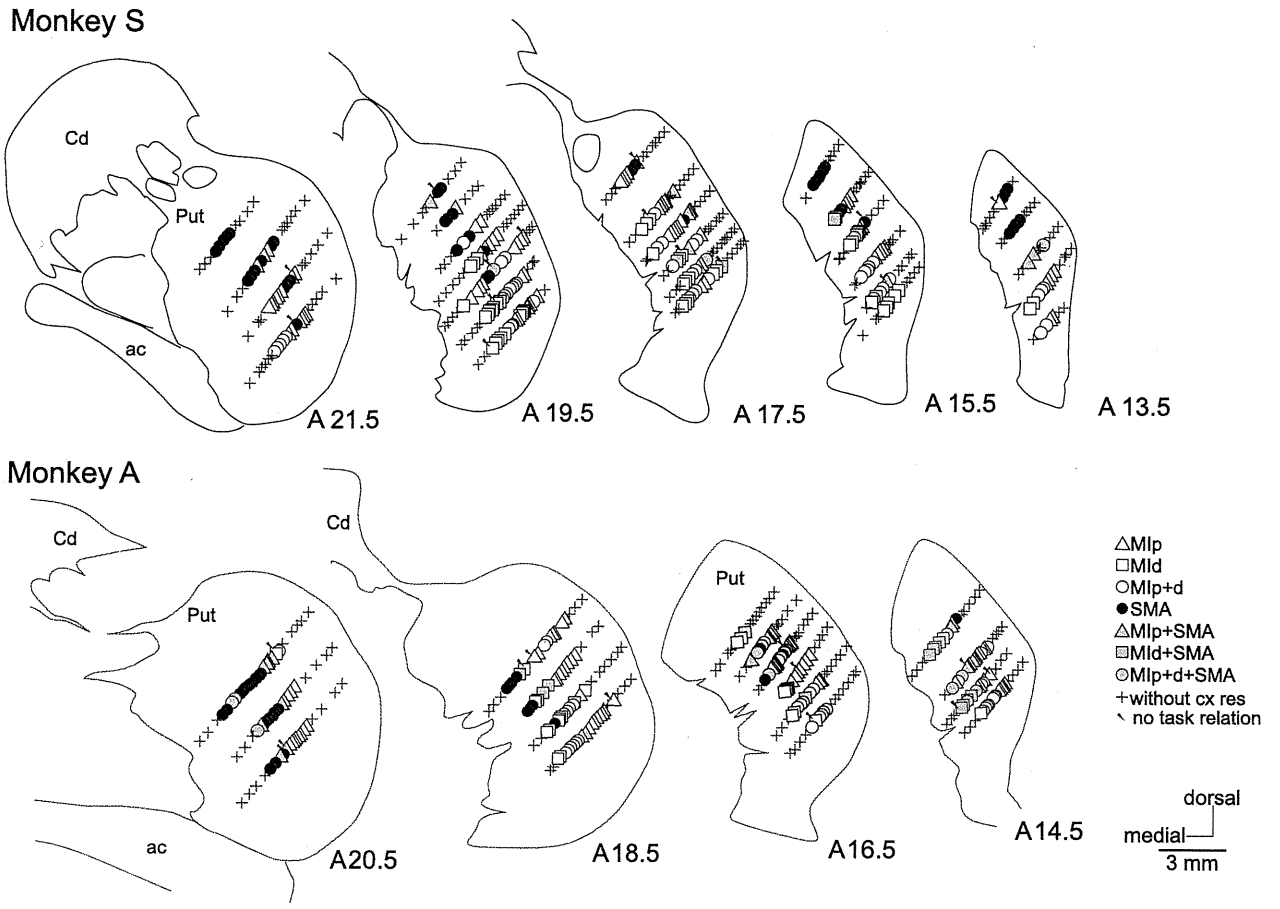

Fig. 10. Locations of putaminal neurons recorded in 2 monkeys were plotted in the frontal sections. Sections are arranged rostrocaudally from *left* to *right*. Neurons with different cortical inputs are indicated by different symbols. Neurons without cortically evoked responses (cx res) and neurons 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.

ACKNOWLEDGMENTS

We thank A. Ito, M. Ohara, S. Sato, and K. Miyamoto for technical assistance and H. Toyoda for MRI scans.

GRANTS

This study was supported by Grant-in-Aid for Scientific Research (A; 21240039) and Grant-in-Aid for Scientific Research on Priority Areas (System study on higher-order brain functions; 18020029) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Uehara Memorial Foundation to A. Nambu.

DISCLOSURES

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

REFERENCES

Alexander GE, Crutcher MD. Preparation for movement: neural representations of intended direction in three motor areas of the monkey. *J Neurophysiol* 64: 133–150, 1990.

Alexander GE, DeLong MR. Microstimulation of the primate neostriatum. I. Physiological properties of striatal microexcitable zones. *J Neurophysiol* 53: 1401–1416, 1985a.

Alexander GE, DeLong MR. Microstimulation of the primate neostriatum. II. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. *J Neurophysiol* 53: 1417–1430, 1985b.

Anderson ME, Horak FB. Influence of the globus pallidus on arm movements in monkeys. III. Timing of movement-related information. *J Neurophysiol* 54: 433–448, 1985.

Aosaki T, Tsubokawa H, Ishida A, Watanabe K, Graybiel AM, Kimura M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *J Neurosci* 14: 3969–3984, 1994.

Bauswein E, Fromm C, Preuss A. Corticostriatal cells in comparison with pyramidal tract neurons: contrasting properties in the behaving monkey. *Brain Res* 493: 198–203, 1989.

Bennett BD, Wilson CJ. Synaptology and physiology of neostriatal neurones. In: *Brain Dynamics and the Striatal Complex,* edited by Miller R and Wickens JR. Amsterdam: Harwood, 2000, p. 111–140.

Crutcher MD, DeLong MR. Single cell studies of the primate putamen. I. Functional organization. *Exp Brain Res* 53: 233–243, 1984a.

Crutcher MD, DeLong MR. Single cell studies of the primate putamen. II. Relations to direction of movement and pattern of muscular activity. *Exp Brain Res* 53: 244–258, 1984b.

Gage GJ, Stoetzner CR, Wiltschko AB, Berke JD. Selective activation of striatal fast-spiking interneurons during choice execution. *Neuron* 67: 466–479, 2010.

Gittis AH, Nelson AB, Thwin MT, Palop JJ, Kreitzer AC. Distinct roles of GABAergic interneurons in the regulation of striatal output pathways. *J Neurosci* 30: 2223–2234, 2010.

Gustafson N, Gireesh-Dharmaraj E, Czubayko U, Blackwell KT, Plenz D. A comparative voltage and current-clamp analysis of feedback and feedforward synaptic transmission in the striatal microcircuit in vitro. *J Neurophysiol* 95: 737–752, 2006.

Ikeda A, Yazawa S, Kunieda T, Ohara S, Terada K, Mikuni N, Nagamine T, Taki W, Kimura J, Shibasaki H. Cognitive motor control in human pre-supplementary motor area studied by subdural recording of discrimination/selection-related potentials. *Brain* 122: 915–931, 1999.

Inokawa H, Yamada H, Matsumoto N, Muranishi M, Kimura M. Juxtacellular labeling of tonically active neurons and phasically active neurons in the rat striatum. *Neuroscience* 168: 395–404, 2010.

Kaneda K, Nambu A, Tokuno H, Takada M. Differential processing patterns of motor information via striatopallidal and striatonigral projections. *J Neurophysiol* 88: 1420–1432, 2002.

Kimura M. Role of basal ganglia in behavioral learning. *Neurosci Res* 22: 353–358, 1995.

Kimura M, Aosaki T, Hu Y, Ishida A, Watanabe K. Activity of primate putamen neurons is selective to the mode of voluntary movement: visually guided, self-initiated or memory-guided. *Exp Brain Res* 89: 473–477, 1992.

Koós T, Tepper JM. Inhibitory control of neostriatal projection neurons by GABAergic interneurons. *Nat Neurosci* 2: 467–472, 1999.

Künzle H. Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. *Brain Res* 88: 195–209, 1975.

Lee IH, Assad JA. Putaminal activity for simple reactions or self-timed movements. *J Neurophysiol* 89: 2528–2537, 2003.

Liles SL. Cortico-striatal evoked potentials in the monkey *(Macaca mulatta)*. *Electroencephalogr Clin Neurophysiol* 38: 121–129, 1975.

Liles SL. Activity of neurons in the putamen associated with wrist movements in the monkey. *Brain Res* 263: 156–161, 1983.

Liles SL, Updyke BV. Projection of the digit and wrist area of precentral gyrus to the putamen: relation between topography and physiological properties of neurons in the putamen. *Brain Res* 339: 245–255, 1985.

Mallet N, Le Moine C, Charpier S, Gonon F. Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum in vivo. *J Neurosci* 25: 3857–3869, 2005.

Merchant H, Zainos A, Hernández A, Salinas E, Romo R. Functional properties of primate putamen neurons during the categorization of tactile stimuli. *J Neurophysiol* 77: 1132–1154, 1997.

Mushiake H, Inase M, Tanji J. Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. *J Neurophysiol* 66: 705–718, 1991.

