Basal Ganglia Mechanisms of Reward-Oriented Eye Movement

OKIHIDE HIKOSAKA

Laboratory of Sensorimotor Research, National Eye Institute, National Institute of Health, Bethesda, Maryland, USA

ABSTRACT: **Expectation of reward facilitates motor behaviors that enable the animal to approach a location in space where the reward is expected. It is now known that the same expectation of reward profoundly modifies sensory, motor, and cognitive information processing in the brain. However, it is still unclear which brain regions are responsible for causing the reward-approaching behavior. One candidate is the dorsal striatum where cortical and dopaminergic inputs converge. We tested this hypothesis by injecting dopamine antagonists into the caudate nucleus (CD) while the monkey was performing a saccade task with a position-dependent asymmetric reward schedule. We previously had shown that: (1) serial GABAergic connections from the CD to the superior colliculus (SC) via the substantia nigra pars reticulata (SNr) exert powerful control over the initiation of saccadic eye movement and (2) these GABAergic neurons encode target position and are strongly influenced by expected reward, while dopaminergic neurons in the substantia nigra pars compacta (SNc) encode only reward-related information. Before injections of dopamine antagonists the latencies of saccades to a given target were shorter when the saccades were followed by a large reward than when they were followed by a small reward. After injections of dopamine D1 receptor antagonist the reward-dependent latency bias became smaller. This was due to an increase in saccade latency on large-reward trials. After injections of D2 antagonist the latency bias became larger, largely due to an increase in saccade latency on small-reward trials. These results indicate that: (1) dopamine-dependent information processing in the CD is necessary for the reward-dependent modulation of saccadic eye movement and (2) D1 and D2 receptors play differential roles depending on the positive and negative reward outcomes.**

KEYWORDS: **saccadic eye movement; caudate nucleus; substantia nigra pars reticulata; substantia nigra pars compacta; superior colliculus; dopamine; D1 receptor; D2 receptor; GABA**

Address for correspondence: Okihide Hikosaka, Laboratory of Sensorimotor Research, National Eye Institute, National Institute of Health, 49 Convent Drive, Bldg. 49, Rm. 2A50, Bethesda, MD 20892-4435, USA. Voice: 301-402-7959; fax: 301-402-0511.
oh@lsr.nei.nih.gov

Ann. N.Y. Acad. Sci. 1104: 229–249 (2007).
doi: 10.1196/annals.1390.012

INTRODUCTION

The initiation of body movements can be influenced by expected rewards. Recent studies using trained monkeys revealed that many neurons in what are usually called cognitive or sensorimotor areas are modulated by reward, including the dorsolateral prefrontal cortex,[1–6] posterior parietal cortex,[7–9] premotor cortex,[10,11] and dorsal striatum.[12–19] Furthermore, other factors that influence behavior, such as learning,[20] memory,[21] and attention,[22] seem dependent on reward. Similar findings have been reported in functional imaging studies using human subjects.[23–25] These data appear to provide a strong background for understanding the neural mechanism of reward-modulated behavior. However, it is still difficult to connect these findings to produce coherent stories. There are at least two problems that prevent our understanding. First, the input–output relationship of the recorded neurons is often unclear. It is unclear whether the neurons really contribute to the reward-dependent modulation of behavior or how they receive reward-related information. Second, the reward-modulated behavior is often not well defined. When the behavior is changed by reward, it is possible that different body movements are used.

Considering the first problem, the basal ganglia seem an ideal place to study the reward-dependent motivational control of behavior. It has been well known that basal ganglia receive substantial reward-related information and strongly influence body movements. First, the motor function of the basal ganglia is illustrated by various kinds of movement disorders (e.g., inability to initiate or suppress movements) in basal ganglia dysfunctions (e.g., Parkinson's disease).[26] This *motor* function is achieved by the outputs of the basal ganglia to the brainstem motor areas (e.g., superior colliculus) and the *movement-related* areas in the cerebral cortex through the thalamus.[27,28] Second, the reward-related information to the basal ganglia is likely to be derived from substantial inputs from the limbic system (e.g., amygdala) to the ventral striatum (e.g., nucleus accumbens)[29,30] and dorsal striatum (i.e., CD nucleus and putamen),[31] and to dopamine (DA) neurons in and around the substantia nigra (SN).[32] In particular, DA neurons, which appear to carry an essential signal for reward-based learning,[33] are an important part of the basal ganglia system and project most heavily within the basal ganglia. Third, sequential and parallel inhibitory connections in the basal ganglia are thought to be suitable for the selection and learning of optimal behavior.[34,35] Fourth, the basal ganglia are thought to play an important role in learning of sensorimotor procedures or habits.[36–38] Finally, sensorimotor-cognitive signals originating from the cerebral cortex are funneled through the basal ganglia and are returned to the cerebral cortex.[39] In short, the basal ganglia are located in a perfect position to control motor behaviors based on reward information.

The basal ganglia are also ideal for solving the second problem mentioned above, that is, to define the kind of body movement as a behavioral measure. It has been well documented that the neural circuits involving the CD and the

SNr exert a powerful control over the generation of saccadic eye movement.[40] Another advantage of using saccadic eye movement is that its mechanism in the brainstem has been studied perhaps more extensively than any other motor behavior.[41] Furthermore, an important component of reward-modulated behavior is orienting movement[31] and an important component of orienting movement is saccadic eye movement.[42] The animal must orient its eye, head, and body to the location where reward is available before procuring it.[43] Saccadic eye movement is particularly important for humans[44,45] and monkeys.[46] As will be shown in this article, the initiation of saccadic eye movement is clearly facilitated or suppressed depending on the reward outcome.

In the present review, I first summarize the neuronal mechanism in the basal ganglia for the control of saccadic eye movement. I will then describe the reward-dependent changes of neuronal activity along the saccade-related neuronal circuit in the basal ganglia and related structures. Finally, I will present evidence that the reward-dependent modulation basal ganglia neuronal activity is caused by dopaminergic inputs to the CD.

OCULOMOTOR CONTROL BY THE BASAL GANGLIA

A fixed, vacant facial expression of patients with Parkinson's disease, which is often called the *Parkinson's mask*, is due to the paucity of movements in the face, including the paucity of eye movements. Similar symptoms were observed in MPTP-induced DA-deficient monkeys (FIG. 1A).[47] Most affected among various kinds of eye movements are smooth pursuit and saccades, which require voluntary control.[40] Parkinsonian patients are often impaired in shifting their gaze from one position in space to another (deficit in saccades). Compared to age-matched control subjects, saccades of parkinsonian patients tend to be small in amplitude (i.e., hypometric), slow, and delayed (i.e., long latency). Curiously, the deficit in saccades is often more severe if there is no visible object and the saccades must rely on memory. Selective deficits in memory-guided saccades are observed in other basal ganglia disorders, including Huntington's disease. The similarity between Parkinson's and Huntington's diseases is noteworthy because they are caused by different mechanisms, the former by a loss of neurons in the SNc and the latter by a loss of neurons in the CD. This suggests that the SN and the CD work together for the control of saccadic eye movements.

