Neurons in the Thalamic CM-Pf Complex Supply Striatal Neurons With Information About Behaviorally Significant Sensory Events

NAOYUKI MATSUMOTO,[1,3] TAKAFUMI MINAMIMOTO,[1] ANN M. GRAYBIEL,[2] AND MINORU KIMURA[1,3]
[1]*Faculty of Health and Sport Sciences, Osaka University, Osaka 560-0043, Japan;* [2]*Department of Brain and Cognitive Sciences, MIT, Cambridge, Massachusetts 02139; and* [3]*Department of Physiology, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan*

Received 1 May 2000; accepted in final form 2 November 2000

Matsumoto, Naoyuki, Takafumi Minamimoto, Ann M. Graybiel, and Minoru Kimura. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. *J Neurophysiol* 85: 960–976, 2001. The projection from the thalamic centre médian–parafascicular (CM-Pf) complex to the caudate nucleus and putamen forms a massive striatal input system in primates. We examined the activity of 118 neurons in the CM and 62 neurons in the Pf nuclei of the thalamus and 310 tonically active neurons (TANs) in the striatum in awake behaving macaque monkeys and analyzed the effects of pharmacologic inactivation of the CM-Pf on the sensory responsiveness of the striatal TANs. A large proportion of CM and Pf neurons responded to visual (53%) and/or auditory beep (61%) or click (91%) stimuli presented in behavioral tasks, and many responded to unexpected auditory, visual, or somatosensory stimuli presented outside the task context. The neurons fell into two classes: those having short-latency facilitatory responses (SLF neurons, predominantly in the Pf) and those having long-latency facilitatory responses (LLF neurons, predominantly in the CM). Responses of both types of neuron appeared regardless of whether or not the sensory stimuli were associated with reward. These response characteristics of CM-Pf neurons sharply contrasted with those of TANs in the striatum, which under the same conditions responded preferentially to stimuli associated with reward. Many CM-Pf neurons responded to alerting stimuli such as unexpected handclaps and noises only for the first few times that they occurred; after that, the identical stimuli gradually became ineffective in evoking responses. Habituation of sensory responses was particularly common for the LLF neurons. Inactivation of neuronal activity in the CM and Pf by local infusion of the $GABA_A$ receptor agonist, muscimol, almost completely abolished the pause and rebound facilitatory responses of TANs in the striatum. Such injections also diminished behavioral responses to stimuli associated with reward. We suggest that neurons in the CM and Pf supply striatal neurons with information about behaviorally significant sensory events that can activate conditional responses of striatal neurons in combination with dopamine-mediated nigrostriatal inputs having motivational value.

INTRODUCTION

The posterior intralaminar nuclei of the thalamus, the centre médian (CM) and parafascicular nucleus (Pf), are small in rodents but are among the largest thalamic nuclei in primates, including humans. These nuclei (together called the CM-Pf complex) are classified as part of the ascending reticulo-thalamo-cortical activating system based on the work of Moruzzi and Magoun (1949), Jasper (1960), and subsequent investigators (see Hu et al. 1989; Mennemeier et al. 1997; Paré et al. 1988; Steriade et al. 1994, 1997). The CM-Pf complex also receives massive inputs from the motor and premotor cortex and from the basal ganglia (Fenelon et al. 1991; François et al. 1991; Macchi and Bentivoglio 1986; Nakano et al. 1990; Sadikot et al. 1992a; Smith and Parent 1986; Steriade et al. 1997). These nuclei do project to the neocortex, but the main outputs of the CM and Pf lead to the striatum (Jones 1997). The CM-Pf complex thus at once is associated with state-setting modulatory systems and with basal ganglia action-gating circuits.

Positron emission tomography (PET) evidence supports a general activating function for the CM-Pf complex, in that the CM is specifically activated when subjects shift from a relaxed waking state to an alert state during performance of an attention-demanding reaction time task (Kinomura et al. 1996). Nothing is yet known, however, about the functional activity of CM and Pf neurons in alert behaving monkeys, and it is not yet known what behaviorally significant effects CM-Pf neurons have on their main cellular targets, neurons in the striatum. In the experiments reported here, we approached these issues by recording the activity of single neurons in the CM and the Pf of macaque monkeys as they learned and performed sensorimotor tasks. We then tested for the effects of blocking CM-Pf activity on the response properties of striatal neurons recorded and on accompanying behavioral responses made in the same tasks. We focused the striatal recordings on the striatal neurons that have irregular tonic activity (the tonically active neurons called TANs). These are thought to be the cholinergic interneurons of the striatum (Aosaki et al. 1995; Kawaguchi 1992; Kimura et al. 1990; Wilson et al. 1990), which have been shown in anatomical experiments to receive a strong input from the CM-Pf complex (Lapper and Bolam 1992; Sidibé and Smith 1999). We have earlier shown that TANs have the property of acquiring motivation-dependent responses to sensory stimuli as a result of reward-based sensorimotor conditioning (Aosaki et al. 1994a,b, 1995; Graybiel et al. 1994). By testing for the effects of CM-Pf inactivation on the acquired responses of striatal TANs, we tried to identify the contribution

Address for reprint requests: M. Kimura, Dept. of Physiology, Kyoto Prefectural University of Medicine, Kawaramachi, Hirokoji Kyoto 602-8566, Japan (E-mail: mkimura@basic.kpu-m.ac.jp).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

of intralaminar thalamic inputs to the motivation-dependent responsiveness of a major class of striatal neurons.

Our findings suggest that a large majority of CM and Pf neurons respond with precisely timed modulations of their discharge rates to one or more modalities of sensory stimuli having behavioral significance. We further demonstrate that the activity of CM-Pf neurons is required for expression of the sensory responses of TANs acquired through sensorimotor learning. We suggest that information about behaviorally significant sensory events provided by the CM-Pf complex could function in cooperation with dopamine-mediated signals transmitting motivational value to provide a basis for the action-selection functions of cortico-basal ganglia circuits.

METHODS

Behavioral paradigms

Three macaque monkeys (*Macaca fuscata*: *monkey TM,* male, 6.5 kg; *monkey AK,* female, 6.7 kg; and *monkey NA,* female, 5.6 kg) were used in this study. The experiments were carried out in compliance with the guidelines for the care and use of experimental animals of the Physiological Society of Japan. Monkeys were trained to sit in a primate chair in a soundproof, electrically shielded room. Ambient illumination was controlled and was dim (*monkeys AK* and *NA;* 1.2 cd/m^2) or dark (*monkey TM;* 0.15 cd/m^2). A small panel (54 × 23 cm) was placed 50 cm in front of *monkeys AK* and *NA,* and 22 cm in front of *monkey TM* (Fig. 1*A*). A light-emitting diode (LED) was attached at the center of the panel. The LED could be illuminated (300 cd/m^2) under computer control. Before conditioning, click noises made by a solenoid valve, beep sounds (1 kHz, 100 ms duration), flashes of the LED (100 ms duration), and drops of reward water on a spoon in front of the monkey's mouth were presented independently in random order at a fixed time interval (7 s; Fig. 1*B*). Two tasks were used for behavioral conditioning. One was the stimulus with reward (WR) task, in which the solenoid clicks were followed by reward water delivered 200 ms later. The second task was the stimulus without reward (WOR) task, in which clicks, beeps, and LED flashes were presented without reward (Fig. 1*B*). The three types of sensory stimuli were presented separately in blocks of 20–30 trials, except in special tests in *monkeys TM* and *AK.* In each block of trials, the stimuli occurred at variable intertrial intervals ranging from 5 to 12 s. The stimuli appeared in random order in *monkey NA.* In *monkey NA,* to test the somatosensory responses of CM-Pf neurons, tactile stimulation was applied manually to the neck, shoulder, back, or hands by means of a stimulus probe.

Surgery

All surgeries were carried out under sterile conditions with the monkeys under deep pentobarbital sodium anesthesia. Anesthesia was induced with ketamine hydrochloride (6 mg/kg im) and pentobarbital sodium (Nembutal, 27.5 mg/kg ip), and supplemental Nembutal (10 mg/kg/2 h, im) was given as needed. Before behavioral training, four head restraint bolts and two stainless steel recording chambers were implanted with stereotaxic guidance on the skull of each monkey. One chamber, for recording neuronal activity in the striatum, was placed

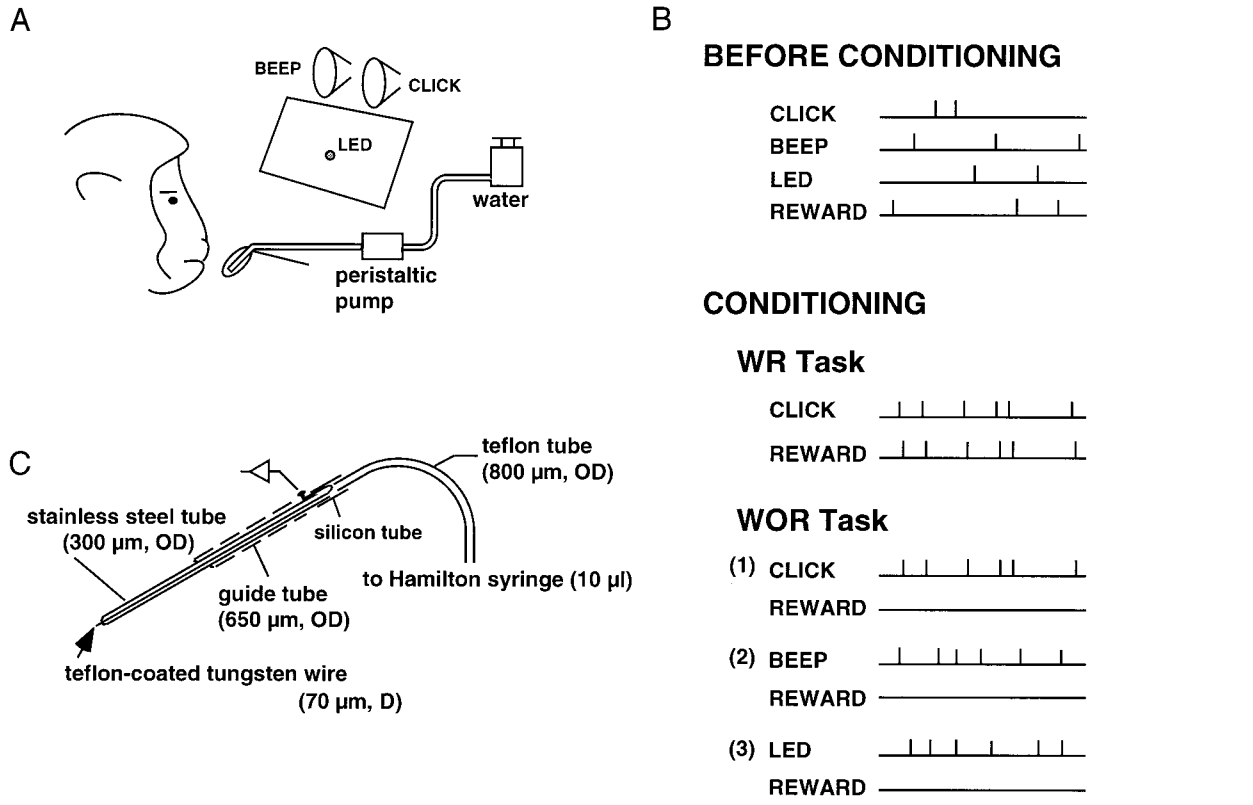

FIG. 1. Experimental paradigm. *A*: monkeys sat in a primate chair facing a panel on which a green light-emitting diode (LED, 2 cm diam) was attached. Beeps and clicks were presented by speakers placed in front of the monkey. For reward, a drop of water was delivered by means of a peristaltic pump onto a spoon in front of animal's mouth. *B*: schematic time charts of events in the behavioral tasks before conditioning and during and after conditioning. Rewards were associated with clicks in the stimulus-with-reward (WR) task, but no reward was associated with beeps or LED flashes in the stimulus-without-reward (WOR) task. *C*: schematic drawing of recording-injection device used for the muscimol injections. OD, outer diameter; D, diameter.

