

## **Role of basal ganglia in initiation and suppression of saccadic eye movements**

O. Hikosaka, M. Matsumura, J. Kojima and T.W. Gardiner

*Laboratory of Neural Control, National Institute for Physiological Sciences, Myodaijicho, Okazaki 444, Japan*

### **Basal ganglia control memory-contingent initiation of saccade**

Disinhibition is a key feature of basal ganglia function (Fig. 1). The basal ganglia normally exert tonic inhibitory influences over their target structures, not only the superior colliculus (SC) but also other brainstem areas and part of the thalamus. The inhibition is maintained by the extremely high spontaneous activity of the output neurons in the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus (GPi). The signals from the striatum, caudate (Cd) and putamen, truncate the inhibition, thus yielding a powerful facilitatory effect.

The saccadic activities in the Cd and the SNr were frequently dependent on how the saccade was initiated [1,2]. Nearly one third of saccadic neurons in the Cd and the SNr were selective for memory-guided saccades; another one third were selective for visually guided saccades. Such strong selectivity, especially the selectivity for memory-guided movement, has not been seen outside the basal ganglia.

Patients of basal ganglia diseases indeed have deficits in initiation of saccades. Moreover, as expected from the characteristic neural activities, the deficits are often selective, apparent only in the task that requires memory-guided saccades [3-5]. Visually guided saccades are comparatively unimpaired; saccade latencies can even be shorter than normal controls. Similar deficits were observed in the monkeys when MPTP was injected into the Cd on one side; memory-guided saccade to the contralateral side was predominantly impaired [6].

### **Basal ganglia may actively suppress saccade**

From the viewpoint of the SC, the basal ganglia input is only a part of an extensive list of cortical and subcortical inputs. But only the basal ganglia input is inhibitory. Without the strong tonic inhibition from the basal ganglia, the SC would be in a chaotic state with excitatory signals, each of which would suggest making a saccade either this way or that way. This in fact happened when we blocked the inhibition by injecting a GABA antagonist in the SC [7] or by injecting a GABA agonist in the SNr [8]; the monkey was unable to maintain fixation and made saccades continually

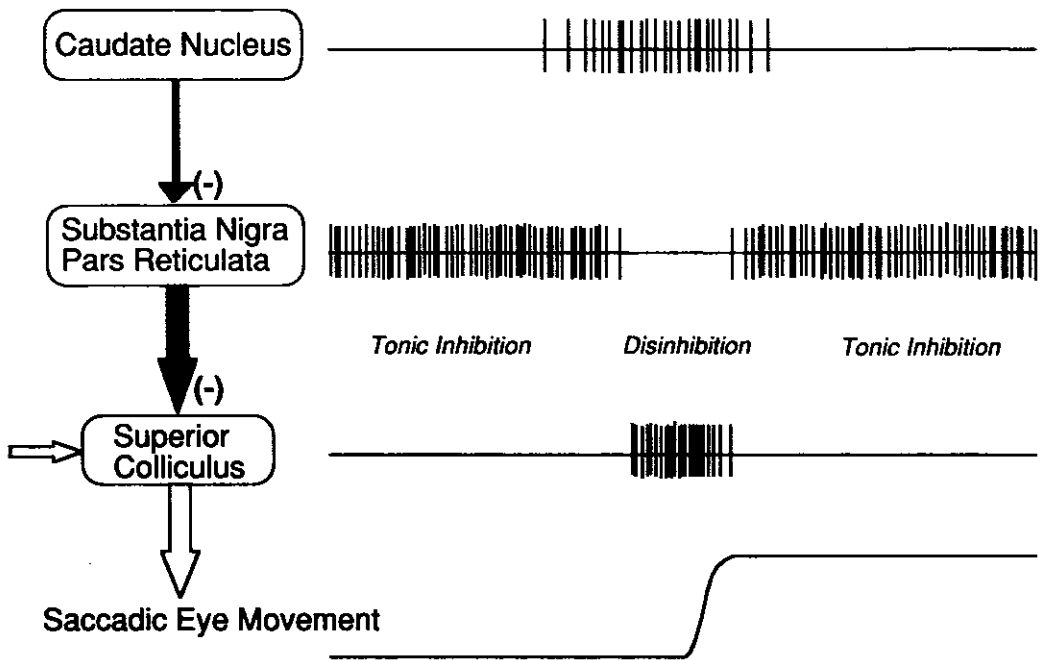


Fig. 1. Neurons in the substantia nigra pars reticulata (SNr) exert strong, sustained inhibition on saccade burst neurons in the superior colliculus (sc). This inhibition is removed by a transient input from the caudate nucleus (Cd), which allows the burst discharge of SC neurons.

