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| **著者**  
| **Author(s)** | Iwamuro, Hirokazu / Tachibana, Yoshihisa / Ugawa, Yoshikazu / Saito, Nobuhito / Nambu, Atsushi |
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Information processing from the motor cortices to the subthalamic nucleus and globus pallidus and their somatotopic organizations revealed electrophysiologically in monkeys

Hirokazu Iwamuro,1,2,3 Yoshihisa Tachibana,1,4 Yoshikazu Ugawa,5 Nobuhiro Saito2 and Atsushi Nambu1

1Division of System Neurophysiology, National Institute for Physiological Sciences and Department of Physiological Sciences, SOKENDAI (Graduate University for Advanced Studies), 38 Nishigonaka, Myodaiji, Okazaki, Aichi 444-8585, Japan
2Department of Neurosurgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
3Department of Research and Therapeutics for Movement Disorders, Juntendo University Graduate School of Medicine, Tokyo, Japan
4Division of System Neuroscience, Kobe University Graduate School of Medicine, Kobe, Japan
5Department of Neurology, School of Medicine, Fukushima Medical University and Fukushima Global Medical Science Center, Advanced Clinical Research Center, Fukushima Medical University, Fukushima, Japan

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Abstract
To understand how the information derived from different motor cortical areas representing different body parts is organized in the basal ganglia, we examined the neuronal responses in the subthalamic nucleus (STN), and the external (GPe) and internal (GPi) segments of the globus pallidus (input, relay and output nuclei, respectively) to stimulation of the orofacial, forelimb and hindlimb regions of the primary motor cortex (MI) and supplementary motor area (SMA) in macaque monkeys under the awake state. Most STN and GPe/GPi neurons responded exclusively to stimulation of either the MI or SMA, and one-fourth to one-third of neurons responded to both. STN neurons responding to the hindlimb, forelimb and orofacial regions of the MI were located along the medial–lateral axis in the posterolateral STN, while neurons responding to the orofacial region of the SMA were located more medially than the others in the anteromedial STN. GPe/GPi neurons responding to the hindlimb, forelimb and orofacial regions of the MI were found along the dorsal–ventral axis in the posterolateral GPe/GPi, and neurons responding to the corresponding regions of the SMA were similarly but less clearly distributed in more anteromedial regions. Moreover, neurons responding to the distal and proximal forelimb MI regions were found along the lateral–medial axis in the STN and the ventral–dorsal axis in the GPe/GPi. Most STN and GPe/GPi neurons showed kinaesthetic responses with similar somatotopic maps. These observations suggest that the somatotopically organized inputs from the MI and SMA are well preserved in the STN and GPe/GPi with partial convergence.

Introduction
To elucidate the functions of the basal ganglia in normal and disease states, it is essential to understand how information derived from the cerebral cortex is processed through the cortico-basal ganglia loop (Alexander et al., 1986; Alexander & Crutcher, 1990a). The striatum and subthalamic nucleus (STN) are the input stations of the basal ganglia and receive excitatory cortical inputs. On the other hand, the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) are the output nuclei of the basal ganglia. Information from the cerebral cortex reaches the output nuclei via the following three major pathways: the cortico-STN-GPi/SNr hyperdirect, cortico-striato-GPi/SNr direct and cortico-striato-external pallido (GPe)-STN-GPi/SNr indirect pathways (Albin et al., 1989; Alexander & Crutcher, 1990a; Nambu et al., 2002a).

One of the key concepts of basal ganglia circuitry is the parallel processing hypothesis vs. the information convergence hypothesis. The parallel processing hypothesis proposes that information...
derived from different cortical areas is processed in parallel through different cortico-basal ganglia loops (Alexander et al., 1986; Hoover & Strick, 1993; Strick et al., 1995). The information convergence hypothesis proposes that inputs derived from different cortical areas are converged and integrated into the cortico-basal ganglia loops (Percheron & Filion, 1991; Percheron et al., 1994). Among them, the motor loop that originates from the primary motor cortex (MI), supplementary motor area (SMA) and premotor cortex (PM) has been most extensively analysed (Nambu et al., 1996; Takada et al., 1998; Nambu et al., 2011), and how information from different cortical areas is transferred to the basal ganglia has long been a focus of attention. Recent studies have suggested that parallel processing and information convergence may both occur within the basal ganglia (Haber et al., 2006; Nambu, 2011; Haynes & Haber, 2013). In fact, in the striatum, projections from the MI, SMA and PM overlap partially (Takada et al., 1998), and one-fourth of striatal neurons receive convergent inputs from both the MI and SMA (Nambu et al., 2002b). On the other hand, in the STN, axon terminals from the MI and SMA are partially intermingled (Nambu et al., 1996), but whether these projections converge at a single neuron level remains to be determined. Additionally, how information from different motor cortical areas is organized in the GPe and GPi remains to be clarified. The first objective of this study is to electrophysiologically investigate how MI- and SMA-inputs are represented at a single neuron level in the STN and GPe/GPi through the cortico-basal ganglia pathway.

Another key concept of basal ganglia circuitry is somatotopic organization. Somatotopy in the striatum has been confirmed by both anatomical and electrophysiological studies (Künzle, 1975; Alexander & DeLong, 1985; Alexander & Crutcher, 1990b; Flaherty & Graybiel, 1993; Takada et al., 1998; Nambu et al., 2002b; Takara et al., 2011). Somatotopy in the STN has also been revealed by anatomical and electrophysiological studies (Monakow et al., 1978; DeLong et al., 1985; Wichmann et al., 1994; Nambu et al., 1996). However, STN neurons have wide dendritic fields that cover large areas of the STN (Yelnik & Percheron, 1979), and their local axon collaterals terminate on neighbouring neurons in rodents (Kita et al., 1983), although they are not identified in primates (Sato et al., 2000). Therefore, somatotopic organization at a single neuron level is still not clear in the STN. On the other hand, somatotopy in the posterior parts of the GPe/GPi that mainly processes MI-inputs has been demonstrated electrophysiologically (DeLong, 1971; Georgopoulos et al., 1983; DeLong et al., 1985; Hamada et al., 1990; Nambu et al., 1990; Yoshida et al., 1993), but the more anterior and medial parts that are thought to process SMA-inputs have not been well studied yet. The second objective of this study is to elucidate somatotopic maps in the STN and GPe/GPi at a single neuron level by electrophysiologically analysing cortical inputs from the MI and SMA at the same time. The importance of somatotopic maps in the STN and GPe should be emphasized given the fact that they are clinically utilized to localize the target areas for stereotactic surgery for the treatment of movement disorders, including Parkinson’s disease, dyskinesia and dystonia (Vitek et al., 1999; Gross et al., 2006; Obeso et al., 2008; Maiti et al., 2016).

Here, we performed recordings of neuronal activity in the STN and GPe/GPi of the monkey, and extensively investigated their responses to stimulation of the orofacial, forelimb and hindlimb regions of the MI and SMA to clarify information processing and somatotopic maps in the STN and GPe/GPi.

