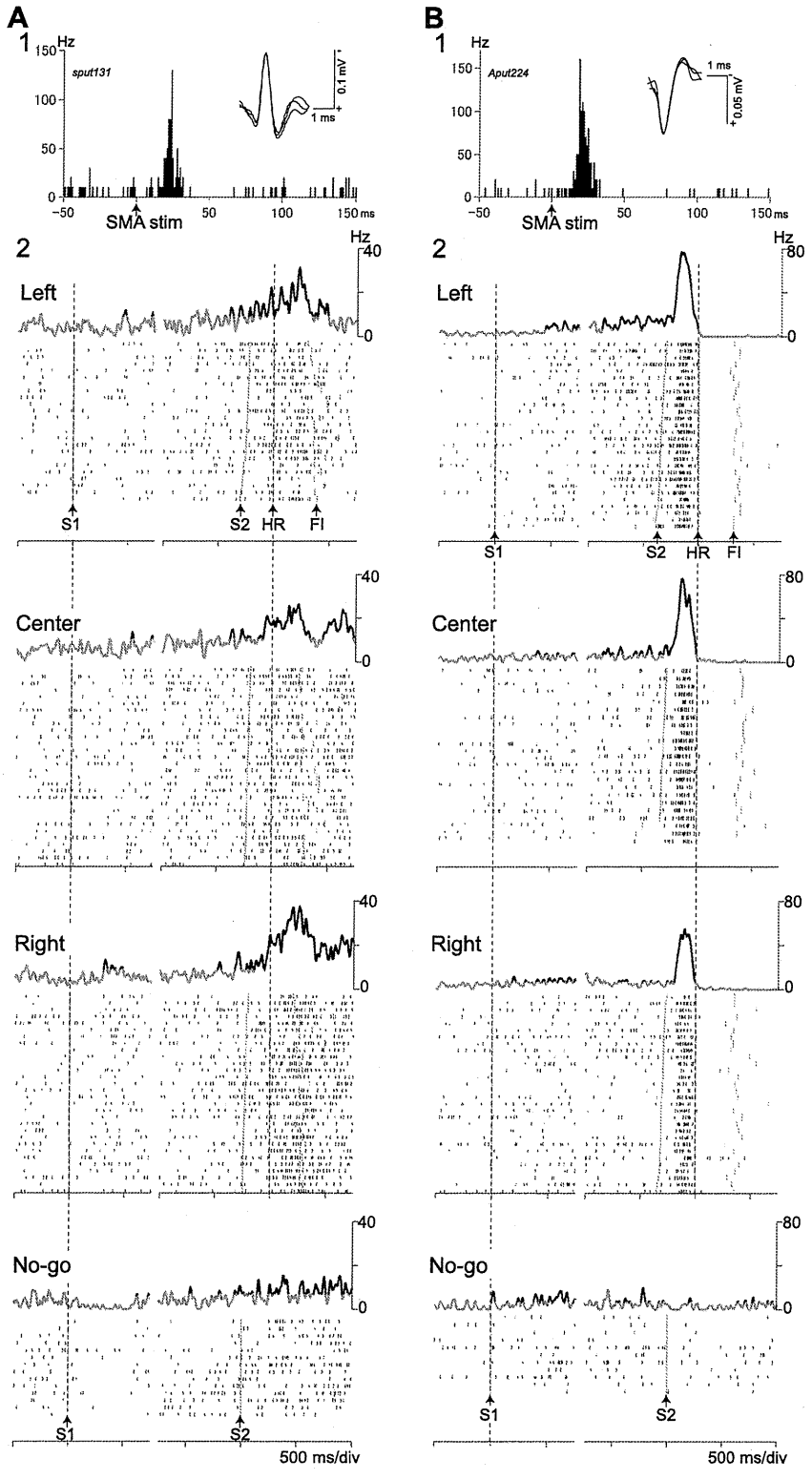

Fig. 5. Two examples (*A* and *B*) of SMA-recipient putaminal neurons. *A1* and *B1*: PSTHs showing responses to SMA stimulation (0.6 mA). *A2* and *B2*: raster display showing the neuronal firing during task performance.

example of SMA-recipient putaminal neurons. This neuron responded to SMA stimulation at a latency of 10 ms (Fig. 5*B1*), whereas stimulation of other cortical areas did not. This neuron exhibited a delay-related activity (directional selectivity, 0.22) and a large movement-related activity increase preceding the HR by 252 ms (Fig. 5*B2*). Directional selectivity of the HR-related activity was 0.38. This neuron was activated by passive shoulder movements.

Figure 6*A* shows a typical example of $MI_{proximal}$ + SMA-recipient putaminal neurons. This neuron received

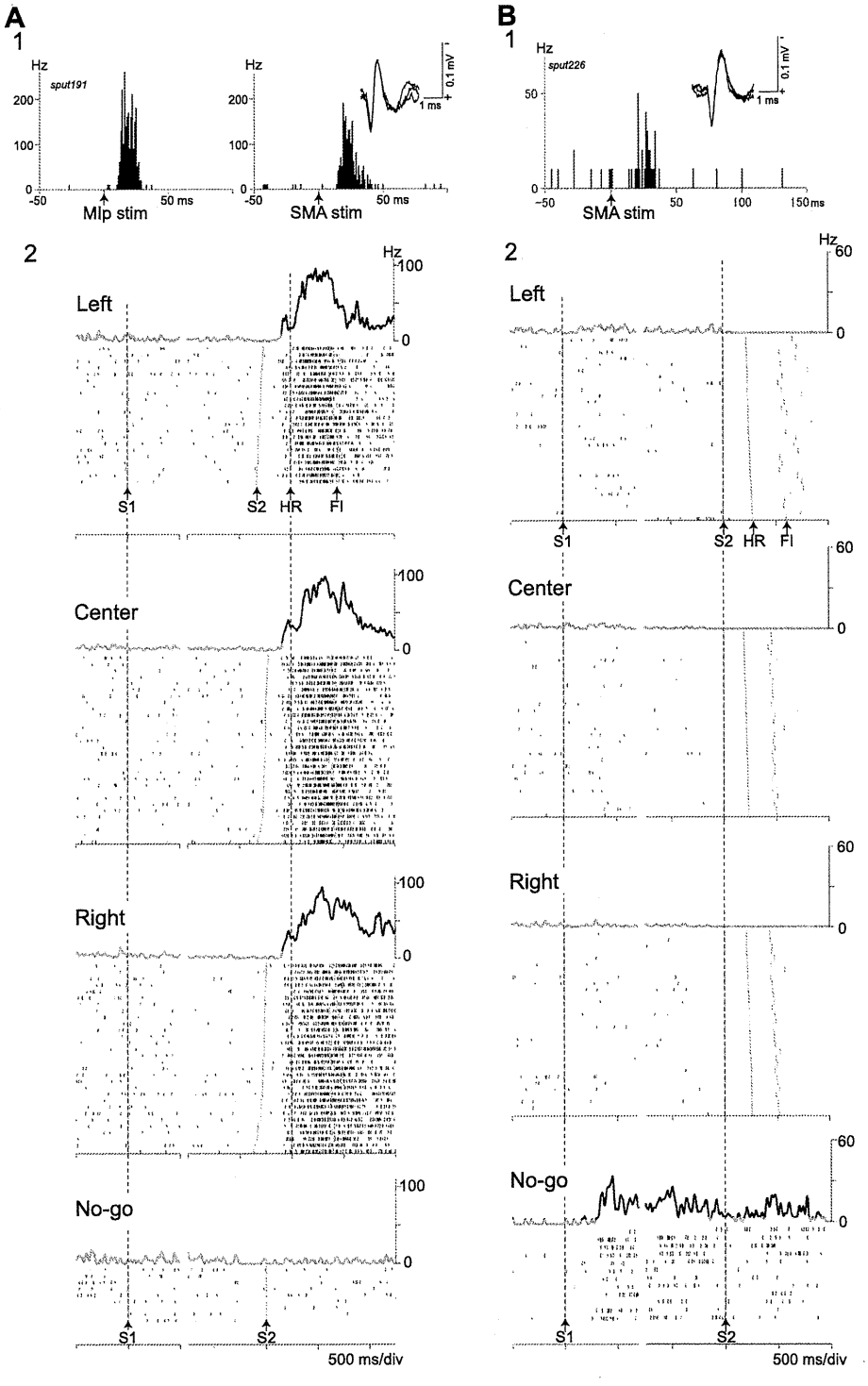

Fig. 6. *A*: typical example of $MI_{proximal}$ + SMA-recipient putaminal neurons. *A1*: PSTHs showing responses to $MI_{proximal}$ stimulation (0.6 mA, *left*) and SMA stimulation (0.5 mA, *right*). *A2*: raster display showing the neuronal firing during task performance. *B*: No-go-specific activity. *B1*: PSTHs showing responses to SMA stimulation (0.6 mA). *B2*: raster display showing the neuronal firing during task performance.

convergent cortical inputs from the $MI_{proximal}$ and SMA. $MI_{proximal}$ and SMA stimulation evoked excitatory responses at latencies of 9 ms and 14 ms, respectively (Fig. 6*A1*), whereas MI_{distal} stimulation did not. This neuron increased activity in relation to arm-reach movements, preceding the HR by 106 ms (Fig. 6*A2*). The amplitude of excitation was comparable among the three target conditions. Directional selectivity of the HR-related activity was 0.15. No activity was observed in No-go trials. This neuron was activated by extension and abduction of the shoulder.

Among 447 putaminal neurons recorded, most neurons (412/447, 92.2%) exhibited activity increases in Go trials and almost no activity in No-go trials. Twenty-two neurons (4.9%) showed no significant activity changes in either Go or No-go trials. Six neurons (1.3%) showed a comparable activity increase in both Go and No-go trials and were classified as MI + SMA-

Table 2. *Activity patterns of putaminal neurons during task performance*

Cortical inputs	Delay-related	Movement-related	Total
MI	39 (16)*	213 (87)†,‡	246
$MI_{proximal}$	23 (20)	107 (92)	116
MI_{distal}	11 (17)	55 (83)	66
$MI_{proximal + distal}$	5 (8)	51 (80)	64
SMA	35 (32)*	78 (71)†	110
MI + SMA	21 (23)	65 (71)‡	91
$MI_{proximal}$ + SMA	13 (28)	32 (70)	46
MI_{distal} + SMA	5 (18)	21 (75)	28
$MI_{proximal + distal}$ + SMA	3 (18)	12 (71)	17
Total	95 (21)	356 (80)	447

Numbers of putaminal neurons showing delay-related and/or movement-related activity are shown according to cortical inputs. Figures in parentheses indicate the percentage to each category of neurons. *,†,‡Significantly different from each other (χ^2 test with Bonferroni correction; $P < 0.05$). Note that some neurons showed both delay- and movement-related activity.

recipient neurons. Seven neurons (1.6%) showed an activity increase in No-go trials and no activity in Go trials (No-go-specific activity), as exemplified in Fig. 6*B*, and were classified as SMA-recipient neurons. SMA stimulation evoked excitatory responses at a latency of 20 ms (Fig. 6*B1*). This neuron increased activity at 395 ms after the S1, maintained activity, and decreased activity before the Reward in No-go trials (Fig. 6*B2*), whereas no activity in Go trials. This neuron was not activated either by passive body movements or by visual stimuli.

Putaminal neurons with different cortical inputs showed different activity patterns during task performance (Table 2). The activity patterns of MI-recipient neurons are significantly different from those of SMA- and MI + SMA-recipient neurons (χ^2 test with Bonferroni correction, $P < 0.05$). Most of MI-recipient neurons (87%) showed movement-related activity, whereas some neurons (16%) showed delay-related activity. More SMA-recipient neurons (32%) showed delay-related activity than MI-recipient neurons, and fewer ones (71%) showed movement-related activity. MI + SMA-recipient neurons showed activity patterns intermediate between MI- and SMA-recipient neurons. The ratio of MI + SMA-recipient neurons showing delay-related activity was smaller than that of SMA-recipient neurons, and the ratio of MI + SMA-recipient neurons showing movement-related activity was smaller than that of MI-recipient neurons.

