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Role of the Basal Ganglia in the Control of Purposive Saccadic Eye Movements

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Hikosaka, Okihide, Yoriko Takikawa, and Reiko Kawagoe. Role of the Basal Ganglia in the Control of Purposive Saccadic Eye Movements. *Physiol Rev* 80: 953–978, 2000.—In addition to their well-known role in skeletal movements, the basal ganglia control saccadic eye movements (saccades) by means of their connection to the superior colliculus (SC). The SC receives convergent inputs from cerebral cortical areas and the basal ganglia. To make a saccade to an object purposefully, appropriate signals must be selected out of the cortical inputs, in which the basal ganglia play a crucial role. This is done by the sustained inhibitory input from the substantia nigra pars reticulata (SNr) to the SC. This inhibition can be removed by another inhibition from the caudate nucleus (CD) to the SNr, which results in a disinhibition of the SC. The basal ganglia have another mechanism, involving the external segment of the globus pallidus and the subthalamic nucleus, with which the SNr-SC inhibition can further be enhanced. The sensorimotor signals carried by the basal ganglia neurons are strongly modulated depending on the behavioral context, which reflects working memory, expectation, and attention. Expectation of reward is a critical determinant in that the saccade that has been rewarded is facilitated subsequently. The interaction between cortical and dopaminergic inputs to CD neurons may underlie the behavioral adaptation toward purposeful saccades.

I. INTRODUCTION

> Animals lacking the striatum always display a certain fatuous, expressionless facies from which the eyes stare vacantly and with morbid intentness.
>
> Mettler (212)

Patients with basal ganglia disorders suffer from excessive or retarded movements of the trunk, arms, or legs. Such movement deficits are so disabling that deficits in eye movements, if present, may remain unnoticed during clinical tests. Notably, however, one of the diagnostic signs of Parkinson's disease is the expressionless face, often called "parkinsonian mask" (283), which is due partly to the paucity of spontaneous gaze shifts (saccadic eye movements). Parkinsonian patients may make a saccade, on command, to a visual object with little difficulty, yet their voluntary saccades are rare. These facts suggest that the basal ganglia are involved in the control of saccades, but in an intricate manner. Recent studies on trained animals and humans have suggested that the basal ganglia are related to both initiation and suppression of saccades in complex behavioral contexts, which we summarize in this review.

Clinical studies have indicated that smooth pursuit is also impaired in basal ganglia disorders (75, 326). However, because to our knowledge there has been no study that suggests how the basal ganglia contribute to the control of smooth pursuit, we do not make further comments on this issue.

This article may be divided roughly into three parts. First, we introduce you to the present topic by speculating how the basal ganglia evolved to control spatial orienting (sects. II and III). In the second part, we summarize the experimental evidence for the specific relation of the basal ganglia to saccadic eye movement (sects. IV–VI). The second part will, hopefully, be continued into the third part smoothly, where we describe the results of recent studies on cognitive or motivational aspects of motor control (sects. VII and VIII). The issues dealt with in the third part are not limited to the control of eye movement but are of more global importance for brain function in general.

II. CONCEPT OF THE BASAL GANGLIA

The basal ganglia are considered to be necessary for voluntary control of body movements (53). This idea is derived mainly from the clinical observations that lesions in the basal ganglia lead to movement disorders ranging from the inability to initiate a movement to the inability to suppress involuntary movements. Anatomically, the basal ganglia are the aggregate of nerve cell nuclei located at the base of the cerebrum (39). Although there are different opinions on the definition (106), the basal ganglia, as a functional entity, are composed of the caudate nucleus (CD) and putamen (PUT) (collectively called striatum), globus pallidus, substantia nigra, and subthalamic nucleus (STN).[1] The globus pallidus is further divided into the external segment (GPe) and the internal segment (GPi); the substantia nigra is divided into the pars reticulata (SNr) and pars compacta (SNc). The CD and PUT are the two input stations, receiving signals from a wide area in the cerebral cortex and part of the thalamus, whereas the GPi and SNr are the two major output stations, sending signals to part of the thalamus and brain stem motor areas. The STN, GPe, and SNc are mostly connected with other basal ganglia nuclei and may act as modulators. The STN, in addition, receives direct inputs from the cerebral cortex. Closely related to, or included in, the basal ganglia is the ventral striatum including the nucleus accumbens, which is a ventral extension of the CD-PUT (199). Although the basal ganglia have limited routes for their inputs and outputs, individual nuclei are often connected with each other, and therefore, it is difficult to understand, solely based on the known anatomical connections, how the information is processed in the basal ganglia.

We propose that the basal ganglia have two ways to control movements using two kinds of output: *1*) control over the thalamocortical networks and *2*) control over brain stem motor networks (Fig. 1). Many studies on trained animals have been done using hand or arm movements in which the thalamocortical networks are mainly involved. However, there are different kinds of movements, such as eye-head orienting, locomotion, mastication, and vocalization. They are different from hand/arm movements in that their movement patterns are determined by specific neural networks in the brain stem or spinal cord. For hand-finger-arm movements, the pattern of movement is acquired largely with practice; for the brain stem-controlled movements, the pattern of movement is largely determined genetically.[2]

The outputs of the basal ganglia are directed to some of the motor networks in the brain stem (106, 233). They include the projection to the superior colliculus (SC) (for

[1] The caudate and putamen arise from a common embryonic structure and have common cell types and, therefore, are often called the striatum collectively (106). In this article, we frequently use the term *striatum*, instead of the caudate, when we (or the authors to which we refer) want to describe a feature common to the caudate and putamen, such as the microstructure of the projection neurons.

[2] This does not necessarily indicate that the brain stem-controlled movements are unrelated to learning. A number of studies have demonstrated motor or sensorimotor learning of saccades, although the learning is usually limited to adaptation of saccade parameters (57). More importantly, skill learning involves spatiotemporal reorganization of a variety of movements, including saccades, toward efficient and quick performance (216), whereas the properties of individual saccades may be unchanged.

eye-head orienting which will be described later), the pedunculopontine nucleus (106, 237) [possibly for locomotion (87, 109, 221)], and the periaqueductal gray [possibly for vocalization (160) and autonomic responses (17, 146)]. Given the fact that the basal ganglia (or their homologs) are present also in lower vertebrates (including reptiles and amphibians), which lack the robust thalamocortical networks, the brain stem projection is probably the primary way in which the basal ganglia operate (200). Most common among the vertebrate species is the connection to the SC (or tectum) (208). According to Marín et al. (200), "in non-mammalian tetrapods, the basal ganglia-tectal pathways constitute the main anatomical basis for the involvement of the basal ganglia in motor control." This consideration suggests that a key feature of the basal ganglia function can be revealed by studying the basal ganglia-SC connection.

III. GENERAL SCHEME OF SACCADIC EYE MOVEMENT

Saccadic eye movement is controlled by many brain areas (Fig. 2). Drive for saccade originates largely from different cortical areas [frontal eye field (FEF), lateral intraperitoneal area (LIP), and supplementary eye field (SEF)], more or less independently (see Ref. 333 for review). The basal ganglia work in a completely different way. They do not provide a drive, but select one that is appropriate, by exerting powerful tonic inhibition and removing it. This feature seems common to other kinds of movements and probably nonmotor functions that the basal ganglia control.

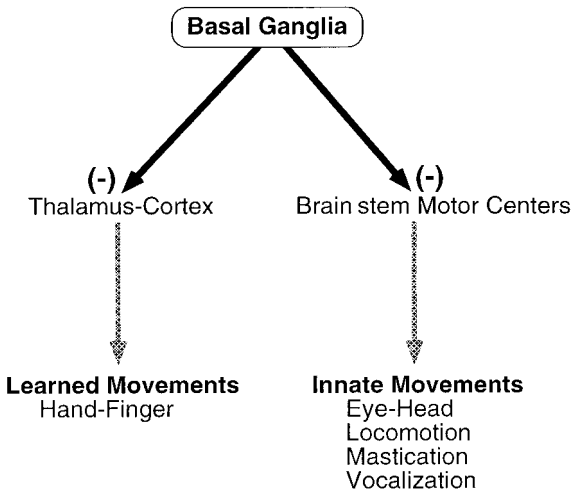

FIG. 1. Two functions of the basal ganglia. The basal ganglia exert inhibitory effects on *1*) brain stem motor centers to control innate movements and *2*) thalamocortical circuits to control learned movements.

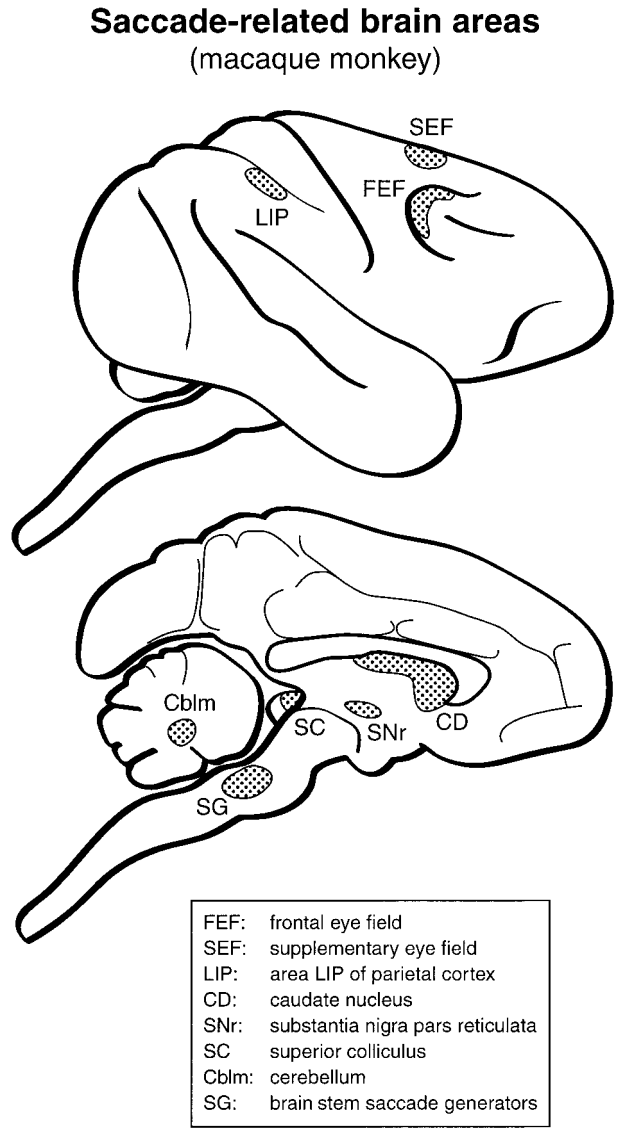

FIG. 2. Major saccade-related areas in the macaque monkey's brain viewed from the lateral (*top*) and mesial (*bottom*) sides.

A. Hierarchy of Oculomotor Mechanisms

To understand the role of the basal ganglia in saccades, we need to know how the SC-brain stem mechanism works for generating saccades. As the result of many studies over 20 years, the detailed networks for saccade control and their functional properties have been elucidated. Figure 3 shows a conceptual scheme to illustrate how oculomotor mechanisms might have evolved. According to Robinson (261), vestibulo-ocular reflex (VOR) is the most primitive form of eye movement that acts to stabilize the image on the retina by compensating for head movements and therefore is crucial for visual perception. However, VOR is induced by head acceleration and therefore is least effective when the head moves at a constant

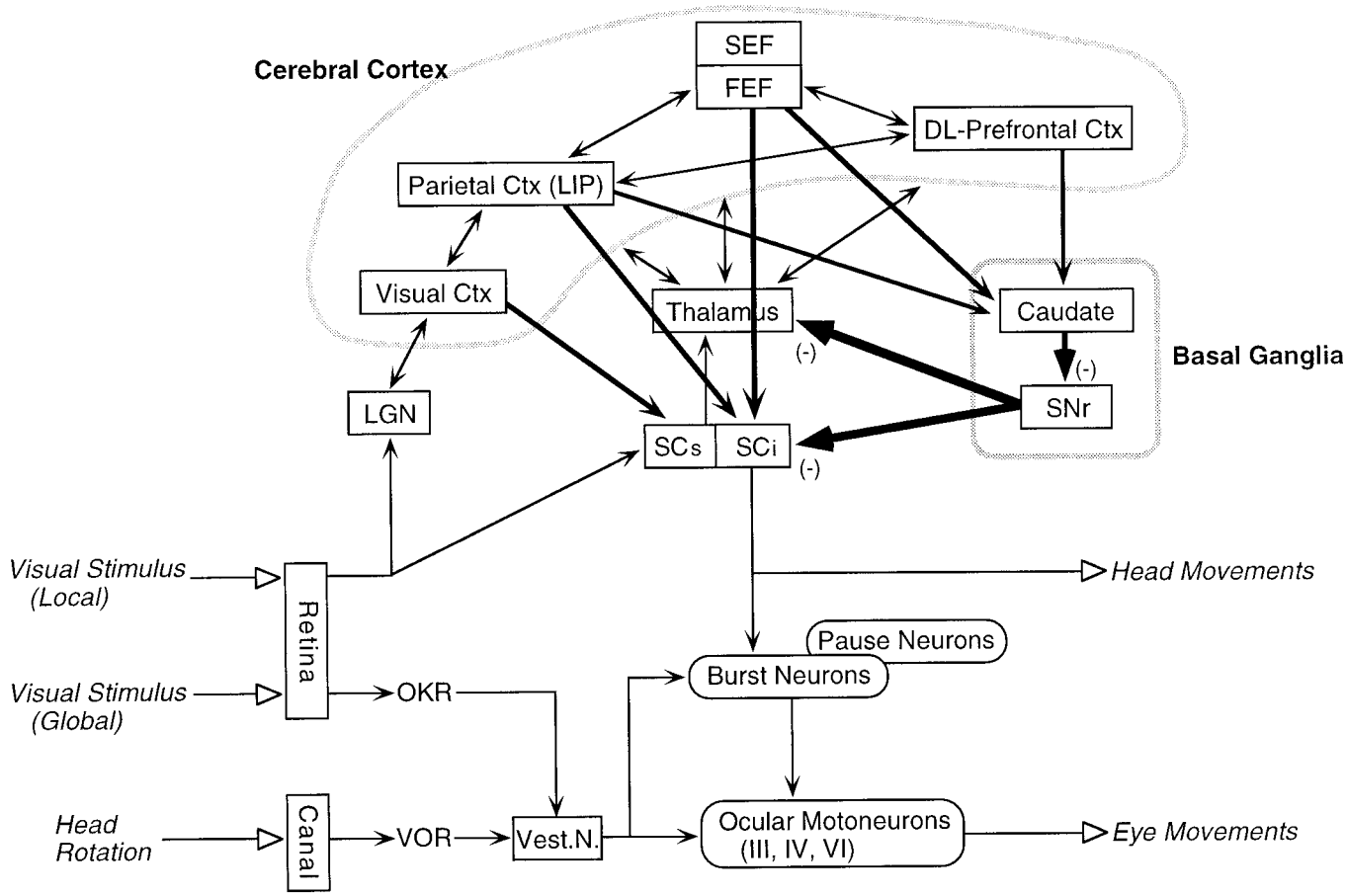

FIG. 3. Hierarchical organization of saccade mechanisms. The neural machinery for saccade is provided by the mechanism of vestibulo-ocular reflex (VOR) and optokinetic response (OKR) as a quick phase generator that includes burst neurons and pause neurons. The connection from the superior colliculus (SC) to the quick phase generator allows the animal to orient its eyes quickly to an object using local visual information, which is generally referred to as "saccadic eye movement." Efferent connections to the SC from the cerebral cortical areas and the basal ganglia (i.e., SNr) enable the selective control of saccades, especially by suppressing unwanted saccades. SCs and SCi, the superficial and intermediate layers of the SC, respectively; Vest. N., vestibular nuclei. See Figure 2 for additional definitions.

speed. Optokinetic response (OKR) would compensate for the deficient performance of VOR in that the eyes follow the motion of the whole visual field. Both VOR and OKR are commonly present in different vertebrate species, such as frogs and turtles (59, 58). One problem here is that both VOR and OKR need to be reset intermittently; otherwise, the eyes may end up in an eccentric position. Even frogs show quick phases, although infrequently (60). However, visual perception is virtually lost during the resetting movement; therefore, the reset must be done very quickly (the so-called quick phases). The quick phases are produced by a specialized set of neurons in the brain stem reticular formation that include burst neurons and pause neurons (121). At some point in evolution, the SC gained synaptic connections to the generators of quick phases. This is probably the origin of saccadic eye movement, as described in the following hypothetical scheme of evolution.

The tectum (the homolog of the SC) is a prominent brain structure in lower vertebrates (e.g., amphibians and reptiles). It is a key station of "orienting response" in which the animal orients its head or body quickly to a newly appearing object (67, 297, 332). The orienting response is essential for the survival of most animals including invertebrates (144). Most vertebrates have multiple sensory organs, and consequently, the orienting response must be determined by taking into account multiple kinds of sensory information (visual, tactile, and auditory). All of these sensory signals converge onto the SC in a topographical manner, forming a spatial map (319). The output of the SC is then led to the motor networks in the spinal cord for head and trunk movements to produce the orienting response (226, 264). In mammals, the SC output is now connected to the brain stem networks for quick phases (46, 102). The eye movement thus produced would be an orienting response to an object (rather than just a reset) and is called a saccadic eye movement. Saccadic eye movement turned out to be

more efficient than head movement because it is faster (19). This is particularly true for primates, since they have larger brains and consequently heavier heads. Clearly, the orienting response is no longer just a reflex for most vertebrates; it requires integration of multimodal sensory information. This in turn necessitates the presence of a mechanism that controls the integration process, with which an appropriate signal is selected. The basal ganglia may have evolved as playing such a role of selection with its connection to the SC (257).

An important event in evolution is that the brain became more complex as spatial information is represented in multiple forms (5, 108). In addition to the SC, there are now many spatial maps in cerebral cortical areas: some of them are specific to sensory modalities (e.g., visual, somatosensory, auditory) or submodalities (e.g., visual motion, shape etc.), whereas others are supramodal or cross-modal. However, the animal can orient to only one location at a time. This means that signals derived from the multiple spatial maps must be integrated to decide to which location the animal orients. Such an integrating function could be accomplished by the convergent connections from many cortical areas to the SC (Fig. 3) (298, 332).