Materials and methods

Animals

Two adult female monkeys (P8, Macaca fuscata and P6, Macaca cyclopis; body weight 4.0–5.0 kg) were used in this study. They were trained daily to quietly sit in a monkey chair. Monkey P8 was trained to be accustomed to passive movements of body parts. The experimental protocols were approved by the Institutional Animal Care and Use Committee of National Institutes of Natural Sciences. All experiments were conducted according to the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Surgery and MRI acquisition

Under general anaesthesia with ketamine hydrochloride (10 mg/kg body weight, i.m.), xylazine hydrochloride (1 mg/kg, i.m.) and sodium thiopental (25 mg/kg, i.v.), the monkeys received a surgical operation to fix their heads painlessly in a stereotactic frame attached to a monkey chair as previously described (Nambu et al., 2000, 2002b). After the skin incision, the skull was widely exposed, and its periosteum was completely removed. Small polyethylene ether ketone (PEEK) screws were attached to the skull as anchors. The exposed skull and screws were completely covered with transparent acrylic resin. Two PEEK pipes were mounted in parallel over the frontal and occipital areas for head fixation. All surgical procedures were performed under aseptic conditions. All materials that were attached to the monkeys’ skulls were compatible with magnetic resonance imaging (MRI). Arterial oxygen saturation and heart rate were monitored during the surgery. Depth of anaesthesia was assessed by heart rate and body movements. Anaesthetic agents were additionally administered when necessary. Antibiotics and analgesics were administered after the surgery.

A few days after the surgery, structural MRI (3D MP-RAGE, 192 axial slices, 0.8 mm thickness, TR/TE = 2500/5.16 ms, 144 × 192 matrix size, yielding to isotropic voxels of 0.8 mm) was acquired by a 3T MRI scanner (3T Allegra; Siemens, Erlangen, Germany) without painless head fixation under anaesthesia with ketamine hydrochloride (10 mg/kg, i.m.) and xylazine hydrochloride (1 mg/kg, i.m.). Arterial oxygen saturation and heart rate were monitored during MRI scanning. Depth of anaesthesia was assessed by heart rate and body movements. The MRI scan helped to localize the STN and GPe/GPi prior to electrophysiological recording and to reconstruct recording sites histologically in the STN and GPe/GPi.

Implantation of stimulating electrodes into the cerebral cortex

After full recovery from the surgery, the skull over the central sulcus and midline was removed under anaesthesia with ketamine hydrochloride (10 mg/kg, i.m.) and xylazine hydrochloride (1 mg/kg, i.m.) with local lidocaine application, and electrophysiological mapping of the MI and SMA was performed (Fig. 1; Nambu et al., 2000, 2002b). According to this mapping, pairs of bipolar intra-cortical stimulating electrodes (composed of 200-μm-diameter enamel-coated stainless steel wires; intertip distance, 2 mm) were chronically implanted into the following regions in the MI (at a depth of 4 mm from the dural surface) and SMA (at a depth of 5 mm from the dural surface): In Monkey P8, the orofacial (MIo), distal forelimb (MIIfd) and proximal forelimb (MIIfp), and hindlimb (MIhl) regions of the MI, and the orofacial (SMAo), forelimb (SMAf) and hindlimb (SMAh) regions of the SMA (Fig. 1), in Monkey P6, the same regions as those in Monkey P8 except for the...
SMAo. In the analyses, MIfd and MIfp were dealt with together as the forelimb region (MIf) of the MI. These stimulating electrodes were fixed to the skull with acrylic resin, and exposed cortical areas were covered with additional acrylic resin except for two openings (10–15 mm diameter) used for accessing the STN and GPe/GPi. A rectangular plastic chamber was attached to cover two openings. Depth of anaesthesia was assessed by body movements, and ketamine hydrochloride and xylazine hydrochloride were additionally administrated when necessary. Antibiotics and analgesics were administered after the above procedures.

**Recording of STN and GPe/GPi neuronal activity**

One week after the implantation of cortical stimulating electrodes, recording neuronal activity in the STN and GPe/GPi was started in the awake state. During the recording sessions, the monkeys were calmly seated in the monkey chair with their heads restrained.

A glass-coated Elgiloy-alloy microelectrode (1.5–2.0 MΩ at 1 kHz for STN recording, 0.8–1.2 MΩ at 1 kHz for GPe/GPi recording) was inserted vertically into the STN or obliquely (50° for Monkey P8, 45° for Monkey P6 from vertical in the frontal plane) into the GPe/GPi with a hydraulic microdrive (Narishige Scientific Instruments, Tokyo, Japan). Neuronal signals in the STN and GPe/GPi were amplified (8000 times), filtered (200–2 kHz) and monitored using an oscilloscope. The unitary activity was carefully isolated, converted into digital data with a home-made time–amplitude window discriminator and then sampled at 2 kHz with a computer. Spontaneous unit activity was recorded for 50 s and confirmed as a single unit activity by checking refractory periods around 0 ms in autocorrelograms. Cortical stimulation (300-μs duration, single pulse, 0.7-mA strength, at 0.7 Hz) was delivered via the stimulating electrodes implanted in the MI and SMA. These stimulation parameters were determined by a series of our previous studies (Nambu et al., 2000, 2002b; Kita et al., 2004, 2005; Tachibana et al., 2008; Takara et al., 2011). Neuronal responses to cortical stimulation were examined and stored on the computer with constructing peristimulus time histograms (PSTHs; bin width of 1 ms; sum of 100 times). Further, in Monkey P8, kinaesthetic responses of each neuron to passive movement of the following body parts were examined: the orofacial part (lip and jaw), contralateral forelimb (digit, wrist, elbow, and shoulder) and hindlimb (ankle, knee and hip). Examination of kinaesthetic response was always performed by the same experimenter. The activity was audiomonitored, and the body part whose movements evoked the strongest response was determined in each neuron.

**Data analysis**

For each PSTH, we calculated the mean and standard deviation (SD) of the discharge rate during the 100-ms period preceding the stimulation, and considered them as the baseline discharge rate. We then indicated the mean and mean ± 1.65 SD (corresponding to $P < 0.05$, one-tailed $t$-test) in each PSTH by grey solid (mean) and dashed (mean ± 1.65 SD) lines, respectively (see Fig. 2). Changes in neuronal activity in response to cortical stimulation were judged to be significant if the discharge rate during at least two consecutive bins (2 ms) exceeded the dashed lines (Nambu et al., 2000; Tachibana et al., 2008). The latency of each response was defined as the
time at which the first bin of the two consecutive bins exceeded the dashed lines. The responses were judged to end when two consecutive bins fell below the dashed lines. Because the latency of each response component was different between MI- and SMA-stimulation (Table 1), we could not set constant values as the latency thresholds for early and late excitations under all stimulus conditions. Instead, based on the observed latencies for biphasic STN responses and triphasic GPe/GPi responses (Fig. 2), we set the latency thresholds for early and late excitations as 13 ms (MI-stimulation) and 17 ms (SMA-stimulation) in the STN and as 19 ms (MI-stimulation) and 22 ms (SMA-stimulation) in the GPe/GPi. The amplitude of each component of cortically evoked responses was defined as the number of spikes during the significant response minus that of the baseline discharge in the PSTH (i.e. the area of the response). Among cortical regions whose stimulation induced a significant response component in a neuron, the major cortical input region was defined as the cortical region whose stimulation induced the maximum amplitude of the response, and the

Fig. 2. Neuronal responses in the subthalamic nucleus (STN), and the external (GPe) and internal (GPi) segments of the globus pallidus evoked by cortical stimulation. Typical response patterns of STN (A1–3), GPe (B1–7) and GPi (C1–7) neurons to the stimulation of the cortex are shown in peristimulus time histograms (PSTH; bin width of 1 ms; 100 stimulus trials). Cortical stimulation (duration 300 μs, single pulse, 0.7 mA) was delivered at time 0 (arrows). The mean and mean ± 1.65 SD (corresponding to $P < 0.05$, one-tailed $t$-test) are indicated in PSTHs by grey solid and dashed lines, respectively. The percentages of the response patterns are indicated in Venn diagrams (A4, B8, C8). An early excitation (Early ex), an inhibition (Inh) and a late excitation (Late ex) are indicated by different colours. Ex, excitation; Inh, inhibition. Ex-inh-ex indicates the response consisting of an early excitation followed by an inhibition and a late excitation.
and the external (GPe) and internal (GPi) segments of the globus pallidus evoked by the stimulation of the orofacial, forelimb and hindlimb regions (MIo, MIf, Mlh, MIf, MIf, MIf). Their distribution according to major cortical inputs was compared among the cortico-striatal stimulation sites. The early and late excitations in STN neurons displayed significant responses to stimulation of the MI and/or SMA (Fig. 1). The spontaneous firing rates of STN, GPe and GPi neurons were 22.2 ± 11.1, 59.1 ± 26.0 and 66.2 ± 22.6 (mean ± SD) Hz, respectively.

