Eye Movements in Monkeys with Local Dopamine Depletion in the Caudate Nucleus. II. Deficits in Voluntary Saccades

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Unilateral infusion of MPTP into the monkey caudate nucleus produced deficits in task-specific saccades, in addition to the deficits in spontaneous eye movements (preceding article). We trained three monkeys to perform two kinds of saccade tasks: (1) saccade task for eliciting visually guided saccades and (2) delayed saccade task for eliciting memory-guided saccades. After the MPTP infusion, dopaminergic function, estimated by tyrosine hydroxylase (TH) immunoreactivity, was shown to be decreased locally around the infusion site at the head–body junction of the caudate. We found that the deficits were prominent in the saccades directed to the side contralateral to the infusion (contralateral saccades). Memory-guided saccades were sometimes misdirected to the ipsilateral side even when the cue stimulus was presented on the contralateral side. Among the parameters of saccades, a selective change was found in the saccade latency: the latency was prolonged consistently in contralateral memory-guided saccades. The amplitude and velocity of saccades decreased in contralateral saccades, either memory guided or visually guided. The duration of saccades tended to increase in visually-guided saccades and memory-guided saccades, in both directions. Only one monkey, in which the decrease in TH activity included a large part of the putamen and the head of the caudate, showed prolongation of manual reaction time for lever release.

[Key words: monkey, MPTP, visually guided saccade, memory-guided saccade, caudate nucleus, dopamine deficiency]

A remarkable feature of the basal ganglia oculomotor mechanism is its strong dependency on memory, expectation, or attention (Hikosaka and Sakamoto, 1986; Hikosaka et al., 1989b; Apicella et al., 1992). The presaccadic changes in spike activity—a pause in the substantia nigra and a burst in the caudate nucleus—are frequently dependent on how the saccade is initiated rather than where the saccade is to be directed. The ac-

tivity change occurs before purposive saccades which are made during the behavioral tasks in order to obtain reward; it is rarely seen during spontaneous, automatic saccades. Unique to the basal ganglia is the presence of neurons that change their activity preferentially before saccades to remembered targets (Hikosaka and Wurtz, 1983; Hikosaka et al., 1989a); in these neurons saccades to visual targets are associated with much less activity.

These characteristics predict that oculomotor deficits in basal ganglia diseases are conditional, depending on how saccades are made. Recent clinical studies have supported this prediction; for example, patients with mild parkinsonism may show nearly normal saccades in the ordinary saccade task but their performance deteriorates in the memory-guided saccade task or anti-saccade task (Carl and Wurtz, 1985; Crawford et al., 1989; Hikosaka et al., 1992; Ventre et al., 1992).

However, it is still uncertain whether these oculomotor deficits are caused by basal ganglia dysfunction. Cell degeneration in Parkinson's disease is not localized to the substantia nigra but includes surrounding dopaminergic areas (e.g., ventral tegmental area) and the locus ceruleus which contains noradrenergic neurons (Greenfield and Bosanquet, 1953; Chan-Palay and Asan, 1989). These non-nigral dopaminergic and noradrenergic neurons project to the frontal cortical areas (Gaspar et al., 1992), unlike nigral dopaminergic neurons which project to the striatum. These facts may lead to the speculation that the oculomotor deficits observed in parkinsonian patients are caused by the dysfunction of the frontal cortex including the frontal eye field. This idea would be supported by the fact that parkinsonian patients may show deficits in a variety of cognitive tasks (e.g., Wisconsin Card Sorting Test) which are generally attributed to frontal cortical dysfunction (Taylor et al., 1986).

In order to differentiate basal ganglia dysfunctions from cortical ones, we needed to have a more localized lesion in the basal ganglia. We used a local infusion of MPTP into the unilateral caudate nucleus for this purpose. We trained monkeys to perform a set of oculomotor tasks, each of which aims at inducing different types of saccades, and examined the effect of local dopamine deficiency in the caudate.

In the preceding article we have shown that dopamine deficiency was largely localized to parts of the striatum around the infusion site (central part of the caudate and, to a lesser extent, anterior portion of the putamen). Spontaneous eye movements of these monkeys were changed after the MPTP infusion, interestingly, without obvious skeletomotor deficits. We report in this article that deficits were also present in saccades made in learned tasks in a selective manner.

Received Mar. 14, 1994; revised July 20, 1994; accepted July 25, 1994.