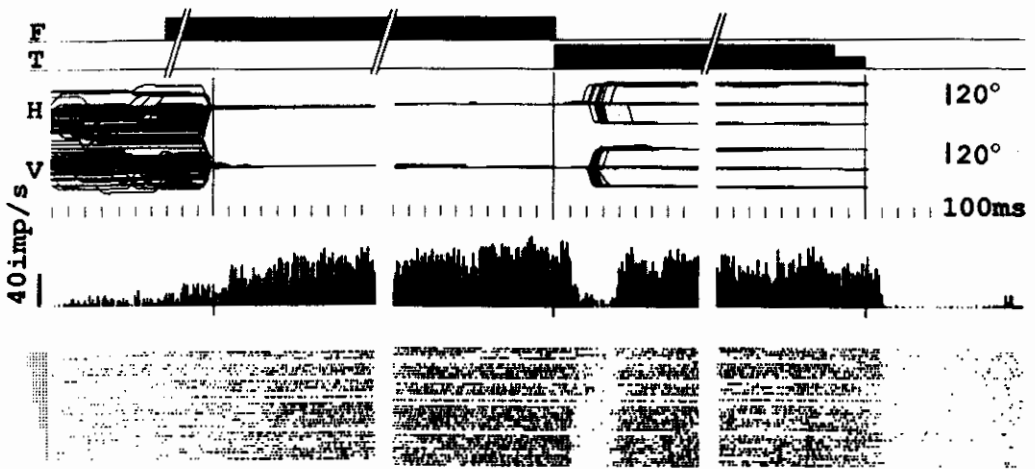
to the contralateral side. This result suggested that suppression of eye movements, not just disinhibition, is an important function of the basal ganglia.

Indeed, it has been shown that the patients with Huntington's disease [4,9] and Parkinson's disease (unpublished observation) have difficulty in suppressing saccades. Even if specifically instructed not to make an eye movement while the central fixation point is present, the patient makes a saccade frequently to a flashed stimulus which is presented as the cue for the future target.

### Dual mode of basal ganglia function

Recent studies suggest the role of the basal ganglia in enhancing movement suppression. A key structure is the subthalamic nucleus (STN). Although clinically outstanding as seen in hemiballismus [10], the function of the STN had been unclear until recently. It was only recently determined that this nucleus sends excitatory signals to the output structures of the basal ganglia – SNr and the GPi [11].

Unlike the disinhibitory mechanism, the external inputs to the subthalamic nucleus, notably from the cerebral cortex, appear to result in an enhancement of the basal ganglia inhibitory outputs [12]. The indirect pathway through the external segment of the globus pallidus (GPe) also leads to the enhancement because it contains two inhibitions.



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*Fig. 2.* A subthalamic nucleus (STN) neuron with activity related to eye fixation. This neuron discharged tonically while the monkey was fixating on either the fixation point (F) or the target point (T). From top to bottom, durations of fixation point (F) and of target point (T), horizontal eye positions (H) (up: rightward, down: leftward), vertical eye positions (V) (up: upward, down: downward), spike frequency histogram, and raster display of spike discharges. The records are aligned with respect to offsets of saccades made to the fixation point (left), fixation point offset (center), and target point offset (right). Because the durations of these events were different across trials, the records are shown as interrupted. Each line in the raster display represents the activity of the neuron during a single trial, each dot indicating a single spike discharge. The target points were located at  $20^\circ$  from the fixation point, in four directions. Their directions are indicated by the dots at the left of the raster line. The raster lines were reordered with respect to the direction of the target point, though direction was selected randomly at the time of the experiment.

