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Saccadic Eye Movements in Parkinsonism

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NEURAL MECHANISM IN THE BASAL GANGLIA RELATED TO SACCADIC EYE MOVEMENTS

Saccadic eye movements, like skeletal movements, are controlled by the basal ganglia. This is accomplished through the inhibitory connection from the substantia nigra pars reticulata to the superior colliculus.[23] Cells in the substantia nigra pars reticulata fire rapidly and tonically and keep suppressing presaccadic burst cells in the superior colliculus (Fig. 1). The nigra cells pause occasionally. This leads to a disinhibition of colliculus cells allowing their spike bursts and consequently a saccade to the contralateral side.[20] This inhibition is mediated by GABA.[21,22] The pause in nigra cells is thought to be the result of another GABAergic inhibition, an inhibition originated at least partly from the caudate nucleus.[24] Cells in the caudate are nearly silent most of the time, but fire before a voluntary saccade in different behavioral contexts.

In short, the saccadic system in the basal ganglia is composed of two serial inhibitions, one from the caudate to the substantia nigra and the other from the substantia nigra to the superior colliculus. The nigro-collicular inhibition is tonically active, thereby preventing excitatory signals from various cortical areas[35] to evoke unlimited eye movements. The caudate-nigral inhibition becomes active only occasionally; it removes the tonic inhibition on the superior colliculus thereby allowing other excitatory inputs to evoke eye movements.

WHY IS DOPAMINE SO IMPORTANT?

The basal ganglia are far more complex, however. GABA is only one of many neurotransmitters highly concentrated in the basal ganglia.[17] Perhaps the most important among them is dopamine. Dopamine is the key factor determining the function of the basal ganglia as a whole (Fig. 2). Without dopamine one would be rendered to be akinetic with involuntary tremor, as seen in Parkinson's disease.[34] Eye movement is not an exception. Deficits in saccadic eye movements and smooth pursuit have been reported repeatedly.[7,8,11,14,27,28,32,33,36]

However, little is known of how dopamine modulates the outputs of the basal ganglia. Dopamine neurons have no efferent connections to the areas outside the basal ganglia; any dopaminergic action must be mediated through the GABAergic output neurons in

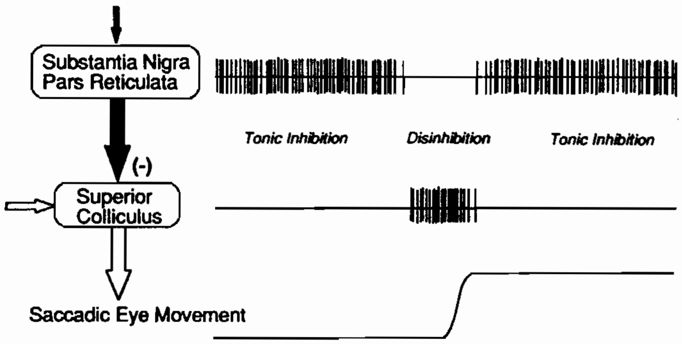

Fig. 1. Nigro-collicular inhibition and disinhibition controls voluntary initiation of saccadic eye movements.

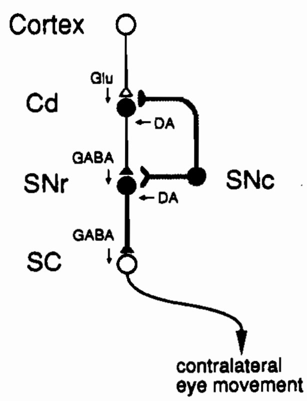

Fig. 2. Hypothetical interaction of GABA and dopamine (DA) in the basal ganglia. Cd, caudate nucleus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; SC, superior colliculus. Excitatory and inhibitory neurons are indicated by open and filled circles, respectively. Presumed neurotransmitters: Glu, glutamate; GABA, γ-amino butyric acid; DA, dopamine. Dopaminergic neuron is shaded indicating the ambiguous nature of its synaptic action.

the substantia nigra pars reticulata or the internal segment of the globus pallidus. Dopaminergic neurons are concentrated in the pars compacta of the substantia nigra and project their axons to the striatum, namely caudate and putamen.[17] The striatum may therefore be the site where dopamine exerts its modulatory action.