Nambu A, Kaneda K, Tokuno H, Takada M. Organization of corticostriatal motor inputs in monkey putamen. *J Neurophysiol* 88: 1830–1842, 2002.

Nambu A, Tokuno H, Hamada I, Kita H, Imanishi M, Akazawa T, Ikeuchi Y, Hasegawa N. Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *J Neurophysiol* 84: 289–300, 2000.

Schultz W, Romo R. Role of primate basal ganglia and frontal cortex in the internal generation of movements. I. Preparatory activity in the anterior striatum. *Exp Brain Res* 91: 363–384, 1992.

Sharott A, Moll CK, Engler G, Denker M, Grün S, Engel AK. Different subtypes of striatal neurons are selectively modulated by cortical oscillations. *J Neurosci* 29: 4571–4585, 2009.

Takada M, Tokuno H, Nambu A, Inase M. Corticostriatal projections from the somatic motor areas of the frontal cortex in the macaque monkey: segregation vs. overlap of input zones from the primary motor cortex, the supplementary motor area, and the premotor cortex. *Exp Brain Res* 120: 114–128, 1998a.

Takada M, Tokuno H, Nambu A, Inase M. Corticostriatal input zones from the supplementary motor area overlap those from the contra- rather than ipsilateral primary motor cortex. *Brain Res* 791: 335–340, 1998b.

Tanji J. The supplementary motor area in the cerebral cortex. *Neurosci Res* 19: 251–268, 1994.

Tepper JM, Wilson CJ, Koós T. Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons. *Brain Res Rev* 58: 272–281, 2008.

Tokuno H, Inase M, Nambu A, Akazawa T, Miyachi S, Takada M. Corticostriatal projections from distal and proximal forelimb representations of the monkey primary motor cortex. *Neurosci Lett* 269: 33–36, 1999.

Turner RS, DeLong MR. Corticostriatal activity in primary motor cortex of the macaque. *J Neurosci* 20: 7096–7108, 2000.

J Neurophysiol 107: 1042, 2012.
doi:10.1152/jn.z9k-1228-corr.2011.

Volume 106, September 2011

Takara et al. Differential activity patterns of putaminal neurons with inputs from the primary motor cortex and supplementary motor area in behaving monkeys. *J Neurophysiol* 106: 1203–1217, 2011; doi:10.1152/jn.00768.2010; http://jn.physiology.org/content/106/3/1203.full.

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.

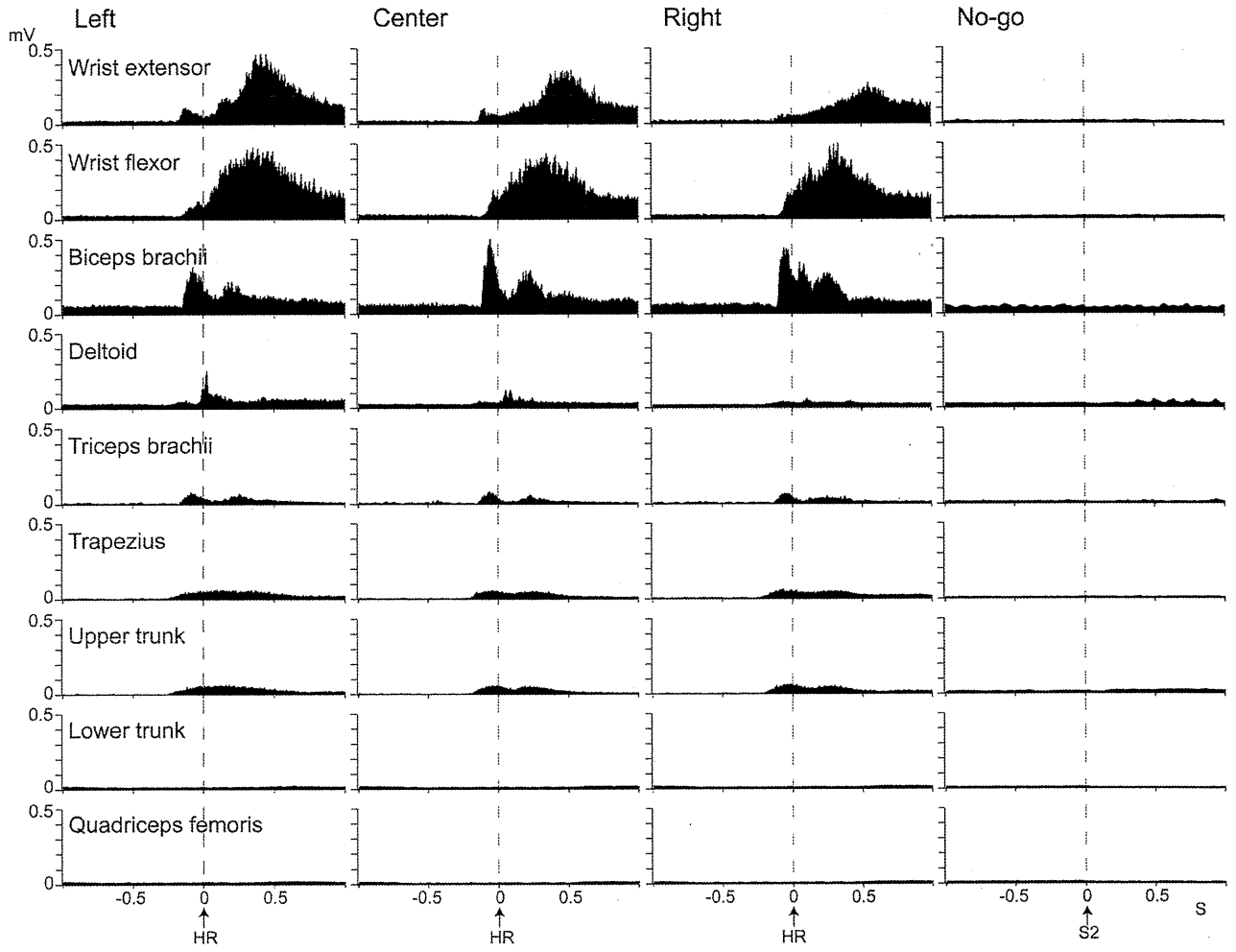

Fig. 2. Electromyogram (EMG) activity during the performance of a goal-directed reaching task with delay. EMG activity was rectified, aligned at the HR (Go trials, at *time 0*) or S2 (No-go trials), and averaged 100 times separately, according to the S1 conditions (Left, Center, and Right targets and 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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PLoS one

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.

Citation: Yumoto N, Lu X, Henry TR, Miyachi S, Nambu A, et al. (2011) A Neural Correlate of the Processing of Multi-Second Time Intervals in Primate Prefrontal Cortex. PLoS ONE 6(4): e19168. doi:10.1371/journal.pone.0019168

Editor: Paul A. Bartell, Pennsylvania State University, United States of America

Received December 17, 2010; **Accepted** March 21, 2011; **Published** April 27, 2011

Funding: This work was supported by Grants-in-Aid for Scientific Research on Priority Areas "Integrative Brain Research" (17021050) to M.T., and Scientific Research (18500247 and 20500293) to X.L. from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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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

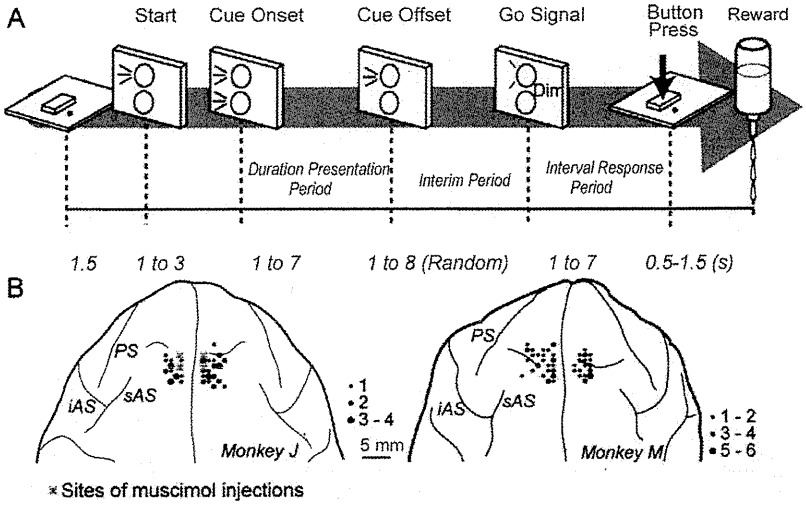

Figure 1. Task schema and recording sites. (A) Behavioral task schema. The monkeys were trained to prepare for and then observe the presentation of a time interval of visual stimuli, and after a variable interim period, then to reproduce this presented interval with a button press, as described in materials 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.
doi:10.1371/journal.pone.0019168.g001

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 $\pm$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