Visual search may be another function that emerged with the establishment of the cortico-SC connections. The detailed analysis of visual features can only be done for inputs to the fovea. This necessitated continual saccades to capture points of interest in visual field with the fovea; the process is called "visual search" (222, 318). Inherent in visual search is the need for selection, attention, or judgment, since there are usually many points of interest, and yet a saccade must be directed to one of them at a time. Possible neural correlates for the selection of saccade or attention have been found in the FEF (97, 188, 270, 335) and the LIP (47, 100, 295). It has been shown that visual and saccadic neurons in the FEF (282, 296) and LIP (241) project to the SC.

However, such an increased demand for the convergent connections to the SC would lead to an information overload if not controlled appropriately. The inhibitory basal ganglia-SC connection would play a crucial role in preventing a chaotic state. Before describing the experimental evidence for basal ganglia-SC connection, let us summarize the more detailed function of the SC.

B. Superior Colliculus: A Key Station for Saccade Control

The SC is unique in that it has both strong sensory functions and strong motor functions (332). Visual inputs from the retina are directly mapped on its superficial layer as a two-dimensional retinotopic representation (262, 271). The visual inputs from one hemifield are mapped onto the surface of the contralateral SC such that the central field is represented at the rostral part while the peripheral field is at the caudal part, and the upper field is at the medial part while the lower field is at the lateral part.

The intermediate layer beneath the visual superficial layer has a motor function (297). Robinson (260) demonstrated that electrical stimulation there evokes a saccade whose direction and amplitude depends on the stimulus location, not its intensity or duration. The vector of the stimulus-induced saccades matches the retinotopic map in the superficial layer such that small saccades are evoked from the rostral part, whereas large saccades from the caudal part and upward saccades are evoked from the medial part while downward saccades from the lateral part.

In addition to visual information, auditory and somatosensory information can drive SC neurons (176, 302). The body surface, including hair or vibrissae, is represented in the deep layer such that the somatotopic representation is roughly aligned on the retinotopic representation. A similar spatial alignment is also present for auditory information. In the cat, for example, neurons in a same region of the SC respond to light and sound that are elicited from the same location in space (213).

Suppose an object or animal appears in the right-upper part of the visual field. A visual signal elicited from it will activate visual neurons in the superficial layer, but only in its medial part. This will be followed by activation of neurons in the intermediate layer just below the activated visual neurons (155, 219). These neurons show a burst of spikes that is followed by a saccadic eye movement that is directed exactly to the location of the object or animal. In fact, the burst of spikes is the command for the saccade; the signal is sent to the saccade generators in the reticular formation to generate the orienting saccade (46, 102, 103, 224).

IV. MECHANISMS OF THE BASAL GANGLIA: DISINHIBITION

Studies on eye movements have largely been focused on the relation between the CD, SNr, and SC (133, 143). The most important conclusion was that the CD inhibits the SNr, which in turn inhibits the SC. With these serial inhibitory connections, the basal ganglia control the wide variety of inputs to the SC. The oculomotor function of the basal ganglia was first suggested by the findings that the neurons in the SNr, one of the output stations of the basal ganglia, project to the intermediate layer of the SC (68, 104, 148, 157, 259, 317). The SNr-SC connection was further confirmed anatomically (20, 21, 78, 206, 207, 256, 322, 329) and physiologically (6, 43, 44, 162).

A. Visuo-oculomotor Activities in the Substantia Nigra Pars Reticulata

The first evidence for the oculomotor role of the basal ganglia originates from the discovery of saccade-related neurons in the SNr in monkeys (137–139) and cats (159). A striking finding then was that almost all SNr neurons were spontaneously very active, discharging at 50–100 Hz. Such high spontaneous spike activity turned out to be a critical determinant of basal ganglia functions (142).

Neurons in the SNr, especially those in its laterodorsal part, showed a saccadic or visual response by decreasing their spike activity. The latency of visual responses was ~110–120 ms after stimulus onset, while saccadic activities preceded saccade onset by 0–240 ms. The pause of activity was present only when the monkey was engaged in saccade tasks; no change in activity was observed when the monkey was making saccades spontaneously. Most of the visuo-oculomotor neurons in the SNr had restricted response fields (visual receptive fields or saccadic movement fields) that were usually centered in the contralateral hemifield (137) A smaller number of neurons showed visual on- and/or off-responses only when the fixation spot turned on or off (138).

A group of SNr neurons showed visual or saccadic responses only when the saccade was made to a remembered location of a visual target (139). Subsequent studies have suggested that the neural mechanisms for memory-guided saccades are distributed in wider cortical and subcortical areas (84, 96). Nonetheless, the basal ganglia are unique in that they contain neurons specifically related to memory-guided saccades (133).

B. Substantia Nigra Pars Reticulata-Superior Colliculus Projection (and Its Experimental Manipulation)

Hikosaka and Wurtz (140) demonstrated, by using antidromic activation, that SNr project their axons to the SC. They use two electrodes, one in the SNr for recording and the other in the SC for stimulation. Many SNr neurons, particularly those with visuo-oculomotor properties, were activated antidromically from the SC. The threshold and latency of antidromic responses of a single SNr neuron changed when the stimulating electrode was moved inside the SC. The depth-threshold and depth-latency patterns thus obtained suggested that the axon of a single SNr neuron entered the SC from its deep layer and arborized profusely in the intermediate layer where saccadic burst neurons are located, consistent with anatomical findings (157, 206).

What is the nature of the SNr-SC connection? The comparison of the visuo-oculomotor activities in the SNr and the SC indicates a mirror image-like relationship; SNr neurons pause while SC neurons burst. Furthermore, the response field of a SNr neuron roughly corresponded to those of SC neurons where the axon of the SNr neuron arborized (140). These results suggested that SNr neurons have inhibitory connections with SC neurons, consistent with anatomical (317) and physiological (6, 43, 162) findings. SNr neurons exert tonic inhibition on presaccadic neurons in the SC but remove the inhibition occasionally to allow the burst of spikes and consequently a saccade to the contralateral side.

The next question was what causes the cessation of SNr neural activity and consequently the removal of the tonic inhibition.

C. Caudate Nucleus as an Input Station in the Basal Ganglia

The striatum, including the CD and the PUT, is a major input station of the basal ganglia (39, 106). The CD is an elongated structure along the lateral ventricle, which often is differentiated into the head, body, and tail (with no obvious demarcations). While the PUT receives inputs predominantly from the somatomotor areas of the cerebral cortex and related thalamic nuclei (74, 191, 307), the CD receives inputs from the large portion of the association cortices and the associational part of the thalamus in a more or less topographical manner (284, 336). A majority of neurons in the striatum are medium-sized spiny neurons that are GABAergic (70, 72, 76, 180) and project their axons out of the striatum (180, 242, 293). A smaller portion of CD neurons is interneurons, which are cholinergic or GABAergic (61, 166). However, the identification of cell types has been done only in slice preparations or in the anesthetized animals. In the alert animals, two types of neurons have been recognized, which appear to correspond to GABAergic projection neurons and cholinergic interneurons (3, 133, 171).

In contrast to the output neurons of the basal ganglia in the SNr or GPi, which show high spontaneous activities, projection neurons in the striatum are usually very quiet and are difficult to detect their presence by extracellular recordings (53, 133). They become active only when the animal performs an appropriate task. These features are thought to be related to unique membrane properties of these neurons; the membrane potential is set either at a hyperpolarized level (down state) or at a depolarized level (up state) (35, 181, 330).

Only a small portion of neurons in the striatum are interneurons. Most prominent among them is a group of neurons that are tonically active. It has been suggested that the tonically active neurons (TAN) are cholinergic interneurons that are large aspiny neurons and comprise <2% of all striatal neurons (251). The TAN respond to

visual or auditory stimuli, but only when they signify future reward (7). It is unknown whether TAN contribute to the control of saccadic eye movements.

Another group of interneurons, which are GABAergic and contain parvalbumin, have recently been characterized morphologically and electrophysiologically (177). They are medium-sized aspiny neurons, slightly larger than projection neurons, and comprise ~3–5% of all striatal neurons. However, their discharge pattern in behaving animals has not been reported.

D. Visuo-oculomotor Activities in the Caudate Nucleus

Unlike the PUT where neurons could be activated in simple movement tasks (3, 172), complex behavioral tasks are usually necessary to activate CD neurons (170, 196, 236, 263, 278). Saccade tasks are also effective in driving CD neurons, but the neurons' relation to saccades can be very complex.

The CD neurons showing visual or saccadic activities were thought to be projection neurons, since their spontaneous discharge rates were very low (usually <1 Hz). They are clustered in the region of the CD where the head changes into the body, mostly posterior to the anterior commissure (133, 134). The visuo-oculomotor region largely includes the region that receives inputs from the FEF (245, 299) and the SEF (288) and partly includes the region that receives inputs from the dorsolateral prefrontal cortex (284, 336). Intermingled with such visual-saccadic neurons were found more complex neurons, such as those related to expectation of task-specific events (135). The complex properties of CD neurons will also be described in section VII.

Because projection neurons in the CD show very low spontaneous activity, the visual or saccadic activities always appear as an increase in discharge rate (133). Like SNr neurons, CD neurons have response fields (visual receptive fields or saccadic movement fields) that are usually centered in the contralateral field. These activities are frequently dependent on the behavioral context in that they tend to be enhanced when the stimulus location must be remembered or attended (134), or when the saccade must be made based on working memory (133). These properties are similar to those of SNr neurons, further suggesting that visuo-oculomotor signals are transmitted from the CD to the SNr.

E. Caudate Nucleus-Substantia Nigra Pars Reticulata Projection

The comparison of visuo-oculomotor activities between the CD and the SNr revealed a mirror image-like relationship; before a contralateral saccade, CD neurons increased while SNr neurons decreased their spike activity. This suggested that the pause of SNr cell activity was caused by the phasic activity of CD neurons. In fact, when the visuo-oculomotor region of the CD was stimulated, the spike activity of SNr neurons, especially those with visuo-oculomotor activities, tended to be suppressed (132), confirming previous studies on alert monkeys (69b). Although the effect was clear with a single pulse stimulation of <100 μA, the latency was quite long (9–33 ms; mean, 17 ms). The effect was nonetheless considered to be monosynaptic, since its latency was comparable to the latency of monosynaptic inhibitory postsynaptic potentials (15–20 ms) induced in SNr neurons by stimulation of the CD (337). SNr neurons that were related to memory-guided saccades, compared with those related to visually guided saccades, were more likely to be affected by CD stimulation (132).

Train stimulation of the CD induces eye-head orienting toward the contralateral side (77, 185, 193, 238). These results are consistent with the hypothesis that the effect of CD stimulation is mediated by the serial connection from the CD through the SNr to the SC. The hypothesis is supported by anatomical (328) and physiological (45) experiments, although the effect could be attributable to the antidromic activation of cortical neurons, especially in the FEF. Interestingly, however, a significant proportion of SNr neurons showed excitation (in addition to inhibition or in isolation) by CD stimulation with similar latencies (132). The excitation is possibly mediated by the indirect pathway through the GPe and the STN. We will come back to this problem in section V.

F. Disinhibition: A Key Feature of Basal Ganglia Function

These experiments led to the conclusion that disinhibition is a key mechanism with which the basal ganglia control saccadic eye movements (122). Although the SNr normally exerts tonic inhibitory influences over the SC, phasic inhibitory signals from the CD interrupt the SNr-induced inhibition, thus yielding a powerful facilitatory effect (Fig. 4). In fact, this scheme seems a general principle of basal ganglia functions (54, 247); as a major mechanism for skeletomotor control, the PUT (instead of the CD) acts to remove the tonic inhibition of the GPi on the thalamus.

Why should the basal ganglia use disinhibition instead of simple excitation? Probably crucial to this question is the fact that the SC receives excitatory inputs from many brain areas. Given this situation, disinhibition would be superior to simple excitation as a control mechanism. 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 to make a saccade in

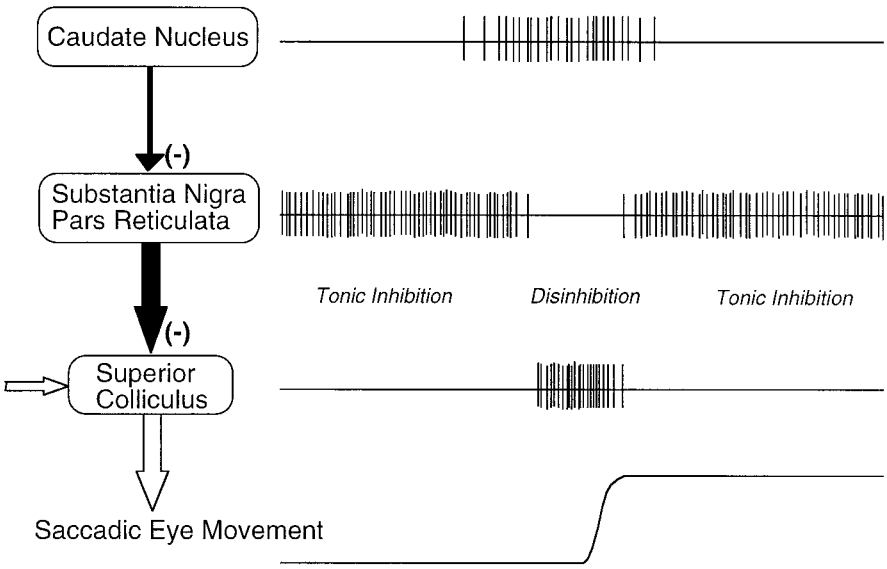

FIG. 4. Disinhibition as a key mechanism for the basal ganglia control of saccade. With their high background activity, GABAergic SNr neurons inhibit SC output neurons tonically, thus preventing unwanted saccades. Phasic activity of GABAergic output neurons in the CD (which are otherwise nearly silent) interrupts the tonic SNr-SC inhibition, thus allowing a saccade to occur.

a different context. Therefore, the primary function of the basal ganglia would be to prevent the convergent excitatory signals from triggering motor output of the SC; the gate for motor outputs is thus kept closed. The second function of the basal ganglia is to open the gate by removing the tonic inhibition.

G. Reversible Blockade of Substantia Nigra Pars Reticulata

If this mechanism is really important, its loss should lead to serious behavioral disorders. However, lesion experiments were apparently very difficult because the SNr is relatively small and surrounded by important motor structures such as the cerebral peduncle. An alternative method was drug-induced reversible inactivation, specifically injection of muscimol (a GABA agonist) (141). The results were striking, and this method is now used widely for behavioral experiments.

Muscimol injected in the SNr would bind to GABA receptors on SNr neurons and stop their otherwise rapid firing. The effect was to temporarily eliminate the tonic inhibitory influences on the SC. After an injection of muscimol in the SNr unilaterally, the monkey became unable to keep fixating a center spot of light and made saccades repeatedly to the side contralateral to the injection, especially when a visual stimulus was presented (142). Similar results were obtained in cats (28) and rats (267). In addition to saccades, rats showed involuntary head and trunk movements toward the contralateral side (267). The result indicates that the SNr-induced tonic inhibition is indeed very important in preventing unnecessary saccades. A similar effect was induced when bicuculline (a GABA antagonist) was injected in the SC (141). These results were complementary in suggesting that the SNr-induced inhibition was blocked at the level of neurons of origin (SNr) or at the level of synaptic terminals (SC).

Involuntary movement is a characteristic feature of basal ganglia diseases. Involuntary eye movements observed after muscimol injection in the SNr may be based on the mechanism common to basal ganglia diseases. Although involuntary eye movements are not commonly reported in basal ganglia diseases, any abnormality of eye movements may be overshadowed by robust involuntary body movements. In Tourette's syndrome, for example, the patients often show involuntary eye movements together with various motor tics (see sect. IX).

V. MECHANISMS OF THE BASAL GANGLIA: ENHANCEMENT OF INHIBITION

As indicated before, many kinds of inputs converge onto the SC, and the input from the SNr is only one of them. What is unique about the SNr input is its inhibitory nature. This function would further be supported by the findings of parallel indirect pathways (Fig. 5). For example, stimulation of the CD sometimes excites SNr neurons (132). This could be mediated by one of the indirect pathways; the striatal outputs are mediated by the external segment of the GPe, which is inhibitory (292), and the STN, which is excitatory (113, 230). The inputs to the striatum would lead to an enhancement of the basal ganglia inhibitory outputs, because the indirect pathway contains two inhibitions, as opposed to one inhibition. This is quite opposite to what the direct pathway does.

It is important to note that output neurons are segregated in the striatum for the direct and indirect path-

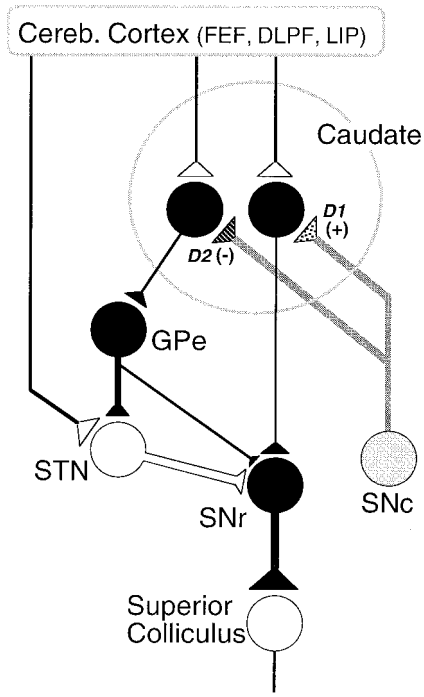

FIG. 5. Two parallel mechanisms in the basal ganglia. In parallel with the CD-SNr-SC serial inhibitions are present pathways mediated by the GPe and/or STN. Inhibitory and excitatory neurons are indicated by solid and open circles, respectively. The effects of the GPe/STN pathways are thought to be opposite to that of the CD-SNr-SC pathway, since they contain two (CD and GPe) or no inhibitions before reaching the SNr. DA neurons in the SNc (and surrounding midbrain regions) connect mainly to striatal output neurons and exert modulatory effects, mostly via D_1 receptors on SNr projecting neurons and via D_2 receptors on GPe-projecting neurons. It is postulated that the corticostriatal input carries spatial information while the DA input carries reward-related information.

ways (69a, 93, 94, 242, 291). Both are GABAergic, but different polypeptides are colocalized: substance P in SNr/GPi-projecting neurons and enkephalin in GPe-projecting neurons (105). Although both types of striatal neurons receive heavy dopaminergic innervation, SNr/GPi-projecting neurons and GPe-projecting neurons have D_1 and D_2 receptors, respectively (91), although the segregation of receptor types is not complete (305). This suggests that the basal ganglia can exert two opposing effects (disinhibition and enhancement of inhibition) depending on which type of striatal neurons is activated.