The nature of dopaminergic action is controversial (Akaike *et al.*, 1987,[1] for review). Dopamine may facilitate or depress synaptic actions mediated by other neurotransmitters such as glutamate[9] or GABA.[6] Furthermore, different types of dopamine receptors are present in the basal ganglia in a non-uniform manner[5]; D1 and D2 receptors would mediate inhibitory and excitatory responses of striatal neurons and lead to antagonistic intracellular chemical processes.[1]

We have no way to deduce the function, not action, of basal ganglia dopamine from these observations. One way to answer this question is to study the signals carried by the dopaminergic neurons. Schultz and his colleagues[30] have demonstrated that dopaminergic cells in the substantia nigra respond to visual or somatosensory stimuli that signal the presence or availability of reward. Another way would be to study the deficiency of dopamine in terms of well-known behaviors in which the basal ganglia play a crucial role; saccadic eye movement is a good candidate.

We found that the deficits in saccades in parkinsonian patients are conditional, depending on how the saccade is initiated.[27]

SACCADE EYE MOVEMENTS IN PARKINSONIAN PATIENTS

Saccade tasks for human subjects are similar to the ones used for monkeys (Fig. 3; see Ref. 24). The subject sits in front of a dome-shaped screen with his head on a chin rest. Eye movements are recorded using EOG. He has a box with a switch button. When he presses the button, a small spot of red light comes on at the center. After a random period of time the red spot steps from the center to the right or left and changes its color to green. If he releases the button immediately then, a pleasant tone comes on. If he fails to do so, an unpleasant beep sound pops up.

We used two kinds of task. In saccade task, the eccentric target comes on at the same

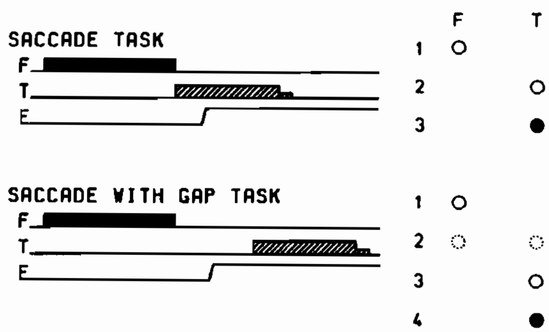

Fig. 3. Saccade tasks for human subjects. Saccade task is used for inducing visually guided saccades; saccade with gap task is for memory-guided (anticipatory) saccades. In saccade task, a central fixation point (F) is replaced with a target point (T), and the subject makes a saccade from F to T. In saccade with gap task, the target point comes on after a time gap; the subject makes a saccade during the time gap by anticipating its appearance.

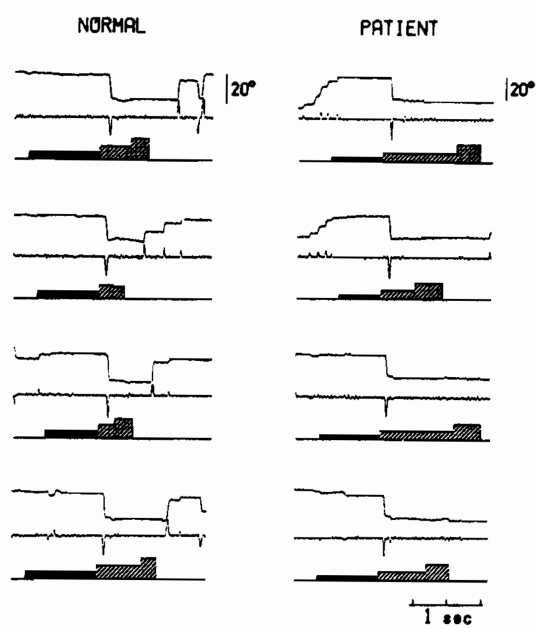

Fig. 4. Visually guided saccades in a normal control subject (left) and a parkinsonian patient (right). Records of four sequential trials are shown for each subject. For each record are shown horizontal eye position (top), horizontal eye velocity (center), and task-related events (bottom). Filled bar indicates fixation point; hatched bar target point.

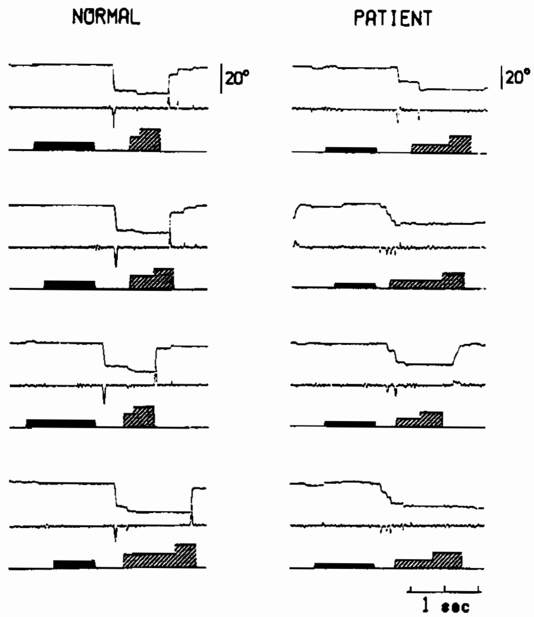

Fig. 5. Memory-guided (anticipatory) saccades in the normal control subject (left) and the parkinsonian patient (right). The same arrangement as in Fig. 4.