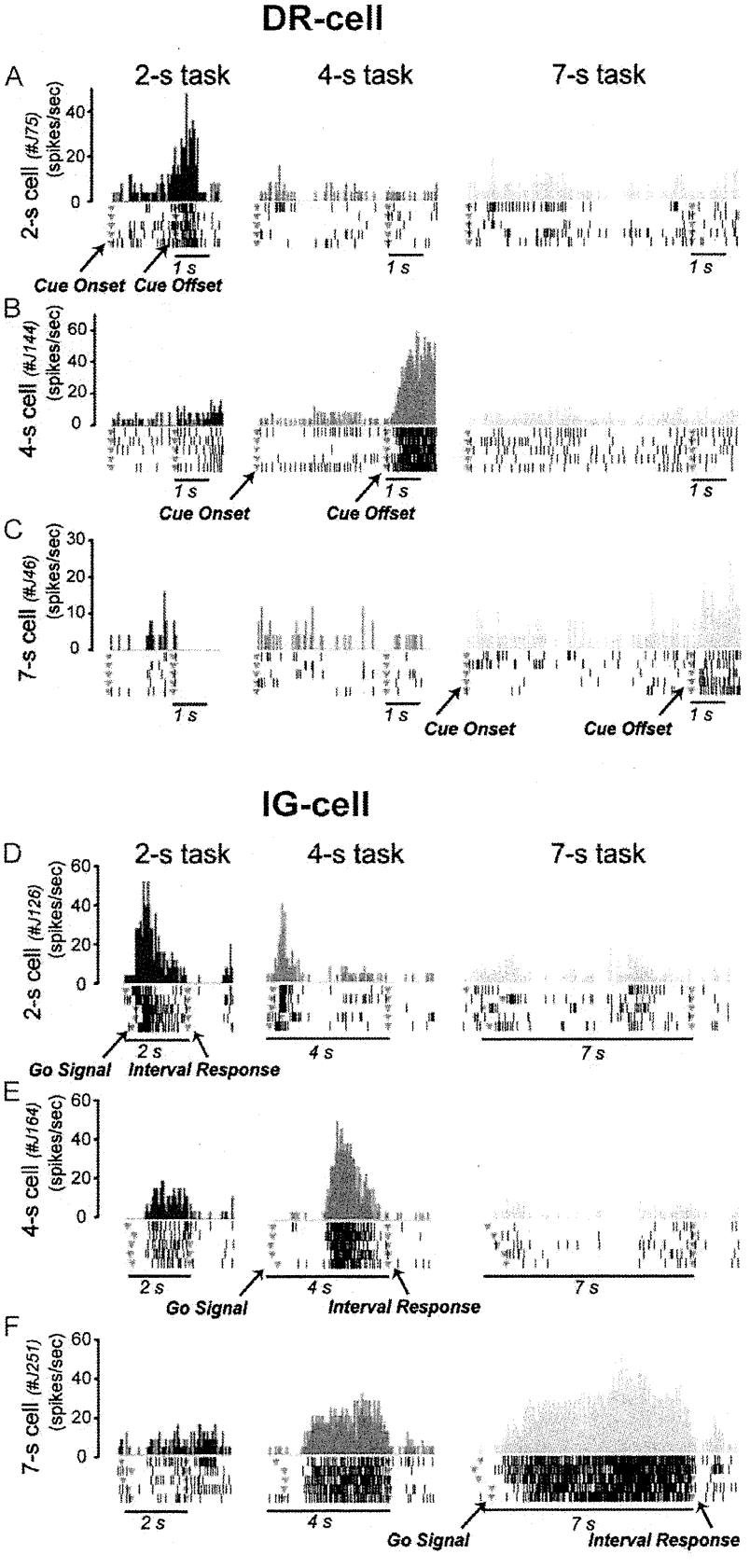
DR-cell
A
2-s task
4-s task
7-s task
2-s cell (#J75) (spikes/sec)
40
20
0
1 s
Cue Onset
Cue Offset
B
4-s cell (#J144) (spikes/sec)
60
40
20
0
1 s
Cue Onset
Cue Offset
C
7-s cell (#J46) (spikes/sec)
30
20
10
0
1 s
Cue Onset
Cue Offset
IG-cell
D
2-s task
4-s task
7-s task
2-s cell (#J126) (spikes/sec)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

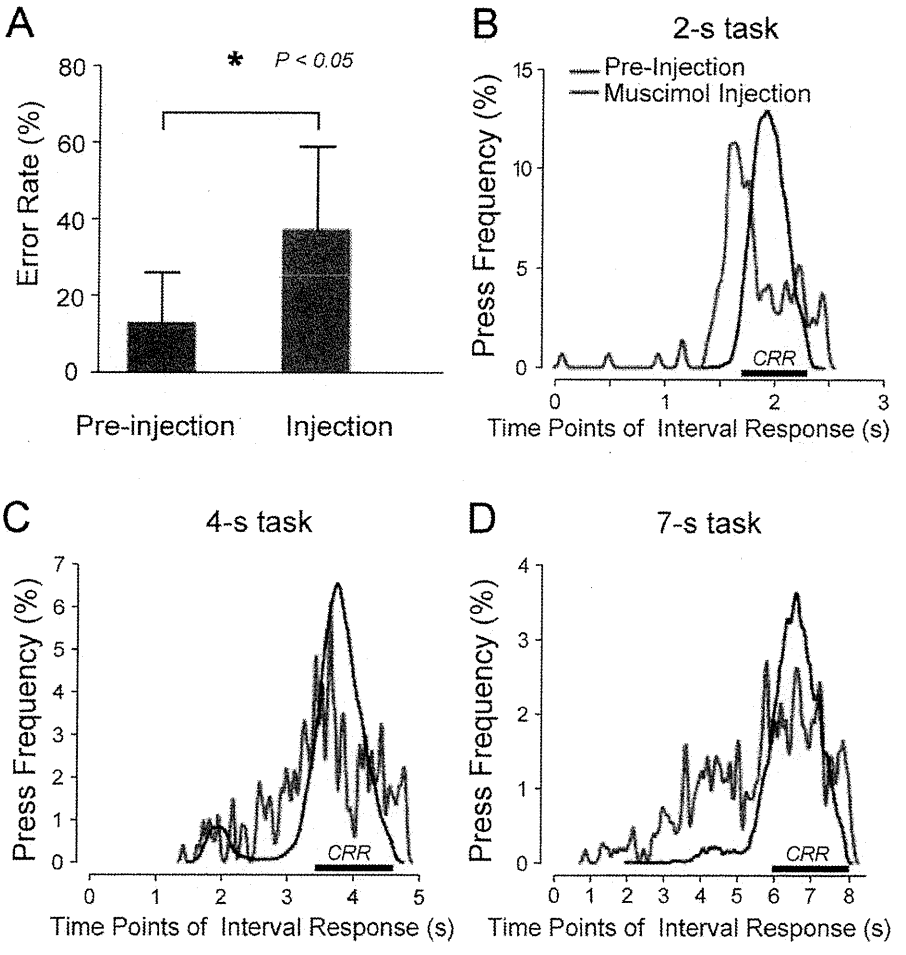

Figure 3. Effect of muscimol injections into area 9 on the accuracy of time reproduction in monkey J. (A) Change in the error rate for all of the 2-s, 4-s, and 7-s tasks. (B–D) Comparison of the frequency of interval responses between the pre- and the post-injections in the 2-s (B), 4-s (C), and 7-s (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.

References

1. Buhusi CV, Meck WH (2005) What makes us tick? Functional and neural mechanisms of interval timing. Nat Rev Neurosci 6: 755–765.
2. Church RM, Meck WH, Gibbon J (1994) Application of scalar timing theory to individual trials. J Exp Psychol Anim Behav Process 20: 135–155.
3. Hinton SC, Meck WH (1997) The 'internal clocks' of circadian and interval timing. Endeavour 21: 82–87.
4. Braitenberg V (1967) Is the cerebellar cortex a biological clock in the millisecond range? Prog Brain Res 25: 334–346.
5. Ivry RB, Keele SW, Diener HC (1988) Dissociation of the lateral and medial cerebellum in movement timing and movement execution. Exp Brain Res 73: 167–180.
6. Ivry RB, Spencer RM (2004) The neural representation of time. Curr Opin Neurobiol 14: 225–232.
7. Xu D, Liu T, Ashe J, Bushara KO (2006) Role of the olivo-cerebellar system in timing. J Neurosci 26: 5990–5995.
8. Pastor MA, Artieda J, Jahanshahi M, Obeso JA (1992) Time estimation and reproduction is abnormal in Parkinson's disease. Brain 115(Pt 1): 211–225.
9. Meck WH, Benson AM (2002) Dissecting the brain's internal clock: How frontal-striatal circuitry keeps time and shifts attention. Brain and Cognition 48: 195–211.
10. Matell MS, Meck WH, Nicolelis MA (2003) Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons. Behavioral Neurosci 117: 760–773.
11. Lustig C, Matell MS, Meck WH (2005) Not "just" a coincidence: frontal-striatal interactions in working memory and interval timing. Memory 13: 441–448.
12. Meck WH (2006) Frontal cortex lesions eliminate the clock speed effect of dopaminergic drugs on interval timing. Brain Res 1108: 157–167.
13. Meck WH (2006) Neuroanatomical localization of an internal clock: a functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. Brain Res 1109: 93–107.
14. Rao SM, Mayer AR, Harrington DL (2001) The evolution of brain activation during temporal processing. Nat Neurosci 4: 317–323.
15. Leon MI, Shadlen MN (2003) Representation of time by neurons in the posterior parietal cortex of the macaque. Neuron 38: 317–327.
16. Harrington DL, Boyd LA, Mayer AR, Sheltraw DM, Lee RR, et al. (2004) Neural representation of interval encoding and decision making. Brain Res Cogn Brain Res 21: 193–205.
17. Janssen P, Shadlen MN (2005) A representation of the hazard rate of elapsed time in macaque area LIP. Nat Neurosci 8: 234–241.
18. Lucchetti C, Ulrici A, Bon L (2005) Dorsal premotor areas of nonhuman primate: functional flexibility in time domain. Eur J Appl Physiol 95: 121–130.
19. Harrington DL, Zimbelman JL, Hinton SC, Rao SMNeural modulation of temporal encodind,maintenance, and decision processes. Cereb Cortex 20: 1274–1285.
20. Koch G, Oliveri M, Torriero S, Caltagirone C (2003) Underestimation of time perception after repetitive transcranial magnetic stimulation. Neurology 60: 1844–1846.

