ABNORMALITIES OF PREDICTIVE SACCADIES IN HEMI-PARKINSON’S DISEASE

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SUMMARY

We studied reflexive and predictive saccades by direct current electro-oculography in nine patients with mild hemi-Parkinson’s disease (hemi-PD) and in 16 age-matched controls. In five patients, the neurological syndrome was predominant on the right side of the body (RPD) and in four patients, on the left side (LPD). Reflexive saccades were elicited in response to the random appearance (timing and location) of a light-emitting diode (LED). Predictive saccades were elicited by alternatively illuminating LEDs at 10 degrees right and left, at various fixed frequencies (0.25 — 1 Hz).

In the reflexive task, latency and amplitude of the saccades were normal in both PD groups. In the predictive task, mean saccade latency was not significantly different between patients and normals but there were two significant abnormalities in timing: first, but only in LPD, a directional asymmetry in latency (left greater than right, e.g. at 0.25 Hz, mean difference of 90 ms); secondly, especially in RPD, an abnormal tracking pattern, reflected by more variability of the mean value (for each group of patients) of saccade latency at each point in time, throughout a period of tracking at a given frequency. Predictive saccades were also strongly hypometric in both PD groups but especially in LPD (e.g. for rightwards saccades: controls = 19 degrees, SD = 1.6; LPD = 14 degrees, SD = 2.7; RPD = 15.7 degrees, SD = 2.3). These defects in saccadic timing and amplitude during predictive tracking were most salient at low frequencies. While these defects were largely bilateral, our findings suggest slightly different contributions of the right and left cerebral hemispheres to the spatial and timing components, respectively, that comprise optimal predictive saccadic behaviour.

INTRODUCTION

Parkinson’s disease (PD) is a degenerative disorder characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNPC). In addition to a somatomotor syndrome consisting of tremor, rigidity and bradykinesia, there are also abnormalities of eye movements (Kennard and Lueck, 1989; Leigh and Zee, 1991). In patients with mild PD, the saccades are delayed and hypometric in tasks that primarily reflect internally generated volitional motor programs, such as the response to targets moving in a predictable fashion (Bronstein and Kennard, 1985; Nomura et al., 1986; Crawford et al., 1989b; Kennard and Lueck, 1989; Lueck et al., 1990). Saccades are less impaired in tasks that test reflexive types of behaviour such as externally triggered responses to novel visual stimuli.

Recent electrophysiological studies in the basal ganglia and in the frontal lobes of monkeys have linked both of these structures to the generation of more volitional saccades, in the context of learned, remembered or anticipated behaviour (Hikosaka and Wurtz, 1983a, b, c, d; Bruce and Goldberg, 1985; Deng et al., 1986; Joseph and Barone, 1987; Goldberg and Segraves, 1989; Hikosaka and Wurtz, 1989; Hikosaka et al., 1989a, b, c).
Clinical studies of patients with PD and of patients with Huntington’s disease (HD) also suggest that the frontal lobes and basal ganglia participate in the control of voluntary saccades (Bronstein and Kennard, 1985; Lasker et al., 1987, 1988; Crawford et al., 1989a, b; Lueck et al., 1990; Tian et al., 1991).

In the present study, we recorded saccadic eye movements in patients with mild hemi-Parkinson’s disease (hemi-PD), using a predictive tracking paradigm to learn (i) if there are directional asymmetries in predictive behaviour and (ii) if the right and left cerebral hemispheres make different contributions to the spatial and the temporal aspects of predictive tracking. Our results confirm a deficit in predictive saccadic tracking in hemi-PD, especially at low frequencies. Surprisingly, the ocular motor deficits were largely bilateral in spite of the striking somato-motor asymmetry. Nevertheless, there was some asymmetry in the ocular motor abnormalities suggesting that there may be a difference between the contributions of the left and right cerebral hemispheres to both the temporal (timing) and the spatial (location) components necessary for generating optimal anticipatory responses during a predictive tracking task.

