INTRODUCTION

The pedunculopontine tegmental nucleus (PPTN) and laterodorsal tegmental nucleus (LDTN) are major sources of cholinergic projections in the brain stem and contain both cholinergic and glutamatergic neurons (Hallanger and Wainer 1988). PPTN is a part of the reticular activating system, which provides background excitation for several sensory and motor systems and is essential for perception (Lindsley 1958) and cognitive processes (Steckler et al. 1994a). Reciprocal connections have been demonstrated between PPTN and the output structures of the basal ganglia: the subthalamic nucleus, the globus pallidus, and the substantia nigra (Edley and Graybiel 1983; Lavoie and Parent 1994), and between PPTN and catecholaminergic systems in the brain stem: the locus coeruleus (LC) and the dorsal raphe nucleus (DRN) (Koyama and Kayama 1993). The basal ganglia–PPTN–catecholaminergic system complex is thought to play an important role in gating movement and controlling several attentive behaviors (Aston-Jones et al. 1996; Garcia-Rill 1991). Despite the abundance of anatomical data, however, the functional role of PPTN neurons for behavioral control is not sufficiently understood.

A role for PPTN in the control of movement has been suggested by a number of observations (arm movement: Matsumura et al. 1997; locomotion and posture control: Garcia-Rill 1991). It has also been shown that lesions of PPTN reduce the frequency of eye movements during REM sleep (Shouse and Siegel 1992). The frontal eye field (FEF) (Bruce and Goldberg 1985) and substantia nigra pars reticulata (SNr) (Hikosaka and Wurtz 1983) are related to controlling saccadic eye movements, and both FEF neurons (Matsumura et al. 2000) and GABAergic SNr neurons (Gerfen et al. 1982; Granata and Kita 1991) project to the PPTN. These findings suggest that PPTN may contribute to controlling eye movements, particularly saccades.

The cholinergic PPTN also strongly innervates the intermediate layer of the superior colliculus (SC) in various mammalian species (Beninato and Spencer 1986; Graybiel 1987; Hallanger and Wainer 1988). The cholinergic PPTN also strongly innervates the intermediate layer of the superior colliculus (SC) in various mammalian species (Beninato and Spencer 1986; Graybiel 1987; Hallanger and Wainer 1988).

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et al. 1989; Henderson and Sherriff 1991; Jeon et al. 1993; Ma et al. 1991; Schnurr et al. 1992). SC is involved in the generation of saccades (Sparks and Hartwich-Young 1989). The neuronal activity of the intermediate layer of SC preceding saccade execution is influenced by attentional shifts (Sheliga et al. 1997), movement selection (Glimcher and Sparks 1992), and the degree of motor preparation (Basso and Wurtz 1998; Dorris and Munoz 1998). To clarify the role of the cholinergic input to the intermediate layer of SC in saccades, we previously examined the effect of microinjection of nicotine into the SC on visually guided saccades in monkeys. After injection of nicotine, the saccadic reaction times decreased dramatically (Aizawa et al. 1999), suggesting that cholinergic inputs to SC influence saccade initiation.

PTPN also projects to the dopaminergic neurons of the substantia nigra pars compacta (SNc) (Beninato and Spencer 1986) that encode an error signal for reinforcement learning (Schultz 1998). PPTN receives limbic inputs from the hypothalamus, the ventral tegmental area (Segma and Fibiger 1992), and the limbic cortex in monkeys (Chiba et al. 2001). A recent computational model (Brown et al. 1999) predicts that PPTN is a major source of the excitatory signal to the SNc and is an important component of reinforcement learning, demonstrating that PPTN may be involved in reinforcement mechanisms.

Performance of the behavioral tasks may depend on the attentive and motivational state of the animal. Many studies suggest that PPTN and LDTN control wakefulness or vigilance levels and may induce a global attentive state in response to a novel stimulus (Datta and Siwek 1997; Koyama et al. 1994; Steriade 1996a,b). Several motivated behaviors of rats driven by rewards are controlled by PPTN (Bechara and van der Kooy 1989; Bechara et al. 1995; Stefurak and van der Kooy 1994).

In conditioned cats, reversible blockage of PPTN by muscimol injection caused elongation of inter-trial intervals in a lever-release task (Condé et al. 1998). Bilateral lesions of PPTN in rats did not affect performance in a simple maze task (the cross-maze task: requiring simple memory of place), but did decrease performance in another maze task (the radial-maze task) which required simple memory of place and sustained attention during search (Dellu et al. 1991). In addition, lesions of PPTN in rats did not produce marked deficits in the accuracy of a delayed nonmatching to position task, although motivational processes were affected (Steckler et al. 1994b).

Overall, these results suggest that PPTN may also be involved in the motivation or sustained attention required for correct performance of the task.

Given these anatomical and physiological results, we hypothesized that PPTN can relay signals related to motor control, limbic function, and motivation and that PPTN may function as an important interface for behavioral control by integrating various signals on each neuron. To investigate how PPTN neurons were related to control of visually guided saccade tasks, we recorded the neuronal activity in relation to saccade execution/initiation, reinforcement processes (reward for the task), and task performance. A preliminary account has been presented in an abstract form (Kobayashi et al. 1999).

METHODS

Electrophysiology

All experimental procedures were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and approved by the Committee for Animal Experiment at Okayama National Institutes. The details of the surgical and data acquisition methods have been published previously (Aizawa and Wurtz 1998; Aizawa et al. 1999). Briefly, three male Japanese monkeys (Macaca fuscata) weighing 7–13 kg were anesthetized with halothane and implanted with scleral search coils (Fuchs and Robinson 1966), a head holder, and a recording chamber tilted 40° posterior to the vertical axis. The monkeys were allowed to recover for ⩾3 wk and then trained to perform a visually guided saccade task for a liquid reward, sitting in a primate chair with their heads in a fixed position. The activity of single neurons was recorded using tungsten microelectrodes (FHC) with an impedance of 1–6 MΩ. Electrodes were positioned through stainless steel guide tubes (23 gauge) using a micromanipulator (Narishage MO-95). The guide tubes were held in position with a delrin grid that was fixed to the recording cylinder (Crist et al. 1988). Eye movements were recorded using the magnetic search coil (Fuchs and Robinson 1966) with a resolution of 0.1 deg. Horizontal and vertical eye positions were sampled at 1 kHz. Single neuronal discharges were also collected at 1 kHz via a template matching spike discriminator (Alpha-Omega MSD) that produced a pulse for each spike that matched a spike waveform template. To examine the relationship between spike width and firing pattern, we also collected 50 action potentials at 40 kHz for each neuron to analyze its spike width.