The mechanism for the enhancement of inhibition includes two additional pathways: *1*) direct connection from the cerebral cortex to the STN (115, 183) and *2*) direct connection from the GPe to the SNr and GPi (293). The actions of these pathways are thought to be an enhancement of inhibition, since the number of inhibitions before entering the SNr is 0 and 2, respectively. However, the direct cortical projection to the STN may be critically different from the pathways through the striatum because it is fast in conveying information (230, 338) and the STN receives less dense dopamine (DA) inputs than the striatum.

An important question here is whether these inhibition-enhancing pathways are used for oculomotor control and, if so, how it is used.

A. Subthalamic Nucleus as a Mechanism for Motor Suppression

The STN is a prominent, though not large, structure overlying the SNr. It is well known that a unilateral lesion of the STN leads to ballistic involuntary movements of body parts on the contralateral side (hemiballism) (50). Unlike most of the other basal ganglia nuclei which use GABA as a neurotransmitter (and therefore inhibitory), the STN is excitatory using glutamate as a neurotransmitter (230). The STN receives inputs from the GPe (287), and frontal cortical areas (41, 115, 231), and sends its outputs to the SNr, SNc, GPi, and GPe (161, 179, 244, 294). These results raise the possibility that the STN is also involved in the oculomotor control.

B. Neural Activity in the Subthalamic Nucleus

Visuo-oculomotor neurons were indeed found in the STN (204). They were located predominantly in the ventral part that receives inputs mainly from the prefrontal association cortex (115), the FEF (152, 300), or the SEF (151). The task-related neural activities were classified into several types: saccadic, visual, fixation, and others. Unlike in the SNr, these responses usually appeared as an increase in spike frequency.

Sustained activity during visual fixation was frequently observed in the STN. Typically, a STN neuron continues to discharge from the onset of the fixation spot until the end of trial, except when a saccade was made to a target. 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 was what the monkey was required to do for completion of task trials.

Visual responses in the STN were phasic and excitatory. Their latencies (70–120 ms) were generally shorter than those of CD visual responses (100–250 ms), suggesting that visual information, at least partly, is sent to the STN directly from the cerebral cortex. 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. This is consistent with the idea that the STN contributes to the maintenance of stable fixation that is prerequisite for performing saccade tasks.

C. Globus Pallidus External Segment as a Mediator for Enhancement of Inhibition

The function of the GPe is less clear compared with other basal ganglia structures. It is connected with almost all nuclei in the basal ganglia but has few connections with brain areas outside the basal ganglia. Inputs to the GPe originate from the striatum (79, 94, 117, 118) and the STN (116), whereas outputs from the GPe are directed to the SNr (243, 293), GPi (174), and STN (40, 178). GPe neurons are considered to be GABAergic (292). The GPe thus plays an important mediator for the so-called indirect pathway: striatum (GABA)-GPe (GABA)-STN (glutamate)-SNr or GPi (GABA). It is possible that visuo-oculomotor information is relayed along this pathway.

D. Neural Activity in the Globus Pallidus External Segment

Visuo-oculomotor neurons were found in the dorsal part of the GPe (163), the region that receives inputs predominantly from the CD (117). Some neurons showed excitatory responses, whereas others were inhibitory. Some were selective for visually guided saccades, whereas others were selective for memory-guided saccades. Spatial selectivity of visual or saccadic activities was generally poor, frequently responding to saccades of any direction or eccentricity. Some GPe neurons showed a sustained increase or decrease of activity while the monkey was fixating, similarly to those in the STN. Some may also combine other responses, such as hand movements. In short, although GPe neurons are related to visual-saccadic behaviors, their activities tended to be nonselective, which is similar to those in the STN but dissimilar to those in the CD or SNr.

E. Focusing and Sequencing of Basal Ganglia Signals

What then is the function of the pathway involving the GPe and/or STN? Given the anatomical data described above, the visuosaccadic activities in GPe neurons are likely to originate in the CD, yet the GPe neurons are less selective than CD neurons (163). The result suggests that there is a large degree of convergence of information for GPe neurons (i.e., divergence for CD neurons) in the CD-GPe connections. This idea may be supported by quantitative anatomical considerations (73, 175, 248). An additional connection from the STN may also contribute to the nonselective feature.

Let us assume that a cortical input activates a population of CD neurons to create a focus of activity that has a spatial gradient decreasing outward (Fig. 6). 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 due to the divergence of information, yielding the nonselectivity of GPe neurons. These signals, when transmitted to the SNr either directly or through the STN, would

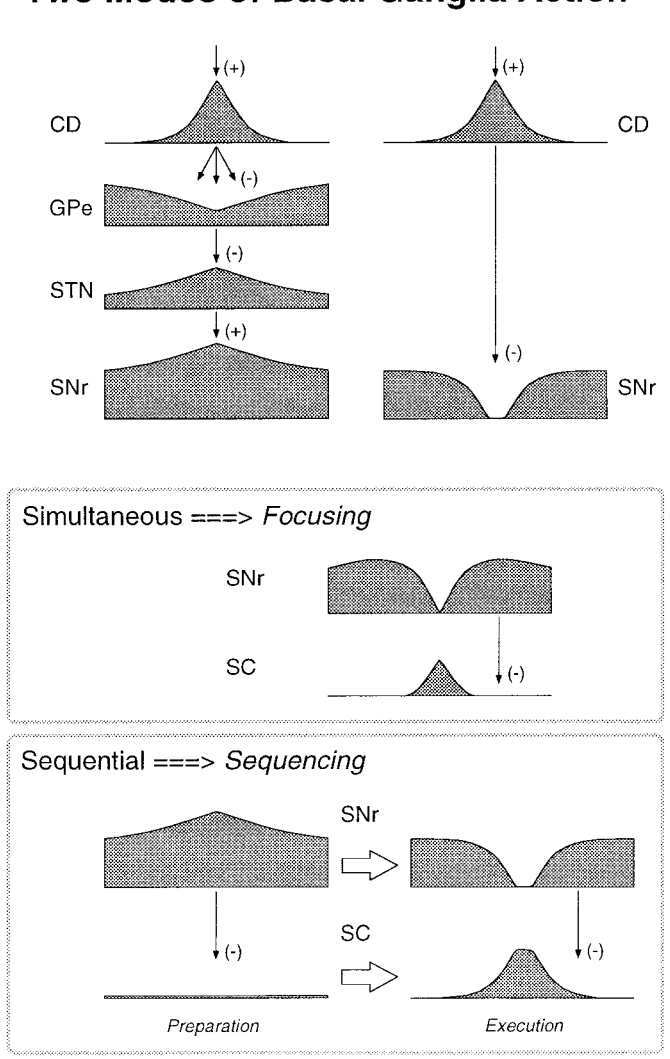

FIG. 6. Two modes of basal ganglia action: focusing and sequencing. The spatial extent of neuronal population activity in each basal ganglia nucleus is schematized along the signal transmission through the indirect pathway (*left*) and the direct pathway (*right*). Through the direct pathway, the CD-SNr connection leads to a spatially selective inhibition of SNr neurons, usually for the contralateral visual field. The indirect pathway through the GPe and/or STN leads to a less selective facilitation of SNr neurons, partly due to the divergent CD-GPe connection. The two opposing effects would interact in SNr neurons either *1*) simultaneously to produce more selective information (due to the interaction between a narrow inhibitory effect by the direct pathway and a wide facilitatory effect by the indirect pathway) or *2*) sequentially to produce switching of behavior from the suppression of movement (when the indirect pathway is dominant) to the initiation of movement (when the direct pathway is dominant).

produce a positive peak (because GPe neurons are inhibitory) that is less steep than the negative peak produced by the direct pathway.

There can be two ways in which these pathways might work: simultaneous mode and sequential mode (Fig. 6). 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 focused. The effect is to enhance the spatial contrast of neural signals. This is similar to the scheme frequently referred to as lateral (or surround) inhibition. In the sequential mode, the effect would be to enhance the temporal contrast. When a movement is in preparation, the indirect pathway would be continuously active so that the target of the basal ganglia (i.e., SC) is continuously inhibited in a nonselective manner. However, once a trigger signal comes in, the direct pathway would start working, now disinhibiting the SC in a selective manner. Both modes of operation seem plausible, since neural activities have been found in the GPe and STN together with the CD and SNr that agree with these schemes.

An important fact here is that there are two distinct groups of neurons in the striatum: one for the direct pathway and the other for the indirect pathway (69a, 242, 291). To test these ideas, it is critical to characterize the functional characteristics of these two groups of striatal neurons. Direct pathway neurons and indirect pathway neurons should be activated antidromically from the SNr and GPe, respectively, but such an experiment has not been done in behaving animals except for the projection from the PUT to the GPe or GPi (173). This is partly because it is often difficult to activate striatal neurons antidromically (83), possibly because action potentials are blocked at a branch point of plexuslike axon collaterals (252).

However, the distinction between the direct and indirect pathways may not be appropriate, if we emphasize the direct cortical input to the STN. Logically, this allows the cerebral cortex to use the dual mechanisms in the basal ganglia independently (rather than in a coordinate manner as implied in Fig. 6). Again, we have had no answer yet, largely because no study has been done to characterize functionally striatum-projecting neurons and STN-projecting neurons in the cerebral cortex. The cortico-STN connection would act as a more direct and quicker way to suppress unnecessary movements (80, 205).

To summarize, depending on whether working together or sequentially, the direct and indirect 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); and *2*) suppression of a forthcoming movement when the movement is in preparation; this is particularly important because the motor program is ready to go but must be kept from being triggered. Without the latter mechanism we would have difficulty in suppressing planned movements, as exemplified in the fixation-breaking saccades in patients of basal ganglia disorders (125).

VI. MECHANISMS OF THE BASAL GANGLIA: ROLE OF DOPAMINE

DA is a critical determinant of basal ganglia function. DA neurons located in the substantia nigra pars compacta (SNc) and its vicinity project to the striatum (in addition to frontal cortical and limbic areas) and exert strong modulatory influences over the corticostriatal signal transmission (101). Patients with Parkinson's disease, which is caused by the degeneration of DA neurons, show deficits in eye movements (see section IX).

Experimentally induced parkinsonism, using 1-methly-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), provides a useful model to determine the role of DA in eye movements. Saccades in MPTP-induced parkinsonian subjects were very infrequent, slow, and hypometric, and the range of eye movements was limited, as initially shown in human subjects (149) and later in macaque monkeys (32, 279). However, the subjects were usually unable to perform any kind of behavioral task due to the strong actions of MPTP, making it impossible to evaluate the normal function of DA.

An alternative method was a local (not systemic) infusion of MPTP in the basal ganglia (154). Kato et al. (164) injected MPTP into the CD unilaterally during the period of 7–14 days using an osmotic mini-pump. Later histological examination using tyrosine hydroxylase immunohistochemistry indicated that DA depletion was restricted in the CD unilaterally, without affecting the ventral part of the PUT. Most of the MPTP-infused monkeys remained active with no clinically detectable parkinsonism, but their eye movements became deficient.

There were three kinds of deficits in relation to eye movements. *1*) There was paucity and restriction of spontaneous saccades. Spontaneous saccades became less frequent, the area scanned by the saccades became narrower and shifted to the hemifield ipsilateral to the MPTP infusion, and the saccade amplitudes and velocities decreased (164). *2*) There were preferential deficits in memory-guided saccades. The saccadic latency was prolonged consistently in contralateral memory-guided saccades, and these saccades were sometimes misdirected to the ipsilateral side (190). *3*) There was saccadic and attention hemineglect. When presented a target and a distractor on each hemifield, the monkeys made a saccade to whichever was presented in the ipsilateral side; they reacted to the ipsilateral stimulus more quickly even in an attention task in which no saccade was allowed (217).

The preferential impairment of MPTP in CD monkeys is in line with the finding that the monkey basal ganglia contain neurons that are selective for memory-guided saccades (135, 143). On the other hand, it was not immediately clear why spontaneous saccades were disturbed by MPTP, since basal ganglia neurons usually show no change in activity with spontaneous saccades. It has been shown that the level of the basal ganglia output is abnormally increased in MPTP-induced parkinsonism (71, 214). The increased SNr-SC inhibition may then prevent saccadic output neurons in the SC from firing and triggering spontaneous saccades.

In human neuropsychology, spatial hemineglect has usually been related to an asymmetric lesion of the parietofrontal cortices (119). In experimental studies, animals with unilateral basal ganglia lesions, especially DA depletion, show hemineglect (38, 69, 197, 321). However, it was unclear whether the basal ganglia-induced neglect was due to sensory, attention, or motor deficits. The saccade and attention tasks applied for trained monkeys (217) suggest that both motor and attention deficits are present in animals with MPTP injected in the CD.

The role of DA in oculomotor control in human patients with DA deficiency is described in section IX.

VII. CONTEXT DEPENDENCY OF NEURAL ACTIVITY IN THE BASAL GANGLIA

We have so far described how the basal ganglia might control saccadic eye movements, specifically on the two parallel mechanisms, one for disinhibition and the other for enhancement of inhibition. However, it is perhaps more important to know how these mechanisms are used. We have already mentioned a preferential relation of basal ganglia neurons to memory-guided saccades. In addition, there are different types of neurons that are not directly related to sensory or motor events but appear to be related to cognitive functions, including attention, working memory, expectation, and procedural memory, as shown below. These sensory, motor, and cognitive activities are likely to form a neural system for goal-directed behavior (135), along with the relevant cerebral cortical areas (4, 304).

A. Relation to Attention

A large amount of information is processed in the brain simultaneously, but an optimal behavior under a particular behavioral context requires the selection of information that is appropriate for the particular context. Attention, in its broadest sense, indicates such a selection process (30, 129). With the assumption that spatial orienting, especially saccadic eye movement, is associated with the orienting of attention (258, 272), the basal ganglia are likely to control attention with the CD-SNr-SC connections.

Earlier studies have shown that lesions of the basal ganglia frequently lead to changes in behavior that were thought to be attention deficits, in addition to well-documented movement disorders (2, 56, 212, 315). Animals with large lesions in the striatum, for example, would not orient to an object presented in front of them; other lesioned animals would follow a person or object that is most conspicuous.

More rigorous examinations using saccade and attention tasks confirmed that the monkey basal ganglia contribute to the oculomotor and attention orienting to the contralateral hemifield (9, 164, 217). Similar hemineglect or attention deficits were found in human patients with unilateral basal ganglia lesions (51, 240, 268) and parkinsonian patients (316). Experiments on rats suggest the role of the basal ganglia in overt (motor) orienting (38, 321), rather than covert (attention) orienting. However, visual responses of CD neurons are enhanced when monkeys attended to the stimulus in the receptive field, suggesting that the CD is related to spatial attention (134), together with frontal and parietal cortices (334).

B. Relation to Working Memory

Working memory is a temporary buffer of information with which motor and cognitive signals are manipulated (16). Earlier studies showed that CD lesions impaired the performance of monkeys in delayed response tasks (18, 156). The deficit was particularly strong in young animals (98). The memory-guided saccade task is an ideal task by which a simple form of working memory can be (and has been) studied. Neural activities selectively related to memory-guided saccades have been found in the SNr (139) and CD (133). Similar activities have been found in the dorsolateral prefrontal cortex (84) and parietal cortex (96). These brain areas are closely connected with each other by the basal ganglia-thalamocortical (BG-TC) loop circuits (284, 336) and corticocortical connections (99). These results suggest that the BG-TC loop circuits are a critical neural mechanism for working memory (122, 196, 306).

There are three types of neurons in the basal ganglia (especially in the SNr and CD) that are related to memory-guided saccades (139): *1*) visual neurons that respond to a visual stimulus only when its location must be remembered as the target of a future memory-guided saccade (134); *2*) memory neurons that show sustained activity while the stimulus location is maintained as a working memory; and *3*) saccadic neurons that become active just before a saccade only when the saccade is guided by memory (133). These neurons have restricted response fields usually in the contralateral hemifield. They would

work in sequence for the preparation and initiation of memory-guided saccades.

Nearly one-third of saccadic neurons in the CD and the SNr were selective for memory-guided saccades. Note, however, another one-third were selective for visually guided saccades (133). Such strong selectivity, especially the selectivity for memory-guided movement, has not been reported in other brain areas.

An important function of working memory is to predict a forthcoming event and prepare for an action. Because the basal ganglia have mechanisms for disinhibition and enhancing inhibition, a major function of the basal ganglia would then be to open the gate based on working memory so that the target motor areas can prepare for an action in a predictive manner.

C. Relation to Expectation

A mental state evoked by a predictive event may be called expectation. Many neurons in the basal ganglia appear to be related to expectation, since they become active before, not after, a particular event (12, 276). In a memory-guided saccade task, for example, reward is obtained after several steps of behavior, such as onset of a central fixation spot, presentation of a cue stimulus, offset of the fixation spot, saccade, onset of a target spot, and finally reward. Interestingly, different groups of CD neurons become active before different events, forming a chain of neural activation toward a goal (135). A common feature among these neurons is that the activity continues until the "expected" event occurs and ceases immediately after the event. The function of the expectation-related activity may or may not be related to the preparation of specific motor actions. For example, some CD neurons show sustained activity before a saccade to the remembered target, which may be related to the preparation of the saccade. Other neurons show sustained activity before the acquisition of reward, which may not directly be related to motor preparation because it is present regardless of how the reward is obtained.

Similar neural activities have been found in neurons in the dorsolateral prefrontal cortex (269, 323) and FEF (33), again suggesting that the BG-TC loop circuit consisting of the prefrontal cortex and the CD may contribute to expectation in addition to working memory. Expectation requires long-term memory for a learned sequential procedure: an event is expected on the basis of the knowledge or long-term memory (be it explicit or implicit) that the event is likely to occur next. Furthermore, expectation is directly related to the goal of behavior, especially reward. It is not surprising, therefore, that there are several lines of evidence that the basal ganglia are tightly related to these two aspects of behavior: sequential procedural learning and reward.