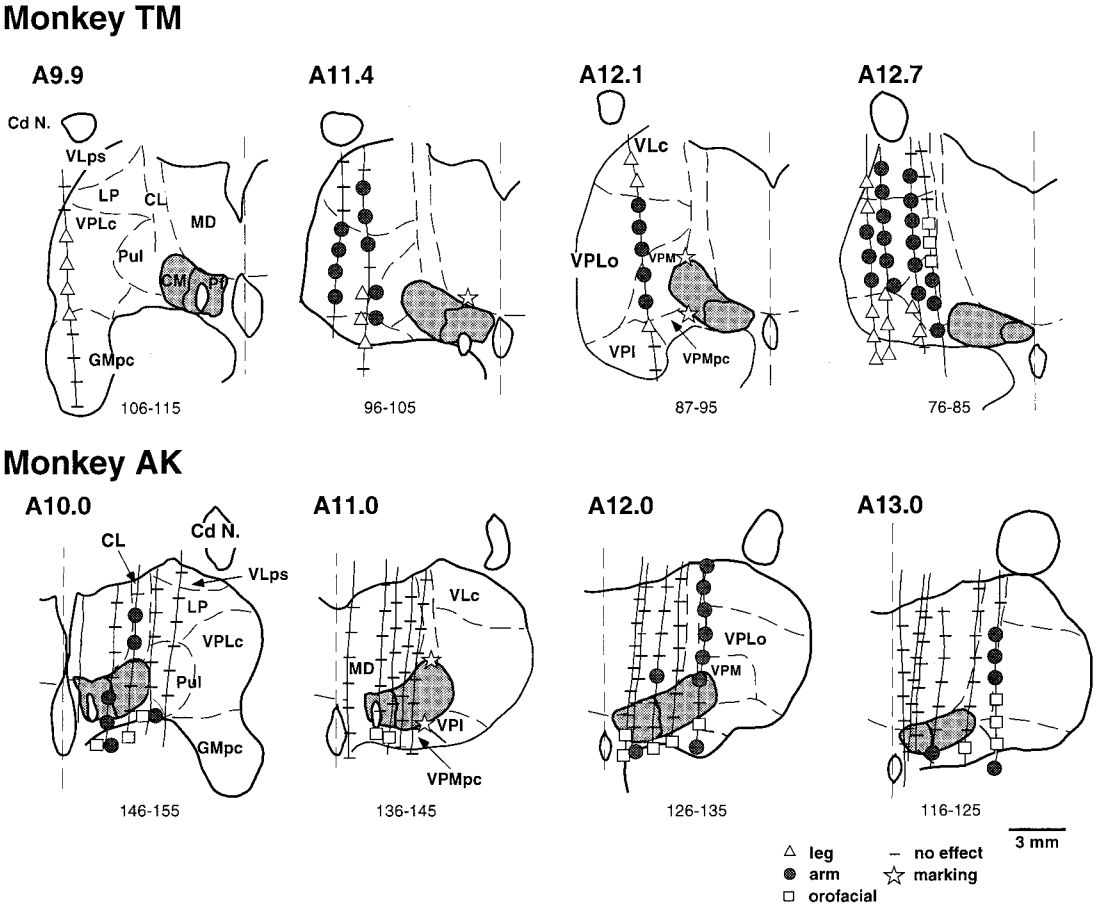

FIG. 2. Histological reconstructions of the electrode tracks in the thalamus of 2 monkeys (*TM* and *AK*) in which the effects of thalamic microstimulation were examined. Sites at which leg, arm, and orofacial movements were evoked are marked by △, ●, and □, respectively. The locations at which current pulse trains at 100 μA evoked no responses are marked by a dash. Stars indicate locations where the electrolytic lesion marks were made. The coronal sections shown are roughly 1 mm apart. Approximate Horsley-Clarke coordinates are indicated above, and section numbers below. Cd N., caudate nucleus; MD, mediodorsal nucleus; VLc, ventrolateral nucleus pars caudalis; VLps, ventrolateral nucleus pars postrema; VPI, ventral posterior inferior nucleus; VPLo, ventral posterolateral nucleus pars oralis; VPLc, ventral posterolateral nucleus pars caudalis; VPM, ventral posteromedial nucleus; VPMpc, ventral posteromedial nucleus pars parvocellularis; GMpc, medial geniculate nucleus pars parvocellularis; CL, centrolateral nucleus; CM, centromedian nucleus; Pf, parafascicular nucleus; LP, lateral posterior nucleus; Pul, pulvinar.

laterally at a 45° angle in *monkeys TM* and *AK* to minimize damage to internal capsule fibers by electrode penetrations. The second chamber, for recording neuron activity in the thalamus, was mounted horizontally for *monkeys TM* and *AK* but was tilted laterally by 5° for *monkey NA*. The centers of the thalamic recording chambers were adjusted according to Horsley-Clark stereotaxic coordinates: lateral = 4 mm and anterior = 13 mm for *monkey TM*, lateral = 3 mm and anterior = 10 mm for *monkey AK*, and lateral = 2 mm and anterior = 10 mm in *monkey NA*.

Recordings

Single neuron activity was recorded extracellularly with glass-insulated elgiloy microelectrodes or epoxy-coated tungsten microelectrodes (Frederic Hair and Co., 26-10-2L or 25-10-2L) with an exposed tip of 15–60 μm and with an impedance of 0.5–1.5 MΩ. The electrodes were inserted through the implanted recording chamber and advanced by means of an oil-drive micromanipulator (Narishige, MO-95). Neuronal activity recorded by the microelectrodes was amplified and displayed on an oscilloscope with conventional electrophysiological techniques. Band-pass filters (50 Hz to 3 kHz band-pass with a 6-dB/octave rolloff) were used. Action potentials of single neurons were isolated by the use of either a time-amplitude window discriminator or a spike sorter with a template matching algorithm (Alpha Omega, MSD4), and the onset times of the action potentials were recorded on a laboratory computer (NEC9801RA, 9821Bf) together with onset and offset times of stimulus and behavioral events occurring during behavioral tasks. The licking movements that occurred during consumption of water reward were monitored by a pressure sensor on the spoon on which a drop of water was delivered. These analog signals were also fed to the computer through the A-D converter interface at a sampling rate of 100 Hz. The responses of neurons were defined in perievent time histograms of neuronal impulse discharges as increases or decreases of discharge rate after a behavioral event relative to discharges prior to the event if the changes achieved a significance level of $P < 0.05$ by a two-tailed Wilcoxon test (Kimura 1986).

Microstimulation

The effects of microstimulation were examined during microelectrode penetrations through the thalamus made to map the location of the CM-Pf complex. Electrical current pulses (40 pulses

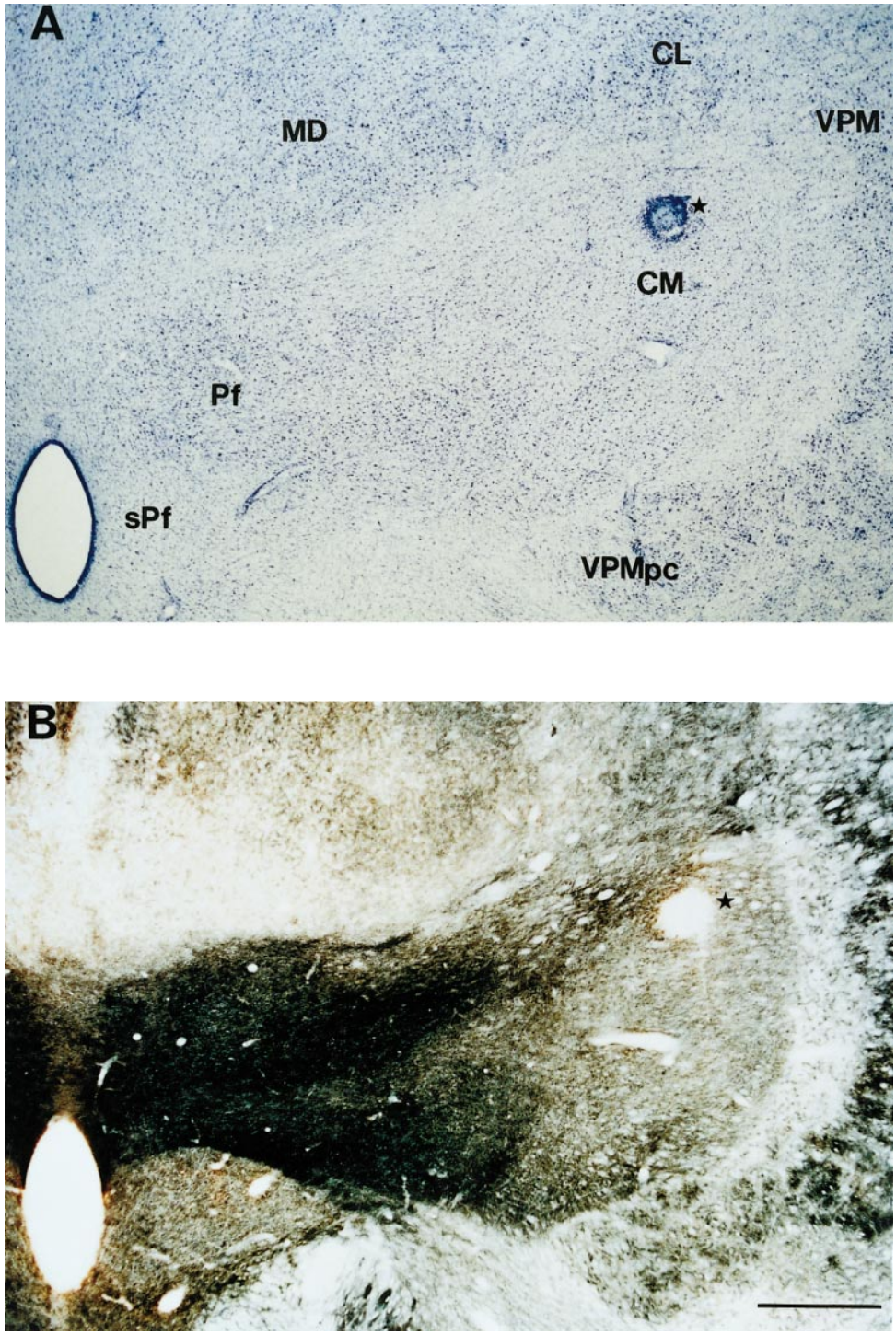

FIG. 3. Photomicrographs of coronal sections through the right thalamus of *monkey NA*. *A*: Nissl-staining. *B*: staining with the acetylthiocholine method to demonstrate acetylcholinesterase (AChE) activity. Stars indicate electrolytic lesion made in the lateral part of CM. Scale bar: 1 mm. s-Pf, subparafascicular nucleus; other abbreviations, as in Fig. 2.

with 0.2 ms duration at 3-ms intervals) were passed through the recording microelectrode at stimulus intensities of <100 μA. The microelectrode served as the cathode. Stimulus-induced movements of the body were carefully observed by two experimenters as the current pulse trains were delivered at a repetition rate of 0.5 Hz.

Injection of muscimol into the CM-Pf complex in the thalamus

To inhibit neuronal activity in the CM-Pf complex, we injected the $GABA_A$ receptor agonist, muscimol, locally into the CM-Pf complex of *monkey TM*. We used a stainless steel injection cannula (300 μm, OD) through which a teflon-coated tungsten wire (70-μm coated diameter, A-M Systems) had been threaded so that its cut tip protruded 0.7–1.0 mm beyond the tip of the cannula (Fig. 1*C*). The cannula was connected by teflon tubing (800 μm OD) to a 10-μl Hamilton microsyringe. A guide tube (650 μm, OD) was fixed to the microdrive, and the recording-injection device was placed inside the guide tube. Once the guide tube had been lowered through the dura mater into the brain, the recording-injection device was advanced 20–23 mm from the tip of the guide tube to reach the CM-Pf complex. The CM-Pf complex was located by recording neuronal activity in the thalamus through the tungsten wire electrode while advancing the

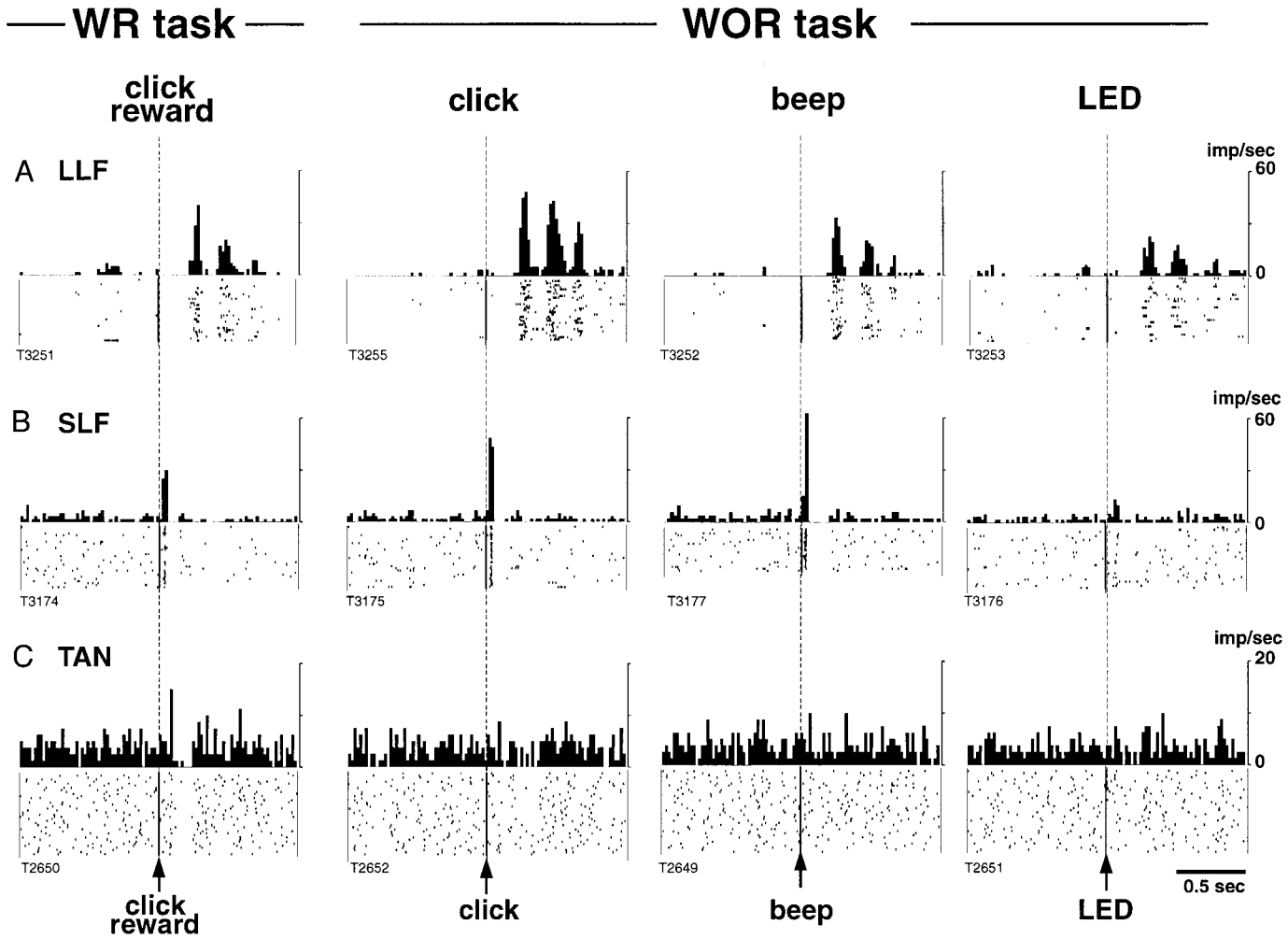

FIG. 4. Sensory responses of 2 types of thalamic CM-Pf neurons and a striatal tonically active neuron (TAN) recorded after behavioral conditioning on the WR and WOR tasks. Spike rasters and accompanying histograms are aligned at the time of presentation of the sensory stimuli indicated. *A*: representative activity of a CM neuron with long-latency facilitation following stimulus presentation (LLF neuron). *B*: activity of a Pf neuron showing short-latency facilitation after stimulus presentation (SLF neuron). *C*: representative activity of a striatal TAN recorded in the putamen. Note that thalamic responses occur in both WR and WOR tasks, whereas the TAN response occurs only in the WR task.

recording-injection device. Muscimol (Sigma, 1 μg/1 μl saline, pH 7.3) was injected at a rate of 0.2 μl/min for total amounts of 1–3 μl. The activity of neurons at the injection site stopped discharging immediately after injection of muscimol. The recording-injection device was removed after recording neuronal activity in the CM-Pf complex and in the striatum, in which conventional elgiloy electrodes were placed. Experiments involving muscimol injection were separated by at least 3–4 days to allow recovery from the effects of the muscimol injections.