21. Machens CK, Romo R, Brody CD (2005) Flexible control of mutual inhibition: a neural model of two-interval discrimination. Science 307: 1121–1124.
22. Brody CD, Hernandez A, Zainos A, Romo R (2003) Timing and neural encoding of somatosensory parametric working memory in macaque prefrontal cortex. Cereb Cortex 13: 1196–1207.
23. Ohmae S, Lu X, Takahashi T, Uchida Y, Kitazawa S (2008) Neuronal activity related to anticipated and elapsed time in macaque supplementary eye field. Exp Brain Res 184: 593–598.
24. Genovesio A, Tsujimoto S, Wise SP (2006) Neuronal activity related to elapsed time in prefrontal cortex. J Neurophysiol 95: 3281–3285.
25. Fortin C, Fairhurst S, Malapani C, Morin C, Towey J, et al. (2009) Expectancy in humans in multisecond peak-interval timing with gaps. Atten Percept Psychophys 71: 789–802.
26. Lu X, Hikosaka O, Miyachi S (1998) Role of monkey cerebellar nuclei in skill for sequential movement. J Neurophysiol 79: 2245–2254.
27. Lu X, Matsuzawa M, Hikosaka O (2002) A neural correlate of oculomotor sequences in supplementary eye field. Neuron 34: 317–325.
28. Lu X, Ashe J (2005) Anticipatory activity in primary motor cortex codes memorized movement sequences. Neuron 45: 967–973.
29. Watanabe M (1996) Reward expectancy in primate prefrontal neurons. Nature 382: 629–632.
30. Tsujimoto S, Genovesio A, Wise SP (2010) Evaluating self-generated decisions in frontal pole cortex of monkeys. Nat Neurosci 13: 120–126.
31. Freedman DJ, Riesenhuber M, Poggio T, Miller EK (2001) Categorical representation of visual stimuli in the primate prefrontal cortex. Science 291: 312–316.
32. Ashe J, Lungu OV, Basford AT, Lu X (2006) Cortical control of motor sequences. Curr Opin Neurobiol 16: 213–221.
33. Machens CK, Romo R, Brody CD. Functional, but not anatomical, separation of "what" and "when" in prefrontal cortex. J Neurosci 30: 350–360.
34. Roesch MR, Olson CR (2005) Neuronal activity dependent on anticipated and elapsed delay in macaque prefrontal cortex, frontal and supplementary eye fields, and premotor cortex. J Neurophysiol 94: 1469–1497.
35. Lucchetti C, Bon L (2001) Time-modulated neuronal activity in the premotor cortex of macaque monkeys. Exp Brain Res 141: 254–260.
36. Coull JT, Vidal F, Nazarian B, Macar F (2004) Functional anatomy of the attentional modulation of time estimation. Science 303: 1506–1508.
37. Mita A, Mushiake H, Shima K, Matsuzaka Y, Tanji J (2009) Interval time coding by neurons in the presupplementary and supplementary motor areas. Nat Neurosci 12: 502–507.
38. Jones CR, Rosenkranz K, Rothwell JC, Jahanshahi M (2004) The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation. Exp Brain Res 158: 366–372.
39. Matell MS, Meck WH (2004) Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes. Brain Res Cogn Brain Res 21: 139–170.
40. Meck WH, Penney TB, Pouthas V (2008) Cortico-striatal representation of time in animals and humans. Curr Opin Neurobiol 18: 145–152.
41. Jin DZ, Fujii N, Graybiel AM (2009) Neural representation of time in cortico-basal ganglia circuits. Proc Natl Acad Sci U S A 106: 19156–19161.
42. Selemon LD, Goldman-Rakic PS (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. J Neurosci 5: 776–794.
43. Joel D, Niv Y, Ruppin E (2002) Actor-critic models of the basal ganglia: new anatomical and computational perspectives. Neural Netw 15: 535–547.

frontiers in
NEUROANATOMY

ORIGINAL RESEARCH ARTICLE
published: 20 April 2011
doi: 10.3389/fnana.2011.00026

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.

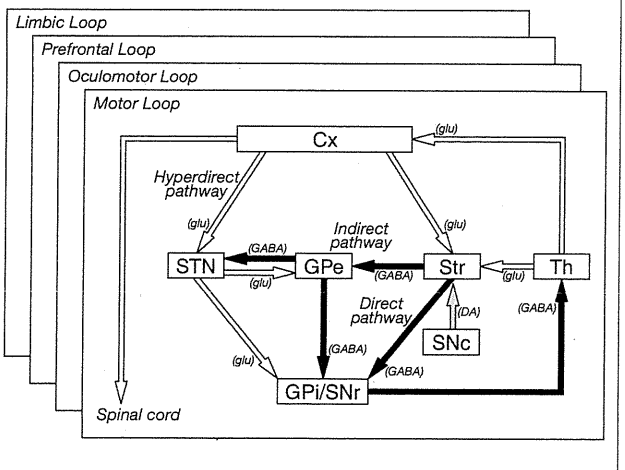

FIGURE 1 | Basic circuitry of the basal ganglia. Open and filled arrows indicate excitatory and inhibitory projections, respectively. Cx, cerebral cortex: DA, dopamine, GABA, gamma-aminobutyric acid; glu, glutamate; GPe and GPi, external and internal segments of the globus pallidus; SNc, substantia nigra 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).

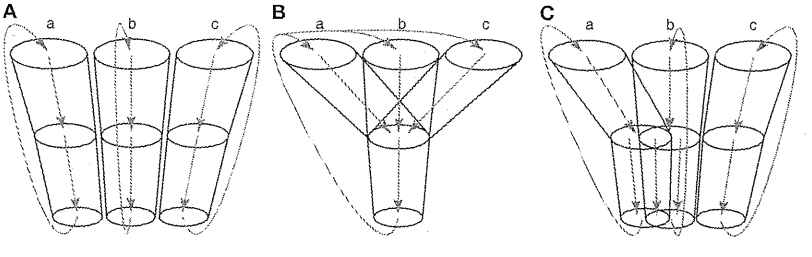

FIGURE 2 | Information processing in the basal ganglia. (A) *Parallel processing* hypothesis. Information originating from different areas (a, b, c) of the cerebral cortex is processed independently in the different parts of the basal ganglia, and returns to the original cortical areas. **(B)** *Information 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).

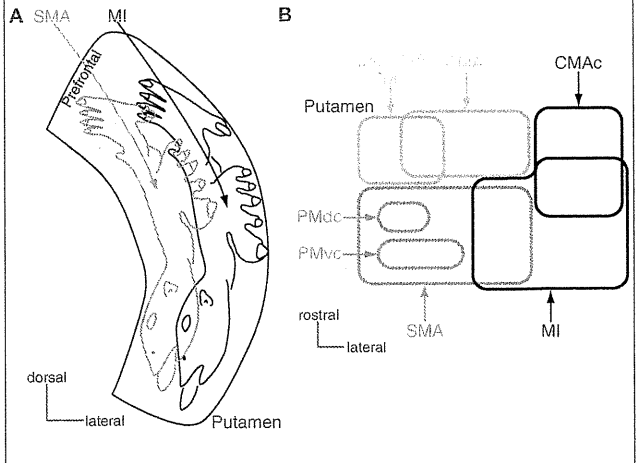

FIGURE 3 | Somatotopy of the putamen. (A) Somatotopy of the putamen is schematically shown in a frontal section. In the caudal aspect of the putamen, the lateral part receives somatotopic inputs from the primary motor cortex (MI), and the medial part from the supplementary motor area (SMA). The somatotopy 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

projection neurons. Activity patterns of other interneurons during task performance remain to be studied. The striatum is classified into μ-opiate receptor-rich patch compartment (or striosome) and matrix compartment (Graybiel, 1990), but the relationship between somatotopy and patch-matrix organization is unclear.

