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Effects of caudate nucleus stimulation on substantia nigra cell activity in monkey

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Abstract. The present study provides evidence that the saccadic signals in the caudate nucleus (caudate) are transmitted to the substantia nigra pars reticulata (SNr). We inserted two microelectrodes into the caudate and SNr of monkeys trained to perform saccade tasks. After identifying the functional characteristics of a SNr neuron recorded, we stimulated the caudate (single pulse, $<100\ \mu A$) to see whether its discharge rate changed. Among 138 SNr cells tested, 60 showed responses to stimulation of the caudate: inhibition only ($n=21$), inhibition-excitation ($n=17$), excitation only ($n=9$), and excitation-inhibition ($n=13$). The latencies were 9.0–32.5 ms (mean 16.7 ms) for the initial inhibitory responses and 6.5–35.0 ms (mean 16.7 ms) for the initial excitatory responses. Pars compacta cells ($n=10$) were unresponsive. The effect of caudate stimulation was selective in terms of (1) functional type of SNr cells, (2) location of SNr cells, and (3) stimulation site within the caudate. Functional type of SNr cells: saccadic, visual, expectation-related cells were more responsive than auditory, mouth/hand/arm movement-related, and reward-related cells. Many of the cells whose functional characteristics were unidentified responded to the caudate stimulation. The preferential effects were seen among the functional subtypes: cells related to memory-guided saccades, not visually guided saccades; cells with conditioned visual responses, not simple visual responses. Location of SNr cells: the stimulus effects were seen preferentially in cells in the central part of the SNr, not in the dorsal part. Stimulus site: stronger effects, whether inhibition or excitation, were obtained when the stimulation was applied to the head-body transitional zone where visuooculomotor cells were clustered. Behaviorally contingent correlation of spike activity was found between the caudate-nigral pair of cells. For example when a SNr cell with memory-contingent saccadic activity was inhibited by the caudate stimulation, a caudate cell at or close to the stimulation site may show memory-contingent saccadic activity with a similar movement field.

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Introduction

The basal ganglia contribute to the initiation of saccadic eye movements through an inhibitory connection from the substantia nigra pars reticulata (SNr) to the superior colliculus. Cells in the monkey SNr discharge rapidly and tonically during background activity. A group of SNr cells, which have axonal projections to the superior colliculus (Hikosaka and Wurtz 1983c), stop firing before an intentional saccade to a visual target (Hikosaka and Wurtz 1983a) or a remembered target (Hikosaka and Wurtz 1983b). The decrease in SNr spike activity is followed by a burst of spikes in cells in the intermediate layer of the superior colliculus, leading to a saccade to the contralateral side. If the tonic activity of SNr cells is blocked by locally injecting a GABA agonist, the monkey makes saccades to the contralateral side continually and irrepressibly (Hikosaka and Wurtz 1985a, b). The same pharmacological treatment in the rat induced a variety of body movements in addition to contralateral saccades and contralateral turning (Sakamoto and Hikosaka 1989). These data, together with other lines of evidence (Chevalier et al. 1981; Di Chiara et al. 1979), have established that the nigrocollicular connection is inhibitory and GABAergic. The SNr tonically inhibits the superior colliculus, thereby suppressing unwanted movements, but removes the inhibition in a particular behavioral context, thereby facilitating a saccade and possibly other movements.

The SNr of the monkey, as in other species, receives massive inputs from the striatum (caudate nucleus and putamen; François et al. 1987; Parent et al. 1984). Therefore, the presaccadic decrease in the SNr cell activity may be the result of the striatal inputs. In a previous series of studies, we found a group of presaccadic cells

in the monkey caudate nucleus whose activity was similar to SNr cells (Hikosaka et al. 1989a); the caudate cells, however, always increased their activity before a saccade, being otherwise almost inactive. Their activity was dependent on how the saccade was initiated, and the presaccadic caudate cells were classified into three types: (1) cells selectively related to memory-guided saccades (SAC/MEM), (2) cells selectively related to visually guided saccades (SAC/VIS), and (3) cells related to both types of saccades (SAC/VM). In addition to such presaccadic activity, the same or other group of caudate cells responded to visual stimuli that were used as the targets for the saccades (Hikosaka et al. 1989b). Their receptive fields were usually centered on the contralateral visual field, much like the movement fields of the presaccadic cells. The magnitudes of the visual responses were contingent on the behavioral contexts in which the stimuli were presented: the response was enhanced (1) when the visual stimulus induced a saccade upon its onset, (2) when the stimulus was remembered as the target for a future saccade, or (3) when the stimulus was expected to appear after a time gap. In addition, we found neurons whose activity was neither sensory nor motor (Hikosaka et al. 1989c). Many of them showed tonic activity which ended with a task-specific event (e.g., appearance of a light target after a time gap), as if anticipating the upcoming event. These saccadic, visual, and expectation-related neurons were found intermingled in the central region of the caudate nucleus (caudate), forming a functional cluster. Their activities must be organized in a sequential manner in order for the monkey to perform the visuomotor tasks. The connection to the SNr would carry such a sequence of information, thereby serving learned behavior.

A number of questions remain unanswered, however. Do all oculomotor and visual signals in the SNr come from the caudate? Or partly from the caudate and partly from other areas? If so, what kind of information is carried by the caudate-nigral connection? Is the caudate-nigral connection topographically organized among other inputs to the SNr? The answer to these questions would give us an important clue to characterizing the functions of the caudate nucleus and the SNr.

The present study was planned as the first step to answer these questions. We studied the effect of intracaudate stimulation on spike activity of SNr cells, whose functional characteristics were identified using behavioral paradigms.

Materials and methods

Experimental animals

We used two adult male Japanese monkeys *(Macaca fuscata)*, weighing 12 kg and 10 kg. The first monkey was used for an extensive survey of caudate neural activity (Hikosaka et al. 1989a). By the time we started the present study of caudate stimulation, we had finished the survey and thus had obtained detailed functional maps of the caudate nucleus as well as the substantia nigra (SN). We therefore were able to compare the distribution of task-related cells and the effective region of stimulation (see Results). The second monkey was used also to observe the effects of caudate nucleus stimulation on eye movements. This allowed us to compare the effective sites for SN cell activity and the effective sites for eye movements (mentioned in Results; this will be dealt with in more detail in a forthcoming paper).

The monkeys were kept in individual primate cages in an air-conditioned room where food was always available. At each experimental session, they were brought to the experimental room. The monkeys were given restricted fluid during periods of training and recording. Their health, including body weight and appetite, was checked daily. Supplementary water and fruit were provided daily.

Surgical procedures

The monkeys were sedated with ketamine (4.6–6.0 mg/kg) and xylazine (1.8–2.4 mg/kg) intramuscularly, and then general anesthesia was induced by intravenous injection of pentobarbital sodium (4.5–6.0 mg/kg per hour). We conducted surgical procedures under aseptic conditions in an operating room. After exposing the skull, we bolted several screws onto it and fixed them with a dental acrylic resin. The screws acted as anchors by which a head holder and chambers for microelectrode recording were fixed to the skull. We used two chambers: one for the SNr and the other for the caudate. The chambers were so arranged as to avoid physical conflict with each other. In the first monkey they were tilted in two planes: laterally (28°) and anteriorly (20°) for the caudate and laterally (25°) and posteriorly (35°) for the SNr. In the second monkey, the caudate chamber was tilted laterally by 35°, the SNr chamber posteriorly by 40°. The materials for these devices were different in each monkey. In the first monkey they were made of stainless steel. In the second monkey we avoided the use of metal to permit magnetic resonance imaging (see below); the screws were acrylic, and the head holder and chambers were made of Delrin. For measurement of eye position we implanted an eye coil over one eye (Judge et al. 1980; Matsumura et al. 1992). The animals received antibiotics (sodium ampicillin 23–30 mg/kg intramuscularly each day) after the operation.

Experimental procedures

Determination of stimulation and recording sites. Visuooculomotor cells were clustered both in the caudate (Hikosaka et al. 1989a) and in the SNr (Hikosaka and Wurtz 1983a). We selected the sites of stimulation and recording such that they included the visuooculomotor regions. This was based on the general survey that we carried out using behavioral tasks (see below).

In some experiments we implanted a guide tube for electrode penetration. It was either a stainless steel tube (1.0 mm OD) or a Teflon tube (1.2 mm OD). The insertion of the guide tube was performed under ketamine hydrochloride anesthesia using the same micromanipulator. It was directed to the location where visuooculomotor cells were clustered and was fixed using acrylic resin. It could be removed and reinserted to different locations within the chamber. The tip of the guide tube was 2–3 mm above the dorsal edge of the caudate nucleus.

The use of the guide tube allowed us to reach the same region repeatedly. We spent several days exploring the region to determine the cell types along the guide tube track, and then started stimulating the same region while recording single SNr cells. We thus were able to compare the distribution of cell types and the effects of stimulation (see Results). There were also some technical advantages in using the guide tube. Recording of a single cell while moving another microelectrode is difficult, because the distortion of the brain caused by the electrode movement is easily transmitted to the recording site. Such a mechanical effect was prevented to some extent by the use of the guide tube. Another technical advantage was that the shock artifact associated with the electrical stimulation could be lessened by using the guide tube (if metal) as the reference electrode.

Stimulation of the caudate nucleus. We inserted microelectrodes both in the caudate and in the SNr. While placing the caudate electrode at the depth close to the center of the visuooculomotor region, we tried to record single cell activity in the SNr. When the SNr cell activity was isolated, we first determined the functional characteristics of the neuron using the behavioral tasks. We then stimulated the visuooculomotor region of the caudate and then changed the depth by at least 1 mm above and below, for further stimulation.