How the basal ganglia might control eye movements has been studied by recording single cell activity in animals trained on the visually guided and memory-guided saccade tasks. Electrical activity of single neurons was recorded with microelectrodes and was correlated with saccadic eye movements. Saccade-related activity has been found in various nuclei in the basal ganglia, including the SN,[48–50] CD,[51] subthalamic nucleus (STN),[52] and globus pallidus (GP).[53] Anatomical studies have shown that these saccade-related

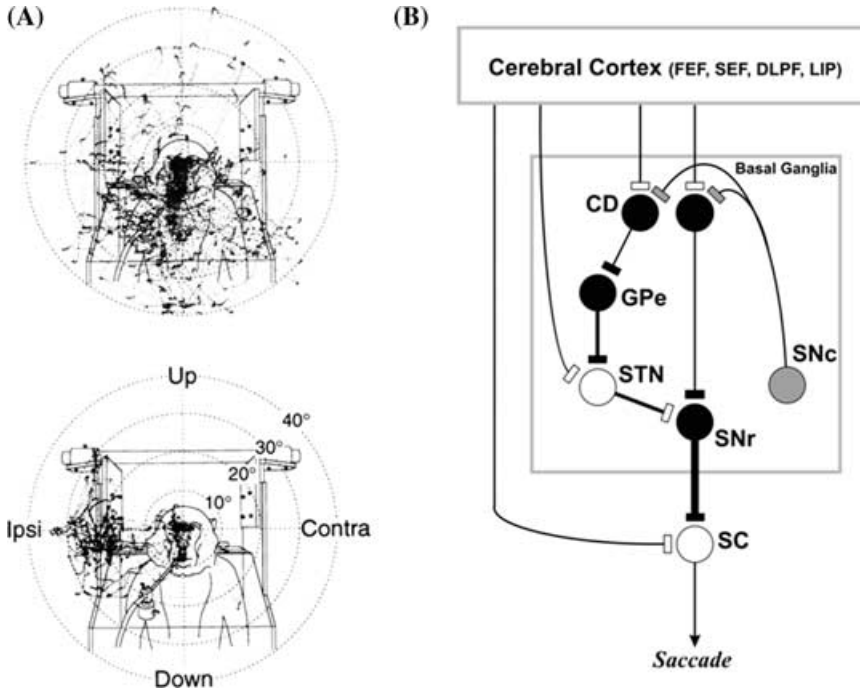

FIGURE 1. Abnormal eye movements in monkeys induced by basal ganglia dysfunctions. (**A**) Eye movements of a monkey while he was looking in a mirror before (*top*) and 31 days after (*bottom*) dopaminergic denervation of the left caudate nucleus by MPTP. Shown are the trajectories of eye movements superimposed on the view seen in the mirror by the monkey.[47] (**B**) Basal ganglia neural network involved in the control of saccadic eye movement. CD = caudate nucleus; SNr = substantia nigra pars reticulata; SC = superior colliculus; SNc = substantia nigra pars compacta; Gpe = globus pallidus external segment; STN = subthalamic nucleus; FEF = frontal eye field; SEF = supplementary eye field; DLPF = dorsolateral prefrontal cortex; LIP = area LIP in parietal cortex. Excitatory and inhibitory neurons and synapses are indicated by open and filled symbols, respectively. Gray symbol indicates dopaminergic neuron, which exerts modulatory effects on CD neurons. The thickness of the line (axon) roughly indicates the level of spontaneous activity. The direct excitation of SC neurons by inputs from the cerebral cortex is gated by the inhibitory input from the SNr.

parts are connected within the basal ganglia and with saccade-related regions outside the basal ganglia[40] (FIG. 1B). For example, the saccade-related part of the CD receives inputs from the frontal eye field and the supplementary eye field in the frontal cerebral cortex[54] while the saccade-related part of the SNr projects their axons to the superior colliculus (SC).[55]

An important feature of the basal ganglia circuits is that they use inhibitory connections as a primary means to convey signals[56] (FIG. 1B). Each area contains projection neurons and interneurons. While cortical inputs to the CD

are excitatory and use glutamate as a transmitter, projection neurons in all areas in the basal ganglia, except the STN, are thought to be GABAergic and inhibitory. This means that the polarity of a signal is reversed each time it passes through projection neurons in one area. There are at least three parallel pathways in which saccade-related signals can be processed in the basal ganglia (FIG. 1B)[57]: (1) direct pathway from the CD to the SNr; (2) indirect pathway from the CD to the SNr through the GPe and/or the STN; (3) hyper-direct pathway from the STN to the SNr. Since the direct pathway consists of a series of two inhibitory connections (CD and SNr), the net effect is facilitatory. Since the indirect pathway and the hyper-direct pathways consist of three and one inhibitory connection, respectively, the net effect is inhibitory. The basal ganglia thus could facilitate or inhibit motor processes by selectively using these pathways. The target area for saccadic eye movement is the SC.

With respect to saccadic motor control in general, the basal ganglia system is situated as a side path, which has been added to the direct effect of the cerebral cortex on the SC (FIG. 1B). Probably the most important question is: How unique is the function of the basal ganglia, compared to the direct cortico-SC effect? The answers to this question should be found in the content of information carried by neurons in the CD and SNr.

The neural circuit in the basal ganglia related to eye movements originates in the CD and converges on the SNr, which then projects to the SC[40] (FIGS. 1B and 2B). The CD is a large structure in the basal ganglia and, together with the putamen, is called the striatum or the dorsal striatum. A majority of inputs to the basal ganglia are destined for the striatum, which thus acts as the input station of the basal ganglia. In addition to the cortical inputs, the entire CD (together with the putamen and the ventral striatum) receives diffuse inputs from dopaminergic neurons in the SNc and its surrounding regions (FIGS. 1B and 2B).[58] It is likely that particular combinations of these inputs create signals unique to CD neurons.

Neurons in the SNr are characterized by their rapid and tonic firing (FIG. 2A). Their firing frequency is usually between 40 and 100 spikes/sec in monkeys.[40] Furthermore, virtually all of them are GABAergic. These facts indicate that neurons in the SC should be kept inhibited by them. This inhibition can be reduced or eliminated by injecting a small amount of a GABA agonist (muscimol) into the SNr. After muscimol injection in the SNr, animals can no longer maintain stable eye position and make saccades continually and probably involuntarily (FIG. 2C). This happens to all animals tested: monkeys,[59] cats,[60] and rats.[61] Rats, compared to monkeys, exhibit a wider range of involuntary movements in addition to eye movements. These findings may be relevant to the fact that patients with basal ganglia dysfunction usually exhibit some type of involuntary movements, such as tremor, dyskinesia, dystonia, ballism, and chorea. These involuntary movements are likely to be caused by a reduction of the basal ganglia-induced inhibition.

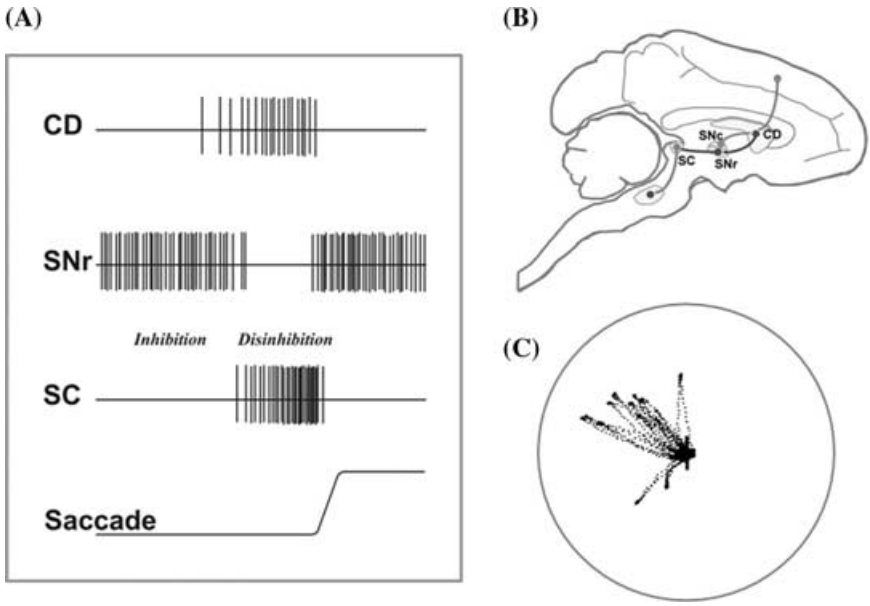

FIGURE 2. Basal ganglia mechanism for control of saccadic eye movement. (**A**) A cardinal saccade mechanism in the basal ganglia. The SC is normally inhibited by rapid firing of GABAergic neurons in the SNr. The tonic inhibition can be interrupted by GABAergic inputs from the CD. This disinhibition, together with excitatory cortical inputs, allows SC neurons to fire in burst, which leads to a saccade to a contralateral location. (**B**) Simplified neural circuits in the basal ganglia for control of saccadic eye movement in a parasagittal view of the macaque brain. (**C**) Involuntary eye movement of a monkey after muscimol injection into right SNr, shown as trajectories of saccades during 2-sec fixation periods. The monkey was unable to keep fixating at the central spot of light.[59]