Behavioral task

Monkeys were trained on two visually guided saccade tasks. Visual stimuli consisted of small squares of light (0.8 deg square) back-projected on a tangential screen positioned 28 cm from the eyes. Visual displays and data storage were controlled using computers running a QNX-based real-time data acquisition system REX (Hays et al. 1982) and a Windows-based real-time data acquisition system (Reflective computing, Tempo for Windows) with a dynamic link to MatLab (MathWorks). At the beginning of each trial, the fixation point (FP) appeared at the center of the screen, and monkeys were required to move their eyes to the FP. To monitor fixation of monkeys, we applied a window (2–7 deg square) that quickly narrowed to approximately 2 deg in every recording session once the monkeys adjusted to the task. If the monkeys did not make a gaze shift to the FP within 3000 ms, the trial was regarded as an error trial. The trial was then aborted and the computer program moved to the next trial. The duration of fixation on the central FP was varied randomly between 400 and 1000 ms. Trials in which monkeys could not maintain fixation to the FP for the duration (400–1000 ms) were rejected as error trials. Data sampling started from 500 ms before FP onset for every trial. The saccade target (ST) was presented at an amplitude of 5–15 deg distant from the FP in eight directions (0, 45, 90, 135, 180, 225, 270, and 315 deg). The target amplitude was determined by the largest saccadic modulation evoked by a target location for each recorded neuron (mean amplitude: 12 deg). If the saccade-related modulation was weak, we set the target amplitude to 10 deg. Three tasks were randomly shuffled within a block of trials. In the Step paradigm, the ST appeared in the peripheral visual field concurrent with the offset of the FP. In the Gap paradigm, the ST appeared 170–200 ms following the disappearance of the FP. On catch trials, the FP disappeared and after a gap of 200 ms, the FP reappeared in the central position. Catch trials comprised <12% of the trials in a block to reduce anticipatory error to the saccade target, but we did not systematically compare the data between blocks that included catch trials and those that did not.

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Saccadic reaction time (SRT) was defined as the interval between ST onset and the saccade onset. The Step and Gap paradigms were included to increase the range of SRT, because SRTs in Gap trials are shorter than those in Step trials (Fischer and Boch 1983; Paré and Munoz 1996). Monkeys were rewarded with fruit juice 200–500 ms after correctly performing a saccade to the ST and then maintaining fixation for 100–300 ms in the ST window (size 2–7 deg), the size of which also gradually decreased during recording sessions. Small percentage of trials with SRTs below 80 ms were considered as trials with anticipatory saccades, because they commonly exhibited lower peak velocities and larger targeting errors as reported in a previous study (Fischer and Weber 1993). Trials with SRTs above 500 ms were considered as error trials and were not rewarded. Inter-trial intervals ranged from 1100 to 2000 ms.

Identification of recording sites

The location of PPTN was verified using penetration record maps and magnetic resonance imaging (MRI; Hitachi MRI system, 2.2T). Recording sites were plotted on sagittal magnetic resonance (MR) images and images parallel to the recording chamber angle for each monkey (e.g., see Fig. 1). To reconstruct the recording sites based on MR images, recordings were made for selected penetrations through implanted guide tubes in the grid chamber system. We used two landmarks to fit the MR image and penetration records: auditory responses in the inferior colliculus, fiber activity of the superior cerebellar peduncle, and reached PPTN. PPTN was located 3–5 mm lateral from midline and 3–7 mm deeper than where auditory responses were observed. We recorded single units in that location and confirmed high-frequency tonic fiber activity (>20 Hz) within 3–5 mm from single units, since PPTN is close to the cerebellar peduncle. Fiber activity was identified as a discharge pattern of spikes including a positive potential and brief spike width (<1 ms).

Histology

At the conclusion of the experiments, one monkey (the other monkeys are still alive) was deeply anesthetized with pentobarbital (Nembutal; >150 mg/kg) and perfused with 10% formaldehyde. The brain was removed, frozen, cut into 50-μm coronal sections, mounted on microscope slides, and stained using cresyl violet. Recording sites were marked by placing electrolytic lesions at selected recording sites and were verified to be in PPTN after reconstruction of the electrode tracks.

Data analysis

For all analyses, we did not prescreen the neurons for any specific firing pattern, and 70 neurons with more than or equal to five completed trials for each condition were used for analysis of task related firing pattern (Gap/Step and 8 directions). Three neurons were used only for the tests pertaining to reward responses. To evaluate the relationship between neuronal discharge and specific events, we produced rasters and continuously varying spike density functions (Richmond et al. 1987) aligned on the events. To generate the spike density function, a Gaussian pulse of fixed width (α-value = 4 ms) was substituted for each spike and then summed together to produce a continuous function in time. A mean spike density function was computed by averaging the spike densities over a series of trials. Onset and offset of saccades were identified by velocity criteria (threshold 30 deg/s) during off-line analysis.

To clarify the relationship between neuronal activity of PPTN and the execution of visually guided saccades, the activity preceding and during saccadic eye movement and its directional property were examined. To examine the contribution of PPTN neurons to saccade initiation, the pretarget activity and its correlation with SRT were analyzed. To examine the activity in relation to reinforcement process, we analyzed the discharges around rewards delivered during the saccade task and the freely given rewards without saccade tasks.

To investigate the relationship between neuronal activity and task performance, we analyzed tonic discharges and responses to the FP with the successful or erroneous outcome of the task. The relationship between the performance and neuronal activity was estimated by success rate and firing rate. The firing rates were calculated in a time-window for every trial, and then the data, which were composed of firing rate and success or error, were collected according to their
firing rate into several bins (i.e., every 2 spikes/s). The success rate was calculated for each bin according to the number of successful and erroneous trials for each firing rate bin.

To investigate performance of the task (preparation for appearance of the FP or a motivational state), we analyzed the reaction time to the FP appearance (RTFP). In the off-line analysis, the RTFP was defined as the interval between the time of FP onset and the time at which the eye entered the computer-controlled FP window (size: 2 deg square). The correlation between the tonic discharges or the responses to the FP and RTFP was also examined. To examine motivation toward the task, we classified error trials into three types depending on which portion of the task the monkey failed to perform and analyzed the relationship between the error type and RTFP. In addition, we analyzed the RTFP in relation to success or error of the task.

Previous studies in cats (Dormont et al. 1998) and rats (Koyama et al. 1998) suggested that the width of the action potential in PPTN neurons correlated with the neurotransmitter that they carry (glutamatergic, brief spikes; cholinergic, broad spikes). To investigate the relationship between various aspects of the task (saccade execution, task performance and activity around reward) and the presumed neuronal transmitter type for each neuron, we examined the correlation between firing pattern and spike width, which was measured as the duration of the negative phase of the spike waveform.