Recording procedures

Single cell activity. We used platinum-iridium electrodes (Wohlbarsht et al. 1969) or Elgiloy electrodes (Suzuki and Azuma 1976), both glass-insulated. Their tips were exposed by 15–20 μm. In the initial experiments the electrode was driven by an electrode manipulator (MO-95; Narishige) with an *x-y* coordinate, which was attached to the implanted chamber (circular, 19 mm ID). In the later experiments we used Delrin-made, rectangular chambers. The electrode manipulator used for these chambers was modified in our laboratory from the Narishige type. The electrical signals, recorded between the microelectrode and a reference electrode, were preamplified, passed through a window discriminator, and fed into a computer with a resolution of 1 ms. The recording chamber, if it was metal, served as the reference electrode; otherwise, a silver wire placed on the dura over the occipital cortex was used for this purpose.

Eye movements. Eye movements were recorded using the magnetic search-coil technique (MEL-2U; Enzanshi-Kogyo) (Robinson 1963). Eye positions were digitized at 250 Hz or 500 Hz and fed continuously into the computer, where they were stored.

Stimulation procedures

We used a rectangular pulse (duration 0.1–0.2 ms, intensity <200 μA) for stimulation. A train of pulses (up to 3 pulses) were also used but only for preliminary survey of the area. The stimulation was monopolar and anodal (i.e., microelectrode, negative); the chamber, or the guide tube (when it was metal), or the silver wire were used as the reference electrodes.

While recording a single SNr cell, we applied the stimulation to see whether cell activity was changed. For each block of experiment we repeated the stimulation 32–50 times and stored all data (spike discharges and eye movements) with a resolution of 1 ms. The interstimulus interval was 1–2 s (randomized). We carried out the stimulation experiment in two behavioral conditions: the monkey was (1) at rest but alert or (2) performing a simple fixation task. In the latter case, the electrical stimulation was applied while the monkey was fixating a central spot.

Visual stimuli

During the experimental sessions the monkey sat in a primate chair with his head fixed. The experimental room was dimly lit. The field coils of a magnetic search coil system were lowered over the chair. In front of the monkey (57 cm) was placed a tangent screen onto which small red spots of light were back-projected. The projection system consisted of a light-emitting diode (LED) light source (TLRA150-C; Toshiba), pinhole aperture, and projector lens. Three LED projectors were used: the first one was for the fixation point, and its light was projected directly onto the screen. The second and third LEDs were for the target point and another irrelevant stimulus, and their lights were reflected via two galvanomirrors, which controlled the horizontal and vertical positions of the light spots. The positions of these stimuli were controlled by a computer or manually. The behavioral tasks, as well as storage and display of data, were controlled by an experimental system: MONK11 operated on a PDP11/73 computer for the first monkey and MN98 operated on a NEC computer (PC9801 RA21) for the second monkey.

Behavioral tasks

The monkey's basic task was to fixate on a small spot of light projected on the screen. The monkey initiated each task trial by depressing a lever attached to the primate chair. A spot of light (fixation point) then came on at the center of the screen. After a random period of time the spot dimmed. If the monkey responded to the dimming by releasing the lever within a short period (usually less than 0.5 s), he was rewarded with a drop of water. To perform the task the monkey had to keep fixating on the spot. 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 s (randomized).

The monkeys were trained in a series of tasks, all of which were based on the dimness-detection procedure. Crucial for the present study were the saccade task and delayed saccade task (see Matsumura et al. 1992, for detail).

The saccade task was designed to induce the monkey to make a saccade to a visual target (visually guided saccade). In most of the trials, the fixation point went off after a random period of time, and another spot of light (target point) came on at the same time. The target point dimmed for 0.5–0.6 s after a random period between 0.5 and 1.5 s. This task required the monkey to move his line of sight from the fixation point to the target point by making a saccade.

The delayed saccade task was designed to elicit a saccade to a remembered target (memory-guided saccade; Hikosaka et al. 1989a). Usually, 0.7–1.0 s after the fixation point appeared, a spot of light came on for a short period (0.1–0.3 s), indicating the location of the target which would appear later (target cue). The monkey was required to continue to fixate for another 2–4 s while the fixation point remained on. After the fixation point went off, the monkey was required to make a saccade to the remembered location of the cue stimulus before the actual target came on, 600 ms later. When the target came on, the monkey then fixated on the target to detect its dimming and released the lever.

Data analyses

Statistical test. The results are shown as raster and histogram displays (bin width 1 ms). We used Wilcoxon's signed-ranks test for the statistical analysis. We set two time windows on the raster display, one just before stimulation (control period) and the other after stimulation (test period). For each trial the number of spikes in the test period was compared with that in the control period. The changes in discharge rates were then rank-ordered for the statistical test. The test window was set such that it covered the period in which a change in discharge rate was suspected. Its duration was usually 10–100 ms. When no effect was appreciated, it was set to 50–100 ms, starting 10–15 ms after the onset of the stimulus. When multiple effects (e.g., excitation followed by inhibition) were appreciated, the test period was set independently for each of them. Changes in discharge rate whose peaks occurred later than 100 ms after the stimulation were not analyzed.

To quantitate the stimulus effect we calculated a response index (RI) which is defined as follows: RI = Freq (test) Freq (control), where Freq (test) is the average discharge rate during the test period and Freq (control) is the average discharge rate during the control period. The response index was calculated for each block of the experiment (32–50 trials) in which the stimulus was applied at the same location (depth). The response indices obtained at different

depths were then compared, which yielded a depth-effect relationship.

Cumulative display. We used a cumulative time histogram to determine the onset and duration of stimulus effects. Normally a cumulative histogram would show a monotonic increase with time, but in this paper a constant value was subtracted for every bin so that no overall change was seen it the prestimulus period (100 ms; see Fig. 1). The constant value was obtained by calculating the mean discharge rate averaged over the prestimulus period. Thus, a stimulus-evoked excitation and inhibition appeared as an upswing and a downswing in the cumulative histogram, respectively.

Reconstruction of stimulation and recording sites

For the first monkey the procedures of histological reconstruction were described in a previous paper (Hikosaka et al. 1989a) in which we quantified the locations of recorded neurons. We adopted the coordinate system proposed by Percheron (1975). The key structures for the coordinate system are the anterior commissure (AC) and posterior commissure (PC). The position of each neuron was obtained at the time of experiments in relation to the recording chamber (from the readings of the electrode manipulator). The chamber-based coordinates were then transformed to the AC-PC coordinates through rotations (because the chamber was tilted) and translations (from the zero point of the chamber coordinate system to the AC). Several electrolytic marks (10–20 μA, 20–30 s, electrode being negative) made during experiments enabled the translation of the coordinate system. The guide tube also served as a useful landmark. These landmarks were later identified in histological sections (embedded in celloidin and stained using the Klüver-Barrera method), and their locations relative to the AC could be calculated (after taking into account of the ratio of shrinkage). The borders of the basal ganglia nuclei were similarly reconstructed in the AC-PC coordinate system. This was done for every histological section in which neurons with a given activity were localized, so that their profiles could be viewed from any perspective.

For the second monkey we used magnetic resonance imaging (MRIS; Hitachi Laboratory; 2.11 T) so that we could determine, roughly, the locations of recorded cells in relation to the caudate nucleus or the SNr. Inside the recording chambers we pasted a sheet of bandage soaked with liquid paraffin. Because of the paraffin, the chambers (their inner borders) were highlighted on the MRI. We then took MRIs in the direction of the chamber; that is, the direction of electrode penetration. Thus, the location of a recorded cell, which was read from the coordinates of the electrode manipulator, was directly mapped on the MRI.

Results

Nigral cell types inhibited / excited by caudate stimulation

We examined the effect of intracaudate stimulation (single pulse, 100 μA) in 148 cells in the SN: 138 cells in the pars reticulata (SNr) and 10 cells in the pars compacta (SNc). Statistically significant changes were produced in 60 SNr cells ($P<0.05$ by Wilcoxon's signed-ranks test). Using a variety of behavioral paradigms we characterized the types of SNr cell activity (see Materials and methods for details). Among them, saccade-related, visual, and expectation-related cells were likely to respond to the caudate stimulation (Table 1). The stimulation was usually ineffective to auditory, mouth, or arm movement-related cells. A large portion of unidentified cells showed the stimulus effects. None of the cells presumed to be in the SNc and to be dopaminergic were affected.

Inhibitory and excitatory effects were observed in 58 and 45 cells, respectively. As shown in Table 1, 21 cells showed only an inhibition (I), while 9 cells showed only an excitation (E); others showed an inhibition followed by an excitation (I-E; $n=17$) or an excitation followed by an inhibition (E-I; $n=13$).