Neurons in the SNr change (usually decrease) their firing rates in preparation for saccadic eye movement[62] (FIG. 2A). Many SNr neurons stop firing in response to a visual stimulus if the animal is ready to make a saccade to it. Other neurons do so just before the saccade. The inhibition of SNr neurons is caused, at least partly, by the GABAergic input from the CD. Electrical stimulation in the CD induces inhibitions and occasionally facilitations in SNr neurons.[63] The former is likely to be mediated by the direct CD-SNr inhibitory connection, while the latter is likely to be mediated by the indirect pathway through the GP (FIG. 1B).

Many of these SNr neurons project to the intermediate layer of the SC[40] and have inhibitory synaptic contacts with saccadic burst neurons.[55,64] This means that the SNr-induced tonic inhibition on SC neurons is removed or reduced before saccades (FIG. 2A). Note that saccadic neurons in the SC receive excitatory inputs from many brain areas, especially saccade-related cortical

areas: the frontal eye field (FEF), supplementary eye field (SEF), and lateral intraparietal area (LIP)[65–67] (FIG. 1B). These excitatory cortical inputs, together with the SNr-induced disinhibition, would make SC neurons fire in a burst and the signal is sent to the brainstem saccade generators. Note, however, SNr neurons may increase their activity before saccade. In such a case, the SC would be less likely to generate a signal to induce saccades.

To summarize, the SNr-induced inhibition on SC neurons acts as a gate for saccade generation (FIG. 2A). SC neurons are constantly bombarded by excitatory inputs from many brain areas because there are so many objects that can attract our attention and gaze. However, these inputs are often incapable of inducing a burst of spikes in SC neurons due to the SNr-induced tonic inhibition. Only when the SNr-induced inhibition is reduced, SC neurons would exhibit a burst of spikes reliably. This is probably a very efficient mechanism to select an appropriate action in a particular context.

NEURONAL ACTIVITY IN THE BASAL GANGLIA IS MODULATED BY EXPECTED REWARD

A feature common to CD and SNr neurons is that their activity is often strikingly dependent on the behavioral context. Another feature is that many CD neurons fire tonically in an anticipatory manner before an expected task-related event occurs, such as before the onset of an expected target or the delivery of an expected reward.[14,68] And *reward* turned out to be a key factor that characterizes the information processing in the basal ganglia, as described below.

To examine the effect of reward on saccadic eye movement, we have used saccade tasks in which the amount of reward is unequal among possible target positions. We chose position as a cue for reward for two reasons. First, the goal of saccadic eye movement is to localize an object in space.[42,44] Second, when an animal forages for food, the most crucial behavior is to localize a place where the food is available.[31] Positional cues have widely been used in learning tasks, such as conditioned place preference task.[69]

In our saccade tasks the target was presented randomly at one out of two or four directions, but only one direction was associated with a big reward while the others were associated with a small or no reward (FIG. 3A). The big-reward direction was fixed in a block of 20–60 trials and is changed in the next block (FIG. 3B). Let us call this 1DR (one-direction rewarded) saccade task. We used visual and memory versions. In the visual-1DR task, the monkey makes a saccade to the target immediately after its onset (FIG. 3A, *top*).[17] In the memory-1DR task, the target position was cued and the monkey has to make saccade to the cued position after a time delay based on memory (FIG. 3A, *bottom*).[12]

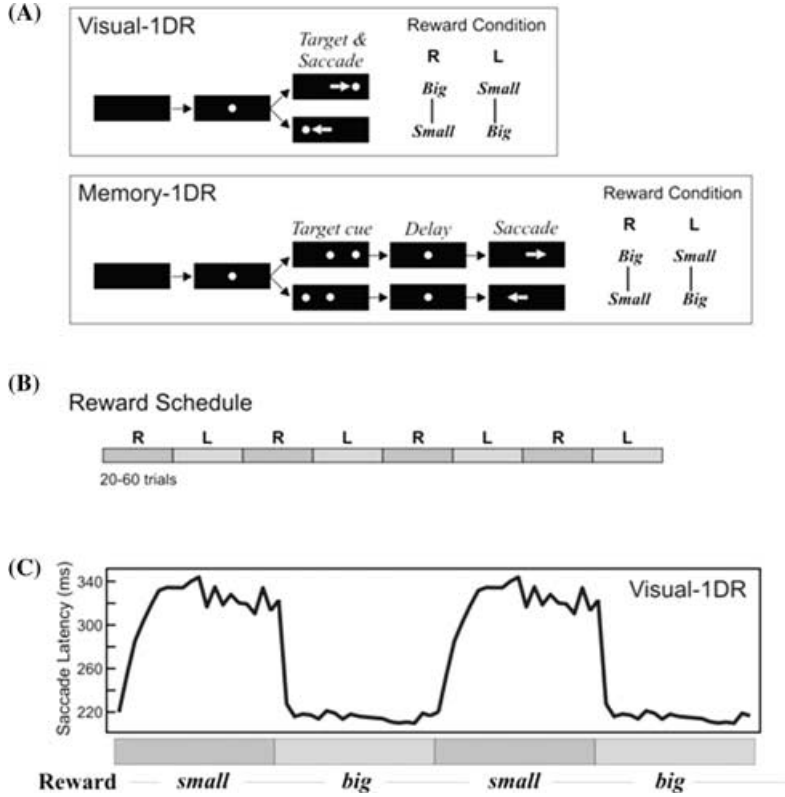

FIGURE 3. Saccade tasks with positional bias of reward, which we call one direction-rewarded (1DR) saccade tasks. (**A**) It has two versions: Visual-1DR task (*top*) and Memory-1DR task (*bottom*). In both tasks the monkey first fixates at the central spot of light and then makes a saccade to the target after the fixation point goes off. The target is chosen pseudo-randomly out of two directions (as shown here) or four directions. In the visual-1DR task (*top*) the target comes on at the same time as the fixation point goes off and hence the saccade is made to the visible target. In the memory-1DR task (*center*) the target is illuminated briefly (target cue) while the monkey is fixating and the monkey must withhold saccade until the fixating point goes off; hence, the saccade is made to the remembered target. Within a block of 20–60 trials of 1DR tasks, the saccade to one particular direction is followed by a big amount of reward, whereas the saccade to any of the other directions is followed by a small amount of reward or no reward. Even for the small or no reward direction, the monkey must make a saccade correctly to the target; otherwise, the trial is repeated until the saccade is made correctly. (**B**) One set of experiments consists of several blocks of trials during which the big-reward direction is alternated (in the two-direction condition, as shown here as R and L, which are indicated in (A) or randomized (in the four-direction condition). (**C**) Changes in saccade latency with the changes in the reward condition in the visual-1DR task.[70] The mean saccade latencies in one monkey are plotted across trials in two blocks in which saccades were followed by small and big rewards, respectively. Two cycles are shown repeated to facilitate visual impression.

