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The Role of Substantia Nigra in the Initiation of Saccadic Eye Movements

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Introduction

It has long been known that the basal ganglia, including the substantia nigra, are involved in the initiation of movement. The role of the basal ganglia in movement is strikingly indicated by diseases such as Parkinson's disease, which produces a paucity of movement and particular difficulty in the initiation of voluntary movements. Similar movement deficits also afflict saccadic eye movements (Cogan, 1956).

The substantia nigra might be regarded as just another in an already extensive list of brain areas involved in the initiation of eye movements that have an uncertain relation to the known oculomotor areas of the brain stem. However, recent anatomical evidence has shown that the pars reticulata of the substantia nigra projects directly to the intermediate layers of the superior colliculus (Rinvik et al., 1976; Jayaraman et al., 1977; Graybiel, 1978). Cells in these intermediate layers discharge before the onset of saccadic eye movements (Schiller & Koerner, 1971; Wurtz & Goldberg, 1972); some cells discharge only before saccades to visual targets (Mohler & Wurtz, 1976) while others discharge before saccades made in the dark or in the light. By studying the relation of discharge patterns of substantia nigra cells to the onset of saccadic eye movement, we will have the opportunity to study the neural mechanisms related to the initiation of eye movements at a stage of processing earlier than that seen in the superior colliculus.

Methods

Cells were studied in awake rhesus macaques trained to fixate a spot of light on the tangent screen in front of them and to follow that spot of light if it went off at one position and came on at another (Wurtz, 1969b; Goldberg & Wurtz, 1972a). This behavioral training allowed analysis of the relation of the cell activity to eye movement when the monkey made saccades from the fixation point to a visual target point. The visual responsiveness of cells was also explored while the monkey fixated by presenting a second spot of light which could be placed at different points in the visual field. In addition, the modulation of the visual response was studied by comparing a cell's response to a passive visual stimulus presented while the monkey looked at the fixation point with the same cell's response when the monkey used the stimulus as the target for a saccadic eye movement.

The activity of single cells was recorded using movable platinum microelectrodes (Evarts, 1966) while the monkey sat in a primate chair with his head restrained. At the end of the series of experiments, the monkeys were perfused and the recorded cells were located approximately on brain sections with the aid of marking lesions made at the time of recording (10–20 μA for 60 sec). The cells considered in this report were identified as lying in the pars reticulata of the substantia nigra either (1) by being at a mark made at the recording site, (2) by lying between such a mark above and the cerebral peduncle below, or (3) by lying on a penetration adjacent to a mark and at a depth that would ensure that the location of the cell was within the substantia nigra. The area of the substantia nigra studied is indicated in Fig. 1.

Results

Cells in the substantia nigra generally had a steady high rate of discharge ranging between 40 and 100 spikes/sec. Many of these cells (but by no means all) showed a decrease in the rate of discharge before the onset of visually guided saccadic eye movements. This report is based on a sample of 125 cells from four monkeys that were related to visually guided saccadic eye movements. The discharge of some of the other cells was modulated during licking and chewing movements as reported previously (Delong & Georgopoulos, 1978). A few cells showed an increase of discharge before saccades, but as these cells were seen only infrequently and were not clearly within the pars reticulata, we will not consider them further. We will describe two types of cells found in the pars reticulata of the substantia nigra: one whose discharge rate decreased before saccades, and one whose discharge rate decreased after the visual target guiding the saccade.

Saccade-Related Cells

The discharge rate of saccade-related cells decreased when the monkey made a saccade to a stimulus in a particular part of the visual field but did not change when the monkey did not make a saccade to the stimulus. In Fig. 2*A* the dot pattern and histograms are aligned on the onset of a saccadic eye movement, and the discharge of the cell decreased about 50 msec before the onset of the saccade and continued for about 150 msec, well beyond the end of the 5 deg saccade. In Fig. 2*B* the same trials are aligned on the onset of the stimulus target. The latency of the decrease in activity to the stimulus onset appears to be a little more variable than to the saccade

Fig. 1. Coronal section through the brain stem of a rhesus macaque showing substantia nigra, pars reticulata. Shaded area indicates where we found cells related to saccades or visual stimuli. Abbreviations: CI, capsula interna; CP, cerebral peduncle; LGN, lateral geniculate nucleus; PC, pars compacta of substantia nigra; PR, pars reticulata of substantia nigra; RN, red nucleus; VPL, nucleus ventralis posterior lateralis; VPM, nucleus ventralis posterior medialis.

