Voluntary Control of Saccadic Eye Movement in Patients with Frontal Cortical Lesions and Parkinsonian Patients in Comparison with that in Schizophrenics

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To investigate whether the abnormalities of antisaccades in schizophrenics could be explained by a dysfunction of the frontal cortex, we examined 10 patients with frontal cortical lesions and 22 patients with idiopathic Parkinson's disease with mild symptoms (Yahr I-II) using the same tasks, and compared the results with those obtained in schizophrenics. The frontal patients with lesions covering the frontal eye field and prefrontal cortex showed more errors, longer latencies, and lower peak velocities in the antisaccade task, despite giving normal results in the visually guided saccade task. This was similar to the results observed in schizophrenics. Parkinsonian patients did not consistently show a significant difference in the antisaccade task. These results indicate specific abnormalities of antisaccades in schizophrenics and patients with frontal cortical lesions but not consistently in Parkinsonian patients. This suggests that the abnormalities of antisaccades in schizophrenics might be explained by a frontal cortical dysfunction.

Key Words: Saccade, antisaccade, schizophrenics, parkinson's disease, patients with frontal lesions, frontal cortical dysfunction

Introduction

We reported previously that many schizophrenic patients showed higher error rates, longer latencies, and lower peak velocities in the antisaccade task, despite giving normal results in the visually guided saccade task (Fukushima et al 1988, 1990a,b; Thaker et al 1989). These abnormalities were correlated with frontal cortical atrophy in computed tomography (CT) scans, but not with age or quantities of medication; and even nonmedicated schizophrenics showed the above-mentioned abnormalities (Fukushima et al 1990a,b).

The frontal eye field and prefrontal cortex are known to control saccadic eye movements (Bruce and Goldberg 1985; Guitton et al 1985; Goldberg and Segraves 1989; Pierrot-Deseuiligny et al 1991). Abnormalities in the antisaccade task, therefore, suggest a frontal cortical dysfunction in schizophrenics. To examine whether or not the frontal cortex is involved in abnormalities in the antisaccade task in schizophrenics, it is necessary to examine patients with lesions localized in the frontal cortex using the same task.
Another important area in the control of saccadic eye movement is the basal ganglia, particularly the substantia nigra (Hikosaka and Wurtz 1983, 1985). Their animal experiments suggested the possibility that patients with Parkinson's disease might show abnormalities in the inhibition of reflexive saccades. It has been reported that patients with mild Parkinson's disease do not show higher error rates or longer latencies than controls in the antisaccade task, however, although their paradigm was somewhat different from that used in our study (Lueck et al 1990). Therefore, it is necessary to examine Parkinsonian patients using the same task and situation used for schizophrenics. In patients with severe Parkinson's disease, however, various brain areas in addition to the basal ganglia are most probably involved; for example, the frontal cortical atrophy was evident in Yahr III patients in CT scans (T. Warabi, personal communication). To minimize the factors of cortical involvement, it is necessary to examine only mild Parkinsonian patients (Yahr I–II). The purpose of this study is to examine whether or not the abnormality in antisaccades in schizophrenics can be explained by dysfunction of the eye movement-related frontal cortical areas and/or the basal ganglia. For this, we examined patients with lesions in the frontal cortex together with patients with mild symptoms of Parkinson's disease using the same task, and compared the results with those obtained in schizophrenics.

Part of the results was presented in an abstract (Fukushima et al 1991).

**Subjects**

Ten patients with frontal cortical lesions were examined. The mean age was 54.3 (±12.2 SD, range 26–72) years old. Table 1 summarizes the nature of the lesions in these 10 patients. Four of them had had subarachnoidal hemorrhage due to an aneurysm of the anterior communicating artery, and had received surgery; four had cerebral infarction, and the other two had subdural hematoma. The localization of the lesions determined from magnetic resonance imaging (MRI) is illustrated in Figure 1A (Cases 1–5) and 1B (Cases 6–10). Six of the 10 patients had bilateral lesions (Cases 1–4, 6, 7), and the remaining four patients had unilateral lesions (Cases 5, 8–10).

