1-G) \). Although closed-loop gain was decreased by less than 30 per cent for target velocities under 30 deg/s (at 0.25 and 0.5 Hz in the sinusoidal protocols), calculated open-loop gain was decreased by about 70 per cent (Table 4).

\[
G = \frac{\dot{E}}{\dot{T}} = \frac{k}{1 + k}
\]

**DISCUSSION**

This study documents abnormalities of saccadic initiation and trajectory, and smooth pursuit gain, not previously quantified in Parkinson’s disease. We examined patients taking L-DOPA and anticholinergic medications, in combination or alone, as well as untreated patients. Ocular motor dysfunction occurred regardless of medication. We did not study the effects of medications longitudinally. Highstein et al. (1969) recorded improvement in saccadic speed and accuracy after L-DOPA in 2 patients. In our 14 patients the severity of ocular motor impairment correlated with the duration of the disease and the severity of bradykinesia and rigidity.

**Saccadic System**

**Saccadic delay.** The mean latency of saccades to target steps was markedly increased in advanced disease (Table 1). Both patients and normal subjects frequently initiated saccades at short latency when target timing was predictable (fig. 2A). Patients, like normal subjects, made anticipatory movements before the target moved. Most were saccades, but a few were smooth eye movements that did not exceed 1 deg/s. Both our patients and normals generated anticipatory smooth eye movements at velocities up to 10 deg/s before ramp targets. Short latency saccades and anticipatory eye movements to regular target motion signified preserved ocular motor prediction in parkinsonism. This relative integrity of ocular motor prediction contrasts with impairment of anticipatory limb movements (Flowers and Downing, 1978).

The prolonged reaction time for limb movement (akinesia) is disproportionately increased for visually triggered responses when compared with kinaesthetic
responses (Evarts et al., 1981). In our patients, saccadic delay to unpredictably timed targets was disproportionately increased after brief periods of target fixation (Table 2). The large increment in patients' reaction time (approximately 340 ms) compared with that of normals (approximately 150 ms), greatly exceeds the increase in delay of visual evoked potentials in Parkinson's disease (approximately 15 ms) (Bodis-Wollner and Yahr, 1978). This saccadic akinesia cannot be explained by visual afferent delay alone. Since saccadic delay after prolonged fixation was relatively brief (330 ms), the increment in delay after brief fixation (latency 670 ms) cannot be explained by absolute delay in motor efferent pathways.

Normal saccadic responses to visual stimuli usually occur at discrete intervals of approximately 200 ms. A sampled-data system model was proposed to explain this behaviour (Young and Stark, 1962). However, observation of shorter latency responses and visual modification of saccades in flight prompts revision of the sampled-data concept (Hallett and Lightstone, 1976). Robinson (1973) proposed parallel processing for saccades of specific amplitude and direction. According to this hypothesis, each parallel process can initiate a saccade and cancel others. In our patients, saccadic delay increased as sampling time decreased (fixation time; Table 2). The increased time required for sampling could indicate increased refractoriness in sampled-data behaviour. This refractory delay implies that defective selection of channels that trigger saccades might be responsible for saccadic akinesia in Parkinson's disease. This explanation is highly speculative, and other mechanisms might account for refractory delay.

Dementia and cerebral cortical damage also cause prolonged saccadic latency (Pirozzolo and Hansch, 1981; Sharpe et al., 1979). Dementia occurs more frequently in Parkinson's disease than in an age-matched population (Lieberman et al., 1979) and cerebral cortical degeneration can occur without dementia in Parkinson's disease (Boller et al., 1980). Our patients who had advanced motor deficits and normal intellectual function (White et al., 1983) had saccadic delay. The delay may be an otherwise undetected disorder of vigilance that results from cerebral cortical or basal ganglia dysfunction in Parkinson's disease.

Frequent square wave jerks signified fixational instability. Although prominent in cerebellar system disease, they are also common in patients with focal cerebral hemisphere damage (Sharpe et al., 1982). Our recordings indicated that square wave jerks are a feature of Parkinson's disease.

