Remembered Saccades With Variable Delay in Parkinson’s Disease

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Summary: The effect of increasing delay on the metrics of remembered saccades was studied in 10 subjects with mild Parkinson’s disease, none of whom was receiving treatment with l-dopa, and nine age-matched control subjects. Delays of 1 msec, 250 msec, 1000 msec, 2500 msec, and 5000 msec were used, and reflexive saccades used as a control condition. Results were analyzed for the gain of the primary saccade and the accuracy of the final eye position (FEP gain). Reflexive saccades were normal in subjects with Parkinson’s disease, but remembered saccades showed marked hypometria of primary saccade gain at all delays. FEP gain was unimpaired in Parkinson’s disease, and primary saccade gain and FEP gain did not vary as a function of delay. Hypometria of primary saccades is compatible with dysfunction in striato-collicular inhibitory pathways in Parkinson’s disease, arising as a functional consequence of dopamine deficiency in the basal ganglia. Maintenance of an accurate FEP gain suggests no deficit in oculomotor spatial working memory in Parkinson’s disease, at least at delays of up to 5 sec. Key Words: Parkinson’s disease—Remembered saccades—Basal ganglia—Dorsolateral prefrontal cortex—Spatial working memory.

The recent development of a range of behaviorally demanding saccadic paradigms has demonstrated dissociations in performance in individual patient groups which may reflect dysfunction of specific cortical and subcortical areas, and thus aid our understanding of the pathophysiology of these conditions. An example of this is Parkinson’s disease (PD), in which patients show distinctive deficits depending on the behavioral context in which the saccade is elicited.

Reflexive saccades are generally agreed to be normal in PD and antisaccades also appear to be normally executed, except in patients with advanced disease in whom increased distractibility and latency are reported. In contrast, saccades generated in the absence of a visual target, or as part of a sequence of eye movements, appear to display characteristic abnormalities in PD. Early studies reported greater hypometria when patients executed voluntary saccades to verbal commands than visually directed saccades and when patients moved their eyes back and forth either in the dark or to fixed targets. Predictive saccades are also impaired, with hypometria and difficulty in anticipating the stimulus, and asymmetries of this effect are described in patients with unilateral clinical signs. The generation of sequences of saccades is impaired in PD, and this effect can be reversed by the administration of l-dopa.

Similarly, the primary saccade in a remembered saccade task with visual input is hypometric in PD and this effect is also present for remembered saccades with vestibular or cervical input. However, despite primary saccade hypometria, a normal final eye position (FEP gain) is achieved with delays of 500 msec, although hypometria of FEP gain for leftward saccades is reported in a remembered saccade task with delays of 6 sec.

The remembered saccade task provides an oculomotor model with which to study spatial working memory, because it requires the subject to maintain an accurate internal representation of target location during a delay period before the generation of a saccade to the remembered location of the target. Dorsolateral prefrontal cor-
tex (DLPFC) appears to play an important role in spatial working memory, and dopaminergic blockade in this area induces inaccuracy of final eye position in a remembered saccade task. Subjects with PD are known to display mild deficits across a range of cognitive functions early in the course of their disease, and many of these impairments resemble those commonly attributed to frontal lobe dysfunction, including significant disruption of performance on visuospatial working memory tasks. Depletion of dopamine and its metabolites is reported in the prefrontal cortex of PD patients, and this deficiency may underlie the frontal cognitive deficits reported in PD, perhaps through frontostriatal projections. These findings suggest that dopamine deficiency in the prefrontal cortex of subjects with PD may predispose them to spatial inaccuracy in the reproduction of target location in the remembered saccade task manifest as errors in FEP gain. However, although primary saccade hypometria in the remembered saccade task has been well characterized in PD, few studies have systematically investigated the effect of delay on the spatial accuracy of the final eye position achieved in PD. The intention of this study was therefore to investigate the effect of increasing delay on the metrics of remembered saccades with particular reference to the accuracy of the FEP gain.

METHODS

Ten patients with mild to moderate Parkinson’s disease (Hoehn and Yahr stage 2 or 3) and nine age-matched control subjects were recruited. The mean age of patients was 62.5 years (range, 51–75 yrs) and that of control subjects 61.0 years (range, 53–74 yrs). No patient or control subject was taking medication known to affect oculomotor function: four patients were taking selegiline but none were taking L-dopa or anticholinergics. The mean disease duration from the time of diagnosis to when tested was 14.5 months (range, 2 mos–3 yrs). No subject showed evidence of dementia as assessed by the Mini Mental State Examination or had abnormalities of saccadic eye movements or smooth pursuit on bedside examination. The study had been approved by the local ethics committee and all subjects gave informed consent.