Reconstruction of recording sites

At the end of the recording sessions, anatomically important landmarks, such as dorsal borders of the STN and GPe and border between the GPe and GPi, were marked by passing cathodal DC current (20 μA for 30 s) through the recording electrode. Then, monkeys were deeply anaesthetized with sodium pentobarbitol (50 mg/kg, i.v.) and perfused transcardially with 0.1 M phosphate buffer (pH 7.3) followed by 10% formalin in 0.1 M phosphate buffer, 0.1 M phosphate buffer containing 30% sucrose at 4 °C. They were extracted and kept in the same buffer containing 30% sucrose. The brains were extracted and the external (GPe) and internal (GPi) segments of the globus pallidus evoked by the stimulation of the orofacial, forelimb and hindlimb regions (MIo, MIf, Mlh) of the primary motor cortex (MI) and the orofacial, forelimb and hindlimb regions (SMAo, SMAf, SMAd) of the supplementary motor area (SMA). *Significantly different between MI-induced and SMA-induced responses (unpaired t-tests, P < 0.01).

Minor cortical regions were defined as other cortical regions. If a neuron showed a significant response to a single cortical region, the major cortical input region was defined as this cortical region.

Overview of cortically evoked responses of STN and GPe/GPi neurons

In this study, a total of 777 STN (463 neurons in Monkey P8; 314 neurons in Monkey P6), 503 GPe (331 in P8; 172 in P6) and 435 GPi (292 in P8; 143 in P6) neurons were recorded. Among them, we analysed 398 STN (254 in P8; 144 in P6), 343 GPe (197 in P8; 146 in P6) and 247 GPi (147 in P8; 100 in P6) neurons that displayed significant responses to stimulation of the MI and/or SMA (Fig. 1). The spontaneous firing rates of STN, GPe and GPi neurons were 22.2 ± 11.1, 59.1 ± 26.0 and 66.2 ± 22.6 (mean ± SD) Hz, respectively.

Stimulation of the MI and/or SMA induced 772 significant responses in 398 STN neurons (several neurons responded to the stimulation of more than one cortical region). As shown in Fig. 2A, a biphasic response consisting of an early excitation followed by a late excitation was the most commonly induced (Fig. 2A1), and responses only with an early excitation (Fig. 2A2) or a late excitation (Fig. 2A3) were occasionally observed (see also Fig. 2A4). The response patterns and their distributions were similar among the cortical stimulation sites. The early and late excitations in STN neurons induced by MI-stimulation had significantly shorter latencies than those induced by SMA-stimulation (unpaired t-tests, P < 0.01; Table 1).

Similarly, stimulation of the MI and/or SMA induced 740 significant responses in 343 GPe neurons and 485 significant responses in 247 GPi neurons. As shown in Fig. 2B,C, a triphasic response consisting of an early excitation followed by an inhibition and a late excitation was the most frequently induced in both the GPe and GPi (Fig. 2B1,C1). Other types of responses lacking one or two of these components were also observed (Fig. 2B2–C2–C7), that is, an excitation followed by an inhibition, biphasic excitations and an inhibition followed by an excitation (see also Fig. 2B8,C8). The response components in GPe and GPi neurons evoked by MI-stimulation had significantly shorter latencies than those induced by SMA-stimulation (unpaired t-tests, P < 0.01; Table 1).

Results

Overview of cortically evoked responses of STN and GPe/GPi neurons

Table 1. Latency of each response component to MI- and SMA-stimulation

| Cortical stimulating site | STN | GPe | GPi |
|--------------------------|-----|-----|-----|
| Early excitation | Late excitation | Early excitation | Inhibition | Late excitation | Early excitation | Inhibition | Late excitation |
| MI | 6.7 ± 1.8* | 17.8 ± 3.8* | 9.2 ± 2.0* | 16.7 ± 3.0* | 28.1 ± 4.4* | 10.0 ± 2.6* | 19.4 ± 4.6* | 28.2 ± 5.2* |
| MIo | 7.0 ± 1.9 | 16.5 ± 3.1 | 10.3 ± 2.1 | 16.1 ± 2.8 | 27.3 ± 4.1 | 10.4 ± 2.0 | 19.0 ± 5.6 | 27.0 ± 5.0 |
| MIf | 6.2 ± 1.6 | 18.5 ± 3.7 | 8.9 ± 2.0 | 16.7 ± 3.3 | 27.4 ± 4.4 | 10.2 ± 3.0 | 20.1 ± 4.2 | 27.8 ± 4.4 |
| Mlh | 7.3 ± 1.6 | 18.2 ± 4.6 | 9.2 ± 1.8 | 16.8 ± 2.4 | 29.4 ± 4.3 | 9.4 ± 2.3 | 18.5 ± 4.2 | 30.9 ± 5.9 |
| SMA | 9.4 ± 2.0* | 25.8 ± 5.5* | 12.4 ± 2.1* | 22.6 ± 4.1* | 34.8 ± 5.5* | 13.7 ± 3.6* | 25.6 ± 5.5* | 38.5 ± 7.3* |
| SMAo | 9.9 ± 1.9 | 32.8 ± 3.8 | 13.5 ± 1.9 | 27.8 ± 5.7 | 41.4 ± 5.2 | 14.0 ± 2.3 | 29.0 ± 4.8 | 43.8 ± 6.0 |
| SMAf | 9.2 ± 2.0 | 25.2 ± 4.7 | 12.2 ± 2.2 | 22.4 ± 2.9 | 35.3 ± 5.1 | 14.2 ± 4.5 | 25.9 ± 5.7 | 37.6 ± 7.1 |
| SMAd | 9.3 ± 2.0 | 24.6 ± 5.3 | 11.6 ± 1.8 | 20.5 ± 2.4 | 31.9 ± 4.4 | 12.0 ± 2.5 | 22.1 ± 3.4 | 34.2 ± 5.1 |

Numbers indicate latencies in ms (mean ± SD) of each response component (early excitation, inhibition and late excitation) in the subthalamic nucleus (STN) and the external (GPe) and internal (GPi) segments of the globus pallidus evoked by the stimulation of the orofacial, forelimb and hindlimb regions (MIo, MIf and Mlh) of the primary motor cortex (MI) and the orofacial, forelimb and hindlimb regions (SMAo, SMAf, SMAd) of the supplementary motor area (SMA). *Significantly different between MI-induced and SMA-induced responses (unpaired t-tests, P < 0.01).
responded exclusively to a single somatotopic region, and the remaining 20% of neurons responded to two adjacent somatotopic regions, such as orofacial and forelimb regions of the MI (Mo + f) and forelimb and hindlimb regions of the MI (MIf + h). SMA-recipient STN neurons tended to receive more convergent inputs from two adjacent somatotopic regions, and this tendency was more evident in MI + SMA-recipient STN neurons (Table 2).

