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Function of the Indirect Pathway in the Basal Ganglia Oculomotor System: Visuo-Oculomotor Activities of External Pallidum Neurons

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A recent model of the basal ganglia has suggested that there are two main pathways, the direct and indirect pathways [1] (fig. 1). The direct pathway is thought to facilitate the target structures through double inhibitions, as shown for the oculomotor part of the basal ganglia [2, 3]. In a resting state, caudate neurons discharge with very low frequencies, whereas substantia nigra pars reticulata (SNr) neurons discharge with very high frequencies. The tonic firing of SNr neurons inhibits the superior colliculus (SC), thus suppressing saccadic eye movements. Activation of caudate neurons by cerebral cortical inputs leads to inhibition of SNr neurons, and consequently disinhibition of SC neurons, and therefore facilitates saccadic eye movements.

Activation of the indirect pathway would have effects opposite to the direct pathway, as judged by the signs of anatomical connections. Activation of caudate neurons would inhibit external pallidum (GPe) neurons, which leads to disinhibition of subthalamic nucleus (STN) neurons, facilitation of SNr neurons, thus increasing the tonic inhibition upon the SC. However, it is still unclear how these two pathways work in natural behavioral conditions. Do they compete with each other? Or do they work in different behavioral contexts? To answer these questions, we recorded single cell activities from the GPe in the monkey performing visuo-oculomotor tasks.

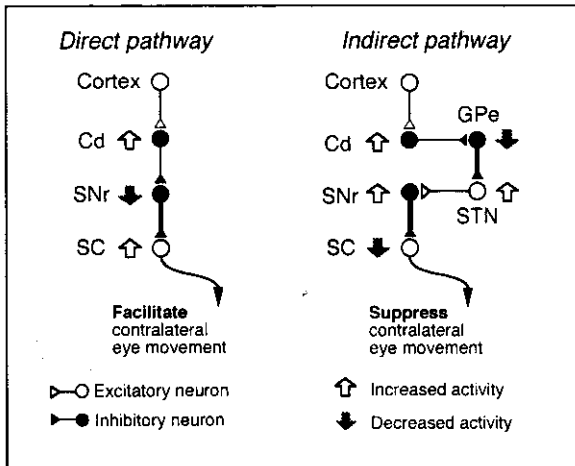
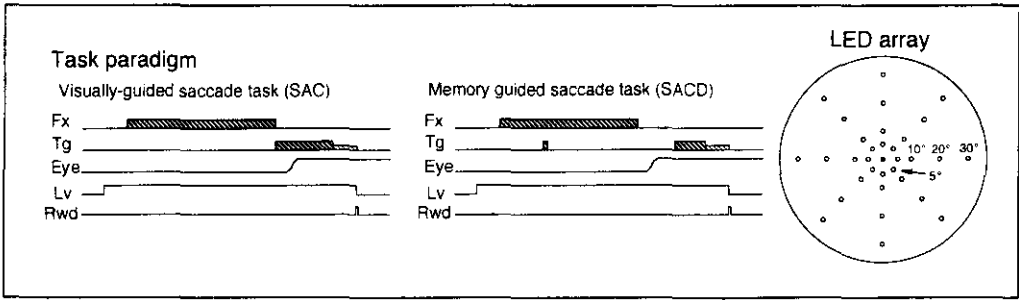


Fig. 1. Connections and hypothetical activity changes of oculomotor areas through the direct (left) and indirect (right) pathways in the basal ganglia. Open and filled neurons indicate inhibitory and excitatory neurons, respectively. Open upward arrows indicate increases in activity changes; hatched downward arrows indicate decrease in activity changes. Cd = Caudate nucleus; GPe = external segment of globus pallidus; SC = superior colliculus; SNr = substantia nigra pars reticularis; STN = subthalamic nucleus.