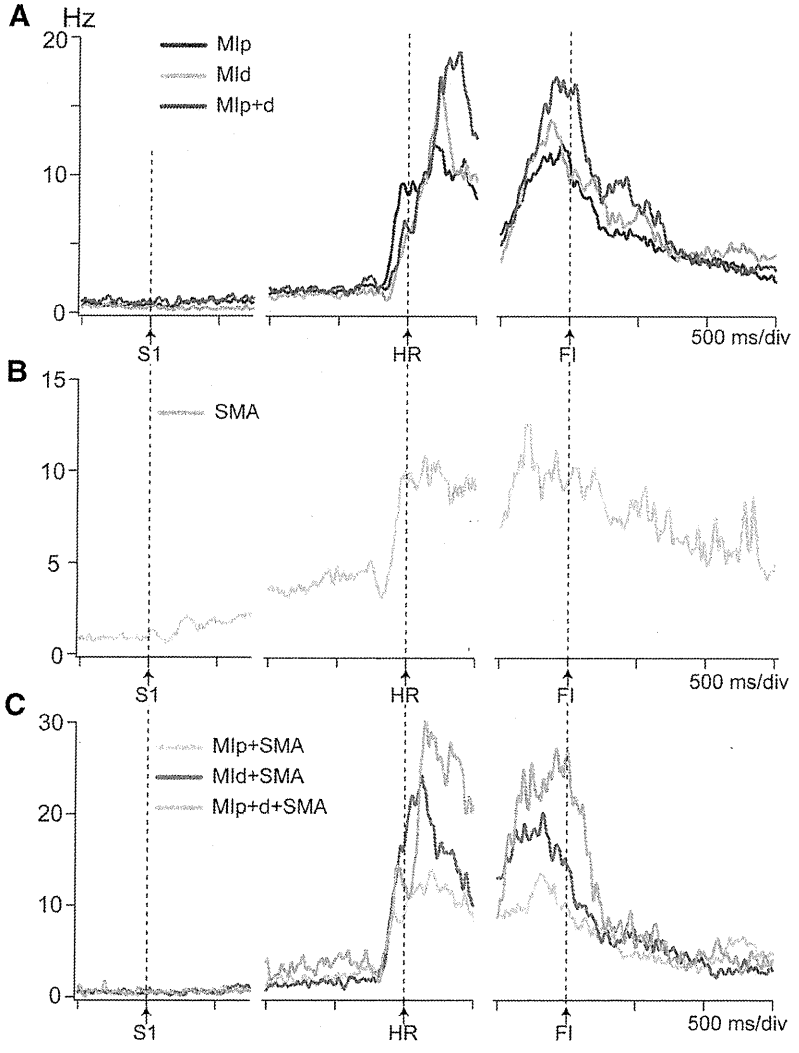

Fig. 7. Population activity of putaminal neurons during task performance. *A*: population activity of $MI_{proximal}$-, MI_{distal}-, and $MI_{proximal + distal}$-recipient putaminal neurons (shown in different colors) aligned with the S1 (*left*), HR (*middle*), and FI (*right*). *B*: population activity of SMA-recipient putaminal neurons. *C*: population activity of $MI_{proximal}$ + SMA-, MI_{distal} + SMA-, and $MI_{proximal + distal}$ + SMA-recipient putaminal neurons (shown in different colors).

Characteristics of putaminal neuronal activity during task performance were also observed in population activity (Fig. 7). MI-recipient neurons showed very little changes during the delay period (Fig. 7*A*). The firing rate increased abruptly before the HR, preceding the HR by 154 ms in $MI_{proximal}$-recipient neurons, by 119 ms in MI_{distal}-recipient neurons and by 123 ms in $MI_{proximal\ +\ distal}$-recipient neurons. Activity increase reached its peak before the FI. SMA-recipient neurons showed a gradual activity increase during the delay period, beginning 197 ms after the S1 (Fig. 7*B*). They showed additional activity increase in relation to arm-reach movements, preceding the HR by 303 ms. MI + SMA-recipient neurons also showed a gradual activity increase during the delay period (Fig. 7*C*). They showed additional activity increase in relation to arm-reach movements, preceding the HR by 134–138 ms ($MI_{proximal}$ + SMA-, 135 ms; MI_{distal} + SMA-, 138 ms; $MI_{proximal\ +\ distal}$ +SMA-, 134 ms).

Timing of activity changes of putaminal neurons. The onset timing of movement-related activity changes in relation to the HR was shown in cumulative distributions (Fig. 8). Very early activity changes that preceded the HR by more than 400 ms in SMA-recipient neurons were considered to reflect activity during the delay period. Approximately one-half of $MI_{proximal}$ (47%)-, SMA (49%)-, $MI_{proximal}$ + SMA (57%)-, M_{distal} + SMA (44%)-, and $MI_{proximal\ +\ distal}$ + SMA (54%)-recipient neurons changed activities before the HR, whereas a smaller number of MI_{distal} (28%)- and $MI_{proximal\ +\ distal}$ (40%)-recipient neurons did. The earliest EMG changes began 170 ms before the HR (Fig. 3). In some of $MI_{proximal}$ (9%)-, MI_{distal} (7%)-, $MI_{proximal\ +\ distal}$ (9%)-, SMA (21%)-, $MI_{proximal}$ + SMA (17%)-, MI_{distal} + SMA (5%)-, and $MI_{proximal\ +\ distal}$ + SMA (15%)-recipient neurons, their activity changes preceded the earliest EMG changes.

The onset latencies of delay-related activity after the S1 were comparable among MI (502 ± 47 ms)-, SMA (469 ± 47 ms)-, and MI + SMA (471 ± 96 ms)-recipient neurons.

Direction selectivity. The amplitude of activity during task performance was modulated by the target direction. Directional selectivity of delay-, HR-, and FI-related activity was calculated in each neuron group (Table 3 and Fig. 9). Concerning HR-related activity, MI-recipient putaminal neurons showed significantly higher directional selectivity than SMA- and MI + SMA-recipient neurons (Bonferroni/Dunn post hoc tests; $P < 0.05$). Among them, $MI_{proximal}$-recipient putaminal neurons showed the highest directional selectivity. One-third of $MI_{proximal}$-recipient neurons (32%) had directional selectivity ≥0.5, whereas a smaller number of other neuron groups did (Fig. 9). Concerning FI-related activity, MI-recipient putaminal neurons showed significantly higher directional selectivity than MI + SMA-recipient neurons ($P < 0.05$). Directional selectivity of delay-related activity was comparable among MI-, SMA-, and MI + SMA-recipient putaminal neurons.

Locations of recorded putaminal neurons. The locations of putaminal neurons recorded were plotted in frontal sections (Fig. 10). The neurons that responded to stimulation of the forelimb regions of the MI and/or SMA were distributed in a band extending from the ventrolateral to dorsomedial part in the caudal aspect of the putamen. Within this band, MI-recipient neurons were located mainly in the ventral part, whereas SMA-recipient neurons were found in the dorsal part. MI + SMA-recipient neurons were located in between. In

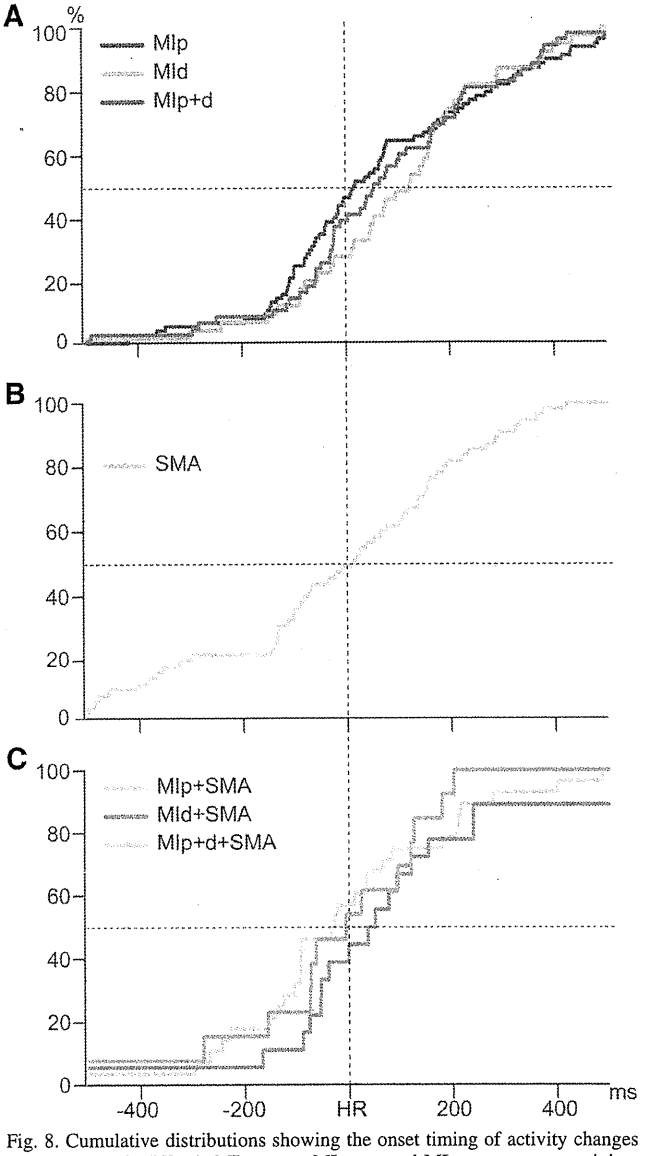

Fig. 8. Cumulative distributions showing the onset timing of activity changes in relation to the HR. *A*: $MI_{proximal}$-, MI_{distal}-, and $MI_{proximal\ +\ distal}$-recipient putaminal neurons (shown in different colors). *B*: SMA-recipient putaminal neurons. *C*: $MI_{proximal}$ + SMA-, MI_{distal} + SMA-, and $MI_{proximal\ +\ distal}$ + SMA-recipient putaminal neurons (shown in different colors).

MI-recipient neurons, MI_{distal}- and $MI_{proximal\ +\ distal}$-recipient neurons were situated predominantly in the ventral-most part. MI- and SMA-recipient neurons showed different activity patterns during task performance (Table 2). Thus neurons in the ventrolateral part of the putamen receive inputs from the MI and show movement-related activity, whereas neurons in the dorsomedial part receive inputs from the SMA and show both movement- and delay-related activity.

The neurons that did not show task-related activity were distributed randomly in the MI- and SMA-recipient band (Fig. 10). The neurons that did not respond to the MI and SMA stimulation were distributed dorsolaterally or ventromedially to the band. Putaminal neurons situated dorsally to the MI-recipient zone often responded to manipulation of the hip joint, and microstimulation in this area evoked movements of the hip

Table 3. *Directional selectivity of putaminal neurons*

Cortical inputs	Directional selectivity (mean ± SD)		
	Delay-related	HR-related	FI-related
MI	0.27 ± 0.18	0.39 ± 0.21*,†	0.37 ± 0.20‡
$MI_{proximal}$	0.23 ± 0.14	0.41 ± 0.23	0.39 ± 0.20
MI_{distal}	0.34 ± 0.25	0.33 ± 0.18	0.33 ± 0.20
$MI_{proximal + distal}$	0.29 ± 0.15	0.37 ± 0.17	0.38 ± 0.20
SMA	0.31 ± 0.19	0.33 ± 0.19*	0.35 ± 0.19
MI + SMA	0.22 ± 0.12	0.31 ± 0.19†	0.29 ± 0.17‡
$MI_{proximal}$ + SMA	0.18 ± 0.09	0.31 ± 0.19	0.32 ± 0.18
MI_{distal} + SMA	0.36 ± 0.12	0.38 ± 0.17	0.29 ± 0.15
$MI_{proximal + distal}$ + SMA	0.16 ± 0.06	0.17 ± 0.11	0.18 ± 0.11

Directional selectivity of Delay-related, Hand Release (HR)-related, and Finger In (FI)-related activity is shown according to cortical inputs. *,†,‡Significantly different from each other (Bonferroni/Dunn post hoc tests; $P < 0.05$).

joint. In contrast, putaminal neurons situated ventrally to the MI-recipient zone responded to manipulation of the orofacial region, and microstimulation in this area evoked orofacial movements. Neurons in the orofacial areas of the putamen increased activity in relation to orofacial movements, such as licking juice at reward periods.