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Saccade task (visually guided saccade)

Delayed saccade task (memory-guided saccade)

Figure 1. Behavioral paradigms to induce visually guided saccades (*saccade task*) and memory-guided saccades (*delayed saccade task*). For each task are shown the durations of the central fixation point and the peripheral target point (*bottom*) and the corresponding sequence of the task events with the light spots and eye position (*top*; open and solid circles, respectively).

Preliminary reports of some of these data have appeared elsewhere (Miyashita et al., 1990; Kori et al., 1991).

Materials and Methods

The same monkeys (RO, PE, IG) were used as in the preceding article.

Behavioral tasks

The details of stimulus presentation were described in a previous article (Matsumura et al., 1992). The monkey sat in a primate chair in a dimly lit and sound attenuated room with his head fixed. In front of him was a tangent screen (57 cm from his face) onto which small red spots of light (diameter, 0.2°) were backprojected using three LED projectors. The first projector was used for a fixation point, the second for a target point, and the third for another irrelevant stimulus. The positions of the stimuli were controlled by reflecting the lights via two orthogonal (horizontal and vertical) galvanomirrors.

We used two basic saccade tasks: *saccade task*, which was designed to elicit visually guided saccades, and *delayed saccade task* to elicit memory-guided saccades (Fig. 1). A trial of either task was initiated when the monkey pressed a lever, and thus a fixation point appeared at the center of the screen; it was completed, if successful, when the monkey released the lever in response to dimming of a peripheral target point and thus obtained a small amount of water as a reward. If he released the lever earlier or later, the trial terminated with neither reward nor punishment. The trial also terminated without reward when eye position deviated from the fixation point by more than a prefixed value (usually 3° in a horizontal or vertical direction) during the fixation period. Successive trials were separated by an intertrial interval of 1–3 sec (randomized).

In *saccade task*, the target point came on at the same time when the fixation point went off. The monkey followed the jump of the light spot by making a saccade. The saccade was guided by visual information from the target. The durations of the fixation point and the target point were randomized for each trial between 1.5 and 2.5 sec and between 0.5 and 2.0 sec, respectively. The target point then became dim for a short period (0.5 sec) during which the monkey had to release the lever to obtain the reward.

In *delayed saccade task*, the target point came on some time (usually 0.6 sec) after the fixation point went off. The monkey made a saccade in a predictive manner within this gap period, because the location of the target had been indicated by flashing of a light spot (subsequently called *target cue*) beforehand while the monkey was fixating at the center. The target cue was presented 1 sec after the fixation point came on; its duration was 50 msec. The fixation point remained on thereafter, usually for 2–3 sec (randomized). The monkey was allowed to make a saccade only after the fixation point went off. The saccade usually occurred during the gap period toward the position where the target cue had been presented. It was guided by memory. The target point then came on to which the monkey would make a corrective saccade if necessary. This procedure encouraged the monkey to make an accurate saccade before the onset of the target point, because otherwise the monkey might have failed to detect its dimming.

Experimental procedures

The daily experimental session was composed of (1) examination of spontaneous eye movements, and (2) examination of task-related saccades (*saccade task*, *delayed saccade task*, *saccade task with gap*, and additional tasks if necessary). The results of spontaneous eye movements are presented in the preceding companion article (Kato et al., 1994).

Figure 2. Effects of the unilateral caudate MPTP infusion on visually guided saccades (*left*) and memory-guided saccades (*right*), before MPTP (*top*) and 10 d after starting MPTP infusion (*bottom*). Saccades to six horizontal targets (10, 20, and 30° from the fixation point to the right and to the left) are superimposed (two to three traces each). Horizontal eye positions (up, ipsilateral; down, contralateral) are aligned on the offset of the fixation point (solid vertical line). The onset of the target point is shown by an interrupted line in the delayed saccade task (*right*); it was simultaneous with the offset of the fixation point in the saccade task (*left*). The sequence of the visual stimuli was as indicated at the top except that the brief presentation of the target (cue) was actually 2–3 sec before the offset of the fixation point. During the experiment, the target was selected randomly for each trial from 32 possible locations (8 directions, 4 eccentricities); here are shown only the saccades to horizontal 10, 20, and 30° targets. The data were obtained from the monkey RO. Note that, after MPTP infusion, memory-guided saccades to the left targets (contralateral to the MPTP infusion) were delayed and tended to be hypometric. Visually guided saccades remained nearly normal.

Eye movements were recorded using the magnetic search-coil technique (Robinson, 1963).