Injection of retrograde tracer into the striatum

After recordings of neuronal activity in the CM-Pf complex and striatum had been completed in *monkey TM,* we injected into the striatum the beta-subunit of cholera toxin (CTB, Sigma) as a retrograde tracer. The CTB was prepared as a saturated solution by adding 0.5 mg of CTB to 20 μl of saline, stirring vigorously, and letting the precipitate settle for 5 min before filling the microsyringe (Flaherty and Graybiel 1993). CTB was injected by means of a 1-μl Hamilton microsyringe (needle, 700 μm OD) that was attached to the micromanipulator (Narishige, MO-95) and inserted through the striatal recording chamber. Based on recordings of neuronal activity in the striatum made with elgiloy microelectrodes, we injected CTB at striatal sites where the activity of TANs had previously been identified. Three injections were made, at two sites in the putamen and one site in the caudate nucleus (see Fig. 13*A*). A total 0.05 μl CTB was injected at each site.

Histology

At the end of all recording experiments, small electrolytic lesions were made at several locations along selected electrode tracks both in the CM-Pf complex and in the striatum. Direct anodal current (20 μA) was passed for 30 s through either elgiloy or tungsten microelectrodes.

Four days after injection of CTB, *monkey TM* was deeply anesthetized with Nembutal (60 mg/kg ip) and was perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer. Coronal 40-μm-thick sections through the thalamus and striatum were stained with cresylecht violet. In addition, CTB was demonstrated immunohistochemically in 30 sections of interest separated by 200 μm. Sections were incubated with polyclonal antiserum against the beta-subunit of CTB (List Biolabs; 1:2,000 dilution) for 2 days, then incubated with a biotinylated secondary antibody, stained with the DAB-avidin-biotin peroxidase technique (Vector Labs), mounted, de-

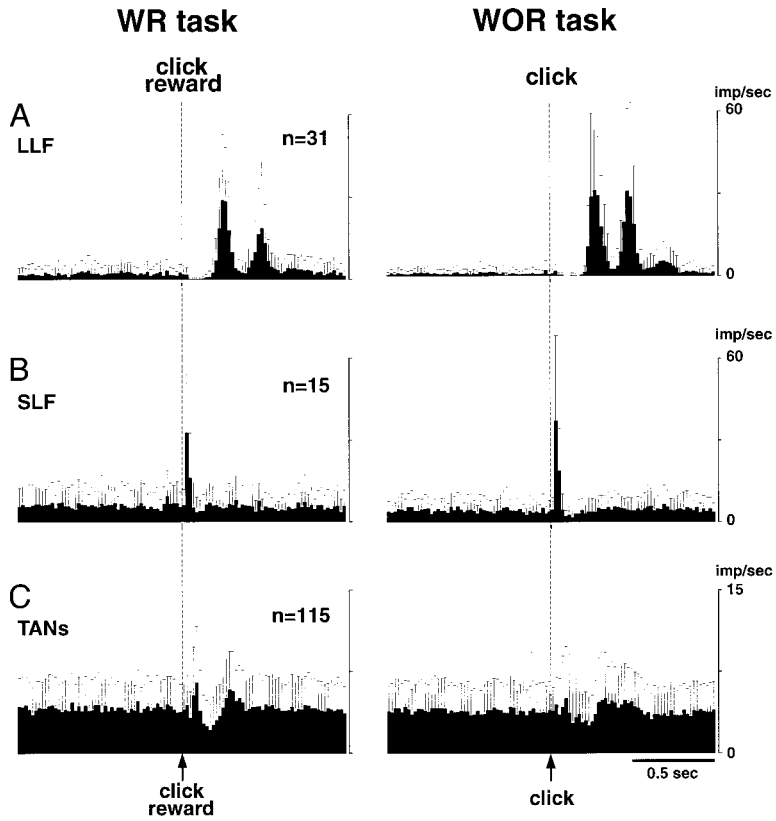

FIG. 5. Population responses of intralaminar thalamic neurons (*A* and *B*) and of TANs (*C*) in *monkeys TM* and *AK* during performance of the WR and WOR tasks. Population histograms were obtained by calculating the ensemble average of responses of different neurons, each one of which was recorded during performance of the 2 tasks. The histograms are aligned on the click onset. The thin vertical bars indicated for each bin of the histogram bins represent the standard deviation (SD) of the responses of the neurons summed in that bin. The numbers of neurons of each type are indicated in the response histogram of WR task.

hydrated, and coverslipped. *Monkey AK* was perfused with 10% formaldehyde, and *monkey NA* was perfused with 4% paraformaldehyde after completion of the physiological experiments. Coronal 50-μm-thick sections through the striatum and CM-Pf complex of both hemispheres were stained with cresylecht violet or with the thiocholine method (*monkey NA*) to demonstrate acetylcholinesterase (AChE) activity (Graybiel and Berson 1980; Hardy et al. 1976).

RESULTS

Altogether, 136 recording tracks were made in the thalamus, and 98 tracks were made in the striatum (Fig. 2). In the striatal recordings, we analyzed the activity of TANs identified on the basis of their low (2–10 spikes/s) spontaneous discharge rates and the broad waveforms of their extracellularly recorded action potentials (Alexander and DeLong 1985; Aosaki et al. 1994b; Apicella et al. 1991; Kimura et al. 1984; Raz et al. 1996). To identify neuronal activity in the CM-Pf complex, we carried out microstimulation mapping experiments and mapped neuronal responses elicited in the behavioral tasks. These stimulation and recording maps were combined with postmortem histological reconstructions of the electrode tracks in each monkey (Figs. 2 and 3). The CM and Pf were identified in Nissl-stained sections based on the histological criteria of Olszewski (1952) and Jones (1997) and, in addition, in *monkey NA*, on the basis of AChE staining. We recorded the activities of 208 TANs in the striatum, 36 neurons in the CM, and 10 neurons in the Pf on the left side in *monkey TM;* 102 TANs and 24 neurons in the CM and 23 neurons in the Pf on the right side in *monkey AK;* and 60 neurons in the CM and 29 neurons in the Pf bilaterally in *monkey NA.*

Microstimulation mapping in the thalamus

Microelectrode penetrations were made over a broad mediolateral extent of the thalamus (Fig. 2). In these penetrations, we recorded the activity of thalamic neurons while advancing the electrode and delivered current pulses for microstimulation while withdrawing the electrode. The effects of microstimulation were examined systematically at 0.5- to 1.0-mm intervals. Consistent with previous reports (Buford et al. 1996; Vitek et

TABLE 1. *Multimodal properties of CM-Pf neuron activity*

	Neurons	
	LLF	SLF
Monkey NA		
Auditory + tactile + visual	14 (47)	3 (34)
Auditory + tactile	11 (36)	4 (44)
Auditory + visual	2 (7)	1 (11)
Tactile + visual	1 (3)	0
Auditory	2 (7)	0
Visual	0	1 (11)
Total	30	9
Monkeys TM and AK		
Auditory + visual	43 (66)	19 (38)
Auditory	21 (32)	29 (58)
Visual	1 (2)	2 (4)
Total	65	50

Figures indicate number of neurons responsive to either auditory or visual or tactile stimuli and corresponding percentages (in parentheses). Tactile responses were examined in only *monkey NA.* CM-Pf, centre médian–parafascicular; LLF, long-latency facilitatory; SLF, short-latency facilitatory.

al. 1996), clear effects of microstimulation were observed in the laterally located motor nuclei of the thalamus, the ventral posterolateral nucleus (VPL) and the ventral posteromedial nucleus (VPM), indicative of a leg-lateral, face-medial somatotopy. By contrast, in the more medially located thalamic nuclei, including the CM-Pf complex, the mediodorsal nucleus (MD) and the centrolateral nucleus (CL), we observed no stimulation-induced bodily movements. Marker lesions (see Fig. 3) allowed verification of the stimulation sites.

Activation patterns of CM and Pf neurons

By recording neuronal activity as the microstimulation electrodes were advanced vertically through the thalamus, we were able to identify patterns of activity characteristic of CM and Pf neurons. We found the CM and Pf approximately 3–6 mm below the surface of the thalamus, with the medial part of the complex <3 mm lateral from the midline. The recording microelectrodes passed through the MD before reaching the CM and Pf. Neurons in the CM and Pf had lower firing rates (4.1 ± 3.3 spikes/s; mean ± SD) than those in the MD (7.2 ± 4.0 spikes/s), and small-amplitude spikes. The CM-Pf neurons had characteristic grouped, repetitive discharges. These properties meant that special care was necessary to isolate the activity of single CM and Pf neurons, but they helped in on-line recognition of the nuclei as recording electrodes entered or left the CM and Pf.

Very high percentages of neurons recorded in the CM-Pf complex (97%, 177/182 neurons examined) exhibited activity changes as the monkeys performed the behavioral tasks. Two classes of neurons were identified in the CM and Pf, based on their different task-related activity patterns. One type showed long-latency increases in firing rate both after clicks (latency 227 ± 30 ms, $n = 40$) in the WR task and after presentations of clicks (latency 233 ± 29 ms, $n = 93$), beeps (latency 251 ± 57 ms, $n = 70$), and LED flashes (latency 281 ± 56 ms, $n = 58$) in the WOR task (Fig. 4*A*). The background discharge rate of these neurons was 4.4 ± 3.6 spikes/s. Many neurons of this type showed characteristic single or periodic repeating activations after the sensory stimuli, as illustrated in Fig. 4*A*. For purposes of classification, we refer to these neurons as the long-latency facilitation (LLF) type.

The second subpopulation of CM-Pf neurons responded with short-latency single burst discharges after the clicks (latency 24 ± 9 ms, $n = 23$) in the WR task and clicks (latency 30 ± 13 ms, $n = 51$), beeps (latency 44 ± 37 ms, $n = 33$), and LED flashes (latency 90 ± 31 ms, $n = 26$) in the WOR task (Fig. 4*B*). The background discharge rate of these neurons was 3.5 ± 2.5 spikes/s. We call this type of CM-Pf neuron the short-latency facilitation (SLF) type. In the example shown in Fig. 4*B*, the neuron responded briskly with a single burst to clicks both in the WR and in the WOR tasks and beeps in the WOR task, but had only a small, single burst in response to LED flashes in the WOR task. For comparison, the activity of a striatal TAN recorded during the WR and WOR tasks is illustrated in Fig. 4*C*. The TAN showed brief initial activation at a latency of 69 ± 30 ms ($n = 34$) followed by a pause in its tonic discharges (latency 131 ± 45 ms, $n = 74$) and rebound facilitation (latency 254 ± 54 ms, $n = 54$) after the click followed by reward in the WR task, but it showed no significant responses to beeps or to LED flashes in the WOR task.