Cortically evoked responses of GPe/GPi neurons by MI- and SMA-stimulation

External segment of the globus pallidus and GPi neurons were classified into MI-, SMA- and MI + SMA-recipient neurons based on the cortically evoked early excitation, inhibition and/or late excitation (Tables 3 and 4). Around two-thirds of GPe neurons and around three-fourths of GPi neurons were classified as MI- or SMA-recipient neurons, and the remaining one-third of GPe neurons and one-fourth of GPi neurons as MI + SMA-recipient neurons. Around 80% of the MI-recipient GPe/GPi neurons received inputs from a single somatotopic region, and the remaining 20% of neurons received inputs from two adjacent somatotopic regions (Tables 3 and 4). SMA-recipient GPe/GPi neurons also received inputs from a single somatotopic region; however, they tended to receive more convergent inputs from two adjacent somatotopic regions. These convergent inputs were more evident in MI + SMA-recipient GPe/GPi neurons.

Locations of recorded STN neurons

Locations of STN neurons were plotted according to the cortically evoked early excitation in *Monkey P8* (Figs 3A and 4). Neurons

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**Table 2. Classification of STN neurons according to cortical inputs**

|                | Early excitation | Late excitation | Total     | Late excitation |
|----------------|------------------|-----------------|-----------|----------------|
|                | P8               | P6              | N = 379   | N = 144        |
| STN neurons    |                  |                 | N = 325   |                |
| MI-recipient   |                  |                 | N = 179   |                |
| Single body part | 49   | 68              | 117 (31%) | 15            |
| Mo             | 29              | 33              | 10        | 2              |
| MIf            | 10              | 6               | 3         | 3              |
| MIf + h        | 7               | 14              | 21 (18%)  | 0             |
| MI + f         | 7               | 7               | 0         | 0              |
| MI + f + h     | 0               | 7               | 0         | 0              |
| Other combinations | 0   | 0               | 0 (0%)    | 0             |
| SMA-recipient  |                  |                 | N = 128   |                |
| Single body part | 25   | 25              | 77 (51%)  | 63            |
| SMAo           | 15              | 12              | 17        | 11             |
| SMAf           | 17              | 8               | 30        | 21             |
| SMA + f        | 58              | 5               | 63 (42%)  | 30             |
| SMA + f + h    | 20              | 5               | 15        | 15             |
| Other combinations | 10   | 0               | 10 (7%)   | 1              |
| SMA + f + h    | 10              | –               | 1         | –              |
| MI + SMA-recipient | 75  | 37              | 112 (29%) | 36            |
| Single body part | 27   | 7               | 34 (30%)  | 27            |
| (MI + SMA)o    | 0               | –               | 0         | 0              |
| (MI + SMA)f    | 27              | 6               | 27        | 7              |
| (MI + SMA)h    | 0               | 1               | 0         | 1              |
| Two adjacent parts | 37   | 24              | 61 (55%)  | 8             |
| Mo + SMAo      | 1               | 1               | 0         | 0              |
| Mo + (MI + SMA)f | 2   | 6               | 0 (10)    | 2             |
| SMAo + (MI + SMA)f | 4   | –               | 0         | –              |
| MIf + SMAo     | 0               | 5               | 0         | 0              |
| MIf + SMAo + MIf | 0   | 0               | 0         | 0              |
| MIf + SMAo + MIf + MIf | 16 | 2               | 2         | 3              |
| MIf + (MI + SMA)h | 0   | 5               | 0         | 3              |
| (MI + SMA)h + h | 0               | 3               | 1         | 4              |
| SMAf + MIf     | 10              | 1               | 5         | 1              |
| SMAf + (MI + SMA)o | 4  | 1               | 0         | 1              |
| Other combinations | 11   | 6               | 17 (15%)  | 1             |
| Mo + SMAah     | 1               | 0               | 0         | 1              |
| Mo + SMAah + h | 2               | 1               | 1         | 2              |
| Mo + f + SMAah | 0               | 1               | 0         | 3              |
| Mo + (MI + SMA)f + SMAah | 3 | 4               | 0         | 3              |
| Mo + f + (MI + SMA)h | 0 | 0               | 0         | 1              |
| SMAo + f + MIf | 4               | –               | 0         | –              |
| SMAo + f + (MI + SMA)h | 1 | –               | 0         | –              |

Numbers of STN neurons in two monkeys (P8 and P6) are shown according to responses (early and late excitations) evoked by cortical stimulation (Mo, MIf, MIf, SMAo, SMAf and SMAh).

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receiving inputs from the MI and/or SMA were located in the dorsal and central STN. MI-recipient neurons were predominantly found in the posterolateral domain, while SMA-recipient neurons were mainly found in the anteromedial domain (Fig. 3A1). MI + SMA-recipient neurons were distributed in both the MI and SMA domains, especially in the transition zone between the MI and SMA domains. These distribution differences between MI-, SMA- and MI+ SMA domains were mainly found in the anteromedial domain (Fig. 3A1).

Dorsal and central STN. MI-recipient neurons were predominantly receiving inputs from the MI and/or SMA were located in the most lateral and the most medial parts, respectively, and MI-recipient neurons were found in between them (Fig. 4A1). MIo-recipient neurons were found more ventrally than MIf- and MIh-recipient neurons. These distribution differences of MIo-, MIf- and MIh-recipient neurons were found in between them (Fig. 4A1).