RESULTS

Recorded neurons

We analyzed 73 neurons (11 neurons in monkey A, 15 neurons in monkey B, and 47 neurons in monkey C) in PPTN. Reconstructions of the locations of recorded PPTN neurons on the coronal sections through the midbrain and pons in monkey A are shown in Fig. 1A, and recording sites were plotted on sagittal MR images for this monkey (Fig. 1B). The average firing rate of the 73 PPTN neurons during inter-trial intervals ranged from 0.1 to 74 spikes/s with a mean of 15 spikes/s. The width of action potentials of PPTN neurons varied from 0.2 to 1.4 ms. For the analyses of discharge in every condition of the task, 70 neurons with more than or equal to 15 spikes/s were used. For the other three neurons, we investigated activity only in the Step paradigm and examined activity around the time of reward delivery. For the 70 neurons, the total trial number was 9391 for the three monkeys, and the success rate on all trials was 82.5%. Among the error trials, the monkeys did not make a gaze shift to the FP or did not fixate to the FP in 87% of error trials, while the monkeys did not make a correct saccade to the ST in the remaining 13%.

Neuronal activity related to saccade execution

To quantify the relationship between the activity of PPTN neurons and the execution of visually guided saccades, the activity during saccades to the targets located in different directions was examined. Typical saccade-related activities toward the target for two separate neurons are shown in Fig. 2, A and B. Both rastergrams and spike density histograms are aligned with the time of saccade onset. A sudden increase (Fig. 2A) or decrease (Fig. 2B) in activity could be observed before the saccade. These modulations of activity were associated with the onset of saccade rather than that of target appearance (indicated by open circles in Fig. 2). We did not classify saccade-related activities into either visually evoked or movement-related; however, the responses to the saccade target were not observed in the error trials where the monkeys did not make a saccade to the presented target (data not shown).

To investigate the contribution of PPTN activity to saccade execution, we classified neurons as burst type or pause type according to the saccade-related activity. The saccade-related activity was defined by either an increase or a decrease in discharge at the time of saccade onset as opposed to the ST onset, by averaging the number of spikes occurring −50 to +50 ms from saccade onset in the Step task for eight directions. We defined the fixation activity as the firing rate between 250 and 350 ms before the ST onset in the Step task. The percentage change was computed as a percentage ratio (the Gap-related activity divided by the pretarget activity in the Step task).

Neurons were defined as saccade burst neurons if the largest modulation in saccadic activity (subtraction of the fixation activity from the saccade-related activity) for stimuli in eight directions was above 10 spikes/s. This criteria was similar to that used in a study of saccade-related activity in FEF (Everling and Munoz 2000). Thirty-seven percent of PPTN neurons were classified as saccade burst neurons (26/70). Their mean firing rate was 39.8 spikes/s (ranging from 20.9 to 111.7 spikes/s) for...
Neurons were defined as saccade pause neurons if all the modulations in saccadic activity for stimuli in eight directions reflected a reduction in discharge rate (i.e., <0 spikes/s). Twenty-seven percent of PPTN neurons were classified as saccade pause neurons (19/70). The saccade pause neurons exhibited tonic discharges (mean = 28.5 spikes/s, ranging from 11.5 to 74.2 spikes/s) while fixating a target spot and exhibited a pause in firing (mean decrease = −13.3 spikes/s, ranging from −34.2 to −5.7 spikes/s) during saccades (Fig. 2B).

The influence of saccadic direction on saccade-related activity in a burst neuron and a pause neuron is shown in Fig. 3, A and B, respectively. The saccade amplitude was 10° during the recordings. Burst neurons were strongly modulated by saccade direction, whereas pause neurons were not. Figure 3, C and F, shows the population data for directional tuning among the burst neurons (n = 26) and the pause neurons (n = 19), respectively. The amplitudes of saccades were within 5–15 deg. The peak and valley of the curves were centered on the best modulated directions for each neuron.

To quantify the relationship between saccade-related activity in PPTN and saccade direction, we used a linear regression analysis. Saccade-related activities in eight directions were fitted to a cosine function as follows: $f = f_0 + A \cos (w - w_p)$, where $f_0$ is the intercept of the regression equation, $A$ is the change in firing rate of the neuron as a function of direction ($w$; 0, 45, 90, 135, 180, 225, 270, and 315 deg), and $w_p$ is the preferred direction of the neuron. The correlation coefficients between the discharge and the cosine function of the direction were statistically significant in 18 of 26 burst neurons and in 7 of 19 pause neurons ($P < 0.05$). The correlation coefficients between the discharge and the cosine function of the direction were larger in burst-type neurons [0.71 ± 0.21 (SD), n = 26] than in the pause-type neurons [0.55 ± 0.24 (SD), n = 19; $P < 0.05$, t-test]. This result suggests that the burst activity was modulated as a cosine function of the saccade direction, but the pause in firing was less directionally dependent.

The burst neurons exhibited strong tuning for the cosine function of the saccade direction; however, the preferred directions for each burst neuron were not distributed in directions aligned with horizontal or vertical meridians. Furthermore, the preferred directions of burst neurons were not biased into either the ipsilateral (15/26) or the contralateral (11/26) hemifields (Fig. 3D). Although the directional selectivity was weak, the computed preferred directions of pause neurons were not distributed in directions aligned with horizontal or vertical meridians, but biased to the ipsilateral side (14/19) rather than the contralateral side (5/19) (Fig. 3E).

**Neuronal activity related to saccade initiation**

To examine whether PPTN controls the initiation of the visually guided saccade, we analyzed neuronal discharges and SRTs in the Gap and Step tasks. Figure 4, A and B, shows the distribution and cumulative percentage of SRTs, respectively, obtained from three monkeys performing the Gap and Step tasks while the 70 PPTN neurons were recorded. Consistent with previous findings (Fischer and Boch 1983; Paré and Munoz 1996), responses in the Gap task exhibited shorter

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**FIG. 3.** Directional selectivity in burst neuron and pause neuron. Activity of a burst (A) and a pause (B) neuron in response to stimuli in 8 directions. Rastergrams (for 5 trials) and spike density functions are aligned with saccade onset (0 ms). The population data of directional tuning is shown for burst neurons (C) (n = 26) and pause neurons (F) (n = 19). The peak and valley of the curves are centered on the best modulated directions for each neuron. Each data point represents the mean. Vertical bars indicate the SE. Dotted lines indicate the average firing rate during fixation. Preferred directions in burst neurons (D) and pause neurons (E). IPSI, ipsilateral; CONTRA, contralateral; UP, upward; DOWN, downward.
SRTs than in the Step task [Gap task, 145.5 ± 18 (SD) ms, n = 3511 and Step task, 158.6 ± 24 (SD) ms, n = 3537, P < 0.01, t-test]

Pretarget activity was computed as the mean activity spanning 50 ms before to 50 ms after target presentation for the Gap task and Step task in eight directions. To estimate the motor preparation processes related to the shorter SRT in the Gap task, we used the methods of Dorris and colleagues (1997). The Gap-related activity was defined as the modulation in activity during the end of gap period (by subtracting the pretarget activity in the Step task from the pretarget activity in the Gap task). The percentage change in modulation was computed as a percentage ratio (the Gap-related activity divided by the pretarget activity in the Step task).