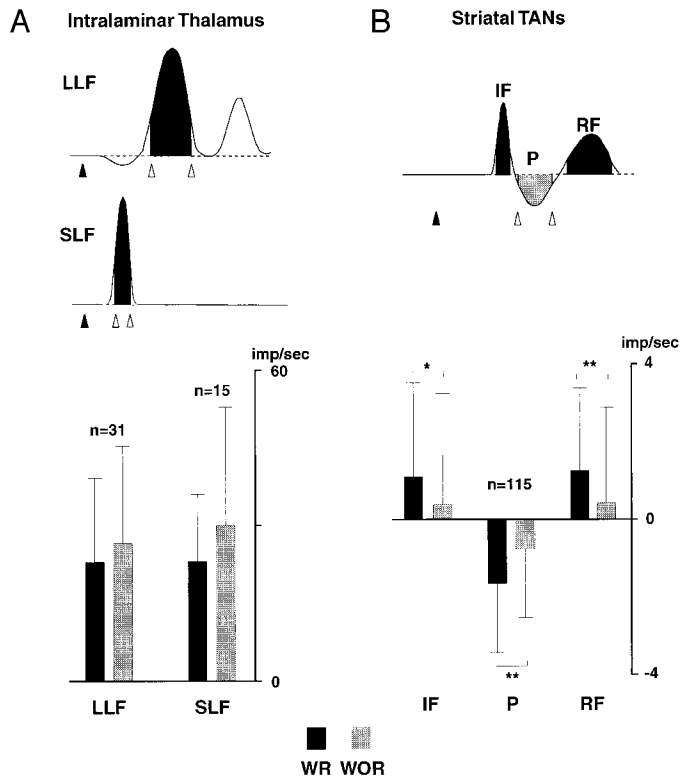

FIG. 6. Comparison of the magnitude of thalamic CM-Pf and striatal TAN responses during performance of the WR and WOR tasks. *A*: responses of SLF and LLF neurons of the CM-Pf complex. *B*: responses of striatal TANs. The *top panels* of *A* and *B* illustrate schematically how the components of the responses were defined. The activity of LLF neurons was measured for the time window (white arrowheads) extending to between 230 and 300 ms after the click (black arrowhead); the activity of SLF neurons was measured between 20 and 50 ms after the click. Initial facilitation (IF), pause (P), and later rebound facilitation (RF) of TANs were measured at 65–125 ms, 130–210 ms (white arrowheads), and 250–330 ms, respectively, after the click (black arrowhead) * and **: $P < 0.05$ and $P < 0.01$ in 2-tailed *t*-tests, respectively. Responses are plotted as either an increase or a decrease of firing rate from the baseline firing frequency measured during the 0- to 3,000-ms period before stimulus presentation.

The differential responses of LLF and SLF neurons in the CM-Pf complex of *monkeys TM* and *AK* are illustrated in Fig. 5, which shows population response histograms for the two types of neuron and, for comparison, the population responses of TANs in the striatum in the WR and WOR tasks. The population response histograms for the LLF type (Fig. 5*A*) shows two or three discrete, periodic burst discharges (period ~200 ms) after clicks in both the WR and WOR tasks. As a population, this class of neurons had long but similar latencies of activation after the clicks in the two tasks. However, the two to three periodic burst discharges after the clicks were mainly observed in *monkey TM*, whereas single burst discharges after the clicks were the dominant responses in *monkey AK* (and also in *monkey NA*, not shown). Although the activation of these neurons in response to the clicks occurred at a long latency, this long-latency activation was preceded by a suppression of discharges at a short latency (50 ± 27 ms). The SLF neurons (Fig. 5*B*) exhibited responses that were tightly locked to the clicks in both the WR and the WOR tasks.

As shown in Fig. 5, *A* and *B*, both LLF and SLF neurons showed responses not only to auditory but also to visual stimuli. In *monkey NA*, in which the responsiveness of 30 LLF

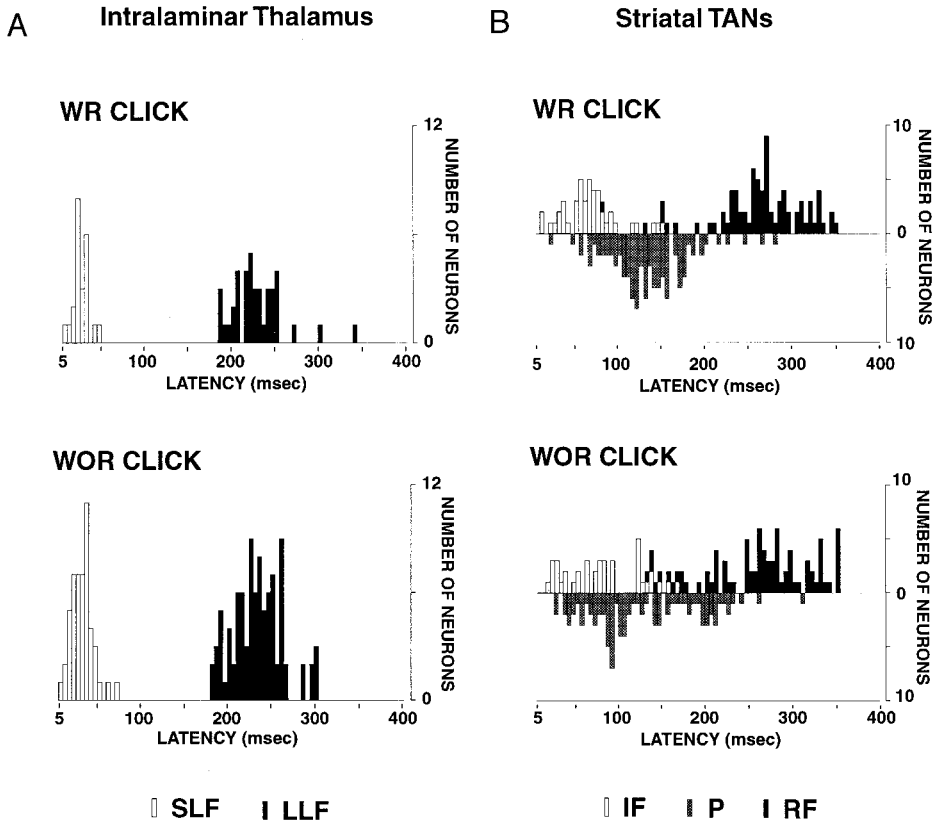

FIG. 7. Onset latencies of click responses of thalamic CM-Pf neurons and striatal TANs during WR and WOR tasks. *A*: SLF and LLF neurons in the intralaminar thalamus. *B*: striatal TANs. Both SLF and LLF neurons showed similar distributions of response latencies (LLF; $P = 0.63$, SLF; $P = 0.28$, Siegel-Turkey test). By contrast, TANs showed significant differences in their response latencies in the WR and WOR tasks ($P < 0.02$ for IF, $P < 0.0001$ for P, $P = 0.08$ for RF). Abbreviations are the same as in Fig. 6.

and 9 SLF to auditory (click and beep), visual (LED), and somesthetic (tactile) stimuli was examined, nearly all LLF (93%) and SLF (89%) neurons showed multimodal responses (Table 1). In *monkeys TM* and *AK*, in which auditory and visual stimuli were used, about half of the LLF and SLF neurons responded to both auditory and visual stimuli, and the other half responded either to auditory or visual stimulus (Table 1).

In the striatum, TANs ($n = 115$) showed responses to the clicks followed by reward (Fig. 5*C*, WR task). The responses to the reward-associated clicks consisted of three consecutive components, an initial short-latency facilitation (IF), a pause (P), and a later rebound facilitation (RF). However, when the click sounds were not associated with reward (WOR task), the magnitudes of these characteristic responses decreased markedly (Fig. 5*C*).

To determine whether the neuronal responses of the CM-Pf neurons to the click stimuli were different in the WR and WOR tasks, we compared the neuronal responses in the two conditions quantitatively. We did the same for the striatal TANs recorded. Figure 6 shows the response magnitudes of SLF and LLF neurons in the thalamus (Fig. 6*A*) and TANs in the striatum (Fig. 6*B*). Increases and decreases in firing rate relative to baseline levels are plotted for each neuronal type. In the thalamus, the SLF and LLF neurons showed no significant difference in click responses in the WR and WOR tasks (Fig. 6*A*, $P = 0.32$ for the LLF, $P = 0.42$ for the SLF, paired 2-tailed *t*-tests). By contrast, all three components of the responses of striatal TANs (IF, P, and RF) were significantly larger in the WR task than in the WOR task (Fig. 6*B*, $P < 0.05$ for the IF, $P < 0.01$ for the P and RF, paired 2-tailed *t*-tests).

Next, we examined the onset latencies of the click responses of individual neurons in the WR and WOR tasks (Fig. 7). Variations in the onset latency of facilitatory responses of the LLF and SLF neurons in the WR task (Fig. 7*A*) were not significantly different from those in the WOR task ($P = 0.63$ for the LLF, $P = 0.28$ for the SLF, Siegel-Turkey test). By contrast, the variations in the latency distributions of the IF and P responses of TANs in WOR condition were larger than those in WR condition (Fig. 7*B; P* < 0.02 for IF, $P < 0.0001$ for P, Siegel-Turkey test). The RF responses of the TANs were not significantly different ($P = 0.08$, Siegel-Turkey test). Thus there was a contrast between the CM-Pf neurons of both LLF and SLF types, which showed similar latencies of response to clicks whether they were associated with reward or not, and the striatal TANs, which showed much more sharply timed response latencies to reward-associated clicks.

Table 2 summarizes the responsiveness of the two types of intralaminar neurons to beep, LED, tactile, and click stimuli in the WOR and WR conditions. More than 90% of both LLF and SLF neurons responded consistently to the click noise not only in WOR but also in WR conditions in *monkeys TM* and *AK*, and values were similar for the responses of *monkey NA*, which was tested only in the WOR task. By contrast, there were considerable differences among the three monkeys in the responsiveness of the intralaminar neurons to the beeps and LED flashes. The SLF and LLF neurons in *monkey TM* showed much higher responsiveness to these stimuli than did intralaminar neurons in the other two monkeys. These differences may reflect differences in the conditions under which the stimuli were presented to the monkeys. For *monkey TM*, the stimuli were presented in much darker ambient light conditions than for *monkeys AK* and *NA*, and the LED was much closer to *monkey TM* (22 cm) than to the other two monkeys (50 cm, see

TABLE 2. *Responsiveness of intralaminar neurons to sensory stimuli*

	Conditions				
	WOR				WR
Stimuli	Beep	LED	Click	Tactile	Click
Short-latency facilitation type					
Monkey TM	6/6 (100.0)	5/6 (83.3)	3/3 (100.0)		8/8 (100.0)
Monkey AK	12/26 (46.2)	7/25 (28.0)	22/26 (84.6)		15/16 (93.8)
Monkey NA	15/32 (46.9)	14/32 (43.8)	26/32 (81.3)	8/10 (80.0)	
Long-latency facilitation type					
Monkey TM	31/32 (96.9)	21/22 (95.5)	26/26 (100.0)		36/38 (94.7)
Monkey AK	12/17 (70.6)	8/16 (50.0)	16/17 (94.1)		4/5 (80.0)
Monkey NA	27/57 (47.4)	29/57 (50.9)	51/57 (89.5)	22/23 (95.7)	

Figures indicate number of neurons (responsive/examined) and corresponding percentages (in parentheses). In *monkey NA*, responses to click in WR condition were not examined. WOR, without reward; WR, with reward; LED, light-emitting diode.

METHODS). Thus the stimuli might have had stronger alerting or orienting effects on *monkey TM*.

Additional characteristics of the sensory responsiveness of neurons in CM and Pf became evident in tests of their responsiveness, which were performed for most of the neurons recorded. Considerable numbers of both LLF and SLF neurons responded to unexpected stimuli such as handclaps and knocks on the door or walls of the room in which the monkey was sitting. In many instances, the neurons responded to such alerting stimuli only for the first several times that they occurred; after that, the same stimuli gradually became ineffective in evoking responses. To test more systematically for habituation of such responses, we compared the responsiveness of 26 CM and Pf neurons of both SLF and LLF types in two sets of trials: trials in which clicks, beeps, and LED flashes were presented in random order in a 75-trial-long block (Fig. 8, *A* and *B*), and trials in which only clicks appeared, repeatedly, in a 25-trial-long block (Fig. 8, *C* and *D*). We found that 13 of 16 LLF neurons examined exhibited habituation, as evident by comparing the population histograms in Fig. 8, *A* and *C*, and the raster plots of Fig. 8, *B* and *D*. Smaller numbers of short-latency facilitation neurons (5 of 10) showed the habituation responses.

Sudden taps to the skin also evoked brisk responses from both CM and Pf neurons. We did not identify the receptive fields of the somatosensory responses, but the fields seemed large because taps to the neck, shoulder, back, or hands of the animal were similarly effective in evoking responses in most of the neurons. We did not explore the entire body surface and examined tactile responses only in *monkey NA*.

Locations of task-related neuronal activity in the thalamus

We recorded thalamic neuronal activity during the presentation of sensory stimuli in the WR and WOR tasks not only in the CM-Pf complex, but also in other nuclei, including the MD, CL, VPL pars oralis (VPLo), and VPL pars caudalis (VPLc). Recording sites at which we identified LLF and SLF neurons were located within the CM and Pf. Neurons with activity related to the orofacial movements made to consume reward water, or related to spontaneous limb movements, were observed in the VPLo and VPLc.

There was a clear tendency for the LLF and SLF neurons to be in separate locations within the CM-Pf complex (Fig. 9). It was rare to record both types of neuron in a single vertical electrode track; single penetrations tended to isolate neurons of either the LLF or the SLF type. LLF neurons were almost exclusively found in the CM, whereas SLF neurons were predominantly found in the Pf and the medial part of CM (Fig. 9).