SNr cells whose first responses were an excitation (excited cells) tended to have higher background discharge rates than other types: excited cells, 89.4 ± 35.0 spikes/s; inhibited cells, 69.5 ± 34.3 spikes/s; "no response" cells, 65.5 ± 32.5 spikes/s (mean ± SD). The dif-

Table 1. Effects of intracaudate stimulation on different types of substantia nigra cells

Area	Functional types	Total	Effects		Type of response			
			No response (*n*)	Response (*n*)	I	I–E	E–I	E
SNr	Visual	45	29	16	4	5	5	2
	Auditory	12	11	1	0	0	1	0
	Saccade	64	37	27	11	6	8	2
	Mouth	3	3	0	0	0	0	0
	Hand and arm	1	1	0	0	0	0	0
	Reward	5	3	2	2	0	0	0
	Expectation	11	4	7	2	2	2	1
	Unknown	34	19	15	4	5	1	5
SNc		10	10	0	0	0	0	0
Total		185	117	68	23	18	17	10
Total no. of neurons		148	88	60	21	17	13	9

For each cell, single pulses of 100 μA were applied while changing the depth of the stimulating electrode for more than 2 mm in the caudate. The sum of the numbers in each column exceeds the total number of neurons, because single cells could show more than one type of behavioral responses (e.g., visual and saccade)

SNr, pars reticulata; SNc, pars compacta; The responses were further classified into: I, pure inhibition; E, pure excitation; I–E, inhibition followed by excitation; E–I, excitation followed by inhibition

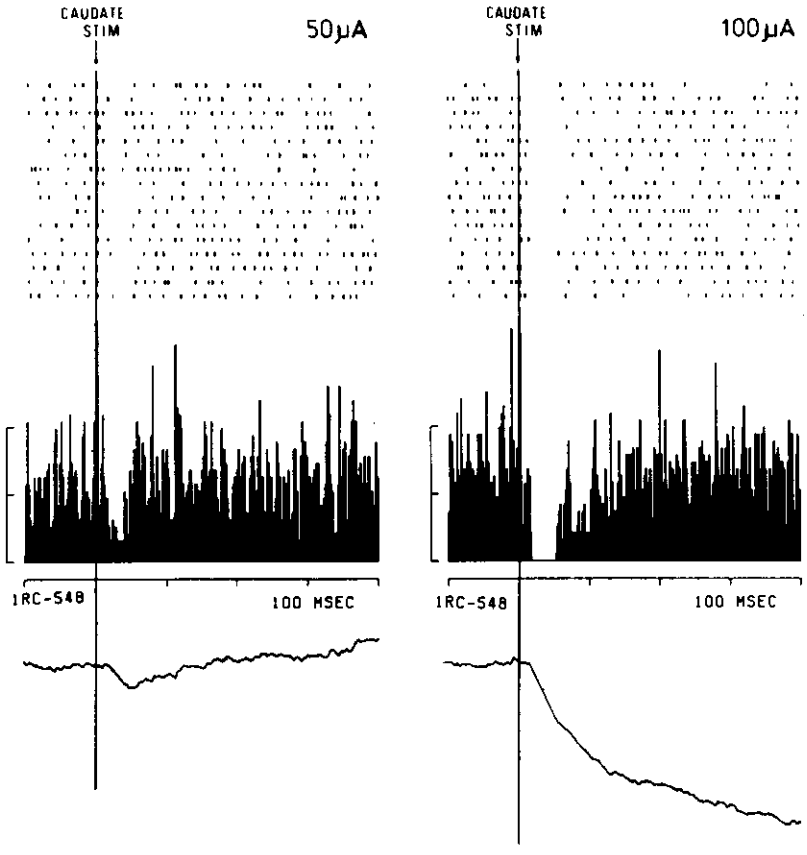

Fig. 1. Effects of single-pulse caudate stimulation of different intensities: 50 μA *(left)* and 100 μA *(right)*. Spike discharges of a single substantia nigra pars reticulata cell are shown as raster displays *(top)*, time histograms *(center)*, and cumulative time histograms *(bottom)*. *Vertical lines* indicate the time of stimulation. A *dot* in the raster display indicates a single action potential. Calibrations on the *left* of the histograms indicate 50 and 100 spikes/s. The onsets of the stimulation effects are readily observed in the cumulative time histograms

ferences were significant (Mann-Whitney *U*-test) between the excited cells and inhibited cells ($P<0.05$) and between the excited cells and no response cells ($P<0.01$).

Spatial and temporal characteristics of caudate-induced inhibition / excitation of nigral cells

Effects of stimulus intensity. Figure 1 shows an example of caudate-induced inhibition. A single pulse of current as low as 50 μA induced a decrease in discharge rate of a SNr cell (Fig. 1, left). Its tonic activity was silenced by stronger stimulation (100 μA; Fig. 1, right). The latency of inhibition (12.5 ms) did not change, however, as indicated by cumulative time histograms. The effect of stimulation also depended on where in the caudate the stimulus was delivered, as shown below.

Sites of stimulation in caudate. In the first monkey we placed guide tubes at two different sites (at different times during the experiments) which were separated in the anteroposterior direction (Fig. 2, left). Through these guide tubes we inserted microelectrodes into the caudate. The anterior penetration was approximately 1 mm posterior to the AC; the posterior one, 5 mm posterior to the AC. Stimulation in the second monkey was applied to the more posterior portion of the caudate, approximately 7 mm posterior to the AC.

The task-related cells were found in the central/ventral region of the caudate, which is elongated in the

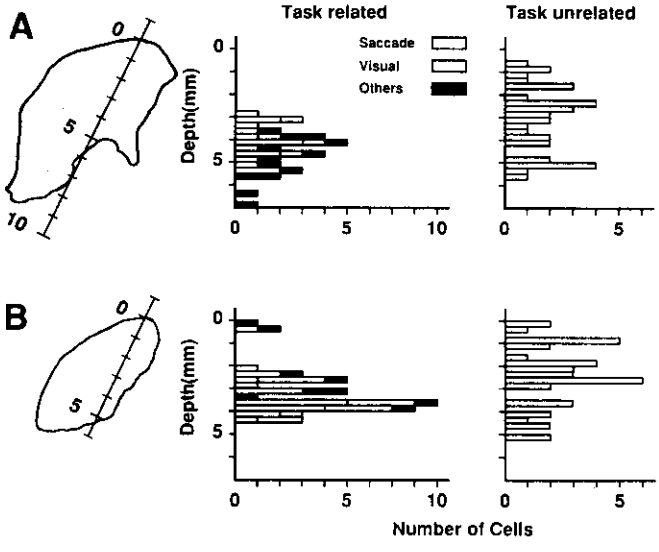

Fig. 2A, B. Determination of the visuooculomotor region in the caudate nucleus. *Left*, two electrode tracks are shown which passed through the caudate at different rostrocaudal levels; *top*, 1 mm caudal to the anterior commissure (AC); *bottom*, 5 mm caudal to the AC. *Center* and *right*, types of caudate cells recorded along the anterior *(top)* and posterior *(bottom)* electrode tracks. The depth was measured from the dorsal end of the caudate nucleus, and the number of cells at each depth is plotted for different types of cells (bin width 250 μm): *center*, task-related (saccade-related, visual, others); and *right*, task-unrelated cells

rostrocaudal direction (see Hikosaka et al. 1989a). In the course of the penetrations for stimulation, the electrode passed the task-related region. In Fig. 2 (center and right) the relationship between the depth in the caudate nucleus and the subtypes of cells recorded along the electrode penetration is illustrated for the first monkey. Saccade-related and visual cells were clustered approximately 2–4.5 mm from the upper border of the caudate in the posterior section (Fig. 2, center-bottom); similar, but more scattered, clustering was seen in the anterior penetration near a depth of 3–5.5 mm (Fig. 2, center-top).

The electrical stimulation was applied along these electrode tracks at different depths. In the first monkey, responses were found in 46 out of 114 SNr cells by stimulation through the posterior guide tube and 7 out of 18 SNr cells from the anterior guide tube. In the second monkey responses were obtained in 7 out of 16 SNr cells.

Inhibition / excitation of SNr cell changes with depth of caudate stimulation. Along with such clustering of task-related cells in the caudate, the effect of stimulation on SN cell activity changed with the depth of caudate stimulation (Fig. 3). We calculated the response indices as shown in Materials and methods and plotted them against the depth of stimulation. The effect of stimulation on this SNr cell was inhibitory, and the inhibition peaked at 3–4 mm where saccade-related and visual cells were clustered (see Fig. 2, bottom; posterior penetration).

The matching of the task-related cell cluster in the caudate and the effect of stimulation on SN cells is more clearly seen in Fig. 4. On the right are superimposed the depth profiles of caudate stimulation on different types of SN cells. The profiles, especially for inhibitory responses, were similar to the distributions of task-related subtypes in the caudate (Fig. 4, left). There might be some tendency toward excitatory responses having multiple peaks.

Latencies of inhibition and excitation. Caudate-induced inhibition and excitation had similar latencies (Fig. 5).

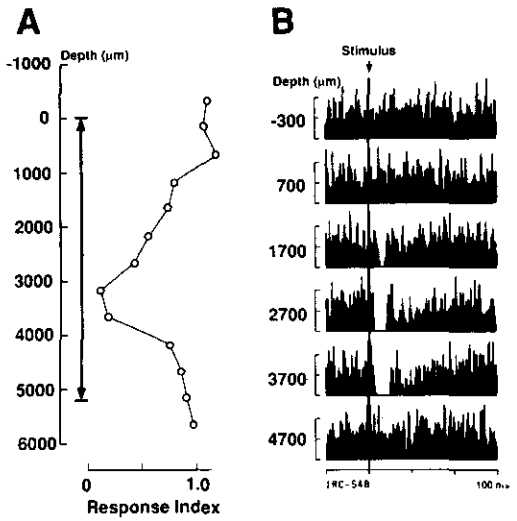

Fig. 3A, B. Effects of stimulation depend on the depth in the caudate nucleus. While a single SNr cell was recorded, stimulation was applied at different depths in the caudate nucleus by moving the stimulating electrode. The change in the stimulus effect is shown by peristimulus spike time histograms (**B**) and the response indices (**A**). The penetration was made through the posterior guide tube (see Fig. 2B, left). The response index was defined as the ratio of the discharge rate in a 50-ms response period (starting 13 ms after the stimulation) to the discharge rate in a 50-ms control period immediately before the stimulation. See Materials and methods for details

The latencies were 9.0–32.5 ms (mean 16.7 ms) for the initial inhibitory responses (top) and 6.5–35.0 ms (mean 16.7 ms) for the initial excitatory responses (bottom). The latencies tended to be shorter when stimulation was applied to the more posterior parts of the caudate. The mean latencies of the inhibitory/excitatory responses from the three major sites for stimulation – 1 mm, 5 mm, and 7 mm posterior to the AC – were 22.7 ms, 16.4 ms, and 11.6 ms, respectively. The differences were statistically significant ($P < 0.05$, Mann-Whitney U-test). A second component (e.g., an excitation following and inhibition) was present in 29 cells and its latency ranged from 15 to 75 ms (mean 34.6 ms; not shown).