The activities related to Gap/Step task for a burst (Fig. 5, A and B) and a pause neuron (Fig. 5, C and D) are shown, contrasting the activities during the Step task (Fig. 5, A and C) and the Gap task (Fig. 5, B and D). Most burst neurons (21/26) exhibited the Gap-related activity above 0 spikes/s [3.3 ± 9.1 (SD) spikes/s; 116 ± 293% (SD) in percentage change; Fig. 5E], and most pause neurons (13/19) exhibited modulation below 0 spikes/s [−5.7 ± 9.4 (SD) spikes/s; −34% ± 36 (SD) in percentage change; Fig. 5F]. Gap-related activity, assessed both by the difference of firing rate and by percentage modulation, was larger in burst neurons than in pause neurons (P < 0.05, t-test). The small arrows in Fig. 5, B and D, indicate the time at which the activity exceeded a significant level (P < 0.05, t-test) compared with activity during fixation (250–350 ms before the ST onset).

Those burst neurons that showed a significant percentage modulation toward the end of the gap period (n = 10), gradually increased their firing rate up until saccade onset (Fig. 5B). The activities 50–100 ms after FP offset were significantly different from those during fixation (P < 0.05, t-test). In contrast, the pause neurons that showed a significant percentage modulation toward the end of the gap period (n = 8) gradually decreased their firing rate up until saccade onset (Fig. 5D). The activities after FP offset were significantly different from those during fixation (P < 0.05, t-test).

We analyzed how SRT varied with changes in activity during the end of the gap period on a trial-by-trial basis. For this analysis, we selected data from neurons for which the number of successful trials toward the best modulated direction was above 20 (35 of 45 saccade related neurons; 24 burst neurons and 11 pause neurons). The slope and intercept of the regression line and correlation coefficient between SRTs and firing rate were calculated. The correlation coefficients were small in both burst and pause neurons [the absolute value of r, estimator of a contribution of activity to SRT, 0.18 ± 0.11 (SD), n = 35], and a significant correlation was found for only a few neurons [2 of 35 (2 burst neurons), P < 0.05] between the two parameters. The absolute value of correlation coefficient was smaller than that for neurons in the intermediate layers of SC (about 0.5 for buildup neurons) (Dorris and Munoz 1998).

If the activity of burst and pause neurons in PPTN was related to the SRT, the slope of the regression line would be expected to be negative for burst neurons and positive for pause neurons. There was, however, no significant difference (P = 0.46, t-test) in the slopes of the regression lines for trial-by-trial analyses between burst neurons [−0.07 ± 0.21 (SD) ms/(spikes/s), n = 22] and pause neurons [−0.01 ± 0.18 (SD) ms/(spikes/s), n = 13]. This result indicates that the correlation between neuronal activity of burst/pause neurons in PPTN during the gap period and SRTs for visually guided saccade is smaller than that for SC neurons.

**Neuronal activity around onset of reward**

A group of PPTN neurons exhibited abrupt increases in activity around reward onset (juice drop) after appropriate saccade to the ST in the saccade task. These peri-reward activities were observed in 22 of the 70 neurons, and their mean firing during −200 to +300 ms from reward onset [22.5 ± 24.5 (SD) spikes/s] were significantly larger than control activity [11.3 ± 14.3 (SD) spikes/s, the mean firing rate 400–500 ms before the reward onset, P < 0.05, t-test]. In this analysis, we did not measure any EMG related to licking or the precise timing of the reward drop, we carefully monitored facial and licking movements during recording session with a video monitor. These changes in activities around reward onset were not associated with any distinct orofacial sensory event or movement (data not shown). We suspect that the activity around reward was auditory response induced by click noise produced by the opening of the valve. Unfortunately we did not control this condition in the present study.

The latency of the peri-reward responses was defined as the time at which the firing rate first exceeded the control activity from onset of the electronic feeder pulse [P = 0.05, Kolmogorov-Smirnov test (K-S test)] (Shidara and Kawano 1993).
Figure 6A shows the results from an experiment in which rewards were given twice in each trial, 200–350 ms after the saccade end. The neuron responded to repetitive reward pulses with the 152-ms latency for the first pulse. The response may not be a specific after-saccadic response, because the burst onset was synchronized with each reward onset (Fig. 6A). During saccade task, the responses after the reward onset were observed in 13 of the 22 neurons [response latencies exceeded 50 ms after reward onset; mean 210 ± 65 (SD) ms (n = 13)].

Interestingly, the other neurons’ (9/22) activity around reward preceded onset of reward [mean –102 ± 90 (SD) ms from reward onset]. In Fig. 6B rewards were also given at a relatively constant interval (200–300 ms) from the saccade end during task and the neuron exhibited an increase in activity preceding the reward (195 ms before reward onset or about 100 ms after saccade end).

To dissociate the peri-reward activity from the other task-related factors, we recorded the response to freely given reward in 7 of 73 neurons (free-reward task). In testing responses to free rewards, we stopped the control of visual display, and rewards were given at random intervals in the darkness, regardless of the eye movements. Five of seven neurons tested exhibited responses to free rewards, and the onset of the responses to free rewards were 100–220 ms after reward [mean of latencies; 142 ± 46 (SD) ms]. These neurons did not show any responses after spontaneous saccade in the dark. A typical response to free rewards is shown in Fig. 6C, data from the same neuron as in Fig. 6B. The neuron exhibited an increase in

FIG. 5. Gap-related activity of a burst neuron and a pause neuron. The activity of a burst neuron during a Step task (A) and a Gap task (B). The activity of a pause neuron during a Step task (C) and a Gap task (D). Rastergrams are aligned with the ST onset (0 ms). Triangles in the rastergrams indicate saccade onsets. The spike density function of each neuron is below the rastergram. Gray bars with arrows indicate the offset of FP. Small arrows in (B) and (D) indicate the time at which the activity exceeded significance (P < 0.01, t-test) compared with activity during fixation. Histograms of percentage change in Gap-related activity in burst neurons (E) and pause neurons (F).
activity before reward onset during the saccade task (Fig. 6B), but was activated after approximately 200 ms from reward onset if rewards were given independently of the saccade task (Fig. 6C). Thus the activity preceding reward onset during the saccade task may be either an after-saccadic response (visual or motor-related and so on) or a response associated with reward. However, the possibility that the pre-reward response was evoked only by after-saccadic events may be rejected because this neuron did not exhibit increased responses in after-saccadic period, when the monkey made saccade toward the FP (data not shown) and was not activated after spontaneous saccades in the dark in free-reward task. One possible account for the pre-reward activity during the saccade task is that it may reflect the behavioral context in which the saccade was performed or be a prediction of reward given after successful saccades.