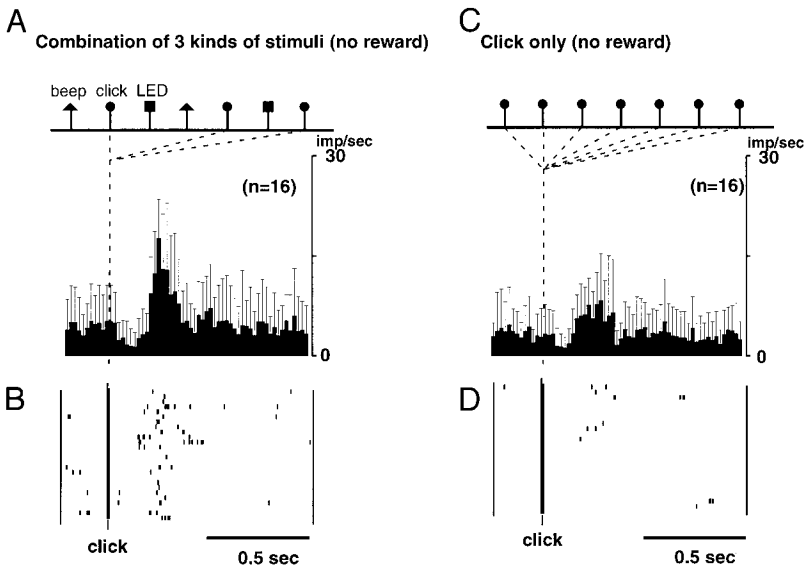

FIG. 8. Habituation of sensory responses of intralaminar thalamic neurons. In 26 neurons recorded in CM and Pf, neural responses were 1st examined in a 75-trial-long block in which beeps, clicks, and LED flashes appeared in a random order with equal probabilities and at equal intervals (*A* and *B*). The neural activity shown is centered at the onset of the 25 presentations of the click that occurred during a 75-trial-long block for both the population response histogram (*A*) and the raster display (*B*). The same neurons were then examined in a 25-trial-long block in which only clicks were delivered and the activity was again displayed by centering on click onsets (*C* and *D*). The histograms in *A* and *C* are ensemble averages of the activities of 16 LLF neurons. The thin vertical bars indicate standard deviation (SD) of responses. The raster displays in *B* and *D* show impulse discharges in chronological order with the 1st trial at the *top* and the last trial at the *bottom*.

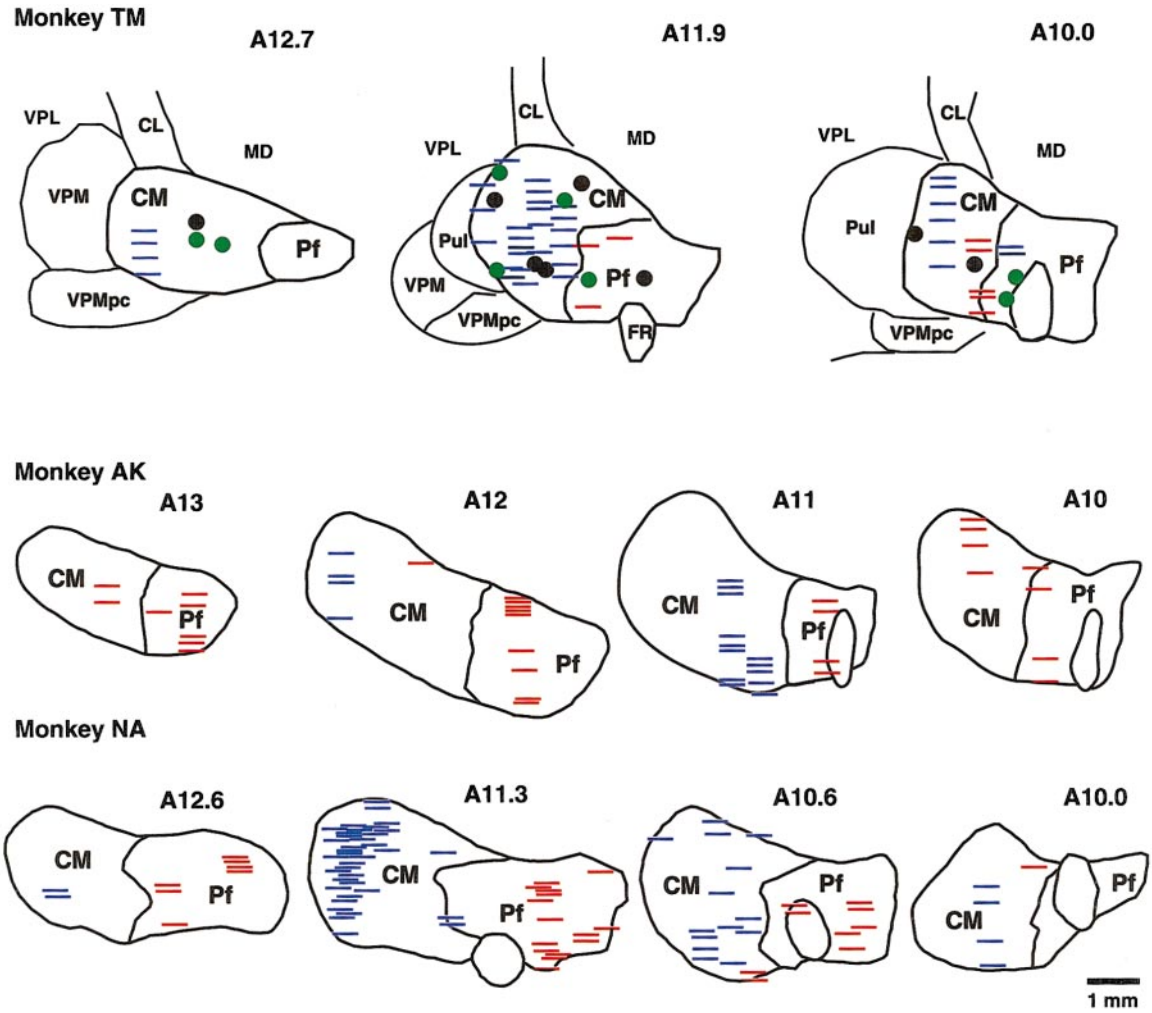

FIG. 9. Sites at which short-latency and long-latency facilitatory responses were recorded in the CM and Pf of all monkeys. Recording sites were reconstructed from brain sections postmortem and are shown on reconstructed electrode tracks. Red bars indicate SLF neurons, and blue bars indicate LLF neurons. Sites of injection of muscimol and saline in the CM and Pf in *monkey TM* are indicated by filled black and green circles, respectively. FR, fasciculus retroflexus; other abbreviations, same as in Fig. 2.

Inactivation of the CM and Pf nuclei in the thalamus markedly reduces the sensory responses of TANs in the striatum

To determine whether the neurons of the CM-Pf complex supply task-dependent input to striatal TANs during performance of the WR and WOR tasks, we identified TANs in *monkey TM* as it performed the behavioral tasks and compared the TANs' activity before and after blocking neural activity in CM and Pf by local infusion of the $GABA_A$ receptor agonist, muscimol (Fig. 10*A*).

We injected 1–3 μl of muscimol (1 μg/1 μl saline, pH 7.3) into the CM-Pf complex in eight experiments (Fig. 9). Before injection of muscimol, we confirmed that the tip of the injection cannula was in the CM or Pf by recording neuronal activity through the tungsten electrode protruding from the tip of the cannula (Fig. 10*A*). Figure 10*B* shows a population response histogram of TANs recorded before muscimol injection, with the histograms centered at the time of presentation of clicks in the WR task. Clear-cut initial activation followed by suppression and subsequent facilitation of discharges is evident. The number of TANs responsive to the clicks in the WR task was much lower in TANs following injection of muscimol (Fig. 10*D*), and the population histogram of activity of these TANs (Fig. 10*D*) showed a much smaller response after the click, mainly an initial facilitation.

Quantitative analysis of these responses (Fig. 11) indicated that the main effects of the muscimol injection into the CM-Pf complex was on the amplitudes of the pause (P) and rebound facilitation (RF; Fig. 11*A*), both of which were significantly smaller after muscimol injection than before it ($P < 0.0001$ for the P and RF, 2-tailed *t*-test). The initial facilitation response (IF), by contrast, showed only a tendency to decrease without a statistically significant decline ($P = 0.33$). There was also a clear change in the distribution of onset latencies of the TAN responses. After muscimol injection into the CM-Pf, the variance of the onset latency of pause (P; Fig. 11*B*) and rebound facilitation (data not shown) became significantly larger ($P < 0.002$ for the P, $P < 0.05$ for the RF, Siegel-Turkey test). The latency of the initial facilitation (IF) did not change ($P = 0.3$).

These strong effects of inactivation of the CM and Pf complex on the responses of striatal TANs continued for more than 5 h. The population histogram in Fig. 10*D* is based on the

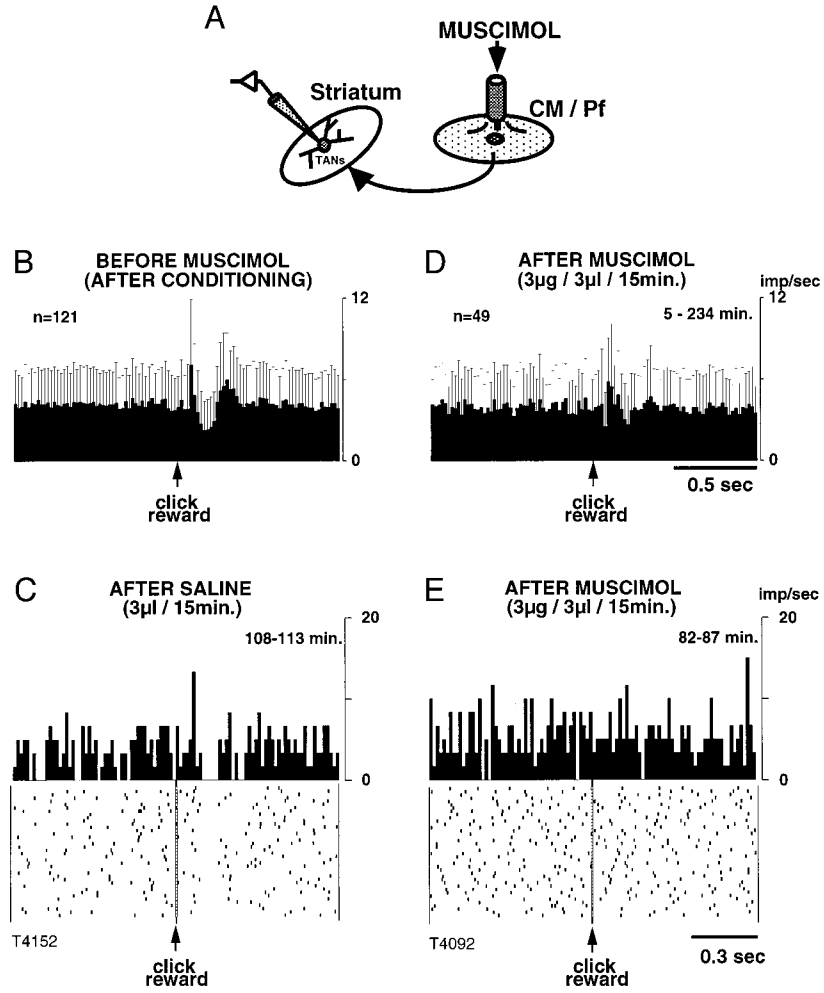

FIG. 10. Effects of inactivation of neuronal activity in CM and Pf on the activity of TANs recorded concurrently during performance of the WR task. *A*: schematic illustration of the experimental setup. *B*: population response of TANs to the clicks associated with reward prior to muscimol injection into the CM-Pf complex. Numbers above the histogram indicate total number of neurons sampled; thin vertical bars indicate SDs. *C*: an example of TAN responses to the clicks after saline injection into the CM-Pf complex. The TAN continued to respond to the reward-associated clicks. *D*: population response of TANs to the clicks after muscimol injection into the CM-Pf complex. *E*: an example of the activity of a TAN recorded after muscimol was injected into the CM-Pf complex. The TAN showed no response to the reward-associated clicks.

activity of TANs recorded between 5 and 234 min after muscimol injection. Figure 10*E* illustrates a representative raster plot of the activity of a single TAN during the WR task recorded from 82 to 87 min after muscimol injection. Responses to the clicks were undetectable following the muscimol injection. Figure 10 also shows that the muscimol injections into CM and Pf did not have significant effects on the background firing rate or discharge pattern of the TANs. Before muscimol injection, the background discharge rate of the 121 TANs recorded was 4.2 ± 1.3 impulses/s (Fig. 10*B*), whereas after injection the firing rate was 4.0 ± 1.4 impulses/s (49 TANs, Fig. 10*D*).

To test whether the effects of muscimol injection into the CM and Pf resulted from mechanical damage to the CM-Pf or nearby neurons, we injected the same amount of physiological saline (3 μl) into the same part of the CM-Pf complex in which muscimol had been injected in a previous experiment, and then recorded the activity of 38 TANs during the WR task (Fig. 9). There was a tendency for reduction of the pause response ($P = 0.04$, 2-tailed *t*-test), but the magnitude of the rebound facilitation (RF) was not significantly different from that before saline injection ($P > 0.99$ for RF, 2-tailed *t*-test). The magnitudes of the pause and rebound facilitatory responses after muscimol injection were significantly smaller than those after saline injection ($P < 0.05$ for P, $P < 0.01$ for RF, 2-tailed *t*-tests). One example of the activity of a TAN after saline

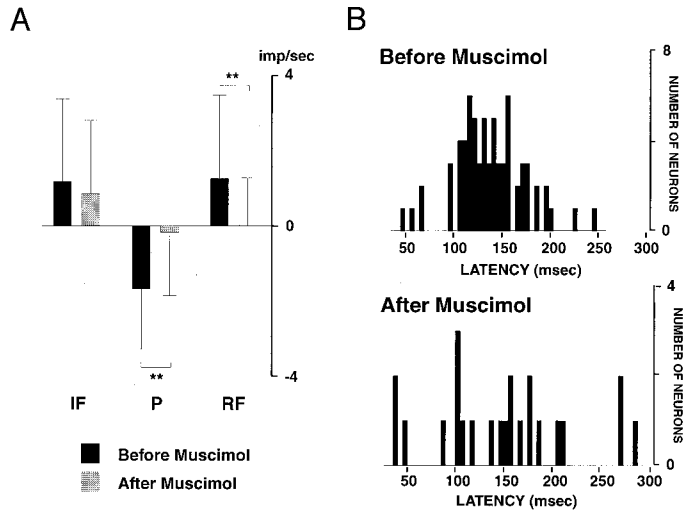

FIG. 11. Responsiveness of striatal TANs to the reward-associated click before and after muscimol injection into the CM-Pf complex. *A*: initial facilitation (IF), pause (P), and later rebound facilitation (RF) measured as an increase or decrease of firing rate of TANs relative to background firing rate, before and after the muscimol injection into the CM-Pf complex. **, $P < 0.001$, 2-tailed *t*-test. *B*: distribution of onset latencies of pause responses to the click in the WR task before and after muscimol injection into the CM-Pf complex. The variance of the latency distribution for the pause response after muscimol injection was significantly larger than the variance of the responses before muscimol injection ($P < 0.002$, Siegel-Turkey test).

injection is shown in Fig. 10*C*. Injection sites, locations of tip of injection needle, of muscimol and saline into the CM-Pf complex are illustrated in Fig. 9. Most of the injections of muscimol and saline were made into the CM-Pf complex where activity of SLF and LLF neurons had been frequently recorded.

