Expectation of reward modulates cognitive signals in the basal ganglia

Reiko Kawagoe, Yoriko Takikawa and Okihide Hikosaka

Department of Physiology, School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Correspondence should be addressed to O.H. (hikosaka@med.juntendo.ac.jp)

Action is controlled by both motivation and cognition. The basal ganglia may be the site where these kinds of information meet. Using a memory-guided saccade task with an asymmetric reward schedule, we show that visual and memory responses of caudate neurons are modulated by expectation of reward so profoundly that a neuron's preferred direction often changed with the change in the rewarded direction. The subsequent saccade to the target was earlier and faster for the rewarded direction. Our results indicate that the caudate contributes to the determination of oculomotor outputs by connecting motivational values (for example, expectation of reward) to visual information.

Visual responses of neurons can be modulated by changes in behavioral contexts. Many widely used behavioral tasks require the subject to respond by choosing one stimulus among many or by choosing one feature (for example, color) of a stimulus among many features[1–3]. In this type of procedure, the same reward is given for all correct trials, so that the motivational state of the subject is assumed to be the same no matter which stimulus (or stimulus feature) represents the correct response. This model is therefore ideal for investigating the cognitive aspect of action or attention, but not the motivational aspect.

Action is controlled by both cognition and motivation[4,5], and motivational states vary considerably. The same action can lead to different reward outcomes in different behavioral contexts. Both neural and behavioral responses (for example, speed of action) may co-vary with such motivational changes, which may have different consequences in the subsequent decision-making processes. However, there have been few physiological studies that manipulated the outcome of an action in terms of reward (its amount or kind) while keeping the subject's actions constant[6]. Consequently, little is known about neural mechanisms of the motivational aspect of attention or action selection.

To investigate how expectation of reward affects cognitive information processing, we devised a memory-guided saccade task in which the subject had to make a saccade to a remembered cue location. However, correct performance was only rewarded when the cue had appeared at one of the four possible locations. The cognitive requirement was always the same, in that the subject had to attend to the cue stimulus, remember its location and make a saccade to the location, but the motivational significance varied. Using this model, we studied single-neuron activity in the monkey caudate nucleus, a major input zone of the basal ganglia, as the basal ganglia may be involved in control of action based on motivation[5,7–9]. We found that visual or memory-related responses of presumed projection neurons were frequently modulated by expectation of reward, either as an enhancement or as a reduction of the response.

Results

We trained two monkeys on a memory-guided saccade task in two reward conditions: 'all directions rewarded' (ADR) and 'one direction rewarded' (1DR). In ADR, which is the conventional reward schedule, the monkeys were rewarded each time they made a memory-guided saccade to the cued location for that trial. In 1DR, which we devised specifically for this study, the monkeys were rewarded for making correct memory-guided saccades only in one direction, termed the rewarded direction (Fig. 1). Monkeys were not rewarded (exclusive 1DR) or were rewarded with a smaller amount (relative 1DR) when they made a correct response in one of the other three directions, but they had to make a correct saccade to proceed to the next trial. The rewarded direction was fixed in a block of 60 successful trials, and a total of four blocks were done, with four different rewarded directions. Thus, the cue

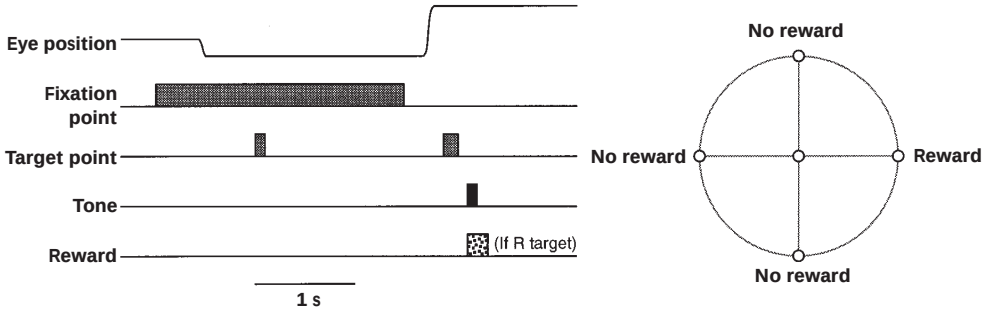

Fig. 1. Memory-guided saccade task in the 'one direction rewarded' condition (1DR). Throughout a block of experiment (60 trials), only one direction was rewarded. (Here the right direction was rewarded.) Different directions were rewarded in different blocks.