Tonic activity in relation to success or error of the task

More than half of recorded PPTN neurons (75%, 52 of 70 analyzed neurons) exhibited tonic activity at the onset of a trial prior to FP onset. The average firing rate of the 52 neurons at the onset of a trial ranged from 0.2 to 76 spikes/s with a mean of 16 spikes/s. In a small population of seven neurons, we observed different levels of tonic activity depending on the
outcome of the upcoming trial. Figure 7A shows the tonic activity in successful trials, which started before FP onset and lasted until a visually guided saccade was made to the ST. Visually guided saccades to the target were executed approximately 1000 ms after FP onset. Figure 7B shows the activity of the same neuron in error trials. These seven neurons exhibited significantly different activities between successful trials and error trials ($P < 0.05$, $t$-test). For these seven neurons, the mean firing rate 0–100 ms before FP onset was $29.4 \pm 19.0$ (SD) spikes/s in successful trials and $21.1 \pm 8.4$ (SD) spikes/s in error trials. The activities of the seven neurons were larger in successful trials than in error trials for all the following intervals examined: 1) 0–100 ms before FP onset; 2) 100–200 ms after FP onset; and 3) 1000–1100 ms after FP onset ($n = 7$, $P < 0.05$, $t$-test). In successful trials, the tonic activities were sustained in the period that began before FP onset and lasted after the execution of the visually guided saccade. To demonstrate the differential distributions in firing rates between successful and error trials, the cumulative percentages of firing rate before FP onset for both successful and error trials are shown in Fig. 7C. Both the intercept and the saturation point of the curves were different between successful trials and error trials.

To evaluate the relationship between performance of task and firing rate, we calculated the success rates against the firing rate before FP onset. The success rates are plotted against firing rates for the neuron shown in Fig. 7A and B (Fig. 7D) and for all seven neurons (Fig. 7E). Each curve in Fig. 7E indicates that the success rates were increasing saturated functions of the firing rates. These results indicate that PPTN neurons vary their level of tonic activity in accordance with the outcome of the upcoming trial.

**Relationship between task performance and RTFP**

To investigate the level of motivation, we measured performance of the task during recording sessions. The monkeys maintained wakefulness throughout all recording sessions even if they succeeded or failed in the trials, because the error ratio was almost constant throughout the session, as shown in Fig. 8A (cumulative error and successful trials were plotted against the elapsed time in the session).

To evaluate the level of motivation or preparation for the FP appearance for each trial, we measured RTFP. RTFPs in the

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**Fig. 7.** Tonic activity related to success or error of the task. Rastergrams and spike densities are aligned with FP onset (0 ms) for 20 successful trials (A) and for 20 error trials (B) in 1 neuron. Open circles indicate successful fixation point (FP) offset; open triangles indicate saccade onset; and asterisks indicate reward onset. C: cumulative percentage of mean firing rate which is calculated between 0 and 500 ms before FP onset for successful trials (solid line) and for error trials (dashed line) of the neuron illustrated in (A) and (B). D: relationship between success rate and mean firing rate before FP onset for data shown in (C). Success rate was calculated every 2 spikes/s. Success and error of trial was defined as 1 and 0, respectively, and success rate was calculated by mean of the value. Vertical bars indicate SE. E: relationship between success rate and firing rate 0–100 ms before FP onset for 7 neurons. Success rates were calculated every 20 spikes/s.

**Fig. 8.** Analysis of performance of the task. A: cumulative successful and error trials in a recording session shown in Fig. 7. A and B, plotted against elapsed time of the session. B: relationship between the level of performance and reaction time to FP appearance (RTFP) for all data. Vertical bars indicate SD. C: cumulative percentage of RTFP for successful trials (solid line) and for error trials (dashed line) in a recording session shown in Fig. 7. A and B. D: relationship between success rate and RTFP for all data (7960 trials, from the 70 neurons). Success rates were calculated every 300 ms of RTFP that ranged from 0 to 2399 ms. Data between 2400 and 2999 ms were omitted, as were Type I errors. Vertical bars indicate SE.
successful trials were shorter than those in the error trials [successful trials; 181 ± 296 (SD) ms, error trials: 2642 ± 930 (SD) ms, for 70 neurons, P < 0.01, t-test]. Note that if the monkey was already fixating on the location where the FP would appear, RTFPs were set to 0 ms. Further, if the monkey did not look to the FP, RTFPs were set to 3000 ms.

We segregated error trials into three types depending on which portion of the task the monkey failed to perform. Type I errors occurred when the monkey did not look to the FP at all. Type II errors occurred when the monkey looked to the FP but failed to maintain fixating FP. Type III errors occurred when the monkey succeeded in fixating the FP but did not look to the ST. The level of motivation was assumed to be the lowest in type I errors and then in Type II errors, then in Type III errors. RTFPs were compared among the type of error in Fig. 8B and were found to be the shortest in the successful trials, and then progressively and significantly longer in Type III, Type II, and Type I errors, respectively (P < 0.05, t-test for all comparisons). Thus RTFP appears to be a good index for the motivation to perform the upcoming trial. The cumulative percentage for RTFP is shown for both successful and error trials in Fig. 8C and demonstrates a differential distribution of RTFP between successful and error trials. To evaluate the relationship between task performance and RTFP, the success rates were plotted against RTFP in Fig. 8D. We observed that the success rate was a decreasing function of RTFP (r = −0.81, RTFP ranged from 0 to 2399 ms). The success or error of the task performance (evaluated by 1 or 0, respectively) was also negatively correlated with RTFP (r = −0.68, P < 0.01, n = 7960 trials [RTFP <2400 ms]). For this analysis, we rejected trials whose RTFPs ranged from 2400 to 2999, because the number of trials was too small. Also, we rejected the trials whose RTFPs were 3000 ms, because these were always Type I errors. Thus we could predict the outcome of the trial via the RTFP.

Correlation between the tonic activity and the RTFP

To test whether the tonic discharges of the neuron that showed a different level of activity between successful and error trials could account for the RTFP, a trial-by-trial correlation between RTFP and mean firing rate (computed 0–100 ms before FP onset) of the tonic activity was analyzed in the successful trials (Fig. 9, A and B) for the seven neurons. A significant negative correlation was found between RTFP and mean firing rate before FP onset (correlation coefficient r = −0.21, n = 156, P < 0.05) for the data shown in Fig. 9B. For every seven neurons, the significant correlation (P < 0.05) was observed in the tonic activity with RTFP. In addition, to examine the temporal profile of the correlation between the tonic activity and RTFP, we computed them in 100-ms bins beginning from −550 ms before to 1550 ms after FP appearance. The significant correlations (P < 0.05) lasted until about 1500 ms after FP onset for these seven neurons (data not shown). Thus the variability of RTFP is related to the variability of tonic discharges, which lasted until the end of a trial.