**METHODS**

**Subjects**

Nine right-handed patients with hemi-PD (four females, five males; mean age 59 yrs, range 51 —69 yrs) and 16 right-handed, age-matched normals (11 females, five males; mean age 54 yrs, range 29 —70 yrs) were investigated (Table 1). The patients were all followed in the movement disorder clinic and the age-matched normals were a mixture of spouses of patients and hospital employees and their relatives. All the patients were clinically examined by a neurologist (S.R.) and the PD disability was scored using the New York University rating scale with a maximal score of 52 (Lieberman, 1974). A score of 0 to 4 is assigned to the following abnormalities: tremor, rigidity, bradykinesia, gait and postural stability. Bradykinesia was evaluated using timed finger and foot tapping. All subjects gave informal consent to participate in this study. The patients were divided into two groups according to the affected side of their neurological syndrome: five patients had a right hemi-PD (RPD) and four patients a left hemi-PD (LPD).

**TABLE 1. CHARACTERISTICS OF PATIENTS**

<table>
<thead>
<tr>
<th>PD patients</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Illness duration (mths)</th>
<th>New York University disability (max. 52)</th>
<th>Tremor Max./side = 8</th>
<th>Rigidity Max./side = 8</th>
<th>Bradykinesia Anti-PD medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPD M.A.R.</td>
<td>F</td>
<td>66</td>
<td>18</td>
<td>9</td>
<td>R L R L</td>
<td>2 0</td>
<td>BL Sinemet</td>
</tr>
<tr>
<td>L.U.T.</td>
<td>F</td>
<td>55</td>
<td>119</td>
<td>5</td>
<td>2 0 2 0</td>
<td>4 2</td>
<td>UL** Artane</td>
</tr>
<tr>
<td>P.J.C.</td>
<td>M</td>
<td>51</td>
<td>40</td>
<td>13</td>
<td>3 0 4 2</td>
<td>3 0</td>
<td>UL** Sinemet, Eldepryl</td>
</tr>
<tr>
<td>B.A.K.</td>
<td>F</td>
<td>56</td>
<td>56</td>
<td>4</td>
<td>0 0 3 0</td>
<td>4 2</td>
<td>UL</td>
</tr>
<tr>
<td>R.K.</td>
<td>F</td>
<td>52</td>
<td>32</td>
<td>10</td>
<td>0 0 0 2</td>
<td>1 2</td>
<td>BL Sinemet, Eldepryl, Amantadine</td>
</tr>
<tr>
<td>LPD A.D.L.</td>
<td>M</td>
<td>69</td>
<td>76</td>
<td>15</td>
<td>0 5 2 4</td>
<td>3 1</td>
<td>UL* Sinemet, Artane</td>
</tr>
<tr>
<td>L.H.</td>
<td>M</td>
<td>65</td>
<td>71</td>
<td>10</td>
<td>0 3 1 3</td>
<td>3 1</td>
<td>UL* Sinemet, Eldepryl, Amantadine</td>
</tr>
<tr>
<td>Q.L.D.</td>
<td>M</td>
<td>63</td>
<td>47</td>
<td>8</td>
<td>0 3 1 3</td>
<td>1 2</td>
<td>BL Sinemet</td>
</tr>
<tr>
<td>S.E.V.</td>
<td>M</td>
<td>57</td>
<td>9</td>
<td>7</td>
<td>0 3 1 2</td>
<td></td>
<td>UL** Sinemet</td>
</tr>
</tbody>
</table>

Tremor was evaluated at the hand and rigidity at the elbow. Bradykinesia was scored on the basis of the timed-finger and foot-tapping tasks. * = mild; ** = severe asymmetry; UL = unilateral; BL = bilateral.
Apparatus and eye-movement recordings

The subjects were seated in a dark room in front of an arc (radius 123 cm) supporting light-emitting diodes (LED). The target lights subtended 0.1 degree of visual angle and were located at 10, 20 and 30 degrees right and left from the centre (0 degree). Head movements were restricted by a chin rest.

Horizontal saccades were recorded from the right eye by direct-current electro-oculography. Eye blinks were monitored by vertical eye movements recordings. Electro-oculography signals were amplified and filtered with a low-pass analogue filter (40 Hz). The filtered analogue signals were digitized at a sampling rate of 100 Hz by computer and saved for off-line analysis.

