Visual and Oculomotor Functions of Monkey Substantia Nigra Pars Reticulata. III. Memory-Contingent Visual and Saccade Responses

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SUMMARY AND CONCLUSIONS

1. The three types of responses described in this report were all related to either saccades to remembered targets or to the targets to be remembered. All the responses were a decrease in discharge rate.

2. The new paradigm frequently used in this study required the monkey to remember the location of a stimulus presented briefly while it was fixating; a later saccade was rewarded if it was made to the position of the no longer present stimulus. The three types of responses were revealed by the use of this paradigm; they were less obvious or undetectable in conventional paradigms in which the monkey responded to the stimulus that was still present.

3. The first type of response was to the visual stimulus that the monkey had to use as the target for a subsequent saccade (memory-contingent visual response); a minimal response occurred if the monkey made a saccade to the stimulus while it was still present or if the monkey continued to fixate. Latencies and receptive fields for this response were similar to those for simple visual responses (17). Of 93 substantia nigra cells with some sensory-oculomotor response, 29 cells (31%) showed this type of response.

4. The second type of response was temporally correlated with a saccade made to the point where a visual stimulus was once present (memory-contingent saccade response). Nearly half of these cells showed no significant response if the saccade was made to the stimulus while it was still present, whereas others showed a comparable response in both conditions. None of them showed a change in activity in relation to spontaneous saccades in darkness.

5. The onset of a memory-contingent saccade response usually preceded the saccade onset by up to 280 ms (most frequently by 70 to 240 ms). The response was usually spatially selective; for most responses, contralateral saccades were associated with an exclusive or greater response compared with ipsilateral saccades. Movement fields were demonstrated for some cells. Of 128 cells tested, 41 cells (32%) showed this second type of response.

6. The third type of response began after the briefly presented stimulus and continued until the saccade made to the stimulus position (memory-contingent sustained response). Of 95 cells tested, 15 cells (16%) showed this type of response. These cells frequently also showed a memory-contingent saccade response.

7. These three types of substantia nigra cell activity are related to the special type of visuooculomotor behavior in which a visual input, particularly its spatial location, must be stored and then used as a target for a saccadic eye movement. One of their efferent connections, the nigrocollicular pathway, may act as a channel for the stored visual-spatial information to be executed as a saccadic eye movement.

8. Discussions of basal ganglia function generally emphasize one of three functions: sensory, motor, or cognitive. All of these three functional aspects appear to be combined in the substantia nigra pars reticulata, which is presumably a final stage of processing in the basal ganglia. In single substantia nigra cells, however, they are combined or gated in different ways so that the sensory or motor activities of the cells are specialized for the different contexts in which behavior occurs.

INTRODUCTION

In a preceding paper (17) we demonstrated a class of substantia nigra pars reticulata cells that showed a decrease in discharge rate in relation to saccades made to visual targets located in one area of the visual field. These cells showed no activity when a similar saccade was made spontaneously in the dark. These visually contingent saccade responses are not unique to the substantia nigra: cells in the superior colliculus, referred to as visually triggered movement cells (24), and cells in the frontal eye fields (3) show a similar contingency for saccade-related activity. In contrast, cells whose discharge is also related to spontaneous saccades have been reported in the superior colliculus (30, 33, 36, 37), the intralaminar nuclei of the thalamus (31), and the pontine and midbrain oculomotor areas (see Ref. 27 for summary).

The visually selective nature of some substantia nigra cells was strengthened by the demonstration that these cells showed no change in discharge in relation to saccades presumably based on the memory of target position derived from previous trials (saccade with gap task) or on visual information currently available. To our surprise, other substantia nigra cells did show activity related to such memory-based saccades. The present experiments describe the characteristics of this response by using a behavioral task that requires the use of spatial memory: a visual stimulus (target cue) is presented briefly during the monkey's fixation and after a certain time delay, when the fixation point goes off, the monkey must make a saccade to the position of the target cue. We find three types of responses in this task: a memory-contingent visual response, which is time-locked to the onset of the target cue, a memory-contingent saccade response, which is time-locked to the onset of the delayed saccade, and a memory-contingent sustained response, which starts after the target cue and ends with the delayed saccade.

The discovery of these cells presumably related to spatial memory emphasizes the distinction between saccades made to visual targets, those made to remembered targets, and those made spontaneously. We will consider the possible neural organization that might underlie these substantia nigra cell activities related to memory-based saccades and the anatomical correlates of this organization. In addition, we will attempt to summarize all the visual and oculomotor activity of substantia nigra cells. Finally, we will attempt to relate our findings on visual and oculomotor activity to more general views on the function of the basal ganglia.

A brief report of this work has appeared previously (16).

METHODS

The general methods used in these experiments were the same as those described in a previous report (17).

The behavioral paradigms used included the fixation task, the saccade task, and the saccade task with overlap and gap, which were described in a preceding paper (17). In addition, a delayed saccade task was also used and it is illustrated in the schematic drawing at the top of Fig. 1*B*. In this task, as in the fixation task, the monkey first touched a bar and a fixation point (F) came on. While the monkey fixated on this spot, another spot of light (T; target cue) was flashed for 50 ms at some point distant from the fixation point. About 1–3 s after this flashed spot appeared the fixation point went off, and the monkey had to make a saccade to the location of the previously flashed spot (a delayed saccade). The reward was given if the end point of the saccade was within a certain distance of the position of the target cue; an error, usually of ±20% of the eccentricity of the target cue, was allowed for both the horizontal and vertical eye positions. Saccades made before the fixation point went off were unrewarded and terminated the trial.

RESULTS

Memory-contingent visual responses

Some substantia nigra cells responded to a visual stimulus but the visual response was markedly improved when the monkey had to make a saccade after a time delay to the position of the stimulus that was no longer