D. Relation to Sequential Procedural Learning

Many human studies have suggested the role of the basal ganglia in execution and learning of sequential procedures. First, patients with basal ganglia disorders (notably Parkinson's disease) show impairments in execution (1, 23, 114, 202, 303, 325) and learning (63, 186, 246) of sequential procedures. Second, imaging studies on normal human subjects have indicated the involvement of the basal ganglia in execution (26, 211) and learning (66, 147, 158, 255) of sequential procedures, including oculomotor sequence (168, 250). The role of the basal ganglia in sequential procedures is further supported by the results of animal experiments using single-unit recording (170, 225) and local inactivations (or lesions) (25, 215, 311). The possible role of the basal ganglia in learning has now been extended to other kinds of learning, notably implicit learning (187) and problem solving (266). The relationship between the sequential procedural learning and implicit learning is still unclear. On the basis of these experimental findings, neural network models have been proposed to account for the role of the basal ganglia in learning and execution of sequential procedures (14, 24, 62, 65, 81, 122, 227). A basic anatomical structure common to these models is the BG-TC loop circuit.

Recent experimental studies have provided some data relevant to these theories. Hikosaka et al. (131) devised a sequential button press task by which both the acquisition of new sequences and the retrieval of learned sequences could be examined in the same subject in one experimental session. During long-term practice, the monkey's performance became progressively more accurate and quicker (254). The improved motor skill was largely attributable to the emergence of anticipatory eye and hand movements (216). The skill was specific to the learned sequence; for a new sequence, the eye and hand did not anticipate but reacted to the target onset. Physiological experiments have shown that different brain areas contribute to the learning of sequential procedures in different ways (128). Local inactivation by injection of muscimol in the striatum revealed the anterior-posterior functional differentiation of the basal ganglia (215); the inactivation of the anterior part of the striatum (including the head of the CD) led to the deficient performance for new sequences, whereas the inactivation of the middle-posterior part of the PUT led to the deficient performance for well-learned sequences. These data suggest that the anterior and posterior parts of the basal ganglia are related to new learning and learned execution of sequential procedures, respectively. This series of studies has also shown that the dorsomedial frontal cortex, especially the presupplementary motor area (pre-SMA), rather than the supplementary motor area (SMA), is related to the learning of new sequences (228, 229), whereas the cerebellar

dentate nucleus is related to the execution of well-learned sequences (198).

Based on these behavioral and physiological data, Hikosaka et al. (130) proposed that multiple BG-TC loop circuits work independently to learn a sequential procedure. Specifically, the loop circuit consisting of the frontoparietal association cortices and the anterior part of the basal ganglia acquires the sequence using the visuospatial coordinates predominantly in the early stage of learning, while the loop circuit consisting of the motor-premotor cortices and the mid-posterior part of the basal ganglia acquires the sequence using the motor coordinates predominantly in the late stage of learning.

However, it is still unclear what kinds of information are processed in the BG-TC loop circuits. One possibility is that the sequence information embedded in the cerebral cortex is decoded along the BG-TC loop circuits and is used for the generation of sequential movements (22, 24, 62, 81). Alternatively, the information derived from the cerebral cortex may be modified or selected in the basal ganglia based on reward-related information (65, 227), as shown in the next section.

VIII. REINFORCEMENT: A KEY FACTOR FOR DECISION MAKING IN THE BASAL GANGLIA

Action is controlled by both cognition and emotion (189). Earlier studies suggested that the nucleus accumbens (or ventral striatum) is the site where these kinds of information meet (218). Many studies have confirmed this hypothesis in relation to dopaminergic functions and related phenomena of drug addiction (331). It is increasingly more likely that the dorsal striatum and its associated structures are also related to motivation (274).

The involvement of the basal ganglia in emotion or motivation has been implicated by the nonmotor symptoms of basal ganglia diseases or lesions. Motor impairments of parkinsonian patients are strongly dependent on the behavioral context so that the patients, otherwise bed-ridden, could move quickly if stimulated externally (95, 265) or emotionally aroused (280). In describing Parkinson's patients, Sacks (265) wrote, "some of them would sit for hours not only motionless, but apparently without any impulse to move, although they might move quite well if the stimulus or command or request to move came from another person. Such patients were said to have an absence of the will or 'abulia'." Abulia turned out not to be unique to Parkinson's disease. Focal lesions in the basal ganglia, especially the CD, lead to abulia, even though the subjects show no other clinical symptoms (37, 210). These reports provide an important insight into the function of the basal ganglia, but it is difficult to evaluate them objectively. However, recent anatomical and behavioral studies are beginning to solve the seemingly mysterious symptoms of basal ganglia patients, as shown below.

Anatomically, it is known that the basal ganglia receive inputs both from the neocortical areas and limbic areas, which are assumed to carry cognitive and emotional signals, respectively. However, these signals are segregated, to some extent, in the striatum, which is composed of two compartments, striosome (or patch) and matrix (88, 106). These compartments, which are delineated by the differential distribution of transmitter-related substances (e.g., acetylcholine esterase, dopamine receptors, calbindin) (90, 107), have differential input-output relationships (92). Although the matrix receives inputs mainly from the neocortical areas, the striosomes receive inputs mainly from the limbic areas (e.g., amygdala, parahippocampal formation) (64, 253). Although the matrix projects mainly to the GPi, SNr, or GPe, the striosomes project heavily to the SNc (89). It is suggested, but not proven, anatomically that there is some exchange of information between the striosomes and matrices through cholinergic interneurons or GABAergic interneurons (166).

Behaviorally, many neurons in the basal ganglia respond to reward or sensory stimuli that indicate the upcoming reward. Included are tonically active neurons in the striatum (which are likely to be cholinergic interneurons) (7, 8, 10, 13, 171), presumed projection neurons in the striatum (11, 29, 135, 236, 263, 276), dopaminergic neurons in and around the SNc (273, 275), and basal ganglia output neurons in the SNr or GPi (220, 234, 235).

These results have provided possible neural correlates for the integration of cognitive and emotional information in the basal ganglia. Recent studies from our laboratory have indicated how the visuo-oculomotor mechanisms in the basal ganglia are modulated by reward, specifically expectation of reward (165).

A. Experimental Approach to Motivation and Oculomotor Action

Investigators studying sleep are aware that the onset of sleep is reliably indicated by the slowing of saccades (120). This is partly due to a change in the operation of the brain stem saccade generator (i.e., the lack of the omnipauser-induced inhibition of burst neurons) (120). Careful observers would further notice that, even during arousal, the speed of saccades depends on the emotional or motivational state of the subject. According to the discussion above, the basal ganglia may contribute to the motivational modification of saccades. In fact, it has been shown that the speed of saccade (especially memory-guided saccade) is increased by the blockade of the SNr-SC inhibition (142) while decreased by the artificially enhanced inhibition of the SC (141). These results indicate that the

basal ganglia are capable of modifying saccade parameters but do not indicate that the basal ganglia actually do it. To test this hypothesis, it was necessary to devise a behavioral paradigm with which the animal's motivation can be manipulated systematically.

B. Modulation of Caudate Nucleus Neural Activity by Expectation of Reward

A promising strategy to manipulate the animal's motivation is to change the kind or amount of reward depending on the context of the task (145, 324). To understand how motivation affects cognitive information processing, we modified the memory-guided saccade task such that only one of four locations was rewarded (165) (Fig. 7*A*). This task was called one-direction rewarded task (1DR) compared with all-directions rewarded task (ADR).

In 1DR, one of four directions was presented randomly as a cue stimulus. The monkey had to remember its location and then had to make a saccade to the remembered location even if it was not rewarded. Otherwise, the monkey could not proceed to the next trial. The rewarded direction was fixed in a block of 60 successful trials, and a total of 4 blocks was performed with 4 different rewarded directions. Thus the cue stimulus had two meanings: *1*) the direction of the saccade to be made later and *2*) whether or not a reward was to be obtained after the saccade.

According to this procedure, it was expected that the monkey knew, after several trials of a particular block of 1DR, which cue (i.e., which direction) indicated that reward was to be given after the saccade. It was further assumed that the monkey desired that the reward-indicating cue appear, and if it appeared, the monkey was more motivated to perform the task. This assumption was corroborated by the result that the latencies were shorter and the velocities were higher when the cue indicated reward than when it indicated no reward (165).

The behavior of CD neurons was correlated with the change in saccade behavior. Figure 7*B* shows a typical cell showing a post cue visual response, which was recorded in the right CD nucleus. In ADR, it responded to the left (contralateral) cue stimulus most vigorously, whereas the response to the right cue was meager. The cell's direction selectivity is shown at the top as a polar diagram. In 1DR, however, the cell's direction selectivity changed completely. For example, when the rewarded direction was right, the cell responded to the right cue stimulus much better than to the other directions. In the same way, the cell changed its preferred direction in other blocks so that its response was most vigorous for the rewarded direction.

Another type of visual neurons maintained its direction selectivity regardless of the rewarded direction, but its response magnitude was enhanced or depressed depending on whether the cell's preferred direction was rewarded or not. A small number of visual neurons showed the pattern opposite to the one shown in Figure 7*B*, in that the response was suppressed specifically when the cue indicated reward (165).

The reward-dependent modulation of CD visual response occurred gradually after the change in the rewarded direction and was maximal usually after 10 trials. For example, the neuron shown in Figure 7*B* initially responded to the cue stimulus in any direction equally well, but the response became differentiated gradually such that the response to the reward-indicating cue increased slightly and the response to the no-reward-indicating cue decreased greatly (the sequence of trials was from bottom to top).

These visual neurons had low spontaneous activity and were presumably projection neurons that are GABAergic (330). The striatal projection neurons are characterized by numerous spines on their dendrites (167, 184, 252) to which glutamatergic corticostriatal axons and DA axons make synaptic contacts (111, 290). DA cells in the SNc show responses to sensory stimuli that predict the upcoming reward (275, 277). Thus a CD cell could receive spatial information via the corticostriatal inputs (245) and reward-related information via the dopaminergic input (275). These results together suggest that the efficacy of the corticostriatal synapses is modulated by the dopaminergic input (150, 277, 327).

C. Possible Role of Dopamine Neurons

A key factor underlying the activity modification of CD neurons may be DA. The idea that dopaminergic neurons carry the information on pleasure or reward is not new. If a stimulating electrode is implanted in the brain and the animal is allowed to press a lever to stimulate its own brain, the animal may continue to press the lever as if it feels pleasure (239). This effect is particularly strong when the electrode is implanted in the DA pathway (48). Another line of evidence comes from the study on drug addiction. It has commonly been shown that addiction to cocaine, morphine, tobacco, alcohol, and coffee is closely correlated with long-lasting changes in DA metabolism in the basal ganglia, especially the nucleus accumbens (331). Support for this idea came from recent findings by Schultz et al. (275) that midbrain DA neurons respond preferentially to reward. A striking feature is that DA neurons respond to a sensory stimulus that reliably indicates the upcoming reward.

Experiments using 1DR indicate that DA neurons also play an important role in oculomotor control (Hikosaka et al., unpublished observations). Dopaminergic neurons fire tonically and irregularly with low frequencies, and their action potentials have a long duration (101, 273).

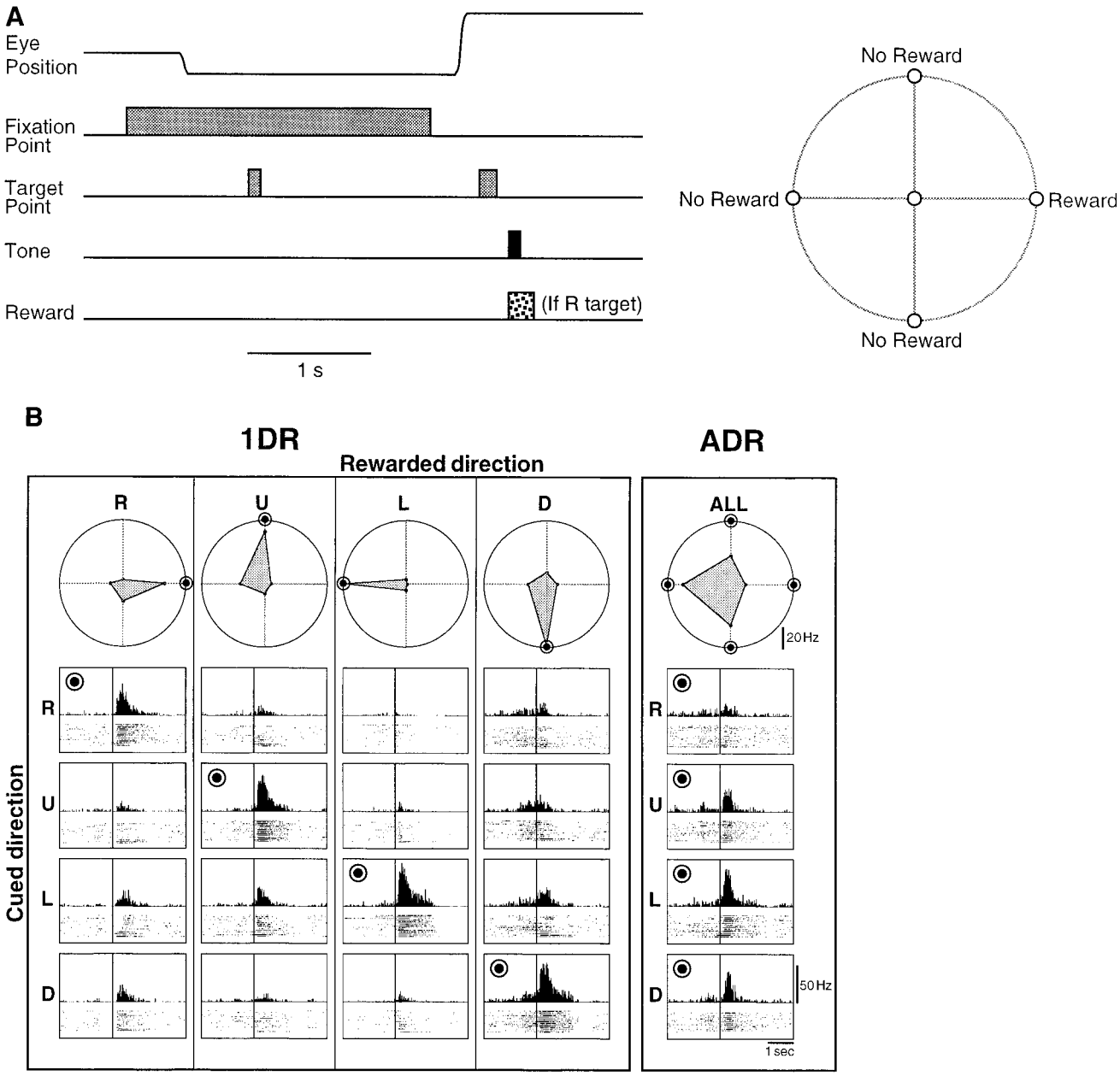

FIG. 7. Visual response of CD neuron modulated by reward expectation. *A*: memory-guided saccade task in one-direction rewarded condition (1DR). Throughout a block of experiment, only one direction was rewarded (the right direction was rewarded in this case). Different directions were rewarded in different blocks. *B*: for a neuron in the right CD, the data were obtained in one block of all-directions rewarded (ADR; *right*) and four blocks of 1DR (*left*). In the histogram/raster display, the cell discharge aligned on cue onset is shown separately for different cue directions (R, right; U, up; L, left; D, down). For each cue direction, the sequence of trials was from *bottom* to *top*. The rewarded direction is indicated by a bull's eye mark. Polar diagram on *top* shows the magnitudes of response for four cue directions. Target eccentricity was 10°. The cell's response was strongest for the rewarded direction in any block of 1DR, whereas its preferred direction was left in ADR. [From Kawagoe et al. (165).]

Many of them responded to reward by increasing its activity phasically (275). However, the reward response disappeared when the monkey obtained the same reward by performing the ADR task. The reward response was also absent in the 1DR task, but instead, the same neuron responded to the cue stimulus phasically only if the cue indicated an upcoming reward; they either did not respond to the cue stimulus that indicated no reward or responded to it by decreasing their activity.

D. Scheme of Reinforcement Learning

The results of the experiments using 1DR are consistent with the hypothesis that the coactivation of the cor-

ticostriatal input and the DA input leads to a change in the efficacy of corticostriatal synapses (36, 123, 150, 274, 327). They further suggest that the corticostriatal input carries spatial information while the DA input carries reward-related information (Fig. 5).

Most CD neurons are direction selective such that information from the contralateral visual field is dominant, but here let us consider a CD neuron that receives information from the left visual fields. If the cue comes on in the left and this direction is to be rewarded, DA neurons fire so that these two synapses are concurrently active. The corticostriatal synapse would be strengthened due to the coactivation with the DA synapse, and the corticostriatal excitatory postsynaptic potentials would be enhanced subsequently (327). On the other hand, if the cue comes on in the left field and this direction is not to be rewarded, DA neurons are suppressed. This would attenuate the output of the CD neuron.

The DA-induced enhancement of the CD output would lead to a stronger suppression of SNr neurons, a stronger disinhibition and hence a stronger burst of SC neurons, and consequently an earlier and quicker saccade. This indeed happened in 1DR when the animal knew that reward would be given later (and therefore presumably more motivated). What is important here is that the mechanisms in the basal ganglia may be sufficient to express motivation behaviorally.

Unlike the CD neurons described above (which might be called "reward-facilitated" type) (Fig. 7), there are a small number of CD neurons that show the selective response to the no-reward-indicating cue ("reward-suppressed" type) (165). For these neurons, the coactivation of corticostriatal and DA inputs would lead to depression (not enhancement) of corticostriatal synapses. Although no evidence is available, it is tempting to speculate that such reward-suppressed neurons project to the GPe (Fig. 5); the activation of these neurons in the nonrewarded trials would lead to a stronger inhibition of SC neurons.

The contrasting behaviors of reward-facilitated neurons and reward-suppressed neurons might be mediated by different DA receptors (Fig. 5). CD neurons projecting directly to the SNr (which are supposed to be reward-facilitated type) possess D_1 receptors preferentially, whereas CD neurons projecting to the GPe (which are supposed to be reward-suppressed type) possess D_2 receptors preferentially (91, 305). Many studies examined the effects of D_1 and D_2 receptor activations and gave mixed results (34). Relevant to the above hypothesis is the finding that *N*-methyl-D-aspartate (NMDA)-induced excitations are enhanced by D_1 receptor-activation and attenuated by D_2 receptor activation (42). NMDA receptor activation is necessary for the occurrence of long-term potentiation in corticostriatal synapses (34, 327) and is necessary for response-reinforcement learning when tested in the nucleus accumbens (169). On the other hand, long-term depression requires both D_1 and D_2 receptor activation and does not require NMDA receptor activation (36). Instead, both D_1 and D_2 receptor activations attenuate non-NMDA-induced excitations (42). To summarize, although at least some of the results on the DA effects on striatal neurons are consistent with the scheme described above, many other studies have shown inconsistent results. Moreover, the relationship between CD neurons and DA neurons may not be so simple. As anatomy suggests, the output of CD neurons is likely to be fed back to dopaminergic neurons either directly or indirectly through SNr neurons (110, 112, 308, 312). How the network might behave based on such a mutual relationship is difficult to understand and probably requires model simulation.