DISCUSSION

The present study revealed the following results. *1*) Putaminal neurons with inputs from different cortical areas showed distinct activity patterns during the performance of a goal-directed reaching task with delay. *2*) MI-recipient neurons increased activity in response to arm-reach movements, whereas SMA-recipient neurons increased activity during delay periods as well as during movements. The activity pattern of MI + SMA-recipient neurons was of an intermediate type between those of MI- and SMA-recipient neurons. *3*) Approximately one-half of $MI_{proximal}$-, SMA-, and MI + SMA-recipient neurons changed activities before the onset of movements, whereas a smaller number of MI_{distal}- and $MI_{proximal + distal}$-recipient neurons did. *4*) MI-recipient neurons showed higher directional selectivity during arm-reach movements than SMA- and MI + SMA-recipient neurons. *5*) MI-recipient neurons were located mainly in the ventrolateral part of the caudal aspect of the putamen, whereas SMA-recipient neurons were located in the dorsomedial part. MI + SMA-recipient neurons were found in between.

Methodological considerations. Electrophysiological recording at the distance of 2.5 mm from the electrode implantation sites showed no excitation of cortical neurons after stimulation (up to 0.7 mA) in our previous work (Nambu et al. 2002). Therefore, the extent of the current spread from stimulating electrodes implanted in the cortex was estimated to be <2.5 mm. $MI_{proximal}$ and MI_{distal} electrode implantation sites were 2.5–3.2 mm apart (Fig. 1*B*), and stimulation in the $MI_{proximal}$ and MI_{distal} evoked movements in the proximal and distal forelimb regions, respectively, in the present study. Thus stimulation in the $MI_{proximal}$, MI_{distal}, and SMA is considered to have excited each cortical area specifically.

The orthodromic responses evoked by cortical stimulation in the present study are considered to be mediated by direct corticostriatal projections as discussed below. The excitatory responses followed well the double-cortical stimulation with short intervals (20–50 ms), suggesting that they are monosynaptic responses. The distribution of the orthodromically activated putaminal neurons corresponds well to that of $MI_{proximal}$-, MI_{distal}-, and SMA-derived corticostriatal terminals reported previously (Künzle 1975; Liles and Updyke 1985; Takada et al. 1998a, b; Tokuno et al. 1999). The latency of MI-evoked orthodromic responses of putaminal neurons in this study was within the same range as that of corticostriatal-evoked responses in the monkey (Liles 1975; Nambu et al. 2002) and putamen-evoked antidromic activation of MI neurons (Bauswein et al. 1989; Turner and DeLong 2000).

MI + SMA-recipient putaminal neurons in the present study are considered to receive converging inputs directly from the MI and SMA. It might be argued that excitatory responses in MI + SMA-recipient putaminal neurons evoked by SMA stimulation could be mediated by the SMA-MI and MI-putamen projection but not by the direct SMA-putamen projection. If this were the case, the neurons in the center of the MI-recipient putaminal zone might also be expected to respond to SMA stimulation. However, the MI + SMA-recipient putaminal neurons were located only in the intermediate zone between the laterally situated MI-recipient and medially situated SMA-recipient zones (Fig. 10), corresponding well to the distribution patterns of corticostriatal terminals from these cortical areas (Takada et al. 1998a, b). The fact that the latency of MI + SMA-recipient putaminal neurons to SMA stimulation was similar to that of SMA-recipient putaminal neurons to SMA stimulation (Fig. 3) also supports the argument that SMA stimulation does not activate MI + SMA-recipient putaminal neurons indirectly.

Another issue is whether MI and SMA stimulation can excite entire forelimb regions of the MI and SMA, respectively. Two pairs of bipolar-stimulating electrodes in the MI cover large areas of the forelimb region of the MI (Fig. 1*B*). A pair of bipolar-stimulating electrodes in the SMA covers most of the forelimb region of the SMA. MI- and SMA-recipient zones studied by orthodromic responses evoked by cortical stimulation correspond well to the zones examined by somatosensory inputs, movements evoked by intrastriatal microstimulation (Nambu et al. 2002), and corticostriatal terminals (Takada et al. 1998a, b). Outside of the MI- and SMA-recipient zones, putaminal neurons responded to manipulation of the hip joint or the oral region. These results suggest that cortical stimulation successfully covers the forelimb regions of the MI and SMA.

Information processing through the corticostriatal projections. On the basis of previous anatomical (Takada et al. 1998a, b; Tokuno et al. 1999) and electrophysiological (Nambu et al. 2002) studies, the forelimb region of the MI projects mainly to

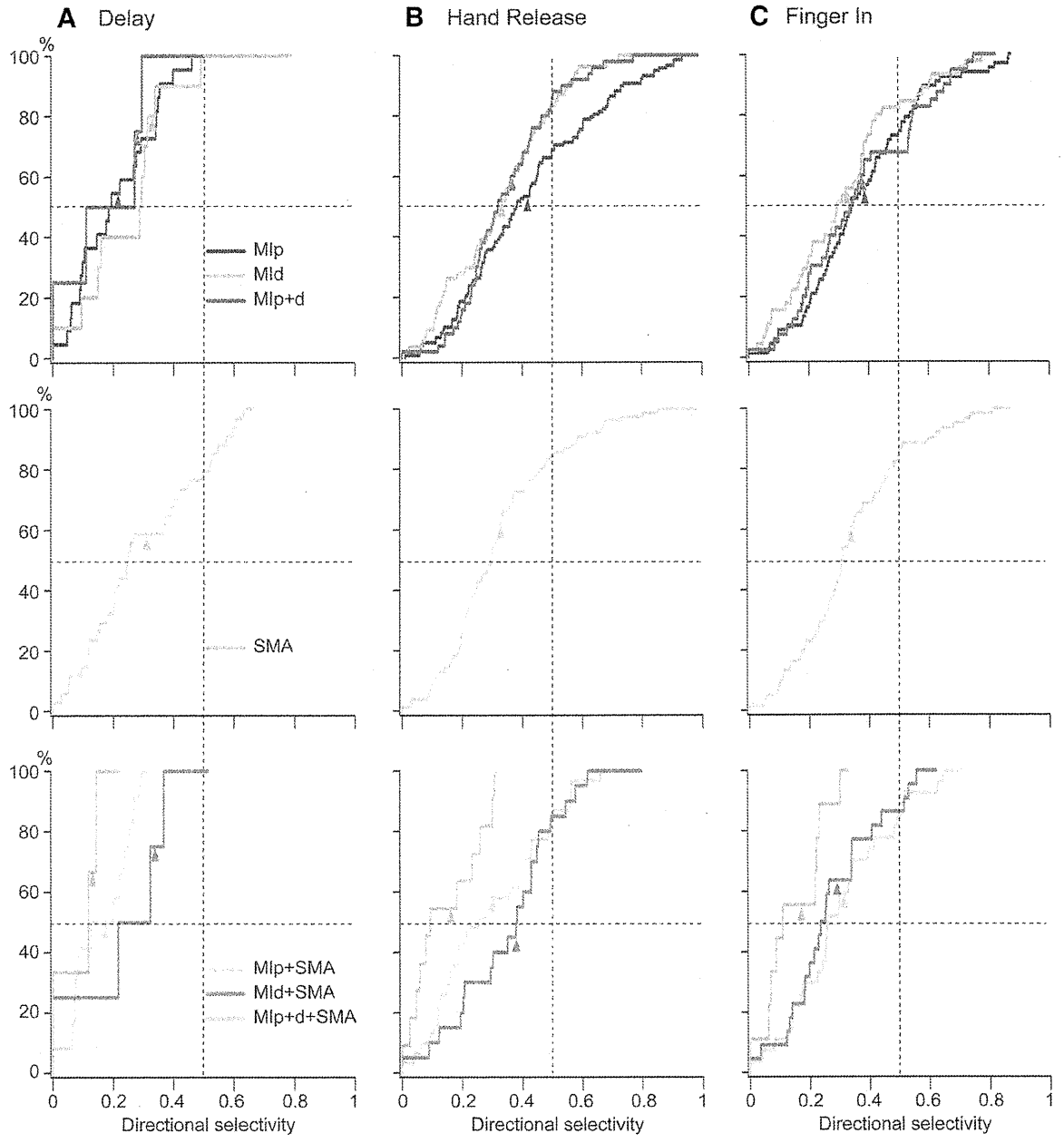

Fig. 9. Cumulative distributions showing the directional selectivity of delay (*A*)-, HR (*B*)-, and FI (*C*)-related activity of $MI_{proximal}$-, MI_{distal}-, and $MI_{proximal + distal}$ (*top row*)-, SMA (*middle row*)-, and $MI_{proximal}$ + SMA-, MI_{distal} + SMA-, and $MI_{proximal + distal}$ + SMA (*bottom row*)-recipient putaminal neurons. Small arrowheads indicate mean.

the lateral part of the caudal aspect of the putamen, whereas that of the SMA projects predominantly to its medial counterpart. In addition, a substantial number of neurons in the mediolateral central zone of the putamen receive convergent inputs from both the MI and SMA (Nambu et al. 2002; Takada et al. 1998a, b). Within the MI- and MI + SMA-recipient zones of the putamen, input from the MI_{distal} enters more ventrally than that from the $MI_{proximal}$ (Nambu et al. 2002; Tokuno et al. 1999). These distributions agree with the present results (Fig. 10). The latency of responses evoked by cortical stimulation was comparable with the previously reported one (Nambu et al. 2002).