Other motor cortices also project to the striatum (**Figure 3B**; Takada et al., 1998a,b, 2001; Inase et al., 1999; Tachibana et al., 2004). The highest motor cortices, such as pre-SMA, PMdr, and CMAr, project to the anterior part of the striatum, especially to the bridge region connecting the caudate nucleus and putamen. The forelimb regions of the PMdc and PMvc project to two independent regions in the SMA territory of the putamen. On the other hand, the CMAc, which shows activity similar to that of the MI, projects to the MI territory. Projections from the primary somatosensory cortex also project to the MI territory (Flaherty and Graybiel, 1993). The projection patterns seem to obey the following rules: The motor cortices whose functions are distinct project to the different regions of the striatum, whereas the motor cortices whose functions are similar project to the common striatal regions in a convergent manner. The prefrontal cortex projects to the rostral part of the putamen anterior to the anterior commissure and the head of the caudate nucleus (prefrontal territory of the striatum), and the limbic cortex projects to the ventral striatum (limbic territory; Selemon and Goldman-Rakic, 1985; Haber et al., 1990; Parent, 1990). Eye movement-related neurons are located in the central part of the caudate nucleus (oculomotor territory; Hikosaka et al., 1989).

SUBTHALAMIC NUCLEUS (STN)

The STN, another input station of the basal ganglia, receives cortical inputs from the frontal lobe. The dorsal part of the STN is the motor territory and shows somatotopic organization (**Figure 4A**; Monakow et al., 1978; Nambu et al., 1996). The MI projects to the lateral part (MI territory), and the SMA projects to the medial part (SMA territory). The orofacial, forelimb, and hindlimb regions of the MI project to the lateral to medial parts of the lateral STN, while those of the SMA project to the medial to lateral parts of the medial STN. Therefore, two sets of somatotopic representations, which are mirror images of each other, are represented in the lateral and medial parts of the STN. The MI also partly projects to the somatotopically corresponding body parts in the SMA territory, and the SMA partly projects to the MI territory, vice versa. Thus, inputs from the MI and SMA partly converge in the STN. The forelimb regions of the PMdc and PMvc also project to the forelimb region of the SMA territory (**Figure 4B**; Nambu et al., 1997). The somatotopy of the STN reflects not only input organization, but also output organization, because similar somatotopy is observed after transneuronal retrograde labeling of rabies virus by its injection into the MI (Miyachi et al., 2006).

The somatotopy of the STN has also been confirmed by electrophysiological methods. Cortical stimulation of the MI and SMA induces a short latency excitation and a subsequent long latency excitation (Nambu et al., 2000), which are mediated by the cortico-STN (hyperdirect) and cortico-striato-GPe-STN (indirect) pathways, respectively. By observing cortically evoked responses, similar somatotopy can be drawn, with some neurons receiving convergent inputs from the MI and SMA. STN neurons in the MI territory change their activity (mostly excitation) in relation to active or passive movements of the corresponding body parts on the contralateral side (DeLong et al., 1985; Wichmann et al., 1994). STN neurons in the SMA territory may also show task-related activity. Microstimulation in the MI and SMA territories does not evoke movements, while that in the most lateral part of the STN often evokes movements probably because of the current spread to the internal capsule (Wichmann et al., 1994).

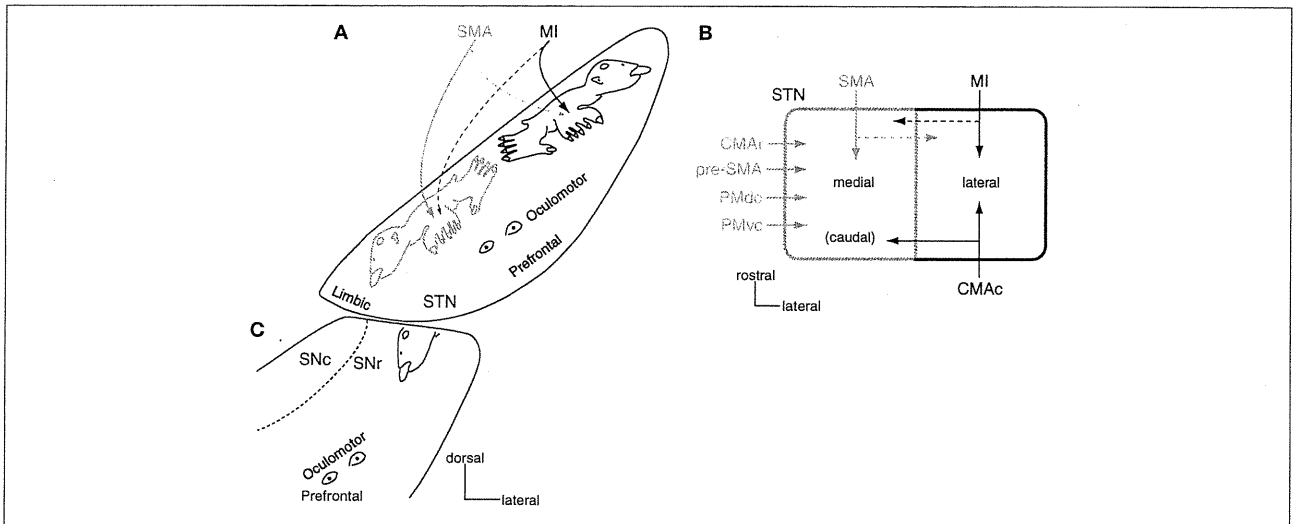

FIGURE 4 | Somatotopy of the subthalamic nucleus (STN) and substantia nigra (SN). (A) Somatotopy of the STN is shown in a frontal section. In the dorsal part of the STN, the lateral part receives somatotopic inputs from the MI, and the medial part from the SMA. The MI also projects partly to the medial part, and the SMA to the lateral part. Ventral to the motor territory, there exist the oculomotor and prefrontal territories. The most medial part is occupied by the limbic territory. Modified from Nambu et al. (2002b). **(B)** Input from motor cortices to the STN is schematically shown in a horizontal section. Modified from Takada et al. (2001). **(C)** Somatotopy of the SNr is shown in a frontal section. The orofacial region of the SNr is a continuation of that of the GPi (see **Figure 5**). Ventral to the motor territory, there exist the oculomotor and prefrontal territories.

Concerning other motor cortical inputs, the CMAc projects to the MI territory of the STN, and the pre-SMA and CMAr project to the SMA territory (**Figure 4B**; Inase et al., 1999; Takada et al., 2001). Thus, more convergence may occur in the cortico-STN projections than in the cortico-striatal projections (compare **Figure 4B** with **Figure 3B**), suggesting that the hyperdirect pathway assembles information from more wide areas of the motor cortices than the direct and indirect pathways do. Ventral to the motor territory in the STN, there exist the oculomotor territory (Matsumura et al., 1992) and the prefrontal territory (Monakow et al., 1978; Parent, 1990; **Figure 4A**). The most ventromedial part of the STN is occupied by the limbic territory (Parent, 1990).

EXTERNAL AND INTERNAL SEGMENTS OF THE GLOBUS PALLIDUS (GPe AND GPi)

The motor territory of the striatum (i.e., the caudal aspect of the putamen) projects to the ventral two-thirds of the caudal GPe and GPi, and thus, these areas are the motor territories of the globus pallidus (Smith and Parent, 1986; Parent, 1990) that show somatotopic organization (**Figure 5**). In GPe/GPi neurons, cortical stimulation evokes a triphasic response composed of early excitation, inhibition, and late excitation, which are mediated by the cortico-STN-GPe/GPi (cortico-STN-GPi: hyperdirect), cortico-striato-GPe/GPi (cortico-striato-GPi: direct), and cortico-striato-GPe-STN-GPe/GPi (cortico-striato-GPe-STN-GPi: indirect) pathways, respectively (Nambu et al., 2000; Kita et al., 2004; Tachibana et al., 2008). The somatotopy in the GPe/GPi can be drawn by observing responses evoked by the stimulation of the MI and SMA. Neurons responding to the orofacial, forelimb, and hindlimb regions of the MI are located along the ventral-to-dorsal axis in the GPe and GPi (MI territory, **Figure 5**; Yoshida et al., 1993). Neurons responding to the corresponding regions of the SMA are also located along the ventral-to-dorsal axis, but in more rostral and dorsal parts of the GPe/GPi (SMA territory). Stimulation of the PM also evokes responses in the SMA territory. GPe/GPi neurons rarely respond to cortical stimulation of multiple body parts, and thus, the orofacial, forelimb, and hindlimb regions of GPe/GPi are clearly and distinctly identified. On the other hand, many neurons respond to the stimulation of both the MI and SMA, and the somatotopic representation in the MI territory and that in the SMA territory are partly fused in the rostro-caudal central zone. Most GPe/GPi neurons show triphasic responses evoked by cortical stimulation, suggesting that the hyperdirect, direct, and indirect pathways originating from a certain body region in the cortex converge at a single GPe/GPi neuronal level.

The above-mentioned somatotopy is also supported by anatomical studies. The injection of anterograde tracers into the MI, SMA, and convergent territories in the putamen revealed the terminals in the GPe/GPi (Kaneda et al., 2002). Terminals from the SMA territory of the putamen are located more anterior and dorsal to those from the MI territory. The convergent territory of the putamen projects to the area in-between, and these three projection territories do not overlap. Transsynaptic anterograde and retrograde labeling studies by injecting herpes simplex virus into the MI reported similar results (Hoover and Strick, 1993, 1999; Strick et al., 1995; Akkal et al., 2007), although there is some discrepancy, such as that the PMv territory of the GPe/GPi is located ventrally to the MI territory. Dendritic fields of GPe/GPi neurons extend widely in the direction perpendicular to the striato-pallidal fibers, and this is considered to be the basis for information convergence (Percheron et al., 1984; Yelnik et al., 1984). However, somatotopic organization through the striato-pallidal projections is well preserved as described above.