IX. CLINICAL APPLICATION

Deficits in saccadic eye movements have been reported in patients of Parkinson's disease (49, 52, 209, 285, 286, 309, 314, 326) and Huntington's disease (15, 27, 192, 195, 301, 310). Saccades in parkinsonian patients tend to be hypometric and slow with prolonged latencies. A saccade to a visual target could be broken down to a series of small saccades. However, these results are not specific to the basal ganglia disorders and could be induced by lesions in the cerebral cortex and cerebellum.

More detailed studies have suggested several features that may characterize the oculomotor deficits induced by lesions of the basal ganglia. First, parkinsonian patients show a preferential deficit in memory-guided saccades (31, 126, 136, 313). This may reflect the fact that many neurons in the SNr and CD change their activity preferentially for memory-guided saccades (133, 139). This phenomenon may also be related to "kinesie paradoxale" of parkinsonian patients (55); for example, an akinetic patient could move easily if sensory guidance is present (i.e., could not move if relying on memory) (95, 201). Similar deficits in memory-guided saccades are present in Huntington's disease (192, 195, 310). Second, parkinsonian patients show difficulty in suppressing visually guided saccades (127). In the memory-guided saccade task in which the target location to be remembered is indicated as a cue stimulus, patients often are unable to suppress a saccade to the cue stimulus. Third, the patients may have difficulty in controlling coordinated movements. This includes deficits in eye-head coordination (301) and eye-hand coordination (320).

Further studies have shown that similar deficits are present in different kinds of basal ganglia disorders. They include several forms of DA deficiencies and lesions in the basal ganglia. DA deficiency, for example, occurs at different ages (as young as 2 yr of age) (281), frequently due to specific defects of DA-related genes (153, 182). They

show different motor symptoms in that young-onset patients tend to show dystonia as a major symptom, rather than general rigidity (281, 232). Nonetheless, these DA-deficient patients share two kinds of saccadic deficits: difficulty in making memory-guided saccades and difficulty in suppressing visually guided saccades (124). Focal lesions of the CD also lead to a preferential deficit in memory-guided saccades (203).

One problem in interpreting the oculomotor deficits is that saccadic performance changes dramatically with development and aging. Saccade latency decreases steeply until ~12 yr of age during development and increases gradually after 30 yr of age (223). The age-related changes are more prominent in memory-guided saccades than in visually guided saccades (82); young children (<12 yr old) and aged people (>50 yr old) make memory-guided saccades less reliably and yet are distracted by a visual stimulus more frequently by making a visually guided saccade to it. These phenomena are similar to what are observed in basal ganglia disorders. A speculation derived from these results is that the function of the basal ganglia is under development until about 12 yr of age, whereas it undergoes deterioration after 50 yr of age. Nonetheless, the saccadic performance of patients of basal ganglia disorders described above is mostly out of the normal age-related change.

Many more neurological disorders have recently been found to be related to the basal ganglia. Tourette's syndrome is one of them, which is characterized by chronic motor tics and obsessive-compulsive disorders (194). Tourette's patients may have reduced volume of the basal ganglia (249). DA-related drugs may be effective in reducing motor tics (289). Remarkably, Tourette's patients may react to a visual target more quickly than age-matched controls, both with hand movement and with eye movement (i.e., shorter latencies in visually guided saccades). In the memory-guided saccade task, the Tourette's patients have great difficulty in suppressing visually guided saccades and some difficulty in making a memory-guided saccades, similarly to the patients with DA deficiency (Hikosaka et al., unpublished data). The results suggest that, in Tourette's syndrome, the basal ganglia-induced suppression over brain stem motor areas, especially the inhibition of the SC by the SNr, is abnormally low or leaky so that excitatory inputs, especially from other brain areas, give rise to inappropriate saccadic motor outputs.

X. CONCLUSIONS

Although the basal ganglia control a wide variety of movements and nonmotor functions, their output to the SC (or tectum) is best preserved in evolution and robust among all vertebrate species that possess the basal ganglia. The SC acts as a key station for orienting response in which the animal orients its body, head, and eyes to an object of interest. Saccadic eye movement constitutes the dominant component of orienting response. The SC translates visual information originating in the retina (in addition to other sensory information) to oculomotor information, thereby eliciting a saccade to the object of interest. The SC receives, in addition, inputs from many cortical areas, such as the visual cortex, LIP, and FEF. It also receives strong inputs from the SNr, one of the outputs regions of the basal ganglia. This SNr input is unique in that it is inhibitory and tonically active, whereas other inputs are excitatory.

Cortical regions, together with the retina, would facilitate the initiation of saccades by sending excitatory signals to the SC based on their unique information processing. Such excitatory signals would be additive with each other. They would act cooperatively but could not modulate each other. The additive, cooperative signals would lead to excessive demands for motor outputs. One way, perhaps the only way, to control the potential chaos would be to exert a powerful, sustained inhibition. This is what SNr neurons normally do.

However, sustained inhibition alone could never be a control mechanism. In fact, the basal ganglia have two different functions. The first function is to contribute to the initiation of movements by removing the sustained inhibition (disinhibition). This occurs when neurons in the caudate (CD), a major input area of the basal ganglia, fire phasically and inhibit SNr neurons. Because the information carried by the basal ganglia is often related to memory and expectation, the basal ganglia contribute to the initiation of movements on the basis of memory or expectation. Indeed, the basal ganglia contain many neurons that are preferentially related to memory-guided saccades, not visually guided saccades, and the dysfunction of the basal ganglia leads to a preferential deficit in memory-guided saccades.

The second function of the basal ganglia is to enhance the inhibition. This is accomplished by another, parallel route, which includes the GPe and the STN. The signals through the indirect pathways would lead to an elevated activity of SNr neurons and, consequently, suppression of SC neurons. Furthermore, the STN receives direct inputs from the cerebral cortex, which also leads to suppression of target neurons. Indeed, some neurons in the GPe and STN show activity that is appropriate for such an enhancement of inhibition; they are activated when sustained eye fixation is required, such as before a goal-directed saccade.

These two mechanisms are useful in selecting an appropriate action (i.e., saccade) in a particular behavioral context. The basal ganglia indeed carry signals that are heavily dependent on the behavioral context, including working memory, spatial attention, and expectation.

Another important determinant of basal ganglia neural activity is motivation or reward expectation. Recent studies have shown that visual, memory, and saccade-related activities of CD neurons are enhanced (attenuated in some cases) if reward is expected after the saccade and the animal is more motivated. DA neurons show similar changes depending on reward expectation but carry no spatial information. These results, together with other studies on striatal neurons, suggest that the efficacy of corticostriatal synapses is enhanced or depressed across several trials depending on whether DA inputs are present concurrently with the corticostriatal spatial information. Owing to these mechanisms, the saccade that has been rewarded previously is more likely to occur with a shorter latency and a faster speed, at the expense of a saccade that has not been rewarded. This means that the basal ganglia play a principal role in selection of purposeful action (in this case, saccadic eye movement), since reward is a definitive goal or purpose of behavior for any animal, including humans.

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REFERENCES

1. AGOSTINO R, BERARDELLI A, FORMICA A, ACCORNERO N, AND MANFREDI M. Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia. *Brain* 115: 1481–1495, 1992.
2. AKERT K AND ANDERSSON B. Experimenteller beitrag zur physiologie des nucleus caudatus. *Acta Physiol Scand* 22: 281–298, 1951.
3. ALEXANDER GE AND DELONG MR. Microstimulation of the primate neostriatum. II. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. *J Neurophysiol* 53: 1417–1430, 1985.
4. ALEXANDER GE, DELONG MR, AND STRICK PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9: 357–381, 1986.
5. ANDERSEN RA, SNYDER LH, BRADLEY DC, AND XING J. Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annu Rev Neurosci* 20: 303–330, 1997.
6. ANDERSON M AND YOSHIDA M. Axonal branching patterns and location of nigrothalamic and nigrocollicular neurons in the cat. *J Neurophysiol* 43: 883–895, 1980.
7. AOSAKI T, KIMURA M, AND GRAYBIEL AM. Temporal and spatial characteristics of tonically active neurons of the primate's striatum. *J Neurophysiol* 73: 1234–1252, 1995.
8. AOSAKI T, TSUBOKAWA H, ISHIDA A, WATANABE K, GRAYBIEL AM, AND KIMURA M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *J Neurosci* 14: 3969–3984, 1994.
9. APICELLA P, LEGALLET E, NIEOULLON A, AND TROUCHE E. Neglect of contralateral visual stimuli in monkeys with unilateral striatal dopamine depletion. *Behav Brain Res* 46: 187–195, 1991.
10. APICELLA P, LEGALLET E, AND TROUCHE E. Responses of tonically discharging neurons in the monkey striatum to primary rewards delivered during different behavioral states. *Exp Brain Res* 116: 456–466, 1997.
11. APICELLA P, LJUNGBERG T, SCARNATI E, AND SCHULTZ W. Responses to reward in monkey dorsal and ventral striatum. *Exp Brain Res* 85: 491–500, 1991.
12. APICELLA P, SCARNATI E, LJUNGBERG T, AND SCHULTZ W. Neuronal activity in monkey striatum related to the expectation of predictable environmental events. *J Neurophysiol* 68: 945–960, 1992.
13. APICELLA P, SCARNATI E, AND SCHULTZ W. Tonically discharging neurons of monkey striatum respond to preparatory and rewarding stimuli. *Exp Brain Res* 84: 672–675, 1991.
14. ARBIB MA AND DOMINEY PF. Modeling the roles of basal ganglia in timing and sequencing saccadic eye movements. In: *Models of Information Processing in the Basal Ganglia*, edited by J. C. Houk, J. L. Davis, and D. G. Beiser. Cambridge, MA: MIT Press, 1995, p. 149–162.
15. AVANZINI G, GIROTTI F, CARACENI T, AND SPREAFICO R. Oculomotor disorders in Huntington's chorea. *J Neurol Neurosurg Psychiatry* 42: 581–589, 1979.
16. BADDLEY A. Working memory. *Science* 255: 556–559, 1992.
17. BANDLER R, CARRIVE P, AND ZHANG SP. Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: viscerotopic, somatotopic and functional organization. In: *Role of the Forebrain in Sensation and Behavior*, edited by G. Holstege. Amsterdam: Elsevier, 1991, p. 269–305.
18. BATTIG K, ROSVOLD HE, AND MISHKIN M. Comparison of the effects of frontal and caudate lesions on delayed response and alternation in monkeys. *J Comp Physiol Psychol* 53: 400–404, 1960.
19. BECKER W. Metrics. In: *The Neurobiology of Saccadic Eye Movements*, edited by R. H. Wurtz and M. E. Goldberg. Amsterdam: Elsevier, 1989, p. 13–67.
20. BECKSTEAD RM, EDWARDS SB, AND FRANKFURTER A. A comparison of the intranigral distribution of nigrotectal neurons labeled with horseradish peroxidase in the monkey, cat, and rat. *J Neurosci* 1: 121–125, 1981.
21. BEHAN M, LIN C-S, AND HALL WC. The nigrotectal projection in the cat: an electron microscope autoradiographic study. *Neuroscience* 21: 529–539, 1987.
22. BEISER DG AND HOUK JC. Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. *J Neurophysiol* 79: 3168–3188, 1998.
23. BENECKE R, ROTHWELL JC, DICK JPR, DAY BL, AND MARSDEN CD. Disturbance of sequential movements in patients with Parkinson's disease. *Brain* 110: 361–379, 1987.
24. BERNS GS AND SEJNOWSKI TJ. A computational model of how the basal ganglia produce sequences. *J Cogn Neurosci* 10: 108–121, 1998.
25. BERRIDGE KC AND WHISHAW IQ. Cortex, striatum and cerebellum: control of serial order in an grooming sequence. *Exp Brain Res* 90: 275–290, 1992.
26. BOECKER H, DAGHER A, CEBALLOS-BAUMANN AO, PASSINGHAM RE, SAMUEL M, FRISTON KJ, POLINE J-B, DETTMERS C, CONRAD B, AND BROOKS DJ. Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with $H_2{}^{15}O$ PET. *J Neurophysiol* 79: 1070–1080, 1998.
27. BOLLEN E, REULEN JPH, DEN HEYER JC, VAN DER KAMP W, ROOS RAC, AND BURUMA OJS. Horizontal and vertical saccadic eye movement abnormalities in Huntington's chorea. *J Neurol Sci* 74: 11–22, 1986.
28. BOUSSAOUD D AND JOSEPH JP. Role of the cat substantia nigra pars reticulata in eye and head movements. II. Effects of local pharmacological injections. *Exp Brain Res* 57: 297–304, 1985.
29. BOWMAN EM, AIGNER TG, AND RICHMOND BJ. Neural signals in

the monkey ventral striatum related to motivation for juice and cocaine rewards. *J Neurophysiol* 75: 1061–1073, 1996.
30. BROADBENT DF. *Perception and Communication*. New York: Pergamon, 1958.
31. BRONSTEIN AM AND KENNARD C. Predictive ocular motor control in Parkinson's disease. *Brain* 108: 925–940, 1985.
32. BROOKS BA, FUCHS AF, AND FINOCCHIO D. Saccadic eye movement deficits in the MPTP monkey model of Parkinson's disease. *Brain Res* 383: 402–407, 1986.
33. BRUCE CJ, GOLDBERG ME, BUSHNELL MC, AND STANTON GB. Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *J Neurophysiol* 54: 714–734, 1985.
34. CALABRESI P, DE MURTAS M, AND BERNARDI G. The neostriatum beyond the motor function: experimental and clinical evidence. *Neuroscience* 78: 39–60, 1997.
35. CALABRESI P, MERCURI NB, AND BERNARDI G. Synaptic and intrinsic control of membrane excitability of neostriatal neurons. II. An in vitro analysis. *J Neurophysiol* 63: 663–675, 1990.
36. CALABRESI P, PISANI A, MERCURI NB, AND BERNARDI G. The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. *Trends Neurosci* 19: 19–24, 1996.
37. CAPLAN LR, SCHMAHMANN JD, KASE CS, FELDMANN E, BAQUIS G, GREENBERG JP, GORELICK PB, HELGASON C, AND HIER DB. Caudate infarcts. *Arch Neurol* 47: 133–143, 1990.
38. CARLI M, EVENDEN JL, AND ROBBINS TW. Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. *Nature* 313: 679–682, 1985.
39. CARPENTER MB. Anatomy of the corpus striatum and brain stem integrating systems. In: *The Nervous System*, edited by V. B. Brooks. Bethesda, MD: Am. Physiol. Soc., 1981, p. 947–995.
40. CARPENTER MB, FRASER RAR, AND SHRIVER JE. The organization of the pallidosubthalamic fibers in the monkey. *Brain Res* 11: 522–559, 1968.
41. CARPENTER MB AND JAYARAMAN A. Subthalamic nucleus of the monkey: connections and immunocytochemical features of afferents. *J Hirnforsch* 31: 653–668, 1990.
42. CEPEDA C, BUCHWALD NA, AND LEVINE MS. Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. *Proc Natl Acad Sci USA* 90: 9576–9580, 1993.
43. CHEVALIER G, THIERRY AM, SHIBAZAKI T, AND FÉGER J. Evidence for a GABAergic inhibitory nigrotectal pathway in the rat. *Neurosci Lett* 21: 67–70, 1981.
44. CHEVALIER G, VACHER S, AND DENIAU JM. Inhibitory nigral influence on tectospinal neurons, a possible implication of basal ganglia in orienting behavior. *Exp Brain Res* 53: 320–326, 1984.
45. CHEVALIER G, VACHER S, DENIAU JM, AND DESBAN M. Disinhibition as a basic process in the expression of striatal functions. I. The striato-nigral influence on tecto-spino/tecto-diencephalic neurons. *Brain Res* 334: 215–226, 1985.
46. CHIMOTO S, IWAMOTO Y, SHIMAZU H, AND YOSHIDA K. Functional connectivity of the superior colliculus with saccade-related brain stem neurons in the cat. In: *Extrageniculostriate Mechanisms Underlying Visually-Guided Orientation Behavior*, edited by M. Norita, T. Bando, and B. E. Stein. Amsterdam: Elsevier, 1996, p. 157–165.
47. COLBY CL, DUHAMEL J-R, AND GOLDBERG ME. Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J Neurophysiol* 76: 2841–2852, 1996.
48. CORBETT D AND WISE RA. Intracranial self-stimulation in relation to the ascending dopaminergic systems of the midbrain: a moveable electrode mapping study. *Brain Res* 185: 1–15, 1980.
49. CORIN MS, ELIZAN TS, AND BENDER MB. Oculomotor function in patients with Parkinson's disease. *J Neurol Sci* 15: 251–265, 1972.
50. CROSSMAN AR, SAMBROOK MA, AND JACKSON A. Experimental hemichorea/hemiballismus in the monkey. *Brain* 107: 579–596, 1984.
51. DAMASIO AR, DAMASIO H, AND CHUI HC. Neglect following damage to frontal lobe or basal ganglia. *Neuropsychologia* 18: 123–132, 1980.
52. DEJONG JD AND MELVILL-JONES G. Akinesia, hypokinesia, and bradykinesia in the oculomotor system of patients with Parkinson's disease. *Exp Neurol* 32: 58–68, 1971.
53. DELONG MR AND GEORGOPOULOS AP. Motor functions of the basal ganglia. In: *The Nervous System*, edited by V. B. Brooks. Bethesda, MD: Am. Physiol. Soc., 1981, p. 1017–1061.
54. DENIAU JM AND CHEVALIER G. Disinhibition as a basic process in the expression of striatal functions. II. The striato-nigral influence on thalamocortical cells of the ventromedial thalamic nucleus. *Brain Res* 334: 227–233, 1985.
55. DENNY-BROWN D. Clinical symptomatology of diseases of the basal ganglia. In: *Diseases of the Basal Ganglia*, edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North Holland, 1968, p. 133–172.
56. DENNY-BROWN D AND YANAGISAWA N. The role of the basal ganglia in the initiation of movement. In: *The Basal Ganglia*, edited by M. D. Yahr. New York: Raven, 1976, p. 115–149.
57. DEUBEL H. Separate adaptive mechanisms for the control of reactive and volitional saccadic eye movements. *Vision Res* 35: 3529–3540, 1995.
58. DIERINGER N, COCHRAN SL, AND PRECHT W. Differences in the central organization of gaze stabilizing reflexes between frog and turtle. *J Comp Physiol* 153: 495–508, 1983.
59. DIERINGER N AND PRECHT W. Compensatory head and eye movements in the frog and their contribution to stabilization of gaze. *Exp Brain Res* 47: 394–406, 1982.
60. DIERINGER N, PRECHT W, AND BLIGHT AR. Resetting fast phases of head and eye and their linkage in the frog. *Exp Brain Res* 47: 407–416, 1982.
61. DIFIGLIA M, PASIK P, AND PASIK T. A Golgi study of neuronal types in the neostriatum of monkeys. *Brain Res* 114: 245–256, 1976.
62. DOMINEY PF AND ARBIB MA. A cortico-subcortical model for generation of spatially accurate sequential saccades. *Cerebral Cortex* 2: 153–175, 1992.
63. DOMINEY PF AND JEANNEROD M. Contribution of frontostriatal function to sequence learning in Parkinson's Disease: evidence for dissociable systems. *Neuroreport* 8: 3–9, 1997.
64. DONOGHUE JP AND HERKENHAM M. Neostriatal projections from individual cortical fields conform to histochemically distinct striatal compartments in the rat. *Brain Res* 365: 397–403, 1986.
65. DOYA K. What are the computations of the cerebellum, the basal ganglia and the cerebral cortex? *Neural Networks* 12: 961–974, 1999.
66. DOYON J, GAUDREAU D, LAFORCE R, CASTONGUAY M, BEDARD PJ, BEDARD F, AND BOUCHARD J-P. Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. *Brain Cogn* 34: 218–245, 1997.
67. EWERT J-P. *Neuroethology*. Berlin: Springer, 1980.
68. FAULL RLM AND MEHLER WR. The cells of origin of nigrotectal, nigrothalamic and nigrostriatal projections in the rat. *Neuroscience* 3: 989–1002, 1978.
69. FEENEY DM AND WIER CS. Sensory neglect after lesions of substantia nigra or lateral hypothalamus: differential severity and recovery of function. *Brain Res* 178: 329–346, 1979.
69a. FÉGER J AND CROSSMAN AR. Identification of different subpopulations of neostriatal neurones projecting to globus pallidus or substantia nigra in the monkey: a retrograde fluorescence double-labeling study. *Neurosci Lett* 49: 7–12, 1984.
69b. FÉGER J AND OHYE C. The unitary activity of the substantia nigra following stimulation of the striatum in the awake monkey. *Brain Res* 89: 155–159, 1975.
70. FELTZ P. γ-Aminobutyric acid and a caudate-nigral inhibition. *Can J Physiol Pharmacol* 49: 1113–1115, 1971.
71. FILION M AND TREMBLAY L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* 547: 142–151, 1991.
72. FISHER RS, BUCHWALD NA, HULL CD, AND LEVINE MS. The GABAergic striatonigral neurons of the cat: demonstration by double peroxidase labeling. *Brain Res* 398: 148–156, 1986.
73. FLAHERTY AW AND GRAYBIEL AM. Input-output organization of the sensorimotor striatum in the squirrel monkey. *J Neurosci* 14: 599–610, 1994.
74. FLAHERTY AW AND GRAYBIEL AM. Motor and somatosensory