Neuronal activity related to FP appearance and task performance

In another subpopulation of neurons, an increase in activity in response to FP onset was observed with a latency of approximately 100 ms. The FP-related activity was evaluated by comparing the mean firing rate 100–200 ms before FP onset with that 100–200 ms after FP onset [34 of the 70 neurons were significant, P < 0.05, t-test, 11.8 ± 17.4 (SD) spikes/s for before FP onset and 24.5 ± 24.9 (SD) spikes/s for after FP onset]. The latency of the FP-related activity was taken as the time at which the frequency exceeded the control frequency (0–100 ms before FP onset) at the significant level (K-S test, P = 0.05) (Shidara and Kawano 1993). The mean response latency to FP onset was 115 ± 13.1 (SD) ms (n = 34). The temporal pattern of FP-related activity was also investigated. The FP-related activities were classified into two groups. One group (n = 29) of neurons exhibited a tonic increase in activity in response to FP, whereas another minor group (n = 5) exhibited only a phasic increase.

In some of these neurons, either the tonic (8/29) or the phasic (2/5) response to FP onset was related to success or error of the task (P < 0.05, t-test). For example, Fig. 10, A and B, shows the response of a tonic neuron in successful trials (Fig. 10A) and error trials (Fig. 10B), respectively. Ten of the 34 neurons showed differential responses 100–200 ms after FP onset between successful and error trials [successful trials: 35.0 ± 24.8 (SD) spikes/s; error trials: 21.5 ± 18.5 (SD) spikes/s, P < 0.01, t-test]. Four of these 10 neurons also exhibited the tonic activity related to success or error, which started before the FP onset as shown in Fig. 7. As shown below, this difference between successful and error trials cannot be explained simply by the position of the eye at FP onset. Figure 10, A and B, shows discharges to FP appearance in successful and error trials, respectively, ordered by RTFPs (recall that RTFPs of 0 ms indicate that the monkey was already fixating the location where the FP would appear). As shown in the lower raster traces in Fig. 10A, if the RTFP was longer, the response following FP onset was weaker or the same as the tonic activity shown above. Further, the rastergram

![Image](http://jn.physiology.org/)

FIG. 9. Trial-by-trial correlation between RTFP and mean firing rate of tonic discharge. A: rastergram and spike density illustrating both spike and RTFP (the time eyes reached the FP indicated by open squares). This neuron is the same as shown in Fig. 7A (for only successful trials). B: RTFP plotted against mean firing rate before FP onset for each trial. The regression line is illustrated on the plot.
is more finely locked to FP onset than the time when the eyes reached the FP, and the spike density function shows an abrupt rise after FP onset. The result suggests that the response to the FP is visually evoked.

An alternative explanation for the difference in FP-related activity between successful and error trials was suggested that it is due to the retinal position of the FP when it appeared. To examine this possibility, the following analyses were performed. In Fig. 10, C and D, the plotted positions indicate the retinal position of the FP when it appeared, and the size of the plotted squares indicates the mean firing rate 100–200 ms after the FP appeared. In the horizontal axis, positive numbers indicate ipsilateral and negative numbers indicate contralateral. In the vertical axis, positive numbers indicate upward and negative numbers indicate downward, respectively. E: the FP-related responses were classified by dividing the plotted data in (C) and (D) into four quadrants by horizontal and vertical axes. Mean of firing rate for successful and error trial for each quadrant is plotted by closed circle and open triangle, respectively. F: relationship between eccentricity of retinal position of FP and mean firing rate for successful and error trial. Vertical bars in (E) and (F) indicate SEM.

FIG. 10. FP-related activity. Responses to FP appearance in successful trials (A) and in error trials (B) are illustrated. Rastergrams are aligned with the FP onset (0 ms). The trials are sorted according to RTFP (indicated by open squares). The spike density of each neuron is below the rastergram. Spatial property of FP-related activity, which was affected by success or error of the trial (C–F). FP-related activity for successful trials (C) and error trials (D). The location of each square indicates the retinal position when the FP onset and the size of each square indicates the average firing rate 100–200 ms after the FP appeared. In the horizontal axis, positive numbers indicate ipsilateral and negative numbers indicate contralateral. In the vertical axis, positive numbers indicate upward and negative numbers indicate downward, respectively. E: the FP-related responses were classified by dividing the plotted data in (C) and (D) into four quadrants by horizontal and vertical axes. Mean of firing rate for successful and error trial for each quadrant is plotted by closed circle and open triangle, respectively. F: relationship between eccentricity of retinal position of FP and mean firing rate for successful and error trial. Vertical bars in (E) and (F) indicate SEM.

In addition, we analyzed the firing rate in successful or error trials as a function of eccentricity of the retinal position of the FP (Fig. 10F). The firing data were assigned into four bins (0–5 deg, 5–10 deg, 10–20 deg, and >20 deg) according to the retinal position from fovea. In Fig. 10F, although a center-peaked receptive field property was observed in both successful and error trials, the firing rates were significantly larger in successful trials than in error trials for each distance bin (P < 0.05, t-test). All 10 neurons showed significantly larger responses in successful than in error trials for small eccentricities (0–5 deg, P < 0.05, t-test), and at least one more eccentricity bin (P < 0.05, t-test). Thus the responses to FP onset were larger in successful trials than in error trials regardless of FP location. We also confirmed that RTFPs were less dependent on the retinal position of the FP when it appeared (data not shown). Thus for this subset of neurons, the activity in re-
Response to FP varies the level of firing with performance of the task.

**Distribution of location, spike width, and response to the events for neurons**

To investigate the distribution of neurons within the PPTN, the location of recorded neurons was examined in relation to its activity pattern (Fig. 11). Neurons were classified into four task-related groups, as follows: 1) the performance-related group, which exhibited differential activity between successful and error trials ($n = 13$), with tonic discharge ($n = 7$) or response only to the FP appearance ($n = 6$); 2) saccade pause ($n = 19$); 3) saccade burst ($n = 26$); and 4) reward-related group (with response around reward onset, $n = 22$). Neurons that exhibited performance-related, saccade-burst, saccade-pause, and reward-related activity were distributed almost evenly throughout PPTN. There was no tendency for a differential distribution of different types of neurons (Fig. 11, B and C). Because previous studies in cats (Dormont et al. 1998) and rats (Koyama et al. 1998) have suggested that the spike width and firing rate of PPTN neurons are correlated with the type of transmitter (glutamatergic neurons, carry brief spikes, and high-frequency; cholinergic neurons, carry broad spikes, and low frequency), we measured the width of the action potentials in 30 of 70 neurons and compared the spike width and 1) neuron distribution; 2) spontaneous firing rate during inter-trial intervals; and 3) the four activity patterns during the task. There was no apparent segregation between the spike width and either distribution of neuron or spontaneous firing rate and firing rate and response related to the events. The width of the action potential was measured as the duration of the negative phase of the spike waveform.
between the firing rate and activity pattern during the tasks (data not shown). However, a slight segregation in spike width was found for the performance-related group neurons versus for the reward-related group neurons (Fig. 12, A–C). Action potentials for the performance-related group neurons and for the reward-related group neurons are shown in Fig. 12, A and B, respectively. Hump-like slow positive potentials (arrows in Fig. 12, A and B), which were suggested to be generated by cholinergic neurons (Koyama et al. 1998), were more frequently observed in performance-related group neurons than reward-related group neurons. Spike widths were compared (Fig. 12C) between performance-related group [0.42 ± 0.17 (SD) ms, n = 9] and reward-related group [0.31 ± 0.10 (SD) ms, n = 10]; however, the difference was not significant (P = 0.09, t-test). In addition, in each group of the response pattern, the distribution of neurons was not segregated by their width of action potential.