time as the central fixation point goes off. The evoked saccade is visually guided. In saccade with gap task, the target comes on after a time gap of between 0.4 and 1 s. Without instruction, the subject makes a saccade before the target. The saccade is memory-guided and anticipatory. In this case, of course, the target position is fixed throughout a block of 10–20 trials. This is very natural, requiring no instruction. Most subjects are even unaware that their eye movements precede the target.

Using these paradigms we compared eye movements in parkinsonian patients ($n=11$; male: 5, female: 6) and normal controls ($n=8$, male: 5, female: 3). They are roughly age-matched: patients, 41–74 y.o. (mean: 60.4); controls: 33–73 y.o. (mean: 55.5).

Figure 4 shows examples of visually guided saccades. The central fixation point was turned on, and then replaced with a target which came on at 20 degrees to the left. Horizontal eye position and velocity are shown for individual trials. The saccades were similar in these two subjects: latencies of about 200 ms, nearly normometric, and peak velocities of about 400 deg/s. After each trial the normal subject returned his gaze to the point close to the center with a single saccade. In the parkinsonian patient, however, the centering eye movements were sometimes delayed and staircase-like (1st and 2nd trials). This might suggest a deficit in parkinsonian patients in the initiation of voluntary movements without a sensory trigger.

The deficits became clear in memory-guided, anticipatory saccades (Fig. 5). Although somewhat hypometric, the normal subject made a saccade which brought his gaze close to the remembered target. The parkinsonian subject did make anticipatory saccades, but their amplitudes were much smaller. The targeting movements were sometimes staircase-like.

The selectivity of saccadic deficits is also evident in Fig. 6 which shows the velocity-amplitude relationships of these two types of saccades. Data points are much more scattered for anticipatory saccades in the parkinsonian patient (Fig. 6, bottom) with many saccades with small amplitudes and low peak velocities. The small saccades, however, appear to follow the inherent correlation between saccadic velocity and

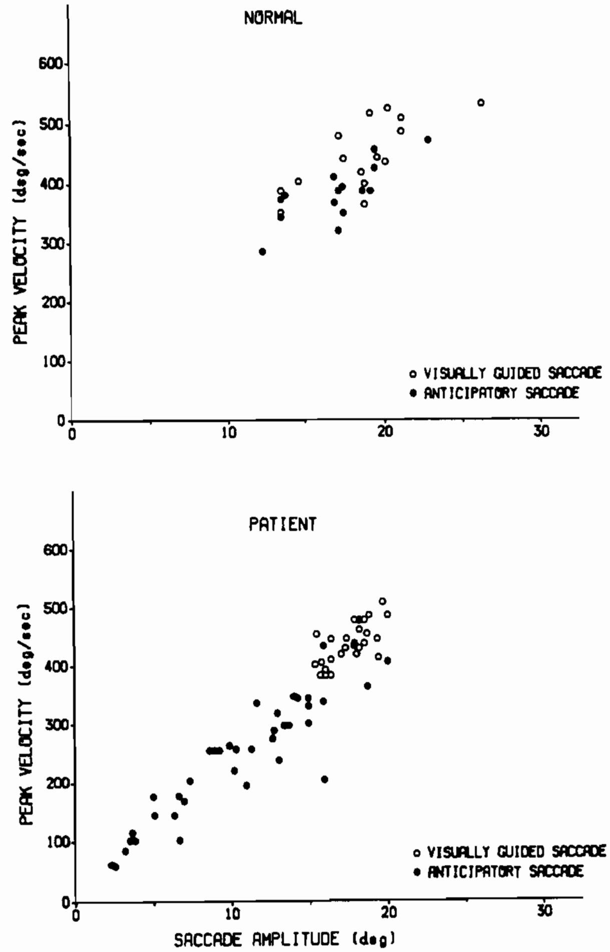

Fig. 6. Saccadic peak velocity-amplitude relationships in the normal subject (top) and in the parkinsonian patient (bottom), for visually guided saccades (open circles) and anticipatory saccades (filled circles).

amplitude.[4] Figure 6 shows another aspect of parkinsonian symptoms: the deficit is not consistent across trials; the patient could make anticipatory saccades that appeared to be normal.