In two further control experiments with *monkey TM*, we injected muscimol into the motor nuclei of the lateral thalamus, including the VPL and VPM. In both experiments, the monkey showed signs of paralysis of the contralateral arm after the muscimol injection. In the ipsilateral striatum, however, TANs that had responses to the reward-predictive click in the WR task before the muscimol injection kept on responding. This observation excluded a possibility that the muscimol injected into the CM and Pf, which are located medial to VPL and VPM, inactivated the activity of TANs because the muscimol diffused laterally into the lateral thalamus or even the striatum.

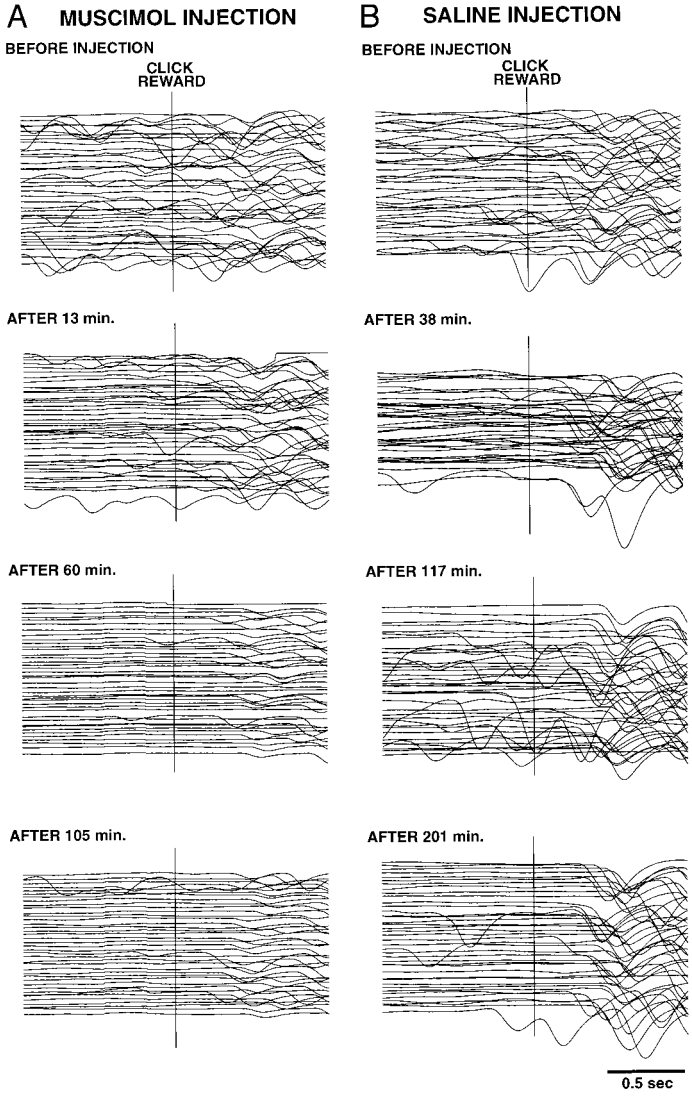

FIG. 12. Effects of inactivation of neuronal activity in CM and Pf on the pattern of licking movements after click with reward water. *A*: superimposed traces of pressure patterns recorded on reward-delivery spoon before and after injection of muscimol (3 μg/3 μl/15 min). The torques generated by tongue movements made in licking were detected; a drop of water was delivered following each solenoid click. The traces were centered at the time of the clicks. *B*: similar to *A*, but after injection of physiological saline (3 μl/15 min). The order of the traces is arranged chronologically from *top* (earliest trace) to *bottom* (last trace).

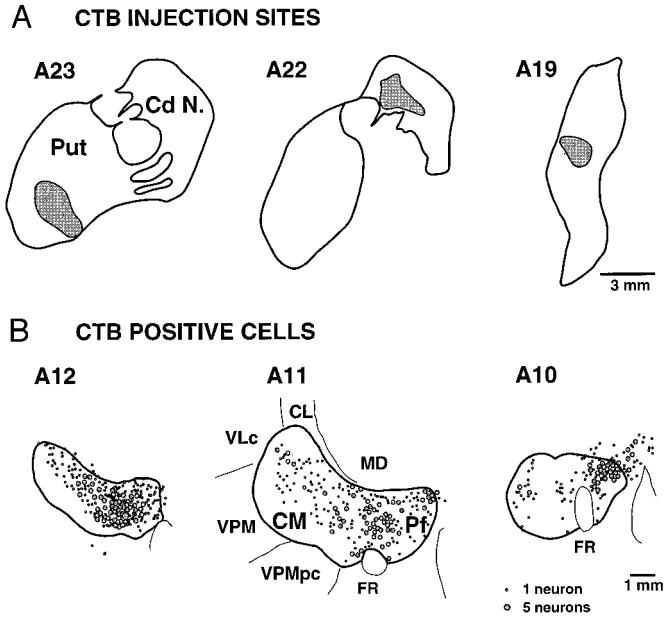

FIG. 13. Retrograde labeling of CM and Pf neurons following injection of cholera toxin beta-subunit (CTB) into the striatum of *monkey TM* at sites at which the responses of TANs were recorded. *A*: schematic drawings of 3 CTB injection sites (shown in stipple) in the putamen (*left* and *right*) and in the caudate nucleus (*middle*). *B*: distribution of retrogradely labeled CM and Pf neurons after injection of CTB at the sites shown above. The charts show superimposed plots of the locations of retrogradely labeled neurons (dots) observed in 3 sections spaced 2 mm apart. Sizes of the gray dots indicate the number of CTB-positive cells at each site. Approximate Horsley-Clarke coordinates are shown for each chart. Abbreviations as in Figs. 2 and 3.

Behavioral effects of inactivation of the CM-Pf complex

To determine whether an inactivation of the CM-Pf complex would significantly affect behavioral attentiveness to salient stimuli, we analyzed the licking movements of *monkey TM* in the WR task before and after muscimol injection. Figure 12 shows examples of the pressure recordings made before and after injection of muscimol (Fig. 12*A*), and before and after injection of physiological saline (Fig. 12*B*). In the WR task, the monkey made anticipatory licks of the spoon before the click with reward and then it made strong, repetitive licks to consume the reward that was delivered after the click. Following inactivation of the CM-Pf complex, however, the pattern of orofacial movements in the WR task changed. The number of anticipatory licks before the click decreased, and the rate of repetition and strength of the licks after reward delivery diminished. These changes in the pattern of orofacial movements were observed in five of eight cases of muscimol injection. In seven of the eight cases of saline injection, no clear change in pattern was observed, and in one case, the lickings after reward decreased but there was no change in anticipatory licks. These observations are consistent with the hypothesis that the monkey's attentiveness to salient behavioral events (click with reward) was compromised by inactivation of the CM-Pf complex.

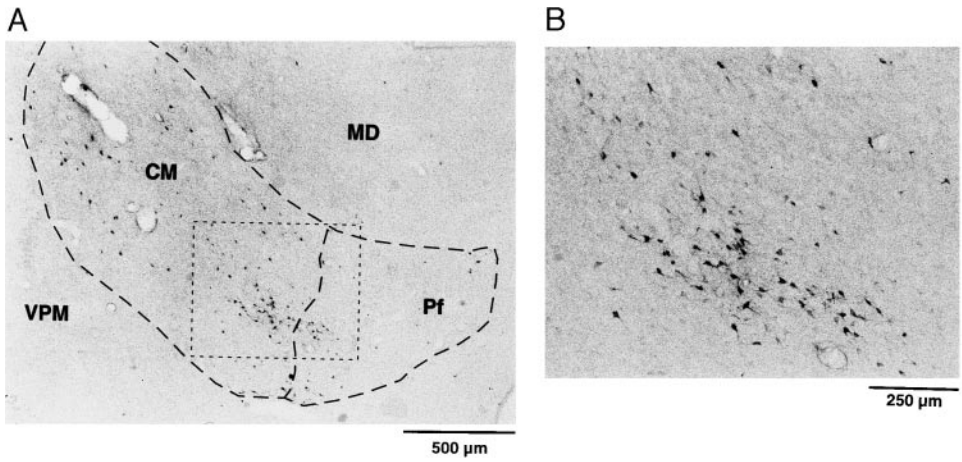

FIG. 14. Photomicrographs of retrogradely labeled neurons in the CM-Pf complex following injection of CTB into the caudate nucleus and putamen. *A*: low magnification view. *B*: high magnification view of region indicated by rectangle in *A*.

Retrograde tracer injections placed in sites of striatal TAN recording label neurons in the CM and Pf nuclei of the thalamus

To obtain anatomical confirmation that the striatal sites at which we recorded the activity of TANs receive direct, strong axonal projections from the CM and Pf, we deposited CTB into the putamen and caudate nucleus after recording the activity of TANs and mapped the distributions of retrogradely labeled neurons in the thalamus. These experiments were carried out in *monkey TM* after completion of all other experiments. We injected the CTB at three sites in the striatum (Fig. 13*A*), two in the putamen and one in the caudate nucleus, at each of which we had recorded the activity of TANs and had observed strong suppressive effects of CM-Pf muscimol injections on the responses of TANs. The retrogradely labeled neurons were concentrated almost exclusively in the CM and Pf (Figs. 13 and 14). Small numbers of labeled neurons were observed medial and dorsal to the Pf, especially at caudal levels. This thalamic distribution corresponded well to the distribution of neurons responding to sensory stimuli in the WR and WOR tasks in this monkey (Fig. 9), strongly suggesting that the sites at which we recorded TANs in the striatum receive direct strong projections from the CM and/or Pf nuclei in the ipsilateral thalamus.

DISCUSSION

Neurons in the CM-Pf complex of primates exhibit temporally discrete responses to salient sensory stimuli

We have identified three key response characteristics of intralaminar CM-Pf neurons recorded in behaving monkeys. First, a large number of CM-Pf neurons exhibited responses to auditory and/or visual stimuli presented in sensorimotor conditioning tasks, and many of these CM-Pf neurons also responded to unexpected auditory, visual, and/or somatosensory stimuli presented to the monkeys outside of these tasks. These findings extend to behaving primates, evidence suggesting that CM-Pf neurons have multimodal response properties (Albe-Fessard and Besson 1973; Grunwerg and Krauthamer 1992; Irvine 1980). Second, the responses of most of the CM-Pf neurons identified showed sharp temporal tuning. They fell into early and late facilitation types. The short-latency (SLF) neurons had brief, phasic responses. The long-latency (LLF) neurons had single or two to three repeating, phasic increases in discharge rate, and they often exhibited an early depressive response as well. These characteristics suggest that neurons in the primate CM-Pf complex can generate discrete, coherent signals in response to a wide variety of sensory stimuli. Third, the sensory responses of the CM-Pf neurons seemed to be largely unaffected by the reward-predictive nature of the stimuli they responded to. They discharged equivalently to the sensory stimuli presented with (WR task) and without (WOR task) reward, but these responses often habituated rapidly when the same stimuli were presented repeatedly.

Given these properties, we suggest that CM-Pf neurons may signal the onsets, offsets, and modulations of behaviorally relevant sensory events rather than the detailed physical properties of the events. Neurons in the internal medullary lamina of the primate thalamus also have been reported to have very large receptive fields and to be insensitive to stimulus size, shape, and brightness but responsive to changes of visual scene (Schlag and Schlag-Rey 1984). Studies of attention have shown that novel or unexpected stimuli tend to shift attention, and that changes in predictable sequences of stimuli, like those used in the present study, often elicit overt orienting responses in human subjects and in experimental animals (Pashler 1998; Rohrbaugh 1984). The present findings suggest that neurons in the CM-Pf complex of primates preferentially process stimuli that have attentional value, thus acting as detectors of behaviorally significant events. These functions are likely to be distinct from those of thalamostriatal inputs reported to originate in the ventral anterior-ventral lateral (VA-VL) complex (McFarland and Haber 2000).