For task-related saccades, the location of the target point was selected from 32 points (eight directions with 5, 10, 20, and 30° eccentricities). In most experiments we used subsets of these target positions; for example, P8E20 (eight directions, eccentricity of 20°), RL5-30 (5, 10, 20, and 30° from the center in horizontal direction to right and left). A block of experiment typically consisted of 32 trials with the target set "P8E20." The target position was selected in a pseudo-random manner such that all targets appeared in one cycle of trials (in this case, eight trials); in other words, each target location was examined four times in each block. The target sets and their combination used for experiments were slightly different between the monkeys. In the monkey RO all 32 targets were examined in single blocks; P8E20 for the monkey PE and P8E20 and RL5-30 for the monkey IG were used for routine experiments.

The behavioral tasks as well as storage and display of data were controlled by computer (PC 9801RA, NEC, Tokyo). On the computer monitor were presented, as a two-dimensional display, current eye position, fixation and target positions, trajectories of task-related saccades; horizontal and vertical eye positions were also displayed relative to the time after offset of the fixation point. Eye positions were digitized at 500 Hz and stored continuously during each block of trials.

The monkey's behavior was continuously monitored by an infrared camera. The camera system, using mirrors, allowed us to observe body movements of the monkey in two perspectives: (1) gross movements (hand/arm movements associated with manipulation of the lever, pos-

tural changes, and foot/leg movements), and (2) movements in the face (eye movements, eye blinks, oral movements associated with water intake).

Time schedule for examination

Pre-MPTP data. We first trained the monkeys to perform the saccade tasks intensively on a daily basis. The data acquisition was started after their performance became stable. We also checked whether their task performance changed by experimental procedures such as implantation of guide tubes; no changes were noticed by any of the procedures. For the pre-MPTP data to be analyzed, we pooled 5 d sessions just before starting MPTP infusion. The daily menu of the examination was basically unchanged, always including both saccade task and delayed saccade task.

Post-MPTP data. We examined the task performance daily after starting MPTP infusion because the drug effects changed dramatically in this period. The interval of the examination was thereafter prolonged gradually. For the representative post-MPTP data to be analyzed, we pooled five consecutive sessions for monkeys RO (day 11–20) and PE (day 13–19) and nine consecutive sessions for the monkey IG (day 1–31) during which MPTP had the maximal effects on saccades.

The daily menu of the examination was also fixed for the initial period, but was sometimes modified in later examinations to seek for different aspects of the deficits.

Recovery data. The monkeys' behavior became stable or started showing slight recovery after 1 month. In monkeys RO and PE the exami-

Memory-guided saccade

Figure 3. The MPTP-induced deficits in memory-guided saccades became clearer by lengthening the delay period (1–10 sec). Saccades (horizontal eye positions) to the right (ipsilateral) target and the left (contralateral) target (eccentricity, 20°) are superimposed. The experiments were done in blocks, each with a single delay period. When the delay was 10 sec (*bottom*), the supposedly contralateral saccade was misdirected twice to the ipsilateral side; however, visually guided correction was quick after onset of the target point. Data from the monkey RO, post MPTP day 7.

Figure 4. Changes in trajectories of saccades after MPTP infusion. The first saccades after the offset of the fixation point are superimposed. The target was randomly selected for each trial from 32 locations (see Fig. 2), but here are shown only the saccades to the 20° targets in eight directions (two to three trials for each). Note that, after MPTP, memory-guided saccades became more curved and tended to be directed to the side ipsilateral to the infusion; visually guided saccades appeared unchanged. Data from the monkey RO, post-MPTP day 6.

nation continued to be performed at least once a week; in the monkey IG the examination was made more infrequent at this stage to see if the frequency of examination affected the monkey's performance.

Several new tasks were introduced at this stage to see different aspects of the deficits in saccades, attention, and memory.

Data analyses

The stored data were composed of two sets of files, an event-data file and an analog-data file. The off-line analyses were performed in two stages: (1) determination of eye movement-related parameters for each task trial, and (2) statistical analyses and displays of the parametric data.

In the present study we focussed on the first saccade after the offset of the fixation point, the main saccade aiming at the visual or remembered target. Parameters of saccade produced by the computer analyses were amplitude, duration, peak velocity, time to peak velocity, accuracy in amplitude, accuracy in angle. Reaction time of lever release was measured, in addition. Statistical analyses were performed using Mann-Whitney *U* test.

Results

We examined different types of saccades. Changes in spontaneous saccades are described in the preceding companion article

(Kato et al., 1994). In this article, we concentrate on two types of saccades: visually guided and memory-guided. We reasoned the distinction to be important because single cells in the basal ganglia frequently show selective activity between these two types of saccades (Hikosaka and Wurtz, 1989; Hikosaka et al., 1989a).

