Antisaccades and remembered saccades in Parkinson’s disease

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Abstract

Antisaccades were studied in ten patients with mild to moderate Parkinson’s disease and ten age-matched normal controls. Remembered saccades and reflex saccades were assessed for comparison. In the population of patients who showed the previously reported abnormalities of remembered saccades, antisaccades were indistinguishable from those of controls in latency, gain and peak velocity. This finding implies that antisaccades are mediated through pathways which are unaffected by Parkinson’s disease, and which are therefore presumably distinct from pathways mediating other voluntary saccades.

There has recently been much interest in the way in which disorders of the basal ganglia affect eye movements, particularly saccadic eye movements. This has been stimulated by neurophysiological work which suggests that the basal ganglia are involved in the generation of some types of saccade but not of others. Briefly, saccades may be divided into reflex, spontaneous and voluntary types. Reflex saccades are those in which a novel visual, auditory or somatosensory stimulus directly precedes a saccade made to that stimulus; they may be mediated primarily via the superior colliculus, as are spontaneous saccades. Voluntary (or internally-generated) saccades comprise a variety of different types, including volitional (that is, saccades made to direct command), predictive (anticipatory saccades made to a predictable target), remembered (saccades made to the remembered location of a target), and antisaccades (saccades made in a direction opposite to that of a target). These voluntary saccades may be mediated through higher centres, including the frontal eye fields and the basal ganglia, in addition to the superior colliculus. Thus, the substantia nigra, pars reticulata has recently been shown to be particularly involved in generating remembered saccades in monkeys, and this concurs with the clinical finding that remembered saccades are abnormal in patients with Parkinson’s disease. Antisaccade paradigms were originally used in normal subjects when they formed part of a series of tests of internal manipulation of visual stimuli: subjects were instructed to look at a point in space which was an equal distance from fixation as the target light, but in exactly the opposite direction (that is, its “mirror image”). Lasker et al found that patients with Huntington’s disease showed greater difficulty than normal controls in suppressing unwanted (reflex) saccades to the target light itself when performing this task. This they termed increased “distractibility”. They also found increased latency and decreased velocity of correctly-executed antisaccades in their patients. Similarly, Guitton et al showed that patients with frontal lobe lesions exhibited increased distractibility, as well as prolonged latency of antisaccades.

Volitional, remembered, reflex and predictive saccades have all been studied in Parkinson’s disease. However, to our knowledge, antisaccades have not. Previous work on remembered and predictive saccades has suggested that the Parkinsonian saccadic deficit may be bypassed in situations in which a novel visual stimulus is followed by a saccade made directly to that stimulus. A possible mechanism which has been put forward is that the new visual stimulus allows some form of “unlocking” of visual fixation, or “attentional capture”, the latter being abnormally strong in Parkinson’s disease. If the observed improvement in saccadic performance is due to such “unlocking”, it is desirable to know if fixation may be unlocked only by the future target for a saccade, or whether it can be unlocked by a new visual event occurring anywhere in the field of view, that is, the process of “unlocking” may not be specifically linked to saccade destination. In the antisaccade paradigm, a novel visual stimulus is followed by a saccade, but not by one made to that stimulus. Thus, if Parkinsonian subjects were able to make antisaccades normally this would imply that “unlocking” is not a property of saccadic targets, but of sudden changes occurring anywhere in the visual field.

Assessment of antisaccades in Parkinson’s disease was thus considered to be important for two reasons. First, it would give information relating to the visual field specificity of the “unlocking” process. Second, it would provide further insight into the involvement of the basal ganglia in the generation of voluntary saccades by comparison with the abnormalities which have been previously demonstrated in Huntington’s disease. In case Parkinsonian patients should show no difference from normal controls it was thought important to...
repeat the remembered saccade study to demonstrate that the subjects concerned did show the expected Parkinsonian abnormality. It was further decided that it was important to use Parkinsonian subjects who were only mildly to moderately (that is, Hoehn-Yahr grade I–III) affected. This was because only in these stages of the disease is the disorder likely to be confined to the basal ganglia—in the more advanced stages other brain structures show pathological changes and it becomes inappropriate to assign abnormalities to dysfunction solely of the basal ganglia. This study was therefore designed to test random, remembered and antisaccades in patients with mild to moderate Parkinson’s disease.