Procedure and paradigms

Both non-predictive and predictive saccades were tested.

Non-predictive paradigm (non-predictive stimulus). Each trial began with fixation of the centre LED. A peripheral LED was illuminated and simultaneously the centre LED was switched off and a non-localized beep, 100 ms in duration, sounded. The peripheral LED was presented at a random time (1400–2400 ms), direction (right or left) and amplitude (10, 20 or 30 degrees). Subjects were told to move their eyes towards the peripheral light as quickly and accurately as possible.

Predictive paradigm (predictive stimulus). Targets alternated between two fixed locations (10 degrees right and left) at various fixed frequencies in the following sequence: 0.25, 0.5, 1, 0.33 and 0.75 Hz. For each target frequency, 25 cycles of responses were collected. Subjects were told to move their eyes in time with the movement of the light.

Data analysis

An interactive computer program was used for saccade analysis; the accuracy of saccade identification was verified by visual inspection of each trial on a video monitor. For the non-predictive paradigm, saccades were calibrated independently for each eccentricity of targets. For the predictive paradigm, separate calibrations were obtained for each frequency of target motion. This calibration procedure minimized inaccuracy due to any fluctuations in the amplitude of the corneo-retinal potential.

For the non-predictive paradigm, the latency and the amplitude of the initial saccade in response to the target stimulus were computed.

For the predictive paradigm, saccades initiated within 100 ms of, or prior to, the target jump were classified as anticipatory. A negative latency indicated that the saccade was initiated before the target jumped. At each frequency of target motion, responses were divided into two groups: the anticipatory and the non-anticipatory saccades. The percentage of anticipatory saccades was calculated. For all of the predictive saccades (anticipatory and non-anticipatory saccades) and for each of the subgroup of non-anticipatory and anticipatory saccades, the analysis of latency and amplitude was performed independently for the rightwards and the leftwards responses.

A normal range for each parameter was established from the mean ±2 SD of the control group. Data were analysed using ANOVA, the Student’s t test and the Mann-Whitney test, performed by the STATGRAPHICS software package. For ANOVA, within-group factors were the subject, the direction of the target and the frequency of the target motion. The dependent variables were the saccade latency and the saccade amplitude for the non-predictive and predictive paradigms, and also the percentage of anticipatory saccades for the predictive paradigm. A 95% confidence interval was used to establish statistical significance.

RESULTS

Non-predictive paradigm

The latency of visually triggered saccades was slightly but not significantly ($P > 0.05$, $t$ test) increased in both directions for both hemi-PD groups (Table 2). The amplitude for 20 degree saccades was normal ($P > 0.05$, $t$ test) for each hemi-PD group (Table 2) though one RPD patient (R.K.) showed an abnormal amplitude (11.1 ±3.2 degrees) for leftward saccades (control group: mean = 18.7 degrees; 2 SD = ±2.8).
TABLE 2. NON-PREDICTIVE PARADIGM: LATENCY AND AMPLITUDE FOR RIGHTWARD AND LEFTWARD SACCADIES IN CONTROL, RPD AND LPD GROUPS

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 16)</th>
<th>RPD (n = 5)</th>
<th>LPD (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Mean</td>
<td>259.0</td>
<td>281.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>37.0</td>
<td>44.0</td>
</tr>
<tr>
<td>Left</td>
<td>Mean</td>
<td>263.0</td>
<td>288.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>49.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Mean</td>
<td>18.2</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Left</td>
<td>Mean</td>
<td>18.7</td>
<td>17.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.4</td>
<td>3.4</td>
</tr>
</tbody>
</table>

SD = standard deviation; eccentricity of target = 20 degrees.

Predictive paradigm

Saccade latency

Although mean latency tended to be higher in patients versus controls (Fig. 1), there was no significant difference between the groups [group effects, F(2,228) = 2.7, P = 0.065, ANOVA].

Frequency effect. Latency depended on frequency in both patient groups and in the control group [frequency effect: F(4,228) = 13, P < 0.0001]. Mean latency was higher at low and high frequencies (0.25, 0.33, 1 Hz). This effect was greater in patients than in controls [control group: F(4,139) = 11, RPD group: F(4,16) = 26, LPD group: F(4,12) = 39] (Fig. 1).