The activity of one neuron that exhibited both FP-related response affected by task performance and additionally exhibited saccade-related response to ST onset is shown in Fig. 13. The neuron showed a differential activity between successful and error trials, which was time-locked to FP onset (Fig. 13, A and B, for successful and error trials, respectively) and response to ST (Fig. 13C). The responses to FP against retinal position of the FP when it appeared are shown in Fig. 13D. The responses to ST against retinal position of the ST when it appeared are shown in Fig. 13E. Response to ST was directionally selective (directed to left-up); however, FP-related response was less directionally selective and had a wider response field to visual stimulus than the response to ST. Thus the response aligned to the onset of a stimulus was altered by its behavioral context, in which the target was presented as FP or ST.

Figure 14 shows the classification of the recorded 70 neurons into the four groups. The majority (56/70) of neurons exhibited some response in visually guided saccade task. Interestingly, 22 of these 56 neurons (39%) exhibited response patterns that were characteristic of two or more groups. Thus a population of PPTN neurons exhibited activity patterns in various combinations related to task performance, reward and the execution of visually guided saccades.

DISCUSSION

Neuronal activity of PPTN related to saccade

This study, for the first time, showed that PPTN neurons may be involved in regulation of saccadic eye movements. To clarify the contribution of neuronal activity of PPTN to saccade execution, we will discuss the saccade-related burst and pause, and their directional property.

The preferred directions of saccade-related activity in PPTN was not biased ipsiversively or contraversively nor aligned with horizontal or vertical axes (Fig. 3, D and E). The source of this saccade-related activity has several possibilities. Crossed descending projections from SC terminate in the pedunculopontine/parabrachial area in rats (Redgrave et al. 1993).
 Recent studies have shown that a gradual increase in “buildup” activity during the gap period, which can be observed in a group of neurons in the intermediate layers of SC, is highly correlated with the initiation of saccades and SRT (Dorris et al. 1997; Dorris and Munoz 1998; Sparks et al. 2000). Moreover, it has been shown that the activity of fixation neurons in the rostral pole of SC, which decreases during the gap period, suppresses initiation of saccades (Dorris and Munoz 1995). Recent studies suggest that a candidate for the origin of the activity in buildup and fixation neurons during the gap period is FEF (Dias and Bruce 1994; Everling and Munoz 2000). Because PPTN neurons massively innervate to SC in several mammalian species (Beninato and Spencer 1986; Graybiel 1978; Hall et al. 1989; Henderson and Sherriff 1991; Jeon et al. 1993; Ma et al. 1991; Schnurr et al. 1992), PPTN may also be a source of buildup activity in SC. A recent study in our laboratory demonstrated that in slice preparations of the rat SC, activation of nicotinic acetylcholine receptors on neurons in the intermediate layer of SC induced inward currents and depolarization, which may gate the signal transmission in the direct visuomotor pathway from the superficial to the intermediate layer of SC (Ilsen et al. 1998). Another recent result suggests that the cholinergic system may facilitate initiation of saccades through SC, indicating that neural mechanism observed in SC slice of rats also applies to behaving monkeys (Aizawa et al. 1999). Thus PPTN may contribute to SC in giving rise to buildup activity and controlling SRT with cholinergic input to the intermediate layer of SC through the activation of nicotinic acetylcholine receptors. During the gap period, PPTN burst neurons increased their firing rate, whereas pause neurons decreased their firing rate (Fig. 5). Although the contrast in Gap-related activity between burst and pause neurons became apparent in averaged data, an obvious correlation between SRTs and Gap-related activity was not observed on a trial-by-trial basis. These results suggest that the contribution of a single PPTN neuron to SRT is weaker than that of buildup neurons in SC, where the neural activity is significantly correlated to SRT (Dorris et al. 1997; Dorris and Munoz 1998).

Although the ongoing influence of PPTN activity on SRT of visually guided saccades was weak, the present results suggest that PPTN may integrate several saccade-related signals coming from SC, basal ganglia, and cerebral cortex and send them back to these areas. Therefore PPTN is ideally situated to work cooperatively for initiation and execution of saccade.

**Neuronal activity of PPTN around reward onset**

Recent studies have emphasized that the dopaminergic neurons of SNCs process reward-related information necessary for reinforcement learning (for review see Schultz 1998). PPTN is thought to be one of the most important input sources to SNCs (Futami et al. 1995; Takakusaki et al. 1996). Accordingly, we observed an increase in the activity of PPTN neurons around reward onset (Fig. 6).

PPTN receives limbic inputs from the hypothalamus, the ventral tegmental area (Semb and Fibiger 1992; Steininger et al. 1992), and the limbic cortex in monkeys (Chiba et al. 2001), all of which may be sources of the activity around reward observed in the present study. The glutamatergic and cholinergic inputs from PPTN make synaptic connections with dopaminergic neurons in SNc (Futami et al. 1995; Takakusaki et al. 1996). Electrical stimulation of PPTN induces a time-locked burst in dopaminergic neurons in the rat SNc (Lokwan et al. 1999). The mean latency of responses to the freely delivered reward was slightly shorter in the PPTN (100–220 ms; mean, 146 ms) than in SNc (151 ms; Mirenowicz and Schultz 1994). Thus the reward-related activity in dopaminergic neurons of SNc may come from PPTN. In a recent study of cats, reinforcement-related single-unit activity in PPTN has been demonstrated, which was preferentially observed on broadly spiking neurons presumed to be cholinergic (Dormont et al. 1998). These results suggest that cholinergic reward-related signals from PPTN may be sent to dopaminergic neurons of SNc (Takakusaki et al. 1996).

In monkeys, PPTN contains both cholinergic and other types of neurons, but it is not known which type of neuron contributes to the specific processing. In the present study, we observed no preferential distribution in spike-width and location of neurons and little correlation of spike-width with several firing properties (the performance of the trial, saccade execution, and reward) and with average firing rate. We speculate the possibility that, in monkeys, there is little correlation between response pattern and the neurotransmitter type of PPTN. However, it is difficult to measure spike-width precisely using metal extracellular recording electrodes.

**Neuronal activity of PPTN related to arousal and motivation**

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain and is thought to control activity that depends on selective attention (Perry et al. 1999). It may be possible that the cholinergic PPTN, noradrenergic LC, and serotonergic DRN in the brain stem act together in the control of arousal and global attention, as previously hypothesized (Garcia-Rill 1991).