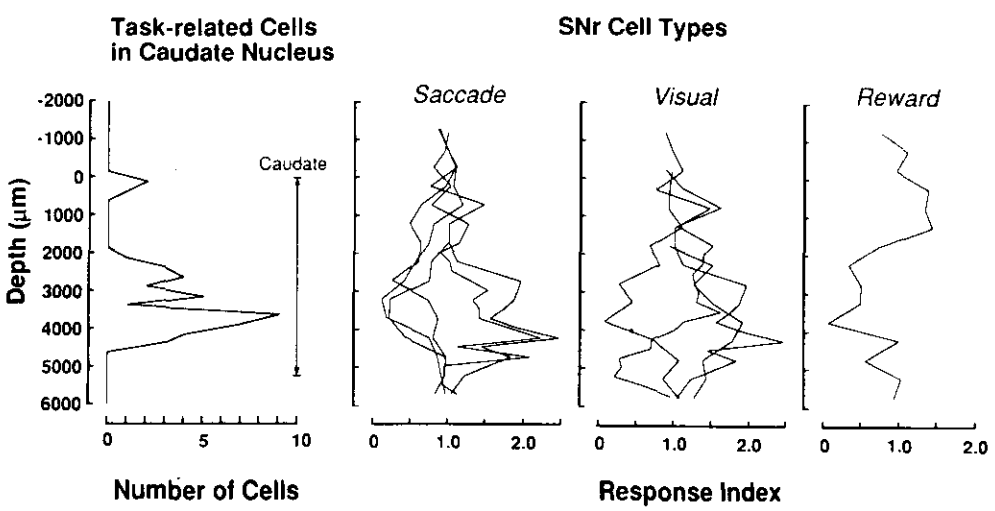

Fig. 4. Stimulation in most effective from the task-related region in the caudate. *Left*, the numbers of task-related cells at different depths (see Fig. 2). *Right*, the response indices for different SNr cells *(abscissa)* are plotted against the depth of the stimulation site in the caudate *(ordinate:* five saccade-related cells, four visual cells, and one reward-related cell. The peaks of inhibitions as well as excitations roughly matched the cluster of task-related cells

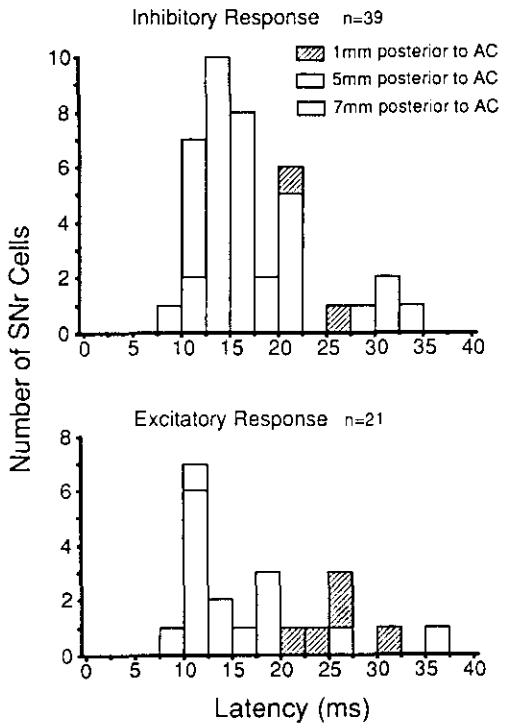

Fig. 5. Latencies of caudate-evoked inhibitions *(top)* and excitations *(bottom)* in SNr cells. The effects from three stimulation tracks are shown by different symbols: *hatched column*, 1 mm posterior to anterior commissure (*AC*); *open column*, 5 mm posterior to AC; *dotted column*, 7 mm posterior to AC

Differential effects of caudate stimulation on functional cell types in substantia nigra

SAC/MEM cells are most likely to be affected. Twenty-seven out of sixty-four saccade-related SNr cells responded to caudate stimulation (Table 1). Using saccade task and delayed saccade task we further classified 53 of the saccade-related cells into three types. The effects of caudate stimulation varied depending on the functional types (Table 2). SAC/MEM cells were more likely to respond to caudate stimulation than SAC/VIS cells; the difference was statistically significant by chi-square test ($P<0.02$); SAC/VM cells were in-between. Any of the three types could receive excitation or inhibition, but pure excitation was seen in only one cell, which was classified as SAC/VIS.

Conditioned visual cells are most likely to be affected. Sixteen out of 45 visual cells responded to caudate stimu-

Table 2. Differential effects of caudate stimulation on saccade-related cells

Primary effect	Inhibition	Excitation	No response	Total
SAC/VIS	1	3	17	21
SAC/VM	3	3	7	13
SAC/MEM	9	4	6	19
Total	13	10	30	53

Cells preferentially related to memory-guided saccades (SAC/MEM) were more likely to be affected (especially inhibited) than cells preferentially related to visually guided saccades (SAC/VIS) or cells equally related to these types of saccades (SAC/VM)

Table 3. Differential effects of caudate stimulation on visual cells

Primary effect	Inhibition	Excitation	No response	Total
Simple visual	1	4	20	25
Complex visual	6	2	5	13
Total	7	6	25	38

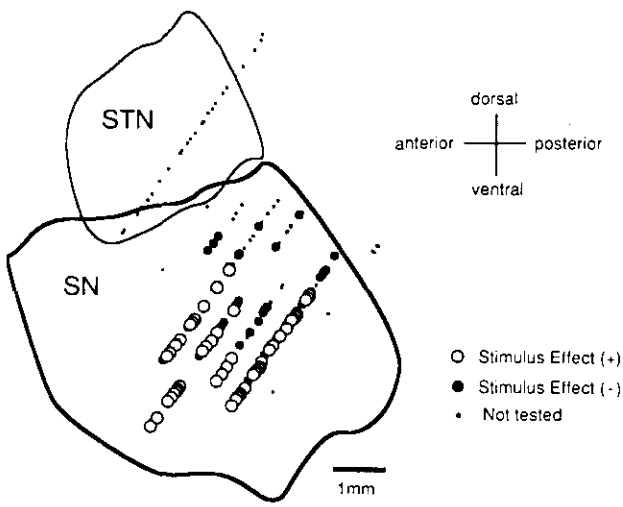

Fig. 6. Intranigral distribution of cells affected by caudate stimulation (lateral view). Inhibited or excited cells *(open circles)* were located more ventrally than unaffected cells *(filled circles)*. The profiles of the substantia nigra (*SN*) and the subthalamic nucleus (*STN*) are also shown, as if projected on a parasagittal plane. *Dots* represent cells for which caudate stimulation was not thoroughly tested

Table 4. Preferential effects of caudate stimulation on single-modal cells

SNr cell modality	Total	Effects		Type of response			
		No response (*n*)	Response (*n*)	I	I–E	E–I	E
Single	109	56	53	19	16	10	8
Multiple	39	32	7	2	1	3	1
Total no. of neurons	148	88	60	21	17	13	9

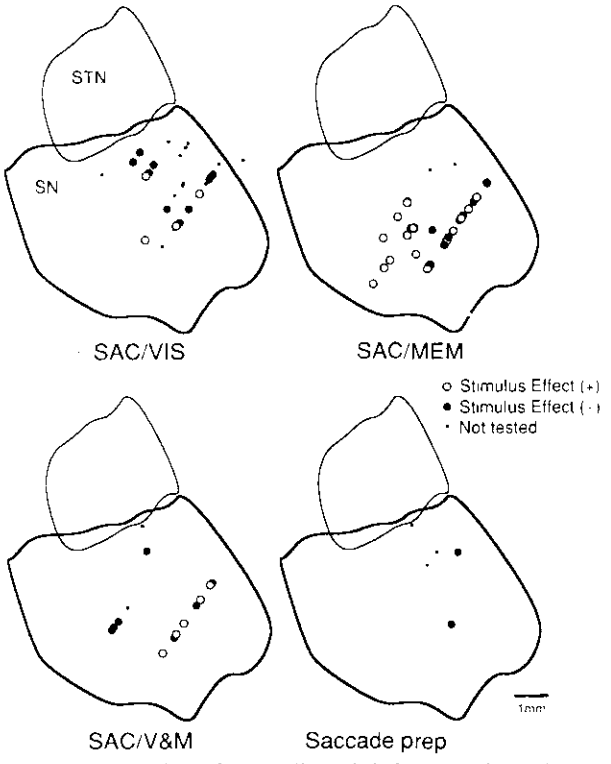

Fig. 7. Distribution of SNr cells and their inputs from the caudate: saccade-related cells (lateral view). Cells inhibited or excited *(open circles)* and cells unaffected by caudate stimulation *(filled circles)* are shown for different functional types. *SAC/MEM*, cells preferentially related to memory-guided saccade; *SAC/VIS*, cells preferentially related to visually guided saccade; *SAC/V&M*, cells equally related to both types of saccade; *Saccade prep*, cells related to preparation of saccades. *Dots* represent cells for which caudate stimulation was not thoroughly tested. The profiles of the SN and STN are shown as if projected on a parasagittal plane