Direction effect. The latency of saccades was consistently asymmetrical (left greater than right) only in LPD patients [direction effect in RPD: F(1,16) = 2.2, P = 0.16 and in LPD: F(1,12) = 10.6, P = 0.0068]. In the LPD group, the difference in latency between right and left saccades was greater at low frequencies and this effect was marked in two subjects (A.D.L. and S.E.V) [frequency/direction interactions: F(4,12) = 4.5, P = 0.019, and subject/direction interactions: F(3,12) = 9.9, P = 0.0014]. These findings are represented in Fig. 2.

Pattern of tracking. In the control subjects, the degree of anticipation depended upon the frequency of target motion; the lowest latencies, corresponding to the best anticipation, were at the intermediate stimulus frequencies (0.5, 0.75 Hz).

The pattern of predictive tracking in controls and in patients is illustrated for leftwards saccades in Fig. 3. We plotted the mean latencies, for each group, at each point in time, during the entire period of tracking at a given frequency. For instance, at 0.5 Hz in controls, mean saccade latency decreased in the first few trials and then became less variable and plateaued in the last 10 trials. However, at lower or higher frequencies, the values of saccade latencies showed more fluctuation.

Although the mean latency was not significantly different between the control group and the patient groups (based on the ANOVA analysis), the pattern of prediction was different (Fig. 3). The pattern in patients was more variable, especially at the lower and higher target frequencies.

To quantify these abnormalities, the last 20 mean values of the latencies throughout the period of tracking were analysed using the Mann-Whitney test. For leftward tracking
Fig. 1. Rightward and leftward saccade latencies during predictive tracking as a function of the target frequency.

A, comparison between control (●) and RPD (○) group. B, comparison between control (●) and LPD (○) group.

(see Fig. 3), there were significant differences compared with normal for both patient groups at low frequencies (0.50, 0.33, 0.25 Hz) and for RPD patients also at 1 Hz. For rightward tracking, there were significant differences ($P < 0.05$) only in RPD patients and only at some frequencies (0.25, 0.5, 1 Hz).

To summarize, the mean latency was normal in both patient groups. In the LPD group only, a directional asymmetry in latency was found between rightward and leftward saccades (left greater than right). Furthermore, especially in RPD, the pattern of tracking was abnormal as reflected in more variability of the mean values of saccadic latency over time, at a given frequency. These defects in latency were usually more pronounced at low frequencies.

Saccade amplitude

Patients showed a considerable decrease in saccade amplitude compared with normals [group effect: $F(2,228) = 42, P < 0.0001$, ANOVA]. The decrease in mean amplitude was greater in LPD than in RPD patients [$F(1,70) = 5, P = 0.026$] (Fig. 4).
Frequency effect. The decrease in amplitude depended on frequency (frequency effect: $F(4,228) = 11, \ P < 0.0001$, ANOVA): the lower the target frequency, the lower the saccade amplitude (Fig. 4).

Direction effect. The mean amplitude depended on saccade direction: the mean amplitude was slightly higher for rightward saccades in the control group and more so for leftward saccades in both hemi-PD groups. The effect of saccade direction on the accuracy within each patient group was analysed.

In RPD, all patients except one (R.K.) showed a significant difference in amplitude between right and left saccades (left greater than right); this effect was independent of the stimulus frequency (Fig. 5) [main effect of the direction factor $F(1,16) = 17.7$, $P = 0.0007$; subject/direction interactions $F(4,16) = 19, \ P < 0.0001$; frequency/direction interactions: $F(4,16) = 1, \ P = 0.38$].
Fig. 3. Pattern for leftward saccades during predictive tracking at different target frequencies (0.25, 0.50, 1 Hz), for control, RPD and LPD group. Each vertical bar represents the saccade latency averaged at each trial for all the subjects in each group. Significant abnormalities ($P < 0.05$, Mann-Whitney test) in the variability of the tracking pattern are noticeable between the control and the patient groups. NS = no significance.