Slow saccades. Peak velocities for saccades of defined amplitudes, although within the normal range, were significantly reduced and more variable in patients (fig. 2b; Table 1). Slowing was more marked in patients with advanced disease (Table 1). Saccades are probably initiated by supranuclear trigger signals that inhibit pause cells in the midline pontine tegmentum (Robinson, 1975). Pause cells, in turn, are thought to inhibit presaccadic burst units in the pons. In the monkey, van Gisbergen et al. (1981) recorded from motor neurons in the abducens nuclei, and from medium-lead burst neurons in the pontomedullary reticular formation, which discharge before saccades. Burst cells fire for saccades in all directions. Motor
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neurons discharge for saccades in both horizontal directions but their firing sequence varies with the direction of saccades, thereby defining on and off directions. The on-direction burst drives the saccade, and subsequent off-direction firing of burst cells on the opposite side of the pons may be responsible for dynamic braking of the eye at the end of saccades.

The difference between on-direction burst rate and off-direction burst rate correlates with instantaneous eye velocity. Inhibitory burst neurons in the medullary reticular formation are thought to inhibit motor neurons reciprocally during saccades in off-directions (Hikosaka et al., 1978). The reciprocal agonist-antagonist discharge of motor neurons is determined by synchronized activity of on-direction burst neurons, off-direction burst neurons and inhibitory burst neurons.

The slowed saccades recorded in our patients indicate disordered regulation of motor neuron innervation. The pontine tegmentum is the only supranuclear site where damage is proven, by pathological correlation, to cause marked slowing of saccades (Sanders, 1975). Progressive supranuclear palsy is a parkinsonian syndrome in which slow hypometric horizontal saccades accompany vertical ophthalmoplegia (Troost and Daroff, 1977). Degeneration of the pontine reticular formation (Steele et al., 1964) is a feature of the disorder that can explain slowed saccades. However, the pontine reticular formation is considered to be structurally intact in idiopathic Parkinson's disease (Alvord et al., 1974). The occurrence of many saccades with normal peak velocities in our patients implies a normal complement of burst cells in the pons.

Slatt et al. (1966) and Chaco (1971) recorded slowed development of the electromyographic (EMG) interference pattern is agonist ocular muscles, in association with inappropriate coactivation of antagonist muscles during saccades. We suggest that the slowed saccades of our patients are caused by impaired reciprocal activation of agonist on-direction burst cells, antagonist off-direction burst cells and inhibitory burst cells.

Cofiring of muscles can cause ocular retraction. For example, patients with paralysis of upward saccades from dorsal midbrain damage exhibit retraction of the eyes when they attempt to make upward saccades (Gay et al., 1963). We did not observe ocular retraction during saccades in our patients. The amount of coactivation required simply to slow saccades would not be expected to cause visible retraction.

Hypometric saccades. Patients, unlike normal subjects, frequently require multiple saccadic steps to attain desired eye position. Inappropriate coactivation of agonist and antagonist ocular muscle pairs may explain slow saccades but not hypometric saccades. After a brief (40 ms) target flash, patients achieve final desired eye position in complete darkness, without the benefit of continuous visual feedback, indicating that desired eye position is correctly coded by the retinal error in Parkinson's disease. Robinson (1975) proposed a model in which desired eye position signals the duration of burst cell discharge while a trigger signal inhibits the pause cells, thus releasing the burst cell discharge. According to this hypothesis, collaterals of burst
cells maintain inhibition of the pause cell and an internal copy of eye position signal (efference copy) is fed back to inhibit the burst cell. When the efference copy of eye position is equal to desired eye position, burst cells cease firing, pause cells resume activity and the saccade stops.

Stimulation of pause cells in the medial pontine reticular formation of monkeys stops saccades while in progress, and if the stimulus is sufficiently brief, saccades subsequently resume their course to near correct final eye position (Keller, 1977). The hypometric saccades of parkinsonism could be explained by inappropriate pause cell activation while a saccade is in progress. Pause cell activity might explain the irregular development of the EMG interference pattern in agonist ocular muscles (Slatt et al., 1966; Chaco, 1971), thereby causing the slow saccadic acceleration recorded in our patients.

Following an initial hypometric step, further saccades were generated at intervals ranging from 10 to 1000 ms. These corrective saccades might be preprogrammed, but a strategy of multiple saccades would delay refoveation. After pathologically hypometric steps, corrective saccades could be mediated by visual feedback, orbital proprioceptive feedback or by an internal (nonretinal) efference copy of eye position. The occurrence of corrective saccades in the target flash condition indicated that visual feedback was not required to generate corrective saccades. Known latencies of orbital proprioceptive responses via the cerebellum or superior colliculi, proposed relays for orbital proprioception, are too long to explain corrective intervals less than about 30 ms (Kimura and Maekawa, 1981; Ron and Robinson, 1973; Rose and Abrahams, 1978; Wurtz and Albano, 1980). Corrective saccades after shorter intervals must be determined by mismatch of desired eye position with an internal efference copy of eye position. The short latency corrective saccades indicate that pathways transmitting internal feedback of eye position are intact in Parkinson's disease.