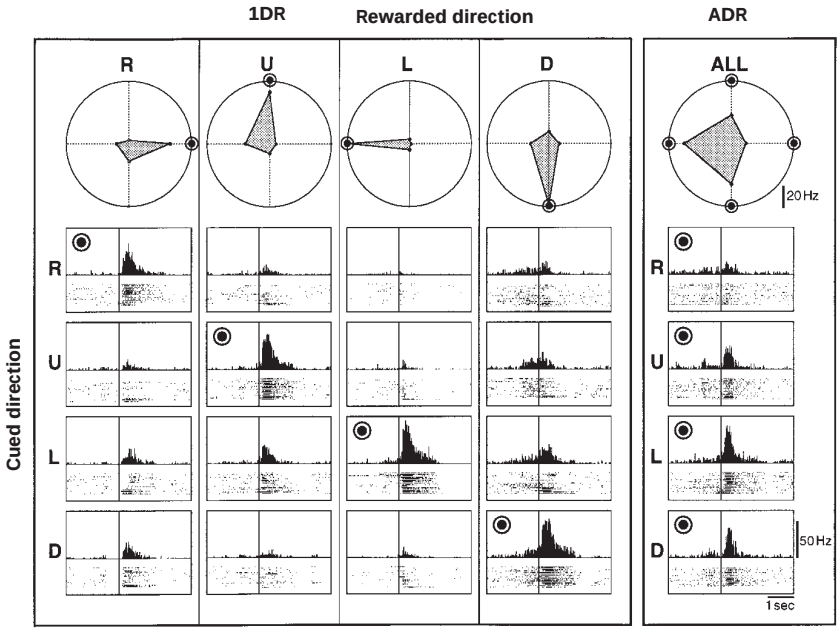

Fig. 2. Reward-dependent visual response (reward-facilitated type) of a neuron recorded in the right caudate nucleus. The data obtained in one block of ADR (right) and four blocks of 1DR (left) are shown in columns. In the histogram/raster display, the neuron discharge aligned on cue onset is shown separately 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 diagrams (top row) show the magnitudes of response for four cue directions. Target eccentricity was ten degrees. The neuron's response was strongest for the rewarded direction in any block of 1DR, whereas its preferred direction was to the left in ADR.

stimulus signified two things: the direction of the saccade to be made later, and whether or not a reward (or a larger reward) was to be obtained after the saccade.

Among 241 neurons that we recorded in the caudate nucleus, there were neurons showing phasic visual responses to the cue stimulus (visual response; $n = 114$), sustained activity during the delay period (memory-related response; $n = 79$), saccadic responses ($n = 92$) and activity preceding the cue stimulus ($n = 89$). Here we studied 87 neurons with visual or memory-related responses, in which four blocks of 1DR and one block of ADR were fully examined. Among the fully examined neurons, 27 of 45 neurons (60%) with visual responses and 20 of 50 neurons (40%) with memory-related responses showed clear direction selectivity when tested in ADR (one-way ANOVA (cued direction), $p < 0.01$; eight neurons showed both visual and memory responses). The preferred direction was usually contralateral (70%), as reported[10].

We found, however, that such spatial selectivity depended on the reward condition. A typical neuron in the right caudate nucleus (Fig. 2) responded to the left (contralateral) cue stimulus most vigorously in ADR, whereas the response to the right cue was meager. The neuron's direction selectivity is shown as a polar diagram (Fig. 2, top row). In 1DR, however, the neuron's direction selectivity changed. For example, when the rewarded direction was right, this neuron responded to the right cue stimulus much better than to the other directions. Similarly, the neuron changed its preferred direction in other blocks so that its response was most vigorous for the rewarded direction. The response depended strongly on the reward condition (two-way ANOVA (reward condition × cued direction), main effect of reward condition; $p < 0.0001$). Another type of caudate neuron also depended on reward expectation, but in the opposite manner (Fig. 3). In ADR, this neuron showed almost no response to any of the four cue stimuli. In 1DR, however, it showed vigorous responses to the cue that indicated no reward, whereas it showed no response to the rewarded cues, no matter which direction was rewarded. A