Table 3. Classification of GPe neurons according to cortical inputs

|                   | Early excitation | Inhibition | Late excitation |
|-------------------|------------------|------------|-----------------|
|                   | P8     | P6     | Total | P8  | P6  | Total | P8  | P6  | Total |
| GPe neurons       |        |        |       |      |      |       |      |      |       |
| MI-recipient      | 59     | 62     | 121 (39%) | 25  | 39  | 64 (24%) | 25  | 40  | 65 (23%) |
| Single body part  | 56     | 50     | 106 (88%) | 24  | 26  | 50 (78%) | 25  | 27  | 52 (80%) |
| Mio               | 10     | 12     | 22    | 4   | 11   | 15    | 4   | 9    | 13 |
| MIf               | 15     | 21     | 36    | 4   | 4    | 8    | 1   | 5    | 6 |
| MIh               | 31     | 17     | 48    | 16  | 11   | 27    | 20  | 13   |
| Two adjacent parts| 3      | 12     | 15 (12%) | 1   | 13   | 14 (22%) | 0   | 13   | 13 (20%) |
| Mio + f           | 1      | 3      | 4     | 0   | 10   | 10    | 0   | 11   | 11 |
| MIf + h           | 2      | 9      | 11    | 1   | 3    | 4     | 0   | 2    | 2 |
| Other combinations| 0      | 0      | 0 (0%) | 0   | 0    | 0 (0%) | 0   | 0    | 0 (0%) |
| SMA-recipient     | 90     | 21     | 111 (35%) | 85  | 23   | 108 (40%) | 76  | 26   | 102 (35%) |
| Single body part  | 55     | 18     | 73 (66%) | 62  | 22   | 84 (78%) | 55  | 25   | 80 (78%) |
| SMAo              | 19     | –      | 19    | 16  | 4    | 20    | 4   | –    | – |
| SMAf              | 33     | 13     | 46    | 37  | 15   | 52    | 45  | 17   | 62 |
| SMAh              | 3      | 5      | 8     | 9   | 7    | 16    | 6   | 8    | 14 |
| Two adjacent parts| 35     | 3      | 38 (34%) | 23  | 1    | 24 (22%) | 21  | 1    | 22 (22%) |
| SMAo + f          | 30     | –      | 30    | 20  | –    | 20    | 19  | –    | – |
| SMAf + h          | 5      | 3      | 8     | 3   | 1    | 4     | 2   | 1    | 3 |
| Other combinations| 0      | 0      | 0 (0%) | 0   | 0    | 0 (0%) | 0   | 0    | 0 (0%) |
| MI + SMA-recipient| 36     | 46     | 82 (26%) | 34  | 63   | 97 (36%) | 43  | 78   | 121 (42%) |
| Single body part  | 24     | 19     | 43 (52%) | 20  | 10   | 30 (31%) | 29  | 14   | 43 (36%) |
| (MI + SMA) o       | 0      | –      | 0     | 0   | –    | 0     | –   | –    | – |
| (MI + SMA) f       | 15     | 12     | 27    | 11  | 3    | 14    | 18  | 9    | 27 |
| (MI + SMA) h       | 9      | 7      | 16    | 9   | 7    | 16    | 11  | 5    | 16 |
| Two adjacent parts | 10     | 25     | 35 (43%) | 13  | 41   | 54 (56%) | 13  | 50   | 63 (52%) |
| Mio + SMA          | 1      | 5      | 6     | 0   | 4    | 4     | 3   | 6    | 9 |
| Mio + (MI + SMA)f | 1      | 2      | 3     | 5   | 14   | 19    | 1   | 5    | 6 |
| SMAo + (MI + SMA)f| 3      | –      | 3     | –   | 1    | 1     | 0   | –    | – |
| Mif + SMAh         | 0      | 3      | 3     | 0   | 3    | 3     | 0   | 3    | 3 |
| (MI + SMA)f + MIh  | 0      | 0      | 0     | 0   | 2    | 2     | 2   | 4    | 4 |
| (MI + SMA)f + SMAh | 0      | 3      | 3     | 0   | 1    | 1     | 0   | 0    | 0 |
| Mif + (MI + SMA)h  | 6      | 5      | 11    | 0   | 9    | 9     | 0   | 14   | 14 |
| (MI + SMA)f + h    | 0      | 5      | 5     | 0   | 7    | 7     | 1   | 7    | 8 |
| SMAf + Mlh         | 2      | 1      | 3     | 5   | 0    | 5     | 3   | 0    | 3 |
| SMAf + (MI + SMA)h | 3      | 1      | 4     | 2   | 1    | 3     | 3   | 1    | 4 |
| Other combinations | 2      | 2      | 4 (5%) | 1   | 12   | 13 (13%) | 1   | 14   | 15 (12%) |
| Mio + SMAh         | 0      | 0      | 0     | 0   | 1    | 1     | 0   | 2    | 2 |
| Mio + SMAf + h     | 0      | 1      | 1     | 0   | 1    | 1     | 0   | 1    | 1 |
| Mio + f + SMAh     | 0      | 0      | 0     | 0   | 3    | 3     | 0   | 1    | 1 |
| Mio + (MI + SMA)f + SMAh | 0 | 3 | 3 | 0 | 3 | 3 |
| Mio + f + (MI + SMA)h | 0 | 1 | 1 | 0 | 3 | 3 |
| Mio + (MI + SMA)f + h | 0 | 0 | 0 | 0 | 3 | 3 |
| SMAo + (MI + SMA)f + MIh | 0 | 0 0 |
| SMAo + (MI + SMA)f + h | 0 | 0 0 |
| SMAo + f + (MI + SMA)h | 0 | 0 0 |

Numbers of GPe neurons in two monkeys (P8 and P6) are shown according to responses (early excitation, inhibition and late excitation) evoked by cortical stimulation (Mio, MIf, MIh, SMAo, SMAf and SMAh).
evoked responses was a biphasic response consisting of an early excitation and a late excitation (Fig. 2A), and as the categorization of STN neurons based on the early and late excitations showed similar results (Table 2).

**Locations of recorded GPe/GPi neurons**

Locations of GPe/GPi neurons were plotted according to the cortically evoked early excitation in *Monkey P8* (Figs 3B and 6). Neurons receiving inputs from the MI and/or SMA were located in the posterior section of the GPe/GPi, MI-recipient neurons were mainly located in the posterolateral domain, while SMA-recipient neurons were found in the more anterior and medial domain (Fig. 3B1). This distribution difference between MI- and SMA-recipient neurons was significant (Bonferroni test, *P* < 0.05; Fig. 3B2,3). MI + SMA-recipient neurons were distributed in both the MI and SMA domains, especially in the transition zone between the MI and SMA domains. In the MI domain, MII-, MIF- and MIh-recipient neurons were distributed in the ventral parts in the GPe/GPi (Fig. 6A1). The distribution of MIh-, MIF- and MIh-recipient neurons along the dorsal–ventral axis was significant (Bonferroni test, *P* < 0.05; Fig. 6A2,3). In the SMA domain, a

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**Table 4. Classification of GPi neurons according to cortical inputs**