**Smooth Pursuit System**

Smooth pursuit gain, the ratio of eye velocity to target velocity, is lowered in Parkinson's disease. By holding target acceleration constant while changing target velocity, amplitude and frequency, Lisberger et al. (1981) demonstrated that normal pursuit system gain is insensitive to changes in target velocity or frequency. Then while holding target velocity constant by changing target amplitude and frequency inversely, they showed that pursuit gain decreases at high target accelerations. This acceleration limitation on normal pursuit gain is called a saturating nonlinearity in engineering terms; it is depicted by the box containing a sigmoid curve in fig. 7.

One of the advantages of negative feedback systems such as smooth pursuit (fig. 7) is that the closed-loop gain \( \frac{k}{l+k} \) is relatively insensitive to changes in open-loop gain \( k \). However, the open-loop gain is determined by neural circuits; it is the pursuit parameter that assesses neurological dysfunction. Direct measures of open-loop gain require artificial stabilization of a retinal image (Pola and Wyatt, 1981) or monocular ophthalmoplegia. We calculated open-loop gain from the measured
closed-loop gain (G). At frequencies of 0.25 and 0.5 Hz, gain was reduced uniformly at all target velocities, whether target acceleration was large or small. Changes in the saturating nonlinear element that limits acceleration would reduce eye acceleration and thereby reduce the frequency at which saturation (gain decrease) occurred. However, changes in the saturating nonlinear element would not affect the low frequency performance where target acceleration is minimal. The uniform reduction in gain at low frequencies (fig. 5) indicates that the pursuit defect in Parkinson’s disease is a disorder of the gain element, not the saturating nonlinearity alone.

Reduction in pursuit gain at all target frequencies in Parkinson’s disease is similar to that recorded in cerebellar system degeneration in man (Zee et al., 1976), and after flocculectomy in monkeys (Zee et al., 1981). It differs from impaired pursuit after cerebral cortical damage, when low frequency pursuit gain approaches unity but decreases (saturates) as frequency increases (Sharpe et al., 1979). The difference in the pursuit performance suggests that cerebral cortical lesions damage the nonlinear saturating element of the pursuit loop, whereas Parkinson’s disease, like cerebellar degeneration, involves the gain element. Little is known about the anatomical substrates for smooth pursuit. We infer that dopaminergic nigrostriatal pathways affect the gain element of the pursuit system.

Several sites of potential dysfunction could disrupt saccadic performance. Schiller et al. (1980) demonstrated that combined lesions of frontal eye fields and superior colliculus produce slowed small saccades. The frontal eye fields project to the corpus striatum (Künzle and Akert, 1977), which in turn has a major outflow via the substantia nigra pars reticulata to the superior colliculus (Nauta, 1979). Wurtz and Hikosaka (1981) recorded from cells in the substantia nigra pars reticulata which modulate with saccades and project to the superior colliculus. Microstimulation in the superior colliculus activates pause cells in the pontine reticular formation (Raybourn and Keller, 1977) and elicits retinotopically coded saccades (Stryker and Schiller, 1975). Lesions of the superior colliculus produce delayed, slowed and hypometric saccades (Schiller et al., 1980) similar to those in Parkinson’s disease. We suggest that involvement of this nigrocolliculoreticular circuit may explain the saccadic deficits that we have described in Parkinson’s disease.

ACKNOWLEDGEMENTS

This work was supported by MRC of Canada Grants ME 5509 and MT 5404 and by the Physicians Services Incorporated Foundation of Ontario (Dr Sharpe). Dr White was a Fellow in Neuro-ophthalmology, supported by the PSI grant and by the Department of Medicine Fund, Toronto Western Hospital.

We thank Drs R. D. G. Blair, G. Sawa and R. Yufe for referring patients for study, Dr W. G. Tatton for invaluable technical assistance and C. D. Sherret for computer programming. We thank Mrs R. Armstrong for editorial assistance.
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(Received July 7, 1982. Revised November 23, 1982)