J Neurophysiol 102: 2946–2954, 2009.
First published August 19, 2009; doi:10.1152/jn.91288.2008.

Substantia Nigra Output to Prefrontal Cortex Via Thalamus in Monkeys. II. Activity of Thalamic Relay Neurons in Delayed Conditional Go/No-Go Discrimination Task

Ikuo Tanibuchi,[1] Hiroyuki Kitano,[1,2]✠ and Kohnosuke Jinnai[1]
[1]*Departments of Physiology and* [2]*Neurosurgery, Shiga University of Medical Science, Ohtsu, Japan*

Submitted 1 December 2008; accepted in final form 14 August 2009

Tanibuchi I, Kitano H, Jinnai K. Substantia nigra output to prefrontal cortex via thalamus in monkeys. II. Activity of thalamic relay neurons in delayed conditional go/no-go discrimination task. *J Neurophysiol* 102: 2946–2954, 2009. First published August 19, 2009; doi:10.1152/jn.91288.2008. The present report investigated the involvement of primate nigro-thalamo-cortical projections in discrimination of visual signals with behavioral meaning. We tested the extracellular unit activity of mediodorsal (MD) and ventral anterior (VA) thalamic neurons monosynaptically receiving inhibitory input from the substantia nigra pars reticulata (SNr) and projecting to the frontal cortex in Japanese monkeys performing a delayed conditional go/no-go discrimination task. In the task two colored stimuli (S1, S2) intervened by delay period required the monkeys lifting a lever (go) or not (no-go); the same and different colored pairs of S1 and S2 meant go and no-go signals, respectively. Prominent task-relevant responses were sustained activity with color preference to S1 during delay period and S2-related activity with different firing rates between go and no-go trials. In particular, a high proportion of such go/no-go differential S2-related activity was found in thalamic relay neurons, receiving input from the caudolateral SNr and projecting to the prefrontal area (PSv) ventral to the principal sulcus, in the rostrolateral MD. The findings suggest that the caudolateral SNr–rostrolateral MD–PSv pathways may be possible conduits of signals coding the behavioral meaning of the visual stimuli and thus may be responsible for generating similar neuronal activity in the PSv.

INTRODUCTION

It is widely appreciated that chronic extracellular unit recording studies using behavioral tasks have made a contribution to the elucidation of primate higher-order functions. Nearly all of them, however, have investigated task-relevant neurons but not directed attention to their afferent and efferent connections. On the basis of their results, neurophysiologists have speculated on the functional properties of the neural networks in which the task-related cells could be involved. In the present study we tested task-related unit discharge of single neurons with afferents and efferents electrophysiologically identified.

In our companion paper (Tanibuchi et al. 2009), we recorded thalamic relay neurons in the mediodorsal (MD), ventral anterior (VA), and ventral lateral (VL) thalamus, which received inhibitory input from the substantia nigra pars reticulata (SNr) monosynaptically and projected primarily to the prefrontal cortex (PFC); the majority of them terminated in the cortical area (PSv) ventral to the principal sulcus (PS), including Walker's area 45. The functional specificity of the nigro-thalamo-PFC pathways still remains enigmatic, despite many intriguing studies performed in the nigral, thalamic, and PFC regions that belong to the ascending pathways (e.g., Freedman et al. 2001; Fuster and Alexander 1973; Hikosaka and Wurtz 1983a,b,c; Miller et al. 1996; Niki 1974a,b,c; O'Scalaidhe et al. 1997; Rao et al. 1997; Sakagami and Niki 1994; Sakagami et al. 2001; Tanibuchi and Goldman-Rakic 2003, 2005; Watanabe 1986a,b; Watanabe and Funahashi 2004a,b; Wilson et al. 1993).