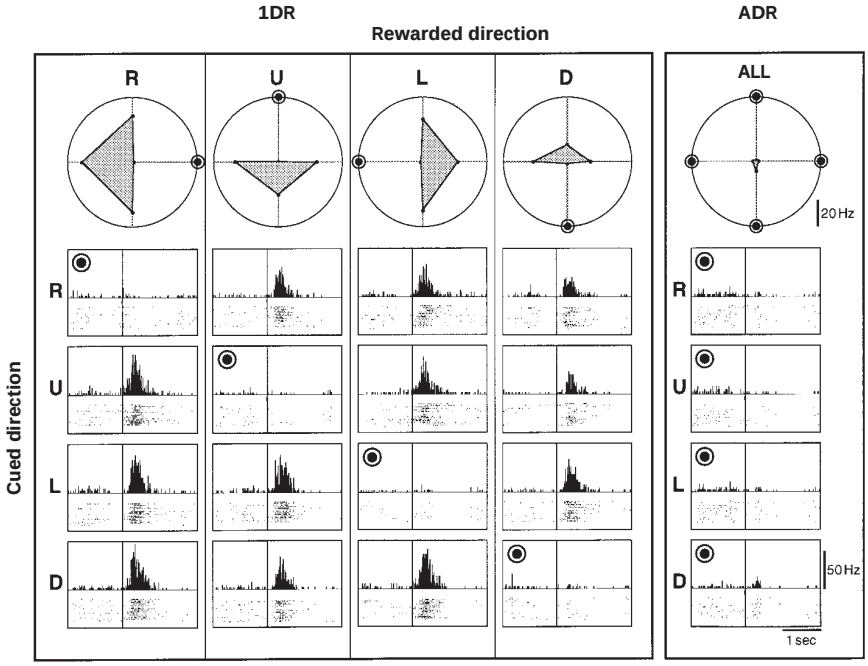

Fig. 3. Reward-dependent visual response (reward-suppressed type) of a neuron recorded in the left caudate nucleus. Target eccentricity was 20 degrees. The neuron showed vigorous responses exclusively to the non-rewarded cues. See legend to Fig. 2 for explanation of layout.

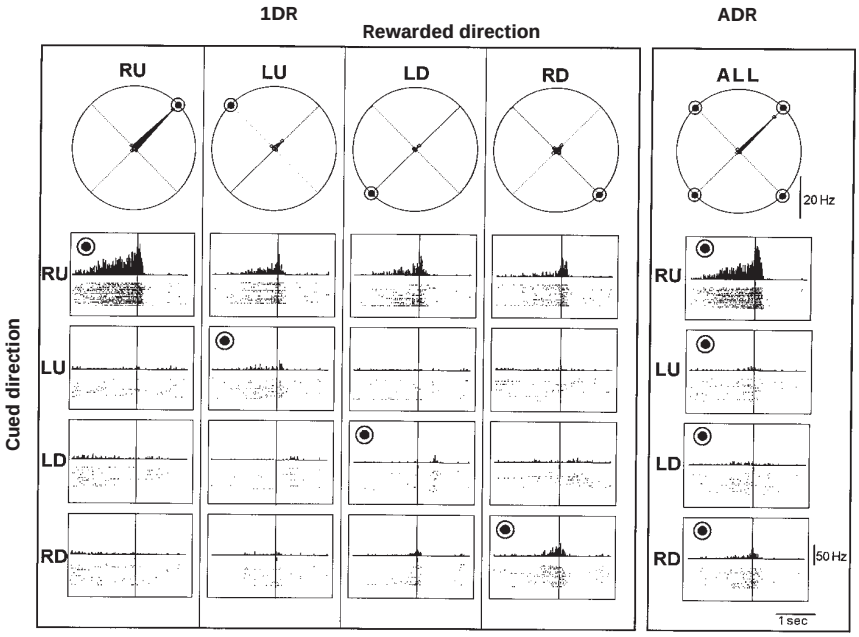

Fig. 4. Reward-dependent memory response (reward-facilitated type) of a neuron recorded in the left caudate nucleus. See legend to Fig. 2 for format. Here the neuron discharge was aligned on saccade onset. Cued/rewarded direction: RU, right-up; LU, left-up; LD, left-down; RD, right-down. Target eccentricity was 20 degrees. The neuron showed sustained memory-related activity and phasic saccadic activity for the right-up direction, both of which were stronger when this direction was rewarded.

third type of response is illustrated by a neuron in the left caudate nucleus (Fig. 4), which showed sustained activity in ADR after the cue was presented in the right-up (RU) direction; the activity reached its peak at the time of the saccade. In 1DR, the neuron's activity for the RU direction was reduced considerably when this direction was not rewarded (columns 2–4), whereas some activity appeared in the right-down (RD) and left-up (LU) directions when they were rewarded.