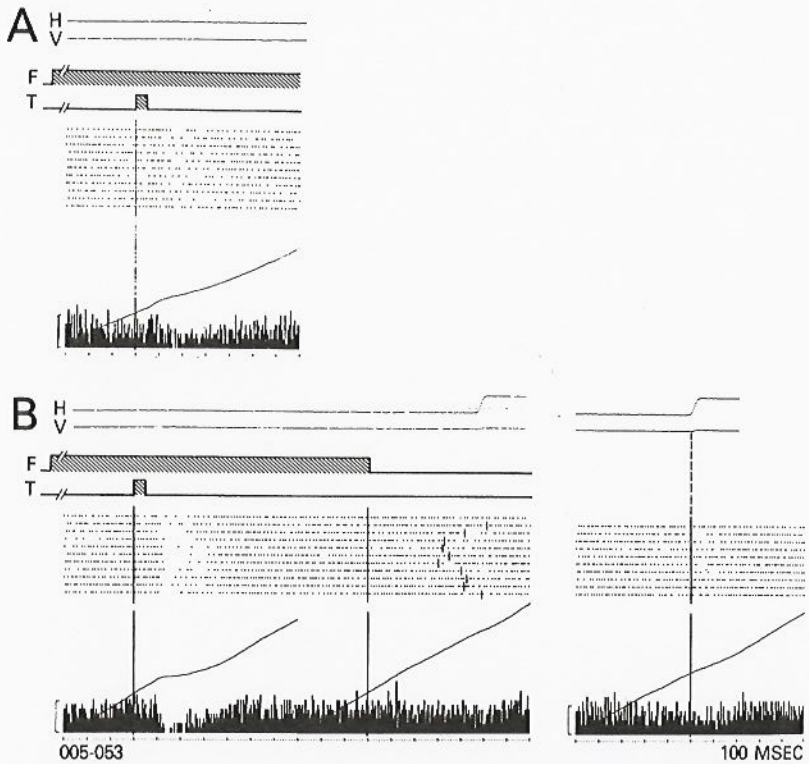

FIG. 1. Response to a spot of light when the spot is remembered as the target for a saccade (memory-contingent visual response). *A*: slight response to a spot of light (T) of short duration (50 ms) while the monkey looked at the fixation point (F) without making a saccade (fixation task). The monkey was rewarded for release of the bar in response to the dimming of the fixation point (not shown). *B*: clear response (a decrease in discharge rate) to the same spot of light (T) of the same duration while the monkey looked at the fixation point (F) but made a delayed saccade to the position of the flashed spot of light (delayed saccade task). The monkey was rewarded if he made a correct saccade after the fixation point went off. T was located 20° into the contralateral visual field in both *A* and *B*. H and V: sample horizontal and vertical eye-position traces. The raster shows consecutive trials for each condition. F, duration of the fixation point; T, duration of the target point. Single dots in the raster indicate single action potentials. Each raster is aligned on an event: the onset of T (*A* and *B*), the offset of F (*B*, left), or the onset of the saccade (*B*, right). Vertical small bars on the raster in *B* (left) indicate onsets of the delayed saccades. The same trials are aligned on the saccade onset in *B* (right). Note that the monkey failed to make a correct saccade on the first trial and, consequently, this trial is not shown in *B* (right). The trials are summed to produce time histograms and cumulative time histograms. Calibration to the side of the time histogram indicates 100 spikes/s per trial. Bin width on the time histogram is 6 ms. The interval between large dots on the time scale is indicated in lower right corner. Number in lower left corner indicates monkey and cell number. All subsequent figures use these values and conventions unless otherwise stated.

present but, instead, had to be remembered. An example is shown in Fig. 1. In the fixation task (Fig. 1*A*), the cell showed only a slight decrease in discharge rate following the onset of a spot of light (T) turned on for 50 ms at a point 20° contralateral to the fixation point. In the delayed saccade task (Fig. 1*B*), we again flashed on the spot of light for 50 ms, but then after 1 s the fixation point went off and the monkey had to make a saccade to the previous location of the target in order to get a reward. The response of the cell (a decrease in discharge rate) to the spot of light (T) was clearly more pronounced in Fig. 1*B* than in Fig. 1*A*, although both the eye position and the physical characteristics of the stimulus were identical. There was little change in discharge rate in relation to the saccade (Fig. 1*B*, right). The same experiments done in total darkness in order to eliminate effects of any visual stimuli in the field of view, except for the fixation point and the target point, gave essentially the same results.

Note that the response of the cell in the delayed saccade task (Fig. 1*B*) was somewhat variable trial by trial. This seemed to be related to the performance of the task by the monkey: when the decrease in discharge rate was greater or longer (Fig. 1*B*, 4th–7th trials), the latency of the delayed saccade to the offset of the fixation point tended to be shorter; when the response was weaker (1st–3rd, 8th–11th trials), the monkey failed to make a correct saccade (1st trial) or did so with longer latencies.

The more pronounced visual response in the delayed saccade task could be related to a change in general arousal or selective attention to the target. The effect of arousal and a shift of attention could be checked by requiring the monkey to make a saccade to the target while it was still present. It has been argued that this type of visually guided saccade is accompanied by a shift of selective attention as well as a change in general arousal, and in several areas of the brain such a saccade produces an enhanced visual response to the saccade target (as discussed in a preceding paper, Ref. 17). The experiments shown in Fig. 2 (the same cell as in Fig. 1), which compared the responses to the same spot of light during the fixation task (Fig. 2*A*)

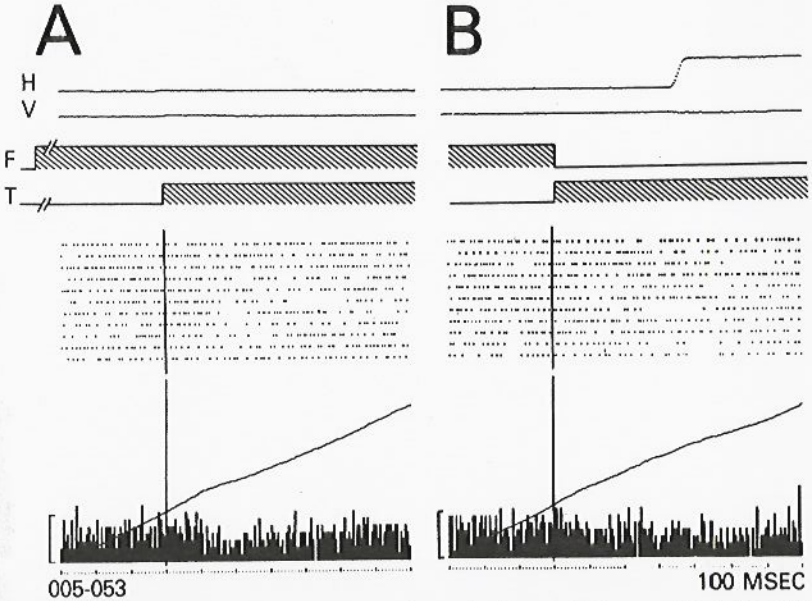

FIG. 2. Lack of response of a cell with a memory-contingent visual response during a saccade task. The same cell and the same stimulus as in Fig. 1. *A*: fixation task; the target point T came on 20° into the contralateral visual field for 1 s (offset not shown) and the monkey was rewarded if he released the bar when the fixation point (F) dimmed. *B*: saccade task; T came on at the same time as the fixation point went off; the monkey made a saccade to T and was rewarded if he released the bar when T dimmed. The monkey's use of the spot as a "current" target, rather than as a "future" target, for a saccade did not produce a clear visual response to the spot.

the saccade task (Fig. 2*B*), suggest that changes in arousal or attention are unlikely to be related to the stronger visual response. The response remained very subtle, even when the monkey made a saccade to the spot of light while it was still present (Fig. 2*B*). For this cell to produce a clear visual response to the target stimulus the monkey had to make a saccade with a delay after the disappearance of the target. Since in this case the visual information, particularly its spatial aspect, must be stored and maintained for the delayed saccade to be enabled and since this storage mechanism is most easily referred to as "memory," we will refer to this response as a memory-contingent visual response. Of 93 substantia nigra cells with some visual or oculomotor responses, 29 cells (31%) had this type of response.