The present study has shown that neuronal activity in the putamen is dominated by its cortical inputs. Moreover, a variety of task-related information from different cortical areas might converge onto single putaminal neurons. Many MI-recipient neurons exhibited movement-related activity, whereas SMA-recipient neurons displayed delay-related activity, as well as movement-related activity. The activity onset of the SMA-recipient neurons preceded that of MI-recipient neurons. In addition, some of the SMA-recipient neurons showed No-go-specific activity (Fig. 6*B*). The spontaneous firing rate of MI-recipient neurons was lower than that of the SMA-recipient neurons (Table 1). Such activity patterns of putaminal neurons seem to reflect activities of MI and

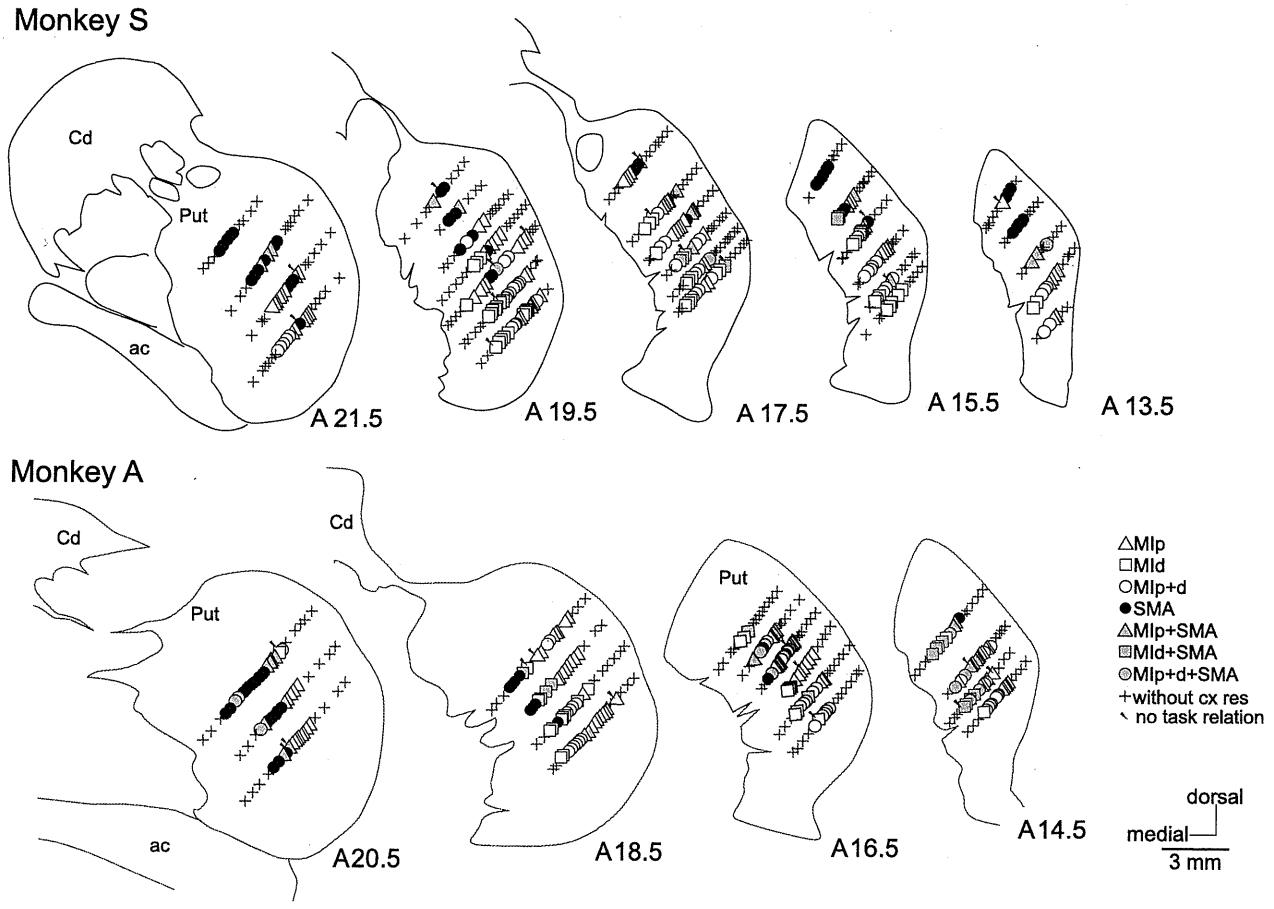

Fig. 10. Locations of putaminal neurons recorded in 2 monkeys were plotted in the frontal sections. Sections are arranged rostrocaudally from *left* to *right*. Neurons with different cortical inputs are indicated by different symbols. Neurons without cortically evoked responses (cx res) and neurons showing no task-related activity are also indicated. The distance of the sections from the auditory meatus is shown in millimeters. ac, anterior commissure; Cd, caudate nucleus; Put, putamen.

SMA neurons, giving rise to the corticostriatal projections, because similar activity patterns were reported for these motor areas (Ikeda et al. 1999; Mushiake et al. 1991, Tanji 1994), especially in MI neurons projecting to the putamen (Turner and DeLong 2000). Moreover, there were a substantial number of neurons receiving convergent inputs from both the MI and SMA. These neurons showed activity changes that were intermediate between those of MI- and SMA-recipient neurons, indicating that both inputs from the MI and SMA contribute putaminal activity during task performance. Thus convergent inputs from the MI and SMA should have functional significance. The activity onset of $MI_{proximal}$-recipient neurons preceded that of MI_{distal}-recipient neurons. This difference can be explained by the observation that EMG activity of the distal forelimb part was late compared with that of the proximal part (see Fig. 2). The thalamus—especially the intralaminar thalamic nuclei—also projects to the striatum. However, the contributions of thalamic input to the task-related activity in the striatum may be small, because striatal activity patterns primarily reflected cortical activity in the MI and SMA.

The activity of putaminal neurons observed in the present study may also be modulated by feedback and feedforward GABAergic circuits within the striatum. The striatum is composed of projection neurons that represent a majority of cells (80–95%) and a smaller number of interneurons (representing 5–20% of all striatal neurons) (Bennett and Wilson 2000). The projection neurons are inhibitory GABAergic neurons and have extensive local axon collaterals that form synapses with other neighboring projection neurons (Gustafson et al. 2006; Tepper et al. 2008). On the other hand, the interneurons are classified into several groups, including parvalbumin (PV)-containing GABAergic neurons and large cholinergic neurons (Bennett and Wilson 2000). The PV-containing GABAergic interneurons especially receive inputs from the cerebral cortex and innervate the projection neurons (Koós and Tepper 1999; Mallet et al. 2005; Tepper et al. 2008). Thus GABAergic networks in the striatum, comprising feedback inhibition through the axon collaterals of the projection neurons and feedforward inhibition through the GABAergic interneurons (Gage et al. 2010), are thought to control the activity of striatal projection neurons.

Putaminal activity. In the present study, only PANs were studied (see MATERIALS AND METHODS). PANs are originally considered medium, spiny, GABAergic-projection neurons; however, recent studies reported electrophysiologically distinct subtypes of PANs in the striatum (Gittis et al. 2010; Mallet et al. 2005; Sharott et al. 2009). Actually, based on the recent juxtacellular-labeling study of rats, the majority of PANs are

medium-sized, spiny GABAergic-projection neurons, whereas a smaller number are GABAergic interneurons, including fast-spiking interneurons. In the present study, we have noticed another type of neurons, which is characterized by *1*) higher spontaneous firing rate, *2*) short spike duration, and *3*) short latency excitation to the cortical stimulation. These neurons are considered as fast-spiking interneurons (Mallet et al. 2005) and excluded from the analysis in the present study.

The locations of putaminal neurons recorded in the present study are largely consistent with the somatotopic organization in the putamen. On the basis of somatosensory responses (Alexander and DeLong 1985a, b), evoked movements by microstimulation (Alexander and DeLong 1985a, b), movement-related neuronal activities (Crutcher and DeLong 1984a, b), and corticostriatal projections (Künzle 1975; Liles 1975; Nambu et al. 2002; Takada et al. 1998a, b), it has been reported that there is a dorsolateral-to-ventromedial topography of representation from the hindlimb to the orofacial area, with the forelimb represented in an intermediate zone. Neurons in the orofacial areas of the putamen increased activity in relation to orofacial movements, such as licking juice at reward periods.

Previous studies reported that neurons in the lateral and medial parts of the putamen exhibited activity changes in different aspects of motor behaviors. Putaminal neurons in the lateral part had firing patterns that closely resembled the activity in agonist muscles, whereas those in the medial part did not (Liles 1983). Putaminal neurons with preparatory activity were located more rostrally and medially than those with movement-related activity only (Alexander and Crutcher 1990). On the basis of the present results, the activity differences along the mediolateral axis of the putamen are likely to be attributable to distinct cortical inputs from the MI and SMA.

The present results demonstrated that the activity of some putaminal neurons was modulated prior to the earliest changes in EMG, whereas most of their activity changes occurred thereafter (Figs. 7 and 8). This temporal distribution agrees well with the previous data (Crutcher and DeLong 1984a, b; Liles 1983; Liles and Updyke 1985; Merchant et al. 1997). Such movement-related activity is considered to be transmitted through the basal ganglia circuitry and the thalamus, reach the MI and SMA, and finally, contribute to movement-related activity in these motor areas, at least, to later activity in relation to the movement onset. On the other hand, delay-related activity of SMA- and MI + SMA-recipient putaminal neurons may contribute to delay-related activity in the SMA and the premotor cortex through basal ganglia-thalamo-cortical pathways.

Functional significance. The present study suggests that the striatum is composed of multiple compartments that receive nonconvergent input from single cortical areas and convergent inputs from multiple cortical areas, which retain specific information related to motor tasks. Our previous anatomical study showed that putaminal regions with MI, SMA, and MI + SMA inputs project to different parts of the globus pallidus (Kaneda et al. 2002). Therefore, specific information retained in multiple compartments of the striatum is transmitted independently through the basal ganglia circuitry, projects to the motor areas via the thalamus, and finally, contributes to the formation of cortical activity related to motor tasks. Further studies are necessary to clarify how the activity of each compartment of the putamen is processed through the basal ganglia-thalamo-cortical pathways.

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DISCLOSURES

The authors declare no conflict of interest (financial or otherwise).

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We now substitute the original incorrect Fig. 2 with the correct figure. The legend remains the same as originally published. The results and conclusions of this study stand.

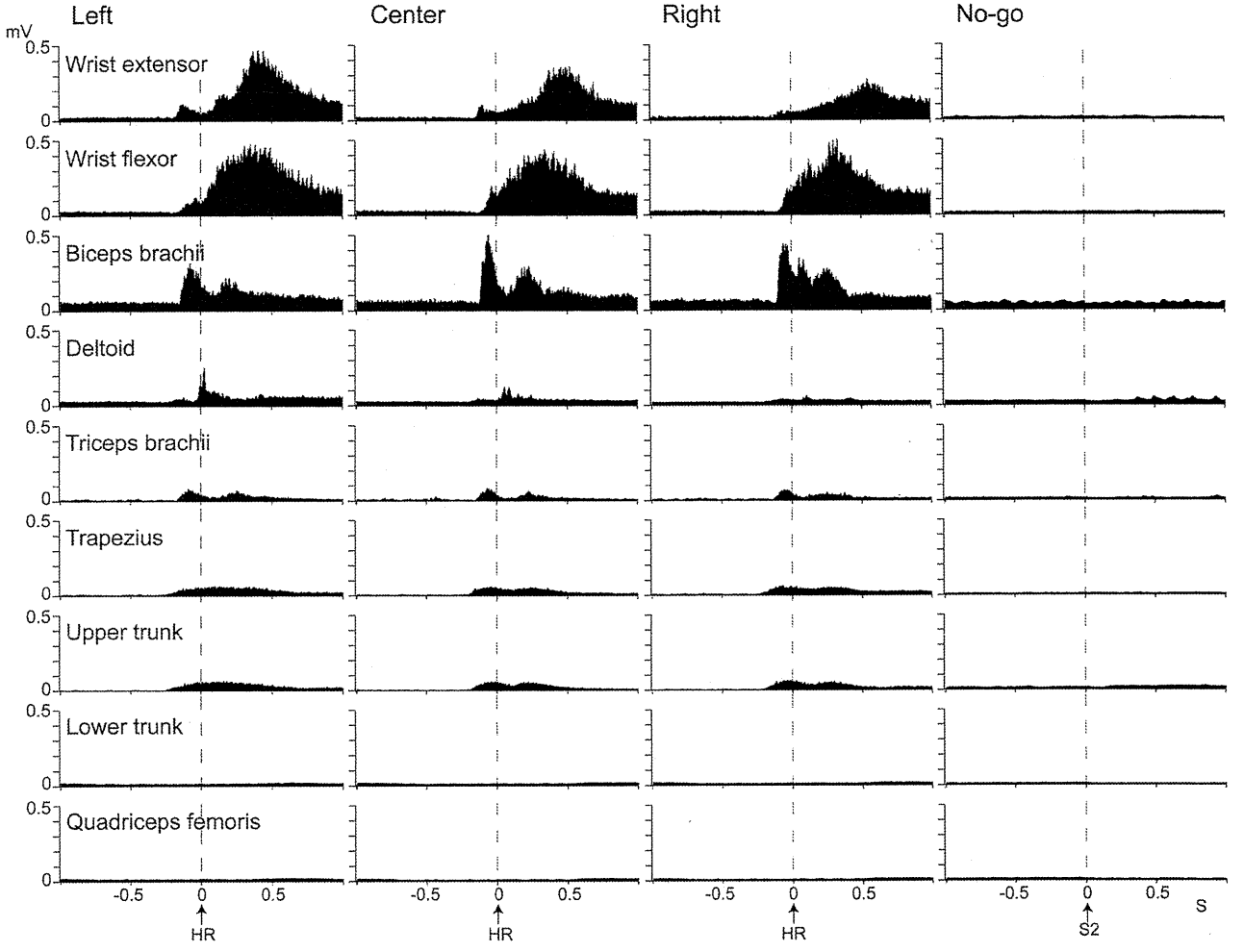

Fig. 2. Electromyogram (EMG) activity during the performance of a goal-directed reaching task with delay. EMG activity was rectified, aligned at the HR (Go trials, at *time 0*) or S2 (No-go trials), and averaged 100 times separately, according to the S1 conditions (Left, Center, and Right targets and No-go trials). In Go trials, EMG activity was observed in the forelimb and upper-trunk muscles but not in the lower-trunk and hindlimb muscles. No EMG activity was observed in No-go trials.