To our knowledge, no research has explored the normal functions of the nigro-thalamo-PFC projections. Thus a major question guiding this study was what signals are carried by thalamocortical neurons with SNr input projecting to the PFC in a delayed conditional go/no-go discrimination task. The PSv and its adjacent cortical areas are considered to participate in processing of visual objects' attributes such as color and form ("what" visual processing) and in making the association between visual information with behavioral meaning and purposive behavior (Freedman et al. 2001; Miller et al. 1996; O'Scalaidhe et al. 1997; Sakagami and Niki 1994; Sakagami et al. 2001; Watanabe 1986a,b; Wilson et al. 1993). Specifically, in unit recording studies (Sakagami and Niki 1994; Sakagami et al. 2001; Watanabe 1986a) using go/no-go discrimination tasks similar to that in the present study, some PSv neurons responded to visual stimuli, irrespective of their physical properties, but differentially according to behavioral meaning (i.e., go or no-go signals). We thus expected that thalamocortical neurons with nigral input projecting to the PSv might have discriminative functions similar to those just mentioned. We tested task-related activity of thalamocortical neurons with nigral input using the delayed conditional go/no-go discrimination task. As expected, thalamocortical neurons with nigral input projecting to the PSv exhibited task-related responses similar to those in the PSv, indicating that the centripetal signals carried by the thalamocortical neurons with nigral input might contribute to some of discriminative processing carried out in the PSv. This study therefore elucidated the coding properties of thalamocortical neurons with nigral input projecting to the PFC and, moreover, provided important insight into the role of the PFC–basal ganglia (BG)–thalamic loop circuitry with respect to cognitive operations (Alexander et al. 1986).

✠ Deceased September 25, 2007.

Address for reprint requests and other correspondence: I. Tanibuchi, Department of Physiology, Shiga University of Medical Science, Seta Tsukinowa-cho, Ohtsu, Shiga 520-2192, Japan (E-mail: buchi@belle.shiga-med.ac.jp).

METHODS

Animals

Two Japanese monkeys that served as subjects in this study also served in our preceding study (Tanibuchi et al. 2009). All procedures in training, surgery, recording, and housing of the monkeys were done in accordance with the Guidelines for Animal Experimentation at Shiga University of Medical Science and National Institutes of Health Guide for the Care and Use of Laboratory Animals. This experimental protocol was approved by the Animal Care Committee of Shiga University of Medical Science. After the experimental session, the monkeys were returned to their home cages and given unrestricted access to water, food, and fruit. Their body weight was regularly monitored.

Experimental procedures

The surgical, recording, and histological procedures used in this study were as described in the companion paper (Tanibuchi et al. 2009). Training sessions began after full recovery from the surgery. The monkeys, sitting in a primate chair with their head restrained, faced a screen (36 × 51 cm) in a dimly lit and sound-attenuated room during experimental sessions. They were trained on the delayed conditional go/no-go discrimination task with color as the discriminanda, as illustrated in Fig. 1. An experimental program on a DP-1000 signal processor (NEC San-ei Tokyo) presented visual stimuli on the screen.

DELAYED CONDITIONAL GO/NO-GO DISCRIMINATION TASK. In the delayed conditional go/no-go discrimination task, each trial was initiated by a light-emitting diode (LED, 0.2° circle) lit in the center of the screen. A first cue (S1: green or red) was illuminated on the LED for 0.8 s and, after a delay period (1.8 s), a second cue (S2: either of the two colors) was presented as an imperative stimulus for 2.3 s. All cues (green and red in both S1 and S2) displayed by LED were isoluminous and thus did not connote the go or no-go responses. This task required the monkeys to discriminate between the color of a previously presented S1 and that of the currently presented S2. If S2 was illuminated in the same color as S1, the monkeys had to lift a lever with the left hand within 0.5 s after the appearance of S2 (go trial). If S2 was illuminated in a color different from that of S1, they were required to withhold lifting the lever (no-go trial) while S2 lasted. A few drops of juice were delivered as a reward for successful go and no-go responses (Fig. 1). Go/no-go signal delivery was pseudorandomized across trials so that the monkeys could not predict the go or no-go signal in each trial. The ratio of go trials to no-go trials, as well as that of green S1 to red S1, was set to 1.0. When the monkeys attained ≥95% of successful responses, the training session was completed. Single-neuron activity in the MD, VA, and VL pars medialis (VLm) of the right thalamus was recorded with glass-coated Elgiloy microelectrodes. Thalamic neurons receiving inhibitory SNr input and projecting to various areas of the frontal cortex (FRC) were identified by antidromic and orthodromic stimulation, as reported in the companion paper (see Tanibuchi et al. 2009 for details). Task-related activity of the isolated thalamic relay neurons was examined while the monkeys were performing the delayed go/no-go discrimination task. The on-line computer system sampled neuronal signals with a resolution of 1 ms and stored these data in relation to task events. Eye movements were monitored by recording horizontal electrooculograms (hEOGs) with surface electrodes (time constant: 2 s). Electromyographic (EMG) activity of the responding hand during task performance was recorded from the forearm muscles of the left upper limb. Recording sessions of several hours were held every 3 or 4 days. When the monkeys did not maintain ≥95% of successful responses, we finished the recording session.