Inputs from the CM-Pf complex to the striatum affect the sensory responsiveness of striatal neurons

Our experiments with muscimol demonstrate that the sensory responses of TANs depend on inputs from the thalamic CM-Pf complex. The decline in the TAN pause and rebound facilitatory responses that we found after inactivation of the CM-Pf complex likely reflects in part blockade of direct thalamostriatal projections to TANs. The physiological characteristics of TANs closely resemble those of the cholinergic interneurons of the striatum, and anatomical evidence suggests that these are densely innervated by intralaminar thalamic

inputs from the CM-Pf complex (Kawaguchi 1992; Lapper and Bolam 1992; Sidibé and Smith 1999). Neurons in CM and Pf also project to other interneurons in the striatum, however, as well as to medium spiny projection neurons there, especially those of the direct pathway (Fenelon et al. 1991; François et al. 1991; Nakano et al. 1990; Sadikot et al. 1992a,b; Sidibé and Smith 1999; Smith and Parent 1986). The effects of the muscimol injections could thus in part reflect blockade of indirect thalamostriatal projections from CM-Pf neurons to striatal projection neurons or interneurons that in turn project to TANs. We favor this view because of evidence that local intrastriatal blockade of $GABA_A$ transmission in the striatum can abolish the pause response of TANs at the site of the infusion (Watanabe and Kimura 1998).

Indirect thalamo-cortico-striatal connections might also contribute to the decline in TAN responses observed after CM-Pf inactivation, but many more CM-Pf neurons project to the striatum than to the neocortex (Jones 1997; Macchi and Bentivoglio 1986; Sadikot et al. 1992b), and few CM-Pf neurons have branched axonal projections to both striatum and neocortex (Deschenes et al. 1996). It is unlikely, therefore that the nearly complete abolition of TAN responses that we found resulted mainly from inactivation of an indirect thalamo-cortico-striatal pathway. This conclusion is consistent with earlier work in acute preparations demonstrating that the multimodal responses of striatal neurons survive lesions of the neocortex (Albe-Fessard et al. 1960; Rogers and McKenzie 1973). Other possible indirect routes from CM-Pf to the striatum include connections via the subthalamic nucleus (Feger et al. 1994; Sadikot et al. 1992a) and subthalamo-pallido-striatal connections (Sidibé and Smith 1996; Smith et al. 1998).

Learning circuits in the striatum can be modulated by thalamic inputs from the CM-Pf complex

The sensory responsiveness of TANs can be strongly modulated by sensorimotor conditioning (Aosaki et al. 1994b), a process that depends on dopamine-containing nigrostriatal input (Aosaki et al. 1994a; Apicella et al. 1997). The TANs of the striatum thus appear to be part of learning circuits in the basal ganglia (Graybiel et al. 1994). The experiments we report here suggest that these learning circuits are strongly modulated by thalamic inputs from the CM-Pf complex. Most of the CM-Pf neurons we recorded responded to sensory stimuli whether or not they were associated with reward, whereas a majority of the TANs responded to sensory stimuli presented in the same experiment only after the monkeys had learned to associate the stimuli with rewards. We examined reward-dependency in a smaller number of CM-Pf neurons than TANs. The differences in reward-dependency between the CM-Pf neurons and TANs could be significant, however, because the activity of CM-Pf neurons was more influenced by other environmental events, such as unexpected noises, than was that of the TANs recorded under the same environmental conditions. CM-Pf neurons responded consistently to the click of the solenoid valve without reward when the clicks, beeps, and LED flashes appeared at random order, but the responses habituated when the no-reward click appeared repeatedly. CM-Pf neurons showed no sign of habituation to the click followed by reward. The reward may enhance the attentional importance of otherwise habituating stimuli and thus enhance the responsiveness of CM-Pf neurons.

These findings suggest a model in which TAN-based learning circuits in the striatum receive inputs both from the CM-Pf carrying sensory signals with attentional and orienting value and inputs from the substantia nigra pars compacta carrying reward-related information (Schultz 1998). The integration of these extensive inputs in turn may be influenced by, or be controlled by intrinsic GABAergic striatal neurons (Watanabe and Kimura 1998).

The responses of TANs tend to be triphasic, with an early, phasic activation followed by a prolonged decrease in firing rate and then a postpause facilitation. All three of these components show learning-dependent changes during sensorimotor conditioning (Aosaki et al. 1994b, 1995). The inactivation of CM-Pf neurons induced by injection of muscimol sharply decreased the TANs' pause response and subsequent rebound facilitation, but did not abolish the short-latency facilitation of the TANs. The facilitatory responses of the LLF neurons in the thalamus were too late (~220–280 ms) to affect the pause responses of the TANs (~130 ms), but these LLF neurons did have early suppressive responses (~50 ms) that could have affected the pause and rebound phases. The early facilitation of the thalamic SLF neurons (~25–90 ms) clearly could have affected these responses as well, through excitatory thalamostriatal projections (Wilson et al. 1983), but this effect would require a sign reversal, possibly via other striatal neurons acting via $GABA_A$ receptors.

We observed a striking predominance of LLF neurons in the CM, which projects to the putamen, and a relative predominance of SLF neurons in the Pf, which projects to the caudate nucleus (Sadikot et al. 1992a). TAN responses in both striatal nuclei were affected by the CM-Pf inactivation. TAN responses in different striatal regions have overlapping latencies (Aosaki et al. 1995), but as a group, the pause responses of TANs in the caudate nucleus to click stimuli occurred earlier (116.7 ± 40.3, $n = 12$) than did those in the putamen (138.2 ± 35.6, $n = 109$). The CM and Pf nuclei both receive inputs from some regions of the brain stem, including the midbrain reticular formation, the superior colliculus, and the pedunculopontine nucleus. Other inputs to these nuclei, however, are known to differ. The CM receives basal ganglia inputs from the internal pallidum, but the Pf receives inputs from the substantia nigra pars reticulata. Cortical inputs to these thalamic nuclei also are different (Künzle 1977, 1978). These differences could contribute to the latency differences we observed. LLF neurons have consistent suppressive sensory responses that have short latencies compared with those of the facilitatory responses of SLF neurons. Sensory stimuli might drive SLF neurons through excitatory circuits, but drive CM neurons through inhibitory-excitatory circuits in the thalamus.

The short-latency initial facilitatory response of TANs (~70 ms) showed at most only a small decrease during inactivation of the CM-Pf complex. This early response also remains after damage to the dopamine-containing inputs to the striatum, despite almost complete loss of the pause and succeeding facilitation of activity that normally follow (Aosaki et al. 1994a). Thus inactivation of the CM-Pf complex and damage to the dopamine-containing inputs have similar suppresive effects on the activity of TANs in the striatum. One possible source for the short-latency initial facilitatory response is input

from the neocortex. Thomas et al. (2000) have described cortical inputs to the distal dendrites of cholinergic interneurons in the monkey. One of major effects of nigrostriatal dopamine depletion is a neglect of stimuli appearing on the side contralateral to the depletion (Kato et al. 1995; Matsumoto et al. 1999; Miyashita et al. 1995). Blockade of thalamostriatal signals after dopamine depletion in the striatum might be responsible for the loss of attentiveness to contralateral events in both monkey and human. In the thalamus, contralateral visual neglect is observed after thalamic lesions involving the internal medullary lamina (Orem et al. 1973; Watson and Heilman 1979) and impairment of attentional orienting has been observed after lesion of reticular nucleus (Weese et al. 1999). In the present study, lowered attentiveness after inactivation of the CM-Pf complex was suggested by behavioral evidence for reduced licking response to click stimuli associated with forthcoming rewards.

If, as evidence suggests, the TANs are cholinergic interneurons (Aosaki et al. 1995), the TANs could be integrating inputs from at least four sources: the substantia nigra pars compacta, the CM-Pf complex of the thalamus, local neurons of the striatum, and the neocortex.

Thalamo-striatal loop circuits may critically influence action-selection functions of cortico-basal ganglia circuits

The CM and Pf have long been considered as "loop nuclei" of the basal ganglia, because they project to the striatum and receive inputs from the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr) (Graybiel and Ragsdale 1979; Parent and Hazrati 1995a,b). Compared to other basal ganglia loop nuclei, the CM and Pf are unique in having the striatum as their principal output targets. Thus Pf-caudate nucleus-SNr-Pf and CM-putamen-GPi-CM circuits may be true "internal loops" of the basal ganglia, operating in parallel with cortico-basal ganglia loops but having a major point of access to cortico-basal ganglia circuits at the level of the striatum.

Our findings suggest two possible functions for these internal thalamo-striatal loops. One is to supply the striatum with attention-gated multimodal sensory information. Given the low modality specificity and the rapid habituation of the CM-Pf responses, it seems likely that this input could provide the striatum (and cortico-basal ganglia circuits) with information about the appearance, disappearance, or change of attention-demanding, behaviorally significant events. This view expands on earlier observations on activity in the intralaminar thalamus (Kinomura et al. 1996) and evidence that unilateral sensory neglect can result from striatal dysfunction (Denny-Brown and Yanagisawa 1976; Ljungberg and Ungerstedt 1976; Vargo and Marshall 1996). Multiple brain stem inputs to the intralaminar thalamus could contribute to such functional characteristics of CM-Pf neurons. Candidates include inputs from the midbrain reticular formation (McCormick and Bal 1994; Moruzzi and Magoun 1949; Steriade et al. 1993), the deep layers of the superior colliculus (Ichinohe and Shoumura 1998; Royce et al. 1991), the pedunculopontine nucleus (Aizawa et al. 1999; Curro-Dossi et al. 1991; Isaacson and Tanaka 1986), and the locus coeruleus (Royce et al. 1991; Usher et al. 1999).

A second function of thalamo-striatal loops suggested by our findings is a contribution to functions of the basal ganglia related to the selection of forthcoming actions (Boussaoud and Kermadi 1997; Cools 1980; Fukai and Tanaka 1997; Graybiel 1998; Graybiel and Kimura 1995; Hikosaka et al. 1989; Jueptner et al. 1997; Kimura et al. 1993; Mink 1996). The GABAergic projection neurons of the GPi and SNr send strong, tonic suppressive inputs to target neurons in the VA-VL nuclei of the thalamus through their high-frequency discharges, and these GPi and SNr neurons are under the control of the striatum, which sends them direct suppressive inputs and indirect facilitatory inputs via the subthalamic loop. This characteristic opponent-circuit design has suggested the view that the basal ganglia act broadly to inhibit competing behavioral mechanisms that would otherwise interfere with intended actions and, simultaneously, to remove focally inhibition of the desired behavior so as to allow the selected action to proceed (Fukai and Tanaka 1997; Mink 1996). Selections of actions are made on the basis of particular behavioral contexts. An adequate program for action can be selected if a particular behavioral context triggers function in the relevant circuit. Thus a crucial condition for adequate operation of these circuits is the presence of context-dependent signals indicating when and how to activate ensembles of output neurons in the striatum. Information about behaviorally significant sensory events originating in the CM-Pf complex could provide such signals. Striatal TANs, as points of convergence of this information with dopamine-mediated nigrostriatal signals having motivational value, could operate to bias the action-selection functions of cortico-basal ganglia circuits.

This study was supported by research grants from the Ministry of Education Japan (07408035, 08279106, JSPS-RFTF96L00201) and Special Coordination Fund to Brain Science to M. Kimura, by Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Japan (09780770) to N. Matsumoto, and by National Institute of Neurological Disorders and Stroke Javits Award NS-25529 to A. M. Graybiel.

REFERENCES

AIZAWA H, KOBAYASHI Y, YAMAMOTO M, AND ISA T. Injection of nicotine into the superior colliculus facilitates occurrence of express saccades in monkeys. *J Neurophysiol* 82: 1642–1646, 1999.

ALBE-FESSARD D AND BESSON J. Convergent thalamic and cortical projections—the non-specific system. In: *Handbook of Sensory Physiology. Somatosensory System*, edited by Iggo A. New York: Springer Verlag, 1973, vol. 2, p. 489–560.

ALBE-FESSARD D, OSWALDO E, AND ROCHA-MIRANDA C. Activités évoquées dans le noyau caudé du chat en réponse à des types divers d'afférences. I. Étude macrophysiologique. *Electroencephalogr Clin Neurophysiol* 12: 405–420, 1960.

ALEXANDER GE AND DELONG MR. Microstimulation of the primate neostriatum. I. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. *J Neurophysiol* 53: 1417–1430, 1985.

AOSAKI T, GRAYBIEL AM, AND KIMURA M. Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys. *Science* 265: 412–415, 1994a.

AOSAKI T, KIMURA M, AND GRAYBIEL AM. Temporal and spatial characteristics of tonically active neurons of the primate's striatum. *J Neurophysiol* 73: 1234–1252, 1995.

AOSAKI T, TSUBOKAWA H, ISHIDA A, WATANABE K, GRAYBIEL AM, AND KIMURA M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensory-motor conditioning. *J Neurosci* 14: 3969–3984, 1994b.

APICELLA P, LEGALLET E, AND TROUCHE E. Responses of tonically discharging neurons in the monkey striatum to primary rewards delivered during different behavioral states. *Exp Brain Res* 116: 456–466, 1997.

APICELLA P, SCARNATI E, AND SCHULTZ W. Tonically discharging neurons of monkey striatum respond to preparatory and rewarding stimuli. *Exp Brain Res* 85: 388–392, 1991.

BOUSSAOUD D AND KERMADI I. The primate striatum: neuronal activity in relation to spatial attention versus motor preparation. *Eur J Neurosci* 9: 2152–2168, 1997.

BUFORD JA, INASE M, AND ANDERSON ME. Contrasting locations of pallidal-receiving neurons and microexcitable zones in primate thalamus. *J Neurophysiol* 75: 1105–1116, 1996.

COOLS AR. Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: facilitation of processes involved in selecting the best strategy in a stressful situation. *Behav Brain Res* 1: 361–378, 1980.

CURRO DOSSI PARE D AND STERIADE M. Short-lasting nicotinic and long-lasting muscarinic depolarizing responses of thalamocortical neurons to stimulation of mesopontine cholinergic nuclei. *J Neurophysiol* 65: 393–406, 1991.