In LPD, all patients except one (S.E.V.) showed a difference in amplitude between right and left saccades (left greater than right); this effect was greater at low frequencies (Fig. 5) [main effect $F(1,12) = 13$, $P = 0.0035$; subject/direction interactions: $F(3,12) = 8$, $P = 0.003$; frequency/direction interactions: $F(4,12) = 5.6$, $P = 0.0087$].

To summarize: the mean amplitude for saccades in both directions was decreased in both groups of hemi-PD patients. This amplitude defect was more pronounced in LPD group and for the saccades directed to the right.

**Amplitude variability.** Saccade amplitude was highly variable over the 25 cycles of tracking, especially in the LPD patients. This variability was quantified by calculating the standard deviation of the mean value of amplitude for each subject over the last 20 trials, at each frequency (Fig. 6). Then, a mean value of the standard deviations was calculated for all subjects in each group. We found a significant increase ($P < 0.05$, student’s $t$ test) in the mean value of the standard deviations in both patient groups, mainly at low frequencies (Fig. 6).
Anticipatory and non-anticipatory saccades. We further analysed saccades during predictive tracking by separating responses into anticipatory and non-anticipatory. An anticipatory saccade was defined as a saccade initiated with a latency before or within 100 ms of the target jump. The percentage of anticipatory saccades in the patient groups was slightly but not significantly decreased with respect to the normal group [F(2, 228) = 2.8, P = 0.064, ANOVA]. The percentage of anticipatory saccades depended on stimulus frequency in both patient and control groups [F(4, 228) = 24, P < 0.0001]. As the frequency increased, the percentage increased, only to fall again when the frequency reached 1 Hz (Fig. 7).

There was, however, a highly significant abnormality in the amplitude of anticipatory saccades in both PD groups [group effect: F(2, 225) = 67, P < 0.0001]; the amplitude deficit depended on frequency [frequency effect: F(4, 225) = 21, P < 0.0001] and was more prominent in the LPD group [F(1, 70) = 4.5, P = 0.04] (Fig. 8). The decrease in the amplitude of anticipatory saccade was independent of the response direction.
Fig. 5. Difference of amplitude between right and left saccades during predictive tracking at different target frequencies (0.25, 0.33, 0.50, 1 Hz). The mean values are represented for the control group (with standard deviation) and for each individual of the patient groups. Negative bars indicate hypometria of rightwards saccades.

[direction factor effect: F(1,225) = 2.2, P = 0.13]. This result was confirmed by computing a t test on the difference of the mean amplitude between right and left saccades in each patient group (RPD: t = 1.2, P = 0.28; LPD: t = -0.11, P = 0.92).

The amplitude of the non-anticipatory saccades during predictive tracking was slightly decreased only in the LPD patients [group effect: F(2,221) = 9.5, P = 0.0001]. The non-anticipatory saccade amplitude was independent of the stimulus frequency (Fig. 8). Both ANOVA and a t test showed significant asymmetry in the amplitude of non-anticipatory saccades due to a decrease in the amplitude for rightward saccades in patients groups (RPD, t = -3.6, P = 0.02; LPD, t = -16, P = 0.00008; Student's t test) (Fig. 8).
To summarize: the decrease of saccade amplitude was mainly apparent in the anticipatory responses in both hemi-PD groups; this amplitude defect depended upon frequency and was more marked in LPD patients, but it did not correlate with response direction.

**Latency-amplitude correlation**

By a linear regression analysis, we found a significant positive correlation between saccade latency and amplitude at low frequencies, in both patient groups ($P < 0.0001$...
Fig. 8. Mean amplitude of the non-anticipatory (filled symbols) and of the anticipatory (open symbols) saccade as a function of the target frequency. A, the control group; B, the RPD group; and C, the LPD group.

at 0.33 and 0.25 Hz, $P < 0.05$ at 0.5 Hz) but not in controls. At high frequencies (1 Hz), a significant latency-amplitude correlation was found mainly for leftwards saccades in both patient groups.
DISCUSSION

The main finding of this study is that patients with mild hemi-PD show abnormalities of saccades during tracking of targets jumping with predictable timing and location, but not to targets jumping to random locations at unpredictable times. This effect was independent of the side affected. The patients demonstrated hypometria of saccades and increased variability in the pattern of tracking. The deficits, usually greatest at low frequencies of target motion, were largely bilateral in both RPD and LPD. However, in patients with LPD, overall saccadic hypometria (for saccades in both directions) was greater and saccade latency was asymmetric (left latency greater than right latency). On the other hand, in patients with RPD, the pattern of timing during prediction was more variable.