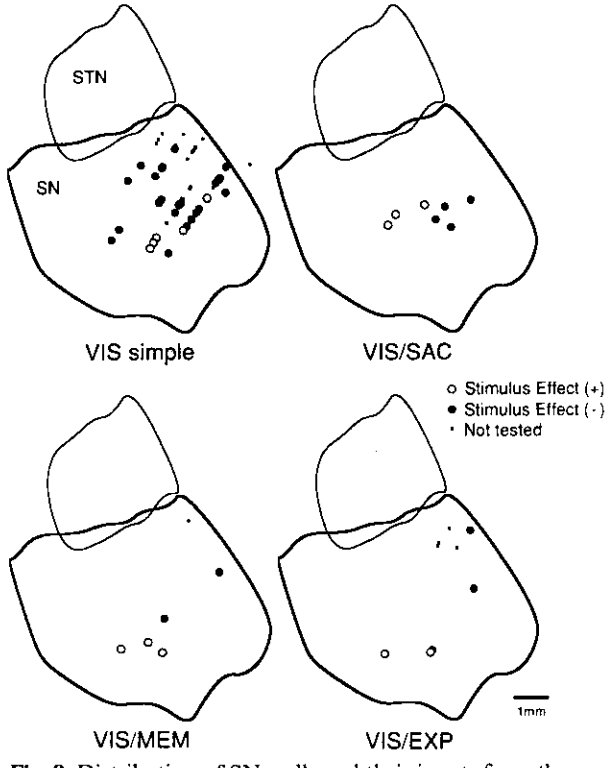

Fig. 8. Distribution of SNr cells and their inputs from the caudate: visual cells. Cells inhibited or excited *(open circles)* and cells unaffected by caudate stimulation *(filled circles)* are shown for different functional types. *VIS simple*, cells with unconditioned visual responses; *VIS/SAC*, cells with visual responses which were enhanced by a saccade to the stimulus; *VIS/MEM*, cells with visual responses which were enhanced when the stimulus had to be remembered; *VIS/EXP*, cells with visual responses which were enhanced when the stimulus had been expected to appear. Other details as in Fig. 7

lation (Table 1). For 38 cells we further classified the visual responses into the simple type and the conditioned type, depending on whether the response was modulated (enhanced) by specific behavioral contexts. The effects of caudate stimulation were differential (Table 3). SNr cells with conditioned visual responses were more likely to respond to caudate stimulation, predominantly with inhibition. The effects on SNr cells with simple visual responses were uncommon and tended to start with excitation.

Single-modal SNr cells are most likely to receive inputs from the caudate. Single SNr cells could show more than one type of activity (e.g., visual and saccade-related; see Hikosaka and Wurtz 1983a). We found that the SNr cells that showed only one type of activity were more likely to respond to the caudate stimulation (Table 4). Among 60 caudate-recipient cells, only 7 were multimodal. Such a tendency was especially clear in the SNr cells that showed

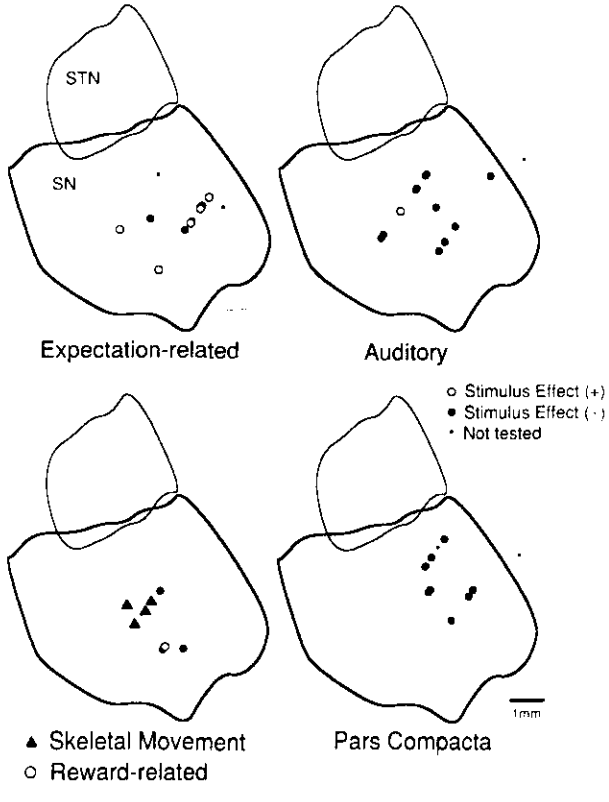

Fig. 9. Distribution of nigral cells and their inputs from the caudate: other types of cells. Cells inhibited or excited *(open circles)* and cells unaffected by caudate stimulation *(filled circles)* are shown for different functional types. Other details as in Fig. 7

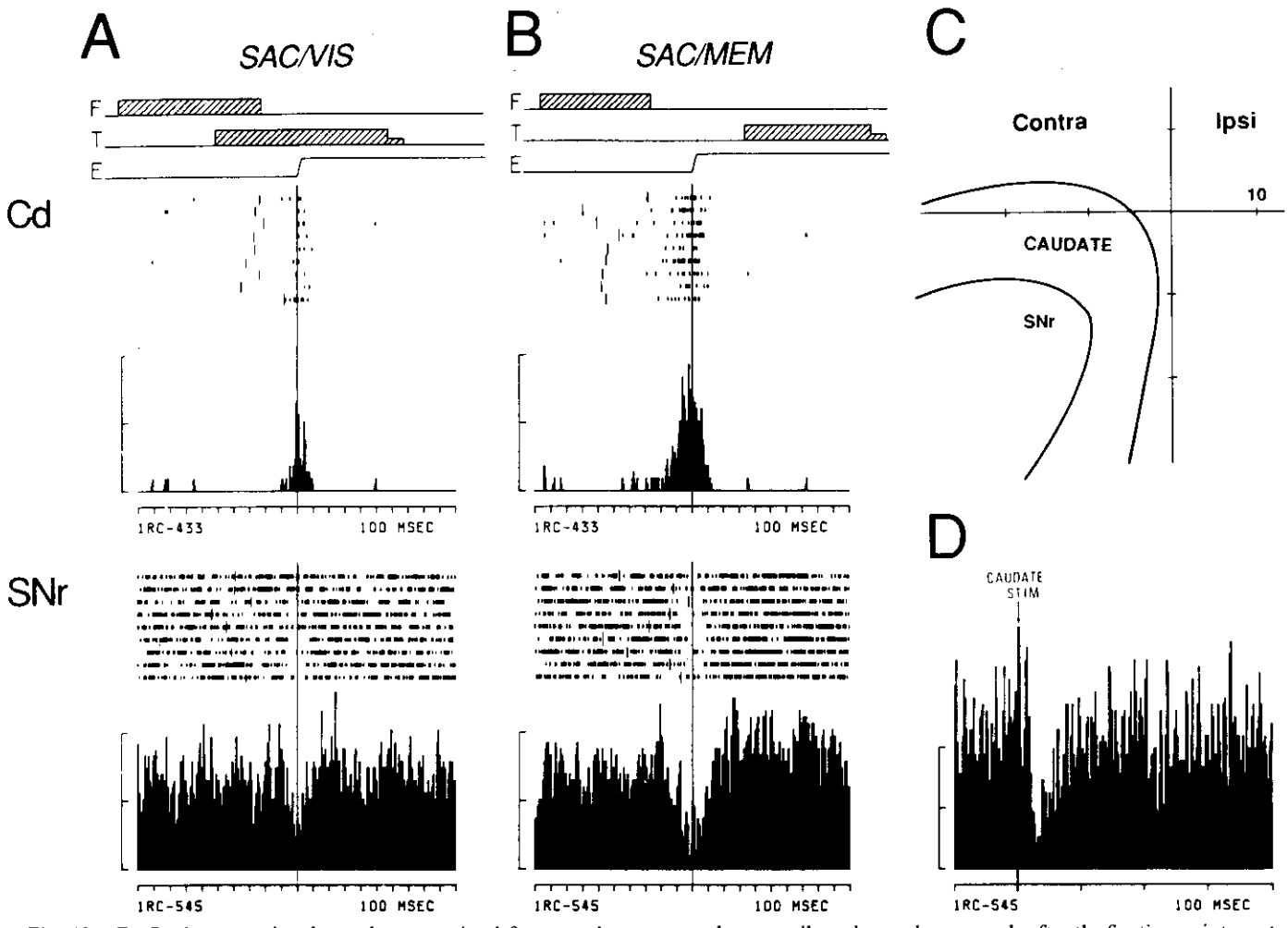

Fig. 10A–D. Oculomotor signal may be transmitted from caudate to substantia nigra: memory-contingent saccadic activity. Spike activities of a caudate cell *(Cd, top)* and a substantia nigra pars reticulata cell *(SNr, bottom)* were compared in two different modes of saccades: visually guided saccade *(SAC/VIS)* (**A**), memory-guided saccade *(SAC/MEM)* (**B**). The spike activities, shown by spike rasters and histograms, were aligned on the onsets of the saccades, as indicated by the task schemes above: *F* central fixation point; *T*, target point located within the movement fields of the cells (20°, contralateral and down); *E*, schematic eye position. **A** The target came on while the fixation point was still present, and the monkey was allowed to make a saccade after the fixation point went off. **B** The position of the target was indicated 2–3 s before the fixation point went off (not shown), and the monkey made a saccade to the remembered location of the cue stimulus. *Short vertical bars* in the spike rasters indicate the offsets of the fixation point. **C** movement fields of the caudate and the SNr cells. **D** Inhibition of the SNr cell by stimulation (100 μA, single pulse) applied at the point close to the caudate cell; further away from the caudate cell, the effect became smaller. *Calibrations* on the *left* of the histograms indicate 50 and 100 spikes/s

an inhibition as the first response to the stimulation; 35 of the 38 cells were single-modal.

Distribution of nigral cells inhibited / excited by caudate stimulation

Intranigral locations of stimulus-affected cells. We then asked whether the caudate-recipient cells were differentially distributed in the substantia nigra. Figure 6 shows the lateral view of all cells recorded in the substantia nigra region, together with the profiles of the SN and subthalamic nucleus (STN). Stimulus-responsive cells (open circles) tended to be deeper and more anterior than nonresponsive cells (filled circles).