However, this is still just a circuit diagram. We still do not know how the circuit works or what kind of information is conveyed by the new pathway. We therefore undertook an experiment to study the visuo-oculomotor signals in the monkey STN [13].

### Visuo-oculomotor activities in the monkey subthalamic nucleus (STN)

The STN is not a large but a prominent structure overlying the SNr. We found visuo-oculomotor cells in its ventral part. The task-related neural activities were classified into several types: saccadic, visual, fixation, and others. Unlike in the SNr, these responses appeared as an increase in spike frequency.

Sustained activity during visual fixation was frequently observed in the STN (Fig. 2). This neuron started discharging after the monkey started fixating the central spot. The discharge continued until the end of trial, except when a saccade was made to a target. The activity was present irrespective of the target directions.

The sustained activity in the STN would keep activating SNr neurons, maintain the tonic inhibition on presaccadic neurons in the SC, and therefore tend to suppress saccades. This is what was required of the monkey for completion of task trials.

Visual responses in the STN were phasic and excitatory. Their receptive fields were usually close to the fovea or included the fovea. If this visual signal is sent to the SC via the SNr, saccades tend to be suppressed when the stimulus is close to the fovea but to be released when the stimulus is somewhere in the periphery. Both situations are desirable.

Sustained activity was sometimes observed during the delay period when the monkey was waiting and preparing for a saccade to a remembered location. The sustained activity was frequently selective for the direction of the upcoming saccade. This type of activity has been found in other brain areas, such as the frontal and parietal association cortices, Cd and SNr. There have usually been two ways to interpret such activity: short-term memory and preparation of movement. In this case, however, such interpretation seems untenable, given the position of the STN in the basal ganglia network. Instead, we would like to propose another interpretation, that is that the sustained activity may be used to suppress an upcoming movement.

Preparation and suppression might appear totally different or even antagonistic, but in fact they must coexist. When we mentally prepare for some motor act, we at the same time suppress the movement. This is what the monkey had to do during this delay period. One must remember that the patients of basal ganglia disorders have difficulty in suppressing saccades during this period. In those patients this type of STN neuron may not be working properly.

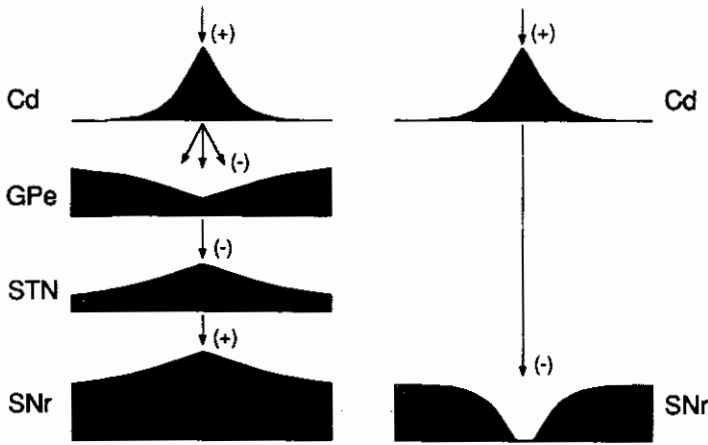
A similar function may be found for hand movements. Our monkeys were usually required to release the lever in response to target dimming to obtain reward. Some STN neurons showed vigorous sustained activity while the monkey was preparing for the lever release. But when the task was changed so that the monkey was now rewarded just by eye fixation, the same neuron stopped firing. This activity was specific to hand movement. It may thus be used to suppress the upcoming hand movement.

### **Visuo-oculomotor activities in the monkey globus pallidus**

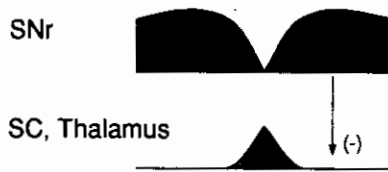
The activities in the STN should at least partly be determined by the external segment of the globus pallidus. This nucleus consists of GABAergic neurons and is now known to project to the SNr directly or indirectly via the STN. This was our next target.