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A Neural Correlate of the Processing of Multi-Second Time Intervals in Primate Prefrontal Cortex

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Abstract

Several areas of the brain are known to participate in temporal processing. Neurons in the prefrontal cortex (PFC) are thought to contribute to perception of time intervals. However, it remains unclear whether the PFC itself can generate time intervals independently of external stimuli. Here we describe a group of PFC neurons in area 9 that became active when monkeys recognized a particular elapsed time within the range of 1–7 seconds. Another group of area 9 neurons became active only when subjects reproduced a specific interval without external cues. Both types of neurons were individually tuned to recognize or reproduce particular intervals. Moreover, the injection of muscimol, a GABA agonist, into this area bilaterally resulted in an increase in the error rate during time interval reproduction. These results suggest that area 9 may process multi-second intervals not only in perceptual recognition, but also in internal generation of time intervals.

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Introduction

Time is a fundamental element in living systems [1]. When we speak, or play sports and music, we sense the elapsed time intervals to monitor the events, and even generate preferred durations for the completion of the performance of the task. Other species also rely on perception of time to coordinate their behavior [1–3]. Brain mechanisms for tracking temporal features of external stimuli are known to utilize neuronal assemblies of the cerebellum [4,5], olivo-cerebellar system [6,7], basal ganglia [8], cortico-striatal circuits [9–13] and cerebral cortex [14–19]. Subcortical areas, particularly within the olivo-cerebellar system, can process measures of time for motor control on the order of milliseconds [6]. Cortical areas, particularly frontal or prefrontal cortex (PFC), may be involved in cognitive tasks such as time estimation [20], time discrimination [21], frequency timing [22], and timing of delay [23]. Recognition of multi-second intervals of external stimuli may require processing in PFC [24]. However, it remains unclear whether the PFC is involved in generation of multi-second time intervals, without reference to environmental stimuli. To address this question, we devised a time-reproduction task similar to tasks studied in human subjects [25], which required two macaque monkeys to estimate specific multi-second time intervals during stimuli (durations of 2, 4, and 7 s for monkey J, and 1 and 5 s for monkey M), and then later to reproduce these intervals by pressing a button based on an internally generated estimate of the elapsed time (Fig. 1 A). The principal features of our task were as follows: (1) The target duration was presented for a specific multi-second interval (from among a set of intervals for which the monkey had been trained); (2) The monkey needed to perceive the time elapsed during this presentation period, in order to reproduce the interval later; (3) After a variable interim period, the monkey had to actually reproduce the time interval that matched the interval previously presented, in order to receive the reward. Thus, this task enabled us to investigate the neuronal activity associated with both perception and reproduction of time by means of extracellular single unit recording in area 9 of the PFC during performance of the task. In addition to the extracellular single unit recording in area 9, we performed muscimol blockage in area 9 to investigate whether reversible ablation of this site would induce behavioral changes on comparing pre-versus post-injection data.

Methods

Animals

We used two macaque monkeys (Macaca fuscata): monkey J (6.1 kg) and monkey M (5.6 kg). This study was carried out in strict accordance with the Guideline for the Care and Use of

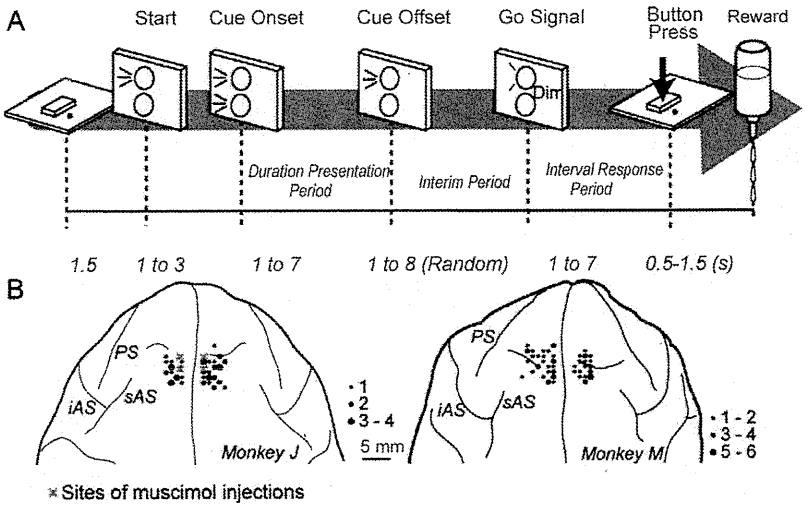

Figure 1. Task schema and recording sites. (A) Behavioral task schema. The monkeys were trained to prepare for and then observe the presentation of a time interval of visual stimuli, and after a variable interim period, then to reproduce this presented interval with a button press, as described in materials and methods. (B) Sites of single unit recordings and muscimol injections. Each dot indicates an electrode track where cellular activity was recorded in relation to the behavioral task. The size of the dot is proportional to the number of task-related cells in area 9. Red crosses denote sites of muscimol injection, which was performed to analyze effects on performance of the behavioral task. iAS, inferior limb of the arcuate sulcus; PS, principal sulcus; sAS, superior limb of the arcuate sulcus.
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Animals (Tokyo Metropolitan Institute for Neuroscience 2000). All surgical and experimental protocols were approved by the Animal Care and Use Committee of the Tokyo Metropolitan Institute for Neuroscience (Permit Number:08–1815). All efforts were made to minimize suffering in accordance with the recommendations of the "The use of non-human primates in research". For example, the monkeys were kept in individual primate cages in an air-conditioned room where food was always available. Their health condition, including factors such as body weight and appetite, was checked daily. Supplementary water and fruit were provided daily. All surgery was performed under general anesthesia (intravenous injection of pentobarbital sodium).

Behavioral procedures

The time-reproduction task required the monkey to estimate specific multi-second durations during signal presentations, and then to reproduce these durations by planning the interval response (button press) based on estimates of the elapsed times. During each stimulus-response trial, the time task began with moving a hand to a light sensor, a black dot beside button, and continuously leaving the hand on the sensor for 1.5 s (Fig. 1A). A control LED on a vertical plate fixed directly in front of the monkey was turned on. After 1–3 s, another LED (instruction LED) was turned on and lasted 2, 4, or 7 s for monkey J and 1 or 5 s for monkey M, to signal the time intervals that they had to reproduce later. Following an additional interim period (randomly assigned as 1–8 s), the control LED dimmed (Go signal). On observing a dimming of the LED (the "Go signal", to signal the start of the interval response period), the monkey had to reproduce the time interval that matched the interval previously presented; then the monkey pressed a button to signal the end of the interval response period (reproduced intervals) (Fig. 1 A). Successful trials were defined as intervals reproduced within±15% of the interval previously presented, which was defined as the "correct response range (CRR)". The successful trials were always followed by supply of liquid reward.

Surgical and electrophysiological recording procedures

The monkeys were trained to perform the task consistently with greater than 80% accuracy (i.e., with 80% of responses of generated intervals that fell within the CRR). At the final stage of the training period, a head holder and a chamber for unit recordings were implanted. The surgical and electrophysiological recording procedures were described in detail elsewhere [26,27]. We performed single unit recordings using a glass-coated Elgiloy-alloy microelectrode (0.5–1.5 MOhm at 1 kHz). During the recording, the time was chosen from a set either of 2, 4, and 7 s, or of 1 and 5 s. In order to prevent habituation to the performance of specific times, times were presented pseudo-randomly for each repetition, at least five repetitions for each cell. Eye and hand movements were monitored by a video camera while the monkey's head was fixed to the primate chair.

We identified the sites of single unit recordings primarily as area 9 according to the following procedures: (1) pre-operative MRI images (Hitachi, AIRIS, 0.3 T) to determine the best position of a recording chamber [26]; (2) anatomical location (dorso-medial) PFC, 1–6 mm from midline, anterior to the near end of the superior arcuate sulcus; (3) cortical surface reconstruction of electrode penetrations in the post-mortem brains (see Fig. 1B).

Muscimol injections

We used a stainless-steel tube (inner diameter 0.06 mm, outer diameter 0.14 mm, length 180 mm) with a sharp angle at the tip, to which a tungsten microelectrode (impedance 0.5–2.0 MOhm at 1 kHz) was attached side by side with an instant glue, where the tip of the electrode protruded from the tip of the injection tube by 0.2–0.3 mm. The injection tube was connected to a 10-µl Hamilton microsyringe by a polyethylene tube (diameter, 0.3 mm). We carried out a total of three muscimol injection experiments in monkey J, each on a separate day in order to make reversible inactivation of the PFC. During an injection experiment, we first recorded neuronal activities using the microelectrode attached to the injection tube. Injections were made at the depth that the task-related neurons were

observed. The injections were always done into both hemispheres of the brain, two sites on each hemisphere (Fig. 1B). An aqueous solution of muscimol (Sigma; 5 μg/μl) was pressure-injected in 5–7 steps (0.2 μl for each step) with an interval of 20 s between steps. A total amount of 1.0–1.4 μl was deposited for each injection site. We collected behavioral data for 3 hours after the injections.

We chose not to perform saline control injections at this site, given evidence that there was no effect after a similar amount of saline was injected into multiple areas of the primate brain, such as cortex [28], or cerebellar dentate nuclei through the same procedure [26], we did not perform saline injections for the current study.

Data analysis

To define "duration-recognizing" (DR) neurons and "interval-generating" (IG) neurons, we first examined whether discharge rates during the interim period and the interval-response period significantly varied among different presented intervals (2 s, 4 s, and 7 s for monkey J; 1 s and 5 s for monkey M; ANOVA, $P<0.05$). Second, if the discharge rate for a certain interval (e.g. 2 s) was significantly higher than those for the others (4 s or 7 s) (Fisher's SLD test, $P<0.05$) during the interim period, the neuron was defined as the DR neuron, specific for the interval (e.g., DR neuron, 2-s specific neuron). If the discharge rate for a certain interval (e.g. 2 s) was significantly higher than those for the others (4 s or 7 s) (Fisher's SLD test, $P<0.05$) during the interval-response period, the neuron was defined as the IG neuron, specific for the interval (e.g., IG neuron, 2-s specific neuron).