Twenty-two (9 men and 13 women) patients with idiopathic Parkinson's disease were examined. The mean age was 56.9 (±7.2 SD, range 40–70) years old. A summary of the clinical characteristics of these Parkinsonian patients is shown in Table 2. The clinical symptoms were evaluated according to Hoen-Yahr staging (Hoen and Yahr 1967) and the modified Columbia Scale (Lehmitte et al 1978). None of the Parkinsonian patients showed dementia as defined by the Mini-mental scale (Folstein et al 1975). Fifteen of the 22 patients were receiving medication at the time of testing (L-DOPA, carbidopa, anticholinergics, amantadine, and bromocriptine), whereas the other seven patients had never been treated before with antiparkinsonian drugs.

Twenty age-matched control subjects for the Parkinsonian patients were examined (control A). The mean age was 57.3 (±9.2 SD, range 45–72) years old. They were also used as normal controls for the patients with frontal lesions, because these patients were relatively old (range for 9 patients, 45–72 years old, see Table 1) except for one (26 years old).

The present study for schizophrenic patients consisted of 18 (13 men and 5 women) subjects who fulfilled DSM-III-R criteria for schizophrenic disorder. Ten patients had been admitted in the Department of Psychiatry of Hokkaido University Hospital, and eight were outpatients there. Their clinical findings were similar to those already reported previously (Fukushima et al 1990a). Briefly, the mean age for the schizophrenic patients in the present study was 30.6 (±8.0 SD, range 16–43) years old. Fifteen paranoid, two disorganized, and one residual type patients were included. Their mean duration of illness was 7.2 (±7.5 SD) years. All the schizophrenics showed negative symptoms and some of them revealed mild hallucination and/or delusion, but they were in a relatively stable state and they could understand the eye movement tasks in this study sufficiently. All of them were receiving medication at the time of this study except for one. The medication received consisted of a major tranquilizer and anticholinergics but no lithium, antidepressants, or anticonvulsants were used. The antipsychotics received were converted to chlorpromazine according to Davis's criteria (Davis 1976) and the mean was 614.5 (±456.3 SD) mg. No side effects (drowsiness or Parkinsonism) due to the medication were noted. None of the subjects showed tardive dyskinesia, according to the criteria of Schooler and Kane (Schooler and Kane 1982).

Although we had examined the saccade- and antisaccade-
Figure 1. Extent of frontal lesions in 10 patients determined by MRI studies. Lesions are shown with different lines in A (Cases 1-5) and B (Cases 6-10). Abbreviations: PFC = prefrontal cortex; FEF = frontal eye field; PPC = posterior parietal cortex; sfs = superior frontal sulcus; pre-cs = precentral sulcus; cs = central sulcus; post-cs = postcentral sulcus; ips = intraparietal sulcus.

tasks on schizophrenic patients previously (Fukushima et al 1988, 1990a,b), we reexamined schizophrenics in this study, because the saccade task used this time was slightly different from the previous one; patients examined in this study were also different from the previous studies. In those studies, the target position was randomized only in direction (i.e., left or right); whereas in the present study, the target position was randomly changed not only in direction, but also in amplitude (i.e., 8°, 12°, or 24°). This reexamination of the saccade task was because some studies reported that schizophrenics revealed longer latencies than controls in the saccade task in which the target position was randomly changed not only in direction, but also in amplitude (Yee et al 1987).

The normal controls for the schizophrenics (control B) were nine age-matched healthy subjects who had no history of psychiatric disorder. The mean age for control B was 31.1 (±7.0 SD, range 19–39) years old. Informed consent was obtained from all the subjects.

Methods

Each subject sat on a chair in the dark, facing a screen that was placed 100 cm away from the subject's eyes. The visual targets consisted of 7 light-emitting diodes (LEDs). One of them was used as a central fixation point, and the others were positioned at 8°, 12°, and 24° to the right and left of the central LED. When the LEDs were not turned on, their position could not be seen by the subjects. The behavioral paradigms are similar to those in previous studies (Fukushima et al 1990b), and are schematically summarized in Figure 2C.

In the saccade task (Figure 2C), the central LED was turned on for 4–6 sec randomly to avoid prediction, and the subjects were instructed to keep their gaze fixed on the light. The central light was then extinguished, and at the same time, one of the 6 targets was turned on for 500 msec. As described above, the selection of the target was randomized in both direction (i.e., left or right) and amplitude (i.e., 8°,
12°, or 24°) to prevent prediction. Subjects were instructed to look at the target as quickly as possible. A total of 60 runs were assigned to each subject; these 60 runs consisted of 10 runs of 8°, 12°, and 24° saccades to the left and right.