onset, although this relationship is ambiguous in this case since the monkey made saccades with relatively constant latencies. These results suggest that the decrease in discharge rate of this cell is related to the saccade and not the stimulus target. In fact, no decrease in discharge rate occurred when the stimulus came on and the monkey did not make a saccade to it (Fig. 2*C*). Since we have not studied the

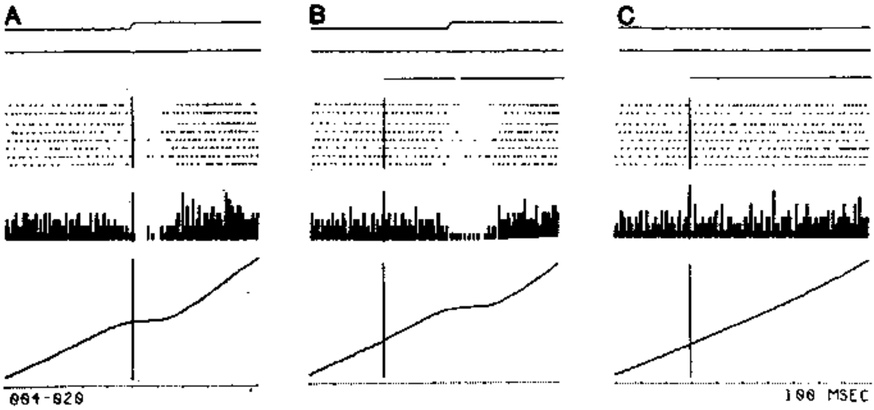


Fig. 2. Cell discharge related to onset of saccades recorded in the left substantia nigra. In *A*, the discharge of the cell decreased before onset of a saccade to a visual target 5 deg to the right. In *B*, trials are aligned on the onset of the stimulus which was the target for the saccade. In *C*, the target came on while the monkey continued to fixate; no decrease in cell discharge occurred with the visual stimulus alone. Lines above the rasters and histograms show horizontal (upper trace) and vertical (middle trace) eye position and period of the visual stimulus (bottom trace). Unless otherwise indicated, the visual stimulus was a spot, 0.1 deg in diameter, produced by a light-emitting diode. The vertical line extending through all three segments indicates the event used to align the traces: onset of the saccade in *A*, onset of the stimulus used to guide the saccade in *B*, or onset of the stimulus while the monkey fixated in *C*. Each dot in the raster display indicates a single discharge of the cell. The histogram shows the sum of the raster lines in 6 msec bins, and the line below the histogram is a cumulative record of the number of discharges based also on the above raster lines. The period between large dots on the time base is 100 msec.

discharge of these cells during saccades made in total darkness, we cannot say whether the response is completely independent of visual input. For saccade-related cells, the onset of the decrease in discharge rate ranged from 120 msec before to just at the onset of the saccade, while the end of the decrease ranged between 40 and 150 msec after the onset of the saccade.

There was a gradient in the change of discharge rate preceding saccades to different parts of the visual field. For a saccade-related cell, the percent decrease in discharge rate before saccades in different directions is indicated by the length of the line on a polar plot (Fig. 3*A*). For most saccade-related cells, the greatest decrease in discharge accompanied a saccade to the stimulus in the visual field contralateral to the substantia nigra in which the cell was located. Vertical saccades were frequently accompanied by a decrease in discharge, while purely ipsilateral saccades almost always had less effect on discharge rate. Thus, saccade-related cells had a limited, but usually large, "movement field."

Visually Related Cells

The discharge of visually related cells decreased after the onset of a spot of light in a particular part of the visual field, even when the monkey did not make a saccade to it. Figure 4 shows an example of the visual response of one of these cells to a spot of