Data analysis

TASK EVENTS. Average firing rates were measured in different task events defined in the following text. Each go trial was divided into S1, delay, S2, and movement (Mvt) epochs, whereas each no-go trial was divided into S1, delay, and S2 epochs. The S1 and S2 epochs were determined over a 200-ms time segment starting 50 ms after the onsets of S1 and S2, respectively. However, for S1- and/or S2-responsive neurons having biphasic changes in firing rate (e.g., increases were followed by decreases in firing rate) within the 200-ms time segment, we set a 150-ms time segment starting 50 ms after the cue(s) to avoid statistically missing such responses. The delay epoch spanned an 1,800-ms period extending from the end of S1 until the onset of S2. The Mvt epoch was a 300-ms period spanning from 200 ms preceding the initiation of the lever lifting to 100 ms after its initiation in go trials.

STATISTICAL ANALYSIS. The average firing rates during three epochs (S1, delay, and S2) were analyzed to find significant changes in firing rates during S1, delay, and S2 epochs (paired *t*-test, $P < 0.01$); a statistical comparison was made between firing rates during each of the three epochs and those during a 1.0-s intertrial interval (ITI) in each trial. The same statistical comparison was also made between

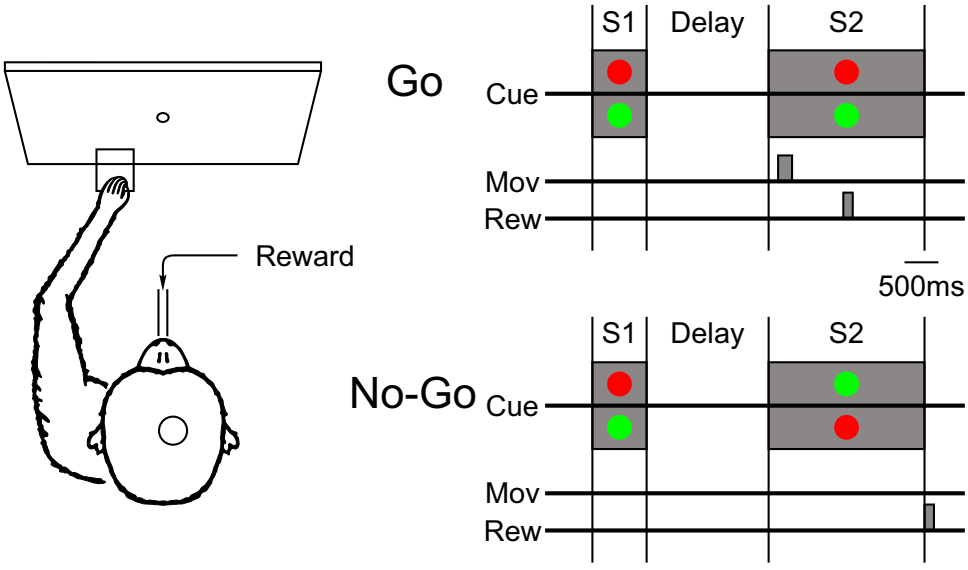

FIG. 1. Paradigm of a delayed conditional go/no-go discrimination task with color discriminanda. If a second cue (S2) was illuminated in the same color as a first cue (S1), the monkey was required to lift a lever within 0.5 s after the appearance of S2 (go trial; *top right*). If S2 was illuminated in a color different from that of S1, the monkey was required to withhold lifting the lever while S2 was lit (no-go trial; *bottom right*). See METHODS for detailed description.

TABLE 1. *Task event-related activity of task-tested neurons projecting to cortical areas*

Projection Areas	Tested Units	Responsive Units	Task Events			
			S1	Delay	S2	Mvt
PSv	33	28	7	20	20	3
Other PFC						
PSd	2	1	1	1	1	1
PFd	4	1		1		
PFm	3	2	1			2
OF	1	1		1	1	1
Motor areas						
PMd	2	2		1		2
PMv	3	2	1	2		1
SMA	1	1	1	1		
M	1	1		1		
Multiple areas						
OF and PMd	2	1		1		
PFd and PMd	1					
Total	53	40	11	29	22	10

firing rates during the Mvt epoch and those during a 1.0-s ITI in each go trial (paired *t*-test, $P < 0.01$) to detect hand movement-related activity.