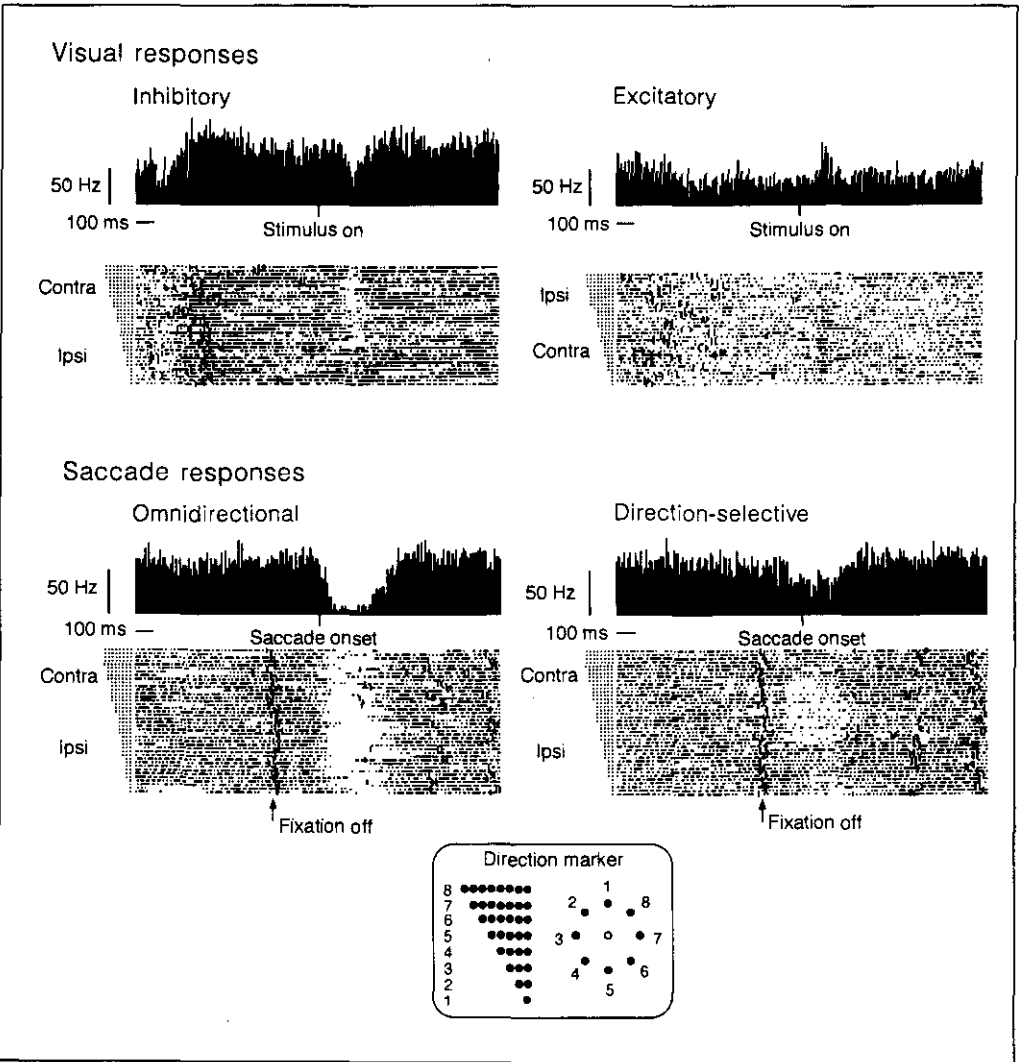
Materials and Methods

We used two Japanese monkeys trained to perform mainly two tasks, visually guided and memory-guided saccade tasks [4] (fig. 2). The tasks were controlled by a conventional microcomputer. The animal sat on a monkey chair in a quiet, dimly lit shielded room facing a dome-shaped black panel implanted with an array of small yellow LEDs (8 direction and 4 eccentric amplitudes plus the center). After sufficient training using these tasks, the animal was anesthetized with pentobarbital sodium (5 mg/kg/h), and underwent an operation for mounting a head holder and a recording chamber stereotaxically on its head and for implanting an eye coil. At the time of experiment, the head of the animal was fixed to the chair by the head holder and eye position was monitored with the search coil method [5]. A glass-insulated elgiloy electrode was introduced into the target area through the chamber for recording extracellular spikes with a conventional amplifier. The spikes were converted into pulses by a discriminator with spike amplitude and duration windows. The pulses, task events, and AD-converted eye position signals were stored in the computer for later offline analysis. Small electrolytic lesions were made at several selected points in and around the GPe by passing weak DC currents (+5 μ A, 100 s) through the recording electrode. After the series of experiments, the animal was deeply anesthetized with pentobarbital sodium (50 mg/kg) and perfused with saline containing heparin, followed with 10% formalin. The brain was cut into several blocks, sectioned at 50 μ m thickness, and stained with cresyl violet for reconstruction of recording sites.