In the antisaccade task, as soon as the central light was turned on for 500 msec (Figure 2C). The subjects were told not to look at the target but to look immediately in the opposite direction, at an approximately equal distance from the fixation point. In this task, the selection of the target was randomized only in direction (i.e., left or right). Thus, 20 runs of 12° of antisaccade task were tested first, followed by 20 runs of 8° and 20 runs of 24° (i.e., a total of 60 runs) of antisaccades.

Horizontal eye movements were recorded electrooculographically (EOG) using surface electrodes applied to the outer canthus of each eye; direct-current (DC) recording with a high frequency cutoff of 100 Hz was used. Eye position and LED signals were displayed using a thermal array recorder and were stored on a data recorder for later analysis with a computer. Eye velocities were derived by the electric differentiation of eye position records and were displayed on a computer screen (sampling clock 10 msec).

We checked all the data by visual inspection on a recorder and also on the computer with an expanded time scale, and any run that included saccades during the fixation period was excluded.

The onset and end points of saccades that were initiated by targets were determined from the eye velocity and position traces. In the antisaccade task, we judged all saccades that were made toward the direction of the target as errors. Latencies, peak velocities, durations, and amplitudes of saccades were measured in the saccade and antisaccade tasks when the subjects did not make errors as described previously (Fukushima et al 1990b). Only the first main saccades were examined; corrective saccades were not included in this analysis. The error rate was calculated as the number of errors divided by the total number of trials. Means and SDs were calculated for each subject. Statistical significance was calculated using ANOVA. Latencies of errors (i.e., latencies of saccades that were made toward the direction of the target in the antisaccade task) were also measured separately. The peak velocities of all the saccades and antisaccades were plotted against the amplitudes for each patient and control. The peak velocities at 8°, 12° and 24° saccades were calculated from the best-fit logarithm curve as described by Bahill et al (1975).

Because it is well known that aging affects the performance of saccadic eye movements (e.g., Tedeschi et al 1987; Fletcher and Sharpe 1986), a direct comparison among the three patients groups cannot be made. We therefore compared frontal and Parkinsonian patients data with age-matched old controls (control A), and schizophrenics data to age-matched young controls (control B).

All of the subjects could understand the instructions well and were cooperative in the study. When they complained of fatigue or sleepiness, the experiment was halted and the subjects were allowed to rest or quit altogether.
Table 3. Summary of the Results of all Subject Groups

<table>
<thead>
<tr>
<th></th>
<th>Control A</th>
<th>Frontal</th>
<th>Parkinson</th>
<th>Control B</th>
<th>Schizophrenic</th>
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<tbody>
<tr>
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<td>10</td>
<td>22</td>
<td>9</td>
<td>18</td>
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<tr>
<td>Age</td>
<td>57.3 (9.2)</td>
<td>54.3 (12.2)</td>
<td>56.9 (7.3)</td>
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<td>Visually-guided</td>
<td>253.6 (37.4)</td>
<td>267.0 (32.1)</td>
<td>239.8 (33.4)</td>
<td>232.8 (33.2)</td>
<td>233.2 (39.7)</td>
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<tr>
<td>mean latency (msec)</td>
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<tr>
<td>Mean peak velocity (deg/sec)</td>
<td>255.8 (42.4)</td>
<td>233.5 (32.6)</td>
<td>247.1 (35.0)</td>
<td>222.1 (20.7)</td>
<td>218.4 (37.6)</td>
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<tr>
<td>8 deg</td>
<td>318.6 (45.7)</td>
<td>289.8 (39.7)</td>
<td>310.2 (32.7)</td>
<td>287.7 (33.2)</td>
<td>280.2 (54.7)</td>
</tr>
<tr>
<td>12 deg</td>
<td>423.3 (56.4)</td>
<td>383.8 (60.3)</td>
<td>416.3 (39.9)</td>
<td>397.2 (60.8)</td>
<td>367.2 (76.3)</td>
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<td>24 deg</td>
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<tr>
<td>Antisaccade</td>
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<td>error(%)</td>
<td>14.9 (10.8)</td>
<td>41.0 (31.5)</td>
<td>24.5 (18.5)</td>
<td>3.9 (4.7)</td>
<td>33.6 (20.6)</td>
</tr>
<tr>
<td>mean latency (msec)</td>
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<td>398.3 (45.9)</td>
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<td>283.1 (14.3)</td>
<td>346.1 (81.7)</td>
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<td>Mean peak velocity (deg/sec)</td>
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<td>211.4 (27.4)</td>
<td>246.4 (43.8)</td>
<td>231.5 (39.3)</td>
<td>221.9 (45.3)</td>
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<td>8 deg</td>
<td>303.1 (43.9)</td>
<td>266.1 (24.0)</td>
<td>299.9 (39.9)</td>
<td>284.7 (45.2)</td>
<td>264.6 (60.0)</td>
</tr>
<tr>
<td>12 deg</td>
<td>394.6 (62.8)</td>
<td>357.2 (42.3)</td>
<td>389.1 (44.9)</td>
<td>373.5 (61.6)</td>
<td>335.8 (88.6)</td>
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<td>24 deg</td>
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Mean (SD) values are shown for each group. < > indicates the mean value of the schizophrenics with abnormal latency or/and error rate in the antisaccade task. *indicates a significant difference compared to the age-matched controls (p < 0.01).