Overview of saccadic deficits

All of the three monkeys developed deficits in task-specific saccades by local injection of MPTP into the unilateral caudate nucleus. The deficits were not obvious until 3 d after beginning of the MPTP infusion. Instead, acute, facilitatory effects were consistently observed within the first 24 hr. Shorter latencies and increased amplitudes and velocities were observed for saccades to the side contralateral to the MPTP infusion. The monkey RO tended to break fixation to the contralateral side, especially when the target cue was presented on that side.

This initial change disappeared on the following day, and the first sign of near-permanent deficits appeared as early as 3 d

Table 1. Changes in oculomotor and skeletomotor parameters by unilateral caudate infusion of MPTP

	Visually guided saccade						Memory-guided saccade					
	Ipsi			Contra			Ipsi			Contra		
	RO	PE	IG	RO	PE	IG	RO	PE	IG	RO	PE	IG
Saccade												
Latency	▼	—	—	—	—	△	—	△	△	△	△	△
Amplitude	—	—	—	—	▼	▼	—	—	—	▼	▼	—
Velocity	—	—	—	—	▼	—	△	▼	—	—	▼	—
Duration	—	—	△	△	△	—	—	△	—	—	△	—
Lever release												
Latency	—	—	△	—	—	△	—	—	△	—	—	—

The statistical comparison (Mann–Whitney *U* test) was made between the pre- and post-MPTP data (each consisting of 5–10 d data) for visually guided saccades (left) and memory-guided saccades (right) for each monkey (RO, PE, and IG). The data were selected for the task trials in which the target was presented at 20° from the fixation point and were analyzed separately for the contralateral (Contra) and ipsilateral (Ipsi) directions, each consisting of three directions (horizontal, oblique up to 45°, and oblique down 45°). Solid downward triangles indicate significant decreases in post-MPTP data; open upward triangles indicate significant increases ($p < 0.005$).

after beginning of the MPTP infusion (day 3). The maximum effects were observed on day 7–15, followed by a gradual recovery.

Figure 2 provides an intuitive picture of the saccadic deficits. In this monkey, MPTP was injected into the right caudate nucleus. No gross changes were seen in visually guided saccades (left), except that the latencies became shorter for the saccades directed to the side ipsilateral to the MPTP infusion.

In contrast, memory-guided saccades (right) showed a clear asymmetry after MPTP. Memory-guided saccades were slower than visually guided saccades in the normal monkey (top), as has been well documented (Hikosaka and Wurtz, 1985; Smit et al., 1987). After MPTP (bottom), initiation of saccades to the left (contralateral to the MPTP infusion) became delayed and hypometric.

In this paradigm (delayed saccade task) the target appeared 0.6 sec after offset of the fixation point, as indicated by a hatched line, to which the monkey made a corrective saccade. Such a visually guided saccade was made briskly with latencies around 200 msec, apparently with no asymmetry. This result again indicates that visually guided saccades were relatively intact.

Deficits in mnemonic process for saccade initiation

In the delayed saccade task, the monkey had to retain the information of the target location while he was fixating and preparing for the saccade. In the experiment shown in Figure 3, we asked whether this mnemonic process was disrupted by MPTP. The delay period (between presentation of the target cue and offset of the fixation point) was changed from 1 sec to 10 sec, each of which was examined as a block of trials. The ipsi/contra asymmetry was present regardless of the delay periods. The asymmetry was less clear with 2 sec delay, which was close to the routine schedule of this task. A qualitative difference was noted for the longest delay (10 sec): two out of four saccades to the contralateral target were directed to the ipsilateral side; in these cases, however, a correction was made quickly, perhaps as an express saccade (Fischer and Boch, 1983).

Misdirection of saccade

In Figure 4, the first saccades after offset of the fixation point are displayed as two-dimensional trajectories. No clear changes

were observed in visually guided saccades (left) between the pre-MPTP (top) and post-MPTP (bottom) conditions. The trajectories of memory-guided saccades (right), even in the normal monkey (top), were sometimes curved and ended short of the target positions, especially those in the lower visual field, as shown previously (Gnadt et al., 1991). The curved nature of the memory-guided saccades was enhanced after MPTP (bottom). The number of saccades to the contralateral side was reduced, indicating that the supposedly contralateral saccades were misdirected to the ipsilateral side.

In the following sections, we examined changes in saccade parameters. The results are summarized in Table 1.