The cells shown in Figs 2–4 were not exceptional. Most caudate neurons showed either a strong enhancement (data points close to the ordinate) or a reduction (data points close to the abscissa) of response by expectation of reward (Fig. 5a). A statistically significant modulation was found in 76 of 87 neurons (87%) in visual or memory-related responses: visual response, 36/45 (80%); memory response, 43/50 (86%; two-way ANOVA (reward condition × cued direction), main effect of reward condition; $p < 0.01$). Among the 76 modulated neurons, 64 neurons (visual, 31; memory, 36) showed an enhancement ('reward-facilitated neurons'), whereas 12 neurons (visual, 5; memory, 7) showed a reduction of response ('reward-suppressed neurons'). The results were the same for exclusive 1DR and relative 1DR.

The caudate contributes to the initiation of saccades with its connection to the superior colliculus through the substantia nigra[11]. The modulation of caudate neuron activity by reward expectation might therefore produce changes in the characteristics of the subsequent saccade to the remembered cue location. Our data confirmed this prediction; the latencies were shorter (Fig. 5b) and the peak velocities were higher (Fig. 5c) when the saccades were followed by reward than when they were not (paired t-test, $p < 0.0001$). The saccade latencies were significantly different in the two monkeys, but the difference between the rewarded and non-rewarded conditions was evident for each monkey. In addition, saccades to the rewarded direction were more accurate than those to the non-rewarded directions; the monkeys occasionally made incorrect saccades on non-rewarded trials.

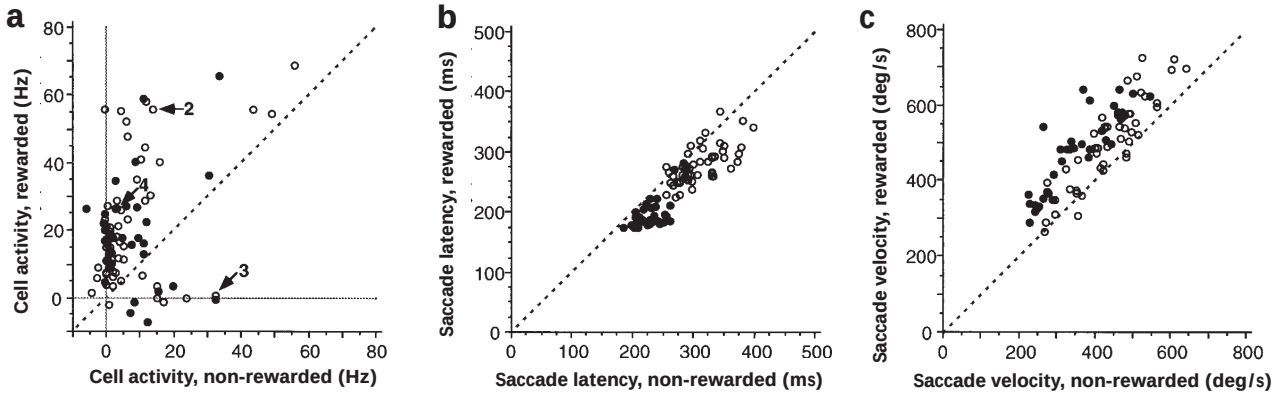

Fig. 5. Effects of reward expectation on caudate neuron activity **(a)**, saccade latency **(b)**, and saccade velocity **(c)**. Values in the rewarded (ordinate) and non-rewarded (abscissa) conditions are compared. After determining the preferred direction for each neuron, we calculated the mean magnitude (test-control, Hz) of the neuron's response to its preferred cue in two conditions: when the preferred direction was rewarded (one block) and when the preferred direction was not rewarded (three blocks). Data from two monkeys are shown with different symbols. Both visual and memory-related responses are included. Arrows 2–4 indicate the data for the neurons shown in Figs 2–4, respectively. The saccade parameters were obtained for each neuron by averaging across saccades to the neuron's preferred direction separately for the rewarded and non-rewarded conditions (b and c).