Results

Saccade Task

LATENCY. Because 4 of the 10 patients with frontal lesions (Cases 5, 8, 9, 10) had unilateral lesions (Table 1, Figure 1), latencies were calculated with respect to the side of the lesion. Only Case 10 showed a significant asymmetry in latencies between saccades toward the lesion and those away from it; the mean latency toward the lesion was 248.7 ± 84.2 msec, whereas the mean latency away from the lesion was 301.0 ± 70.5 msec. Cases 5, 8, and 9 who had unilateral lesions showed no significant asymmetry in their saccade latencies. Although Case 1 had bilateral lesions with a larger lesion to the right (Figure 1A), he also showed an asymmetry. His mean latencies of leftward and rightward saccades were 260.5 ± 83.5 and 353.1 ± 125.5 msec, respectively. Except for Cases 1 and 10, the remaining eight patients showed no significant differences between leftward and rightward saccades. Table 3 summarizes mean latencies (±SD) for all saccades for all subjects group. The frontal patients did not show a significant difference compared to the control A. The mean of all the saccades for the patients was 267.0 ± 32.1, range 233.4–317.1, Figure 2A) msec, whereas the mean of all saccades of the control A was 253.6 ± 37.4 SD, range 204.8–330.5, Figure 2A, Table 3) msec.

Parkinsonian patients did not show an asymmetry between left and right saccades. Mean latencies were not significantly different from that of the control B (young controls, 232.8 ± 33.2, range 183.8–276.2 msec, Table 3). These findings confirm previous reports showing that schizophrenics do not exhibit abnormalities in the visually guided saccade task (e.g., Iacono et al 1981; Levin et al 1981; Fukushima et al 1988, 1990a,b), even when the position of the target is presented randomly in both amplitude and direction.

AMPLITUDE AND PEAK VELOCITY. The amplitudes of the saccades were compared between the patients with frontal lesions and control A. Mean amplitudes for the patients with frontal lesions were 7.6° (±0.1 SD), 12.2° (±1.0 SD), and 20.5° (±0.9° SD) for the saccade tasks of 8°, 12° and 24°, whereas the mean values for control A were 8.6° (±0.9 SD), 12.0° (±1.2 SD), and 22.4° (±2.2° SD), respectively. The difference was significant in only the 8° saccade task, indicating that these frontal patients generally performed saccades with appropriate amplitudes.

The mean amplitudes for the Parkinsonian patients were 8.2° (±0.9 SD), 11.6° (±1.2 SD), and 21.4° (±2.4° SD) for the 8°, 12°, and 24° saccade tasks. These values were not significantly different compared to the control A.

Schizophrenics did not show significant difference in saccade amplitudes compared to the control B. The mean values (±SD) in the 8°, 12°, and 24° saccade task were 8.0° (±1.1), 11.9° (±1.3), and 21.0° (±3.0°) for schizophrenics and 8.1° (±0.7), 11.9° (±1.0), and 20.6° (±1.9°) for the control B.