S2-RELATED AND MVT-PHASE RESPONSES. Neurons significantly (paired *t*-test, $P < 0.01$) responding to both S2 and the movement were tested to assess whether their activity in go trials was related to S2, the movement, or both, by comparing two summed histograms (5 ms/bin) of their firing rate aligned at the onset of S2 and the movement, respectively. If the firing rate increased (or decreased) more steeply in the summed histograms aligned at the onset of S2, it was classified into S2-related responses, and vice versa (see Tanji and Kurata 1982 for details). The responses occurring during the Mvt epoch were mostly not directly linked to the lever lifting, as described in RESULTS, so that we refer to the responses as *Mvt-phase activity*.

COLOR PREFERENTIAL AND GO/NO-GO DIFFERENTIAL ACTIVITY. S1- and delay-related responses, respectively, were statistically further examined with regard to color preference for S1; the average firing rates during S1 and delay epochs, respectively, were compared between green S1 and red S1 trials by unpaired *t*-test ($P < 0.05$). S2-related responses were also statistically tested with respect to color preferential activity to S2 and differential activity between go and no-go trials; two-way ANOVA ($P < 0.05$) was applied to S2-related neurons with behavioral response (two levels: go and no-go signals of S2) and color (two levels: green and red of S2) as factors during S2 epoch (i.e., 200 ms spanning from 50 to 250 ms after the S2 onset), whereby S2-related responses were classified into four classes: *1*) only go/no-go differential activity [*P* of response factor: $P(\text{resp}) < 0.05$; *P* of color factor: $P(\text{color}) \geq 0.05$; and *P* of interaction between response and color: $P(\text{resp} \times \text{color}) \geq 0.05$]; *2*) only color preferential activity to S2 [$P(\text{color}) < 0.05$; $P(\text{resp}) \geq 0.05$; and $P(\text{resp} \times \text{color}) \geq 0.05$]; *3*) go/no-go differential activity with color preference for S2 [$P(\text{resp}) < 0.05$ and $P(\text{color}) < 0.05$]; and *4*) go/no-go nondifferential activity with color nonpreference for S2 [$P(\text{resp}) \geq 0.05$ and $P(\text{color}) \geq 0.05$].

MEASUREMENT OF LATENCY. We measured latencies of S1- and S2-related and Mvt-phase responses detected by paired *t*-test. Latencies of S1-related responses were determined by using summed histograms (5 ms/bin) of unit activity aligned at the onset of S1 in all trials. The control period was 500 ms before the S1 onset and the mean and SD of the firing rates during the control period, determined from the summed histograms, established a 95.45% confidence interval. The latency detection was made within 200 ms starting 50 ms after the S1 onset. When the response was sustained for at least two consecutive bins beyond the upper or lower limit of the confidence interval (i.e., beyond ±2SD), the response latency was defined as the time between the S1 onset and the first bin of the consecutive bins. Latencies in S2-related responses were determined in the same manner as those in S1-related responses, setting the control period to 500 ms before the S2 onset. Latency detection of Mvt-phase neurons was also determined similarly using as the control period 500–1,000 ms before the initiation of the lever lifting in the summed histograms aligned at the onset of the movement. When the firing rates of S1- and S2-related and Mvt-phase responses did not reach the upper or lower limit of the confidence interval, these responses were excluded from S1- and S2-related and Mvt-phase responses, respectively.

Reconstruction and nomenclature

Histological examination and nomenclature in this study were as detailed in our companion paper (Tanibuchi et al. 2009).

RESULTS

Of 70 thalamocortical neurons with nigral input identified (Tanibuchi et al. 2009), we tested 53 thalamic relay neurons with the delayed conditional go/no-go discrimination task. Forty thalamic neurons exhibited significant event-related (cue-related, delay-related, and/or Mvt-phase) changes in firing rate during task performance, as shown in Table 1. With respect to these response types, the mean and SD values of the spontaneous and responsive firing rates in the 40 neurons are detailed in Table 2. We analyzed the 40 task-related neurons in terms of the relationship between the task events (cue, delay, and movement) to which their changes in firing rate were related and their connectional anatomy (nigral sourcing portions, thalamic recording sites, and cortical projection areas).