Neurons in the MI and SMA territories of the GPe/GPi change their activity in relation to active and passive movements of the corresponding body parts on the contralateral side (DeLong, 1971; Georgopoulos et al., 1983; DeLong et al., 1985; Hamada et al., 1990). However, response patterns are different between these territories. Neurons in the MI territory show movement-related activity, while those in the SMA territory show delay-related activity (Nambu et al., 1990). On the other hand, response patterns in the GPe and GPi neurons during task performance are very similar. Microstimulation in the GPe/GPi does not induce any movements.

The prefrontal territory of the striatum projects to the rostral GPe and dorsal one-third of the caudal GPe/GPi, and thus, these areas are the prefrontal territory (Smith and Parent, 1986; Parent, 1990). Ventral striatum projects to the VP, the most rostral part of the GPe and the most medial part of the GPi, and thus, these areas correspond to the limbic territory (Haber et al., 1990; Parent, 1990).

SUBSTANTIA NIGRA (SN)

The SNr and GPi are the output nuclei of the basal ganglia and considered to be a continuum, which is divided into the SNr and GPi by the internal capsule. The motor territory of the striatum projects to the dorsal one-third of the SNr, and thus, this area is considered to be the motor territory of the SNr (**Figure 4C**; Smith and Parent, 1986; Parent, 1990). Neurons in the dorsolateral part

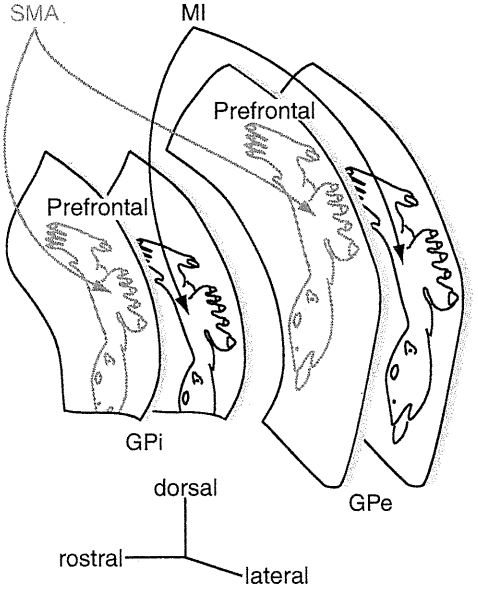

FIGURE 5 | Somatotopy of the external and internal segments of the globus pallidus (GPe and GPi). The GPe and GPi have their own somatotopic representations. The somatotopy in the SMA territory is located rostrodorsally to that in the MI territory. Two territories overlap partly in the rostro-caudal zone. Dorsal one-third of the GPe/GPi is occupied by the prefrontal territory.

of this area respond to the stimulation of the MI, especially to that of the orofacial region, and change their activity in relation to active or passive movements of the orofacial region (DeLong et al., 1983; Kitano et al., 1998). The orofacial region of the SNr is considered to be a continuation of the orofacial region of the GPi (see **Figures 4C and 5**). SNr neurons in the part ventral to the orofacial region receive inputs from the SMA territories of the putamen, and change their activity during task performance. However, the somatotopy is not clearly organized, and their activity is not so distinct compared to that of GPi neurons (Wichmann and Kliem, 2004). The prefrontal territory of the striatum projects to the rostromedial two-thirds of the SNr (Smith and Parent, 1986) that also include the oculomotor territory (Hikosaka and Wurtz, 1983; **Figure 4C**). The limbic territory of the striatum projects to the most medial part of the SNr (Haber et al., 1990).

The SNc is composed of dopaminergic neurons, and projects to the striatum and other basal ganglia nuclei. Dopaminergic projections from the SNc to the striatum display weak topography, and the terminal fields of a single dopaminergic neuron are large (Parent et al., 1983; Parent, 1990; Matsuda et al., 2009). SNc neurons do not respond to active or passive body part movements, but respond to novel sensory stimuli and/or rewards (DeLong et al., 1983; Schultz and Romo, 1990). Recent studies suggest that SNc neurons code the difference between the expected reward and the real reward (a temporal difference error in reinforcement learning). These observations suggest that the SNc has no clear somatotopy.

THALAMUS

The motor thalamus is a target structure of the basal ganglia, and also shows somatotopy (**Figure 6**). Subnuclei located in the rostral part of the motor thalamus receive inputs from the basal ganglia. The oral part of the ventrolateral nucleus (VLo) and the principal part of the ventroanterior nucleus (VApc) receive inputs from the GPi. The medial part of the ventrolateral nucleus (VLm) and the magnocellular part of the ventroanterior nucleus (VAmc) receive inputs from the SNr. On the other hand, subnuclei located in the caudal part, such as the oral part of the ventroposterolateral nucleus (VPLo), the caudal part of the ventrolateral nucleus (VLc) and area X, receive cerebellar inputs (Jones, 2007). Thus, projections from the SNr, GPi and cerebellar nuclei terminate in the rostral to caudal parts of the motor thalamus, and the overlap of their terminals is minimal. The VApc, VLo, VPLo, and VLc project to the motor cortices, and thus, most of the motor cortices receive inputs from both the basal ganglia and the cerebellum through the motor thalamus (Jones, 2007). The MI receives basal ganglia inputs through the VLo, and cerebellar inputs through the VPLo (Holsapple et al., 1991).

The VLo and VPLo display clear somatotopic organization (**Figure 6**). The orofacial, forelimb, and hindlimb regions are represented in the medial to lateral parts (Asanuma et al., 1983; Vitek et al., 1994). VLo neurons change their activity in relation to active movements of the corresponding body parts (Anderson and Turner, 1991; Nambu et al., 1991; Vitek et al., 1994). However, sensory inputs are not clearly identified, and the microstimulation in the VLo does not induce any movements (Buford et al., 1996; Vitek et al., 1996). On the other hand, VPLo neurons respond clearly to active and passive movements of discrete body parts (one to several joints) on the contralateral side. Microstimulation in the VPLo induces movements in the corresponding body parts, contralateral to the stimulation side. The somatotopy can also be confirmed by the anatomical study of the thalamo-cortical projections (Asanuma et al., 1983; Holsapple et al., 1991). Therefore, the thalamus has at least two sets of somatotopic representations: one in the GPi-receiving region (VLo) and the other in the cerebellar-receiving region (VPLo).

FUNCTIONAL SIGNIFICANCE OF THE SOMATOTOPY

Each nucleus of the basal ganglia shows clear somatotopic organization, and information originating from cortical regions representing different body parts rarely converges in the cortico-basal ganglia circuitry. These observations suggest that information related to different body parts, such as forelimb and hindlimb, is processed independently through the cortico-basal ganglia loop. On the other hand, information from different but related cortical areas, such as the forelimb regions of the MI and SMA, is processed in both convergent and non-convergent manners. However, the functional roles of such convergence remain to be elucidated.

SOMATOTOPY AND MOVEMENT DISORDERS

The pathophysiology of movement disorders can be explained by the changes of the firing rates and patterns in the basal ganglia, especially in the GPe, GPi, and STN. In addition, changes in the somatotopy have been reported in movement disorders. In a normal state, GPe and GPi neurons respond specifically to the movement of one direction of a single joint on the contralateral side. On the other hand, GPe/GPi neurons in a Parkinsonian state respond to multiple movements of multiple joints, sometimes of the upper and lower limbs and of both sides (Filion et al., 1988). Loss of functional segregation was also reported in the GPi-receiving thalamus (Pessiglione et al., 2005). Dopamine is considered to contribute to

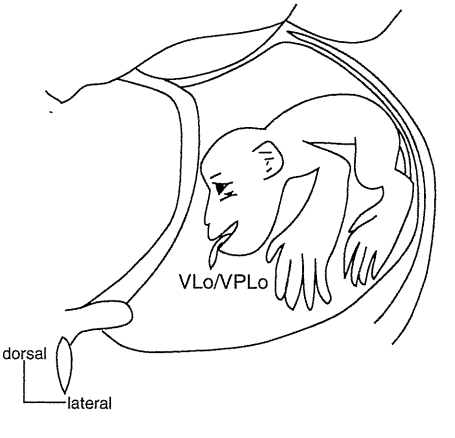

FIGURE 6 | Somatotopy of the thalamus. Somatotopy of the thalamus is shown in a frontal section. Both the oral part of the ventrolateral nucleus of the thalamus (VLo) receiving pallidal projections and the oral part of the ventroposterolateral nucleus of the thalamus (VPLo) receiving cerebellar projections have their own somatotopic representations. Their somatotopic representations are continuous rostrocaudally. Modified from Asanuma et al. (1983).

isolate information related to movements of specific body parts. Loss of dopamine may induce a crosstalk of information related to different body parts (Bergman et al., 1998).