Cell locations are shown in Figs. 7–9 for different functional types. Among saccade-related types (Fig. 7), SAC/MEM cells were most likely to receive inputs from the caudate. Figure 7 also shows that SAC/MEM cells were significantly more ventral than SAC/VIS cells. Among visual types (Fig. 8), simple visual cells were generally unresponsive to caudate stimulation and were located in the dorsal part of the SN. We classified conditioned visual cells based on the nature of the significant behavioral contexts: enhanced when a saccade was made to the stimulus (VIS/SAC), when the stimulus had to be remembered (VIS/MEM), and when the stimulus had been expected (VIS/EXP). These conditioned visual cells, especially deeper ones, received inputs from the caudate. Auditory, expectation-related, skeletal movement, or reward-related cells were found in the central part of the SN (Fig. 9); except for the expectation-related cells, they were poorly responsive. SNc cells, which were identified

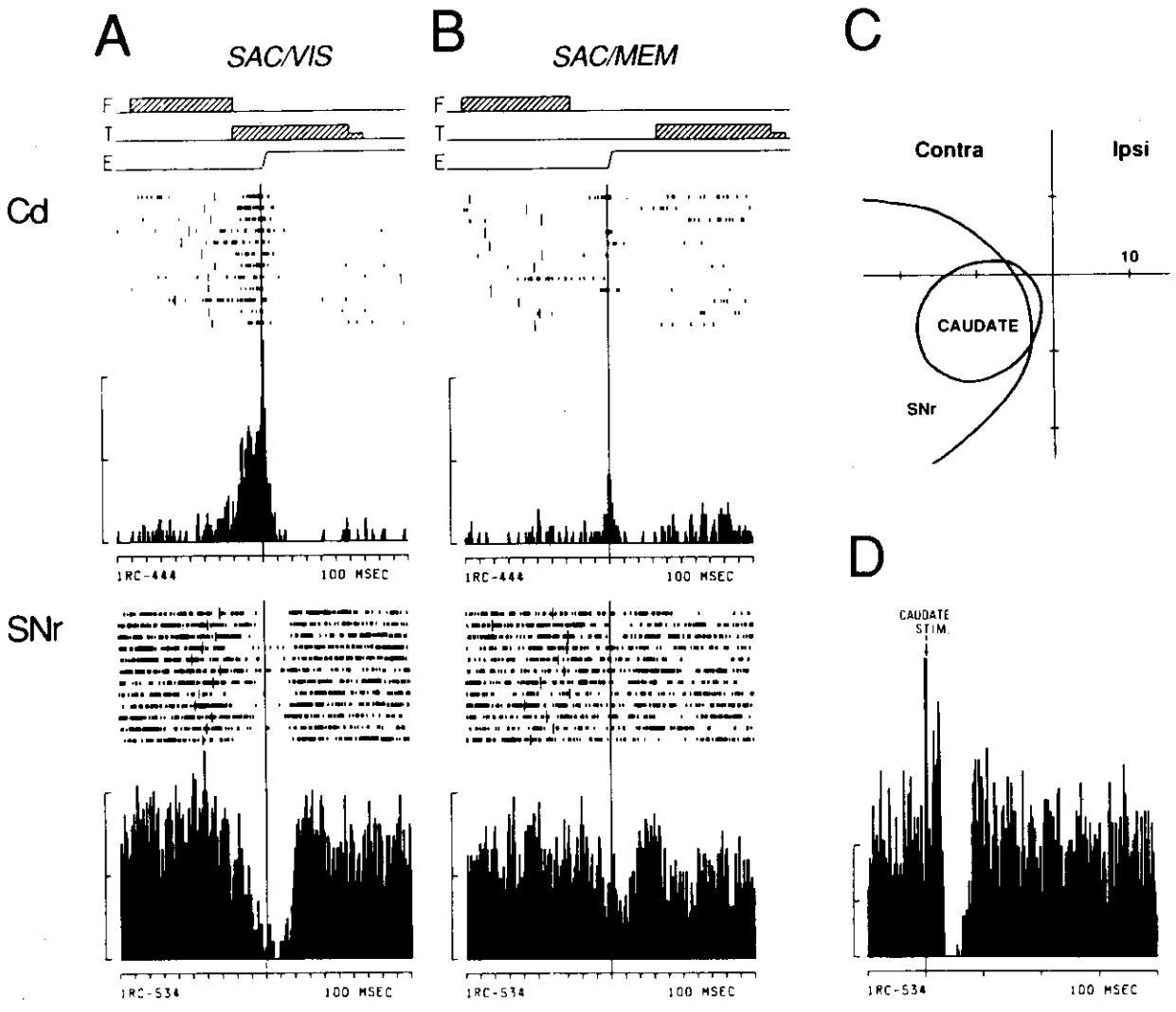

Fig. 11A–D. Oculomotor signal may be transmitted from caudate to substantia nigra: visually guided saccadic activity. Details as in Fig. 10

as showing low-frequency, irregular, broad spikes, were in the caudal part and were unaffected by caudate stimulation.

Task-specific oculomotor / complex signals transmitted by inhibitory caudate-nigral connection

Reciprocal relationships between caudate and SNr cell activities related to saccades. The stimulation experiments suggested that behaviorally significant signals were transmitted from the caudate to the SNr. Temporal correlations would therefore be expected between the activities of caudate-recipient SNr cells and those of the caudate cells near the stimulation site. Indeed, we sometimes found a mirror image-like relationship.

Figure 10 shows a typical example. The SNr cell was inhibited by caudate stimulation (Fig. 10D). We were able to record from a single caudate cell near the site from which the SNr cell was inhibited with the lowest threshold. Using the saccade tasks (Fig. 10A, B) we found that this pair of cells had similar functional characteristics: both the caudate cell (top) and the SNr cell (bottom) changed their activity before memory-guided saccades (Fig. 10B), but only slightly before visually guided saccades (Fig. 10A). In accordance with the stimulus effect, the tonic activity of the SNr cell was suppressed while the caudate cell showed a burst of spikes. In addition, their movement fields overlapped (Fig. 10C). These results suggested that the caudate-nigral connection carried the memory-contingent saccadic information and this was inhibitory.

Visually contingent saccadic information may also be transmitted through the caudate-nigral connection. The pair of neurons shown in Fig. 11, one caudate (top) and the other SNr (bottom), were both related to visually guided saccades (Fig. 11A); their activities changed little when the saccade was made to remembered targets (Fig. 11B). Again they had similar movement fields (Fig. 11C). Stimulation applied near the site where the caudate cell was recorded induced a brief increase followed by a clear suppression of the activity of the SNr cell (Fig. 11D).

We were able to observe such coincident response patterns in five pairs of caudate-nigral cells, all in relation

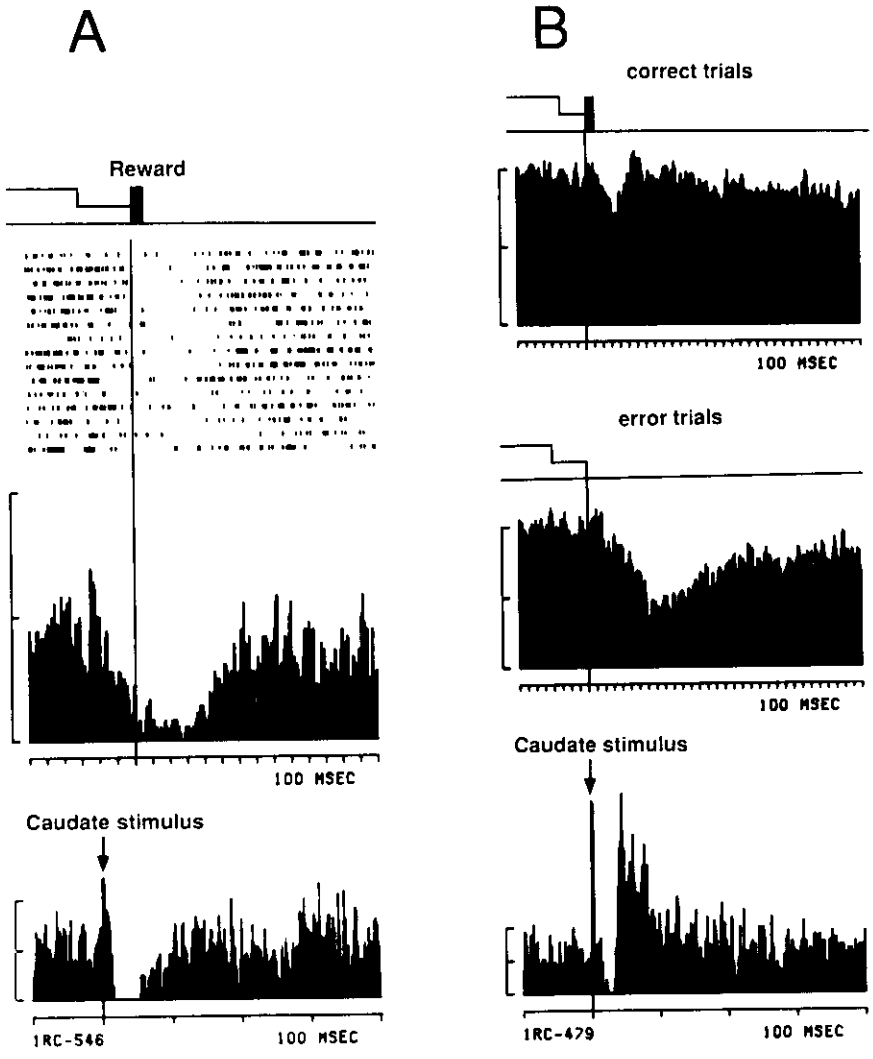

Fig. 12A, B. Other examples of SNr cells affected by caudate stimulation. **A** A SNr cell related to reward-obtaining behavior; its activity was suppressed before and after the delivery of reward. The raster and histogram were aligned on the onsets of the reward (indicated by a *filled rectangle* in the task scheme *above*) which was delivered when the monkey released the lever in response to the dimming of the target point (indicated schematically by a *depression* of the *open column*). This SNr cell was inhibited by caudate stimulation (100 μA, single pulse; *bottom*). **B** A SNr cell related to task failure. The period of target dimming was made short so that the monkey failed about half of the trials, getting no reward. The cell decreased its activity after such error trials (*center*); only slight inhibitions were seen after correct trials (*top*). These trials were intermingled during the experiment, but here are grouped separately. The spike time histograms were aligned on the offsets of the target point, which corresponded to the onset of reward in correct trials. Caudate stimulation (100 μA, single pulse) induced a transient inhibition followed by an excitation (*bottom*)