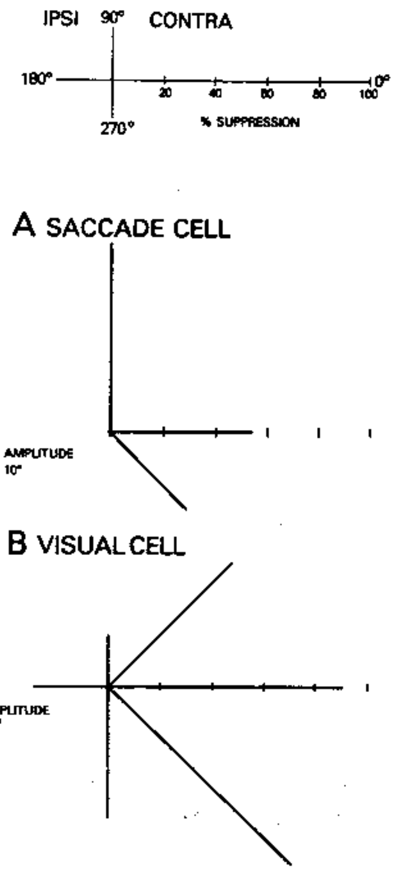


Fig. 3. Decrease in discharge with different saccade directions for a saccade-related cell (*A*) and with different visual stimulus positions for a visual cell (*B*). In *A*, saccades were all 10 deg from the fixation point along the axis indicated. Response magnitude for each direction, expressed as the length of a bar in the polar plot, was calculated as a percent decrease of discharge rate during the response period relative to the discharge rate during the control period. For the saccade-related cell (*A*), the control and response periods began 500 msec before and 60 msec before the saccade onset, respectively, and had the same duration of 200 msec. For the visual cell (*B*), the stimuli were all 2.5 deg from the fixation point; the control and response periods began 300 msec before and 90 msec after the onset of visual stimulus, respectively, and had the same duration of 100 msec.

light coming on in the receptive field. When the monkey made a saccade to the visual target, and the dot display and histograms were triggered on the onset of the saccadic eye movement, the decrease in discharge (Fig. 4*A*) is similar to that of the saccade-related cell shown previously (Fig. 2*A*). Figure 4*B* shows the same trials aligned on the onset of the visual stimulus; the decrease in discharge began about 150 msec after the stimulus onset. Figure 4*C* shows that the visual stimulus in the absence of a saccade still produced the decrease in discharge rate. The decrease in discharge began about 150 msec after the stimulus onset and lasted for about 200

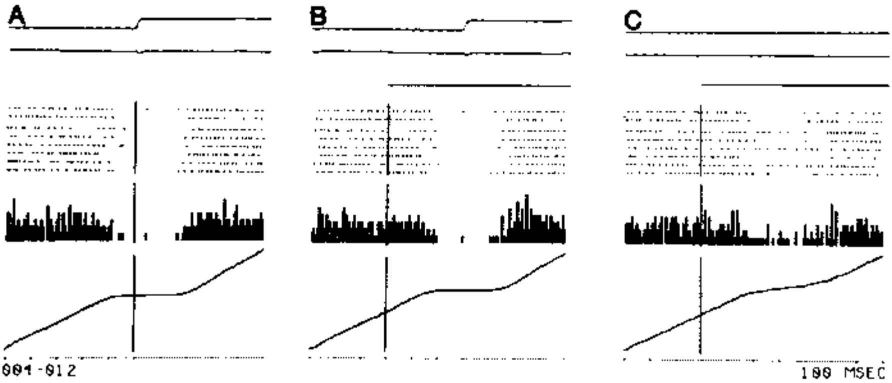


Fig. 4. Cell discharge related to the visual stimulus guiding a saccade recorded in the left substantia nigra. In *A*, the cell discharge decreased before onset of a saccade, and in *B* the same records are aligned on the onset of the stimulus used as a target for the saccades. In *C*, the decrease in discharge persisted when the same stimulus came on but the monkey made no saccade to the target. The saccade target was 10 deg to the right of the fixation point. Data presentation as in Fig. 2.

msec. In general, the latency of the visual response varied from 70 to 150 msec among cells.

Like the movement fields, the visual receptive fields were located primarily in the contralateral visual field and frequently included the vertical meridian. The receptive fields varied in size from a few degrees near the fixation point to nearly a hemifield. A gradient of response to a stimulus existed in these fields (Fig. 3*B*).

Modulation of the Visual Response

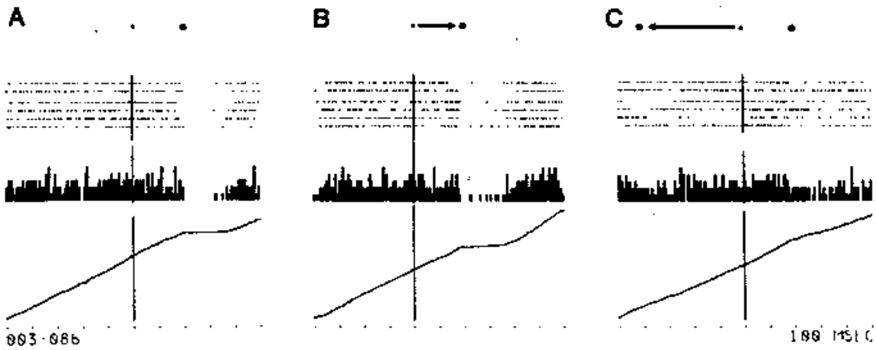
The decrease in discharge rate was more striking when the monkey used the stimulus as a target for a saccade (Fig. 4*B*) than when he did not (Fig. 4*C*). This enhanced response was present in about half of the cells that had a visual response and is reminiscent of the enhancement of visual responses seen in superior colliculus (Goldberg & Wurtz, 1972b; Wurtz & Mohler, 1976), frontal eye fields (Mohler et al., 1973; Wurtz & Mohler, 1976a; Bushnell & Goldberg, 1979) and parietal cortex (Bushnell et al., 1978). However, the sign of the response and the modulation differs: i.e., there is an enhancement of an *increased* rate of discharge to a stimulus in the case of the superior colliculus, frontal eye fields and parietal cortex, but an enhancement of a *decreased* rate of discharge in the substantia nigra.