Eye Movement Recordings

Subjects were seated in total darkness 150 cm from a flat, translucent screen in which red light-emitting diodes (LEDs) were embedded. Eye movements were recorded using an infrared scleral reflection device (Skalar, Delft, Holland) which was linear over 29°, and a head rest was used to minimize movements of the head itself. Each recording session was preceded by a calibration sequence in which subjects fixated horizontal targets with known positions, and one practice run in each paradigm was given to ensure that subjects fully understood their instructions. Target presentation was controlled by a PDP11 computer (Digital Equipment Corp., Reading, U.K.) with a CED 502 interface. Details of oculomotor paradigms used are given below.

Reflexive Saccades

The subject fixated a central LED (Fig. 1). After 800 msec this LED was extinguished, and a peripheral LED appeared for 1000 msec at any one of eight possible locations in a horizontal plane (3.75°, 7.5°, 11.25°, or 15° to either side of fixation); a buzzer sounded for 200 msec simultaneously with onset of the peripheral LED. The subject was instructed to make a saccade as accurately and rapidly as possible to the peripheral LED and then return to fixation ready for the next trial. A total of 48 trials in two blocks of 24 trials each were recorded for this paradigm.

Remembered Saccades

The subject again fixated a central LED (Fig. 1). After 800 msec a peripheral LED at any one of four horizontal locations (±7.5° or ±15°) was presented for 200 msec but the subject was instructed to maintain central fixation. Five delay periods were then introduced at random (1 msec, 250 msec, 1000 msec, 2500 msec, 5000 msec), and following this delay a buzzer sounded and simultaneously the center LED was extinguished. This was the cue for the subject to make a saccade as rapidly and accurately as possible to the remembered location of the target and then return to fixation ready for the next trial. Data was collected for a total of 48 trials at all delays.

Data Analysis

Saccadic data was analyzed for primary saccade gain (primary saccade amplitude/target amplitude) and the accuracy of the final eye position achieved (FEP gain: final eye position amplitude/target amplitude) using an interactive computer program (ASYST, Asyst Software Technology, Rochester, NY, U.S.A.). Saccades to remembered targets that were initiated before or less than 100 msec after the buzzer sounded were considered anticipatory saccades and excluded from analysis. Statistical analysis was performed using analysis of variance with repeated measures (ANOVA) and the level of significance set at p <0.05.

RESULTS

All results of saccadic analysis are given in Table 1 and represented graphically in Figure 2.
Reflexive Saccades

Primary saccade gain and FEP gain did not differ significantly between the two groups (primary saccade gain: control 0.96 ± 0.07, PD 0.89 ± 0.16; FEP gain: control 1.02 ± 0.07, PD 1.02 ± 0.16). The latency of reflexive saccades was not significantly different between the two groups (control: 249 msec ± 47.4; PD: 235 msec ± 44.6).

TABLE 1. Saccadic data (mean ± 1 standard deviation) for primary saccade gain and FEP gain as a function of delay in a remembered saccade task for control and PD subjects

<table>
<thead>
<tr>
<th>Delay</th>
<th>1 ms</th>
<th>250 ms</th>
<th>1000 ms</th>
<th>2500 ms</th>
<th>5000 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary saccade gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.88 ± 0.39</td>
<td>0.87 ± 0.24</td>
<td>0.98 ± 0.03</td>
<td>0.96 ± 0.32</td>
<td>0.93 ± 0.17</td>
</tr>
<tr>
<td>PD</td>
<td>0.65 ± 0.28*</td>
<td>0.56 ± 0.24*</td>
<td>0.66 ± 0.29*</td>
<td>0.65 ± 0.3*</td>
<td>0.76 ± 0.23*</td>
</tr>
<tr>
<td>FEP gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.03 ± 0.15</td>
<td>1.08 ± 0.2</td>
<td>1.00 ± 0.17</td>
<td>1.05 ± 0.17</td>
<td>1.08 ± 0.21</td>
</tr>
<tr>
<td>PD</td>
<td>0.91 ± 0.12</td>
<td>1.00 ± 0.16</td>
<td>1.03 ± 0.17</td>
<td>0.91 ± 0.18</td>
<td>1.02 ± 0.3</td>
</tr>
</tbody>
</table>

FEP, final eye position; PD, Parkinson’s disease.
There is significant primary saccade hypometria in the remembered saccade task in PD subjects at all delays, with preservation of FEP gain.

Remembered Saccades

Latency

The mean latency of remembered saccades across all delays did not differ significantly between the two groups (control: 312 msec ± 116; PD: 287 msec ± 124).

FIG. 1. Schematic representation of the reflexive (A) and remembered (B) saccade paradigms. Full details of the target configuration and subject instructions are given in the text.
Primary Saccade Gain
There was a main effect of group with PD subjects displaying marked hypometria ($F[1, 16] = 5.26; p = 0.03$). However, there was no main effect of delay and no significant interaction between group and delay. The mean primary saccade gain across all delays was 0.61 ± 0.28 for PD subjects and 0.92 ± 0.28 for control subjects.

FEP Gain
Mean FEP gain across all delays was 0.93 ± 0.22 for subjects with PD compared with 1.05 ± 0.17 for control subjects, and statistical analysis showed no main effect of group ($F[1, 16] = 0.98, p = 0.34$). There was also no main effect of delay, and no interaction between group and delay.