The visual receptive fields of the cells with memory-contingent visual responses were similar to those of cells with simple visual responses (17); they were large with the most sensitive areas located in the contralateral visual field. Latencies of the memory-contingent visual responses (e.g., 115 ms for the cell in Fig. 1) were well within the range of latencies found for simple visual responses. These results suggest that common visual inputs underlie the visual and the memory-contingent visual responses.

Memory-contingent saccade response

We found some cells in the substantia nigra whose activity was correlated primarily with a saccade made to the point where a visual stimulus was once present but was no longer present. For example, the discharge of the cell shown in Fig. 3 showed little change in the ordinary saccade task either to the target onset (Fig. 3*A*, left) or to the saccade onset (Fig. 3*A*, right). In the delayed saccade task (Fig. 3*B*), however, this cell showed a clear decrease in discharge rate in relation to saccades made to the previously present target. The high discharge rate started decreasing nearly 200 ms before the onset of a saccade and recovered gradually after the saccade, as seen in the raster in Fig. 3*B*, right, which is aligned on the onset of the saccade.

The clear saccade-related response in the delayed saccade task (Fig. 3*B*) compared with the weak response in the ordinary saccade task (Fig. 3*A*) cannot be attributed to the difference in the physical properties of the saccade: they were virtually the same, as exemplified by the traces showing eye position. The response was not correlated with offset of the fixation point, since in some trials (the 8th and 10th trials in Fig. 3*B*) the response started clearly before the offset of the fixation point but still in close temporal relation to the onset of the saccade. The possibility that the monkey used some landmarks on the screen to guide saccades in the absence of a target in the delayed saccade task was excluded because the response was still present when the same delayed saccade task was done in total darkness. These results suggested that the decrease in discharge rate of this cell was correlated with a particular type of saccade, one that used the stored information (memory), on the location of a target as opposed to one that used the visual information currently available. Therefore, we will refer to this response as a memory-con-

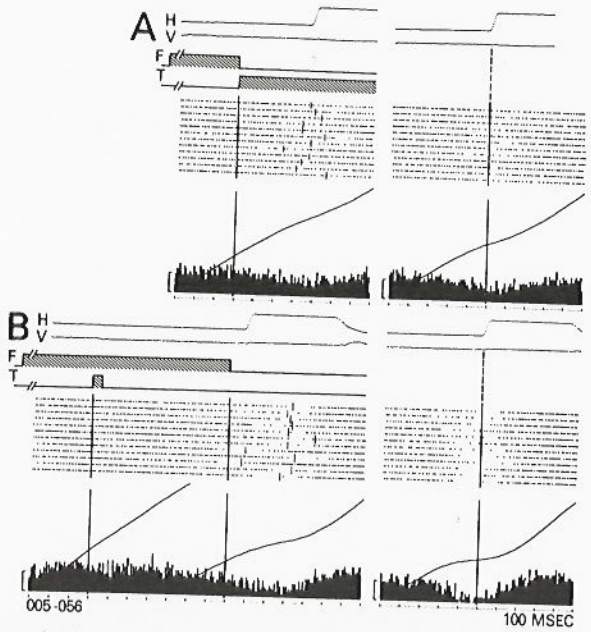

FIG. 3 Response related to a saccade to a previously flashed spot of light (memory-contingent saccade response). In *A* (saccade task), saccades to the target (T) were associated with only a slight decrease in discharge rate. In *B* (delayed saccade task), saccades with the same direction and amplitude but to the point where the target was flashed previously but was no longer present were associated with a clear decrease in discharge rate. The target was located 20° into the contralateral visual field. In both *A* and *B*, the same trials are aligned on stimulus changes on the left and saccade onsets on the right. Vertical small bars on the raster lines on the left indicate saccade onsets.

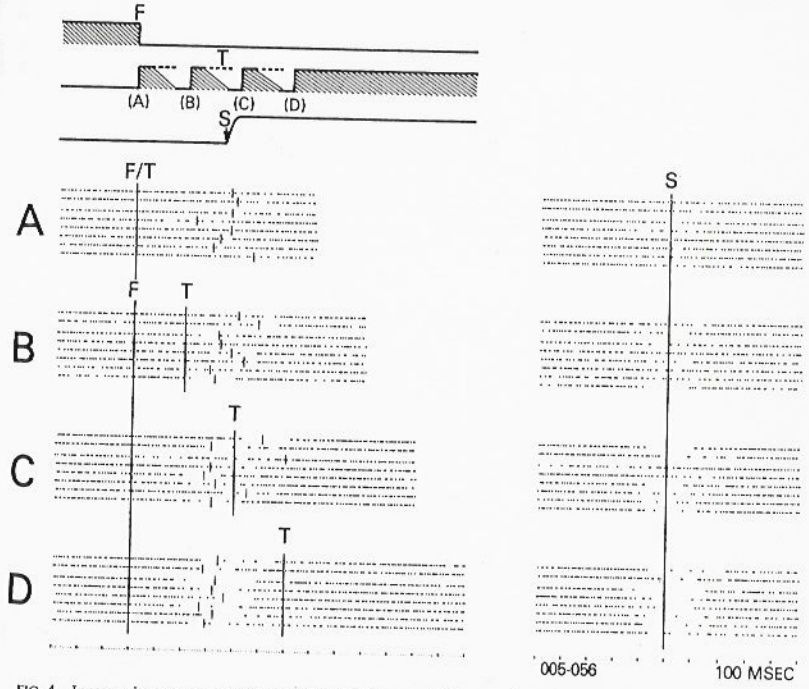

FIG. 4. Increase in memory-contingent saccade response with increased gap between offset of the fixation point (F) and onset of the target point (T). The duration of the gap was 0 (*A*), 200 (*B*), 400 (*C*), and 600 (*D*) ms. When the duration of the gap was long (*C* and particularly *D*), the monkey was able to make an accurate saccade to the location of the target before it came on, since the target position was fixed in this series of experiments (20° into the contralateral visual field), and such saccades were associated with a clear decrease in discharge rate. The monkey was always rewarded for detecting the dim of the target, not for making the correct saccade.

tingent saccade response. Of 128 substantia nigra cells with some visual or oculomotor response, 41 cells (32%) showed this type of response. It should be noted that about half of these cells showed a visually contingent saccade response as well (see Fig. 9) but none of them showed activity related to spontaneous saccades (see Fig. 5).