Saccadic parameters changed dramatically in 1DR tasks. In the visual-1DR task, latencies were much shorter when saccades were followed by a big reward than when they were followed by a small reward.[17,70] In the schematic example shown in FIGURE 3A *top*, the latencies of rightward saccades are shorter in the reward condition R (rightward saccades associated with bigger rewards than leftward saccades) than in the condition L (leftward saccades associated with bigger rewards). Conversely, the latencies of leftward saccades are shorter in the condition L than in the condition R. During the experiment the reward conditions R and L were alternated usually every 20 trials with no external instruction (FIG. 3B), but the saccade latency changed reliably (FIG. 3C). One interesting finding common to all monkeys tested was that saccade latency decreased quickly during a small-to-big reward transition and increased more slowly during a big-to-small reward transition (FIG. 3C).[70] Thus, saccadic eye movement provides a solid and reliable behavioral measure to study the neural mechanisms of reward-oriented behavior. A series of experiments, reviewed below, suggest that the basal ganglia play a key role in the reward-dependent modulation of saccades.

The memory-1DR task allowed us to study the effects of expected reward on the preparatory process of saccadic eye movements. Kawagoe *et al*.[12] found that visual responses of CD projection neurons were modulated strongly by the expected reward. It has been known that many CD neurons respond to the target cue in the memory-guided saccade task, especially when it is presented in the contralateral hemifield.[71] Such visual responses are greatly enhanced and diminished if the saccade to the visual stimulus is expected to be followed by a bigger and smaller reward, respectively (FIG. 4 *bottom*).[12] The reward modulation was often so strong that the neuron's original direction selectivity was shifted or reversed. Other CD neurons maintained their direction preference, but their selectivity was enhanced or depressed depending on the expected reward. A minority of CD neurons showed the opposite pattern: they responded to the visual cue only or preferentially when it indicated no reward.[12] Overall, statistically significant modulation by the expected reward was observed in about 80% of visually responsive CD neurons. Similar reward-dependent modulation was found among SNr neurons.[72]

How have CD and consequently SNr neurons come to acquire activity dependent on expected reward? One possibility is that CD neurons receive signals from other brain areas that have already been modulated by expected reward. In fact, neurons exhibiting visuomotor activities that are modulated by expected reward are found in the FEF,[10] SEF,[73,74] dorsolateral prefrontal cortex,[2–4] and LIP,[7] all of which project to the saccade-related region of the CD. A second possibility is that the reward-modulation first occurs in the basal ganglia, not in the cerebral cortex. In this case, the cerebral cortex would receive reward-modulated signals from the basal ganglia through the thalamus.[75] A recent study by Pasupathy s Miller[76] seems consistent with this idea. In the following

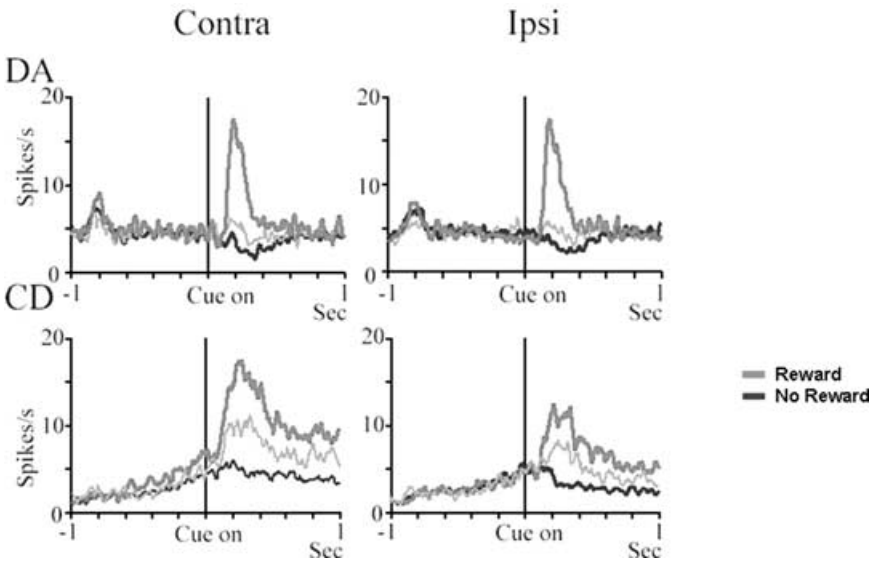

FIGURE 4. Comparison of cue responses between DA neurons and CD neurons. Population cue responses in 1DR-rewarded (*red*), 1DR-nonrewarded (*blue*), and ADR (*gray*) conditions are shown separately for contralateral (*left*) and ipsilateral (*right*) cues.[84]

section we will examine the hypothesis that the reward-modulation occurs, at least partly, in the basal ganglia depending on the inputs from DA neurons.

DOPAMINERGIC MODULATION OF INFORMATION PROCESSING IN THE CAUDATE NUCLEUS (CD)

Studies from our laboratory, including those described above, indicated that there are mechanisms in the basal ganglia that modify saccadic eye movements depending on whether or not the saccades are followed by reward. An important question was: Where does the reward-related information originate from? A candidate for the reward information carrier would be dopaminergic neurons that are located in and around the SNc and project to the CD in addition to other brain areas. To test this hypothesis we carried out two types of experiments: (a) comparison of information carried by CD neurons and DA neurons, and (b) test of DA causality.

Direct evidence for the relationship of DA to reward is based on recent single unit studies on midbrain DA neurons in trained animals. Schultz and colleagues demonstrated that DA neurons respond to the delivery of reward.[77] A key finding was that the response was correlated with the difference between the expected reward and the actual reward. Thus, the response to a reward is stronger if it is not expected.[78] The response is negative (i.e., a decrease in

firing) if the expected reward is not given.[79] In short, DA neurons encode *reward prediction error*.[33] This signal corresponds nicely to a principal factor in learning theories that account for classical conditioning[80] as well as in reinforcement learning theory that was developed more recently.[20,81–83]

DA neuronal activity in the memory-1DR task followed this principle.[84] In an animal trained extensively in 1DR, DA neurons responded to the cue positively (with a phasic increase in firing) if the cue indicated an upcoming reward (FIG. 4 *top*, red); they responded to the cue negatively (with a phasic decrease in firing) if the cue indicated no reward (FIG. 4 *top*, blue). DA neurons showed no spatial selectivity: they responded to the cue at any position equally as long as it indicates an upcoming reward or as long as it indicates no reward. DA neurons exhibited no response to the cue when all positions were equally rewarded (FIG. 4 *top*, gray). DA neurons now represented the difference between the expected value of reward cue and the actual value of reward cue, consistent with an extension of the *reward prediction error* theory.[85] DA neurons' *positive* and *negative* responses are correlated respectively with the increase and decrease in reward prediction. If all positions are equally rewarded, the likelihood of reward is 100% before the cue and this is not changed by the presentation of the cue; hence, DA neurons show no response.

Here we see an intriguing relationship between CD projection neurons and DA neurons (FIG. 4).[84] In both CD and DA neurons, the visual responses in 1DR task are strongly modulated by the expected reward, although CD projection neurons exhibit only a positive response while DA neurons exhibit positive and negative responses. They are different in that CD projection neurons, not DA neurons, show spatial selectivity. The reward sensitivity of DA and CD neurons developed similarly (1) in a short time course after the reward-position contingency was reversed and (2) in a long time course while the animal learned this task.[86] These results suggest that DA neurons, with their connection to CD neurons, modulate the spatially selective signals in CD neurons in the reward-predicting manner and CD neurons in turn modulate saccade parameters with their polysynaptic connections to the oculomotor brainstem.