|                  | Early excitation | Inhibition | Late excitation |
|------------------|------------------|------------|-----------------|
|                  | *P8*  | *P6* | Total | *P8*  | *P6* | Total | *P8*  | *P6* | Total |
| GPi neurons      |       |       |       |       |       |       |       |       |       |
| MI-recipient     | 34    | 59   | 93 (41%) | 15    | 45   | 60 (30%) | 16    | 49   | 65 (32%) |
| Single body part | 31    | 51   | 82 (88%) | 14    | 33   | 47 (78%) | 15    | 33   | 48 (74%) |
| Mio              | 6     | 23   | 5     | 2     | 2    | 4     | 21    |       |       |
| MIF              | 13    | 15   | 28    | 2     | 2    | 4     | 2     | 2     | 4     |
| MIh              | 12    | 13   | 25    | 7     | 12   | 19    | 9     | 10    | 19    |
| Two adjacent parts | 3    | 8    | 11 (12%) | 1     | 12   | 13 (22%) | 1     | 16   | 17 (26%) |
| Mio + f          | 2     | 5    | 7     | 1     | 9    | 10    | 1     | 12    | 13    |
| MIF + h          | 1     | 3    | 4     | 0     | 3    | 3     | 0     | 4     | 4     |
| Other combinations | 0    | 0    | 0 (0%) | 0     | 0    | 0 (0%) | 0     | 0    | 0 (0%) |
| SMA-recipient    | 74    | 13   | 87 (38%) | 67    | 15   | 82 (40%) | 79    | 14   | 93 (46%) |
| Single body part | 46    | 11   | 57 (66%) | 50    | 14   | 64 (78%) | 51    | 11   | 62 (67%) |
| SMAo             | 32    | 25   | 57    | 28    | 31   | 61 (71%) | 27    | 31   | 61 (71%) |
| SMAf             | 11    | 5    | 16    | 20    | 25   | 40 (80%) | 21    | 5     | 26 (50%) |
| SMAh             | 3     | 6    | 9     | 5     | 9    | 14 (28%) | 7     | 6     | 13 (28%) |
| Two adjacent parts | 27   | 2    | 29 (33%) | 16    | 1    | 17 (21%) | 28    | 3    | 31 (33%) |
| SMAo + f         | 24    | 2    | 26    | 11    | 1    | 12 (31%) | 26    | 1    | 12 (31%) |
| SMAo + h         | 3     | 2    | 5     | 5     | 1    | 6 (20%)  | 2     | 3     | 5 (20%)  |
| Other combinations | 1    | 0    | 1 (1%) | 1     | 0    | 1 (1%)  | 0     | 0    | 0 (0%)  |
| SMAo + f + h     | 1     | –    | –     | 1     | –    | –      | 0     | –    | –      |
| MI + SMA-recipient | 31   | 18   | 49 (21%) | 37    | 24   | 61 (30%) | 10    | 33   | 43 (22%) |
| Single body part | 16    | 4    | 20 (41%) | 22    | 13   | 35 (58%) | 7     | 7     | 14 (32%) |
| (MI + SMAo)      | 0     | –    | –     | 0     | –    | –      | 1     | –    | –      |
| (MI + SMAf)      | 7     | 3    | 10    | 11    | 10   | 21 (21%) | 3     | 3     | 6      |
| (MI + SMAh)      | 9     | 1    | 10    | 12    | 3    | 15 (25%) | 3     | 4     | 7      |
| Two adjacent parts | 13   | 12   | 25 (51%) | 15    | 9    | 24 (39%) | 2     | 19   | 21 (49%) |
| Mio + SMAf       | 1     | 2    | 3     | 1     | 0    | 1      | 0     | 6     | 6      |
| Mio + (MI + SMA)f | 2     | 4    | 6     | 2     | 3    | 5      | 0     | 7     | 7      |
| (MI + SMAo) + SMAf | 1   | –    | –     | 1     | –    | –      | 0     | –    | –      |
| (MI + SMAo) + f   | 1     | –    | –     | 1     | –    | –      | 0     | –    | –      |
| SMAo + (MI + SMA)f | 3  | –    | –     | 5     | –    | –      | 0     | –    | –      |
| MIF + SMAh       | 0     | 4    | 4     | 0     | 4    | 4      | 0     | 4     | 4      |
| (MI + SMAf) + SMAh | 0 | 0    | –     | 1     | 0    | –      | 1     | 0     | –      |
| MIF + (MI + SMA)h | 0 | 0    | –     | 1     | 0    | –      | 0     | 1     | –      |
| (MI + SMAf) + h   | 0     | 1    | 1     | 0     | 0    | –      | 0     | 1     | –      |
| SMAf + MIh       | 2     | 1    | 3     | 1     | 0    | 1      | 0     | 2     | 2      |
| SMAf + (MI + SMA)h | 3  | 0    | 3     | 0     | 3    | 3      | 0     | 3     | 3      |
| Other combinations | 2    | 2    | 4 (8%) | 0     | 2    | 2 (3%)  | 1     | 7     | 8 (19%) |
| Mio + SMAh       | 0     | 1    | 1     | 0     | 0    | –      | 0     | 0     | –      |
| Mio + SMAf + h   | 0     | 1    | 1     | 0     | 0    | –      | 0     | 1     | –      |
| Mio + (MI + SMA)f + SMAh | 0 | 0    | –     | 1     | 0    | –      | 0     | 1     | –      |
| Mio + f + SMAh   | 0     | 0    | 0     | 0     | 0    | –      | 0     | 1     | –      |
| Mio + f + (MI + SMA)h | 0 | 0    | –     | 0     | 0    | –      | 0     | 2     | –      |
| Mio + (MI + SMA)f + h | 0 | 0    | –     | 1     | 0    | –      | 0     | 1     | –      |
| Mio + SMAf + (MI + SMA)h | 0 | 0    | –     | 0     | 0    | –      | 0     | 1     | –      |
| SMAo + (MI + SMA)f + h | 1 | 0    | –     | 0     | 0    | –      | 0     | 1     | –      |
| SMAo + f + MIh   | 0     | –    | –     | 0     | –    | –      | 0     | 0     | –      |
| SMAo + f + (MI + SMA)h | 1 | –    | –     | 0     | –    | –      | 0     | –    | –      |
similar somatotopy along the dorsal–ventral axis could be observed, but was more ambiguous (Fig. 6B1–3). SMAo-recipient neurons were found in the most anterior part of the GPe/GPi (Fig. 6B2,3). (However, see the ‘Somatotopic arrangements in the GPe/GPi’ in the Discussion section.) GPe/GPi neurons receiving convergent inputs from two adjacent somatotopic regions were located in the transition zone between two somatotopic regions of the GPe/GPi. These distributions of GPe/GPi neurons were found in both Monkeys P8 and P6, although their responses to SMAo-stimulation were not tested in Monkey P6.

We also drew somatotopic maps of the GPe and GPi based on the inhibition and late excitation and obtained similar results to those based on the early excitation described above (Fig. 5B for MIf-stimulation). Again, these distributions are expected, as the major response pattern of cortically evoked responses was a triphasic response consisting an early excitation followed by an inhibition and a late excitation (Fig. 2B,C), and as the categorization of GPe/GPi neurons based on the early excitation, inhibition and late excitation showed similar results (Tables 3 and 4).

**Detailed cortical inputs from the forelimb region of the MI to the STN and GPe/GPi**

We further analysed the responses to stimulation of the distal (MIfd) and proximal (MIfp) forelimb regions of the MI. Among STN, GPe and GPi neurons responding to MIf- or MIf + SMA-stimulation, a

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**Fig. 3.** Distribution of primary motor cortex (MI)- and/or supplementary motor area (SMA)-inputs in the subthalamic nucleus (STN) and GPe/GPi. Locations of STN (A1) and GPe/GPi (B1) neurons that showed an early excitation evoked by MI- and/or SMA-stimulation are indicated with different colours in Monkey P8. Crosses and bars represent no early excitations and no responses to MI- and/or SMA-stimulation, respectively. Sections along the anterior–posterior axis are arranged from left to right. The distance of the sections from the auditory meatus is shown in millimetres. Histograms show the locations of STN (A2), GPe (B2) and GPi (B3) neurons with MI- and/or SMA-inputs according to Horsley–Clark stereotaxic coordinates along the anterior–posterior (AP), medial–lateral (ML) and dorsal–ventral (DV) axes. Dashed vertical lines indicate means of the locations. *Significantly different (one-way ANOVA with Bonferroni post hoc test, P < 0.05).
certain number of them responded to stimulation of only MI\(d\), only MI\(p\) or both MI\(d\) and MI\(p\) (MI\(d+p\)) (Table 5). The locations of these STN and GPe/GPi neurons were plotted according to the early excitation evoked by MI\(d\)- and MI\(p\)-stimulation (Fig. 7). In the STN, MI\(d\)-recipient neurons were found more laterally than MI\(p\)-recipient neurons (Fig. 7A1, 2; Bonferroni test, \(P < 0.05\)), and MI\(d+p\)-recipient neurons were located in between. In both the GPe and GPi, MI\(d\)-recipient neurons were found more ventrally than MI\(p\)-recipient neurons (Fig. 7B1 – 3; Bonferroni test, \(P < 0.05\)), and MI\(d+p\)-recipient neurons were located in between.

Kinaesthetic responses of STN and GPe/GPi neurons

In Monkey P8, kinaesthetic responses of STN, GPe and GPi neurons exhibiting a cortically evoked early excitation were also examined (Table 6). Most of the MI-recipient and MI + SMA-recipient STN, GPe and GPi neurons showed kinaesthetic responses, typically transient increase (or occasionally decrease) of firing rates during passive joint movements and/or muscle palpation, while less of the SMA-recipient neurons did. The majority of them responded to a single body part, and the remaining neurons responded to two adjacent body parts.

Locations of neurons were plotted according to the body part whose movements evoked the strongest response in each neuron (Fig. 8). In the STN, the neurons responding to the orofacial movements were located in the most lateral and the most medial parts, and the neurons responding to movement of the contralateral hindlimb were located in the central part (Fig. 8A). The neurons responding to movement of the contralateral forelimb were located in between. In the GPe and GPi, the neurons responding to the hindlimb, forelimb and orofacial movements were arranged from the dorsal to the ventral parts of the GPe and GPi (Fig. 8B). Such somatotopic organizations in the STN and GPe/GPi based on kinaesthetic responses agreed well with the somatotopic map based on cortically evoked responses (compare Fig. 8A with Fig. 4, and Fig. 8B with Fig. 6). In the GPe/GPi, the SMA\(o\)-recipient neurons were found widely in the anterior part while lacked sensory inputs (Figs 6B1 and 8B) (see the ‘Somatotopic arrangements in the GPe/GPi’ in the Discussion section).