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Results

Out of 400 GPe neurons, 100 were responsive to the tasks. Sixty-four neurons showed responses time-locked to saccades and 34 neurons showed responses time-locked to visual events. Many saccadic neurons also responded to other events such as visual stimulus, reward or lever release, and in addition showed tonic responses during eye fixation.

Visual responses were observed in response to a brief flash of the LED light (on-response) or to the offset of fixation light (off-response). Figure 3 shows representative visual on-responses of 2 cells with a decrease and an increase in discharge rate. On-responses were obtained in 23 neurons with decreased ($n = 13$) or increased ($n = 10$) activity. These neurons had large receptive fields, including,

Fig. 2. Schematic diagrams of a visually guided saccade (left) and memory-guided saccade (center) task. Fx = Fixation light; Tg = target light; Eye = eye position; Lv = lever switch. Right: schematic illustration of distribution of an array of small yellow LEDs (the center, and 8 direction and 4 eccentric amplitudes) implanted on a dome-like black panel. The task was initiated with a lever press by the monkey. For the visually guided saccade task, a LED light of a fixation point turned on at the center of the panel. The monkey had to fixate the fixation point. And after 1.5–3 s, the fixation point turned off, and simultaneously, another LED light (target point) turned on. The animal had to make a saccade to the target point. After 0.5–1.5 s, the target point dimmed for 0.5 s. The animal had to release the lever during the dim. If successful, a drop of water was delivered. For memory guided saccade task, a LED light turned on briefly at 1 s after the onset of the fixation light, as the cue to indicate where the target point would appear. After the fixation point turned off, the monkey must make a saccade according to his memory to where the cue had appeared. The target point turned on at 0.6 s after the fixation point turned off, and thereafter dimmed.

Fig. 3. Raster-histograms of representative visual-on and saccade responses. For visual-on responses (top), inhibitory (left) and excitatory (right) responses were obtained during the memory guided saccade task. While the monkey was fixating the center spot light, another spot light (visual stimulus) was presented at one of 8 directions with a 20° eccentric amplitude. These raster-histograms were aligned at the onset of the stimulus; they have been rearranged according to the direction of the stimulus. Direction markers are indicated at the left to each raster line. The bottom inset shows what direction the marker indicates. 'Contra' and 'Ipsi' indicate that the stimulus was presented in the visual field contralateral and ipsilateral to the recording site of the neuronal activity, respectively. For saccade responses (bottom), omnidirectional (left) and direction-selective (right) saccade responses were obtained during the visually guided saccade task. Saccade amplitudes were 20°. These raster-histograms were aligned at the onset of saccades; they have been rearranged according to the direction of the saccade. 'Contra' and 'Ipsi' indicate that the saccade was directed to the visual field contralateral and ipsilateral to the recording site of the neuronal activity, respectively.