The memory of target location need not be updated on each trial for this type of cell to produce the memory-contingent saccade response. We also trained one monkey to make a saccade without giving him any target cue on a series of trials. After an initial series of trials in the delayed-saccade task with the position of the target cue fixed, we stopped presenting the target cue but continued to reward the monkey for the correct saccades. Although this task was difficult for the monkey, the response related to the saccade was as clear as that shown in Fig. 3*B*.

Since the ways in which the monkey obtained a reward were different in the saccade task (releasing the bar) and in the delayed saccade task (correct saccade), the difference in cell response in the two tasks might be related to differences in the strategy that the monkey used in performing the task. In the series of experiments shown in Fig. 4, we always rewarded the monkey for detecting the dimming of the target point so that differences in the monkey's strategy to obtain a reward should be minimized. In these experiments, we increased the gap between the offset of the fixation point (F) and the onset of the target point (T) from 0 (Fig. 4*A*, saccade task) to 600 ms (Fig. 4*D*, saccade with gap task). In the trials with relatively long

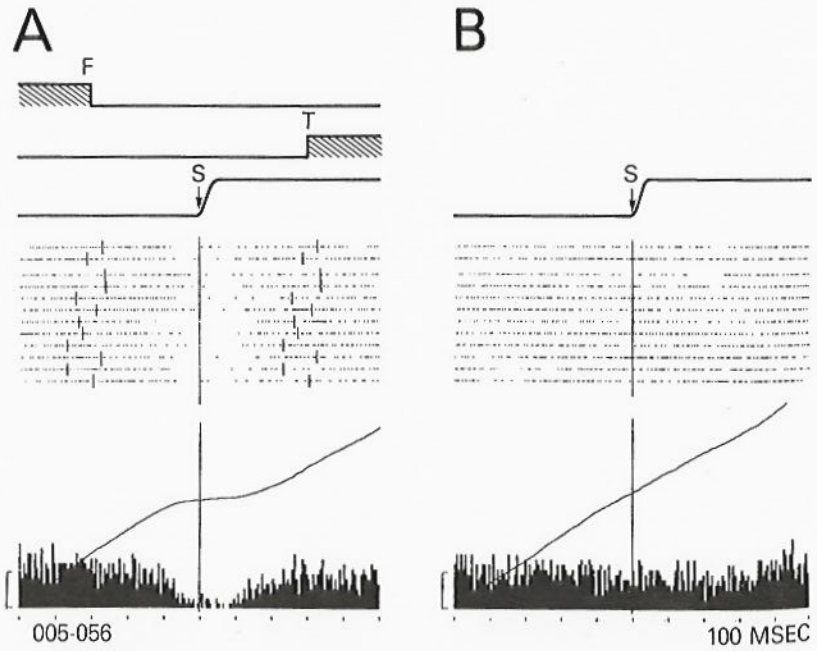

FIG. 5. Lack of response with spontaneous saccades in a cell with a memory-contingent saccade response. *A*: clear response related to saccades made during a long time gap between the offset of the fixation point (F) and the onset of the target point (T). The experiment was done in total darkness except for F and T. *B*: no response related to saccades made spontaneously in total darkness. Saccades with similar amplitude and direction to those in *A* were selected.

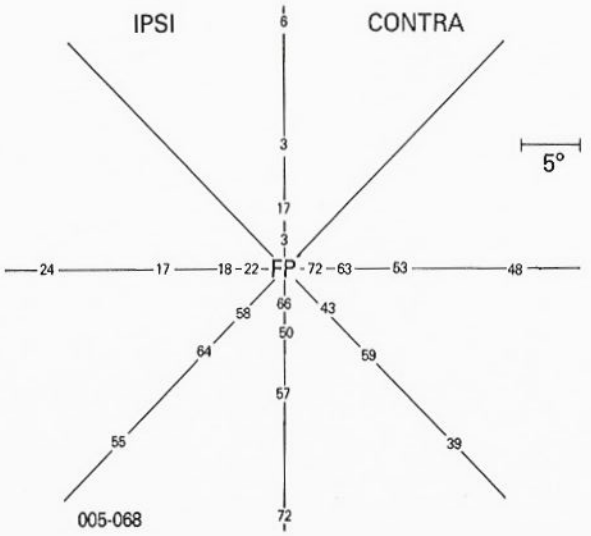

FIG. 6. Movement field of a cell with a memory-contingent saccade response. Results of more than eight trials of the saccade task with a long gap (more than 600 ms) were summarized to obtain the response magnitude for each location of the target. Response magnitude (% D) was defined by the following equation: % D = (B − R)/B × 100; B is the total spike number within the background period (500 ms before to 350 ms before the saccade onset) and R is the total spike number within the response period (50 ms before to 100 ms after the saccade onset). This cell showed little response in the ordinary saccade task.

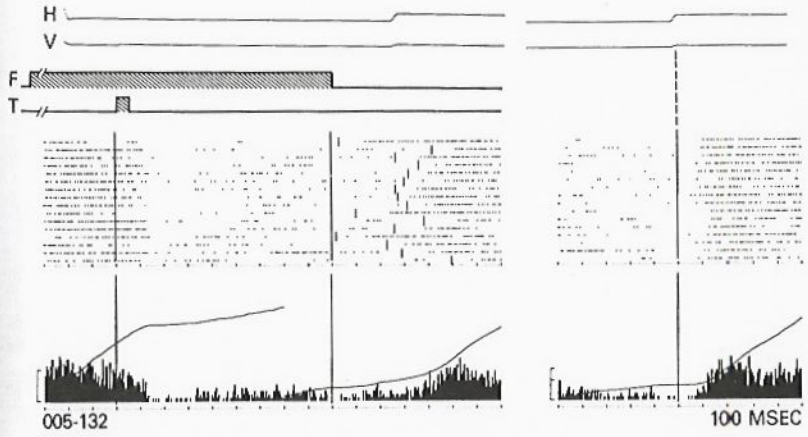

FIG. 7. Maintained decrease in discharge rate of a cell during the delay period of the delayed saccade task (memory-contingent sustained response). Discharge rate decreased usually after the target point (T) was flashed and remained low through the delay period until the delayed saccade occurred. The task was performed in the dark.

time gaps (Fig. 4*C* and *D*), the monkey made saccades to the target point before it actually came on (as indicated by the small vertical bars on the raster lines). This was possible because the position of the target was fixed throughout this series of experiments. On these trials, the cell showed a clear decrease in discharge rate at the time of these early saccades in contrast to little response in the ordinary saccade task with no gap (Fig. 4*A*). The saccade task with a long gap (as in Fig. 4*D*) can be regarded as a variation of the delayed saccade task: instead of a target cue for each trial, the target point in previous trials (with an interval of about 3.5 s) acts as the cue for the target. All 18 cells with a memory-contingent saccade response that were tested in both the delayed-saccade task and the saccade with gap task showed about the same response in both tasks.