In dystonia, somatotopy of the basal ganglia is also disorganized (Vitek et al., 1999; Chiken et al., 2008). GPe/GPi neurons respond to stimulation of multiple body parts, and they are intermingled. Dystonic patients show a phenomenon known as "motor overflow." Such a phenomenon may be explained by disorganization of the somatotopy. When patients try to move one body part, for example, a hand, not only the hand region, but also other regions, such as the neck region, of the GPi could be inhibited by somatotopic disorganization. This may lead to unintended movements of other body parts, such as the neck, that accompany intended movements of a hand.

Hemiballism is caused by lesions in the STN, such as a hemorrhage or infarction. Hemiballism in the lower limb is common, while that in the orofacial regions is rare (Carpenter et al., 1950; Hamada and DeLong, 1992). Hemiballism in the upper limb is associated with that in the lower limb. These characteristics can be explained by the mirror image organization of the somatotopy in the STN (**Figure 4A**; Nambu et al., 1996). It is supposed that the inactivation of both the MI and SMA territories of the corresponding body parts is necessary to produce hemiballism. Small lesions in the central STN affect both lower limb regions of the MI and SMA territories, and thus cause hemiballism in the lower limb. Large lesions affecting both upper limb regions of the MI and SMA territories also affect both lower limb regions, and thus hemiballism in the upper limb is accompanied by that in the lower limb. Lesions affecting both orofacial regions of the MI and SMA territories should be rare because they are remotely located.

Abnormal firing rates and patterns in the motor territory of the basal ganglia cause motor symptoms of the movement disorders. The target of stereotaxic surgery, including deep brain stimulation (DBS), for treatment of movement disorders aimed at the motor territory of the basal ganglia, such as the GPi and STN. The somatotopy gives us useful indices to identify the targets during stereotaxic surgery (Kaplitt et al., 2003). STN-DBS sometimes induces side effects of mood changes. This may be explained by the current spread from the motor territory to the limbic and prefrontal territories of the STN because of the small size of the STN. On the other hand, GP-DBS does not induce psychological side effects, probably because the motor territory is remotely located from the limbic and prefrontal territories in the GPi.

CONCLUSION

In this article, I have described that each nucleus of the basal ganglia shows clear somatotopic organization, and that information related to different body parts is processed independently through the cortico-basal ganglia loop. I would like to point out the following unsolved questions: In the topographic projections from one nucleus to another nucleus, what kind of information is added? What kind of information is originated? How do converging inputs from multiple motor cortices contribute to the execution of voluntary movements? How is the somatotopy in each nucleus of the basal ganglia organized during development? These are important questions closely related to the functions of the basal ganglia. The somatotopic perspective way of view will be a good clue and guide for further understanding of the basal ganglia.

ACKNOWLEDGMENTS

Studies in the author's laboratory were supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The author is grateful to the current and former collaborators.

REFERENCES

Akkal, D., Dum, R. P., and Strick, P. L. (2007). Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J. Neurosci.* 27, 10659–10673.

Alexander, G. E., and Crutcher, M. D. (1990a). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.* 13, 266–271.

Alexander, G. E., and Crutcher, M. D. (1990b). Preparation for movement: neural representations of intended direction in three motor areas of the monkey. *J. Neurophysiol.* 64, 133–150.

Alexander, G. E., and DeLong, M. R. (1985). Microstimulation of the primate neostriatum. II. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. *J. Neurophysiol.* 53, 1417–1430.

Alexander, G. E., DeLong, M. R., and Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9, 357–381.

Anderson, M. E., and Turner, R. S. (1991). Activity of neurons in cerebellar-receiving and pallidal-receiving areas of the thalamus of the behaving monkey. *J. Neurophysiol.* 66, 879–893.

Aosaki, T., Kimura, M., and Graybiel, A. M. (1995). Temporal and spatial characteristics of tonically active neurons of the primate's striatum. *J. Neurophysiol.* 73, 1234–1252.

Asanuma, C., Thach, W. R., and Jones, E. G. (1983). Anatomical evidence for segregated focal groupings of efferent cells and their terminal ramifications in the cerebellothalamic pathway of the monkey. *Brain Res.* 286, 267–297.

Bergman, H., Feingold, A., Nini, A., Raz, A., Slovin, H., Abeles, M., and Vaadia, E. (1998). Physiological aspects of information processing in the basal ganglia of normal and Parkinsonian primates. *Trends Neurosci.* 21, 32–38.

Buford, J. A., Inase, M., and Anderson, M. E. (1996). Contrasting locations of pallidal-receiving neurons and microexcitable zones in primate thalamus. *J. Neurophysiol.* 75, 1105–1116.

Carpenter, M. B., Whittier, J. R., and Mettler, F. A. (1950). Analysis of choreoid hyperkinesia in the Rhesus monkey; surgical and pharmacological analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of Luys. *J. Comp. Neurol.* 92, 293–331.

Chiken, S., Shashidharan, P., and Nambu, A. (2008). Cortically evoked long-lasting inhibition of pallidal neurons in a transgenic mouse model of dystonia. *J. Neurosci.* 28, 13967–13977.

DeLong, M. R. (1971). Activity of pallidal neurons during movement. *J. Neurophysiol.* 34, 414–427.

DeLong, M. R., Crutcher, M. D., and Georgopoulos, A. P. (1983). Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. *J. Neurosci.* 3, 1599–1606.

DeLong, M. R., Crutcher, M. D., and Georgopoulos, A. P. (1985). Primate globus pallidus and subthalamic nucleus: functional organization. *J. Neurophysiol.* 53, 530–543.

Filion, M., Tremblay, L., and Bedard, P. J. (1988). Abnormal influences of passive limb movement on the activity of globus pallidus neurons in Parkinsonian monkeys. *Brain Res.* 444, 165–176.

Flaherty, A. W., and Graybiel, A. M. (1993). Two input systems for body representations in the primate striatal matrix: experimental evidence in the squirrel monkey. *J. Neurosci.* 13, 1120–1137.

Gage, G. J., Stoetzner, C. R., Wiltschko, A. B., and Berke, J. D. (2010). Selective activation of striatal fast-spiking interneurons during choice execution. *Neuron* 67, 466–479.

Georgopoulos, A. P., DeLong, M. R., and Crutcher, M. D. (1983). Relations between parameters of step-tracking movements and single cell discharge in the globus pallidus and subthalamic nucleus of the behaving monkey. *J. Neurosci.* 3, 1586–1598.

Graybiel, A. M. (1990). Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci.* 13, 244–254.

Haber, S. N., Kim, K. S., Mailly, P., and Calzavara, R. (2006). Reward-related cortical inputs define a large striatal region in primates that interface with

associative cortical connections, providing a substrate for incentive-based learning. *J. Neurosci.* 26, 8368–8376.

Haber, S. N., Lynd, E., Klein, C., and Groenewegen, H. J. (1990). Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study. *J. Comp. Neurol.* 293, 282–298.

Hamada, I., and DeLong, M. R. (1992). Excitotoxic acid lesions of the primate subthalamic nucleus result in transient dyskinesias of the contralateral limbs. *J. Neurophysiol.* 68, 1850–1858.

Hamada, I., Delong, M. R., and Mano, N. (1990). Activity of identified wrist-related pallidal neurons during step and ramp wrist movements in the monkey. *J. Neurophysiol.* 64, 1892–1906.

Hikosaka, O., Sakamoto, M., and Usui, S. (1989). Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movements. *J. Neurophysiol.* 61, 780–798.

Hikosaka, O., and Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. I. Relation of visual and auditory responses to saccades. *J. Neurophysiol.* 49, 1230–1253.

Holsapple, J. W., Preston, J. B., and Strick, P. L. (1991). The origin of thalamic inputs to the "hand" representation in the primary motor cortex. *J. Neurosci.* 11, 2644–2654.

Hoover, J. E., and Strick, P. L. (1993). Multiple output channels in the basal ganglia. *Science* 259, 819–821.

Hoover, J. E., and Strick, P. L. (1999). The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1. *J. Neurosci.* 19, 1446–1463.

Inase, M., Tokuno, H., Nambu, A., Akazawa, T., and Takada, M. (1999). Corticostriatal and corticosubthalamic input zones from the presupplementary motor area in the macaque monkey: comparison with the input zones from the supplementary motor area. *Brain Res.* 833, 191–201.

Jones, E. G. (2007). *The Thalamus.* New York: Cambridge University Press.

Kaneda, K., Nambu, A., Tokuno, H., and Takada, M. (2002). Differential processing patterns of motor information via striatopallidal and striatonigral projections. *J. Neurophysiol.* 88, 1420–1432.

Kaplitt, M. G., Hutchinson, W. D., and Lozano, A. M. (2003). "Target localization in movement disorders surgery," in *Surgical Treatment of Parkinson's Disease and Other Movement Disorders*, eds D. Tarsy, J. L. Vitek, and A. M. Lozano (Totowa: Humana Press), 87–98.

Kita, H., Nambu, A., Kaneda, K., Tachibana, Y., and Takada, M. (2004). Role of ionotropic glutamatergic and GABAergic inputs on the firing activity of neurons in the external pallidum in awake monkeys. *J. Neurophysiol.* 92, 3069–3084.