Saccade latency

Distributions of saccade latencies are shown in Figure 5. The data were obtained in the monkey RO. The mean latency of visually guided saccades was about 180 msec, and the distributions showed a single peak in the pre- and post-MPTP conditions, for both the ipsi- and contralateral saccades. By the administration of MPTP a significant *decrease* was observed in the saccades made to the ipsilateral side; this effect, however, was not observed in the other monkeys (Table 1).

The changes in memory-guided saccades were more pronounced. The latencies of contralateral saccades became longer and more variable; the same change was also observed in the other two monkeys (Table 1). Some saccades occurred after 600 msec, especially around 800 msec. Since the target appeared at 600 msec, these saccades were in fact visually guided, preceded by no memory-guided saccades. The number of incorrect (misdirected) saccades also increased (indicated by open columns). The latencies of ipsilateral memory-guided saccades became more variable, but showed no significant change in their mean.

In summary, the only effect common to all of the three monkeys was the increase in the latency of contralateral memory-guided saccades (Table 1).

Saccade amplitude

In the polar diagrams in Figure 6, the mean amplitudes of saccades before and after the MPTP infusion are plotted for each of eight targets (20° eccentricity, eight directions). This figure shows that the saccades tended to become more hypometric

A

Visually guided saccade

B

Memory-guided saccade

after the MPTP infusion. The effect was more consistent in the saccades directed to the side contralateral to the infusion, especially in the memory-guided saccades (Fig. 6, right).

In the monkey PE, for example, memory-guided saccades became smaller when the target was in one of the three contralateral directions and the upward direction, but not in the ipsilateral directions. Visually guided saccades also became smaller in the contralateral directions; this effect was less pronounced than in the case of memory-guided saccades but was nonetheless statistically significant (Table 1), because visually guided saccades were less variable in amplitude in the pre- and post-MPTP conditions.

To summarize, two monkeys showed a significant decrease in amplitude for contralateral visually guided saccades (monkeys PE and IG) and for contralateral memory-guided saccades (monkeys RO and PE).

Saccade velocity

The peak velocity generally decreased by the MPTP infusion (Fig. 7). The effect was clearly seen in monkeys PE in both directions, especially in memory-guided saccades. In the normal (pre-MPTP) monkeys, the peak velocity was slower in memory-guided saccades than in visually guided saccades. The difference became enhanced by the MPTP infusion, as typically seen in the monkey PE. In the monkey RO, however, the ipsilateral memory-guided saccades became faster after the MPTP infusion (Table 1).

In summary, one monkey PE showed a significant decrease in peak velocity in both visually guided and memory-guided saccades. Somewhat unlike the saccade amplitude, the decrease in peak velocity was significant in both directions, except for the ipsilateral visually guided saccade in the monkey PE (Table 1).

Saccade duration

The effect of MPTP on saccade duration was less selective (Table 1). In monkey PE, clear changes were observed in memory-guided saccades in both directions and in visually guided saccades in the contralateral direction; saccades with extremely long durations were alternated with close-to-normal saccades. Small but significant prolongation of saccade duration was found in contralateral visually guided saccades in monkey RO and in ipsilateral visually guided saccades in monkey IG.

Hand movements were less impaired

In our saccade tasks, the monkeys responded to dimming of the target point by releasing their hands from the lever. This allowed us, to some extent, to examine possible changes in hand movements by MPTP. In Figure 8 are shown the latencies (reaction times) of the lever response before and after MPTP. No significant changes were observed in the monkey RO. The reactions of the monkey PE, who was the youngest, became even slightly faster, presumably because of extensive repetition of the tasks.

In contrast, the monkey IG's reactions became significantly slower (Table 1).

We did not require the monkeys to use a particular hand to depress and release the lever. As a consequence, the manner of lever manipulation was variable between the monkeys. Their own styles, once established, did not change even after starting MPTP administration. The side of the lever-manipulating hand with respect to the MPTP infusion site was ipsilateral in monkeys RO and IG; the monkey PE kept using both hands for lever manipulation.

Lack of continuity in task performance

There were some occasions during the examination after MPTP administration in which the monkeys stopped working for unknown reasons and would not restart. They did not seem irritated or nervous; they simply stopped pressing the lever. The monkeys could then be encouraged to resume the task performance when the investigators made social contacts with them. The monkeys then went on performing the task at least for 10 or so trials. This phenomenon was prominent in monkeys RO and PE. Note, however, that the latencies of lever release were not increased in these monkeys (see Fig. 8).