Laterality Effects
Data for both primary saccade gain and FEP gain were also analyzed by saccade direction to see if there was any evidence of lateralization of effect. There was no significant main effect of saccade direction and no interaction between group and direction for either measure.
DISCUSSION

The results of this study demonstrate that there is no decay in the spatial accuracy of the FEP gain of remembered saccades in PD at delays of up to 5 sec. Although primary saccades displayed marked hypometria at all delays, this did not vary as a function of increasing delay. Evidence from existing studies provides a framework within which to interpret these results in terms of both spatial working memory and motor programming.

Dorsolateral prefrontal cortex appears to play a pivotal role in the performance of delayed response tasks, and neurons in this area show individual activity in relation to the cue, delay, and response phases of an oculomotor delayed response task. The responses of delay period neurons are maximal to targets in specific locations of the visual field with the same neuron always encoding the same target location. Pharmacologic antagonism of dopaminergic (D1) receptors in the DLPFC of monkeys induces errors in the final eye position of remembered saccades, and the magnitude of this effect is sensitive to the length of the delay period with significant effects emerging only with delays of greater than 1.5 sec. The effects of D1 blockade on primary saccade gain were not reported in these studies.

Cognitive deficits are well recognized in PD, and many authors have stressed the frontostrial nature of these deficits. Among these, impairment of delayed response and visuospatial working memory tasks appear to be relatively early and sensitive findings, even in patients with clinically mild disease; performance in these tasks has been reported to improve after the administration of L-dopa. It has been suggested that these deficits reflect functional disruption of neural loops linking the striatum to the frontal cortex through the thalamus and pallidum arising either from dopamine deficiency in the prefrontal cortex or striatum.

Hence, dopamine deficiency in DLPFC or its striatal inputs may be expected to impair the accuracy of spatial responses in a remembered saccade task but the results of the current study do not support this contention, at least at delays of up to 5 sec. A previous study has reported unilateral hypometria of FEP gain in PD subjects performing a remembered saccade task with a 6-sec delay; this effect was not reversed by the administration of L-dopa. The differences between these two studies may reflect the longer disease duration of the patients recruited (a mean of 9 years as opposed to 14.5 months in the current study) or differences in the experimental paradigm and recording technique.

In addition, the patients in the current study were not medicated with L-dopa (although four were taking sele-giline), and this may be an important factor to consider when interpreting the data and drawing comparisons with the results of other studies. Treatment with L-dopa has been reported to affect the performance of both reflexive and volitional saccades, and adverse cognitive effects of L-dopa are well recognized in a clinical setting. There is greater depletion of dopamine in the motor putamen than in the prefrontal cortex or caudate in Parkinson’s disease, and doses of L-dopa required to correct the motor effects of dopamine lack in the putamen may act adversely on areas where dopamine concentrations are relatively intact both in the short-term and by long-term regulation of dopaminergic receptors.

The failure to demonstrate an effect of 5-sec delays on FEP gain in PD subjects may have several explanations. Clearly, the delay may not be long enough to expose a deficit in spatial working memory or the patients selected may be too mildly affected. Studies in primates that have demonstrated inaccuracies of FEP gain with delays of greater than 1.5 sec after dopaminergic blockade in DLPFC have been more spatially demanding than the paradigms used in people, using a large number of randomly presented targets, and achieved high levels of local dopaminergic antagonism which are not pharmacologically feasible in people.

The somatomotor features of PD, particularly akinesia, have been attributed to dopamine deficiency in the striatum, and a similar mechanism appears likely to underlie primary saccade hypometria in the remembered saccade task. GABA-ergic inhibitory caudate-nigral and nigro-collicular pathways act to modulate the effects of excitatory cortical input into the superior colliculus, and these pathways are preferentially active during saccades to remembered targets. Pharmacologic accentuation of inhibitory input into the superior colliculus from the caudate nucleus and substantia nigra, pars reticulata induces striking primary saccade hypometria, particularly in a remembered saccade task, and depletion of dopamine in the caudate nucleus by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has a similar effect. Further support for this thesis is provided by the finding that schizophrenic subjects treated with dopaminergic antagonists develop similar deficits in saccadic performance to subjects with PD.

However, the effect of dopamine on primary saccade metrics in the remembered saccade task has been addressed by only one study in which the administration of L-dopa was shown to have no effect on saccadic hypometria. Further studies to clarify the role of treatment with dopaminergic drugs on saccadic performance in PD, with particular reference to primary saccade hypometria, would be valuable.
The results reported in this study, with primary saccade hypometria but preservation of FEP gain, may reflect the relative severity of loss of dopaminergic transmission in the striatum and prefrontal cortex in PD. Although striatal dopamine deficiency may manifest as primary saccade hypometria at short delays in a remembered saccade task, a delay which places greater demands on spatial working memory may be required to reveal deficiencies in mechanisms involving prefrontal cortex.

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REFERENCES


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