Kitano, H., Tanibuchi, I., and Jinnai, K. (1998). The distribution of neurons in the substantia nigra pars reticulata with input from the motor, premotor and prefrontal areas of the cerebral cortex in monkeys. *Brain Res.* 784, 228–238.

Künzle, H. (1975). Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. *Brain Res.* 88, 195–209.

Matsuda, W., Furuta, T., Nakamura, K. C., Hioki, H., Fujiyama, F., Arai, R., and Kaneko, T. (2009). Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. *J. Neurosci.* 29, 444–453.

Matsumura, M., Kojima, J., Gardiner, T. W., and Hikosaka, O. (1992). Visual and oculomotor functions of monkey subthalamic nucleus. *J. Neurophysiol.* 67, 1615–1632.

McFarland, N. R., and Haber, S. N. (2000). Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate. *J. Neurosci.* 20, 3798–3813.

Miyachi, S., Lu, X., Imanishi, M., Sawada, K., Nambu, A., and Takada, M. (2006). Somatotopically arranged inputs from putamen and subthalamic nucleus to primary motor cortex. *Neurosci. Res.* 56, 300–308.

Monakow, K. H., Akert, K., and Künzle, H. (1978). Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. *Exp. Brain Res.* 33, 395–403.

Nakano, K., Hasegawa, Y., Tokushige, A., Nakagawa, S., Kayahara, T., and Mizuno, N. (1990). Topographical projections from the thalamus, subthalamic nucleus and pedunculopontine tegmental nucleus to the striatum in the Japanese monkey, *Macaca fuscata*. *Brain Res.* 537, 54–68.

Nambu, A., Kaneda, K., Tokuno, H., and Takada, M. (2002a). Organization of corticostriatal motor inputs in monkey putamen. *J. Neurophysiol.* 88, 1830–1842.

Nambu, A., Tokuno, H., and Takada, M. (2002b). Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. *Neurosci. Res.* 43, 111–117.

Nambu, A., Takada, M., Inase, M., and Tokuno, H. (1996). Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. *J. Neurosci.* 16, 2671–2683.

Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., Ikeuchi, Y., and Hasegawa, N. (2000). Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *J. Neurophysiol.* 84, 289–300.

Nambu, A., Tokuno, H., Inase, M., and Takada, M. (1997). Corticosubthalamic input zones from forelimb representations of the dorsal and ventral divisions of the premotor cortex in the macaque monkey: comparison with the input zones from the primary motor cortex and the supplementary motor area. *Neurosci. Lett.* 239, 13–16.

Nambu, A., Yoshida, S., and Jinnai, K. (1990). Discharge patterns of pallidal neurons with input from various cortical areas during movement in the monkey. *Brain Res.* 519, 183–191.

Nambu, A., Yoshida, S., and Jinnai, K. (1991). Movement-related activity of thalamic neurons with input from the globus pallidus and projection to the motor cortex in the monkey. *Exp. Brain Res.* 84, 279–284.

Parent, A. (1990). Extrinsic connections of the basal ganglia. *Trends Neurosci.* 13, 254–258.

Parent, A., and Hazrati, L. N. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res. Rev.* 20, 91–127.

Parent, A., Mackey, A., and De Bellefeuille, L. (1983). The subcortical afferents to caudate nucleus and putamen in primate: a fluorescence retrograde double labeling study. *Neuroscience* 10, 1137–1150.

Percheron, G., and Filion, M. (1991). Parallel processing in the basal ganglia: up to a point. *Trends Neurosci.* 14, 55–59.

Percheron, G., Francois, C., Yelnik, J., Fenelon, G., and Talbi, B. (1994). "The basal ganglia related system of primates: Definition, description and information analysis," in *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, eds G. Percheron, J. S. McKenzie, and J. Feger (New York: Plenum Press), 3–20.

Percheron, G., Yelnik, J., and Francois, C. (1984). A Golgi analysis of the primate globus pallidus. III. Spatial organization of the striato-pallidal complex. *J. Comp. Neurol.* 227, 214–227.

Pessiglione, M., Guehl, D., Rolland, A. S., Francois, C., Hirsch, E. C., Feger, J., and Tremblay, L. (2005). Thalamic neuronal activity in dopamine-depleted primates: evidence for a loss of functional segregation within basal ganglia circuits. *J. Neurosci.* 25, 1523–1531.

Picard, N., and Strick, P. L. (2001). Imaging the premotor areas. *Curr. Opin. Neurobiol.* 11, 663–672.

Sadikot, A. F., Parent, A., Smith, Y., and Bolam, J. P. (1992). Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. *J. Comp. Neurol.* 320, 228–242.

Schultz, W., and Romo, R. (1990). Dopamine neurons of the monkey midbrain: contingencies of responses to stimuli eliciting immediate behavioral reactions. *J. Neurophysiol.* 63, 607–624.

Selemon, L. D., and Goldman-Rakic, P. S. (1985). Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J. Neurosci.* 5, 776–794.

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

Strick, P. L., Dum, R. P., and Picard, N. (1995). "Macro-organization of the circuits connecting the basal ganglia with the cortical motor areas," in *Models of Information Processing in the Basal Ganglia*, eds J. C. Houck, J. L. Davis, and D. G. Beiser (Cambridge: MIT Press), 117–130.

Tachibana, Y., Kita, H., Chiken, S., Takada, M., and Nambu, A. (2008). Motor cortical control of internal pallidal activity through glutamatergic and GABAergic inputs in awake monkeys. *Eur. J. Neurosci.* 27, 238–253.

Tachibana, Y., Nambu, A., Hatanaka, N., Miyachi, S., and Takada, M. (2004). Input-output organization of the rostral part of the dorsal premotor cortex, with special reference to its corticostriatal projection. *Neurosci. Res.* 48, 45–57.

Takada, M., Nambu, A., Hatanaka, N., Tachibana, Y., Miyachi, S., Taira, M., and Inase, M. (2004). Organization of prefrontal outflow toward frontal motor-related areas in macaque monkeys. *Eur. J. Neurosci.* 19, 3328–3342.

Takada, M., Tokuno, H., Hamada, I., Inase, M., Ito, Y., Imanishi, M., Hasegawa, N., Akazawa, T., Hatanaka, N., and Nambu, A. (2001). Organization of

inputs from cingulate motor areas to basal ganglia in macaque monkey. *Eur. J. Neurosci.* 14, 1633–1650.

Takada, M., Tokuno, H., Nambu, A., and Inase, M. (1998a). Corticostriatal input zones from the supplementary motor area overlap those from the contra- rather than ipsilateral primary motor cortex. *Brain Res.* 791, 335–340.

Takada, M., Tokuno, H., Nambu, A., and Inase, M. (1998b). Corticostriatal projections from the somatic motor areas of the frontal cortex in the macaque monkey: segregation versus overlap of input zones from the primary motor cortex, the supplementary motor area, and the premotor cortex. *Exp. Brain Res.* 120, 114–128.

Tepper, J. M., Wilson, C. J., and Koos, T. (2008). Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons. *Brain Res. Rev.* 58, 272–281.

Tokuno, H., Inase, M., Nambu, A., Akazawa, T., Miyachi, S., and Takada, M. (1999). Corticostriatal projections from distal and proximal forelimb representations of the monkey primary motor cortex. *Neurosci. Lett.* 269, 33–36.

Vitek, J. L., Ashe, J., DeLong, M. R., and Alexander, G. E. (1994). Physiologic properties and somatotopic organization of the primate motor thalamus. *J. Neurophysiol.* 71, 1498–1513.

Vitek, J. L., Ashe, J., DeLong, M. R., and Kaneoke, Y. (1996). Microstimulation of primate motor thalamus: somatotopic organization and differential distribution of evoked motor responses among subnuclei. *J. Neurophysiol.* 75, 2486–2495.

Vitek, J. L., Chockkan, V., Zhang, J. Y., Kaneoke, Y., Evatt, M., DeLong, M. R., Triche, S., Mewes, K., Hashimoto, T., and Bakay, R. A. (1999). Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann. Neurol.* 46, 22–35.

Wichmann, T., Bergman, H., and DeLong, M. R. (1994). The primate subthalamic nucleus. I. Functional properties in intact animals. *J. Neurophysiol.* 72, 494–506.

Wichmann, T., and Kliem, M. A. (2004). Neuronal activity in the primate substantia nigra pars reticulata during the performance of simple and memory-guided elbow movements. *J. Neurophysiol.* 91, 815–827.

Yelnik, J., Percheron, G., and Francois, C. (1984). A Golgi analysis of the primate globus pallidus. II. Quantitative morphology and spatial orientation of dendritic arborizations. *J. Comp. Neurol.* 227, 200–213.

Yoshida, S., Nambu, A., and Jinnai, K. (1993). The distribution of the globus pallidus neurons with input from various cortical areas in the monkeys. *Brain Res.* 611, 170–174.

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 August 2010; accepted: 31 March 2011; published online: 20 April 2011.

Citation: Nambu A (2011) Somatotopic organization of the primate basal ganglia. Front. Neuroanat. 5:26. doi: 10.3389/fnana.2011.00026