DOPAMINERGIC MODULATION OF INFORMATION PROCESSING IN THE CD

To test the causal role of DA in reward-dependent signals in the basal ganglia, we blocked dopaminergic synaptic transmission in the CD by injecting DA antagonists locally.[87] According to our model, if the DA input is blocked, the reward-dependent neuronal activity in the CD and consequently the reward modulation of saccade behavior should be diminished. Among at least five types of DA receptors, mainly D1 and D2, receptors are expressed in CD projection neurons. We thus injected a D1 antagonist and a D2 antagonist into the region of the CD where saccade-related neurons are clustered while the

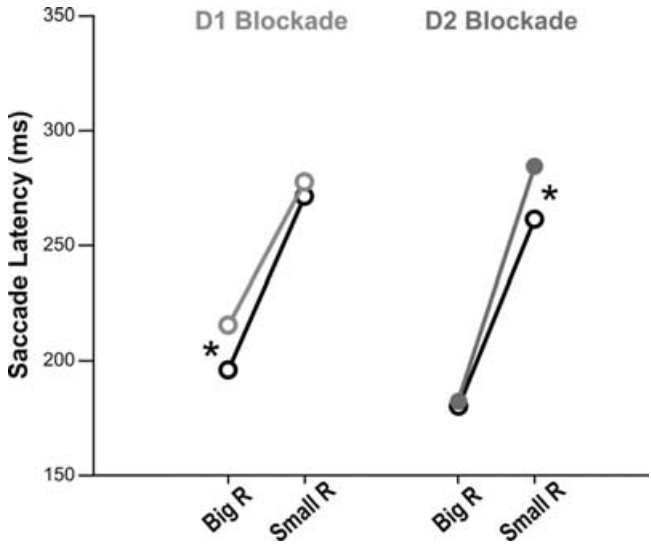

FIGURE 5. The effects of D1 and D2 receptor blockades in the middle part of the CD on the latencies of saccades followed by big and small rewards. Indicated are the mean saccade latencies before blockade (*black*), during D1 blockade (*red*), and during D2 blockade. Asterisk indicates a statistically significant difference (Mann–Whitney U test, $P < 0.01$). The numbers of experiments were 8 for D1 blockade and 13 for D2 blockade.[87]

monkey performed a reward-biased saccade task. We found that D1 antagonist attenuates the reward modulation of saccade behavior (FIG. 5, *left*). In contrast, injecting D2 antagonist into the same region enhanced the reward-dependent changes (FIG. 5, *right*).

I will now discuss possible mechanisms underlying the D1 and D2 blockade effects. The attenuation of the reaction time bias by D1 blockade was due to the prolongation of reaction times on large-reward trials and unchanged reaction times on small-reward trials (FIG. 5, *left*). The prolongation of saccade reaction times can be explained by a change in the function of the basal ganglia circuits, specifically the direct pathway (FIG. 6, *left*). First, in the CD, D1 receptors are preferentially expressed by neurons that belong to the direct pathway (i.e., projecting to the SN directly).[88,89] Second, in the anesthetized animals, DA increases the excitability of CD neurons and this effect was reduced by D1 antagonist.[90,91] These observations suggest that D1-antagonist injection into the CD would attenuate the responses of SN-projecting CD neurons, which leads to a weaker disinhibition of neurons in the SC and consequently the prolongation of saccade reaction time (indicated by *green arrows* in FIG. 6, *left*).

In contrast, the enhancement of the reaction time bias by D2 blockade was due to the prolongation of reaction times on small-reward trials and unchanged

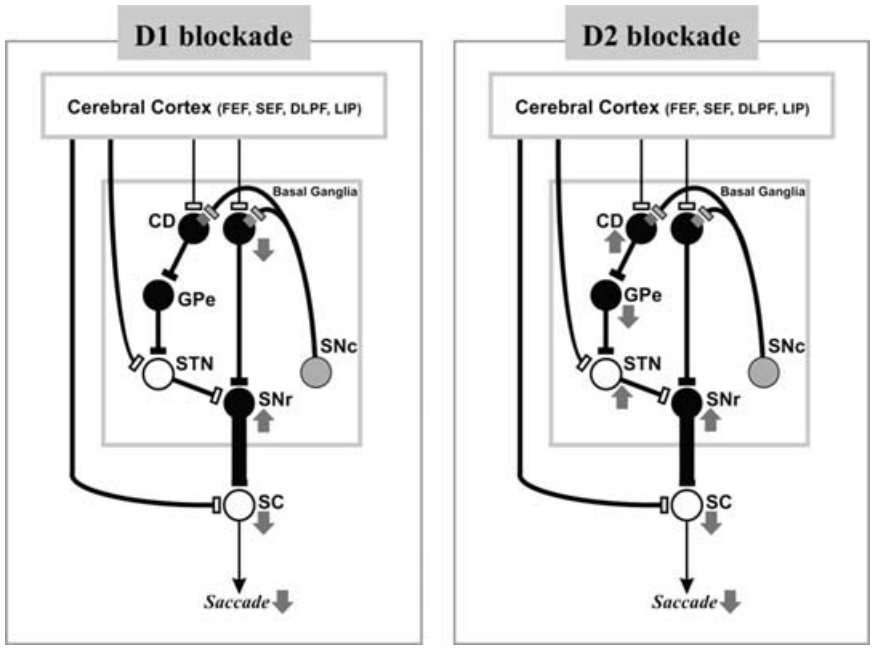

FIGURE 6. A hypothetical scheme showing how the blockade of DA receptor activation might work, assuming that D1 receptors (*red*) and D2 receptors (*blue*) are differentially expressed by CD projection neurons belonging to the direct pathway and those belonging to the indirect pathway. *Left*: The hypothetical effects of the blockade of D1 receptors are shown by green arrows, upward and downward indicating increase and decrease of neuronal activity. The primary effect would be a decrease in CD neuronal activity because D1 receptor-mediated effect is thought to be facilitatory. *Right*: The hypothetical effects of the blockade of D2 receptors. The primary effect would be an increase in CD neuronal activity because D2 receptor-mediated effect is thought to be inhibitory.

reaction times on large-reward trials (FIG. 5, *right*). The prolongation of saccade reaction times can also be explained by a change in the function of the basal ganglia circuits, but in this case the indirect pathway (FIG. 6, *right*). It has been shown that D2 receptors are preferentially expressed by neurons that belong to the indirect pathway[88,89] (FIG. 6, *right*) and that the D2-mediated effect on CD neurons is inhibitory.[91] As indicated by green arrows in FIGURE 6, *right*, D2 blockade would remove the inhibition of CD neurons, increase the CD-induced inhibition of neurons in the globus pallidus external segment (GPe), decrease the GPe-induced inhibition of SNr neurons (directly or indirectly through the STN), increase the SNr-induced inhibition of SC neurons, and consequently the prolongation of saccade reaction times.

But why should the effects of D1 blockade occur selectively for large-reward trials while the effects of D2 blockade occur selectively for small-reward trials?

To solve this puzzle we need to understand that DA neurons exhibit a short burst of spikes in response to unexpected reward[78] or a reward-indicating sensory stimulus[77,84,86] and a pause of firing in response to unexpected omission of reward[79] or a no-reward-indicating stimulus.[84] Let us suppose that D1 receptor activation has a higher threshold than D2 receptor activation. Some support for this postulate can be found in a paper by Richfield *et al*.,[92] which indicates that the sensitivity to DA is higher for D2 receptor than D1 receptor. The differential effects of D1 and D2 blockades could then be explained by the model shown in FIGURE 7. We now represent sensitivity of D1- or D2-mediated effects by *threshold*; the modulatory effects by DA become significant only when available DA is higher than the threshold for each receptor. During the control experiment (FIG. 7, *left*) D1 receptor activation is effective when the phasic increase of DA after the presentation of big-reward-indicating cue exceeds D1 threshold while D2 receptor activation is effective tonically except for a brief dip after the small-reward-indicating cue. By D1 blockade (FIG. 7, *center*), D1 threshold is elevated and therefore the phasic D1 effect for big-reward condition is reduced, leading to prolongation of SRT in the