corticostriatal projection magnifications in the squirrel monkey. *J Neurophysiol* 74: 2638–2648, 1995.
75. FLOWERS KA AND DOWNING AC. Predictive control of eye movements in Parkinson disease. *Ann Neurol* 4: 63–66, 1978.
76. FONNUM F, GOTTESFELD Z, AND GROFOVA I. Distribution of glutamate decarboxylase, choline acetyltransferase and aromatic amino acid decarboxylase in the basal ganglia of normal and operated rats. Evidence for striatopallidal, striatopeduncular and striatonigral GABAergic fibres. *Brain Res* 143: 125–138, 1978.
77. FORMAN D AND WARD JW. Responses to electrical stimulation of caudate nucleus in cats in chronic experiments. *J Neurophysiol* 20: 230–244, 1957.
78. FRANÇOIS C, PERCHERON G, AND YELNIK J. Localization of nigrostriatal, nigrothalamic and nigrotectal neurons in ventricular coordinates in macaques. *Neuroscience* 13: 61–76, 1984.
79. FRANÇOIS C, YELNIK J, PERCHERON G, AND FÉNELON G. Topographic distribution of the axonal endings from the sensorimotor and associative striatum in the macaque pallidum and substantia nigra. *Exp Brain Res* 102: 305–318, 1994.
80. FUJIMOTO K AND KITA H. Responses characteristics of subthalamic neurons to the stimulation of the sensorimotor cortex in the rat. *Brain Res* 609: 185–192, 1993.
81. FUKAI T. Sequence generation in arbitrary temporal patterns from theta-nested gamma oscillations: a model of the basal ganglia-thalamo-cortical loops. *Neural Networks* 12: 975–987, 1999.
82. FUKUDA H AND HIKOSAKA O. Memory-guided saccade, rather than visually guided saccade, is related to human development and aging. *Neurosci Res Suppl* 19: S191, 1994.
83. FULLER DRG, HULL CD, AND BUCHWALD NA. Intracellular responses of caudate output neurons to orthodromic stimulation. *Brain Res* 96: 337–341, 1975.
84. FUNAHASHI S, BRUCE CJ, AND GOLDMAN-RAKIC PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol* 61: 331–349, 1989.
87. GARCIA-RILL E. The pedunculopontine nucleus. *Prog Neurobiol* 36: 363–389, 1991.
88. GERFEN CR. The neostriatal mosaic: compartmentalization of corticostriatal input and striatonigral output systems. *Nature* 311: 461–464, 1984.
89. GERFEN CR. The neostriatal mosaic. I. Compartmental organization of projections from the striatum to the substantia nigra in the rat. *J Comp Neurol* 236: 454–476, 1985.
90. GERFEN CR, BAIMBRIDGE KG, AND MILLER JJ. The neostriatal mosaic: compartmental distribution of calcium-binding protein and parvalbumin in the basal ganglia of the rat and monkey. *Proc Natl Acad Sci USA* 82: 8780–8784, 1985.
91. GERFEN CR, ENGBER TM, MAHAN LC, SUSEL Z, CHASE TN, MONSMA JFJ, AND SIBLEY DR. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 250: 1429–1432, 1990.
92. GERFEN CR, HERKENHAM M, AND THIBAULT J. The neostriatal mosaic. II. Patch-and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J Neurosci* 7: 3915–3934, 1987.
93. GERFEN CR AND YOUNG IWS. Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix compartments: an in situ hybridization histochemistry and fluorescent retrograde tracing study. *Brain Res* 460: 161–167, 1988.
94. GIMÉNEZ-AMAYA JM AND GRAYBIEL AM. Compartmental origins of the striatopallidal projection in the primate. *Neuroscience* 34: 111–126, 1990.
95. GLICKSTEIN M AND STEIN J. Paradoxical movement in Parkinson's disease. *Trends Neurosci* 14: 480–482, 1991.
96. GNADT JW, BRACEWELL RM, AND ANDERSEN RA. Sensorimotor transformation during eye movements to remembered visual targets. *Vision Res* 31: 693–715, 1991.
97. GOLDBERG ME AND BUSHNELL MC. Behavioral enhancement of visual responses in monkey cerebral cortex. II. Modulation in frontal eye fields specifically related to saccades. *J Neurophysiol* 46: 773–787, 1981.
98. GOLDMAN PS AND ROSVOLD HE. The effects of selective caudate lesions in infant and juvenile rhesus monkeys. *Brain Res* 43: 53–66, 1972.
99. GOLDMAN-RAKIC PS. Topography of cognition. Parallel distributed networks in primate association cortex. *Annu Rev Neurosci* 11: 137–156, 1988.
100. GOTTLIEB JP, KUSUNOKI M, AND GOLDBERG ME. The representation of visual salience in monkey parietal cortex. *Nature* 391: 481–484, 1998.
101. GRACE AA AND BUNNEY BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons. 1. Identification and characterization. *Neuroscience* 10: 301–315, 1983.
102. GRANTYN A AND BERTHOZ A. Burst activity of identified tectoreticulo-spinal neurons in the alert cat. *Exp Brain Res* 57: 417–421, 1985.
103. GRANTYN A, JACQUES VO-M, AND BERTHOZ A. Reticulo-spinal neurons participating in the control of synergic eye and head movements during orienting in the cat. II. Morphological properties as revealed by intra-axonal injections of horseradish peroxidase. *Exp Brain Res* 66: 355–377, 1987.
104. GRAYBIEL AM. Organization of the nigrotectal connection: an experimental tracer study in the cat. *Brain Res* 143: 339–348, 1978.
105. GRAYBIEL AM. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci* 13: 244–254, 1990.
106. GRAYBIEL AM AND RAGSDALE CW. Fiber connections of the basal ganglia. In: *Development of Chemical Specificity of Neurons*, edited by M. Cuenod, G. W. Kreutzberg, and F. E. Bloom. Amsterdam: Elsevier, 1979, p. 239–283.
107. GRAYBIEL AM, RAGSDALE CW, YONEOKA ES, AND ELDE RP. An immunohistochemical study of enkephalins and other neuropeptides in the striatum of the cat with evidence that the opiate peptides are arranged to form mosaic patterns in register with the striosomal compartments visible by acetylcholinesterase staining. *Neuroscience* 6: 377–397, 1981.
108. GRAZIANO MSA AND GROSS CG. Spatial maps for the control of movement. *Curr Opin Neurobiol* 8: 195–201, 1998.
109. GRILLNER S AND SHIK ML. On the descending control of the lumbosacral spinal cord from the "mesencephalic locomotor region." *Acta Physiol Scand* 87: 320–333, 1973.
110. GROFOVA I, DENIAU JM, AND KITAI ST. Morphology of the substantia nigra pars reticulata projection neurons intracellularly labeled with HRP. *J Comp Neurol* 208: 352–368, 1982.
111. GROVES PM, LINDER JC, AND YOUNG SJ. 5-Hydroxydopamine-labeled dopaminergic axons: three dimensional reconstructions of axons, synapses, and postsynaptic targets in rat neostriatum. *Neuroscience* 58: 593–604, 1994.
112. HAJÓS M AND GREENFIELD SA. Synaptic connections between pars compacta and pars reticulata neurones: electrophysiological evidence for functional modules within the substantia nigra. *Brain Res* 660: 216–224, 1994.
113. HAMMOND C, DENIAU JM, RIZK A, AND FÉGER J. Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. *Brain Res* 151: 235–244, 1978.
114. HARRINGTON DL AND HAALAND KY. Sequencing in Parkinson's disease. Abnormalities in programming and controlling movement. *Brain* 114: 99–115, 1991.
115. HARTMANN-VON MOAKOW K, AKERT K, AND KÜNZLE H. Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. *Exp Brain Res* 33: 395–403, 1978.
116. HAZRATI L-N AND PARENT A. Convergence of subthalamic and striatal efferents at pallidal level in primates: an anterograde double-labeling study with biocytin and PHA-L. *Brain Res* 569: 336–340, 1992.
117. HAZRATI L-N AND PARENT A. The striatopallidal projection displays a high degree of anatomical specificity in the primate. *Brain Res* 592: 213–227, 1992.
118. HEDREEN JC AND DELONG MR. Organization of striatopallidal, striatonigral, and nigrostriatal projections in the macaque. *J Comp Neurol* 304: 569–595, 1991.
119. HEILMAN KM, BOWERS D, VALENSTEIN E, AND WATSON RT. Hemispace and hemispatial neglect. In: *Neurophysiological and Neuropsychological Aspects of Spatial Neglect*, edited by M. Jeannerod. Amsterdam: Elsevier, 1987, p. 115–150.
120. HENN V, BALOH RW, AND HEPP K. The sleep-wake transition in the oculomotor system. *Exp Brain Res* 54: 166–176, 1984.
121. HEPP K, HENN V, VILIS T, AND COHEN B. Brainstem regions

related to saccadic generation. In: *The Neurobiology of Saccadic Eye Movements*, edited by R. H. Wurtz and M. E. Goldberg. Amsterdam: Elsevier, 1989, p. 105–212.
122. HIKOSAKA O. Role of basal ganglia in initiation of voluntary movements. In: *Dynamic Interactions in Neural Networks: Models and Data*, edited by M. A. Arbib and S. Amari. New York: Springer-Verlag, 1989, p. 153–167.
123. HIKOSAKA O. Role of basal ganglia in control of innate movements, learned behavior and cognition: a hypothesis. In: *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, edited by G. Percheron, J. S. McKenzie, and J. Féger. New York: Plenum, 1994, p. 589–596.
124. HIKOSAKA O, FUKUDA H, KATO M, UETAKE K, NOMURA Y, AND SEGAWA M. Deficits in saccadic eye movements in hereditary progressive dystonia with marked diurnal fluctuation. In: *Hereditary Progressive Dystonia with Marked Diurnal Fluctuation*, edited by M. Segawa. New York: Parthenon, 1993, p. 159–177.
125. HIKOSAKA O, FUKUDA H, SEGAWA M, AND NOMURA Y. Voluntary saccades in normal and in dopamine deficient subjects. In: *Age-Related Dopamine-Deficient Disorders*, edited by M. Segawa and Y. Nomura. Basal: Karger, 1995, p. 59–68.
126. HIKOSAKA O, IMAI H, AND SEGAWA M. Saccadic eye movements in parkinsonism. In: *Vestibular and Brain Stem Control of Eye, Head and Body Movements*, edited by H. Shimazu and Y. Shinoda. Tokyo: Japan Sci. Soc., 1992, p. 405–414.
127. HIKOSAKA O, MATSUMURA M, KOJIMA J, AND GARDINER TW. Role of basal ganglia in initiation and suppression of saccadic eye movements. In: *Role of the Cerebellum and Basal Ganglia in Voluntary Movement*, edited by N. Mano, I. Hamada, and M. R. DeLong. Amsterdam: Elsevier, 1993, p. 213–219.
128. HIKOSAKA O, MIYASHITA K, MIYACHI S, SAKAI K, AND LU X. Differential roles of the frontal cortex, basal ganglia, and cerebellum in visuomotor sequence learning. *Neurobiol Learning Memory* 70: 137–149, 1998.
129. HIKOSAKA O, MIYAUCHI S, AND SHIMOJO S. Orienting of spatial attention: its reflexive, compensatory, and voluntary mechanisms. *Cogn Brain Res* 5: 1–9, 1996.
130. HIKOSAKA O, NAKAHARA H, RAND MK, SAKAI K, LU X, NAKAMURA K, MIYACHI S, AND DOYA K. Parallel neural networks for learning sequential procedures. *Trends Neurosci* 22: 464–471, 1999.
131. HIKOSAKA O, RAND MK, MIYACHI S, AND MIYASHITA K. Learning of sequential movements in the monkey: process of learning and retention of memory. *J Neurophysiol* 74: 1652–1661, 1995.
132. HIKOSAKA O, SAKAMOTO M, AND MIYASHITA N. Effects of caudate nucleus stimulation on substantia nigra cell activity in monkey. *Exp Brain Res* 95: 457–472, 1993.
133. HIKOSAKA O, SAKAMOTO M, AND USUI S. Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movements. *J Neurophysiol* 61: 780–798, 1989.
134. HIKOSAKA O, SAKAMOTO M, AND USUI S. Functional properties of monkey caudate neurons. II. Visual and auditory responses. *J Neurophysiol* 61: 799–813, 1989.
135. HIKOSAKA O, SAKAMOTO M, AND USUI S. Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. *J Neurophysiol* 61: 814–832, 1989.
136. HIKOSAKA O, SEGAWA M, AND IMAI H. Voluntary saccadic eye movement: application to analyze basal ganglia disease. In: *Highlights in Neuro-Ophthalmology*, edited by S. Ishikawa. Amsterdam: Aeolus, 1987, p. 133–138.
137. HIKOSAKA O AND WURTZ RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata. I. Relation of visual and auditory responses to saccades. *J Neurophysiol* 49: 1230–1253, 1983.
138. HIKOSAKA O AND WURTZ RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses related to fixation of gaze. *J Neurophysiol* 49: 1254–1267, 1983.
139. HIKOSAKA O AND WURTZ RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J Neurophysiol* 49: 1268–1284, 1983.
140. HIKOSAKA O AND WURTZ RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. *J Neurophysiol* 49: 1285–1301, 1983.
141. HIKOSAKA O AND WURTZ RH. Modification of saccadic eye movements by GABA-related substances. I. Effect of muscimol and bicuculline in the monkey superior colliculus. *J Neurophysiol* 53: 266–291, 1985.
142. HIKOSAKA O AND WURTZ RH. Modification of saccadic eye movements by GABA-related substances. II. Effects of muscimol in monkey substantia nigra pars reticulata. *J Neurophysiol* 53: 292–308, 1985.
143. HIKOSAKA O AND WURTZ RH. The basal ganglia. In: *The Neurobiology of Saccadic Eye Movements*, edited by R. H. Wurtz and M. E. Goldberg. Amsterdam: Elsevier, 1989, p. 257–281.
144. HINDE RA. *Animal Behavior*. Tokyo*:* McGraw-Hill Kogakusha, 1966.
145. HOLLERMAN JR, TREMBLAY L, AND SCHULTZ W. Influence of reward expectation on behavior-related neuronal activity in primate striatum. *J Neurophysiol* 80: 947–963, 1998.
146. HOLSTEGE G. Descending motor pathways and the spinal motor system: limbic and non-limbic components. In: *Role of the Forebrain in Sensation and Behavior*, edited by G. Holstege. Amsterdam: Elsevier, 1991, p. 307–421.
147. HONDA M, DEIBER M-P, IBÁNEZ V, PASCUAL-LEONE A, ZHUANG P, AND HALLETT M. Dynamic cortical involvement in implicit and explicit motor sequence learning. A PET study. *Brain* 121: 2159–2173, 1998.
148. HOPKINS DA AND NIESSEN LW. Substantia nigra projections to the reticular formation, superior colliculus and central gray in the rat, cat and monkey. *Neurosci Lett* 2: 253–259, 1976.
149. HOTSON JR, LANGSTON EB, AND LANGSTON JW. Saccade responses to dopamine in human MPTP-induced parkinsonism. *Ann Neurol* 20: 456–463, 1986.
150. HOUK JC, ADAMS JL, AND BARTO A. A model of how the basal ganglia generate and use neural signals that predict reinforcement. In: *Models of Information Processing in the Basal Ganglia*, edited by J. C. Houk, J. L. Davis, and D. G. Beiser. Cambridge, MA: MIT Press, 1995, p. 249–270.
151. HUERTA MF AND KAAS JH. Supplementary eye field as defined by intracortical microstimulation: connections in macaques. *J Comp Neurol* 293: 299–330, 1990.
152. HUERTA MF, KRUBITZER LA, AND KAAS JH. Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys. II. Cortical connections. *J Comp Neurol* 265: 332–361, 1986.
153. ICHINOSE H, OHYE T, TAKAHASHI E, SEKI N, HORI T, SEGAWA M, NOMURA Y, ENDO K, TANAKA H, TSUJI S, FUJITA K, AND NAGATSU T. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase l gene. *Nature Genet* 8: 236–242, 1994.
154. IMAI H, NAKAMURA T, ENDO K, AND NARABAYASHI H. Hemiparkinsonism in monkeys after unilateral caudate nucleus infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): behavior and histology. *Brain Res* 474: 327–332, 1988.
155. ISA T, ENDO T, AND SAITO Y. The visuo-motor pathway in the local circuit of the rat superior colliculus. *J Neurosci* 18: 8496–8504, 1998.
156. IVERSEN SD. Behaviour after neostriatal lesions in animals. In: *The Neostriatum*, edited by I. Divac and R. G. E. Oberg. Oxford, UK: Pergamon, 1979, p. 195–210.
157. JAYARAMAN A, BATTON RRI, AND CARPENTER MB. Nigrotectal projections in the monkey: an autoradiographic study. *Brain Res* 135: 147–152, 1977.
158. JENKINS IH, BROOKS DJ, NIXON PD, FRACKOWIAK RSJ, AND PASSINGHAM RE. Motor sequence learning: a study with positron emission tomography. *J Neurosci* 14: 3775–3790, 1994.
159. JOSEPH JP AND BOUSSAOUD D. Role of the cat substantia nigra pars reticulata in eye and head movements. I. Neural activity. *Exp Brain Res* 57: 286–296, 1985.
160. JÜRGENS U. The role of the periaqueductal grey in vocal behaviour 1985. *J Behav Brain Res* 62: 107–117, 1994.
161. KANAZAWA I, MARSHALL GR, AND KELLY JS. Afferents to the rat substantia nigra studied with horseradish peroxidase, with special reference to fibres from the subthalamic nucleus. *Brain Res* 115: 485–491, 1976.
162. KARABELAS AB AND MOSCHOVAKIS AK. Nigral inhibitory termi-