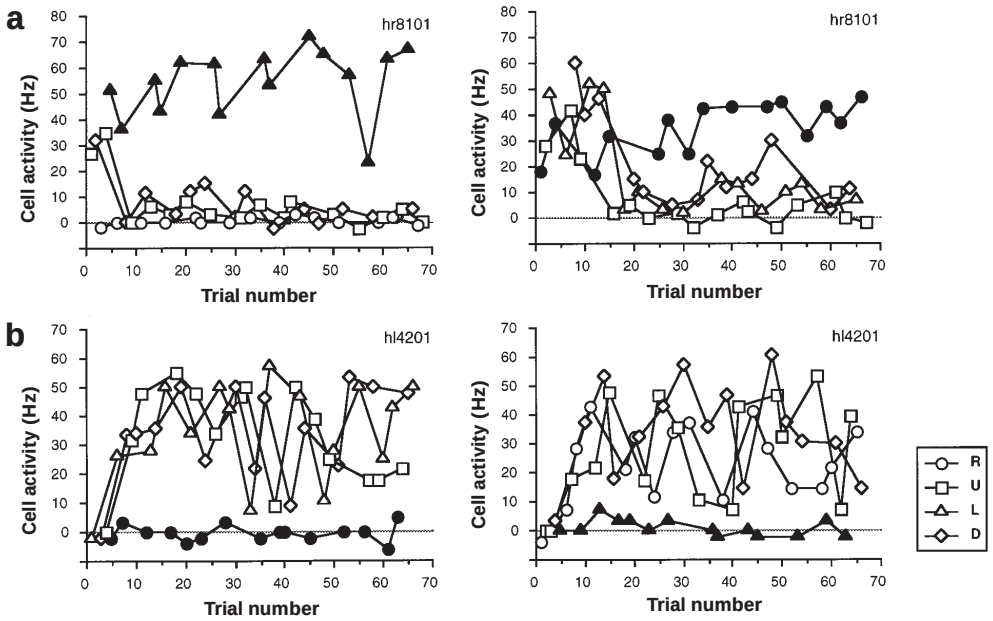

Fig. 6. Change in direction selectivity within one block of 1DR trials. Data for two sequential blocks are shown for two neurons: **(a)** neuron from Fig. 2; **(b)** neuron from Fig. 3. Discharge rates for four cue directions are plotted individually against the trial number. The rewarded cue is indicated by a filled symbol.

We next determined how quickly the caudate neurons changed their response when the rewarded direction was changed (Fig. 6). In the first block of 1DR for the reward-facilitated neuron shown in Fig. 2, the rewarded direction was to the left, which was the neuron's preferred direction in ADR (Fig. 6a, left). The responses were initially strong for all directions except the right, but the responses to the left cue gradually increased, whereas the responses to the other cues decreased rapidly and remained near zero. In the next block (Fig. 6a, right), the rewarded direction was changed to the right, which was the non-preferred direction in ADR. Again, the responses were initially strong for all directions but decreased gradually, with only the response to the right cue persisting. The time course for the reward-suppressed neuron shown in Fig. 3 was opposite to that of the reward-facilitated neuron in Figs 2 and 6a. For each block, the reward-suppressed neuron initially showed almost no response to any direction, but then started responding to the three directions that indicated no reward (Fig. 6b). A similar time course of response modulation was observed in some of the other reward-contingent caudate neurons. For the non-rewarded cues, 27 of 64 reward-facilitated neurons significantly decreased their responses, whereas 4 of 12 reward-suppressed neurons significantly increased their responses, when the initial 15 trials and the subsequent trials were compared (t-test, $p < 0.01$). Reward-contingent neurons were distributed in the caudate nucleus from its head to the body (Fig. 7). There was no distinct tendency for differential distribution of different types of neurons: reward-facilitated versus reward-suppressed (Fig. 7) or visual versus memory (not shown).

Discussion

These data show that visual and memory responses of caudate neurons were strongly modulated by the reward schedule in the memory-guided saccade task. The monkeys were required to complete the same tasks of spatial attention and motor programming on each trial, yet caudate neurons' responses depended selectively on whether a successful trial would be rewarded immediately. This reward-dependent modulation of neural behavior can be viewed as reflecting a form of motivation.