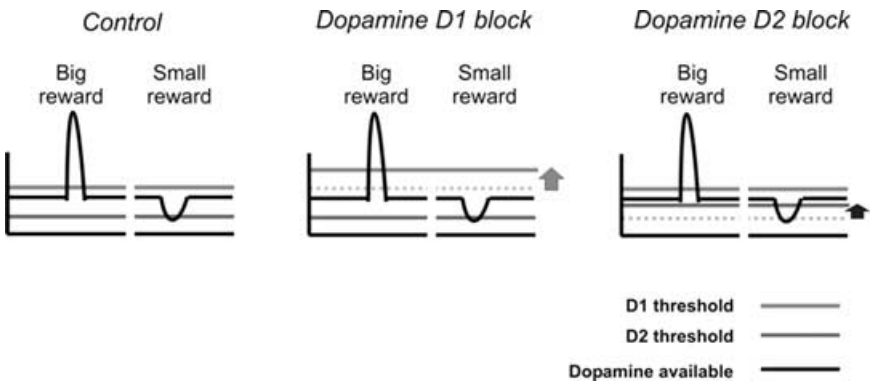

FIGURE 7. A model that explains the different effects by D1 and D2 receptor blockades on the reward-dependent modulation of saccades. In each of the three conditions (Control, D1 block, D2 block), *black lines* indicate the changes in the level of DA in the caudate during the biased-reward saccade task after presentation of the target indicating a large reward (*left*) and a small reward (*right*). The sensitivities of D1 and D2 receptors to DA are expressed as *thresholds,* which are indicated by red and blue lines, respectively (see text). If the level of DA is higher than the threshold of a given receptor type, DA influences the output of caudate projection neurons through the receptor. *Left column:* Before injection of D1 or D2 antagonist, D1 receptor activation occurs phasically after the target indicating a large reward, while D2 receptor activation is sustained except for a brief decrease after the target indicating a small reward. *Middle column:* After D1 antagonist injection, D1 threshold is elevated, which leads to a decrease in the phasic D1 effect in the large-reward condition. *Right column:* After D2 antagonist injection, D2 threshold is elevated, which leads to a further weakening of the D2 effect in the small-reward condition.

big-reward condition (FIG. 6, *left*). By D2 blockade (FIG. 7, *right*), D2 threshold is elevated and therefore the D2 effect is further reduced in the small-reward condition, leading to prolongation of SRT in the small-reward condition (FIG. 6, *right*).

The above interpretation assumes that DA neurons act quickly on CD neurons to change saccade reaction time on a single trial. However, this may not be realistic, considering the modulatory nature of DA actions. An alternative mechanism may be DA-dependent plasticity in corticostriatal synapses.[93–96] A conjunction of presynaptic activity in corticostriatal inputs and postsynaptic activity in CD neurons leads to long-term potentiation only if a large phasic increase in D1 receptor activation occurs simultaneously.[94] In our paradigm, if a particular target is repeatedly associated with a large reward that would cause DA neuron activation,[84] the corticostriatal synapses carrying the target signal should undergo long-term potentiation and therefore CD neurons respond to the target progressively more strongly, leading to shorter saccade reaction times. D1 antagonist should suppress such changes, as we observed as the longer saccade reaction times on large-reward trials. On the other hand, the D2-mediated inhibitory effect on caudate neurons is necessary to keep minimum facilitatory effects on the SC for saccades to be generated even on small-reward trials.

These results suggest that: (1) the reward modulation of saccadic eye movement, at least partly, originates from the CD; (2) the DA input to CD projection neurons is responsible for the reward modulation; (3) the DA effect is mediated by D1 and D2 receptors in differential manners.

FUTURE DIRECTIONS OF RESEARCH ON REWARD-DEPENDENT MOTIVATIONAL BEHAVIOR

We have shown that reward-dependent modulation of saccadic eye movements occurs, at least partly, in the CD where cortical inputs carrying predominantly spatial information and dopaminergic inputs carrying exclusively reward-related information converge. A causal role of DA in the reward modulation was also demonstrated in our study in which DA antagonists injected locally in the CD changed the reward modulation of saccadic eye movements.

The importance of DA neurons becomes more evident as we understand the complexity of information they carry. DA neurons respond to rewards or sensory stimuli that reliably predict the rewards. The response is positive (an increase in activity) or negative (a decrease in activity) if the value of the reward is higher or lower, respectively, than predicted. This kind of information, which is called reward prediction error, is thought to act as a teaching signal for appetitive learning to maximize the gain of reward. However, it is not a trivial task to predict the upcoming reward. Theoretically, it requires the knowledge or memory of the entire past reward history, which is assumed to be extrapolated

to future. Furthermore, the prediction needs to take account of sequential or temporal patterns of reward outcome, if any.[97]

A big problem is that it is virtually unknown which parts of the brain provide DA neurons with such complex reward-related signals. It has been known anatomically that midbrain DA neurons receive inputs from many brain areas, including the ventral and dorsal striatum, subthalamic nucleus, pedunculopontine nucleus, amygdala, lateral hypothalamus, SC, and lateral habenula,[32,98–102] but none of these areas has been proved to be a critical determinant of reward-predictive DA signals. We need to solve this issue to gain a broader perspective on motivational behavior.

REFERENCES

1. INOUE, M. *et al.* 1985. Reward related neuronal activity in monkey dorsolateral prefrontal cortex during feeding behavior. Brain Res. **326:** 307–312.
2. WATANABE, M. 1996. Reward expectancy in primate prefrontal neurons. Nature **382:** 629–632.
3. LEON, M.I. & M.N. SHADLEN. 1999. Effect of expected reward magnitude on the response of neurons in the dorsolateral prefrontal cortex of the macaque. Neuron **24:** 415–425.
4. KOBAYASHI, S. *et al.* 2002. Influence of reward expectation on visuospatial processing in macaque lateral prefrontal cortex. J. Neurophysiol. **87:** 1488–1498.
5. WATANABE, M. *et al.* 2002. Coding and monitoring of motivational context in the primate prefrontal cortex. J. Neurosci. **22:** 2391–2400.
6. BARRACLOUGH, D.J., M.L. CONROY & D. LEE. 2004. Prefrontal cortex and decision making in a mixed-strategy game. Nat. Neurosci. **7:** 404–410.
7. PLATT, M.L. & P.W. GLIMCHER. 1999. Neural correlates of decision variables in parietal cortex. Nature **400:** 233–238.
8. GLIMCHER, P.W. 2001. Making choices: the neurophysiology of visual-saccadic decision making. Trends Neurosci. **4:** 654–659.
9. SUGRUE, L.P., G.S. CORRADO & W.T. NEWSOME. 2004. Matching behavior and the representation of value in the parietal cortex. Science **304:** 1782–1787.
10. ROESCH, M.R. & C.R. OLSON. 2003. Impact of expected reward on neuronal activity in prefrontal cortex, frontal and supplementary eye fields and premotor cortex. J. Neurophysiol. **90:** 1766–1789.
11. ROESCH, M.R. & C.R. OLSON. 2004. Neuronal activity related to reward value and motivation in primate frontal cortex. Science **304:** 307–310.
12. KAWAGOE, R., Y. TAKIKAWA & O. HIKOSAKA. 1998. Expectation of reward modulates cognitive signals in the basal ganglia. Nat. Neurosci. **1:** 411–416.
13. TREMBLAY, L., J.R. HOLLERMAN & W. SCHULTZ. 1998. Modifications of reward expectation-related neuronal activity during learning in primate striatum. J. Neurophysiol. **80:** 964–977.
14. HOLLERMAN, J.R., L. TREMBLAY & W. SCHULTZ. 1998. Influence of reward expectation on behavior-related neuronal activity in primate striatum. J. Neurophysiol. **80:** 947–963.