The daily follow-up of the oculomotor deficits using a series of tasks might itself have affected the deficits. We had three other monkeys who were infused with the same amount of MPTP in the putamen using the same method but were not examined on any behavioral tasks. These monkeys developed strong motor and attentional deficits which were obvious with simple clinical tests. This observation might suggest that the daily motor/mental exercise may prevent behavioral derangement by MPTP. However, there remain several factors which may account for the differences, such as age, nutrition, or site of infusion within the striatum.

Behavioral deficits may be correlated with the distribution of dopaminergic lesion

Table 1 summarizes the oculomotor and skeletomotor deficits in the three monkeys. The latency was prolonged for memory-guided saccades, especially in the contralateral direction. The amplitude tended to be decreased in contralateral saccades, both visually and memory-guided. The decrease in the velocity and the increase in the duration was consistently observed in monkey PE, but not in other monkeys. Except for the duration, the deficits were found more consistently in memory-guided saccades, especially those directed to the side contralateral to the MPTP infusion.

There are individual differences which might be correlated with the differential distribution of dopamine deficiency (Table 2). A prominent feature common to all monkeys was the increase in the latencies of contralateral memory-guided saccades and the dopamine deficiency in the body of the caudate. Thus, the caudate body may be crucial for memory-guided saccades to the contralateral side.

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Figure 5. Pre- and Post-MPTP comparison of the latencies of visually guided saccades (*A*) and memory-guided saccades (*B*). The pre-MPTP data (top for each of *A* and *B*) were obtained from 5 experimental days before MPTP infusion; the post-MPTP data (bottom) from 6 experimental days (7, 11, 13, 15, 17, and 20 days after starting MPTP infusion). Histograms are shown separately for saccades to the ipsilateral targets (*right*) and those to the contralateral targets (*left*), each group including the targets in three directions (oblique up, oblique down, and horizontal); their eccentricities ranged from 5 to 30°. Saccades were judged to be incorrect when they ended in the hemifield opposite to the target, and are shown by open columns. Data are from the monkey RO.

Saccade amplitude

Figure 6. Changes in the amplitude of visually guided saccades (*left*) and memory-guided saccades (*right*), shown separately for the three monkeys (RO, PE, and IG). Each data point in the polar diagrams indicates the average of the amplitudes of saccades ($n = 10\text{--}23$) to the target in the corresponding direction (the targets were 20° from the fixation point in 8 directions); pre-MPTP and post-MPTP data are indicated by *open* and *hatched areas*, respectively. An asterisk indicates the direction in which the pre- and post-values were significantly different (Mann-Whitney U test, $p < 0.005$).

Saccade velocity

Figure 7. Changes in the peak velocity of visually guided saccades (left) and memory-guided saccades (right). The same arrangement as in Figure 6. Each data point in the polar diagrams indicates the mean peak velocity of saccades ($n = 10-23$) to the target in the corresponding direction.

Figure 8. Changes in the reaction time of hand movements for lever release. Percentage histograms are shown separately for the three monkeys; pre-MPTP and post-MPTP data are indicated by *upward* and *downward* histograms, respectively. The data were collected from the saccade task. Only the monkey IG showed the increase in the reaction time.

The monkey IG was different from the other two monkeys in that the latency of lever release was significantly prolonged. In this monkey, unlike the others, the dopamine deficiency included the putamen. Thus, the dopaminergic hypoactivity in the putamen may be responsible for the deficits in hand movements.

The dopamine deficiency in the head of the caudate was weakest in the monkey RO. This monkey showed least deficits in visually guided saccades. This result suggests that the head of the caudate might be involved in some aspects of visually guided saccades.

Lack of effects by saline infusions

As control experiments, we infused saline using the same osmotic mini-pump method in the same three monkeys. The

Table 2. Grade of dopamine deficiency in different regions of the striatum in three monkeys

	Cd head	Cd body	Put ant	Put post
Monkey				
RO	+	+++	±	±
PE	++	+++	—	—
IG	+++	+++	+++	++

The decrease in tryptophan hydroxylase activity (densitometric analysis) was classified into >30% (+++), 20–30% (++), 10–20% (+), 5–10% (±), and <5% (—) and is shown for each of four striatal areas; caudate head (Cd head), caudate body (Cd body), anterior putamen (Put ant), and posterior putamen (Put post).

amount of saline and the infusion period were made the same as MPTP which was injected into the same monkeys. We employed three different schedules in terms of time and location. In the monkey RO, saline was injected 51 d after starting MPTP into the caudate nucleus on the opposite side, at the symmetric location. In the monkey PE, saline was injected before MPTP; 54 d thereafter MPTP was injected at the same location in the caudate nucleus. In the monkey IG, saline was injected simultaneously with MPTP at the symmetric locations in the caudate.