In the dorsal part of the GPe we found a group of task-related neurons (Kato and Hikosaka, Unpublished observation). The response can be an increase or a decrease, unlike Cd, SNr, and STN. Some were selective for visually-guided saccades; others were selective for memory-guided saccades. Saccadic direction selectivity was generally poor, frequently responding to saccades of any direction or eccentricity – a feature never seen in the Cd or SNr. Some may combine other responses, such as lever release as shown here. Such response combinations may appear totally arbitrary, suggesting no straightforward behavioral consequences.

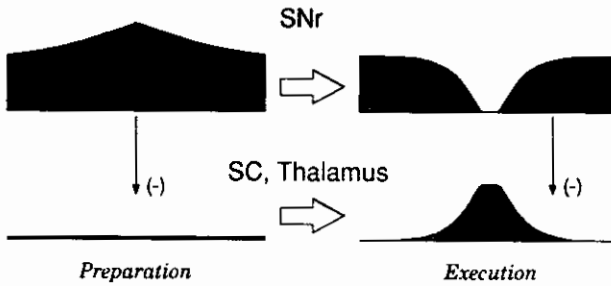
## Two Modes of Basal Ganglia Action



Simultaneous ==> *Focussing*



Sequential ==> *Sequencing*



*Fig. 3.* In addition to the disinhibitory pathway (right), there is an indirect pathway (left) which is intervened by the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN). The outcome of this indirect pathway (suppression) is antagonistic to that of the direct pathway (facilitation). Cd, caudate nucleus; SNr, substantia nigra pars reticulata; SC, superior colliculus.

### Function of the pallido-subthalamic pathway

In a previous series of experiments we studied the neural activity of Cd neurons using similar paradigms. We found saccadic, visual, reward-related, and expectation-related activities. Thus, almost all types of activity seen in the GPe are found

in the Cd. But most Cd neurons show only one type of response, and each response tends to be more specific, say, responding only to contralateral-upward saccades. These results, taken together, suggest that there is a large degree of convergence or divergence in the Cd-GPe connections.

Now let us consider how the two parallel pathways in the basal ganglia might work (Fig. 3). Let us assume that cortical inputs to the striatum have a focus of activity which, however, is not really spot-like but has a gradient decreasing outward. The positive peak of activity in the Cd, on one hand, would directly inhibit SNr neurons, thus producing a negative peak of activity. If a similar positive peak of activity is fed into the indirect pathway, a negative peak would be produced in the GPe. Note that this peak would be less steep because of the divergence, yielding the non-selectivity of GPe neurons. These signals, when transmitted to the SNr either directly or through the STN, would produce a positive peak which is less steep than the negative peak produced by the direct pathway.

There can be two ways in which these pathways work: simultaneous mode and sequential mode. In the simultaneous mode, these two opposing effects should be superimposed in the SNr, yielding a sharper negative peak. The activity in its target structures, SC or thalamus, would thus be more focussed. The effect is to enhance the spatial contrast of neural signals. In the sequential mode, the effect would be to enhance the temporal contrast. When a movement is prepared, the indirect pathway may be continuously active so that the target of the basal ganglia may be continuously inhibited in a non-selective manner. But once a trigger signal comes in, the direct pathway may begin to work, disinhibiting the target neurons in a selective manner.

To summarize, we have demonstrated the dual mode of basal ganglia operation. When working together or sequentially, these pathways would contribute to the following aspects of behavioral organization.

- (1) Suppression of unnecessary or inappropriate movements; its effect is to focus and select movements that are currently required.
- (2) Suppression of a forthcoming movement when the movement is prepared; this is particularly important because the motor program is now ready to go but must remain in a state of idleness or gears disengaged. Without this mechanism we would have difficulty in suppressing anticipated movements, as exemplified in the fixation-breaking saccades of basal ganglia patients.

Our last speculation is that the basal ganglia may contribute to the transition between the motor-overt behavior and mental-covert behavior. For voluntary execution of movement, a motor program or memory must be activated. This information would then activate the lower motor areas to produce an overt movement. When we prepare for but refrain from executing a movement, the outflow of the motor program must be disconnected. The basal ganglia might again be crucial for this process. If such disconnection is maintained, the association cortex would be functionally isolated, its activity being internalized. We would speculate that this was a necessary step toward development of mental activity.

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