We will discuss these results first by reviewing some aspects of the normal physiology of the basal ganglia relevant to saccadic eye movements. Secondly, we will consider the nature of the deficits of prediction in PD. Finally, we will speculate upon the relationship between the ocular motor findings and the asymmetry of the somato-motor deficits in our patients.

Saccade abnormalities in basal ganglia disease

Normal ocular motor physiology of the basal ganglia. The superior colliculus (SC) appears to participate in the generation of all types of saccades. The basal ganglia may gate activity in the SC, to facilitate more volitional types of saccades and to suppress, when necessary, more reflexive types of saccades. By virtue of successive inhibitory pathways from the caudate nucleus (CN), to the substantia nigra pars reticulata (SNPR), and then from the SNPR to the SC, the basal ganglia can modulate activity within the SC (Hikosaka and Wurtz, 1983a,b,c,d, 1985a,b; Hikosaka et al., 1989a,b,c). The frontal and parietal lobes may also modulate activity in the SC by direct projections as well as through projections to the CN (Petras, 1971; Fries 1984, 1985; Komatsu and Suzuki, 1985; Lynch et al., 1985; Selemon and Golman-Rakic, 1985; Huerta et al., 1986; Updyke, 1986; Segraves and Goldberg, 1987; Selemon and Goldman-Rakic, 1988; Stanton et al., 1988).

Pathophysiology of basal ganglia disturbances of eye movements. In HD, there are pathological changes in the CN and probably also in the SNPR (Albin et al., 1989; Oyanagi et al., 1989). Patients with HD show defects in initiating more voluntary saccades (including those in predictive tracking paradigms) and in suppressing, uncalled-for, reflexive saccades (Lasker et al., 1987; 1988; Tian et al., 1991).

In PD, the main pathologic effect is seen in the SNPC. Although the SNPC has no known ocular motor function, it could influence activity in the CN, or even the SNPR, by virtue of its direct projections to both structures (Hikosaka and Wurtz, 1989). Like patients with HD, patients with PD have difficulty initiating voluntary saccades (Bronstein and Kennard, 1985; Crawford et al., 1989a; Lueck et al., 1990).

However, the saccadic eye-movement defects in PD differ in some respects from those in HD. A loss in the ability to suppress uncalled-for reflexive saccades, the oculomotor sine qua non for HD (Lasker et al., 1987), has not been observed in PD (Crawford et al., 1989b). Although patients with either PD or HD have difficulty generating predictive saccades, abnormalities of latencies are more prominent in HD and abnormalities of accuracy more prominent in PD (Crawford et al., 1989b; Tian et al., 1991).
The reasons for the differences in eye movements between HD and PD are not clear. Dysmetric and delayed saccades are produced by acute pharmacological lesions of the SC (Hikosaka and Wurtz, 1985a, 1986; Lee et al., 1988). It is possible that both the level of tonic activity in the SNPR, and the level of phasic activity that occurs in relation to saccades (either in the CN or in the SNPR), determine whether or not there will be hypometria and/or delay in initiating saccades. Which abnormality predominates in patients with HD or PD might depend upon the relative differences between alterations in phasic and in tonic activity emanating from the basal ganglia.

On the other hand, it is difficult to attribute specific ocular motor defects to malfunction in a single structure or in a particular population of neurons, since defects in one structure often lead to changes in distant ones. For instance, in PD, metabolic changes affect not only the substantia nigra and striatum but also the thalamus and the frontal lobes (Wolfson et al., 1985; Ho et al., 1988; Mitchell et al., 1989; Palombo et al., 1990).

**Predictive tracking in normal subjects and in patients**

Accurate predictive saccadic tracking requires that the temporal (timing) and the spatial (location) components of the motion of the target are correctly stored in memory and then used, in lieu of direct visual information, to trigger a saccade of the right amplitude at the right time. In normal subjects, the ability to anticipate the motion of the target in a predictive tracking task is best at a target frequency of about 0.5 Hz. At lower and higher frequencies the degree of anticipation is less though accuracy is relatively maintained.