nation on efferent neurons of the superior colliculus: an intracellular horseradish peroxidase study in the cat. *J Comp Neurol* 239: 309–329, 1985.
163. KATO M AND HIKOSAKA O. Function of the indirect pathway in the basal ganglia oculomotor system: visuo-oculomotor activities of external pallidum neurons. In: *Age-Related Dopamine-Deficient Disorders*, edited by M. Segawa and Y. Nomura. Basal: Karger, 1995, p. 178–187.
164. KATO M, MIYASHITA N, HIKOSAKA O, MATSUMURA M, USUI S, AND KORI A. Eye movements in monkeys with local dopamine depletion in the caudate nucleus. I. Deficits in spontaneous saccades. *J Neurosci* 15: 912–927, 1995.
165. KAWAGOE R, TAKIKAWA Y, AND HIKOSAKA O. Expectation of reward modulates cognitive signals in the basal ganglia. *Nat Neurosci* 1: 411–416, 1998.
166. KAWAGUCHI Y, WILSON CJ, AUGOOD SJ, AND EMSON PC. Striatal interneurones: chemical, physiological and morphological characterization. *Trends Neurosci* 18: 527–535, 1995.
167. KAWAGUCHI Y, WILSON CJ, AND EMSON PC. Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin. *J Neurosci* 10: 3421–3438, 1990.
168. KAWASHIMA R, TANJI J, OKADA K, SUGIURA M, SATO K, KINOMURA S, INOUE K, OGAWA A, AND FUKUDA H. Oculomotor sequence learning: a positron emission tomography study. *Exp Brain Res* 122: 1–8, 1998.
169. KELLEY AE, SMITH-ROE SL, AND HOLAHAN MR. Response-reinforcement learning is dependent on *N*-methyl-D-aspartate receptor activation in the nucleus accumbens core. *Proc Natl Acad Sci USA* 94: 12174–12179, 1997.
170. KERMADI I AND JOSEPH JP. Activity in the caudate nucleus of monkey during spatial sequencing. *J Neurophysiol* 74: 911–933, 1995.
171. KIMURA M. The role of primate putamen neurons in the association of sensory stimuli with movement. *Neurosci Res* 3: 436–443, 1986.
172. KIMURA M. Behaviorally contingent property of movement-related activity of the primate putamen. *J Neurophysiol* 63: 1277–1296, 1990.
173. KIMURA M, KATO M, SHIMAZAKI H, WATANABE K, AND MATSUMOTO N. Neural information transferred from the putamen to the globus pallidus during learned movement in the monkey. *J Neurophysiol* 76: 3771–3786, 1996.
174. KINCAID AE, PENNEY JB JR, YOUNG AB, AND NEWMAN SW. Evidence for a projection from the globus pallidus to the entopeduncular nucleus in the rat. *Neurosci Lett* 128: 121–125, 1991.
175. KINCAID AE, ZHENG T, AND WILSON CJ. Connectivity and convergence of single corticostriatal axons. *J Neurosci* 18: 4722–4731, 1998.
176. KING AJ AND PALMER AR. Integration of visual and auditory information in bimodal neurones in the guinea-pig superior colliculus. *Exp Brain Res* 60: 492–500, 1985.
177. KITA H. Parvalbumin-immunopositive neurons in rat globus pallidus: a light and electron microscopic study. *Brain Res* 657: 31–41, 1994.
178. KITA H, CHANG HT, AND KITAI ST. Pallidal inputs to subthalamus: intracellular analysis. *Brain Res* 264: 255–265, 1983.
179. KITA H AND KITAI ST. Efferent projections of the subthalamic nucleus in the rat: light and electron microscopic analysis with the PHA-L method. *J Comp Neurol* 260: 435–452, 1987.
180. KITA K. GABAergic circuits of the striatum. In: *Chemical Signalling in the Basal Ganglia*, edited by G. W. Arbuthnott and P. C. Emson. Amsterdam: Elsevier, 1993, p. 51–72.
181. KITA T, KITA H, AND KITAI ST. Passive electrical membrane properties of rat neostriatal neurons in an in vitro slice preparation. *Brain Res* 300: 129–139, 1984.
182. KITADA T, ASAKAWA S, HATTORI N, MATSUMINE H, YAMAMURA Y, MINOSHIMA S, YOKOCHI M, MIZUNO Y, AND SHIMIZU N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392: 605–608, 1998.
183. KITAI ST AND DENIAU JM. Cortical inputs to the subthalamus: intracellular analysis. *Brain Res* 214: 411–415, 1981.
184. KITAI ST, KOCSIS JD, PRESTON RJ, AND SUGIMORI M. Monosynaptic inputs to caudate neurons identified by intracellular injection of horseradish peroxidase. *Brain Res* 109: 601–606, 1976.
185. KITAMA T, OHNO T, TANAKA M, TSUBOKAWA H, AND YOSHIDA K. Stimulation of the caudate nucleus induces contraversive saccadic eye movements as well as head turning in the cat. *Neurosci Res* 12: 287–292, 1991.
186. KNOPMAN D AND NISSEN MJ. Procedural learning is impaired in Huntington's disease: evidence from the serial reaction time task. *Neuropsychologia* 29: 245–254, 1991.
187. KNOWLTON BJ, MANGELS JA, AND SQUIRE LR. A neostriatal habit learning system in humans. *Science* 273: 1399–1402, 1996.
188. KODAKA Y, MIKAMI A, AND KUBOTA K. Neuronal activity in the frontal eye field of the monkey is modulated while attention is focused on to a stimulus in the peripheral visual field, irrespective of eye movement. *Neurosci Res* 28: 291–298, 1997.
189. KONORSKI J. *Integrative Activity of the Brain*. Chicago, IL: Univ. of Chicago Press, 1967, p. 531.
190. KORI A, MIYASHITA N, KATO M, HIKOSAKA O, USUI S, AND MATSUMURA M. Eye movements in monkeys with local dopamine depletion in the caudate nucleus. II. Deficits in voluntary saccades. *J Neurosci* 15: 928–941, 1995.
191. KÜNZLE H. Bilateral projections from the precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. *Brain Res* 88: 195–209, 1975.
192. LASKER AG, ZEE DS, HAIN TC, FOLSTEIN SE, AND SINGER HS. Saccades in Huntington's disease: initiation defects and distractibility. *Neurology* 37: 364–370, 1987.
193. LAURSEN AM. Movements evoked from the region of the caudate nucleus in cats. *Acta Physiol Scand* 54: 175–184, 1962.
194. LECKMAN JF, KNORR AM, RASMUSSON AM, AND COHEN DJ. Basal ganglia research and Tourette's syndrome. *Trends Neurosci* 14: 94, 1991.
195. LEIGH RJ, NEWMAN SA, FOLSTEIN SE, LASKER AG, AND JENSEN BA. Abnormal ocular motor control in Huntington's disease. *Neurology* 33: 1268–1275, 1983.
196. LEVY R, FRIEDMAN HR, DAVACHI L, AND GOLDMAN-RAKIC PS. Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks. *J Neurosci* 17: 3870–3882, 1997.
197. LJUNGBERG T AND UNGERSTEADT U. Sensory inattention produced by 6-hydroxydopamine-induced degeneration of ascending dopamine neurons in the brain. *Exp Neurol* 53: 585–600, 1976.
198. LU X, HIKOSAKA O, AND MIYACHI S. Role of monkey cerebellar nuclei in skill for sequential movement. *J Neurophysiol* 79: 2245–2254, 1998.
199. LYND-BALTA E AND HABER SN. Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum. *J Comp Neurol* 345: 562–578, 1994.
200. MARÍN O, SMEETS WJAJ, AND GONZÁLEZ A. Evolution of the basal ganglia in tetrapods: a new perspective based on recent studies in amphibians. *Trends Neurosci* 21: 487–494, 1998.
201. MARTIN JP. *The Basal Ganglia and Posture*. London: Pitman Medical, 1967.
202. MARTIN KE, PHILLIPS JG, IANSEK R, AND BRADSHAW JL. Inaccuracy and instability of sequential movements in Parkinson's disease. *Exp Brain Res* 102: 131–140, 1994.
203. MATSUMURA M, FUKASAWA K, AND KOJIMA J. Saccade abnormalities in patients with caudate lesion. In: *The Basal Ganglia V*, edited by C. E. A. Ohye. New York: Plenum, 1996, p. 269–276.
204. MATSUMURA M, KOJIMA J, GARDINER TW, AND HIKOSAKA O. Visual and oculomotor functions of monkey subthalamic nucleus. *J Neurophysiol* 67: 1615–1632, 1992.
205. MAURICE N, DENIAU J-M, GLOWINSKI J, AND THIERRY A-M. Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the corticosubthalamic circuits. *J Neurosci* 18: 9539–9546, 1998.
206. MAY PJ AND HALL WC. Relationships between the nigrotectal pathway and the cells of origin of the predorsal bundle. *J Comp Neurol* 226: 357–376, 1984.
207. MAY PJ AND HALL WC. The sources of the nigrotectal pathway. *Neuroscience* 19: 159–180, 1986.
208. MEDINA L AND SMEETS WJAJ. Comparative aspects of the basal

ganglia-tectal pathways in reptiles. *J Comp Neurol* 308: 614–629, 1991.
209. MELVILL JONES G AND DEJONG JD. Dynamic characteristics of saccadic eye movements in Parkinson's disease. *Exp Neurol* 31: 17–31, 1971.
210. MENDEZ MF, ADAMS NL, AND LEWANDOWSKI KS. Neurobehavioral changes associated with caudate lesions. *Neurology* 39: 349–354, 1989.
211. MENON V, GLOVER GH, AND PFEFFERBAUM A. Differential activation of dorsal basal ganglia during externally and self paced sequences of arm movements. *Neuroreport* 9: 1567–1573, 1998.
212. METTLER FA. Effects of bilateral simultaneous subcortical lesions in the primate. *J Neuropathol Exp Neurol* 4: 99–122, 1945.
213. MIDDLEBROOKS JC AND KNUDSEN EI. A neural code for auditory space in the cat's superior colliculus. J. *Neurosci* 4: 2621–2634, 1984.
214. MILLER WC AND DELONG MR. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: *The Basal Ganglia II*, edited by M. B. Carpenter and A. Jayaraman. New York: Plenum, 1987, p. 415–427.
215. MIYACHI S, HIKOSAKA O, MIYASHITA K, KARADI Z, AND RAND MK. Differential roles of monkey striatum in learning of sequential hand movement. *Exp Brain Res* 115: 1–5, 1997.
216. MIYASHITA K, RAND MK, MIYACHI S, AND HIKOSAKA O. Anticipatory saccades in sequential procedural learning in monkeys. *J Neurophysiol* 76: 1361–1366, 1996.
217. MIYASHITA N, HIKOSAKA O, AND KATO M. Visual hemineglect induced by unilateral striatal dopamine dificiency in monkeys. *Neuroreport* 6: 1257–1260, 1995.
218. MOGENSON GJ, JONES DL, AND YIM CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14: 69–97, 1980.
219. MOONEY RD, NIKOLETSEAS MM, HESS PR, ALLEN Z, LEWIN AC, AND RHOADES RW. The projection from the superficial layer to the deep layers of the superior colliculus: an intracellular horseradish peroxidase injection study in the hamster. *J Neurosci* 8: 1384–1399, 1988.
220. MORA F, MOGENSON GJ, AND ROLLS ET. Activity of neurons in the region of the substantia nigra during feeding in the monkey. *Brain Res* 133: 267–276, 1977.
221. MORI S. Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. *Prog Neurobiol* 28: 161–195, 1987.
222. MOTTER BC AND BELKY EJ. The guidance of eye movements during active visual search. *Vision Res* 38: 1805–1815, 1998.
223. MUNOZ DP, BROUGHTON JR, GOLDRING JE, AND ARMSTRONG IT. Age-related performance of human subjects on saccadic eye movement tasks. *Exp Brain Res* 121: 391–400, 1998.
224. MUNOZ DP AND GUITTON D. Presaccadic burst discharges of tecto-reticulo-spinal neurons in the alert head-free and -fixed cat. *Brain Res* 398: 185–190, 1986.
225. MUSHIAKE H AND STRICK PL. Pallidal neuron activity during sequential arm movements. *J Neurophysiol* 74: 2754–2758, 1996.
226. MUTO N, KAKEI S, AND SHINODA Y. Morphology of single axons of tectospinal neurons in the upper cervical spinal cord. *J Comp Neurol* 372: 9–26, 1996.
227. NAKAHARA H, DOYA K, HIKOSAKA O, AND NAGANO S. Multiple representations in the basal ganglia loops for sequential decision making. *Technical Report of IEICE* NC97–24: 97–104, 1997.
228. NAKAMURA K, SAKAI K, AND HIKOSAKA O. Neuronal activity in medial frontal cortex during learning of sequential procedures. *J Neurophysiol* 80: 2671–2687, 1998.
229. NAKAMURA K, SAKAI K, AND HIKOSAKA O. Effects of local inactivation of monkey medial frontal cortex in learning of sequential procedures. *J Neurophysiol* 82: 1063–1068, 1999.
230. NAKANISHI H, KITA H, AND KITAI ST. Intracellular study of rat substantia nigra pars reticulata neurons in an in vitro slice preparation: electrical membrane properties and response characteristics to subthalamic stimulation. *Brain Res* 437: 45–55, 1987.
231. NAMBU A, TAKADA M, INASE M, AND TOKUNO H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. *J Neurosci* 16: 2671–2683, 1996.
232. NARABAYASHI H, YOKOCHI M, IIZUKA R, AND NAGATSU T. Juvenile parkinsonism. In: *Extrapyramidal Disorders*, edited by P. J. Vinken, G. W. Bruyn, and H. L. Klawans. Amsterdam: Elsevier, 1986, p. 153–165.
233. NIIJIMA K AND YOSHIDA M. Electrophysiological evidence for branching nigral projections to pontine reticular formation, superior colliculus and thalamus. *Brain Res* 29: 279–282, 1982.
234. NISHINO H, ONO T, FUKUDA M, AND SASAKI K. Monkey substantia nigra (pars reticulata) neuron discharges during operant feeding. *Brain Res* 334: 190–193, 1985.
235. NISHINO H, ONO T, MURAMOTO K, FUKUDA M, AND SASAKI K. Movement and non-movement related pallidal unit activity during bar press feeding behavior in the monkey. *Behav Brain Res* 15: 27–42, 1985.
236. NISHINO H, ONO T, SASAKI K, FUKUDA M, AND MURAMOTO K-I. Caudate unit activity during operant feeding behavior in monkeys and modulation by cooling prefrontal cortex. *Behav Brain Res* 11: 21–33, 1984.
237. NODA T AND OKA H. Nigral inputs to the pedunculopontine region: intracellular analysis. *Brain Res* 322: 332–336, 1984.
238. OHNO T AND TSUBOKAWA H. Regional differences in the cat caudate nucleus as to the effectiveness in inducing contraversive head-turning by electrical stimulation. *Neurosci Res* 4: 497–516, 1987.
239. OLDS J AND MILNER P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 47: 419–427, 1954.
240. OWEN AM, JAMES M, LEIGH PN, SUMMERS BA, MARSDEN CD, QUINN NP, LANGE KW, AND ROBBINS TW. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* 115: 1727–1751, 1992.
241. PARÉ M AND WURTZ RH. Monkey posterior parietal cortex neurons antidromically activated from superior colliculus. *J Neurophysiol* 78: 3493–3497, 1997.
242. PARENT A, BOUCHARD C, AND SMITH Y. The striatopallidal and striatonigral projections: two distinct fiber systems in primate. *Brain Res* 303: 385–390, 1984.
243. PARENT A AND DE BELLEFEUILLE L. The pallidointralaminar and pallidonigral projections in primate as studied by retrograde double-labeling method. *Brain Res* 278: 11–27, 1983.
244. PARENT A AND SMITH Y. Organization of efferent projections of the subthalamic nucleus in the squirrel monkey as revealed by retrograde labeling methods. *Brain Res* 436: 296–310, 1987.
245. PARTHASARATHY HB, SCHALL JD, AND GRAYBIEL AM. Distributed but convergent ordering of corticostriatal projections: analysis of the frontal eye field and the supplementary eye field in the macaque monkey. *J Neurosci* 12: 4468–4488, 1992.
246. PASCUAL-LEONE A, GRAFMAN J, CLARK K, STEWART M, MASSAQUOI S, LOU J-S, AND HALLETT M. Procedural learning of Parkinson's disease and cerebellar degeneration. *Ann Neurol* 34: 594–602, 1993.
247. PENNEY JB JR AND YOUNG AB. Speculations on the functional anatomy of basal ganglia disorders. *Annu Rev Neurosci* 6: 73–94, 1983.
248. PERCHERON G, YELNIK J, AND FRANÇOIS C. A Golgi analysis of the primate globus pallidus. III. Spatial organization of the striatopallidal complex. *J Comp Neurol* 227: 214–227, 1984.
249. PETERSON B, RIDDLE MA, COHEN DJ, KATZ LD, SMITH JC, HARDIN MT, AND LECKMAN JF. Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. *Neurology* 43: 941–949, 1993.
250. PETIT L, ORSSAUD C, TZOURIO N, CRIVELLO F, BERTHOZ A, AND MAZOYER B. Functional anatomy of a prelearned sequence of horizontal saccades in humans. *J Neurosci* 16: 3714–3726, 1996.
251. PHELPS PE, HOUSER CR, AND VAUGHN JE. Immunocytochemical localization of choline acetyltransferase within the rat neostriatum: a correlated light and electron microscopic study of cholinergic neurons and synapses. *J Comp Neurol* 238: 286–307, 1985.
252. PRESTON RJ, BISHOP GA, AND KITAI ST. Medium spiny neuron