Peak velocities were plotted against amplitudes of saccades in the saccade task and compared with those of the control A in Figure 3A. Individual values are shown in Table 3. None of the patient groups showed a significant difference compared to their controls. The mean (±SD) values (°/sec) for 8°, 12°, and 24° saccades were 233.5
SACCADE VELOCITY

A

ANTI-SACCADE VELOCITY

B

Figure 3. Mean ± SD of peak velocities against 8°, 12°, and 24° of saccades (A) and antisaccades (B) in patients with frontal lesion, Parkinsonian patients and control A. *p < 0.05; **p < 0.01.

(±32.6), 289.8 (±39.7), and 383.8 (±60.3) for the patients with frontal lesions; 247.1 (±35.0), 310.2 (±32.7), and 416.3 (±39.9) for Parkinsonian patients; 255.8 (±42.4), 318.6 (±45.7), and 423.3 (±56.4) for the control A; whereas 218.4 (±37.6), 280.2 (±54.7), and 367.2 (±76.3) for schizophrenics and 222.1 (±20.7), 287.7 (±33.2), and 397.2 (±60.8) for the control B.

Antisaccade Task

ERROR RATE. Figure 4 summarizes mean error rates (see Methods) of individual patients. Mean values for each subject group are summarized in Table 3. The frontal patients as a whole showed significantly higher error rates (mean 41.0 ± 31.5 SD, range 3%–100%) than the control (mean 14.9 ± 10.8 SD, range 0–36%, p < 0.0022). Moreover, 40% of the frontal patients examined showed error rates of more than

Figure 4. Histograms of error rates of antisaccades in patients with frontal lesions, Parkinsonian patients and control A. Mean error rates were calculated for individual subjects. Each number in the top histogram (frontal patients group) indicates the Case number in Figure 1. Mean ± SD % of all patients in each group and statistical significance compared to control A are also shown. * > mean +2 SD.
mean +2 SD of the control value (Figure 4, marked with asterisks). The patient with a right lateral frontal lesion (Case 9, Figure 1) showed an error rate of 100% to the targets shown both on her left and right. Case 5 with a left lateral frontal lesion showed a mean error rate of 80%. She showed an error rate of 80% to the targets shown both on her left and right. Case 8 with a left lateral frontal lesion showed a mean error rate of 60%. She showed an error rate of 75% for her left-hand targets, and 47% to her right-hand targets. The difference was significant between the two (p < 0.01). The patient who had a right frontal lesion (Case 10) showed a mean error rate of 40%. His error rate was 60% for the right-hand targets, which was higher than the error rate for the targets presented on the left (21%; p < 0.01). The other patients showed mean error rates below 40%. Although the mean error rate was not high compared to the controls, Case 1 showed an asymmetry in the error rates for right-hand and left-hand targets. His error rate for left-hand targets was 17.2%, whereas that for right-hand targets was 48.3% (p < 0.05). The other patients with frontal lesions showed no asymmetry of error rates for left-hand and right-hand targets.

The patients with Parkinson's disease did not show a significant difference in the error rates for left-hand and right-hand targets. The mean error rate was 24.5 (± 18.5 SD, range 0–65%) with no significant difference compared to control A (Table 3). Six patients (27%) showed error rates of more than mean +2 SD of the control value (Figure 4, marked with asterisks), however.

Consistent with previous results (Fukushima et al 1988, 1990a,b), schizophrenics showed significantly higher overall error rates (mean 33.6 ± 20.6 SD, range 11%–74%) than the control B (mean 3.9 ± 4.7 SD, range 0–10%) in the antisaccade task (p < 0.0003, Table 3). None of them showed a significant difference between left error rates and right error rates.

Consistent with previous studies (Fukushima et al 1988, 1990a,b), schizophrenics showed significantly longer latencies compared to the control B (p < 0.03; 346.1 ± 81.7 SD, range 250–628.4 msec versus 283.1 ± 14.3 SD, range 274.6–320.4 msec, Table 3).