15. TAKIKAWA, Y., R. KAWAGOE & O. HIKOSAKA. 2002. Reward-dependent spatial selectivity of anticipatory activity in monkey caudate neurons. J. Neurophysiol. **87:** 508–515.
16. LAUWEREYNS, J. *et al.* 2002. Feature-based anticipation of cues that predict reward in monkey caudate nucleus. Neuron **33:** 463–473.
17. LAUWEREYNS, J. *et al.* 2002. A neural correlate of response bias in monkey caudate nucleus. Nature **418:** 413–417.
18. WATANABE, K., J. LAUWEREYNS & O. HIKOSAKA. 2003. Neural correlates of rewarded and unrewarded eye movements in the primate caudate nucleus. J. Neurosci. **23:** 10052–10057.
19. CROMWELL, H.C. & W. SCHULTZ. 2003. Effects of expectations for different reward magnitudes on neuronal activity in primate striatum. J. Neurophysiol. **89:** 2823–2838.
20. DAYAN, P. & B. BALLEINE. 2002. Reward, motivation, and reinforcement learning. Neuron **36:** 285–298.
21. BAXTER, M.G. & E.A. MURRAY. 2002. The amygdala and reward. Nat. Rev. Neurosci. **3:** 563–573.
22. MAUNSELL, J.H. 2004. Neuronal representations of cognitive state: reward or attention? Trends Cogn. Sci. **8:** 261–265.
23. DELGADO, M.R. *et al.* 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. J. Neurophysiol. **84:** 3072–3077.
24. KNUTSON, B. *et al.* 2000. FMRI visualization of brain activity during a monetary incentive delay task. Neuroimage **12:** 20–27.
25. O'DOHERTY, J. *et al.* 2001. Representation of pleasant and aversive taste in the human brain. J. Neurophysiol. **85:** 1315–1321.
26. DENNY-BROWN, D. 1962. The Basal Ganglia and Their Relation to Disorders of Movement. Oxford University Press. London.
27. GRAYBIEL, A.M. & C.W. RAGSDALE. 1979. Fiber connections of the basal ganglia. *In*: Development of Chemical Specificity of Neurons. M. Cuenod, G.W. Kreutzberg & F.E. Bloom, Eds.: 239–283. Elsevier. Amsterdam.
28. DELONG, M.R. & A.P. GEORGOPOULOS. 1981. Motor functions of the basal ganglia. *In*: The Nervous System. Vol. sect.1, part 2, vol. II, chapt. 19. V.B. Brooks, Ed.: 1017–1061. American Physiological Society. Bethesda, MD.
29. MOGENSON, G.J., D.L. JONES & C.Y. YIM. 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. **14:** 69–97.
30. HABER, S.N. & N.R. MCFARLAND. 1999. The concept of the ventral striatum in nonhuman primates. Ann. N. Y. Acad. Sci. **877:** 33–48.
31. SWANSON, L.W. 2000. Cerebral hemisphere regulation of motivated behavior. Brain Res. **886:** 113–164.
32. FUDGE, J.L. & S.N. HABER. 2000. The central nucleus of the amygdala projection to dopamine subpopulations in primates. Neuroscience **97:** 479–494.
33. SCHULTZ, W. 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. **80:** 1–27.
34. HIKOSAKA, O. *et al.* 1993. Role of basal ganglia in initiation and suppression of saccadic eye movements. *In*: Role of the Cerebellum and Basal Ganglia in Voluntary Movement. N. Mano, I. Hamada & M.R. Delong, Eds.: 213–219. Elsevier. Amsterdam.

35. MINK, J.W. 1996. The basal ganglia: focused selection and inhibition of competing motor programs. Prog. Neurobiol. **50:** 381–425.
36. SALMON, D.P. & N. BUTTERS. 1995. Neurobiology of skill and habit learning. Curr. Opin. Neurobiol. **5:** 184–190.
37. GRAYBIEL, A.M. 1998. The basal ganglia and chunking of action repertoires. Neurobiol. Learn. Mem. **70:** 119–136.
38. PACKARD, M.G. & B.J. KNOWLTON. 2002. Learning and memory functions of the Basal Ganglia. Annu. Rev. Neurosci. **25:** 563–593.
39. ALEXANDER, G.E., M.R. DELONG & P.L. STRICK. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. **9:** 357–381.
40. HIKOSAKA, O., Y. TAKIKAWA & R. KAWAGOE. 2000. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol. Rev. **80:** 953–978.
41. SPARKS, D.L. 2002. The brainstem control of saccadic eye movements. Nat. Rev. Neurosci. **3:** 952–964.
42. HAYHOE, M. & D. BALLARD. 2005. Eye movements in natural behavior. Trends Cogn. Sci. **9:** 188–194.
43. EWERT, J.-P. 1980. Neuroethology. Springer. Berlin.
44. JOHANSSON, R.S. *et al.* 2001. Eye-hand coordination in object manipulation. J. Neurosci. **21:** 6917–6932.
45. TRIESCH, J. *et al.* 2003. What you see is what you need. J. Vis. **3:** 86–94.
46. MIYASHITA, K. *et al.* 1996. Anticipatory saccades in sequential procedural learning in monkeys. J. Neurophysiol. **76:** 1361–1366.
47. MIYASHITA, N., O. HIKOSAKA & M. KATO. 1995. Visual hemineglect induced by unilateral striatal dopamine dificiency in monkeys. Neuroreport **6:** 1257–1260.
48. HIKOSAKA, O. & R.H. WURTZ. 1983. Visual and oculomotor functions of monkey substantia nigra pars reticulata. I. Relation of visual and auditory responses to saccades. J. Neurophysiol. **49:** 1230–1253.
49. JOSEPH, J.P. & D. BOUSSAOUD. 1985. Role of the cat substantia nigra pars reticulata in eye and head movements. I. Neural activity. Exp. Brain Res. **57:** 286–296.
50. HANDEL, A. & P.W. GLIMCHER. 1999. Quantitative analysis of substantia nigra pars reticulata activity during a visually guided saccade task. J. Neurophysiol. **82:** 3458–3475.
51. HIKOSAKA, O., M. SAKAMOTO & S. USUI. 1989. Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movements. J. Neurophysiol. **61:** 780–798.
52. MATSUMURA, M. *et al.* 1992. Visual and oculomotor functions of monkey subthalamic nucleus. J. Neurophysiol. **67:** 1615–1632.
53. KATO, M. & O. HIKOSAKA. 1995. Function of the indirect pathway in the basal ganglia oculomotor system: visuo-oculomotor activities of external pallidum neurons. *In*: Age-Related Dopamine-Deficient Disorders. Vol. 14. M. Segawa & Y. NOMURA, Eds.: 178–187. Karger. Basal.
54. PARTHASARATHY, H.B., J.D. SCHALL & A.M. GRAYBIEL. 1992. 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.
55. HIKOSAKA, O. & R.H. WURTZ. 1983. Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. J. Neurophysiol. **49:** 1285–1301.