The longer the gap duration, the greater the saccade-related response. When the gap duration was 200 ms (Fig. 4*B*) or 400 ms (Fig. 4*C*), the saccade-related response was obvious but weaker than when the gap duration was 600 ms (Fig. 4*D*). Although in many of these trials saccades started after the target came on, their latencies to the target onset seem too short for the visual input to be solely responsible for the initiation of these saccades. Therefore, the weaker response in Fig. 4*B* and *C* may be correlated with the weaker but consistent contribution of the memory target location in saccade initiation.

It should be emphasized that cells with a memory-contingent saccade response showed no activity in relation to spontaneous saccades (Fig. 5). While the monkey sat in total darkness and without significant sensory

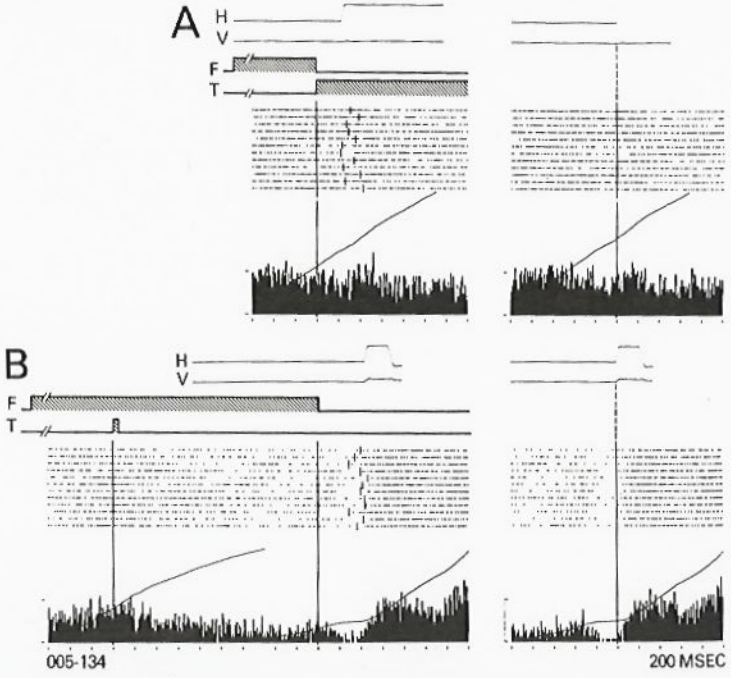

FIG. 8. Gradual decrease in discharge rate of a cell during the delay period of the delayed saccade task (a varient of the memory-contingent sustained response). *A*: no response during the ordinary saccade task. *B*: discharge rate began decreasing after the target point (T) was flashed and continued decreasing until the saccade was made to the position of T.

stimuli, we selected saccades (Fig. 5*B*) whose amplitudes and directions were similar to those studied in the saccade with gap task (Fig. 5*A*). At least some of these spontaneous saccades had time courses similar to those of memory-contingent saccades although others had longer durations. Nonetheless, we found no change in discharge rate associated with any saccade (Fig. 5*B*). Furthermore, this result excludes the possibility that the saccade-related response was simply suppressed by the presence of visual inputs in the ordinary saccade task. Of eight cells with memory-contingent saccade response in which spontaneous saccades were examined systematically, none showed a change in discharge rate in relation to these saccades.

The memory-contingent saccade response was usually spatially selective. We tested saccades in both horizontal directions for 17 cells, and 12 showed exclusive or greater response for contralateral saccades; the remaining cells showed no difference in response for the two directions; none showed an ipsilateral preference. It was difficult to map the movement field of these cells, since frequent changes in the target position lowered the performance of the monkey, but Fig. 6 shows a nearly complete map of the movement field of a cell with a memory-contingent saccade response. By using the saccade with gap task, we collected data on at least eight saccades made to each target point and calculated the response magnitude by the same method as used for visual responses described previously (17). This cell showed a clear response for downward saccades, but the movement field included both the contralateral and the ipsilateral visual fields, with the contralateral side dominant.

Memory-contingent sustained response

Some cells showed a sustained decrease in discharge rate following the flashed target cue in the delayed saccade task. For example, the discharge rate of the cell shown in Fig. 7 decreased after a target cue was flashed and remained low until after a delayed saccade was made. Recovery of the discharge rate was related to onset of the saccade (Fig. 7, raster and histogram on the right) rather than the offset of the fixation point (Fig. 7, left). This cell behaved as if it maintained the information on the approximate location of the

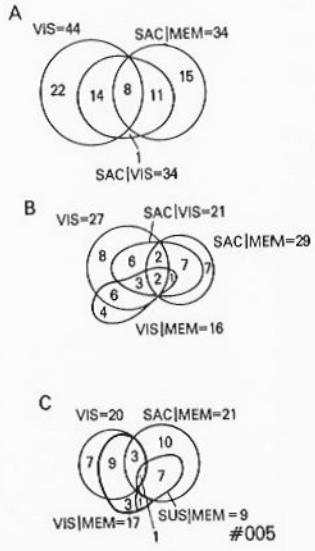

FIG. 9. Diagrams showing the combination of response types in substantia nigra cells. Total number of cells that showed a particular type of response is indicated beside the abbreviation of each response type. Number within each area of the diagram indicate number of cells that showed a particular combination of responses. Abbreviations: VIS, simple visual response; SAC/VIS, visually contingent saccade response; SAC/MEM, memory-contingent saccade response; VIS/MEM, memory-contingent visual response; SUS/MEM, memory-contingent sustained response.

target cue to enable the delayed saccade to the location of the target. Since the experiment shown in Fig. 7 was performed in total darkness except for the fixation point and the briefly flashed target cue, this cell could not respond to some landmark on the screen. We will refer to this response as a memory-contingent sustained response. Of 95 substantia nigra cells with some visual or oculomotor responses, 15 cells (16%) showed this type of response.