Discussion

The present study has shown the following results: (i) stimulation of the MI and/or SMA induced a biphasic response composed of early and late excitations in the STN, and a triphasic response composed of an early excitation, an inhibition and a late excitation in the GPe and GPi (Fig. 2), as previously described (Kitai & Deniau, 1981;
Ryan & Clark, 1991, 1992; Kita, 1992; Fujimoto & Kita, 1993; Yoshida et al., 1993; Maurice et al., 1998; Nambu et al., 2000, 2002a; Kita et al., 2004; Tachibana et al., 2008). (ii) Most of STN and GPe/GPi neurons responded exclusively to stimulation of either the MI or SMA, while one-fourth to one-third of neurons responded to stimulation of both the MI and SMA (Fig. 3, Tables 2–4). (iii) Most of MI-recipient STN and GPe/GPi neurons received inputs from a single somatotopic region. On the other hand, SMA- or MI + SMA-recipient STN and GPe/GPi neurons received inputs from a single somatotopic region or convergent inputs from two adjacent somatotopic regions (Tables 2–4). (iv) In the STN, MI-recipient neurons were predominantly found in the posterolateral domain, while SMA-recipient neurons were mainly found in the anteromedial domain (Fig. 3). MI + SMA-recipient neurons were distributed in both the MI and SMA domains, especially in the transition zone between the MI and SMA domains. (v) STN neurons responding to the hindlimb, forelimb and orofacial regions of the MI were found in the medial to lateral parts of the posterolateral STN, while neurons responding to the orofacial region of the SMA were located more medially than the others in the anteromedial STN (Fig. 4). (vi) In the GPe/GPi, MI-recipient neurons were mainly located in the posterolateral domain, while SMA-recipient neurons were found in the more anterior and medial domain (Fig. 3). MI + SMA-recipient neurons were distributed in both the MI and SMA domains, especially in the transition zone between the MI and SMA domains. (vii) GPe/GPi neurons responding to the hindlimb, forelimb and orofacial regions of the MI were found along the dorsal–ventral axis in the posterolateral GPe/GPi, and neurons responding to the corresponding regions of the SMA were similarly but less clearly distributed in more anteromedial regions (Fig. 6). (viii) Among neurons responding to the forelimb regions of the MI, those responding to the distal forelimb region were located more laterally in the STN and more ventrally in the GPe/GPi than those responding to the proximal forelimb region (Fig. 7). (ix) Most of the MI- and MI + SMA-recipient STN and GPe/GPi neurons showed kinaesthetic responses, while less of the SMA-recipient neurons did (Table 6). The somatotopic maps based on kinaesthetic responses were similar to those based on cortically evoked responses in both the STN and GPe/GPi (Fig. 8; Compare with Figs 4 and 6). Finally, data were obtained from two female monkeys, and the present results should be further explored by extensive data from more animals, including male subjects.

**Cortically evoked responses in the STN and their origins**

In this study, MI- and/or SMA-stimulation commonly induced a biphasic response consisting of early and late excitations in STN neurons (Fig. 2A), as previously reported (Nambu et al., 2000). The early excitation is thought to be mediated by the direct cortico-STN projection, as previously shown in rodents and primates (Kitai & Deniau, 1981; Ryan & Clark, 1992; Fujimoto & Kita, 1993; Maurice et al., 1998; Nambu et al., 2000). The most probable origin of the late excitation is the disinhibition of STN neurons by the cortico-striato-GPe-STN indirect pathway (Maurice et al., 1998; Nambu et al., 2002a), although other possibilities include rebound firings after the inhibition evoked by the cortico-STN-GPe-STN pathway (Nakanishi et al., 1987; Bevan et al., 2002), and a second part of a cortico-STN induced a broad excitation interrupted by a brief inhibition via the cortico-STN-GPe-STN pathway (Fujimoto & Kita, 1993). Thus, cortical information through the cortico-STN and cortico-striato-GPe-STN pathways converges on the same STN neurons, and convergence from the MI and SMA occurred to a similar extent through both projections (Table 2). The latencies of MI-evoked early and late excitations in this study were similar to those previously reported (Nambu et al., 2000) and were shorter than those of SMA-evoked ones in this study (Table 1). This latency difference may be explained by the difference in conduction velocities of axons originating from the MI and SMA, as observed in the putamen (Nambu et al., 2002b).
FIG. 6. Somatotopic distribution of primary motor cortex (MI)- and supplementary motor area (SMA)-inputs in the GPe/GPi. Locations of GPe/GPi neurons that showed an early excitation evoked by cortical stimulation of the somatotopic body parts in the MI (A1) and SMA (B1) in Monkey P8 are indicated. Cortical stimulation sites, such as MIh, MIf, MIo, SMAh, SMAf and SMAo, are marked with different colours. Large circles, small circles and bars represent major cortical inputs, minor cortical inputs and no early excitations to MI- or SMA-stimulation, respectively. Histograms show the locations of GPe (A2, B2) and GPi (A3, B3) neurons with major cortical inputs from the MI (A2, 3) and SMA (B2, 3) along the AP, ML and DV axes. Dashed vertical lines indicate means of the locations. *Significantly different (one-way ANOVA with Bonferroni post hoc test, P < 0.05).
In the present study, around 30% of STN neurons received convergent inputs from the MI and SMA based on the early excitation by the cortico-STN pathway and on the late excitation by the cortico-striato-GPe-STN pathway (Table 2). Similar convergence was reported in the cortico-putaminal projections: 20% of putaminal neurons received convergent inputs from the MI and SMA (Nambu et al., 2002b). In the GPe, convergence from the MI and SMA occurred in around one-third of neurons based on the early excitation by the cortico-striato-GPe pathway, on the inhibition by the cortico-striato-GPe pathway and on the late excitation by the cortico-striato-GPe-GPe/GPi pathway (Table 3). In the GPe, convergence from the MI and SMA occurred in around one-fourth of neurons based on the early excitation by the cortico-STN-GPi pathway, on the inhibition by the cortico-striato-GPi pathway and on the late excitation by the cortico-striato-GPe-GPe/GPi pathway (Table 4). These results indicate that convergence of cortico-striatal or cortico-STN projections occurred to some extent, and that information through the striato-GPe/GPi, STN-GPe/GPi and GPe-STN-GPe/GPi projections is processed in a parallel fashion (Fig. 9A). Kaneda et al. (2002) showed that MI-, SMA- and MI + SMA-recipient neurons in the striatum project to different regions in the GPe/GPi, suggesting that striato-GPe/GPi projections are arranged in a parallel fashion.

When we look closely at the somatic information in the STN and GPe/GPi, most of the MI-recipient STN and GPe/GPi neurons received inputs from a single somatotopic region, while SMA-recipient neurons received inputs from a single somatotopic region or convergent inputs from two adjacent somatotopic regions: a considerable percentage of SMA-recipient neurons received convergent inputs, which is more evident in Monkey P8, likely because the neuronal response to SMAo-stimulation was also included in this subject (Tables 2–4). Moreover, MI + SMA-recipient neurons received more convergent inputs from two adjacent somatotopic regions. These data suggest that somatic information originating from the MI is processed mainly in a parallel fashion and that information from the SMA is processed in a convergent fashion, at least to some extent (Fig. 9A). They also suggest that both functional (i.e. MI and SMA) and somatic information are simultaneously integrated into MI + SMA-recipient neurons. The convergence of somatic information in the STN and GPe/GPi did not occur randomly, that is, convergent inputs came from the same or neighbouring somatotopic regions (Tables 2–4), indicating that the convergence seems to be functionally significant.