Another difference between the modulation of the visual response of cells in the substantia nigra and the other areas was revealed when the monkey made saccades to locations outside the visual receptive field of the cell. In the case of the superior colliculus and frontal eye fields, the response of the cell to the visual stimulus was roughly the same whether the monkey simply fixated and the stimulus came on in the receptive field of the cell or whether the monkey made a saccade to a target outside the receptive field of the cell. This was not the case for many cells in the substantia nigra, which showed a decreased response to the visual stimulus when the monkey made a saccade away from the visual receptive field of the cell (Fig. 5). Figure 5*A* shows the "passive" response of the cell when the stimulus came on in the receptive field while the monkey fixated; a decrease in cell discharge is evident after the stimulus onset. In contrast to the cell in Fig. 4, the decrease in discharge was similar even when the monkey made saccades to the receptive field stimulus (Fig. 5*B*). On the other hand, when the monkey made saccades to a target outside the visual field of the cell, the response of the cell to the stimulus was nearly obliterated (Fig. 5*C*).

Summary and Comment

A class of cells in the pars reticulata of the substantia nigra shows a clear and consistent relation to saccades or the visual targets for the saccades. The saccade-related cells show a decrease in discharge rate before the onset of saccades but in most cases only to saccades made to one area of the visual field, usually the contralateral field. Cells related to visual stimuli have a long latency, never less than 70 msec, and limited visual fields also usually centered in the contralateral visual field. The visual response of these cells is modulated by the relation of the visual stimulus to the saccade. If the stimulus is the target for a saccade, the response is

Fig. 5. Reduction in response of a visual cell when another remote visual stimulus was the target of a saccade. A decrease in discharge rate followed onset of the stimulus 5 deg to the right of the fixation point both when the monkey fixated (*A*) and when it made saccades to the stimulus (*B*). But the response to the same stimulus was reduced when the monkey was required to make a saccade to a point outside the receptive field of the cell 10 deg to the left of the fixation point (*C*). In *C*, some time after the onset of the receptive field stimulus (5 deg to the right), the fixation point went off; at the same time, the control stimulus (10 deg to the left) came on and eventually dimmed. For *A*-*C*, the vertical line indicates the onset of the receptive field stimulus (5 deg to the right). The latency of the visual response is long because the visual stimulus in this experiment was produced by an incandescent bulb with a slow rise time. The cell was located in the left substantia nigra.



enhanced (a greater decrease in discharge rate); if the target of the saccade is remote from the visual stimulus, the response is reduced (little or no decrease in discharge rate).

These relations between cell discharge and saccadic eye movement suggest that the pars reticulata might well be an important efferent pathway from the basal ganglia to the oculomotor system. One anatomically demonstrated route for such a pathway is through the superior colliculus, and it is worth relating the activity of the pars reticulata cells with those they might connect to in the intermediate layers of the superior colliculus. The most striking difference in discharge in the two structures is the direction of the change in discharge before saccades; in the superior colliculus, there is an increased rate while in the pars reticulata there is a decreased rate. Such a reciprocal relation is what might be expected if the pars reticulata cells produced a tonic inhibition of the superior colliculus cells. The decreased rate of discharge in the pars reticulata before saccades would then reduce the tonic inhibition on the colliculus cells and permit their increased rate of discharge before a saccade. Consistent with this idea is the observation in rats that the transmitter released in the colliculus by nerve terminals from the substantia nigra is gamma amino butyric acid (GABA), which is considered to be an inhibitory transmitter (Vincent et al., 1978; Di Chiara et al., 1979).

This hypothetical relation of pars reticulata to superior colliculus requires considerable additional information for substantiation. In addition, which type of cells in the pars reticulata connect to which cells in the intermediate layers of the superior colliculus is unknown, but determination of these connections may provide further insight into the neural mechanisms underlying visually triggered saccades.