The onset of the decrease in discharge rate was frequently time-locked to the onset of the target cue, and there appears to be another component of the response time-locked to the saccade onset (Fig. 7). These presumed visual and saccade-related responses were also present in the fixation or saccade task

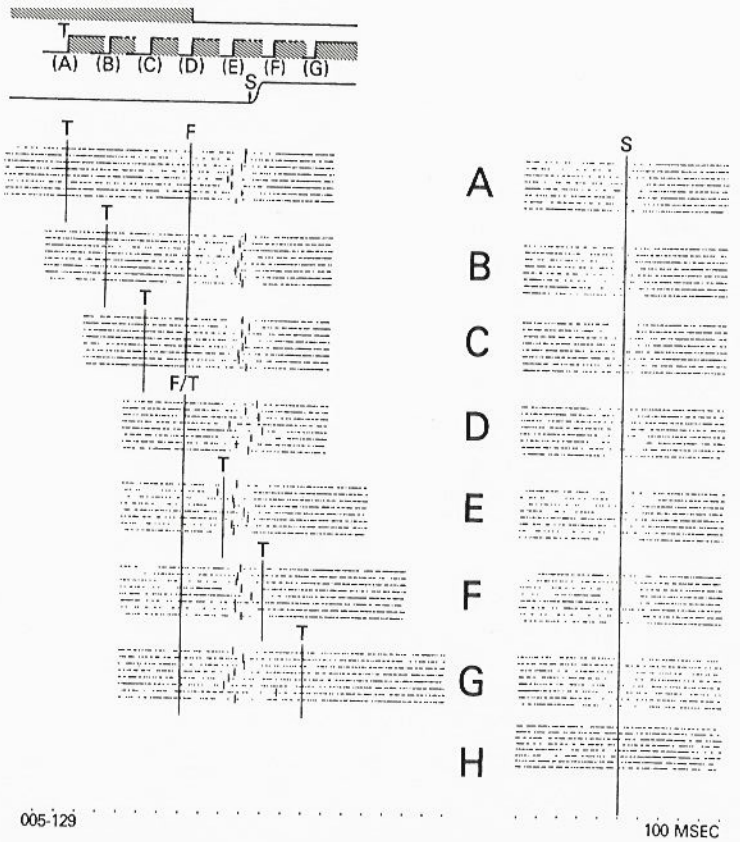

FIG. 10. Combination of visually contingent saccade response and memory-contingent saccade response. *A–C*: target point came on 600 ms (*A*), 400 ms (*B*), and 200 ms (*C*) before the fixation point went off. In these trials (*A–C*) saccades occurred while the visual target was present and, therefore, the response was a visually contingent saccade response. *D*: ordinary saccade task. *E–G*: target point came on 200 ms (*E*), 400 ms (*F*), and 600 ms (*G*) after the fixation point went off. For *E–G* the target point was flashed (50 ms) 1 s before the fixation point offset to facilitate the monkey's performance. In these trials (*E–G*) saccades occurred frequently in the absence of the visual target and, therefore, the response was a memory-contingent saccade response. *H* shows lack of response associated with spontaneous saccades of the same amplitude and direction as that in *A–G* but made in total darkness.

and, according to our classification criteria, this cell therefore had visual and saccade-related responses as well as a memory-contingent sustained response.

The sustained response did not, however, always begin so sharply after the flashed target as for the cell illustrated in Fig. 7. Other cells showed a gradual decrease in discharge rate in the period between the target cue and the occurrence of the saccade. For example, the cell illustrated in Fig. 8, which showed no response in relation to the visual target or the saccade to the visual target in the saccade task (Fig. 8*A*), showed a gradual decrease in discharge rate between the target cue and the onset of the saccade (Fig. 8*B*).

Combination of response types

Different types of responses seen individually in some cells were also seen in combination in other cells (Fig. 9). Cells with a combination of a memory-contingent sustained and a memory-contingent saccade response were common, as the diagrams of Fig. 9*C* show: of nine cells with a memory-contingent sustained response (SUS/MEM) studied on one monkey, eight had a memory-contingent saccade response (SAC/MEM) as well.

Combination of the memory-contingent saccade response and the visually contingent saccade response described in the first paper of this series (17) also occurred. For example, the cell illustrated in Fig. 10 showed a decrease in discharge rate in relation to saccades, whether they were made in the presence of the target (Fig. 10*A–D*, a visually contingent saccade response) or in the absence of the target (Fig. 10*F* and *G*, a memory-contingent saccade response). This type of cell, however, did not show any change in its activity in relation to spontaneous saccades (Fig. 10*H*). Cells with this combination of responses also were common, as indicated in Fig. 9*A*: of 34 cells with a memory-contingent saccade response (SAC/MEM), 19 (8 + 11) showed a visually-contingent saccade response (SAC/VIS) as well.

Time course of saccade-related responses

The two saccade-related responses, a visually contingent saccade response and a memory-contingent saccade response, tended to have different temporal relationships to the saccade onset (Fig. 11). We classified the saccade-related cells recorded in one monkey into three types according to the type of saccade-related responses, and the length of the horizontal bars in Fig. 11 indicates the duration of the response (from the onset to the offset of a decrease in discharge rate) for each cell. Cells in which the memory-contingent saccade response was greater (Fig. 11*C*) had earlier onsets of response than cells in which the visually contingent response predominated (Fig. 11*A*): memory-contingent responses started well before (70–280 ms) the saccade onset, while visually contingent responses started barely before or just after the saccade onset. Cells with a visually contingent and memory-contingent response that were about equal (Fig. 11*B*) tended to have intermediate times for decrease of discharge.

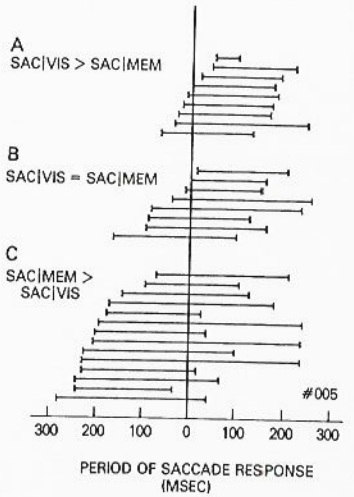

FIG. 11. Different time course of the saccade-related response between three groups of cells. *A*: cells that showed better response related to visually contingent saccades than to memory-contingent saccades. *B*: cells that showed comparable responses to these two types of saccades. *C*: cells that showed better response related to memory-contingent saccades than to visually contingent saccades. The start (left) and the end of each line indicate the onset and the offset of the response (a decrease in discharge rate) of a single cell relative to the saccade onset (vertical line). The onset was defined as the point where the line of the cumulative time histogram started deviating downward from the initial slope; the offset was defined as the point where the line resumed its initial slope. Memory-contingent sustained responses were not included in this analysis.