In none of these experiments were found significant effects in saccades, lever manipulation, or other behaviors.

Discussion

The present study demonstrated that local dopamine deficiency in the unilateral caudate leads to deficits in goal-directed saccades, especially those guided by memory, although the monkeys remained virtually asymptomatic. The deficits were clearer or exclusive in the saccades directed to the side contralateral to the dopamine deficiency. The saccades became delayed, hypometric, and slower.

These results suggest that the caudate nucleus participates in the production of such goal-directed saccades. This portion of the caudate nucleus contains a cluster of neurons related in different manners to initiation of memory-guided or visually guided saccades (Hikosaka et al., 1989a). The present results were therefore anticipated, but were not self-evident. This was because the oculomotor function of the basal ganglia has been thought to be dependent on GABAergic inhibitory mechanisms, not directly related to dopaminergic mechanisms.

Eye movement deficits in parkinsonism

There have been a number of studies on parkinsonian eye movements (DeJong and Melvill-Jones, 1971; Melvill Jones and DeJong, 1971; Corin et al., 1972; Yamazaki and Ishikawa, 1972; Shibasaki et al., 1979; Teravainen and Calne, 1980; White et al., 1983). Earlier studies examined only one type of saccade, visually guided saccade, which were found to be hypometric, slow and delayed. The deficits revealed in these examinations were usually small compared with overall motor disturbances experienced by the patients in their daily lives. Recent studies, however, have revealed the conditional nature of the parkinsonian eye movements. Memory-guided saccades or anti-saccades were deficient, even if visually guided saccades were relatively intact (Bronstein and Kennard, 1985; Carl and Wurtz, 1985; Hikosaka et al., 1987; Crawford et al., 1989; Ventre et al., 1992). In the above two types of saccades, the patients had to rely on the internal image or memory information. This is actually the situation in which many of the basal ganglia neurons

become active (Hikosaka and Wurtz, 1989; Hikosaka et al., 1989a). Furthermore, the deficit fits well with the phenomenon of "akinesia paradoxa" (Schwab and Zieper, 1965) in which immobile parkinsonian patients can move swiftly if appropriate external stimuli are provided or unusual emotional stress is imposed.

Eye movement deficits have also been reported in experimental parkinsonism. A most striking example was demonstrated for human MPTP-induced parkinsonism (Hotson et al., 1986). Their saccades to visual targets were extremely hypometric like a staircase. Similar saccadic deficits were observed in MPTP-administered monkeys. Visually guided saccades were slow and hypometric (Brooks et al., 1986) and had longer latencies (Schultz et al., 1989). Spontaneous saccades were limited in a small range (Schultz et al., 1989). Memory-guided saccades were not investigated in these studies.

Our monkeys showed relatively weak deficits in visually guided saccades. The difference probably reflects the regional differences of basal ganglia functions. In our study the effects of MPTP were largely limited to the caudate nucleus on one side, unlike in the previous studies in which MPTP was administered per-orally or intravenously. Such functional differentiation is also suggested in our study (see Heterogeneity in the basal ganglia, below).

Memory-guided movement initiation

The impairment of memory-guided saccades could be caused by deficits in memory or deficits in movement initiation. Both of these possibilities are plausible because neuronal activities have been found in the caudate and SNr that are selectively related to one of these processes. The memory process should consist of two stages: acquisition and maintenance. The possible neuronal counterparts of these processes have been found: neurons responding to a visual stimulus only when the stimulus must be remembered (acquisition of memory) (Hikosaka and Wurtz, 1983; Hikosaka et al., 1989b) and neurons discharging tonically while the visual stimulus is remembered (maintenance of memory) (Hikosaka and Wurtz, 1983; Hikosaka et al., 1989a,c). The process of movement initiation may be found in the neuronal activity that is selectively related to memory-guided saccades (Hikosaka and Wurtz, 1983; Hikosaka et al., 1989a).

Where and how are the memory signals created? The first candidate for their origin is the dorsolateral prefrontal cortex. Lesions of this area are well-known to produce severe deficits in short-term memory tasks—such as delayed response task or delayed alteration task (Battig et al., 1960; Divac et al., 1967). A recent series of studies from Goldman-Rakic's laboratory is more convincing. Funahashi et al. (1989, 1990) found neurons in this cortical area that show sustained and direction-selective activity in the delay period of the memory-guided saccade task. Sawaguchi and Goldman-Rakic (1991) further demonstrated that focal injection of D1 antagonist into area 46 of monkeys produced selective deficits in memory-guided saccades. The deficits were also spatially selective in that saccades were incorrect only when they were directed to a limited portion of the visual field. This is one of the dominant cortical areas that send inputs to the caudate nucleus, especially to its central portion at which our MPTP infusion was aimed (Selemon and Goldman-Rakic, 1985).