Mean values of saccade parameters are compared between the groups of parkinsonian and control subjects (Table 1). There is no statistical difference in saccade latency for visually guided saccades and anticipatory saccades. In anticipatory saccades, both amplitude and peak velocity are significantly smaller in the parkinsonian subjects than the control subjects; a similar tendency is seen in amplitudes of visually guided saccades, but to a lesser degree.

In summary, parkinsonian patients show deficits in saccadic eye movements especially when saccades are initiated without external sensory guidance, *i.e.*, when they are dependent on internally stored information. This result might be related to a clinical phenomenon characteristic of Parkinson's disease; that is, they need explicit sensory guidance to initiate a movement, notably walking.[10,16,31]

A selective nature of neural activity in the basal ganglia might underlie the context-dependent behavioral deficit.

Table 1. Parameters of visually guided saccades and anticipatory saccades in parkinsonian and control subjects.

Visually guided saccade

	Number	Amplitude (deg)	Peak velocity (deg/s)	Latency (ms)
Parkinsonian	7	17.2±1.4	401±73	217±37
Control	8	18.8±1.2	409±43	234±32
		$p<0.05$	n.s.	n.s.

Anticipatory saccade

	Number	Amplitude (deg)	Peak velocity (deg/s)	Latency (ms)
Parkinsonian	11	10.1±3.3	250±59	359±120
Control	8	15.3±2.2	324±49	389±67
		$p<0.01$	$p<0.02$	n.s.

The mean value of each parameter was calculated for each subject, which was then averaged across the group of parkinsonian and control subjects (mean±s.d.). Below the parameters are shown statistical significance levels for the differences between the two groups (Student's t-test).

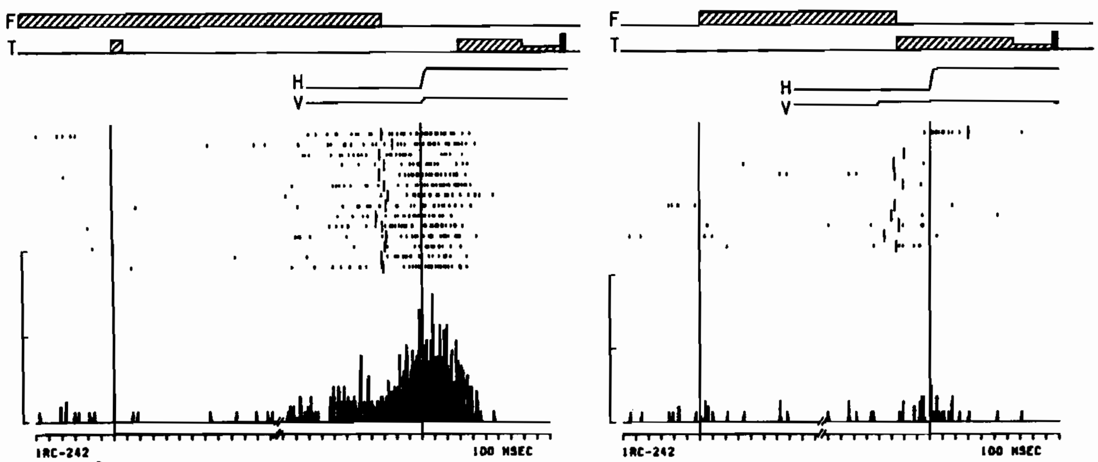

Fig. 7. Neuronal activity in the monkey caudate nucleus selective for memory-guided saccades. In delayed saccade task (left), the monkey made a saccade to the remembered location where the target was flashed 3-4 s before; the caudate neuron showed spike discharges starting before the saccade. In saccade task (right), the same neuron showed no activity although the saccades were similar. The spike activity is shown by a raster display and a summed histogram for each task, both aligned on the onsets of saccades. Each line of the raster display indicates a single trial; each dot a single action potential.

SELECTIVITY IN BASAL GANGLIA NEURAL ACTIVITY

In the substantia nigra as well as in the caudate of the monkey are found cells that change their activity before voluntary saccades.[18,19,24] The term voluntary is used here because such basal ganglia neurons were rarely related to less voluntary, spontaneous saccades. The selectivity is even higher; many of the caudate or nigra neurons are related to memory-guided saccades but not before visually guided saccades (memory-contingent presaccadic response.[18,24] Figure 7 shows an example. This caudate neuron showed little activity in the ordinary saccade task regardless of where the target came on (Fig. 7, right). The same cell showed a vigorous activity before memory-guided saccades (Fig. 7, left). This task is similar to the saccade with gap task used for humans, one difference being that the target position is randomized between trials; instead, it is cued for each trial a couple of seconds before the saccade.