### Somatotopic arrangements in the STN

MI-recipient neurons were mainly located in the posterolateral STN, whereas SMA-recipient neurons were mainly found in the anteromedial STN (Figs 3A and 4). In the MI domain, MIo-, MIf- and MIh-recipient neurons were located in this order from lateral to medial, while in the SMA domain, SMAo-recipient neurons were located more medially than SMAf- and SMAo-recipient neurons (Fig. 4). This somatotopic organization in the STN agrees with previous anatomical studies (Monakow et al., 1978; Nambu et al., 1996) (Fig. 9B). A previous anatomical study also showed that the MI sends minor projections to the medial SMA domain and the SMA to the lateral MI domain in a somatotopic organized manner (Nambu et al., 1996), which supports the current observation that a considerable number of MI + SMA-recipient STN neurons received...
convergent inputs from the same somatotopic regions of the MI and SMA (Table 2).

In the present study, kinaesthetic responses of each neuron were also examined, and many neurons in both the MI and SMA domains of the STN changed their activity in relation to passive movements of the corresponding body parts (Table 6, Fig. 8A). Previous studies examining neuronal responses to active and passive movements of individual body parts revealed a somatotopic map in the STN, that is, along the medial–lateral axis of the nucleus, neurons representing the hindlimb, forelimb and orofacial regions were located (DeLong et al., 1985; Wichmann et al., 1994). This representation agrees well with the somatotopic organization of the MI domain in this study (Figs 4, 8A and 9B). The present study also showed kinaesthetic responses of SMA-recipient neurons with a somatotopic arrangement, and no such movement-related activity was reported previously in the medial part of the STN. Further studies on movement-related activity of SMA-recipient STN neurons are warranted.

Somatotopic arrangements in the GPe/GPi

The ventral two-thirds of the posterior parts of the GPe/GPi is considered to be motor territories and to receive motor cortical inputs via the posterior putamen (Smith & Parent, 1986; Parent, 1990). In the present study, we examined the motor territory of the GPe/GPi and showed that the SMA domain was anterior and medial to the MI domain and that the MI + SMA-recipient neurons were found...
mainly in the transition zone between the MI and SMA domains (Figs 3B and 6), supporting the findings of previous studies (Hedreen & DeLong, 1991; Hazrati & Parent, 1992; Yoshida et al., 1993; Kaneda et al., 2002). In the MI domain, MIh-, MIi- and MIo-recipient neurons were found along the dorsal–ventral axis (Fig. 6). In the SMA domain, a similar somatotopy along the dorsal–ventral axis could be observed, but was not as distinct as that in the MI domain (Fig. 9B). The SMAo-recipient neurons were found widely in the anterior part while lacked sensory inputs (Figs 6B and 8B). This was probably because stimulation of the SMAo, which was a small area, might spread to the pre-SMA and excite pre-SMA-recipient GPe/GPi neurons. Previous transsynaptic anterograde and retrograde labelling studies by injecting herpes simplex virus into the MI showed similar somatotopic maps to those in our current study (Hoover & Strick, 1993, 1999; Strick et al., 2007).

In the present study, many neurons in both the MI and SMA domains of the GPe/GPi changed their activity in relation to passive movements of the corresponding body parts (Table 6, Fig. 8B). Previous studies showed that neurons responding to active and passive movements of the hindlimb, forelimb and orofacial parts were found in this order along the dorsal–ventral axis in the posterior GPe/GPi (DeLong, 1971; Georgopoulos et al., 1983; DeLong et al., 1985; Hamada et al., 1990), which corresponds well to the current somatotopic maps in the MI domain and, to some extent, the SMA domain (Figs 6, 8B and 9B). Further studies on the activity difference between SMA- and MI-recipient GPe/GPi neurons may be warranted.

**Table 6. Numbers of STN, GPe and GPi neurons showing kinaesthetic responses according to cortical inputs**

|                | STN (%) | GPe (%) | GPi (%) |
|----------------|---------|---------|---------|
| All            | 199/249 (80) | 154/185 (83) | 105/139 (76) |
| MI-recipient   | 46/49 (94) | 53/59 (90) | 31/34 (91) |
| Single body part | 36 (78)  | 33 (62)  | 26 (84)  |
| Two adjacent parts | 10 (22)  | 20 (38)  | 5 (16)   |
| SMA-recipient  | 85/125 (68) | 67/90 (74) | 49/74 (67) |
| Single body part | 46 (54)  | 44 (66)  | 28 (57)  |
| Two adjacent parts | 38 (45)  | 23 (34)  | 21 (43)  |
| MI+SMA-recipient | 68/75 (91) | 34/36 (94) | 25/31 (81) |
| Single body part | 43 (63)  | 20 (59)  | 16 (64)  |
| Two adjacent parts | 25 (37)  | 14 (41)  | 9 (36)   |

Numbers and percentage of STN, GPe and GPi neurons with kinaesthetic responses are shown according to responses (early excitation) evoked by MI- and SMA-stimulation in *Monkey P8*. *Includes one STN neuron showing kinaesthetic response to all three body parts.*

**Fig. 8. Somatotopic distribution of kinaesthetic responses in the subthalamic nucleus (STN) and GPe/GPi.** Locations of STN (A) and GPe/GPi (B) neurons that showed kinaesthetic responses to passive movements of body parts in *Monkey P8* are indicated. Each symbol with different colour represents the body part whose movement evoked the largest responses, and a bar indicates no response to any movements examined.

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of the STN and GPi, and microelectrode recordings and kinaesthetic responses are used to localize the targets. Moreover, pallidotomy in one somatotopic region improves symptoms in the corresponding body part, while DBS activates the stimulated structures, including their outputs and inputs, and may not have the same discrete effect (Deogaonkar & Vitek, 2009). Therefore, identification of motor territories and somatotopy in the STN and GPe/GPi is crucial for stereotactic surgery. Detailed analysis and deep understanding of somatotopic maps in the STN and GPe/GPi in non-human primates, such as those performed in the current study, should help to precisely localize the target structure of stereotactic surgery in human patients.

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Conflict of interest

None declared.

Author contributions

HI performed experiments, analysed data and wrote the first draft of the manuscript. YT helped to perform the experiments and reviewed and gave critiques of the manuscript. AN devised the whole experiment, supervised the whole process and wrote the final version of the manuscript. YU and NS reviewed and gave critiques of the manuscript. AN devised the whole experiment, supervised the whole process and wrote the final version of the manuscript.

Data accessibility

The data presented in the current manuscript can be available upon request to the corresponding author (nambu@nips.ac.jp).

Abbreviations

AP, anterior–posterior axis; DV, dorsal–ventral axis; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MI, primary motor cortex; MIh, hindlimb region of the primary motor cortex; ML, medial–lateral axis; MRI, magnetic resonance imaging; PEEK, polyether ketone; PM, premotor cortex; Pre-SMA, pre-supplementary motor area; PSTH, peristimulus time histograms; SD, standard deviation; SMAf, forelimb region of the supplementary motor area; SMAh, hindlimb region of the supplementary motor area; SMAo, orofacial region of the supplementary motor area; SN, substantia nigra pars reticulata; STN, subthalamic nucleus.

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