The above observations, taken together, appear to indicate that the memory signals are generated in the prefrontal cortex or somewhere upstream and sent to the basal ganglia. However,

a detailed analysis by Funahashi et al. (1993) indicated that a dorsolateral prefrontal lesion (in and around the principal sulcus) alone produced no change in saccadic latency and velocity (unlike our observations). The increase in latency and the decrease in velocity, in addition to the inaccuracy, of memory-guided saccades were observed when the lesion included the anterior bank of the arcuate sulcus (frontal eye field), consistent with the previous finding by Deng et al. (1986). Therefore, the memory-related signals in the basal ganglia may originate in the frontal eye field, rather than or in addition to, the principal sulcus area. This idea would be supported by anatomical data (Huerta et al., 1986; Stanton et al., 1988).

The unilateral corticostriatal relationship hypothesized above is not evident, however, because the signals arising from the basal ganglia may, via the thalamus, be fed into the same association areas of the cerebral cortex (Alexander and Crutcher, 1990). Therefore the possibility still remains that spatial memory is generated by the neural networks including the prefrontal cortex, caudate, and SNr.

Heterogeneity in the basal ganglia

As seen in spontaneous eye movements (Kato et al., 1994), our monkeys were not homogeneous in terms of the nature of behavioral deficits. Unlike the other monkeys, the monkey IG clearly showed deficits in visually guided saccades and manual reaction. This might correspond to the fact that in this monkey the decrease in tyrosine hydroxylase included a large part of the putamen. Hand movement is controlled by the putamen (Crutcher and DeLong, 1984; Kimura, 1986) through its efferents via pallido-thalamo-cortical pathways, but probably not by the caudate (Hikosaka et al., 1989a). Neurons are found in the caudate (Hikosaka et al., 1989a) and the substantia nigra (Hikosaka and Wurtz, 1983) that are selectively related to memory-guided saccades. These facts may explain the heterogeneity of our monkeys' performance.

In another series of our preliminary experiments, MPTP injection was aimed at the rostral part of the putamen. The decrease in tyrosine hydroxylase activity included the putamen and, to a lesser extent, the caudate. These monkeys initially showed strong contralateral visual hemineglect in addition to parkinsonian motor symptoms (rigidity, tremor, akinesia) in the contralateral extremities. Deficits in saccades were also severe; both visually guided and memory-guided saccades were impaired, in addition to strong ipsilateral deviation of eye position. These oculomotor deficits, however, could be corrected by daily training of the saccade tasks.

It is unclear, however, why visually guided saccades were affected by dopamine deficiency in the putamen. Although there has been no report that indicates the presence of saccade-related cells in the putamen, anatomical studies have shown that cortical eye fields (frontal and supplementary) project to limited but dispersed regions in the putamen, in addition to the well-documented projections to the central part of the caudate (Stanton et al., 1988; Huerta and Kaas, 1990; Shook et al., 1991). A dichotomy of oculomotor function might be suggested from this consideration: signals for visually guided saccades are carried by the putamen neurons, while signals for memory-guided saccades are carried by caudate neurons. The dichotomy might be maintained in the SNr as well. Stimulation of the oculomotor region of the caudate induces inhibition (and sometimes excitation) of spike activity of substantia nigra neurons (Hikosaka et al., 1993). Interestingly, the caudate-recipient neurons are

found relatively in the ventral part of the substantia nigra and usually are predominantly related to memory-guided saccades. Neurons in the dorsal part (perhaps corresponding to pars lateralis) are non-caudate-recipient and are predominantly related to visually guided saccades. Indeed, the efferents to this part of the substantia nigra originates in the putamen (Parent et al., 1984; François et al., 1987).

Relevant to this idea is the recent study by Kimura et al. (personal communication), who compared the effects of reversible blockade of the caudate and putamen on learned hand movements initiated in different modes. As in saccadic eye movements, memory-guided hand movements were more affected by the caudate blockade while visually guided hand movements were more affected by the putamen blockade.

The relationship between the changes in oculomotor behaviors and the regional differences in dopamine deficiency observed in this and the preceding study (Kato et al., 1994) raises interesting speculations on the functional differentiation within the basal ganglia, although the data so far are limited and it is premature to draw any conclusion.

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