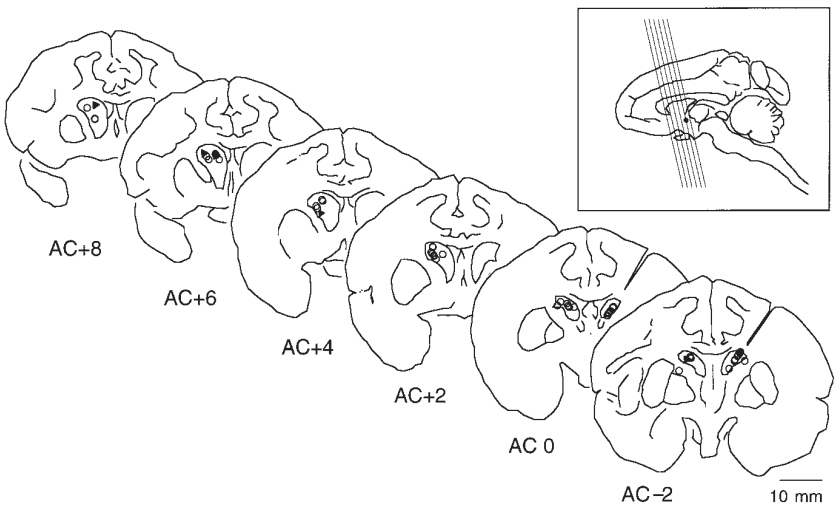

Fig. 7. Recording sites of reward-contingent caudate neurons plotted on coronal sections in one monkey. Open circles, reward-facilitated neurons; filled triangles, reward-suppressed neurons. AC indicates the level of the anterior commissure; the sections anterior and posterior to the AC are indicated by plus and minus numbers (distances in mm), respectively. Inset, a mid-sagittal view, indicating the levels of the coronal sections (anterior to left); the position of the AC is indicated by a dot. To reconstruct the recording sites based on MR images, recordings were made for selected penetrations through implanted guide tubes, which were then visualized on MR images (sections AC –2 and AC 0, right side). One neuron in the section AC –2 (left side) was judged to be inside the neuron cluster bridging the caudate and the putamen.

The modulation of caudate neural activity could instead be considered a kind of attentional modulation. However, this is conceptually different from the type of attention investigated in previous studies. Thus, the previous studies on attention[1–3] were based on the 'attend-versus-ignore' comparison, whereas our study was based on the 'rewarded-versus-nonrewarded' comparison. In the former comparison, cognitive processing was allocated to the to-be-attended location or object, and reward was given consistently. Here the required cognitive processing was identical for different target locations, but the reward outcome was different. The basal ganglia may direct attention to items associated with reward, whereas the cerebral cortex, especially the parietal cortex[12], may direct attention based on task requirements.

The neurons we recorded had low spontaneous activity and were presumably projection neurons, which are GABAergic[13]. They are thought to modulate the final inhibitory outputs of the basal ganglia, either by disinhibition or by enhancement of inhibition[14–16]. Anatomically, the striatal projection neurons are characterized by many spines on their dendrites[17,18], to which glutamatergic cortico-striatal axons and dopaminergic axons make synaptic contacts[19,20]. Dopaminergic neurons in the substantia nigra show responses to sensory stimuli that predict the upcoming reward[21,22]. Thus, a caudate neuron could receive spatial information through the corticostriatal inputs[23] and reward-related information through the dopaminergic input[21].

Given these considerations, our findings are consistent with the view that the efficacy of the corticostriatal synapses is modulated by the dopaminergic input[22,24,25]. The co-activation of these two inputs should produce synaptic enhancement and depression, respectively, in reward-facilitated neurons and reward-suppressed neurons. Such opposing processes might be mediated by different dopaminergic receptors, such as D1 and D2[26,27].

Alternatively, the reward-contingent modulation may occur in the cerebral cortex, especially in the prefrontal cortex[6]. Memory-related sustained activity in prefrontal neurons is modulated by dopaminergic inputs[28,29]. It is thus possible that the reward-contingent activity of caudate neurons may simply reflect the plasticity of the cerebral cortex. Conversely, the caudate neurons may influence the activity in the cerebral cortex through the output nuclei of the basal ganglia and the thalamus[30].