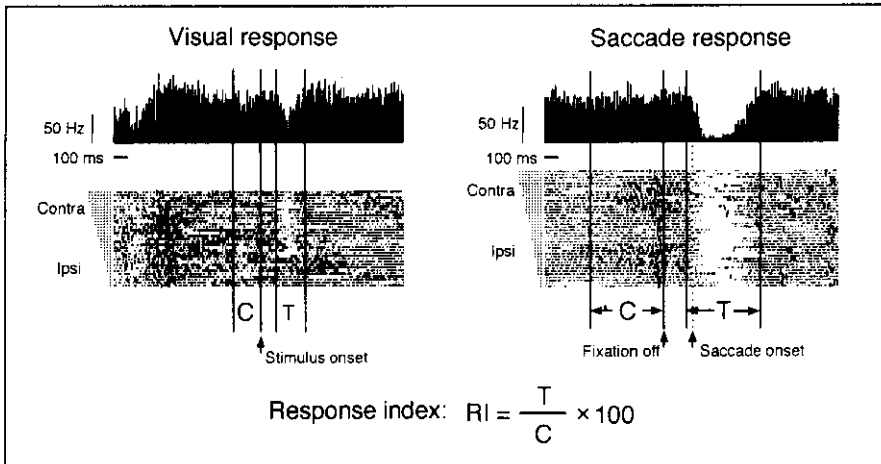


Fig. 4. For quantitative analysis of direction selectivity, a response index (RI) was defined as the ratio of spike activity within a test period (T) to spike activity within a control period (C) (represented in percentage). For visual responses (left), the control period was set just before the visual stimulus onset; for saccade responses, it was set just before the offset of the fixation light. The test period was set during the response phase. Durations of the control and test periods were made the same. Thus the excitatory and inhibition responses are indicated by the response index more than and less than 100, respectively.

the contralateral hemifield. Off-responses were obtained in 11 neurons with decreased ($n = 5$) or increased ($n = 6$) activity.

For quantitative analysis of the direction selectivity of visual on-responses, we calculated the response index for each of 8 directions and made polar diagrams (fig. 4). Figure 5 (upper) shows examples of visual on-responses. Broadly tuned neurons tended to have multiple peaks of response.

For saccade responses, the dominant response was a decrease in activity (40 out of 64 saccadic neurons; fig. 3). We found neurons showing omnidirectional responses ($n = 32$) and direction-selective responses with a contralateral ($n = 11$), ipsilateral ($n = 5$), or up-down ($n = 16$) preference. These direction selectivities were broadly turned as well as those for visual responses.

For quantitative analysis of the direction selectivity, we calculated the response index as well as visual responses (fig. 4). Figure 5 (lower) shows representative polar diagrams of saccade responses. Saccade responses were broadly tuned, including more than 4 responsive directions. Some neurons showed different saccade responses between visually guided and memory-guided saccades. Saccade responses were often associated with responses to other task events such as reward.

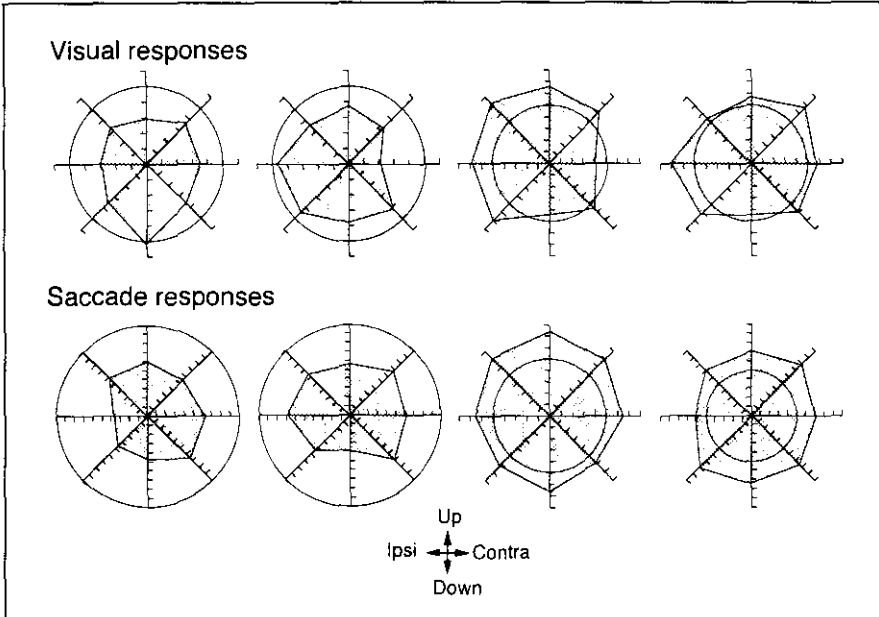


Fig. 5. Polar diagrams of representative visual (upper, 4 neurons) and saccade (lower, 4 neurons) responses in each direction. The right side of each polar diagram indicates the response to the stimulus presented contralaterally to the recording site of the neurons. Circles indicate the control level in spike activity.