projection from the rat striatum: an intracellular horseradish peroxidase study. *Brain Res* 183: 253–263, 1980.
253. RAGSDALE CW AND GRAYBIEL AM. Fibers from the basolateral nucleus of the amygdala selectively innervate striosomes in the caudate nucleus of the cat. *J Comp Neurol* 269: 506–522, 1988.
254. RAND MK, HIKOSAKA O, MIYACHI S, LU X, AND MIYASHITA K. Characteristics of a long-term procedural skill in the monkey. *Exp Brain Res* 118: 293–297, 1998.
255. RAUCH SL, WHALEN PJ, SAVAGE CR, CURRAN T, KENDRICK A, BROWN HD, BUSH G, BREITER HC, AND ROSEN BR. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Hum Brain Mapping* 5: 124–132, 1997.
256. REDGRAVE P, MARROW L, AND DEAN P. Topographical organization of the nigrotectal projection in rat: evidence for segregated channels. *Neuroscience* 50: 571–595, 1992.
257. REDGRAVE P, PRESCOTT TJ, AND GURNEY K. The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience* 89: 1009–1023, 1999.
258. REMINGTON RW. Attention and saccadic eye movements. *J Exp Psychol* 6: 726–744, 1980.
259. RINVIK E, GROFOVA I, AND OTTERSEN OP. Demonstration of nigrotectal and nigroreticular projections in the cat by axonal transport of proteins. *Brain Res* 112: 388–394, 1976.
260. ROBINSON DA. Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res* 12: 1795–1808, 1972.
261. ROBINSON DA. Control of eye movements. In: *The Nervous System*, edited by V. B. Brooks. Bethesda, MD: Am. Physiol. Soc., 1981, p. 1275–1320.
262. ROBINSON DL AND MCCLURKIN JW. The visual superior colliculus and pulvinar. In: *The Neurobiology of Saccadic Eye Movements*, edited by R. H. Wurtz and M. E. Goldberg. Amsterdam: Elsevier, 1989, p. 337–360.
263. ROLLS ET, THORPE SJ, AND MADDISON SP. Responses of striatal neurons in the behaving monkey. I. Head of the caudate nucleus. *Behav Brain Res* 7: 179–210, 1983.
264. ROSE PK, MACDONALD J, AND ABRAHAMS VC. Projections of the tectospinal tract to the upper cervical spinal cord of the cat: a study with the anterograde tracer PHA-L. *J Comp Neurol* 314: 91–105, 1991.
265. SACKS OW. *Awakenings*. New York: Dutton, 1983.
266. SAINT-CYR JA, TAYLOR AE, AND LANG AE. Procedural learning and neostriatal dysfunction in man. *Brain* 111: 941–959, 1988.
267. SAKAMOTO M AND HIKOSAKA O. Eye movements induced by microinjection of GABA agonist in the rat substantia nigra pars reticulata. *Neurosci Res* 6: 216–233, 1989.
268. SAKASHITA Y. Visual attentional disturbance with unilateral lesions in the basal ganglia and deep white matter. *Ann Neurol* 30: 673–677, 1991.
269. SAWAGUCHI T AND GOLDMAN-RAKIC PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science* 251: 947–950, 1991.
270. SCHALL JD, HANES DP, THOMPSON KG, AND KING DJ. Saccade target selection in frontal eye field of macaque. I. Visual and premovement activation. *J Neurosci* 15: 6905–6918, 1995.
271. SCHILLER PH AND STRYKER M. Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *J Neurophysiol* 35: 915–924, 1972.
272. SCHNEIDER WX AND DEUBEL H. Visual attention and saccadic eye movements: evidence for obligatory and selective spatial coupling. In: *Eye Movement Research: Mechanisms, Processes and Applications*, edited by J. M. Findlay, R. W. Kentridge, and R. Walker. Amsterdam: Elsevier, 1995, p. 317–324.
273. SCHULTZ W. Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. *J Neurophysiol* 56: 1439–1461, 1986.
274. SCHULTZ W. Predictive reward signal of dopamine neurons. *J Neurophysiol* 80: 1–27, 1998.
275. SCHULTZ W, APICELLA P, AND LJUNGBERG T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J Neurosci* 13: 900–913, 1993.
276. SCHULTZ W, APICELLA P, SCARNATI E, AND LJUNGBERG T. Neuronal activity in monkey ventral striatum related to the expectation of reward. *J Neurosci* 12: 4595–4610, 1992.
277. SCHULTZ W, DAYAN P, AND MONTAGUE PR. A neural substrate of prediction and reward. *Science* 275: 1593–1599, 1997.
278. SCHULTZ W AND ROMO R. Neuronal activity in the monkey striatum during the initiation of movements. *Exp Brain Res* 71: 431–436, 1988.
279. SCHULTZ W, ROMO R, SCARNATI E, SUNDOSTROM E, JONSSON G, AND STUDER A. Saccadic reaction times, eye-arm coordination and spontaneous eye movements in normal and MPTP-treated monkeys. *Exp Brain Res* 78: 253–267, 1989.
280. SCHWAB RS AND ZIEPER I. Effects of mood, motivation, stress and alertness on the performance in Parkinson's disease. *Psychiatr Neurol* 150: 345–357, 1965.
281. SEGAWA M, NOMURA Y, AND KASE M. Diurnally fluctuating hereditary progressive dystonia. In: *Extrapyramidal Disorders*, edited by P. J. Vinken, G. W. Bruyn, and H. L. Klawans. Amsterdam: Elsevier, 1986, p. 529–538.
282. SEGRAVES MA AND GOLDBERG ME. Functional properties of corticotectal neurons in the monkey's frontal eye field. *J Neurophysiol* 58: 1387–1419, 1987.
283. SELBY G. Parkinson's disease. In: *Handbook of Clinical Neurology*, edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North Holland, 1968, p. 173–211.
284. SELEMON LD AND GOLDMAN-RAKIC PS. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J Neurosci* 5: 776–794, 1985.
285. SHIBASAKI H, TSUJI S, AND KUROIWA Y. Oculomotor abnormalities in Parkinson's disease. *Arch Neurol* 36: 360–364, 1979.
286. SHIMIZU N, NAITO M, AND YOSHIDA M. Eye-head co-ordination in patients with Parkinsonism and cerebellar ataxia. *J Neurol Neurosurg Psychiatry* 44: 509–515, 1981.
287. SHINK E, BEVAN MD, BOLAM JP, AND SMITH Y. The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey. *Neuroscience* 73: 335–357, 1996.
288. SHOOK BL, SCHLAG-REY M, AND SCHLAG J. Primate supplementary eye field. II. Comparative aspects of connections with the thalamus, corpus striatum, and related forebrain nuclei. *J Comp Neurol* 307: 562–583, 1991.
289. SINGER HS AND WALKUP JT. Tourette syndrome and other tic disorders. Diagnosis, pathophysiology, and treatment. *Medicine* 70: 15–32, 1991.
290. SMITH AD AND BOLAM JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. *Trends Neurosci* 13: 259–265, 1990.
291. SMITH Y, BEVAN MD, SHINK E, AND BOLAM JP. Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* 86: 353–387, 1998.
292. SMITH Y AND BOLAM JP. The output neurones and the dopaminergic neurones of the substantia nigra receive a GABA-containing input from the globus pallidus in the rat. *J Comp Neurol* 296: 47–64, 1990.
293. SMITH Y AND BOLAM JP. Convergence of synaptic inputs from the striatum and the globus pallidus onto identified nigrocollicular cells in the rat: a double anterograde labelling study. *Neuroscience* 44: 45–73, 1991.
294. SMITH Y, HAZRATI L-N, AND PARENT A. Efferent projections of the subthalamic nucleus in the squirrel monkey as studied by the PHA-L anterograde tracing method. *J Comp Neurol* 294: 306–323, 1990.
295. SNYDER LH, BATISTA AP, AND ANDERSEN RA. Coding of intention in the posterior parietal cortex. *Nature* 386: 167–170, 1997.
296. SOMMER MA AND WURTZ RH. Frontal eye field neurons orthodromically activated from the superior colliculus. *J Neurophysiol* 80: 3331–3335, 1998.
297. SPARKS DL. Translation of sensory signals into commands for control of saccadic eye movements: role of primate superior colliculus. *Physiol Rev* 66: 118–171, 1986.
298. SPARKS DL AND HARTWICH-YOUNG R. The deep layers of the superior colliculus. In: *The Neurobiology of Saccadic Eye Movements*, edited by R. H. Wurtz and M. E. Goldberg. Amsterdam: Elsevier, 1989, p. 213–255.

299. STANTON GB, GOLDBERG ME, AND BRUCE CJ. Frontal eye field efferents in the macaque monkey. I. Subcortical pathways and topography of striatal and thalamic terminal fields. *J Comp Neurol* 271: 473–492, 1988.
300. STANTON GB, GOLDBERG ME, AND BRUCE CJ. Frontal eye field efferents in the macaque monkey. II. Topography of terminal fields in midbrain and pons. *J Comp Neurol* 271: 493–506, 1988.
301. STARR A. A disorder of rapid eye movements in Huntington's chorea. *Brain* 9: 545–564, 1967.
302. STEIN BE, MEREDITH MA, HUNEYCUTT WS, AND MCDADE L. Behavioral indices of multisensory integration: orientation to visual cues is affected by auditory stimuli. *J Cogn Neurosci* 1: 12–24, 1989.
303. STERN Y, MAYEUX R, ROSEN J, AND ILSON J. Perceptual motor dysfunction in Parkinson's disease: a deficit in sequential and predictive voluntary movement. *J Neurol Neurosurg Psychiatry* 46: 145–151, 1983.
304. STRICK PL, DUM RP, AND MUSHIAKE H. Basal ganglia "loops" with the cerebral cortex. In: *Functions of the Cortico-Basal Ganglia Loop*, edited by M. Kimura and A. M. Graybiel. Tokyo: Springer, 1995, p. 106–124.
305. SURMEIER DJ, SONG W-J, AND YAN Z. Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. *J Neurosci* 16: 6579–6591, 1996.
306. SWEENEY JA, MINTUN MA, KWEE S, WISEMAN MB, BROWN DL, RESENBERG DR, AND CARL JR. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J Neurophysiol* 75: 454–468, 1996.
307. TAKADA M, TOKUNO H, NAMBU A, AND INASE M. Corticostriatal projections from the somatic motor areas of the frontal cortex in the macaque monkey: segregation versus overlap of input zones from the primary motor cortex, the supplementary motor area, and the premotor cortex. *Exp Brain Res* 120: 114–128, 1998.
308. TEPPER JM, MARTIN LP, AND ANDERSON DR. $GABA_A$ receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. *J Neurosci* 15: 3092–3103, 1995.
309. TERÄVÄINEN H AND CALNE DB. Studies of parkinsonian movement. 1. Programming and execution of eye movements. *Acta Neurol Scand* 62: 137–148, 1980.
310. TIAN JR, ZEE DS, LASKER AG, AND FOLSTEIN SE. Saccades in Huntington's disease: predictive tracking and interaction between release of fixation and initiation of saccades. *Neurology* 41: 875–881, 1991.
311. VAN DEN BERCKEN JHL AND COOLS AR. Evidence for a role of the caudate nucleus in the sequential organization of behaviour. *Behav Brain Res* 4: 319–337, 1982.
312. VAN DEN POL AN, SMITH AD, AND POWELL JF. GABA axons in synaptic contact with dopamine neurons in the substantia nigra: double immunocytochemistry with biotin-peroxidase and protein A-colloidal gold. *Brain Res* 348: 146–154, 1985.
313. VENTRE J, ZEE DS, PAPAGEORGIOU H, AND REICH S. Abnormalities of predictive saccades in hemi-Parkinson's disease. *Brain* 115: 1147–1165, 1992.
314. VIDAILHET M, RIVAUD S, GOUIDER-KHOUJA N, PILLON B, BONNET A-M, GAYMARD B, AGID Y, AND PIERROT-DESEILLIGNY C. Eye movements in Parkinsonian syndromes. *Ann Neurol* 420–426, 1994.
315. VILLABLANCA JR, MARCUS RJ, AND OLMSTEAD CE. Effects of caudate nuclei or frontal cortical ablations in cats. I. Neurology and gross behavior. *Exp Neurol* 52: 389–420, 1976.
316. VILLARDITA C, SMIRNI P, AND ZAPPALÀ G. Visual neglect in Parkinson's disease. *Arch Neurol* 40: 737–739, 1983.
317. VINCENT SR, HATTORI T, AND MCGEER EG. The nigrotectal projection: a biochemical and ultrastructural characterization. *Brain Res* 151: 159–164, 1978.
318. VIVIANI P. Eye movements in visual search: cognitive, perceptual and motor control aspects. In: *Eye Movements and Their Role in Visual and Cognitive Processes*, edited by E. Kowler. Amsterdam: Elsevier, 1990, p. 353–393.
319. WALLACE MT, WILKINSON LK, AND STEIN BE. Representation and integration of multiple sensory inputs in primate superior colliculus. *J Neurophysiol* 76: 1246–1266, 1996.
320. WARABI T, NODA H, YANAGISAWA N, TASHIRO K, AND SHINDO R. Changes in sensorimotor function associated with the degree of bradykinesia of Parkinson's disease. *Brain* 109: 1209–1224, 1986.
321. WARD NM AND BROWN VJ. Covert orienting of attention in the rat and the role of striatal dopamine. *J Neurosci* 16: 3082–3088, 1996.
322. WARTON S, JONES DG, ILINSKY IA, AND KULTAS-ILINSKY K. Nigral and cerebellar synaptic terminals in the intermediate and deep layers of the cat superior colliculus revealed by lesioning studies. *Neuroscience* 10: 789–800, 1983.
323. WATANABE M. Reward expectancy in primate prefrontal neurons. *Nature* 382: 629–632, 1996.
324. WATANABE M. Cognitive and motivational operations in primate prefrontal neurons. *Rev Neurosci* 9: 225–241, 1998.
325. WEISS P, STELMACH GE, AND HEFTER H. Programming of a movement sequence in Parkinson's disease. *Brain* 120: 91–102, 1997.
326. WHITE OB, SAINT-CYR JR, TOMLINSON RD, AND SHARPE JA. Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain* 106: 571–587, 1983.
327. WICKENS J AND KÖTTER R. Cellular models of reinforcement. In: *Models of Information Processing in the Basal Ganglia*, edited by J. C. Houk, J. L. Davis, and D. G. Beiser. Cambridge, MA: MIT Press, 1995, p. 187–214.
328. WILLIAMS MN AND FAULL RLM. The striatonigral projection and nigrotectal neurons in the rat. A correlated light and electron microscopic study demonstrating a monosynaptic striatal input to identified nigrotectal neurons using a combined degeneration and horseradish peroxidase procedure. *Neuroscience* 14: 991–1010, 1985.
329. WILLIAMS MN AND FAULL RLM. The nigrotectal projection and tectospinal neurons in the rat. A light and electron microscopic study demonstrating a monosynaptic nigral input to identified tectospinal neurons. *Neuroscience* 25: 533–562, 1988.
330. WILSON CJ AND KAWAGUCHI Y. The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J Neurosci* 16: 2397–2410, 1996.
331. WISE RA. Neurobiology of addiction. *Curr Opin Neurobiol* 6: 243–251, 1996.
332. WURTZ RH AND ALBANO JE. Visual-motor function of the primate superior colliculus. *Annu Rev Neurosci* 3: 189–226, 1980.
333. WURTZ RH AND GOLDBERG ME (Editors). *The Neurobiology of Saccadic Eye Movements*. Amsterdam: Elsevier, 1989.
334. WURTZ RH, GOLDBERG ME, AND ROBINSON DL. Behavioral modulation of visual responses in the monkey: stimulus selection for attention and movement. In: *Progress in Psychobiology and Physiological Psychology*, edited by J. M. Sprague and A. N. Epstein. New York: Academic, 1980, p. 43–83.
335. WURTZ RH AND MOHLER CW. Enhancement of visual responses in monkey striate cortex and frontal eye fields. *J Neurophysiol* 39: 766–772, 1976.
336. YETERIAN EH AND PANDYA DN. Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. *J Comp Neurol* 312: 43–67, 1991.
337. YOSHIDA M AND PRECHT W. Monosynaptic inhibition of neurons in the substantia nigra by caudate-nigral fibers. *Brain Res* 32: 225–228, 1971.
338. YOSHIDA S-I, NAMBU A, AND JINNAI K. The distribution of the globus pallidus neurons with input form various cortical areas in the monkeys. *Brain Res* 611: 170–174, 1993.