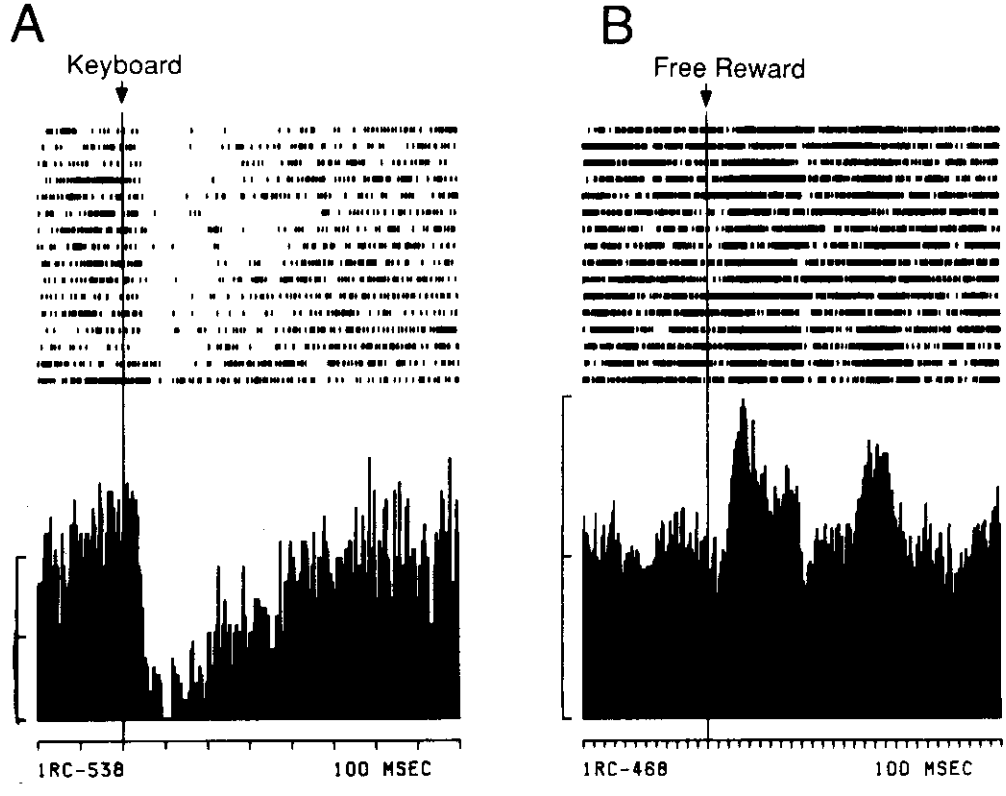

Fig. 13A, B. Examples of SNr cells unaffected by caudate stimulation. **A** A SNr cell inhibited by a sound. While the monkey was at rest, the investigator typed on the computer keyboard with several-second intervals; the cell ceased its tonic activity. The keyboard was located outside the monkey's view in the next room. **B** A SNr cell activated by free reward (water) given outside the tasks; activation appeared to be correlated with tongue protrusion. Caudate stimulation produced no effect in either of these cells

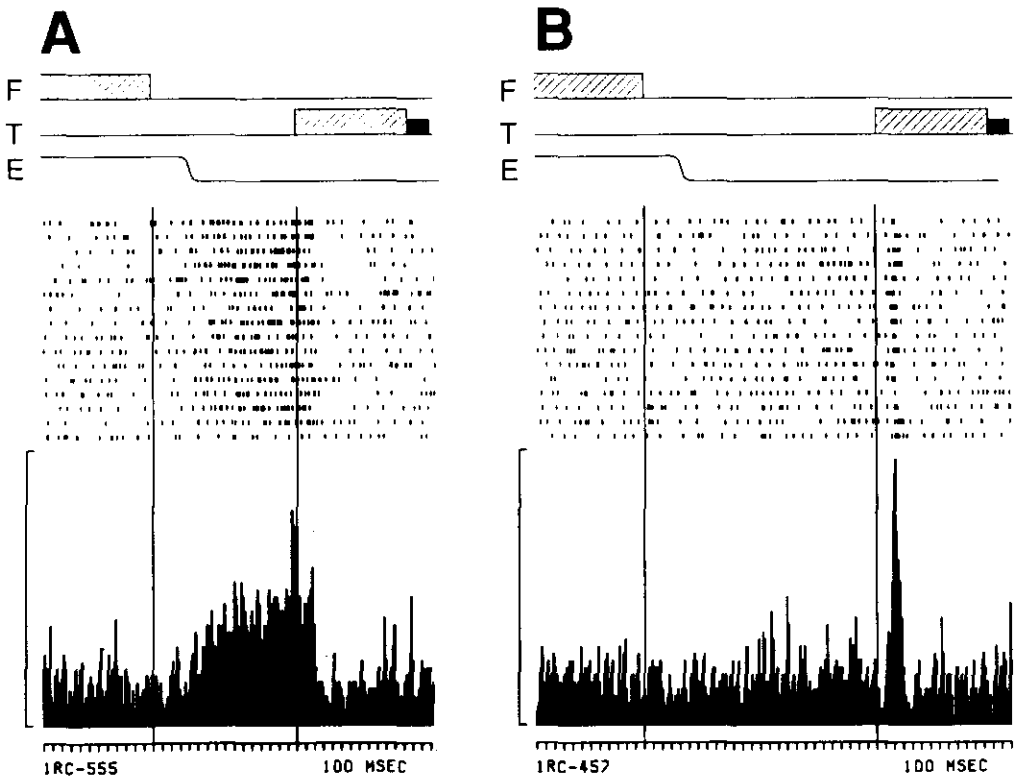

Fig. 14A, B. Substantia nigra pars compacta cells were unresponsive to caudate stimulation. **A** A cell that showed tonic discharge before the expected appearance of the target. **B** Another cell that responded to a visual target only when it appeared after a long time gap. Neither of them responded to caudate stimulation (100 μA). *F*, central fixation point; *T*, target point; *E*, schematic eye position

to saccadic activity. However, such comparison was limited largely because it became difficult after mapping the effective sites of stimulation to record healthy electrical activity from individual caudate cells.

Caudate-nigral connection may carry nonoculomotor signals. SNr cells unrelated to saccades could also be inhibited by caudate stimulation. For example, the SNr cell shown in Fig. 12A decreased its activity before the monkey obtained a reward by releasing the lever. The effect of the caudate stimulation was a pure inhibition. The SNr cell shown in Fig. 12B decreased its activity when the monkey failed to obtain a reward of water as the lever release was delayed. The effect of the caudate stimulation was an inhibition followed by an excitation.

Examples of no stimulus effect – SNr. As shown in Table 1, SNr cells responsive to auditory stimulation or related to skeletal movements were rarely affected by caudate stimulation. The cell shown in Fig. 13A ceased its tonic discharge in response to a sound, e.g., punching of the keyboard in the next room. The cell shown in Fig. 13B showed a cyclic change in its activity after a reward of water; the activity increase appeared to be associated with tongue protrusion. Neither of these cells was responsive to caudate stimulation (not shown).

Examples of no stimulus effect – SNc. No effect was observed in the cells which were thought to be dopaminergic and in the SNc. Unlike the cells in the SNr, these cells typically had triphasic action potentials (positive-negative-positive) with long durations and low background discharge rates (Schultz et al. 1983). Some of them changed their discharge in relation to memory-guided saccades. A first cell (Fig. 14A) showed a sustained increase in discharge rate after the monkey made a saccade to the location where the target was expected to appear. A second cell (Fig. 14B) responded to the appearance of the target point which was expected; no other visual stimulus had similar effects.

Discussion

Mechanisms of caudate-nigral inhibition and excitation

Both suppression and facilitation of spike activity in SNr cells were induced by stimulation of the caudate nucleus. Our data confirmed the results of Feger and Ohye (1975); using alert monkeys, they observed that stimulation of the caudate produced a pure inhibition of half of the nigral cells recorded and an initial excitation followed by an inhibition in the other half.

The suppression is likely to be mediated by monosynaptic inhibitory connections from the caudate to the SNr. A majority of striatal output cells contain GABA and thus are considered to be inhibitory (Graybiel 1990). One of their major targets is the SNr (François et al. 1987; Parent et al. 1984). As demonstrated by Yoshida and Precht (1971) in the cat, stimulation of the caudate induces monosynaptic inhibitory postsynaptic potentials (IPSPs) in SNr cells. The impulse conduction through this pathway is slow; the latencies of the IPSPs ranged from 14.6 to 20 ms. These values roughly correspond to the latencies of the caudate-nigral suppression obtained in our study.

In contrast, the mechanism of the caudate-nigral facilitation is unclear. There are at least three possible mechanisms: (1) direct excitatory connection; (2) disinhibition mediated by the globus pallidus external segment (GPe) and the STN; and (3) disinhibition which occurs within the SNr.

The direct excitatory connection was suggested for substance P-containing neurons (Kanazawa and Yoshida 1980). However, subsequent studies have shown that, within single striatal cells, substance P usually colocalizes with GABA (Graybiel 1990; Penny et al. 1986). Moreover, substance P is now generally considered to have modulatory effects rather than fast synaptic effects (Reid et al. 1990).