We compared the error rate of the post-injection performance with that of the pre-injection performance to assess the effect of muscimol blockade of prefrontal cell activity on the monkey's performance. The error rate was calculated as the ratio of failed trials to the total of failed and successful trials during the performance of a block of 10 successful repetitions. Pre-injection data and post-injection data were collected in 3 paired days separated by one week between pairs, with a pre-injection session on one day and a muscimol injection session on the following day. Statistical comparison (t-test, $P<0.05$) was made for the error rates between the pre- and post-muscimol injections in the three injection experiments. A total of 1080 and 1134 trials of task performance, approximately 360 and 378 trials per time interval, were included in the post- and pre-injection groups, respectively. A button press frequency (a response rate) was calculated as the ratio of the number of responses during 50 ms time bin to the total of 360 or 378 trials.

Results

Activity during duration recognition

We found two groups of time related neurons, with single unit recordings carried out in area 9 of the PFC during performance of the time task. One group showed a higher activity lasting 1–2 s immediately after the duration-presentation period, with specificity of individual neurons to particular intervals (Fisher's SLD test, $P<0.05$). We termed such neurons "duration-recognizing" (DR) neurons. Another group showed increased activity during the interval response period (time-reproduction period), with specificity of individual neurons to particular intervals (Fisher's SLD test, $P<0.05$). We termed these neurons "interval-generating" (IG) neurons. Among 497 cells (154 cells in monkey J; 343 cells in monkey M) recorded from the PFC, the DR cells constituted 39% ($n=60$) in monkey J and 29% ($n=98$) in monkey M, and the IG cells constituted 44% ($n=68$) in monkey J and 32% ($n=111$) in monkey M. Only a small group of neurons, 9% ($n=14$) in monkey J and 3% ($n=10$) in monkey M were active during both the interim and interval response periods. This indicates that DR and IG functions were rarely combined in a single cell.

Typical activities of DR neurons in monkey J are shown in Fig. 2A–C, with examples of one neuron tuned to each of the time intervals (2, 4 and 7 s). Typical activities of DR neurons in monkey M, in cells specific for 1 and 5 s, are depicted in Fig. S1. This is most evident if one compares neuronal discharges during the initial 1-s portion of the interim period across the different time intervals. The cell in Fig. 2A showed higher activity after 2-s interval presentation than after 4-s and 7-s interval presentations (Fisher's SLD test, $P<0.05$). Similarly, the cells in Fig. 2B and 2C were tuned to 4-s and 7-s intervals, respectively (Fisher's SLD test, $P<0.05$). We propose that such time-specific activity may contribute to recognition of particular multi-second time lengths in environmental stimuli.

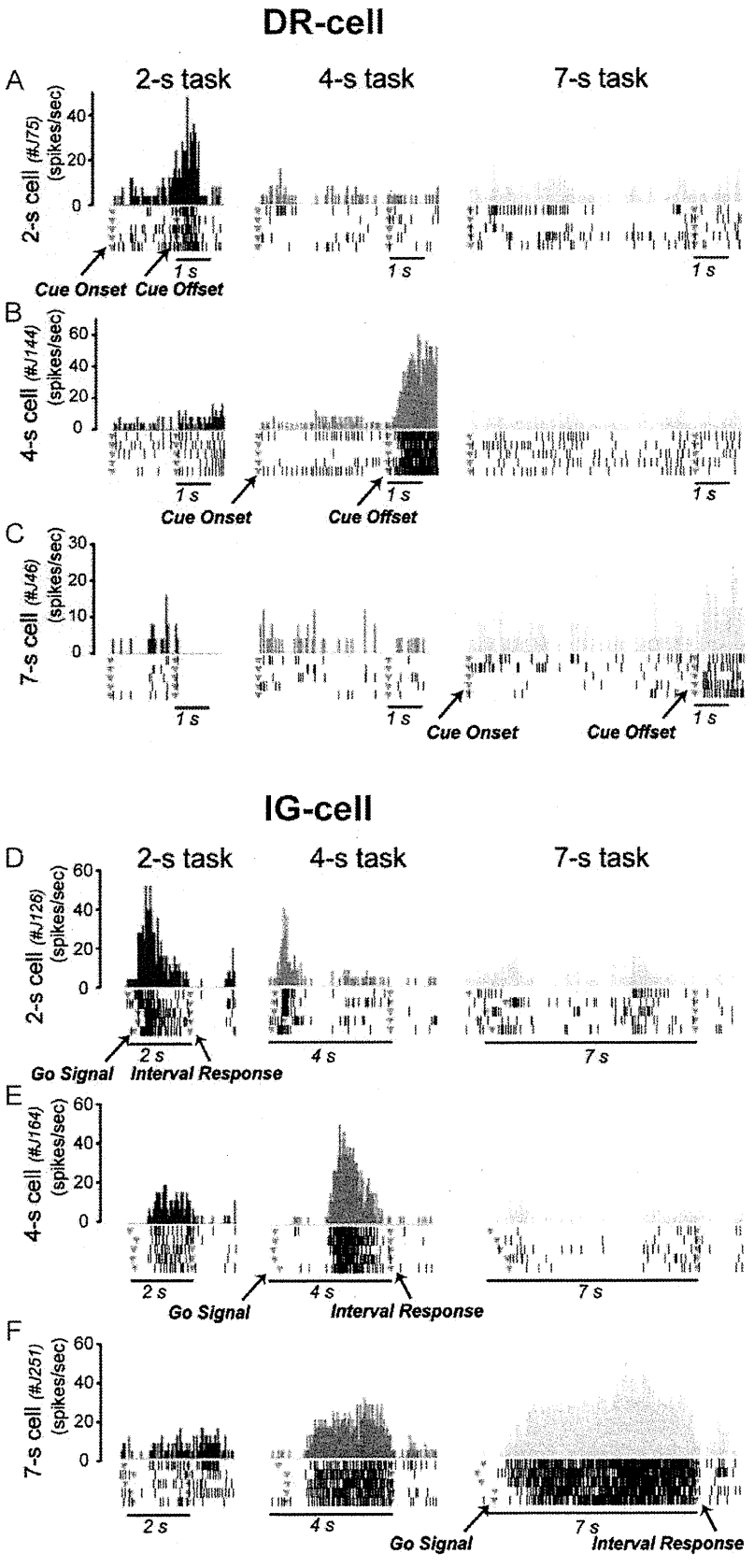
Activity during time interval generation

The IG neurons shown in Fig. 2D–F demonstrated activities specific for 2, 4, and 7 s by increased firing during the interval-response period (Fisher's SLD test, $P<0.05$). Typical activities of IG neurons in monkey M, in cells specific for 1 and 5 s, are depicted in Fig. S2. For example, the cell (J164) in Fig. 2E showed more activity during the reproduction of the 4-s time length than it did during the 2-s and 7-s reproductions (Fisher's SLD test, $P<0.05$). Likewise, the cells J126 and J251 in Fig. 2D and 2F were more active during the reproduction of either the 2-s or the 7-s time period, respectively, than they were during other interval reproductions. We propose that this type of time-specific activity is involved in generating an internal representation of time length that is at least partly independent of external stimuli.

Each monkey had approximately equal proportions of DR neurons and IG neurons tuned to each of the highly practiced time intervals. Among 60 DR cells in monkey J, 38% ($n=23$), 27% ($n=16$), and 35% ($n=21$) of the total exhibited activities specific for presented durations of 2, 4, and 7 s, respectively. Among 68 IG cells in this monkey, 40% ($n=27$), 28% ($n=19$), and 32% ($n=22$) of the total showed 2-s, 4-s, and 7-s specific activities, respectively. Among 98 DR cells in monkey M, 58% ($n=57$) and 42% ($n=41$) of the total were tuned to 1-s and 5-s durations, respectively. Among 111 IG cells in this monkey J, 50% ($n=56$) and 50% ($n=55$) of the total were tuned to 1-s and 5-s durations, respectively.

On the other hand, only a small group of neurons were more active during the duration-presentation period. In monkey J, 3% ($n=5$) and in monkey M 6% ($n=20$) of the total of recorded cells had enhanced activity early during presentation of the time intervals (ANOVA, $p<0.05$). We failed to detect significant relationships between the firing patterns of these neurons and the specific time intervals.

To further test the importance of area 9 neurons in the reproduction of time intervals, we reversibly inactivated the PFC in monkey J, by local injection of muscimol, a GABA agonist [26,28]. The effect of muscimol on the accuracy of interval responses was demonstrated by a significant increase in the error rate for all three injections (Fig. 3A, t-test, $P<0.05$). Fig. 3B–D showed the further details of the behavioral changes with the comparison of the frequency of interval responses based on the estimates of the elapsed times between pre- and post-injection. The response times in the absence of muscimol injection were distributed with single peaks that fell nearly at the mid-point of the CRR and with relatively tight clustering around the CRR, but after muscimol injection the response times were more widely distributed and most errors occurred as excessive shortening of the


DR-cell
A
2-s task
4-s task
7-s task
2-s cell (#J75) (spikes/sec)
40
20
0
1 s
Cue Onset
Cue Offset
B
4-s cell (#J144) (spikes/sec)
60
40
20
0
1 s
Cue Onset
Cue Offset
C
7-s cell (#J46) (spikes/sec)
30
20
10
0
1 s
Cue Onset
Cue Offset
IG-cell
D
2-s task
4-s task
7-s task
2-s cell (#J126) (spikes/sec)
60
40
20
0
2 s
4 s
7 s
Go Signal
Interval Response
E
4-s cell (#J164) (spikes/sec)
60
40
20
0
2 s
4 s
7 s
Go Signal
Interval Response
F
7-s cell (#J251) (spikes/sec)
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2 s
4 s
7 s
Go Signal
Interval Response

Figure 2. Duration-recognizing- and interval-generating-related activity. Activity of individual DR neurons specific for 2 s (A), 4 s (B), or 7 s (C) in monkey J. Shown in histogram and raster format is spike discharge during the duration presentation period and the early interim period of each time task. Note the time-specific activity that is seen during the 1-s period after cue offset. Activity of individual IG neurons specific for 2 s (D), 4 s (E), or 7 s (F) in monkey J. Shown is the spike discharge rate during the interval response period of each time task.
doi:10.1371/journal.pone.0019168.g002

response times (see Fig. 3B–D). It was noteworthy that a peak of the interval response density tended to shift earlier (Fig. 3B–D). The tendency toward excessively early button presses indicated that interference specifically with hand movements was unlikely to be the cause of inaccurate interval signaling. Thus, the PFC inactivation data provided additional evidence for the role of area 9 neurons in time reproduction.

Discussion

Our data demonstrate that time is represented in the PFC or neural networks involving the PFC. Previous studies have shown that neurons in the PFC participate in many aspects of cognitive behaviors based on reward [29], evaluating self-generated decisions [30], categorization [31], procedural learning [32], functional separation of "what" and "when" [33], and time prediction and detection [34]. These earlier observations encouraged our detailed analysis of area 9 neuronal activities in critical aspects of temporal processing.