**PEAK VELOCITY.** Peak velocities against amplitudes of saccades in the antisaccade task were plotted and compared with those of the control A in Figure 3B. These values are also summarized in Table 3. The mean ±SD (°/sec) of the patients with frontal lesions (211.4 ± 27.4, 266.1 ± 24 and 357.2 ± 42.3) were significantly lower than those of the control A (248.2 ± 37.5, 303.1 ± 43.9 and 394.6 ± 62.8) for 8°, 12°, and 24°. Among them, Cases 5, 8, and 10 showed the lowest peak velocities (< mean +2 SD of the control values). These patients also showed abnormality in error rates as described above (Figure 4, i.e., error rates were higher), and there was a significant negative correlation between error rates and peak velocities in the antisaccade task (correlation coefficient = −0.83). Parkinsonian patients showed no significant difference in peak velocities in the antisaccade task (246.4 ± 43.8, 299.9 ± 39.9, and 389.1 ± 44.9 °/sec at 8°, 12° and 24°, Figure 3B, Table 3). Even the six patients who had higher error rates in the antisaccade task (Figure 4) did not show a significant difference.

As we reported previously (Fukushima et al 1990b), peak velocities of antisaccades in 14 (of the 18) schizophrenics who had significant abnormalities in error rate and/or latency (i.e., > mean +2 SD of the control values), were significantly lower at all the amplitudes examined (191.6 ± 34.8, 223.4 ± 42.9, and 276.5 ± 59.0 °/sec) than those of the control B (231.5 ± 39.3, 284.7 ± 45.2, and 373.5 ± 61.6 °/sec) at 8°, 12° and 24° (Table 3). The mean latencies and peak velocities of saccades in the saccade task of these 14 schizophrenics were similar to the mean values of all the 18 schizophrenics described above. When we compared peak velocities of antisaccades for all the 18 schizophrenics with the control B, however, the difference was not significant with the means for the patients being 221.9 ± 45.3, 264.6 ± 60.0, 335.8 ± 88.6 °/sec at 8, 12, and 24° (Table 3), and there was no significant correlation between error rates and peak velocities in the antisaccade task. This was because the schizophrenics group contained patients with normal results as well as those with abnormal results in the antisaccade task, as we reported earlier (Fukushima et al 1988, 1990a).

**Discussion**

**Abnormalities of Antisaccades in Patients with Frontal Lesions**

Since Guitton et al (1985) reported on abnormalities in the antisaccade task in patients with the frontal lesions, higher error rates have been reported for many neurological dis-
eases, such as Alzheimer’s disease (Fletcher and Sharpe 1986), Huntington’s disease (Lasker et al 1987) and progressive supranuclear palsy (Pierrot-Deseilligny et al 1989). These other patients showed abnormalities not only in the antisaccade task, however, but also in the visually guided saccade task. In the present study, none of the frontal patients showed abnormalities in saccade latency, although many of them showed abnormalities in their antisaccades.

The patients with lateral frontal lesions, which probably include the frontal eye field (FEF) and prefrontal cortex (Cases 5, 8, 9, 10 in Figure 1) as well, showed higher error rates in the antisaccade task, but other patients with different frontal lesions, including the medial-rostral parts (Cases 1, 2, 3, 4, 6, 7 in Figure 1) did not. The FEF is reported to play an important role in saccadic eye movement (Goldberg and Segraves 1989; Schlag-Rey et al 1992). The prefrontal cortex has also been reported to contain neurons involved in the saccadic eye movement (Boch and Goldberg 1989). Pierrot-Deseilligny et al (1991) reported that prefrontal lesions cause higher error rates in the antisaccade task in humans. Sawaguchi (personal communication) found that a monkey who had received bicuculline injections in the prefrontal cortex could not perform antisaccades. Therefore, the prefrontal cortex may be responsible for higher error rates in the antisaccade task. Because our patients had lesions that covered both the prefrontal cortex and the FEF (Cases 5, 8, 9) or damaged fibers coming from these areas (Case 10), we cannot tell whether the prefrontal cortex alone contributes to the error rates. Although there is no animal studies on FEF lesions in the antisaccade task, Schlag-Rey et al (1992) reported that microstimulation of the FEF excited superior collicular saccade-cells encoding the same vector but inhibited all others. The FEF may be involved in antisaccades through such functional connections.

Longer latencies in the antisaccade task were observed not only in the patients with FEF or prefrontal lesions (Cases 5, 8, 9, 10 in Figure 1), but also in those with other lesions in the frontal cortex (Cases 1, 3, 4, 6, 7). Our results also indicate that lower peak velocities were observed in patients with the lesions covered the FEF and/or prefrontal cortex (Cases 5, 8, 10). Deng et al (1986) reported that monkeys with FEF lesions showed lower peak velocities in the memory-guided saccade task, despite showing normal velocities in the visually guided saccade task. These results suggest that the FEF and prefrontal lesions may cause longer latencies and lower peak velocities in the antisaccade task.