56. KITA, H. 1993. GABAergic circuits of the striatum. *In*: Chemical Signalling in the Basal Ganglia. G.W. Arbuthnott & P.C. Emson, Eds.: 51–72. Elsevier. Amsterdam.
57. NAMBU, A., H. TOKUNO & M. TAKADA. 2002. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci. Res. **43:** 111–117.
58. UNGERSTEDT, U. 1971. Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiologica Scandinavica **Suppl 367:** 1–48.
59. HIKOSAKA, O. & R.H. WURTZ. 1985. Modification of saccadic eye movements by GABA-related substances. II. Effects of muscimol in monkey substantia nigra pars reticulata. J. Neurophysiol. **53:** 292–308.
60. BOUSSAOUD, D. & J.P. JOSEPH. 1985. 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.
61. SAKAMOTO, M. & O. HIKOSAKA. 1989. Eye movements induced by microinjection of GABA agonist in the rat substantia nigra pars reticulata. Neurosci. Res. **6:** 216–233.
62. HIKOSAKA, O. & R.H. WURTZ. 1989. The basal ganglia. *In*: The Neurobiology of Saccadic Eye Movements. Vol. 3. R.H. Wurtz & M.E. Goldberg, Eds.: 257–281. Elsevier. Amsterdam.
63. HIKOSAKA, O., M. SAKAMOTO & N. MIYASHITA. 1993. Effects of caudate nucleus stimulation on substantia nigra cell activity in monkey. Exp. Brain Res. **95:** 457–472.
64. KARABELAS, A.B. & A.K. MOSCHOVAKIS. 1985. Nigral inhibitory termination on efferent neurons of the superior colliculus: an intracellular horseradish peroxidase study in the cat. J. Comp. Neurol. **239:** 309–329.
65. SOMMER, M.A. & R.H. WURTZ. 2000. Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. J. Neurophysiol. **83:** 1979–2001.
66. TEHOVNIK, E.J. *et al.* 2000. Eye fields in the frontal lobes of primates. Brain Res. Rev. **32:** 413–448.
67. PARÉ, M. & R.H. WURTZ. 2001. Progression in neuronal processing for saccadic eye movements from parietal cortex area LIP to superior colliculus. J. Neurophysiol. **85:** 2545–2562.
68. HIKOSAKA, O., M. SAKAMOTO & S. USUI. 1989. Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. J. Neurophysiol. **61:** 814–832.
69. CARR, G.D. & N.M. WHITE. 1983. Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. Life Sci. **33:** 2551–2557.
70. WATANABE, K. & O. HIKOSAKA. 2005. Immediate changes in anticipatory activity of caudate neurons associated with reversal of position-reward contingency. J. Neurophysiol. **94:** 1879–1887.
71. HIKOSAKA, O., M. SAKAMOTO & S. USUI. 1989. Functional properties of monkey caudate neurons. II. Visual and auditory responses. J. Neurophysiol. **61:** 799–813.
72. SATO, M. & O. HIKOSAKA. 2002. Role of primate substantia nigra pars reticulata in reward-oriented saccadic eye movement. J. Neurosci. **22:** 2363–2373.
73. AMADOR, N., M. SCHLAG-REY & J. SCHLAG. 2000. Reward-predicting and reward-detecting neuronal activity in the primate supplementary eye field. J. Neurophysiol. **84:** 2166–2170.

74. STUPHORN, V., T.L. TAYLOR & J.D. SCHALL. 2000. Performance monitoring by the supplementary eye field. Nature **408:** 857–860.
75. MIDDLETON, F.A. & P.L. STRICK. 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Rev. **31:** 236–250.
76. PASUPATHY, A. & E.K. MILLER. 2005. Different time courses of learning-related activity in the prefrontal cortex and striatum. Nature **433:** 873–876.
77. SCHULTZ, W., P. APICELLA & T. LJUNGBERG. 1993. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci. **13:** 900–913.
78. MIRENOWICZ, J. & W. SCHULTZ. 1994. Importance of unpredictability for reward responses in primate dopamine neurons. J. Neurophysiol. **72:** 1024–1027.
79. HOLLERMAN, J.R. & W. SCHULTZ. 1998. Dopamine neurons report an error in the temporal prediction of reward during learning. Nat. Neurosci. **1:** 304–309.
80. RESCORLA, R.A. & A.R. WAGNER. 1972. A theory of pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. *In*: Classical Conditioning II: Current Research and Theory. A.H. Black & W.F. Prokasy, Eds.: 64–99. Appleton-Century-Croft. New York.
81. BARTO, A.G. 1995. Adaptive critics and the basal ganglia. *In*: Models of Information Processing in the Basal Ganglia. J.C. Houk, J.L. Davis & D.G. Beiser, Eds.: 215–232. MIT Press. Cambridge, MA.
82. HOUK, J.C., J.L. ADAMS & A. BARTO. 1995. A model of how the basal ganglia generate and use neural signals that predict reinforcement. *In*: Models of Information Processing in the Basal Ganglia. J.C. Houk, J.L. Davis & D.G. Beiser, Eds.: 249–270. MIT Press. Cambridge, MA.
83. SCHULTZ, W. & A. DICKINSON. 2000. Neuronal coding of prediction errors. Annu. Rev. Neurosci. **23:** 473–500.
84. KAWAGOE, R., Y. TAKIKAWA & O. HIKOSAKA. 2004. Reward-predicting activity of dopamine and caudate neurons – a possible mechanism of motivational control of saccadic eye movement. J. Neurophysiol. **91:** 1013–1024.
85. TOBLER, P.N., A. DICKINSON & W. SCHULTZ. 2003. Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. J. Neurosci. **23:** 10402–10410.
86. TAKIKAWA, Y., R. KAWAGOE & O. HIKOSAKA. 2004. A possible role of midbrain dopamine neurons in short- and long-term adaptation of saccades to position-reward mapping. J. Neurophysiol. **92:** 2520–2529.
87. NAKAMURA, K. & O. HIKOSAKA. 2006. Role of dopamine in the primate caudate nucleus in reward modulation of saccades. J. Neurosci. **26:** 5360–5369.
88. GERFEN, C.R. *et al.* 1990. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science **250:** 1429–1432.
89. SURMEIER, D.J., W.-J. SONG & Z. YAN. 1996. Coordinated expression of dopamine receptors in neostriatal medium spiny neurons. J. Neurosci. **16:** 6579–6591.
90. GONON, F. 1997. Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum *in vivo*. J. Neurosci. **17:** 5972–5978.
91. WEST, A.R. & A.A. GRACE. 2002. Opposite influences of endogenous dopamine D1 and D2 receptor activation on activity states and electrophysiological properties of striatal neurons: studies combining *in vivo* intracellular recordings and reverse microdialysis. J. Neurosci. **22:** 294–304.
92. RICHFIELD, E.K., J.B. PENNEY & A.B. YOUNG. 1989. Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. Neuroscience **30:** 767–777.

93. CALABRESI, P. *et al.* 1996. The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. Trends Neurosci. **19:** 19–24.
94. REYNOLDS, J.N. & J.R. WICKENS. 2002. Dopamine-dependent plasticity of corticostriatal synapses. Neural Netw. **15:** 507–521.
95. LOVINGER, D.M., J.G. PARTRIDGE & K.C. TANG. 2003. Plastic control of striatal glutamatergic transmission by ensemble actions of several neurotransmitters and targets for drugs of abuse. Ann. N. Y. Acad. Sci. **1003:** 226–240.
96. MAHON, S., J.M. DENIAU & S. CHARPIER. 2004. Corticostriatal plasticity: life after the depression. Trends Neurosci. **27:** 460–467.
97. NAKAHARA, H. *et al.* 2004. Dopamine neurons can represent context-dependent prediction error. Neuron **41:** 269–280.
98. HABER, S.N., J.L. FUDGE & N.R. MCFARLAND. 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci. **20:** 2369–2382.
99. IRIBE, Y. *et al.* 1999. Subthalamic stimulation-induced synaptic responses in substantia nigra pars compacta dopaminergic neurons *in vitro*. J. Neurophysiol. **82:** 925–933.
100. KOBAYASHI, Y. *et al.* 2002. Contribution of pedunculopontine tegmental nucleus neurons to performance of visually guided saccade tasks in monkeys. J. Neurophysiol. **88:** 715–731.
101. DOMMETT, E. *et al.* 2005. How visual stimuli activate dopaminergic neurons at short latency. Science **307:** 1476–1479.
102. SUTHERLAND, R.J. 1982. The dorsal diencephalic conduction system: a review of the anatomy and functions of the habenular complex. Neurosci. Biobehav. Rev. **6:** 1–13.