DISCUSSION

We have described substantia nigra cells that are related to a specific visual and oculomotor behavior in which the monkey made a saccade with a time delay to the location where a spot of light had been previously flashed as a target cue. We could identify three types of responses: cells that de-

creased their discharge rate briefly following onset of the target cue, cells that decreased their discharge rate briefly before and after the onset of such delayed saccades, and cells that decreased their discharge rate in a sustained manner after the target cue came on and until the delayed saccade occurred. Since this delayed saccade task required the monkey to remember the position of a visual stimulus, it is likely that these substantia nigra cells have some interactions with the brain areas that store the spatial information as a short-term memory. We will first consider possible mechanisms and their anatomical correlates. We will then discuss what the results of the present and preceding papers (17, 18) suggest about the function of the basal ganglia in general.

Mechanism of memory-contingent responses

The memory-contingent visual response is a decrease in discharge rate following the onset of a visual stimulus that is evident only when the monkey must make a saccade to the location of the stimulus after it is no longer present. The basic assumption necessary to explain this visual response, as well as the following two types of responses of substantia nigra cells, is the presence of a neural correlate of spatial memory, which would signal the previous location of the visual stimulus. The memory-contingent visual response could be either *1*) a result of a facilitation of a visual response already present by its corresponding spatial memory or *2*) a direct source of the spatial memory. Possible neural mechanisms underlying these relationships are shown in a single schema in Fig. 12*A*. For the first mechanism the neural element of spatial memory (M), which is presumed to be located outside the substantia nigra, facilitates the visual input presynaptically; if the spatial memory is already present when the visual stimulus came on, in other words, if the monkey has a memory of stimulus location before the stimulus came on, the memory element would facilitate the visual input. For the second mechanism the substantia nigra cell has an inhibitory connection onto the memory element; if a response (a decrease in discharge rate) occurs, it would disinhibit the memory element and initiate

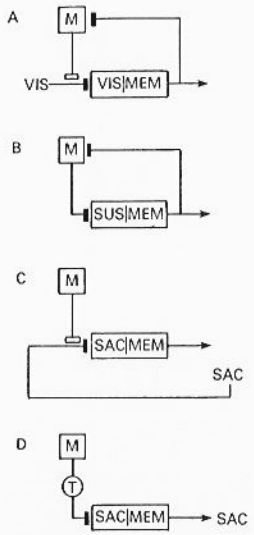

FIG. 12. Possible neural organization underlying a memory-contingent visual response (VIS/MEM) (*A*), a memory-contingent sustained response (SUS/MEM) (*B*), and a memory-contingent saccade response (SAC/MEM) (*C* and *D*). Substantia nigra cells with any of these responses are assumed to have interactions with a neural correlate of spatial memory (M). Details are described in DISCUSSION.

the spatial memory. Although these two mechanisms assume conceptually different roles for the substantia nigra, we do not have enough data to support one as opposed to the other of them. It is also possible that these two mechanisms coexist.

The memory-contingent sustained response is a decrease in discharge rate that starts after the target cue and ends with the delayed saccade. Figure 12*B* shows two connections between the substantia nigra cell and the memory element, either of which could underlie this response. An inhibitory connection from the memory element onto the substantia nigra cell is assumed if this response is merely the reflection of the activity of a memory element. An inhibitory connection from the substantia nigra cell onto the memory element is assumed if the spatial memory is the result of the memory-contingent sustained response in the substantia nigra. Although the second mechanism alone is unlikely (there has been no evidence indicating that the substantia nigra is the neural correlate of spatial memory), it is possible that both of these mechanisms coexist and cooperate to maintain the spatial memory.

The memory-contingent saccade response is a decrease in discharge rate correlated with a saccade made to the location where a stimulus was located. Since such a saccade is not guided by any external stimulus that is currently present, it must be based on the memory of stimulus location. Analogous to the other types of response, two conceptually different mechanisms could underlie this response, as shown in Fig. 12*C* and *D*. If this response is merely the result of the saccade signal originating in some other brain area but conditioned by the presence of the spatial memory, the neural mechanism shown in Fig. 12*C* is possible in which the inhibitory input from the saccade-related area is facilitated presynaptically by the memory element. If the response is the precursor of the saccade, the mechanism shown in Fig. 12*D* is possible; the substantia nigra cell receives an input from the memory element and transmits the signal to the saccade-related area, thereby facilitating the initiation of a saccade; since the memory-contingent saccade response is transient, whereas the memory activity is presumed to be fairly long-lasting, some mechanism underlying this temporal transformation would be necessary, and it is shown by an intervening element T.

Anatomical correlates of visual and spatial memory

Except for the behavioral dependency, the characteristics of the memory-contingent visual responses are similar to those of simple visual responses and, therefore, it is likely that the same brain areas considered in the preceding paper (17) are the sources of the visual input to these cells.

The best currently known candidate for the source of the neural correlate of spatial memory is the prefrontal cortex. Ablation of this area disrupts behaviors that require short-term memory, including spatial memory (see Ref. 28). In the delayed response task or the delayed alternation task, some cells in the prefrontal cortex showed a sustained excitation or inhibition, starting with the presentation of a visual cue and ending with the delayed response (13, 21). Although the paradigms in these experiments differed from ours in that they used a skeletal movement rather than an eye movement as the delayed response, the nature of the cue they used was similar to ours because it was a visual stimulus and required a memory of where the cue was.

If the prefrontal cortex contains the memory elements, the signals related to spatial memory are very likely to be transmitted to the substantia nigra by cells in the caudate nucleus. In fact, after ablation of the caudate nuclei, the performance of the delayed response task is impaired considerably (12, 29). Although Niki et al. (25) did not see sustained activity in the head of the caudate nucleus during the delay period of a delayed alternation task, it is still possible that cells in other parts of this nucleus transmit the memory-related activity.

The possible neural organization related to the memory-contingent responses (Fig. 12) requires a return pathway from the substantia nigra to the memory element. An anatomical connection that might subserve the first step in this pathway is the major efferent connection of the substantia nigra pars reticulata to the thalamus (see Ref. 15, for summary). In the monkey, pars reticulata cells have been shown to project to the medial part of the nucleus ventralis anterior and the nucleus ventralis lateralis (VA-VL complex) as well as to the nucleus medialis dorsalis (MD) (4). These thalamic areas in turn project to the frontal cortex including the frontal eye fields. These nigrothalamocortical connections seem to fit the hypothetical return pathway. Furthermore, the branching of this return pathway from the output pathway to the superior colliculus is justified by experiments showing that single pars reticulata cells frequently project both to the thalamus and the superior colliculus (2, 9).