The second possibility, involvement of the GPe/STN pathway, is quite plausible. This pathway would be trisynaptic (Kitai 1981): caudate-GPe (inhibitory), GPe-STN (inhibitory), and STN-SNr (excitatory). That the STN-SNr connection is excitatory has been established recently (Hammond et al. 1978; Kitai and Kita 1987). Can the trisynaptic pathway carry signals as fast as the monosynaptic caudate-nigral pathway? There is no critical data, to our knowledge, to answer this question. But even if each of the trisynaptic connections takes 3 ms, the latency of the stimulus effect would be less than 10 ms. The oculomotor function of this side pathway was demonstrated by Matsumura et al. (1992): in the ventral part of the STN are a group of neurons which increase spike activity during eye fixation, before and after saccades, or in response to visual stimuli. Such STN cell activities would increase the activity of SNr cells, via their excitatory connections, and thus suppress initiation of saccades. This mechanism may underlie the effect of caudate stimulation observed in the present study.

The third possibility, disinhibition within the SNr, has been suggested by Chevalier et al. (1985). Injection of glutamate in the striatum led to an inhibition of a SNr neuron and in turn excitation (disinhibition) of their target neurons (superior colliculus or ventromedial thalamus). For a given SNr neuron the inhibitory zone was localized in the striatum, and just outside this zone was found the area from which excitatory responses were elicited. The direct striatal effect on SNr cells would be inhibitory, but surrounding SNr cells would be freed from the tonic inhibition exerted by the inhibited SNr cells. In this case, the facilitation should be later than the primary inhibitory effect. The latencies of the facilitation observed in our study were roughly in the same range as those of the inhibition. This possibility is thus still valid.

We would like to add two more possibilities, both involving axon reflexes. First, the electrical stimulation might activate the axon terminals of STN neurons innervating the caudate (Nakano et al. 1990; Parent and Smith 1987), cause axon reflexes to the other branch projecting to the SNr, and produce monosynaptic excitatory postsynaptic potentials (EPSPs). Second, axon reflex may occur via cerebral cortical neurons which directly activate STN neurons, producing disynaptic EPSPs. Further experiments are required to exclude these possibilities.

Oculomotor functions are localized within the caudate-nigral connection

The effect of stimulation was localized within the caudate nucleus where saccadic/cognitive cells were clustered. Furthermore, among several functional types recorded in the SNr, saccadic, visual, and expectation-related neurons tended to receive caudate inputs, whereas auditory, skeletal movement-related, and reward-related neurons did not.

Two implications are raised from these results. The first possibility is that the caudate-nigral system, as a whole, is oriented toward oculomotor or cognitive functions, as suggested previously (Percheron et al. 1984; Selemon and Goldman-Rakic 1985). Indeed, cells related to functions other than visuooculomotor or cognitive functions were in the minority both in the caudate (Hikosaka et al. 1989a) and SNr (Hikosaka and Wurtz 1989).

The second possibility is that the caudate-nigral system consists of different functional sectors. What we observed in this experiment would be the relationship between the oculomotor sectors in these two nuclei (Alexander and Crutcher 1990). In fact, the electrode tracks were limited in both the caudate and SNr, aimed at the locations where visual/saccadic cells were known to be clustered. Auditory cells should be found in the more medial part (Hikosaka et al. 1989b), while skeletal movement cells could be found in the lateral part facing the putamen (Hikosaka et al. 1989c). Stimulation at the medial or lateral part of the caudate would have produced different results.

Finally, we found a group of SNr neurons that received clear inputs from the caudate but whose characteristics could not be identified. This may not be surprising, because close to the stimulation site in the caudate were recorded many unidentified cells, intermingled with oculomotor/cognitive cells. Different behavioral conditions would be required to activate the new, yet identified, functional system.

Memory-related signals are carried by the caudate-nigral pathway

We classified saccadic cells in the SNr into three types based on their dependence on vision versus memory (Hikosaka and Wurtz 1983a, b). The effect of caudate stimulation was found more frequently in SAC/MEM than SAC/VIS. Inhibition was dominant in SAC/MEM cells, whereas pure inhibition was obtained in only 1 out of 21 SAC/VIS cells. A similar feature was found for visual neurons. SNr cells with conditioned visual responses, compared with those with simple visual responses, were more likely to receive caudate inputs. Moreover, inhibition prevailed in conditioned visual cells, whereas excitation was dominant in simple visual cells.

Suggestions are drawn from these results: (1) the caudate-nigral system may largely carry memory-related signals; (2) the signals tend to produce inhibition of SNr cells and probably disinhibition of target neurons (per-

haps in the superior colliculus); (3) although the caudate-nigral system partly carries vision-related saccadic signals, this type of signal appears to be used to enhance, rather than remove, inhibition of the target neurons (due to excitation of SNr cells). In short, the caudate-nigral system may contribute to the initiation of memory-guided behavior while suppressing vision-guided behavior.

However, cells are found in the SNr that *decrease* their activity with visually guided saccades (Hikosaka and Wurtz 1983a). What then are the function and mechanisms of these cells? We found that different types of saccadic cells, to some extent, were segregated in the SNr: SAC/VIS cells were in the dorso-caudal part, SAC/MEM cells in the more ventral-rostral part. Two areas in the striatum are known to project to the dorsal part of the SNr: putamen (François et al. 1987; Parent et al. 1984) and the tail of the caudate (Saint-Cyr et al. 1990). Where in the putamen such signals could be transmitted remains unknown, because no systematic study has been done to reveal visuooculomotor functions, if any, of the putamen. In contrast, the tail of the caudate is known to receive inputs from prestriate-temporal cortices (Saint-Cyr et al. 1990). The caudate (tail)-nigral system would be in a good position to convey visual signals directly (bypassing the frontal cortical areas) down to the superior colliculus. SAC/VIS cells would transmit such vision-oriented signals.

Does caudate stimulation produce behavioral effects?

The present results suggest that caudate stimulation may facilitate, with disinhibition, the initiation of saccadic eye movements. Alternatively, the stimulation may suppress saccades when SNr cells are excited. Such opposing effects have been observed in earlier studies: stimulation of the caudate in cats, monkeys, and humans could induce contraversive eye and head movements (Forman and Ward 1957; Laursen 1962) or suppress ongoing movements (Delgado 1979). The eye/head movement evoked by caudate stimulation was not abolished by removal of the cerebral cortex (Forman and Ward 1957; Laursen 1962).

The study of caudate stimulation was reappraised recently by Ohno and colleagues (Kitama et al. 1991; Ohno and Tsubokawa 1987). They stimulated the caudate nucleus of the "head-free cat" and recorded head and eye movements. Contraversive head turning and saccades were evoked from the body of the caudate, which roughly corresponded to our stimulation sites in the monkey. Miyashita and Hikosaka (unpublished observation) confirmed this finding in the monkey.

However, the latencies of the evoked saccades, in both of these studies, were quite long and variable (100–300 ms). This raised a serious question as to whether the caudate-induced saccades are actually mediated by the disinhibitory mechanism of the caudate-nigrocollicular pathway. Disinhibition could initiate a movement only if there are strong enough excitatory inputs to the target structure, in this case the superior colliculus. By stimulating the caudate nucleus in the midflight of a saccade, Miyashita and Hikosaka (unpublished observation) detected a contraversive change in eye velocity with a short latency (about 20 ms). A similar eye velocity change evoked from the superior colliculus was 10 ms in cats (Munoz et al. 1991) and 8 ms in monkeys (Miyashita and Hikosaka 1991), presumably because, during a saccade, the brainstem saccade burst neurons are released from tonic inhibition by pause neurons. The difference between these values, 12 ms, would correspond to the two inhibitory connections: caudate-nigral (10 ms, close to the minimum value obtained in this study); SNr-superior colliculus (1–2 ms, Hikosaka and Wurtz 1983c). Miyashita and Hikosaka (unpublished observation) also showed that the effective sites in the caudate were localized to the visuooculomotor zone, as was the case in this study. These data would support the hypothesis that the oculomotor effect of caudate stimulation is mediated by the nigrocollicular connection.

Single-modal and multimodal signals may be carried by separate pathways

An unexpected finding of this study was that SNr cells with single response modalities were more responsive to caudate stimulation than multimodal cells. We would suggest two interpretations. First, this could be related to the fact that memory-contingent SNr cells are more likely to receive inputs from the caudate than vision-contingent SNr cells. SAC/VIS cells tend to have visual and saccadic responses in combination, thus they are multimodal. In contrast, SAC/MEM cells tend not to show a visual response, thus they are more likely to be single-modal. The second interpretation assumes two separate pathways, one mediating single-modal signals and the other mediating multimodal signals. The single-modal signals may be carried by the direct connection from the caudate to the SNr, or more generally, the connection linking the input structures (striatum) with the output structures (SNr or internal segment of the globus pallidus, GPi) of the basal ganglia; therefore the caudate stimulation would induce clear effects in SNr cells. In contrast, the multimodal signals may be carried by the indirect connections which are mediated by the GPe and/or the STN; thus, the effect of caudate stimulation would not be readily manifest in SNr cells.

Support for the latter interpretation comes from our recent study on GPe neurons. In the dorsal part of the GPe, which is known to receive afferents from the caudate (Parent et al. 1984; Percheron et al. 1984), were found many neurons that were related to saccades, vision, and reward (Kato and Hikosaka, unpublished observation). But these activities generally lacked selectivity and showed large receptive/movement fields; single cells frequently combine different types of responses, such as saccade and reward. These cells, by their direct connection to the SNr (Smith and Bolam 1991) or indirect connection via the STN (Kita et al. 1983), would act to modulate the outputs of the basal ganglia, particularly of the SNr, rather than to initiate a movement based on

specific signals. What we classified in this study as multimodal SNr cells may be incorporated in such a functional sector and therefore may be less responsive to single-pulse stimulation in the caudate.

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