Methods
Subjects
Ten patients with mild to moderate idiopathic Parkinson’s disease were compared with ten age-matched normal controls. The ages of the Parkinsonian patients ranged from 54 to 72 years (mean 66 years); their clinical features, including disease duration, Hoehn-Yahr staging, and medication are shown in table 1. There was no clinical evidence of dementia in any of the patients. All patients except one (patient 5) were receiving levodopa therapy. The time interval between the last dose of levodopa and eye movement recording was standardised to between three and four hours.

The ages of the controls ranged from 64 to 84 years (mean 70 years). They were not taking any medication known to affect cerebral or oculomotor function. All subjects gave informed consent.

Equipment
Eye movements (left eye) were recorded using the magnetic scleral search coil technique (C-N-C Engineering, Seattle, Washington). Blinks were timed using a DC electro-oculography (EOG). Subjects were seated 150 cm from a tangent screen in which were embedded red lights emitting diode (LED) targets. A buzzer was located behind the subject’s head which was firmly supported in a head rest. All extraneous light was excluded during each paradigm. A whole recording session generally lasted about thirty minutes.

Eye velocity was obtained by on-line electronic differentiation of eye position signals. Eye position and velocity, the stimulus details, and EOG blink recording were all printed on a Mingograph chart recorder (bandwidth 500 Hz) at a paper speed of 25 mm/s. The overall bandwidth for eye position was 300 Hz, linear to ±1% within the range ±20°; the velocity bandwidth was 90 Hz.

Stimulus presentation was controlled by computer (PDP 11/73). Each session consisted of calibration followed by each of three different paradigms. Presentation order of the paradigms was varied on a Latin-square basis to avoid effects of fatigue, practice etc. The paradigms were termed the “random” saccade paradigm, the remembered saccade paradigm, and the antisaccade paradigm. The antisaccade paradigm was based on that used by Lasker et al. and the remembered saccade paradigm was identical to that used by Crawford et al.

Precise details are as follows:
“Random” saccade paradigm (fig 1). A central LED was illuminated at the beginning of each trial and the subject was asked to fixate it. After 800 ms, the central LED was extinguished and, simultaneously, a peripheral LED was illuminated. The peripheral LED could be at any of four possible locations along the horizontal axis (15° left, 7.5° left, 7.5° right, or 15° right). The subject was asked to look as quickly and as accurately as possible at the new light and then to return to the central position, ready for the next trial. The order of peripheral LED presentation was varied pseudo-randomly from trial to trial to prevent prediction by the subject. The buzzer was sounded for 200 ms, starting simultaneously with centre LED offset and peripheral LED onset. This was included to make the paradigm comparable to the remembered and antisaccade paradigms. A complete block consisted of 48 trials. (The term “random” refers only to the spatial location of the target and not to the position of the subject’s head, which was held constant, and was therefore predictable.)

Remembered saccade paradigm (fig 1). A central LED was illuminated. After 800 ms, a peripheral LED was flashed on for 200 ms. The central LED remained on, however, and the subject was instructed not to look at the peripheral LED immediately. The buzzer sounded 500 ms after the flash, and, at this time, the subject was asked to recall the location of the peripheral stimulus.
point, the subject was required to make a saccade to the remembered location of the peripheral LED. The central LED was extinguished with the onset of the buzzer (duration 200 ms). The location of the peripheral LED was again varied pseudo-randomly between 7·5° and 15°, right and left. A total of 48 trials made up each block.  