Motor performance is dramatically reduced by PPTN lesion. Bilateral lesions of PPTN in rats resulted in significant increases in reaction and movement times (Scarmati and Florio 1997), and reversible inactivation of PPTN by lidocaine or muscimol dramatically affects inter-trial intervals and motor execution of a lever-release task in conditioned cats (Conde et al. 1998). It is possible that PPTN is involved in processes related to selecting the appropriate motor program or maintaining the attentional state to perform a task. We observed that a subset of PPTN neurons exhibited tonic activity or activity...
after FP appearance related to the outcome of the trial (Figs. 7 and 10). These activities may contribute to the maintenance of attentional or motivational state required to perform the task.

Many studies suggest that PPTN may induce a global attentive state in response to a novel stimulus (Steriade 1996a,b). Recently, context-dependent activity in PPTN neurons has been demonstrated (Dormont et al. 1998) in operantly conditioned cats performing a lever-release movement. In that study, the neurons were activated shortly after the cue stimulus was presented. We observed similar activity in our visually guided saccade task. Early in a trial, phasic activities immediately following the appearance of the FP were observed. In some neurons, this activity was related to success or error outcome of the trial (Figs. 10 and 13) and was less dependent on the location of the visual stimulus on the retina, compared with the response to ST onset (Fig. 13). Thus the response property (wider visual receptive field to FP or the relationship to performance of task) of PPTN neurons was dynamically modified by the behavioral context and may be commensurate with global attentional or motivational state to perform the task or the level of wakefulness in behaving animals.

Neuronal activity in a brain stem cholinergic nucleus (LDTN) relates to tonic activation processes in thalamocortical systems (Steriade et al. 1990). Projection from PPTN to LGN is known as the reticular activation system, and the projection is cholinergic (McDonald et al. 1993). Electrical stimulation of the brain stem parabrachial region (including PPTN) can also control visual responses of LGN in cats (Uhlrich et al. 1995). Both the tonic activity and the response to FP of PPTN related to behavioral performance (Figs. 7 and 10) were observed. In Fig. 10, we showed that the activity after FP onset was related to the outcome of the trial. The neurons showed a visual response (finitely time-locked to the onset of FP rather than to the onset of fixation), regardless of eye position at FP onset, and also displayed a response depending on the performance of the trial. These activities may enhance the responsiveness of the thalamus and control both sensory and motor processing and may be related to attentional mechanisms required to improve both sensory processing and behavioral performance.

Lesion studies in rats have suggested a relationship between motivation and PPTN (Bechara and van der Kooy 1989; Bechara et al. 1995; Stefurak and van der Kooy 1994). We investigated a correlation between RTFP and success rate to evaluate the level of motivation for the upcoming trial task (or efficacy of the task). We found that the RTFP was a decreasing function of success rate (Fig. 8D), suggesting that RTFP is a parameter that may indicate the level of motivation. We have demonstrated the correlation of the tonic activity and the activity in response to the FP with RTFP, indicating that the relationship between activity of PPTN and motivation.

**Relationship between reinforcement learning and PPTN**

The effects of lesions, receptor blocking, electrical self-stimulation, and drug abuse suggest that midbrain dopaminergic systems (SNc and ventral tegmental area) are involved in processing reward information and learning (for review see Schultz 1998). Most dopaminergic neurons exhibit phasic activity after primary liquid and food rewards as well as conditioned, reward-predicting visual and auditory stimuli. Recently, Brown and colleagues have presented a sophisticated computational model of reinforcement learning in the basal ganglia which includes SNc and PPTN. They successfully simulated the learning process and the activity of PPTN and SNc neurons (Brown et al. 1999; see following text). Dopaminergic neurons were activated by rewards during the early trials of learning sessions, when errors are frequent and rewards unpredictable, but activation by rewards is progressively reduced as performance consolidated and rewards became more predictable. The primary reward signal to SNc may derive from PPTN and suppression of the reward signal after learning may be caused by GABAergic input from striosomes (Gerfen 1992). Thus dopaminergic neurons code errors in the prediction of rewards (Hollerman and Schultz 1998).

In PPTN, neuronal activity around reward was observed even during our fully conditioned task and this activity sometimes precede reward onset. The activity observed after reward onset may be a primary reward signal, whereas pre-reward activity in PPTN may be an excitatory component of the reward prediction signal sent to SNc. We propose that the reward-predictive error signal coded by SNc is composed of an excitatory primary reward signal (derived from PPTN and other limbic systems), and excitatory (from PPTN) and inhibitory (from striosomes) reward prediction signals.

Takikawa and colleagues (1999) showed that during a saccade task, the dopaminergic neurons in SNc are activated phasically by the presence of an FP, only in the first trials of behavioral sessions when the reward is systematically controlled. This response may be related to switching of the task or a prediction of the reward. The FP-related activity of PPTN in our study (Fig. 10) may be a source of the phasic response in SNc and may be inhibited by the basal ganglia (striosomes and so on) in the following trials.

**Signal processing in PPTN**

A population of PPTN neurons exhibited both performance-related activity and activity around reward onset, suggesting that these neurons may create new motivational states by integrating signals related to the current motivational state and the delivery of the reward.

Because PPTN neurons have axon collaterals to both LGN and the intermediate layer of SC (Billet et al. 1999), it is possible that PPTN may contribute to improving visual or motor processing via the thalamus, while sending saccade-related signals to SC.

Neurons responding to both saccades and rewards were also observed (shown in Fig. 14). PPTN may also coordinate the relay of reward information to SNc with information about saccadic execution. In regards to movement control, PPTN may integrate saccade-related signals derived from SC, FEF, and SNr and work cooperatively with SC through their reciprocal connection. Winn and colleagues (Inglis and Winn 1995; Winn et al. 1997) have presented a computational model in which PPTN is one critical site through which limbic information concerned with motivation, reinforcement, and the construction of novel associations gains access to a stream of motor outflow coming from the caudate-putamen and directed toward pontomedullary systems without reference back to the cerebral cortex. These hypotheses view PPTN as an integral
component of the limbic-motor interface and emphasize the importance of pontine systems in cognitive processing.

We hypothesized that PPTN integrates signals for saccade control, reinforcement, and task performance. We observed multimodal responses in relation to execution of the task. Signals related to motivation for behaviors (which may be derived from a conjugating brain stem network, including LC, DRN, and PPTN), saccade control (derived from SC, SNr, and FEF), and reward (derived from limbic systems) might be integrated on each PPTN neuron. PPTN could serve as a critical interface between the variety of the signals and may help create attentional/motivational states and reinforce behaviors, according to the history of attentional/motivational states, action, and reward.

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REFERENCES


ACTIVITY OF PPTN DURING VISUALLY GUIDED SACCADES


KOYAMA Y AND KAYAMA Y. Mutual interactions among cholinergic, noradrenergic and serotonergic neurons studied by ionophoresis of these transmitters in rat brainstem nuclei. Neuroscience 55: 1117–1126, 1993.