DENNY-BROWN D AND YANAGISAWA N. The role of the basal ganglia in the initiation of movement. In: *The Basal Ganglia*, edited by Yahr MD. New York: Raven, 1976, p. 115–149.

DESCHENES M, BOURASSA J, AND PARENT A. Striatal and cortical projections of single neurons from the central lateral thalamic nucleus in the rat. *Neuroscience* 72: 679–687, 1996.

FEGER J, BEVAN M, AND CROSSMAN AR. The projections from the parafascicular thalamic nucleus to the subthalamic nucleus and the striatum arise from separate neuronal populations: a comparison with the corticostriatal and corticosubthalamic efferents in a retrograde fluorescent double-labeling study. *Neuroscience* 60: 125–132, 1994.

FENELON G, FRANÇOIS C, PERCHERON G, AND YELNICK J. Topographic distribution of the neurons of the central complex (centremédian-parafascicular complex) and of other thalamic neurons projecting to the striatum in macaques. *Neuroscience* 45: 495–510, 1991.

FLAHERTY AW AND GRAYBIEL AM. Output architecture of the primate putamen. *J Neurosci* 13: 3222–3237, 1993.

FRANÇOIS C, PERCHERON G, PARENT A, SADIKOT AF, FENELON G, AND YELNICK J. Topography of the projection from the central complex of the thalamus to the sensorimotor striatal territory in monkeys. *J Comp Neurol* 305: 17–34, 1991.

FUKAI T AND TANAKA S. A simple neural network exhibiting selective activation of neuronal ensembles: from winner-take-all to winner-share-all. *Neural Comput* 9: 77–97, 1997.

GRAYBIEL AM. The basal ganglia and chunking of action repertoires. *Neurobiol Learn Mem* 70: 119–136, 1998.

GRAYBIEL AM, AOSAKI T, FLAHERTY A, AND KIMURA M. The basal ganglia and adaptive motor control. *Science* 265: 1826–1831, 1994.

GRAYBIEL AM AND BERSON DM. Histochemical identification and afferent connections of subdivisions in the lateralis posterior-pulvinar complex and related thalamic nuclei in the cat. *Neuroscience* 5: 1175–1238, 1980.

GRAYBIEL AM AND KIMURA M. Adaptive neural networks in the basal ganglia. In: *Models of Information Processing in the Basal Ganglia*, edited by Houk JC, Davis JL, and Beiser DG. Cambridge, MA: MIT Press, 1995, p. 103–116.

GRAYBIEL AM AND RAGSDALE CW JR. Fiber connections of the basal ganglia. In: *Development and Chemical Specificity of Neurons*, edited by Cuénod M, Kreutzberg GW, and Bloom FE. Amsterdam: Elsevier/North-Holland Biomedical, 1979, vol. 51, p. 239–283.

GRUNWERG BS AND KRAUTHAMER GM. Sensory responses of intralaminar thalamic neurons activated by the superior colliculus. *Exp Brain Res* 88: 541–550, 1992.

HARDY H, HEIMER L, SWITZER R, AND WATKINS D. Simultaneous demonstration of horseradish peroxidase and acetylcholinesterase. *Neurosci Lett* 3: 1–5, 1976.

HIKOSAKA O, SAKAMOTO M, AND USUI S. Functional properties of monkey caudate neurons. II. Visual and auditory responses. *J Neurophysiol* 61: 799–813, 1989.

HU B, STERIADE M, AND DESCHÉNES M. The effects of brainstem peribrachial stimulation on perigeniculate neurons: the blockage of spindle waves. *Neuroscience* 31: 1–12, 1989.

ICHINOHE N AND SHOUMURA K. A di-synaptic projection from the superior colliculus to the head of the caudate nucleus via the centromedian-parafascicular complex in the cat: an anterograde and retrograde labeling study. *Neurosci Res* 32: 295–303, 1998.

IRVINE DR. Acoustic properties of neurons in posteromedial thalamus of cat. *J Neurophysiol* 43: 395–408, 1980.

ISAACSON LG AND TANAKA D. Cholinergic and non-cholinergic projections from the canine pontomesencephalic tegmentum (Ch5 area) to the caudal intralaminar thalamic nuclei. *Exp Brain Res* 62: 179–188, 1986.

JASPER HH. Unspecific thalamocortical relations. In: *Handbook of Physiology. Neurophysiology*. Washington, DC: Am. Physiol. Soc., 1960, vol. 2, p. 1307–1321.

JONES EG. Thalamic organization and chemical anatomy. In: *Thalamus. Organization and Function*, edited by Steriade M, Jones EG, and McCormick CD. Amsterdam: Elsevier, 1997, vol. I, p. 31–174.

JUEPTNER M, FRITH CD, BROOKS DJ, FRACKOWIAK RS, AND PASSINGHAM RE. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. *J Neurophysiol* 77: 1325–1337, 1997.

KATO M, MIYASHITA N, HIKOSAKA O, MATSUMURA M, USUI S, AND KORI A. Eye movements in monkeys with local dopamine depletion in the caudate nucleus. I. Deficits in spontaneous saccades. *J Neurosci* 15: 912–927, 1995.

KAWAGUCHI Y. Large aspiny cells in the matrix of the rat neostriatum in vitro: physiological identification, relation to the compartments and excitatory postsynaptic currents. *J Neurophysiol* 67: 1669–1682, 1992.

KIMURA M. The role of primate putamen neurons in the association of sensory stimulus with movement. *Neurosci Res* 3: 436–443, 1986.

KIMURA M, AOSAKI T, AND ISHIDA A. Neurophysiological aspects of differential roles of the putamen and caudate nucleus in voluntary movement. *Adv Neurol* 60: 62–70, 1993.

KIMURA M, KATO M, AND SHIMAZAKI H. Physiological properties of projection neurons in the monkey striatum to the globus pallidus. *Exp Brain Res* 82: 672–676, 1990.

KIMURA M, RAJKOWSKI J, AND EVARTS EV. Tonically discharging putamen neurons exhibit set dependent responses. *Proc Natl Acad Sci USA* 81: 4998–5001, 1984.

KINOMURA S, LARSSON J, GULYÁS B, AND ROLAND PE. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science* 271: 512–515, 1996.

KÜNZLE H. Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. *Exp Brain Res* 30: 481–492, 1977.

KÜNZLE H. An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in *Macaca fascicularis. Brain Behav Evol* 15: 185–234, 1978.

LAPPER S AND BOLAM JP. Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. *Neuroscience* 51: 533–545, 1992.

LJUNGBERG T AND UNGERSTEDT U. Sensory inattention produced by 6-hydroxydopamine–induced degeneration of ascending dopamine neurons in the brain. *Exp Neurol* 53: 585–600, 1976.

MACCHI G AND BENTIVOGLIO M. The thalamic intralaminar nuclei and the cerebral cortex. In: *Cerebral Cortex*, edited by Jones E and Peters A. New York: Plenum, 1986, vol. 5, p. 355–401.

MATSUMOTO N, HANAKAWA T, MAKI S, GRAYBIEL AM, AND KIMURA M. Role of nigrostriatal dopamine system in learning to perform sequential motor tasks in a predictive manner. *J Neurophysiol* 82: 978–998, 1999.

MCCORMICK D AND BAL T. Sensory gating mechanisms of the thalamus. *Curr Opin Neurobiol* 4: 550–556, 1994.

MCFARLAND NR AND HABER SN. Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate. *J Neurosci* 20: 3798–3813, 2000.

MENNEMEIER M, CROSSON B, WILLIAMSON D, NADEAU S, FENNELL E, VALENSTEIN E, AND HEILMAN K. Tapping, talking and the thalamus: possible influence of the intralaminar nuclei on basal ganglia function. *Neuropsychologia* 35: 183–193, 1997.

MINK JN. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 50: 381–425, 1996.

MIYASHITA N, HIKOSAKA O, AND KATO M. Visual hemineglect induced by unilateral striatal dopamine deficiency in monkeys. *Neuroreport* 6: 1257–1260, 1995.

MORUZZI G AND MAGOUN HW. Brain stem reticular formation and the activation of EEG. *Electroencephalogr Clin Neurophysiol* 1: 455–473, 1949.

NAKANO K, HASEGAWA Y, TOKUSHIGE A, NAKAGAWA S, KAYAHARA T, AND MIZUNO N. Topographical projections from the thalamus, the subthalamic nucleus and pedunculopontine tegmental nucleus to the striatum in the Japanese monkey *Macaca fuscata*. *Brain Res* 537: 54–68, 1990.

OLSZEWSKI J. *The Thalamus of Macaca mulatta: An Atlas for Use With the Stereotaxic Instrument*. Basel: Karger, 1952.

OREM J, SCHLAG-REY M, AND SCHLAG J. Unilateral visual neglect and thalamic intralaminar lesions in the cat. *Exp Neurol* 40: 784–797, 1973.

PARÉ D, SMITH Y, PARENT A, AND STERIADE M. Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience* 25: 69–86, 1988.

PARENT A AND HAZRATI LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Rev* 20: 91–127, 1995a.

PARENT A AND HAZRATI LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Rev* 20: 128–154, 1995b.

PASHLER HH. *The Psychology of Attention.* Cambridge, MIT Press, 1998, p. 88–250.

RAZ A, FEINGOLD A, ZELANSKAYA V, VAADIA E, AND BERGMAN H. Neuronal synchronization of tonically active neurons in the striatum of normal and parkinsonian primates. *J Neurophysiol* 76: 2083–2088, 1996.

ROGERS DK AND MCKENZIE JS. Regional differences within the caudate nucleus for suppression of extraleminiscal thalamic units. *Brain Res* 56: 345–349, 1973.

ROHRBAUGH JW. The orienting reflex. In: *Varieties of Attention,* edited by Parasuraman R and Davies DR. New York: Academic, 1984, p. 323–373.

ROYCE GJ, BROMLEY S, AND GRACCO C. Subcortical projections to the centromedian and parafascicular thalamic nuclei in the cat. *J Comp Neurol* 306: 129–155, 1991.

SADIKOT AF, PARENT A, AND FRANÇOIS C. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: A PHA-L study of subcortical projections. *J Comp Neurol* 315: 137–159, 1992a.

SADIKOT AF, PARENT A, SMITH Y, AND BOLAM JP. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. *J Comp Neurol* 320: 228–242, 1992b.

SCHLAG J AND SCHLAG-REY M. Visuomotor functions of central thalamus in monkey II. Unit activity related to visual events, targeting, and fixation. *J Neurophysiol* 51: 1175–1196, 1984.

SCHULTZ W. Predictive reward signal of dopamine neurons. *J Neurophysiol* 80: 1–27, 1998.

SIDIBÉ M AND SMITH Y. Differential synaptic innervation of striatofugal neurons projecting to the internal or external segments of the globus pallidus by thalamic afferents in the squirrel monkey. *J Comp Neurol* 365: 445–465, 1996.

SIDIBÉ M AND SMITH Y. Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins. *Neuroscience* 89: 1189–1208, 1999.

SMITH Y, BEVAN M, SHINK E, AND BOLAM JP. Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* 86: 353–387, 1998.

SMITH Y AND PARENT A. Differential connections of the caudate nucleus and putamen in the squirrel monkey (*Saimiri sciureus*). *Neuroscience* 18: 347–371, 1986.

STERIADE M, CONTRERAS D, AND AMZICA F. Synchronized sleep oscillations and their paroxysmal developments. *Trends Neurosci* 17: 199–208, 1994.

STERIADE M, JONES EG, AND MCCORMICK CD. *Thalamus. Intralaminar nuclei.* Amsterdam: Elsevier, 1997, vol. 1, p. 55–73.

STERIADE M, MCCORMICK DA, AND SEJNOWSKI TJ. Thalamocortical oscillations in the sleeping and aroused brain. *Science* 262: 679–685, 1993.

THOMAS TM, SMITH Y, LEVEY AI, AND HERSCH SM. Cortical inputs to M2-immunoreactive striatal interneurons in rat and monkey. *Synapse* 37: 252–261, 2000.

USHER M, COHEN JD, SERVAN SCHREIBER D, RAJKOWSKI J, AND ASTON JONES G. The role of locus coeruleus in the regulation of cognitive performance. *Science* 283: 549–554, 1999.

VARGO JM AND MARSHALL JF. Frontal cortex ablation reversibly decreases striatal zif/268 and junB expression: temporal correspondence with sensory neglect and its spontaneous recovery. *Synapse* 22: 291–303, 1996.

VITEK JL, ASHE J, DELONG MR, AND KANEOKE Y. Microstimulation of primate motor thalamus: somatotopic organization and differential distribution of evoked motor responses among subnuclei. *J Neurophysiol* 75: 2486–2495, 1996.

WATANABE K AND KIMURA M. Dopamine receptor-mediated mechanisms involved in the expression of learned activity of primate striatal neurons. *J Neurophysiol* 79: 2568–2580, 1998.

WATSON RT AND HEILMAN KM. Thalamic neglect. *Neurology* 29: 690–694, 1979.

WEESE GD, PHILLIPS JM, AND BROWN VJ. Attentional orienting is impaired by unilateral lesions of the thalamic reticular nucleus in the rat. *J Neurosci* 19: 10135–10139, 1999.

WILSON CJ, CHANG HT, AND KITAI ST. Origins of post synaptic potentials evoked in spiny neostriatal projection neurons by thalamic stimulation in the rat. *Exp Brain Res* 51: 217–226, 1983.

WILSON CJ, CHANG HT, AND KITAI ST. Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. *J Neurosci* 10: 508–519, 1990.