In addition, we found neurons showing tonic responses. Figure 6 shows representative tonic responses of 2 cells. Unit 1 showed tonic decreases in activity during fixation and after target light onset. Unit 2 showed a slight tonic increase during fixation followed by an abrupt depression of activity after a saccade, and gradual recovery after target light onset. The decreased activities during fixation to the center and visual target, and waiting for the appearance of the target light may contribute to maintain eye position by preventing external signals from triggering unnecessary eye movements. Tonic responses were often associated with phasic saccade or visual responses.

Response latencies of visual and saccade responses were measured from stimulus and saccade onset, respectively. The latency for a saccadic activity preceding the saccade onset was represented by a minus value. The mean latencies of visual and saccade responses were 128 ($n = 21$) and 4 ms ($n = 59$), respectively. In both visual and saccade responses, the mean latency of the excitatory response (113 and -20 ms, respectively) was slightly shorter than that for the inhibitory response (139 and 4 ms, respectively). Since the signals from the striatum (the

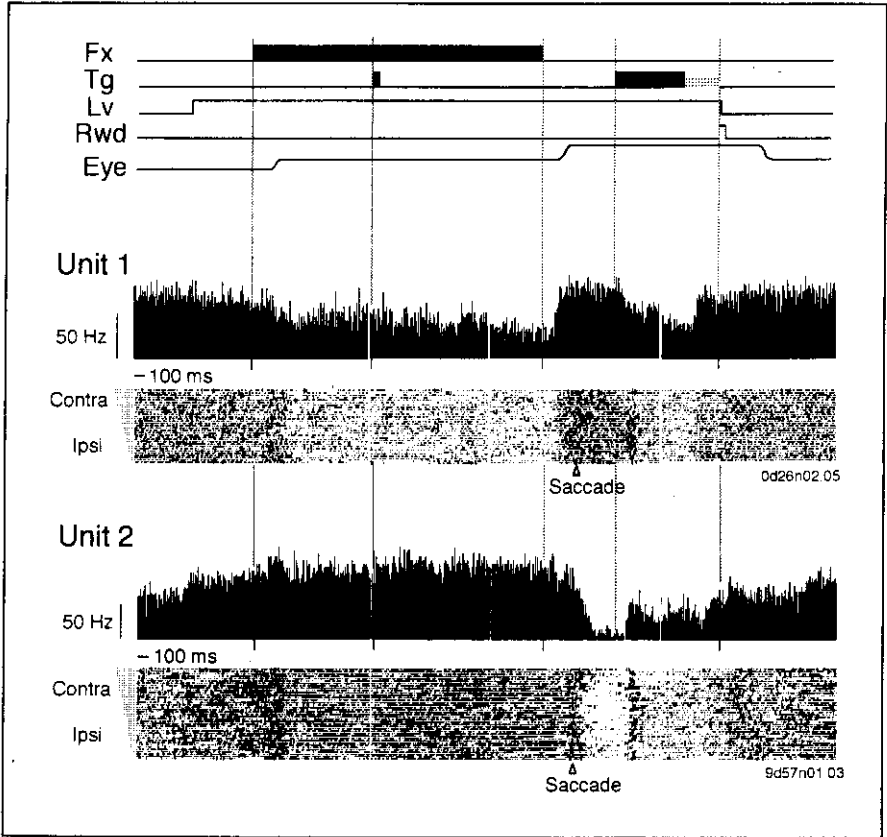


Fig. 6. Raster-histograms of representative tonic responses during the memory guided saccade task obtained from two neurons (Unit 1 and 2). The upper diagram indicates schematic task events. These raster-histograms were aligned at the onset of fixation light, the onset of cue light, the offset of fixation light, the onset of target light, and the lever release, each indicated by a vertical line. They have been rearranged according to the direction of the saccade. Pairs of short lines on each raster indicate the onset and offset of detected saccades. An arrow head under each raster-histograms indicates the approximate time of the occurrence of the memory guided saccades. Other conventions are the same as in figures 2 and 3.

caudate nucleus and putamen) would lead to inhibitions of GPe neurons, the excitatory responses of GPe neurons are probably evoked by the STN inputs. The shorter latency of the excitatory response is consistent with the fact that the excitatory cortico-subthalamo-pallidal pathway is faster than the inhibitory cortico-striato-pallidal pathway [6].