Only a few studies have reported the effects of focal structural lesion on predictive tracking capabilities. Lesions of both frontal and parietal structures have been implicated in predictive tracking deficits but specific details of how the lesions affected amplitude versus timing are scanty (Pyykkö et al., 1984; Bruce and Borden, 1986; Sharpe, 1986; MacAvoy and Bruce, 1989; Ron et al., 1989). In patients with HD, the predominant defect in predictive tracking is an increase in latency; the degree of anticipation is considerably less than that of normal subjects (Tian et al., 1991).

**Abnormalities of predictive tracking in PD**

Patients with PD also show abnormalities during predictive tracking but the degree of defect is subject to the specific nature of the instructions and of the task (Bronstein and Kennard, 1985; Crawford et al., 1989b). Performance was relatively worse if the patient was informed of the predictive nature of the task and relatively better when an auditory cue was substituted for a visual one.

**Amplitude disorders.** The most striking defect of prediction in PD is hypometria of saccades (Bronstein and Kennard, 1985; Crawford et al., 1989b). Our patients, too, showed a decrease in amplitude of predictive saccades and we also found that the degree of hypometria was closely related to the latency; saccades made at lower latencies were smaller. Moreover, the amplitude of saccades during a period of tracking was more variable than in normal subjects. During predictive tracking, as expected, hypometria was present mainly for the anticipatory saccades (latency < 100 ms) since hypometria was not present for saccades made in the reflexive paradigm. Presumably during the predictive paradigm, all saccades made within 100 ms of the target jump had no immediate visual information available to assist in programming saccade amplitude while saccades
made well after the target jumped (e.g. >250 ms) had visual information available to adjust saccade size. Non-anticipatory saccades made with latencies between these extremes probably reflect a mixture of internally generated and visually guided movements. Hence, they would be expected to, and did, show intermediate values of saccade amplitude.

The explanation for the hypometria of anticipatory saccades in PD does not appear to be one of an inaccurate memory of the spatial location of the target, since patients with PD have been reported to make corrective saccades to the actual target location, even without new visual information (Crawford et al., 1989b). Thus, during predictive tracking in PD, the problem is not an inability to register accurately the location of the targets in memory; rather it is an inability to generate an initial saccade of a large enough amplitude.

**Timing disorders.** The abnormality of predictive timing in our patients was not simply a global decrease in the ability to anticipate the position of the target; the mean latencies of the patient groups were not significantly different from those of normal subjects. Rather, the pattern of tracking was less consistent, as reflected in more fluctuation of the mean values of latency throughout each period of tracking at a given stimulus frequency. Whether this defect is part of a generalized loss of fidelity of performance, as is suggested from the increase in the overall variability of saccade latency, or reflects a specific defect in the ability to store and to use timing information during predictive tracking, is not known.

**Frequency dependency of predictive deficits.** In our patients, the defects in timing and amplitude were more prominent at lower frequencies. Occasionally, defects were also seen at higher frequencies. Furthermore, the effect of frequency, per se, was greater in patients than in normal subjects. At low frequencies, prediction may be more impaired because of an inability to sustain the memory trace of target timing, while at 1 Hz, PD patients may falter in prediction in a similar way to that described by Dejong and Jones (1971) for eye movements and by Flowers (1978) and Bloxham et al. (1984) for manual tracking. Whether these effects of frequency are specific to patients with PD or also occur in patients with other conditions in which predictive behaviour is impaired, remains to be determined.

**Asymmetrical ocular motor function in hemi-PD**

**Directional asymmetry in hemi-PD patients.** Why did our patients with hemi-PD not show more directional asymmetry of their saccades abnormalities, considering the remarkable asymmetry of their somato-motor syndrome? Prior studies in hemi-PD have shown minimal or no directional asymmetries in saccades to randomly appearing targets (Carl and Wurtz, 1985; Rascol et al., 1989). Only in memory-guided saccades has a clear-cut asymmetry, in peak velocity (slower to the side of the somato-motor deficit) but not in amplitude or latency, been reported.