**Antisaccade paradigm** (fig 1). As in the other paradigms, a central LED was illuminated to signal the start of each trial. After 800 ms a peripheral LED (chosen pseudo-randomly, as above) was illuminated. This time, however, the subject had to look at an imaginary position in space corresponding to the mirror-image of the peripheral LED, that is, to a point equidistant from the centre, but in exactly the opposite direction. A buzzer (200 ms) was again sounded, its onset being simultaneous with the centre offset and peripheral LED onset. The peripheral LED stayed on for 2000 ms, and at this point, the mirror-image LED was itself illuminated; the subject was asked to fixate this second LED directly so as to provide a measure of accuracy of the initial antisaccade. Again, there were 48 trials per block.  

**Analysis**  
Charted data were analysed using a Tektronix 4052A computer and a bit pad, accurate to 1/200th of an inch. Any saccade occurring within 50 ms of a blink was discarded. In analysing antisaccades, only saccades made in the correct direction were included. Those made in the opposite direction (that is, in the direction of the target LED) were considered "errors" and were analysed separately. In analysing remembered saccades, any saccade occurring before onset of the buzzer was discarded to prevent contamination by predictive saccades.  

Each initial saccade was analysed for latency, amplitude, gain (saccade amplitude divided by target step size, expressed as a percentage), and peak velocity. A regression line was fitted to the peak velocity data when plotted against the logarithm of saccade amplitude, as this relationship is approximately linear within the range 5° to 15°. From this line, calculated peak velocities were derived for hypothetical 7·5°,

10° and 15° saccades. The means and standard deviations of latency, gain and peak velocity (for each of the three amplitudes) were then calculated.

Data for random saccades, remembered saccades, antisaccades and antisaccade "errors" were compared with each other for both normal controls and for Parkinsonian patients. Two-way and three-way analyses of variance were performed for each saccade type. The first (between) factor was always Parkinson's disease versus controls; the second (within) factor was saccade type. If peak velocity was being analysed, a third (within) factor of saccade amplitude was included. Paired or unpaired Student's t tests were then performed as appropriate on data displaying significant F values. A p value of less than 0·05 was considered significant.

For both remembered and antisaccade paradigms, "distractibility indices" were calculated. This was the number of saccades made in the wrong direction (for antisaccades) or too early (remembered saccades) divided by the total number of analysed saccades in each block. Distractibility in the normal and patient groups were compared by Student's t test.

**Results**  
All the results of the saccadic analysis are shown in table 2.

"Random" saccades  
There were no differences between Parkinsonian and control random saccades. This was true in respect of mean gain, mean latency and peak velocity at all three amplitudes: none of these measurements reached significance on analysis of variance.

**Remembered saccades**  
There was a significant difference between the gains of Parkinsonian and control remembered saccades. The mean gain of the former was 73%, whereas that of the latter was 87%. This difference achieved significance at the p < 0·05 level. The peak velocities of Parkinsonian saccades were slightly lower than those of controls, but this difference failed to achieve significance. Similarly, there was no significant difference between the distractibility indices of the two groups. There was no significant difference between Parkinsonian and control latency, but as the time interval between centre LED onset and buzzer was identical for every trial, latency was not considered further.

When remembered saccades were compared with random saccades, there was a significant reduction in gain of the Parkinsonian group, but not of the control group. For both groups, there was a significant drop in peak velocity. This was of the order of 60 to 80% for 15° saccades, and the difference was significant at p < 0·01 for controls and p < 0·001 for Parkinsonian patients (paired t test).

**Antisaccades**  
As with random saccades, there was no difference between Parkinsonian subjects and Parkinsonian patients.
controls. When antisaccades were compared with random saccades, both patients and controls behaved similarly. There was a reduction in gain from about 90% to about 75% (significant for both groups at p < 0.01) and peak velocity was reduced by about 60°/s (p < 0.001 for both groups). Comparison with remembered saccades showed no significant difference for either group in terms of gain or peak velocity.