Visuomotor control and basal ganglia function

The substantia nigra pars reticulata is one of the two major output pathways of the

basal ganglia, and our experimental observations on the cells in this output pathway might yield some insight into the function of the basal ganglia.

In spite of extensive investigations over the last half-century, it is generally agreed that there is no single compelling concept of basal ganglia function (8). At least three views about the function of the basal ganglia have emerged from different lines of experiments. A brief description of these hypotheses allows us to demonstrate how these apparently diverse views might be integrated in the control of eye movements and possibly in the control of skeletal movements as well.

The first view emphasizes the relationship between the basal ganglia and skeletal movements and was originally suggested by clinical data on patients with pathological changes in the basal ganglia such as bradykinesia in Parkinson's disease and choreoid movements in Huntington's disease. Experimental studies supported this view: ablation of the basal ganglia, particularly bilateral ablations, produced severe movement disorders, including akinesia and involuntary movements (see Ref. 10). That a substantial proportion of neurons in the basal ganglia actually have activities related to and sometimes preceding movements of particular parts of the body (8) strengthened the argument for the role of the basal ganglia in the initiation or the facilitation of skeletal movements.

A role of the basal ganglia specifically in oculomotor control is also evident in Parkinson's disease. An increased latency for saccadic eye movements (6, 7, 32) is probably comparable to the bradykinesia seen for skeletal movements. In addition, hypometric saccades (6, 23, 34), limitation of upward gaze (5, 6), and "cogwheel" pursuit (5) have been observed. Of particular interest is the longer time it took patients with Parkinson's disease to make saccades back and forth between targets that were left on all the time (7) or the difficulty that patients with Huntington's disease had in making saccades to a target they were instructed to look at (22). In both of these cases the saccade must be initiated by something other than the onset of a visual target, possibly analogous to saccades to remembered targets.

A second view has emphasized the sensory function of the basal ganglia, particularly the striatum. Bilateral lesions of the striatum lead to striking neglect of sensory stimuli (11). Cells in the striatum receive sensory inputs from different modalities (as discussed in Ref. 17; see Ref. 20 for summary).

A third view has been that the basal ganglia are involved in more complex or cognitive functions (see Ref. 35 for summary). This is largely based on the fact that the ablation of the caudate nuclei disrupts the performance in memory-required tasks (such as the delayed response tasks; 12, 29).

What is striking in the present experiments is that all three factors—motor, sensory, and cognitive—are involved in the activity of substantia nigra cells. Our experiments show that cells within a subset of cells in the substantia nigra pars reticulata receive sensory signals (at least visual or auditory) and/or cognitive (specifically spatial memory) signals and produce an output signal related to the initiation of saccadic eye movements. Cells described in the first paper of this series (17) contribute to the initiation of visually guided saccades, those described in this paper contribute to the initiation of memory-guided saccades, and those in the second paper (18) contribute to the transition between visually guided and nonvisually guided oculomotor behaviors. Thus, sensory, motor, and memory functions are present, not as discrete entities but rather as an interrelated neural organization to produce a saccadic eye movement under specific conditions.

In essence, we envision each type of substantia nigra response as forming a particular channel for saccade initiation, either sensory or memory, which leads to the intermediate layers of the superior colliculus (19). The superior colliculus, which may receive other inputs related to visually guided saccades (possibly from the frontal eye fields as discussed previously) and in addition is likely to generate a signal for the initiation of spontaneous saccades (1), sends the signal of a saccade, now independent of its mode of initiation, to the brain stem oculomotor system (14, 26).

The thread of consistency that runs throughout the activities of the substantia nigra neurons is their dependency on behavioral events. A correlation of cell activity to the sensory or motor events is not enough to reveal the relation of these substantia nigra cells to behavior; their discharge is contingent on the conditions under which such sensory or motor events occur. The contingent nature of the cell activity might also be a larger factor in other basal ganglia neurons whose activity is related to skeletal movements than is apparent from current studies.

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Visual and Oculomotor Functions of Monkey Substantia Nigra Pars Reticulata. IV. Relation of Substantia Nigra to Superior Colliculus

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SUMMARY AND CONCLUSIONS

1. The preceding studies (18–20) have shown that cells in the monkey substantia nigra pars reticulata have responses that are temporally correlated with visual or auditory stimuli and saccadic eye movements. In this study we determined whether these substantia nigra cells project to the superior colliculus.

2. We first recorded from a substantia nigra cell and identified its sensory and oculomotor properties using the behavioral paradigms developed previously (18–20). Then we stimulated the ipsilateral superior colliculus while moving the stimulating electrode through the layers of the colliculus to determine whether and from what depth the substantia nigra cell was activated antidromically. Finally, we identified the visual and oculomotor properties of the colliculus cells located near the points from which the substantia nigra cell was activated antidromically with the lowest thresholds.

3. Of 180 substantia nigra cells studied, 51 were activated antidromically from the ipsilateral superior colliculus. Nearly half of the substantia nigra cells that showed some visual- or saccade-related responses were activated antidromically, whereas cells that did not show such responses were rarely activated.

4. For each of the substantia nigra cells that showed visual- or oculomotor-related responses, we determined the center of the visual receptive or movement field of the cell and compared it with the field center of the superior colliculus cells found at the lowest thresholds. The more eccentric the field centers, the more probable the antidromic activation of the substantia nigra cell, which suggests that each substantia nigra cell projects to the superior colliculus so as to match its own field with that of the colliculus cells in its projection area.

5. The threshold stimulation current for antidromic activation of single substantia nigra cells varied, depending on the depth of the stimulating electrode within the superior colliculus, with several low-threshold points usually seen on a penetration through the colliculus. Regardless of the type of visual or oculomotor response of the substantia nigra cell, the low-threshold point was most commonly found among colliculus cells that showed a burst of spikes before saccades and, therefore, were probably located in the intermediate layers. A low-threshold point was also common in the deep layers but was relatively rare in the superficial layers. The latency of antidromic response ranged from 0.7 to 2.3 ms. The antidromic latency for single substantia nigra cells tended to decrease with the depth of stimulation in the superior colliculus.

6. We compared the visual and oculomotor activity of antidromically activated substantia nigra cells with that of superior colliculus cells near the point of lowest threshold for stimulation. An inverse relationship was found between saccade-related activities of such a neuron pair: a decrease in discharge rate of the substantia nigra cell occurred with an increase in discharge rate (frequently a burst of spikes) of the superior colliculus cell. However, such a relationship depended on how the saccade was initiated