In interpreting results in hemi-PD one must keep in mind several caveats. First, it may be that the ocular motor abnormalities correlate with only one aspect of the somato-motor syndrome, for example the rigidity, the bradykinesia or the tremor. Our patients were heterogeneous with respect to somato-motor abnormalities though there was no obvious correlation between the predominant somato-motor finding and the ocular motor deficit. Secondly, it had been shown with positron emission tomography in patients with hemi-PD that asymmetrical activity in the putamen was correlated with the somato-
motor syndrome, while the decrease of activity with the CN was not (Leenders et al., 1990). Since the latter structure is more likely to be related to the control of eye movements, a large asymmetry in saccade performance might not be expected. Thirdly, predictive tracking in either direction may be behaviour that can be relatively well elaborated by either cerebral hemisphere. With respect to this last point there are bilateral cortical-striatal projections and considerable interhemispheric connections between the frontal lobes (Selemon and Goldman-Rakic, 1985, 1988; Stanton et al., 1988). These anatomical interconnections might account for the largely bidirectional nature of the ocular motor deficits in prediction in hemi-PD.

**Directional asymmetries in experimental hemi-PD.** In contrast, experimental studies in monkeys made acutely hemi-parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, have shown marked asymmetry of saccade function. Saccades were delayed, hypometric and slowed when directed toward the side of the affected limb (Miyashita et al., 1990; Usui et al., 1990). These deficits were greatest for memory-guided saccades; predictive capabilities were not examined. Furthermore, these experimental studies are not directly comparable to our results since, in patients there is often subtle involvement of the non-affected side of the body even when the somato-motor syndrome is predominantly unilateral. Likewise, since the pace of damage in human subjects with hemi-PD is much slower, more compensation would be possible than in the relatively acute animal models of hemi-PD.

**Cerebral hemispheral specialization and PD**

There is some evidence that the right and left cerebral hemispheres contribute to overall motor control in slightly different ways. The right hemisphere is thought to be more involved in the integration for spatial localization of the position of the target and the left hemisphere in programming and learning bilateral motor sequencing (Kimura and Archibald, 1974; Jason, 1983a,b; Haaland et al., 1987; Fisk and Goodale, 1988; Harrington and Haaland, 1991). Although the ocular motor deficits in our patients were largely bidirectional, our patients with hemi-PD did show several side-to-side differences in predictive tracking.

For LPD patients, predictive latencies were greater for leftward saccades. This finding is consonant with the idea that the right cerebrum, including the basal ganglia, may be relatively more important for triggering leftward than rightward saccades, whereas the left cerebral hemisphere may be relatively equi-potent for triggering saccades in either direction. Perhaps related is the finding that hemi-neglect in human patients is usually more prominent with right cerebral lesions. Furthermore, neuropsychological tests have shown a mild left hemispatial neglect in patients with LPD (Starkstein, 1987; Levin et al., 1991). This asymmetric defect in attention may account for the asymmetry in predictive latency in our patients with LPD. It is interesting that there was no asymmetry in latency for more reflexive, visually guided saccades, which suggests the idea that our patients could have neglect that is specific for internally generated, rather than for externally triggering behaviour.

Our patients with LPD also showed a greater degree of overall hypometria, and more variability, than did RPD. Whether or not these findings reflect a specific aspect of right cerebral hemisphere function related to programming the spatial components of predictive tracking remains to be proven.
On the other hand, patients with RPD showed more variability of saccade latency, across a wider range of frequencies, than did LPD patients. This finding suggests that the left cerebral hemisphere may play a more critical role in generating a precise estimate of the timing of the target during prediction.

To summarize, our results suggest that the left and the right cerebral hemispheres make slightly different contributions to the timing and the spatial components that comprise optimal predictive saccadic behaviour. Furthermore, this finding is compatible with the idea that the functions of the basal ganglia are intimately related to cerebral cortex via reciprocal loops (Alexander et al., 1986; Alexander and Crutcher, 1990). Further studies in patients with focal cerebral (and basal ganglia) lesions may confirm or refute these speculations about hemispheric specialization in predictive ocular motor behaviour.

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REFERENCES


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