An important finding in our study was that a group of PFC neurons (DR neurons) displayed activities just after the presentation of the target duration ended, which were specific for multi-second intervals presented during the duration-presentation period. Time-related neuronal activity has been reported in various motor areas of the primate frontal cortex, such as the dorsal premotor cortex [35], the presupplementary motor area (pre-SMA) [36,37] and the supplementary eye field (SEF) (23). Repetitive transcranial magnetic stimulation shows the evidence of role of the dorsolateral prefrontal cortex in short (0.5 s) and long (2 s) interval timing in human subjects [38]. In a rather different task not involving the reproduction of time intervals, Genovesio et al. have shown that there was post-delay spike activity in

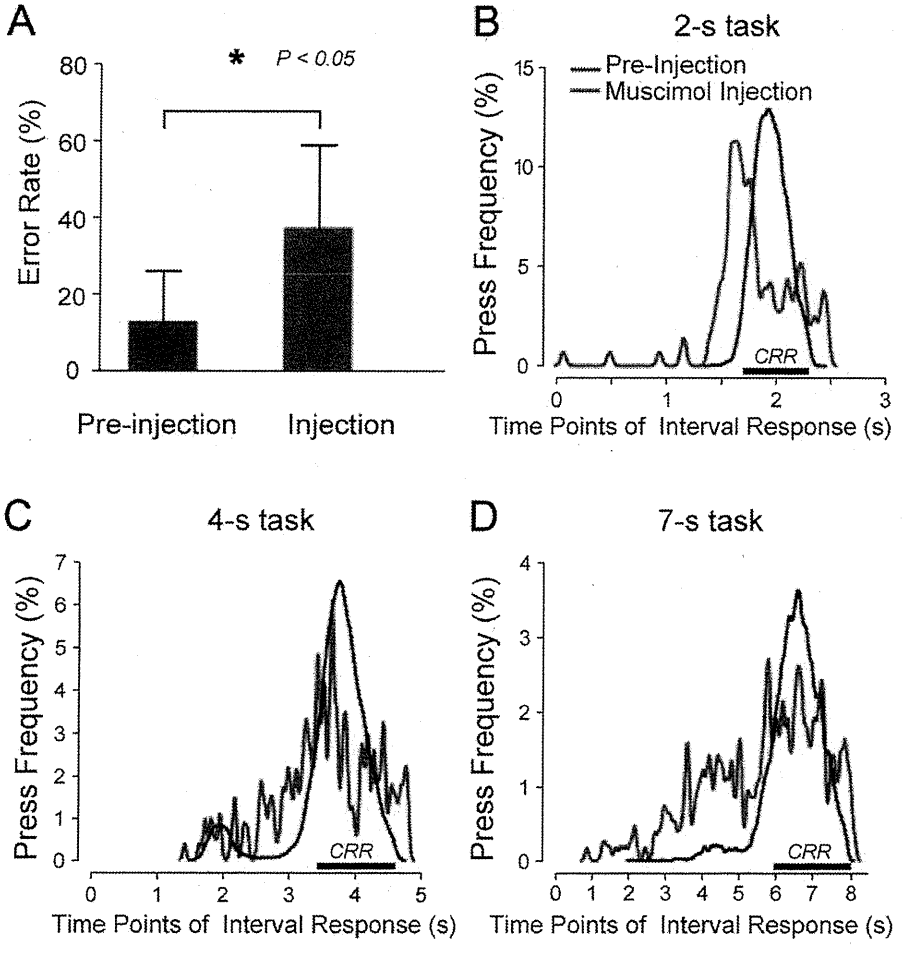

Figure 3. Effect of muscimol injections into area 9 on the accuracy of time reproduction in monkey J. (A) Change in the error rate for all of the 2-s, 4-s, and 7-s tasks. (B–D) Comparison of the frequency of interval responses between the pre- and the post-injections in the 2-s (B), 4-s (C), and 7-s (D) tasks. CRR, correct response range (reproduction accuracy within±15% of the target interval).
doi:10.1371/journal.pone.0019168.g003

areas 46, 8, 9, and rostral 6 that was specific for each of the elapsed delay periods (1 s, 1.5 s, and 2 s) in primates [19]. Yet, Matell, Meck, Jin, and their colleagues have provided strong evidence of neural representation of multi-hundred millisecond time in dorsolateral PFC-basal ganglia circuits [39,40,41]. From these observations, a hypothesis arises that PFC neurons or the related neural networks may change their activities by practice in response to varying elapsed times, thereby detecting or recognizing individual time lengths up to 7 seconds.

Beyond the time-perceptive neurons, the present study has revealed that, during the interval-response period, another group of PFC neurons (IG neurons) displays higher activity specific for different presented time lengths. Our results have clearly demonstrated that, in the primate, there are PFC neurons that can generate distinct time intervals up to 7 seconds. This may provide a useful clue for understanding how signals derived from DR neurons are decoded to motor output, in order to control the timing of the button press after the time interval. We hypothesize that these IG neurons may provide this control.

Given the theory that striatal activity may be the final output of an internal clock [10], and the anatomical evidence that the striatum receives input from area 9 [42], the cortico-striatal projection from area 9 may play a key role in the temporal command for action. Others have suggested that corticostriatal interactions may be critical to reward-enhanced learning [43], and future studies might address how area 9 neurons become tuned to specific multisecond time intervals by simultaneously recording area 9 and striatal neurons during training for such tasks.

Is it possible that the time interval-specific activity that we documented was merely an epiphenomenon? We think not, for several reasons. First, the time interval-specific activity was highly represented among cortical cells in the area 9. The cells involved in time interval, either the DR cells or the IG cells were not a small subpopulation, but approximately formed one out of three of the whole population under study. This proportion of time interval cells in cortical area 9 was similarly observed between two monkeys in the current study. Further, for each of the highly practiced time intervals, each monkey had approximately equal proportions of the DR neurons and of IG neurons, while it was rare that DR and IG functions were combined in a single cell. Second, our recording location, area 9 is characterized by a particular firing pattern of the full layer cortex construction that is distinguishable from the posterior motor areas, which lack layer IV. Accordingly, we did not find evidence that area 9 cells responded to eye movements or hand movements which occurred during the responses used to indicate the internally generated time intervals. The task in our study required only limited eye and hand movements. The monkeys placed the hand on a sensor point at the beginning of the trial, and kept the hand on that point until the end of the trial, after reward delivery. To indicate the internally generated time interval, the monkey needed to move the thumb only a few millimeters to press the button. We monitored eye movements and hand movements, but we did not see individual area 9 neurons that responded to eye or hand movements that occurred during our task. These observations indicated that our recording area was separated from motor areas such as the pre-SMA or SEF. Finally, the most direct evidence of the involvement of prefrontal cortex comes from the results of muscimol interference. We found that the accuracy of time interval production was disrupted.

In conclusion, different groups of PFC neurons in area 9 had enhancement in neuronal discharge just after the duration-presentation period or during the interval-reproduction period, with tuning to specific lengths of time. These results suggest that the PFC neurons contribute to both perception and generation of multi-second time intervals.

Supporting Information

Figure S1 Duration-recognizing-related activity. Activity of individual DR cells specific for 1 s (A) or 5 s (B) in monkey M. Shown in histogram and raster format is spike discharge during the interim (post-duration-presentation) period of each time task. Note the time-specific cell activity that is seen during the 1-s period after cue offset.
(TIF)

Figure S2 Interval-generating-related activity. Activity of individual IG cells specific for 1 s (A) or 5 s (B) in monkey M. Shown in histogram and raster format is spike discharge during the interval-response period of each time task.
(TIF)

Author Contributions

Conceived and designed the experiments: MT NY XL. Performed the experiments: NY SM AN XL. Analyzed the data: TF NY XL TRH SM MT. Wrote the paper: XL NY TRH SM AN TF MT.

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Somatotopic organization of the primate basal ganglia

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Somatotopic organization is a fundamental and key concept to understand how the cortico-basal ganglia loop works. It is also indispensable knowledge to perform stereotaxic surgery for movement disorders. Here I would like to describe the somatotopic organization of the basal ganglia, which consist of the striatum, subthalamic nucleus, globus pallidus, and substantia nigra. Projections from motor cortical regions representing different body parts terminate in different regions of these nuclei. Basal ganglia neurons respond not only to the stimulation of the corresponding regions of the motor cortices, but also to active and passive movements of the corresponding body parts. On the basis of these anatomical and physiological findings, somatotopic organization can be identified in the motor territories of these nuclei in the basal ganglia. In addition, projections from functionally interrelated cortical areas partially converge through the cortico-basal ganglia loop, but nevertheless the somatotopy is still preserved. Disorganized somatotopy may explain, at least in part, the pathophysiology of movement disorders, such as Parkinson's disease and dystonia.

Keywords: striatum, subthalamic nucleus, globus pallidus, substantia nigra, somatotopy, movement disorders

INTRODUCTION

Somatotopic organization in the cerebral cortex, especially in the primary motor and primary somatosensory cortices, is a well-known and fundamental concept to understand the functions of these areas. Each nucleus of the basal ganglia also shows somatotopy, but it has received little attention. Somatotopy of the basal ganglia is disorganized in movement disorders, suggesting its pathophysiological significance. Knowledge on somatotopy of the human basal ganglia is also indispensable to identify the location of the tip of electrodes during stereotaxic surgery for movement disorders. In this article, I would like to describe the somatotopic organization of the basal ganglia comprehensively and in detail. Although the description is mainly based on monkey studies, it should be applicable to the human basal ganglia because the basal ganglia of non-human primates and humans share a number of common properties, despite their size difference.

BASIC CIRCUITRY OF THE BASAL GANGLIA

The basal ganglia are a group of sub-cortical nuclei, and are composed of the striatum, pallidum, subthalamic nucleus (STN), and substantia nigra (SN). The striatum can be classified into the caudate nucleus, putamen, and ventral striatum. The pallidum can be divided into the external (GPe) and internal (GPi) segments of the globus pallidus and ventral pallidum (VP). The SN is composed of pars reticulata (SNr) and pars compacta (SNc). Among these nuclei, the striatum and STN are input stations of the basal ganglia. The striatum receives inputs from the entire cerebral cortex except the primary visual cortex, and the STN receives inputs mainly from the frontal cortex. On the other hand, the GPi and SNr serve as the output nuclei of the basal ganglia, and project outside the basal ganglia. The GPe connects input stations to the output nuclei. The SNc is composed of dopaminergic neurons, which project widely to the whole basal ganglia, especially to the striatum, and modulate their activity.

Cortical information received in the input stations is transferred to the output nuclei through the following three pathways (**Figure 1**; Alexander and Crutcher, 1990a; Nambu et al., 2002b).

Direct pathway: Striatal neurons expressing substance P receive cortical inputs and project directly to the GPi/SNr.
Indirect pathway: Striatal neurons expressing enkephalin receive cortical inputs and project polysynaptically to the GPi/SNr by way of the GPe and STN.
Hyperdirect pathway: STN neurons receive direct cortical inputs and project to the GPi/SNr. This pathway transfers cortical excitation faster to the GPi/SNr than the direct and indirect pathways.

Information originating from the frontal cortex is processed through these three pathways, and mainly returns to the frontal cortex through the thalamus, thus forming the cortico-basal ganglia loop. Some information is transferred to the brainstem from the output nuclei (Alexander and Crutcher, 1990a).

The primary motor cortex (MI), supplementary motor area (SMA) and premotor cortex (PM) are classically defined motor cortices. In addition, the pre-SMA in the mesial side of the hemisphere anterior to the SMA and the cingulate motor areas (CMA) in the cingulate sulcus have been identified (Picard and Strick, 2001). The PM is not homogeneous and was originally divided into dorsal and ventral parts (PMd and PMv), and is now further subdivided into rostral and caudal parts (PMdr, PMdc, PMvr, and PMvc). The CMA is divided into rostral and caudal parts (CMAr and CMAc). Among them, the most rostral motor cortices, such as pre-SMA, PMvr, PMdr, and CMAr, receive inputs from the frontal association cortex and send outputs to the more caudal motor cortices, such as SMA, PMvc, PMdc, and CMAc (Takada et al., 2004). Most of these motor cortices, especially SMA, PMvc, PMdc, CMAc, and MI have their own somatotopy.