**Antisaccade errors**

For both Parkinsonian patients and controls, antisaccade errors displayed a consistent effect. The saccades themselves were of the same peak velocities as random saccades, but gain was reduced and latency prolonged. This latency prolongation was nowhere near the extent of the latency prolongation of correct antisaccades; it was significant for both Parkinsonian patients and controls at p < 0.01.

**Discussion**

The results show that there is no difference in the performance of Parkinsonian patients and controls in the antisaccade task for any of the saccade metrics analysed. However, in both patients and controls, antisaccades are of lower gain, longer latency, and lower peak velocity than random saccades. The lack of difference between Parkinsonians and controls is almost certainly not a false negative finding for two reasons:

1. The same patients and controls did show a difference when they were tested for remembered saccades. The findings of significantly reduced gain and slightly reduced peak velocity in remembered saccades are similar to those described elsewhere. There are no significant changes in either of these during sessions. Note that the buzzer immediately preceded the relevant saccades of each paradigm. Hence, the buzzer itself could be ruled out as a factor contributing to any difference between saccade types.

Several of the findings of this paper agree with previous studies. In the case of reflex saccades as elicited in the random paradigm, we were unable to detect a difference between normal and Parkinsonian performance. This has been reported previously, although some studies have found minor differences; these differences are probably related to variations in procedures used by the respective authors to elicit reflex saccades, in addition to the fact that the studies concerned included severely affected patients. Similarly, the reduced Parkinsonian performance on remembered saccades agrees well with the results of previous studies. The control subjects in the current study also showed a significant difference in the metrics of both remembered saccades and antisaccades when compared with random saccades: this has been previously reported for normal subjects, although a significant reduction in the mean gain of antisaccades was not found.

Concerning the antisaccade distractibility, the indices for both Parkinsonian patients and controls were in the region of 30% to 40%. Laker et al. in their study of Huntington’s disease, found figures of 16-8% for controls and 59-9% for patients. It is possible that the increased distractibility of our patients and controls relative to that of their controls is related to increased age: Laker et al noted that the two of their controls aged 53 and 66 years made over 20% errors.

Thus, when performing antisaccades, Parkinsonian patients appear to behave exactly as normal subjects. This is very different from the behaviour of patients with Huntington’s disease or of patients with lesions of the frontal lobes in whom distractibility is grossly increased (to about 60%), with latency for correct antisaccade response also being considerably elevated. Antisaccade peak velocity is also reduced in Huntington’s disease.

The neurophysiological processes involved...
in the production of antisaccades are quite complex. The peripheral stimulus provides an immediate drive to make a reflex saccade towards it, and this must be suppressed to allow an antisaccade to occur. Having detected the stimulus, a voluntary saccade must be generated to the mirror image location (in the absence of a direct stimulus). The frontal eye fields and basal ganglia are probably involved in the generation of voluntary saccades (see Zee' for review). Thus, the antisaccade paradigm tests simultaneously the generation of voluntary saccades and the suppression of reflex ones.

In the case of Huntington's disease, it has been suggested that the increased distractibility is due to impaired inhibition of the superior colliculus normally mediated via the substantia nigra, pars reticulata.27 The lack of increase in distractibility in Parkinson's disease suggests that there is no abnormality in the level of tonic suppression/inhibition of the superior colliculus in this condition. Similarly, the finding that antisaccades in Parkinson's disease have the same metrics as those of normal controls in Parkinson's disease is destined. This would explain why both reflex saccades,13 compatible with the idea that the Parkinsonian saccadic defect may be bypassed by any novel stimulus, not just one to which a saccade is destined. This would explain why both reflex saccades and antisaccades are indistinguishable from those of normal controls in Parkinson's disease while all other types of voluntary saccade are not. Note, however, that in normal individuals the metrics of antisaccades are different from those of reflex saccades. Further work is in progress to clarify the exact nature of these features of a stimulus which will generate a "normal" response in patients with Parkinson's disease—such clarification may add to the understanding of the pathophysiology of the disease.

References

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