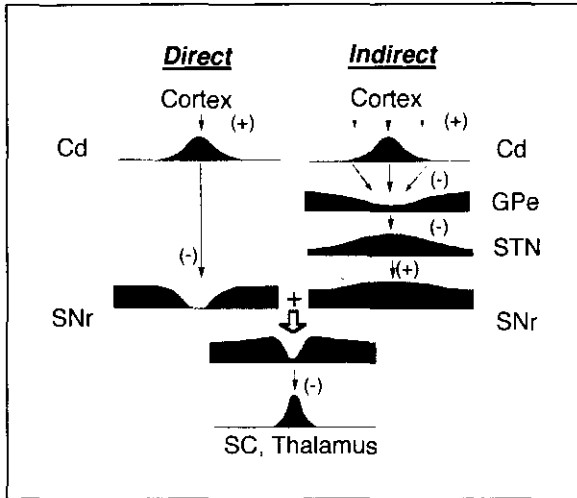


Fig. 7. Schematic diagrams of response fields in each levels of structures involved in the direct and indirect pathways in the basal ganglia. Abbreviations are the same as in figures 1. (+): Excitatory transmission; (-): inhibitory transmission. Details are explained in the Discussion.

Histological analysis for the locations of recorded cells revealed that visuo-oculomotor cells were distributed mainly in the dorsal portion of the GPe. In a recent study [7], these areas received afferents from the caudate. We could not find visuo-oculomotor neurons in the internal pallidum.

Discussion

The present study revealed that GPe neurons have large receptive and movement fields including more than a half of the visual field. Their responses consist of various combinations of phasic and tonic components. Recent studies [3, 8] have suggested that caudate neurons have more specific visuo-oculomotor information. Eccentricities of visual-receptive or movement fields of caudate neurons are less than those of GPe neurons, and the centers of these fields of caudate neurons are distributed in the contralateral visual fields. These results, taken together, indicate that there is a great degree of convergence from caudate neurons onto single GPe neurons (fig. 7). SNr neurons also have relatively specific visuo-oculomotor information [9]. In our laboratory, visuo-oculomotor activity was recorded from STN neurons [10]. Although excitatory responses were domi-

nant, they also had relatively large receptive and movement fields. These results suggest that the indirect pathway provides the SNr with surrounding effects in contrast with specific signals provided through the direct pathway.

Our results are at variance with some previous studies. Georgopoulos et al. [11] reported that the discharge of 41% of internal pallidum (GPi) neurons and 48% of GPe neurons during movement was related to the direction of step-tracking elbow movements. Mitchell et al. [12], using a task with torque loads for dissociating movement direction from EMG pattern, found that 30% of GPi neurons and 30% of GPe neurons had directional responses and only a few neurons (3%) had bidirectional responses. These studies suggested that neuronal signals in the GPe and GPi are not differentiated.

Other studies, however, seem consistent with our results. Mink and Thach [13] reported differences in the population of directional cells between the GPe and GPi during step-tracking wrist movements. They found that 41% of GPi neurons and 28% of GPe neurons were directional, whereas 18% of GPi neurons and 40% of GPe neurons were bidirectional. Using a task with tracking wrist movements, Hamada et al. [14] found that all wrist-related neurons in the GPe were bidirectional. These studies, in agreement with our studies, suggest that neuronal signals conveyed by the GPe are less specific than those in the GPi.

Why are there the discrepancies in the results between the different studies? One possibility is the difference in the degree of the freedom of movement. The elbow movement occurs only in one-dimensional direction, flexion and extension. In contrast, the wrist movement occurs in two-dimensional space, including flexion, extension, abduction and adduction. The eye movement also occurs in two-dimensional space. When wrist and eye movements occur, it is often necessary that they are limited to one dimension by suppressing dimension. In such a condition, the indirect pathway could provide the surrounding effects, in contrast with specific signals provided through the direct pathway. Such a mechanism would be suitable for selecting neuronal signals to facilitate or release a proper movement.

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