There have been two opposing views concerning how information originating from different cortical areas or different somatotopic regions is processed through the basal ganglia (**Figure 2**; Parent and Hazrati, 1995). One is the *parallel processing* hypothesis (Alexander et al., 1986; Hoover and Strick, 1993; Strick et al., 1995) proposing that information from different cortical areas is processed independently in the different parts of the basal ganglia (**Figure 2A**). The other is the *information convergence* hypothesis (Percheron and Filion, 1991; Percheron et al., 1994) proposing that information from different cortical areas converges and is integrated in the basal ganglia (**Figure 2B**). Recent studies suggest that both parallel processing and information convergence occur (**Figure 2C**). Information from cortical areas whose functions are distinct from each other terminates in the different regions in the basal ganglia. On the other hand, information from cortical areas whose functions are close to each other tends to converge in the basal ganglia. For example, projections from the motor, oculomotor, prefrontal, and limbic cortices terminate in different regions in the striatum. These striatal regions project to different regions of other basal ganglia nuclei. Thus, each nucleus of the basal ganglia can be segregated into motor, oculomotor, prefrontal, and limbic territories, and cortico-basal ganglia loops are composed of several independent and functionally distinct, but homological loops: motor, oculomotor, prefrontal, and limbic loops (**Figure 1**). Each loop controls brain functions independently (Alexander et al., 1986; Parent, 1990). Inside the motor loop, projections from the MI, SMA, and PM partly converge in the striatum, while projections from the MI and pre-SMA project to distinct regions of the striatum. Somatotopy is also well defined in each nucleus of the basal ganglia, and information from different body parts of the somatotopy is well preserved through cortico-basal ganglia loops.

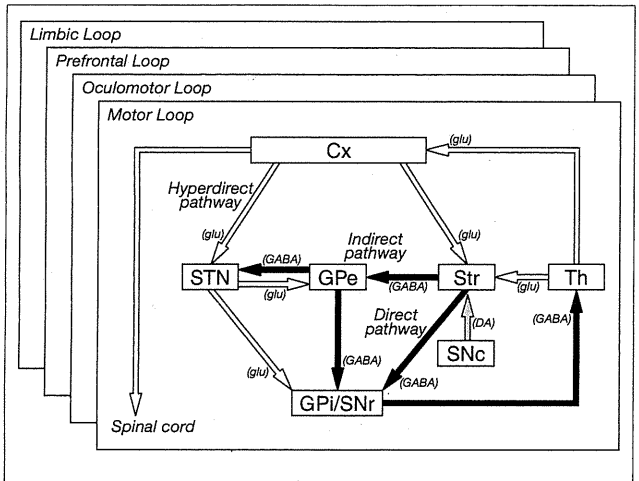

FIGURE 1 | Basic circuitry of the basal ganglia. Open and filled arrows indicate excitatory and inhibitory projections, respectively. Cx, cerebral cortex: DA, dopamine, GABA, gamma-aminobutyric acid; glu, glutamate; GPe and GPi, external and internal segments of the globus pallidus; SNc, substantia nigra pars compacta; SNr substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Modified from Nambu et al. (2002b).

METHODS TO IDENTIFY SOMATOTOPY

Somatotopy of the basal ganglia reflects input and output connections of each nucleus, and can be investigated in several ways. The most basic method is an anatomical method examining fiber connections with other brain areas whose somatotopy is clearly identified. For example, anterograde tracers are injected into the orofacial, forelimb, and hindlimb regions of the MI, and then terminals in the striatum and STN are observed. Transsynaptic anterograde and retrograde tracing can be performed using herpes simplex virus (anterograde or retrograde) and rabies virus (retrograde) as tracers. Fiber connections can also be investigated by electrophysiological methods. Stimulation of the MI induces responses in the corresponding regions in the striatum, STN, GPe, and GPi.

Another useful electrophysiological method is recording neuronal activity in behaving animals. Neurons in the basal ganglia change activity during active movements of the corresponding body parts. These neurons usually respond to passive movements of the corresponding body parts as well, such as manipulations of joints and muscle palpations. Applying microstimulation through recording electrodes in some nuclei of the basal ganglia can induce movements of the corresponding body parts, although more pulses are necessary compared with that for intracortical microstimulation.

In the following sections, somatotopy in each nucleus of the basal ganglia will be discussed. "Cartoons" representing somatotopy will be drawn for each nucleus. However, they are metaphors, and readers should not take them too literally. For example, in **Figure 5**, the orofacial, forelimb, and hindlimb regions are represented in this order along the ventral-to-dorsal axis of the globus pallidus, but it is not known whether each finger is distinctly and orderly represented (Hamada et al., 1990).

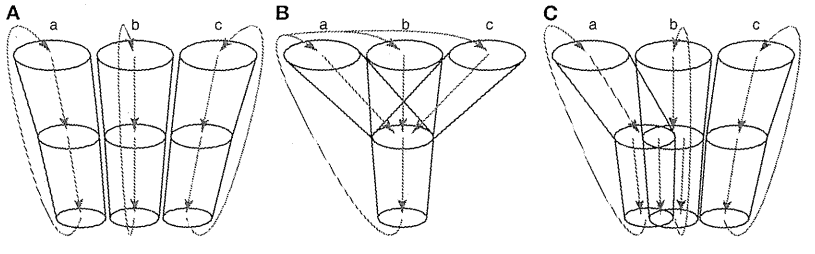

FIGURE 2 | Infomation processing in the basal ganglia. (A) *Parallel processing* hypothesis. Information originating from different areas (a, b, c) of the cerebral cortex is processed independently in the different parts of the basal ganglia, and returns to the original cortical areas. **(B)** *Information convergence* hypothesis. Information originating from different cortical areas converges and is integrated in the basal ganglia, and integrated information returns to all the cortical areas. **(C)** Intermediate hypothesis between parallel processing and information convergence hypotheses, which is supported by recent studies.

STRIATUM

The striatum, as an input station of the basal ganglia, receives excitatory inputs from all areas of the cerebral cortex except the primary visual cortex. The caudal aspect of the putamen, which is posterior to the anterior commissure, is considered to be the motor territory and shows clear somatotopy (**Figure 3A**). Distribution patterns of labeling in the striatum were observed after injection of anterograde tracers into the orofacial, forelimb, and hindlimb regions of the MI and SMA (Künzle, 1975; Flaherty and Graybiel, 1993; Takada et al., 1998b). Labeling consisted of dense and diffuse projection regions as recently proposed (Haber et al., 2006). The dense terminals were found in the lateral part (MI territory) after injection into the MI, and in the medial part (SMA territory) after injection into the SMA. The orofacial, forelimb, and hindlimb regions of the MI project to the ventral to dorsal parts of the lateral putamen. The corresponding regions of the SMA project to the ventral to dorsal parts of the medial putamen, which are mediodorsal to the MI territory. Therefore, the putamen has two sets of somatotopic representations in the medial and lateral parts. The diffuse terminals from the MI extend to the dorsomedial portion, and those from the SMA extend to the ventrolateral portion. Thus, the projections from the orofacial, forelimb, and hindlimb regions of the MI and those from the corresponding regions of the SMA converge in the medio-lateral central zone that occupies one-quarter of each territory. The forelimb region is widely represented in the MI territory. The proximal regions (elbow and shoulder) are located in the mediodorsal part, and the distal regions (wrist and digits) are located in the ventrolateral part (Tokuno et al., 1999).

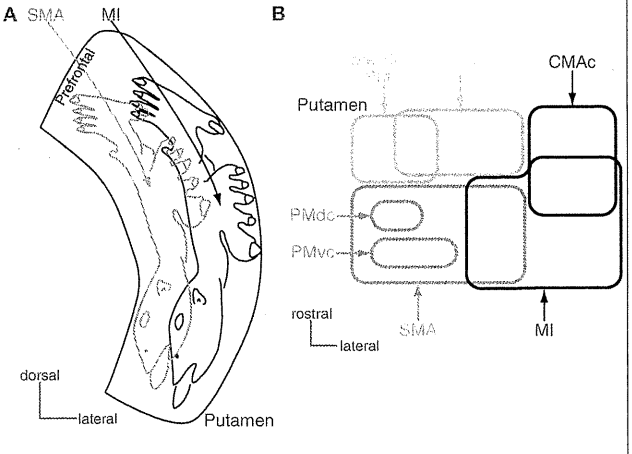

FIGURE 3 | Somatotopy of the putamen. (A) Somatotopy of the putamen is schematically shown in a frontal section. In the caudal aspect of the putamen, the lateral part receives somatotopic inputs from the primary motor cortex (MI), and the medial part from the supplementary motor area (SMA). The somatotopy in the SMA territory is located dorsomedially to that in the MI territory. Projections from the orofacial, forelimb and hindlimb regions of the MI and SMA converge in the medio-lateral central zone in the putamen. The most dorsomedial part receives inputs from the prefrontal cortex. Modified from Nambu et al. (2002a) **(B)** Input from motor cortices to the putamen is schematically shown in a horizontal section. CMAc and CMAr, caudal and rostral parts of the cingulate motor area; PMdc, PMdr, and PMvc, caudal part of dorsal premotor cortex, rostral part of dorsal premotor cortex, and caudal part of ventral premotor cortex. Modified from Takada et al. (2001).

This somatotopy reflects not only cortical inputs revealed by conventional tracers, but also putaminal outputs to the cortex through the direct and indirect pathways. Injection of rabies virus into the MI resulted in retrograde transsynaptic labeling of neurons in the putamen, which showed similar somatotopic organization, especially in its lateral side (Miyachi et al., 2006). Moreover, this study also showed no labeling of neurons in the SMA territory of the putamen, suggesting that the pathways originating from the MI territory of the putamen and from the SMA territory are independent of each other in the basal ganglia. The motor territory of the putamen also receives topographic inputs from the motor thalamus and centromedian and parafascicular nuclei, which are reciprocally connected with motor cortices (Nakano et al., 1990; Sadikot et al., 1992; McFarland and Haber, 2000; Jones, 2007). These projections are also considered to be somatotopically organized.

The somatotopy in the putamen is also confirmed by electrophysiological methods (Nambu et al., 2002a). Cortical stimulation of the forelimb regions of the MI and SMA orthodromically activates projection neurons in the corresponding MI (lateral) and SMA (medial) territories of the putamen, respectively, at a latency of 10–15 ms. Putaminal neurons in the central zones are activated by the stimulation of both the MI and SMA, and thus, convergence from the MI and SMA occurs at a single neuronal level. Putaminal neurons in the MI and SMA territories are activated by passive and/or active movements of the corresponding body parts on the contralateral side (Alexander and DeLong, 1985; Alexander and Crutcher, 1990b; Nambu et al., 2002a). However, putaminal neurons in the MI territory and those in the SMA territory show different activity patterns during task performance. Putaminal neurons in the MI territory are closely related to movements themselves, while neurons in the SMA territory are activated not only by movements themselves, but also during delay periods. Such activity differences of putaminal neurons seem to reflect the activity patterns of MI and SMA neurons that give rise to cortico-striatal projections. Microstimulation in the MI territory of the putamen produces movements of the corresponding body parts, while that in the SMA territory does not (Alexander and DeLong, 1985; Nambu et al., 2002a). The probable pathway for inducing movements by microstimulation is the direct pathway. Stimulation of the striatum may excite direct pathway neurons, inhibit GPi and finally disinhibit thalamic and cortical activity. The microstimulation studies suggest that putaminal neurons in the MI and SMA territories project independently to different territories in the nucleus of the basal ganglia, and that somatotopy is preserved through the basal ganglia circuitry.

Striatal projection neurons are classified into direct and indirect pathway neurons on the basis of the difference in receptors, peptides, and targets. The two groups of neurons may represent similar somatotopy and show similar activity patterns during task performance. The striatum also contains interneurons. Although cholinergic interneurons receive common cortical inputs with neighboring projection neurons, they show reward-related activity (Aosaki et al., 1995), which is different from that of neighboring projection neurons. Parvalbumin (PV)-positive GABAergic interneurons also receive cortical inputs and are thought to regulate the activity of projection neurons through feed-forward inhibition (Tepper et al., 2008). PV-positive interneurons showed task-related activity (Gage et al., 2010), suggesting that they share similar cortical inputs with neighboring