There are cells in the substantia nigra and caudate that are selectively related to visually guided saccades as opposed to memory-guided saccades. Nonetheless, cells related to memory-guided saccades are found more frequently. None of them were related to spontaneous saccades.

The memory-oriented nature of the caudate nucleus is further emphasized by the presence of other types of cells. A number of caudate cells respond to visual stimuli used as the target for saccades.[25] Much like the presaccadic activity, these visual responses are highly dependent on the behavioral contexts in which the visual stimulus was presented. Some respond to a spot of light only when it is used as the cue for a delayed saccade; the visual response is present only when the monkey attempts to remember the location of the stimulus (memory-contingent visual response). Another class of caudate neurons is the one that appears to be related to expectation of target or reward.[26] In this class spike activity precedes the predicted occurrence of a light target or reward. For example, if the target goes off but the monkey knows it will come on somewhere on the screen, those caudate cells keep discharging while the monkey is waiting and searching for the target.

Such basal ganglia activities as a whole might represent different aspects of information processing that allow the conversion between sensory, memory, and motor signals. The memory-contingent visual response might act as a channel through which visual information is converted to memory information. The memory-contingent presaccadic response might act as a channel through which memory information is converted to oculomotor information.

This does not necessarily indicate, however, that such cross-modal signal conversions are carried out within the basal ganglia. The basal ganglia are tightly connected with the cerebral cortices through the thalamus, presumably making up loop circuitries; the signal conversions could take place anywhere along these loops.[2]

Those neurons with memory-related signals are considered to be non-dopaminergic, mostly likely GABAergic. Pathological changes in Parkinson's disease are selective for dopaminergic neurons in the substantia nigra. Nonetheless, there is a significant correlation between parkinsonian behavioral deficits and basal ganglia neural activity. This suggests that dopamine deficiency in parkinsonism might somehow disable these memory-related basal ganglia neurons.

POSSIBLE MECHANISM OF DOPAMINERGIC ACTION IN THE BASAL GANGLIA

As mentioned above, dopaminergic neurons in the substantia nigra have no efferents outside the basal ganglia. Their major target is the striatum (caudate and putamen). Dysfunction of the nigro-striatal dopaminergic connection would lead to the context-specific saccadic deficit. A simple scheme derived from these experiments is as follows. Substantia nigra pars compacta dopaminergic cells would have facilitatory action on caudate output cells. The deprivation of dopaminergic innervation in parkinsonism would remove the facilitatory effect and the caudate cells become more difficult to be driven by excitatory inputs from the cerebral cortices. This would reduce the possibility of the caudate-nigral inhibition. Superior colliculus cells would remain inhibited so that saccades to the contralateral side would be more unlikely to be evoked.

This interpretation is supported by the following observations. Intracollicular injection of muscimol (GABA agonist) mimics the sustained inhibition of the superior colliculus[21]: saccades to the contralateral side are suppressed with longer latencies and smaller amplitudes, much like parkinsonian saccades. Background neural activity in the output areas of the basal ganglia (globus pallidus) increases in MPTP-induced parkinsonian monkeys.[3,15]

However, the actual mechanism of dopaminergic effects is still open to question. First, dopamine could affect the outputs of the basal ganglia through different pathways other than the presumed excitatory nigro-striatal connections: (1) through dendro-dendritic connections inside the substantia nigra from the dopaminergic pars compacta to the GABAergic pars reticulata,[13] or (2) through a polysynaptic pathway from the striatum to the substantia nigra pars reticulata which is mediated by the external segment of the globus pallidus and the subthalamic nucleus.[29] The latter possibility is noteworthy: the polysynaptic pathway is mediated by a group of enkephalin-containing striatal neurons that is different from the substance P-containing one projecting directly to the output areas of the basal ganglia. Furthermore, it is suggested that these two types of striatal neurons react to dopamine in opposite ways including intracellular chemical processes.[12]

In short, dopaminergic action in the basal ganglia is multiple and possibly antagonistic, reflecting the complexity of neural networks and associated neurotransmitters within the basal ganglia. The complexity is further enhanced by the predominantly inhibitory nature of basal ganglia signal flows: a local synaptic action would be reversed at any site in the basal ganglia that is one synapse away. Further studies are required to solve the complexity first by revealing synaptic connections in detail, creating a simulated network model, and finally predicting normal as well as pathological behaviors based on the model.

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