Animal studies indicate that the FEF and prefrontal cortex are involved in memory-guided saccades towards the contralateral side (Deng et al 1986; Sawaguchi personal communication). In the present study, however, no asymmetry in saccade-latencies or antisaccade latencies or in error rates was consistently observed with respect to the side of the lesions. According to the reports by Guitton et al (1985) and Pierrot-Deseilligny et al (1991), none of their patients with unilateral lesions showed asymmetry. These studies suggest that the lesions in humans do not necessarily elicit an asymmetry as found in animal experiments, most probably because of the chronicity of the lesions and/or a compensation mechanism.

This study cannot comment on the involvement of the supplementary eye field (Schlag and Schlag-Rey 1987) in antisaccades, since the medial lesions seen in Case 4 (Figure 1A) were too rostral.

**Antisaccades in Parkinsonian Patients**

Our results confirm the observation reported by Lueck et al (1990) that mild Parkinsonian patients do not show abnormalities in either the saccade or antisaccade task. In this study, however, six patients with mild symptoms showed higher error rates (> mean + 2 SD, Figure 4). It has been reported that even mild Parkinsonian patients show abnormalities in the Wisconsin Card Sorting Test (Lees and Smith 1983). This may suggest an impairment of the frontal cortex. Because these six Parkinsonian patients showed abnormality only in error rates (but not consistently in latencies or peak velocities) in the antisaccade task, the nature of their abnormality is different from that observed in the frontal patients or schizophrenics in this study.

**Abnormalities of Antisaccades in Schizophrenics**

Since we reported abnormalities in the antisaccade task in schizophrenics (Fukushima et al 1988, 1990a,b, 1991), higher error rates in the antisaccade task have been confirmed in schizophrenics by other researchers (Thaker et al 1989; Rosse et al 1993). The present results further indicate specific abnormalities in the control of antisaccades in schizophrenics and patients with frontal lesions but not consistently in Parkinsonian patients.

The saccade task and antisaccade task are quite different, and a direct comparison is difficult. The difference in the latencies between the two tasks should include the time required for the further processing of antisaccades in addition to the time required for processing in the saccade task; that is, in the saccade task, the brain must calculate the retinal error first and eventually produces a saccadic signal that moves eyes to the target position, whereas in the antisaccade task the brain must first suppress the reflexive saccade to the target and at the same time calculate the retinal error and then produces a saccadic signal that moves the eyes to the position opposite (but at an approximately equal distance) from the target. The mechanism for the suppression of the reflexive saccade to the target alone cannot explain the longer latencies in antisaccades in schizophrenics, because similarly longer latencies were also observed in the memory guided saccade task in many schizophrenics.
who showed abnormalities in antisaccades (Fukushima et al 1990b). These results suggest that the central processing that initiates such voluntary saccades to an imagined goal during the initiation of a saccade may be impaired in these patients (Fukushima et al 1990b). To obtain further support for this interpretation, the difference in latencies between antisaccades and saccades was calculated for individual subjects as summarized in Figure 5. Compared to the control A, the patients with frontal cortical lesions (p < 0.01), and compared to the control B, the schizophrenics (p < 0.005) showed significantly larger differences. Parkinsonian patients did not show a significant difference compared to the control A, however. These results are also consistent with our interpretation that frontal patients and schizophrenics (but not Parkinsonian patients) show specific abnormalities in the antisaccade task. These abnormalities in the antisaccade task can be explained by a dysfunction of the saccadic eye movement-related areas of the frontal cortex (e.g., FEF and prefrontal cortex), which might be related to the hypofrontality during the cognitive task found in schizophrenics using the recently developed positron emission tomography (PET) studies (Rubin et al 1991; Buchsbaum et al 1992; Andreasen et al 1992; Wolkin et al 1992).

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References


Davis JM (1976): Comparative doses and costs of antipsychotic medication. Arch Gen Psychiatry 33:858–861.


Hikosaka O, Wurtz RH (1983): Visual and oculomotor function of monkey substantia nigra pars reticulata. IV. Relation of sub-