The reward-contingent modulation of caudate neuron activity was correlated with the changes in saccade latency and velocity. A mechanism underlying the changes may be the serial inhibitory connections from the caudate to the superior colliculus through the substantia nigra pars reticulata[15,31]. An enhancement of caudate neuron activity when reward is expected (Fig. 2) would produce an enhanced disinhibition of the superior colliculus and consequently a reduction of saccade latency and an increase in saccade velocity, especially for memory-guided saccades[32], which we observed here. In contrast, an enhancement of caudate neuron activity when reward was not expected (Fig. 3) might affect the 'indirect pathway' (including the globus pallidus external segment[33] and subthalamic nucleus[34]), which would lead to the suppression of saccades to the non-rewarded cues, as seen here. Consistent with this, dopaminergic denervation in the caudate of monkeys leads to deficits in spontaneous saccades[35] and memory-guided saccades[36]. Dopamine-deficient monkeys also showed spatial hemineglect[37]. Similar oculomotor and attentional deficits have been reported in patients with Parkinson's disease[38,39]. 'Abulia', lack of will, is a symptom that often occurs after a lesion in the caudate[40,41].

The basal ganglia may contribute to the selection of action[42,43]. Our study indicates that the caudate nucleus contributes to the control of oculomotor action by associating motivational values, such as the expectation of reward, to a visual target.

Methods

GENERAL. We used two male Japanese monkeys (*Macaca fuscata*). After each monkey was sedated by general anesthesia, we implanted a head holder, chambers for unit recording and a scleral search coil[31]. All surgical and experimental protocols were approved by the Juntendo University Animal Care and Use Committee and are in accordance with the National Institutes of Health Guide for the Care and Use of Animals. The monkeys were trained to perform saccade tasks, especially a memory-guided saccade task[44]. Eye movements were recorded using the search coil method. We recorded extracellular spike activity of presumed projection neurons, which showed very low spontaneous activity (< 3 Hz)[11], but not of presumed interneurons, which showed irregular tonic discharge[45] .

Here we studied cells that showed visual and/or memory responses. We defined a visual response as phasic activity that started within 200 ms after onset of the cue stimulus and reached its peak within another 200 ms, and a memory-related response as sustained activity that started at least 200 ms after the cue onset and ended before or with the saccade (A neuron could have both types of responses.) For each neuron, we used a set of four target locations of equal eccentricity (either 10 degrees or 20 degrees), arranged at either normal or oblique angles, depending on the neuron's receptive field. The recording sites were verified by MRI (Hitachi, AIRIS, 0.3T).

TASK PROCEDURES. The monkeys did the memory-guided saccade task in two different reward conditions: all-directions-rewarded condition (ADR) and one-direction-rewarded condition (1DR). For every caudate neuron recorded, we required the monkeys to do one block of ADR and four blocks of 1DR (that is, four different rewarded directions). The use of the memory-guided saccade task allowed us to dissociate visually evoked activity from motor-related activity.

In both conditions, a task trial started with the onset of a central fixation point that the monkeys had to fixate (Fig. 1). A cue stimulus (spot of light) came on 1 s after onset of the fixation point (duration, 100 ms), and the monkeys had to remember its location. After 1–1.5 s, the fixation point turned off, and the monkeys were required to make a saccade to the previously cued location. The target came on 400 ms later for 150 ms at the cued location. The saccade was judged to be correct if the eye position was within a 'window' around the target (usually within 3 degrees) when the target turned off. The correct saccade was indicated by a tone stimulus. The next trial started after an inter-trial interval of 3.5–4 s.

In ADR, every correct saccade was followed by the tone stimulus and a liquid reward. In 1DR, an asymmetric reward schedule was used (Fig. 1) in which correct responses in only one of the four directions was rewarded, but correct responses in the other directions were either not rewarded ('exclusive 1DR') or rewarded with a smaller amount (about 1/5) ('relative 1DR'). The highly rewarded direction was fixed in each block of experiments, which consisted of 60 successful trials. Even for the non-rewarded or less-rewarded direction, the monkeys had to make a correct saccade. If the saccade was incorrect, the trial was repeated. The average amount of reward per trial was approximately the same for 1DR and ADR. The target cue was chosen pseudo-randomly such that the four directions were randomized in every sub-block of four trials; thus, one block (60 trials) consisted of 15 trials for each direction. 1DR testing was done in four blocks, each with a different rewarded direction. Other than the actual reward, no indication was given to the monkeys as to which direction was currently rewarded.

DATA ANALYSIS. For each neuron responding to the cue stimulus, we first determined the duration of the response (test duration) based on cumulative time histograms, usually based on the most robust response. A control duration (usually 500 ms) was set just before the onset of the fixation point. The neuron's response was calculated for each trial as the spike frequency during the test duration minus the spike frequency during the control duration.

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