TABLE 2. *Mean ± SD of spontaneous (Sp) and responsive (Resp) firing rates of task event-related neurons projecting to PSv, other PFC, and motor areas*

Projection Areas	Response Types	S1		Delay		S2		Mvt	
		Sp	Resp	Sp	Resp	Sp	Resp	Sp	Resp
PSv	Increase	5.5 ± 2.8	9.5 ± 5.0 ($n = 7$)	7.0 ± 4.8	9.0 ± 6.1 ($n = 10$)	10.7 ± 6.7	20.0 ± 9.8 ($n = 16$)	7.7 ± 2.3	9.8 ± 8.5 ($n = 3$)
	Decrease			13.1 ± 6.5	8.8 ± 6.0 ($n = 10$)	11.2 ± 6.4	6.0 ± 2.9 ($n = 4$)		
Other PFC	Increase	7.5 ± 2.0	10.2 ± 3.6 ($n = 2$)	11.6 ± 4.4	15.5 ± 5.5 ($n = 2$*)	8.8 ± 0.2	12.5 ± 0.9 ($n = 2$)	8.3 ± 2.8	10.5 ± 5.7 ($n = 4$)
	Decrease			8.8 ± 0.2	6.7 ($n = 2$)				
Motor areas	Increase			10.3 ± 5.1	13.4 ± 6.3 ($n = 6$*)			8.7 ± 5.1	15.1 ± 8.4 ($n = 2$)
	Decrease	8.9 ± 3.1	6.7 ± 3.1 ($n = 2$)					6.4	1.1 ($n = 1$)

Values are shown by spikes/s. Spontaneous firing rates (Sp) measured during ITI. *: One neuron projecting to both other PFC and motor areas.

TABLE 3. *Task-responsive neurons classified by projection areas and task events*

			S1		Delay		S2				
							Color Pref(+)		Color Pref(−)		
Projection Areas	Tested Units	Responsive Units	Color Pref(+)	Color Pref(−)	Color Pref(+)	Color Pref(−)	Go/No-Go Diff(+)	Go/No-Go Diff(−)	Go/No-Go Diff(+)	Go/No-Go Diff(−)	Mvt
PSv	33	28		7	**7**	13	**3**		**10**	7	3
Other PFC	13*	6**		2	**1**	3**				2	4
Motor areas	10*	7**		2	**1**	5**					3
Total	53	40		11	**9**	20	**3**		**10**	9	10

Bold numerals: crucial responses for task performance. *: Three neurons projecting to both other PFC and motor areas. **: One neuron projecting to both other PFC and motor areas.

Task-related neurons projecting to PSv

Because the PSv was the main cortical target of the 40 task-responsive neurons (Table 1), we first show the results of 28 task-relevant neurons projecting to the PSv. As shown in Table 3, the 28 neurons (19 MD pars multiformis and pars parvocellularis: MDmf/pc; 9 VA pars magnocellularis: VAmc) were modulated mostly in association with the delay or S2 and less numerously in relation to S1 or the movement, alone or in combination with other types of activity.

S1-RELATED ACTIVITY. Of the 28 task-relevant neurons, 7 showed increasing responses to S1 (Table 2). The onset latencies of the 7 responses to S1 ranged from 55 to 170 ms (mean ± SD = 97.9 ± 36.3 ms). None of the 7 S1-related responses showed color selectivity (Table 3).

DELAY-RELATED ACTIVITY. Of the 28 task-relevant neurons, more than two thirds ($n = 20$) showed sustained increases ($n = 10$) and decreases ($n = 10$) in discharge rate during the delay period (Table 2). About one third ($n = 7$; 4 MDmf/pc, 3 VAmc) of the 20 delay-responsive neurons showed color selectivity (i.e., different delay-related discharge rate between green S1 and red S1 trials) (Table 3). They received nigral input from the rostral ($n = 3$; 1 MDmf/pc, 2 VAmc) or caudal ($n = 4$; 3 MDmf/pc, 1 VAmc) SNr. A neuron with prominent color-selective responses during the delay period is illustrated in Fig. 2, showing an elevated discharge rate during the delay period only after green S1 was presented (and also exhibiting S2-related nondifferential activity between go and no-go trials; Fig. 2, *A-1* and *A-2*). This neuron received inhibitory input from the caudal SNr and projected to the PSv (Fig. 2, *B* and *C*).

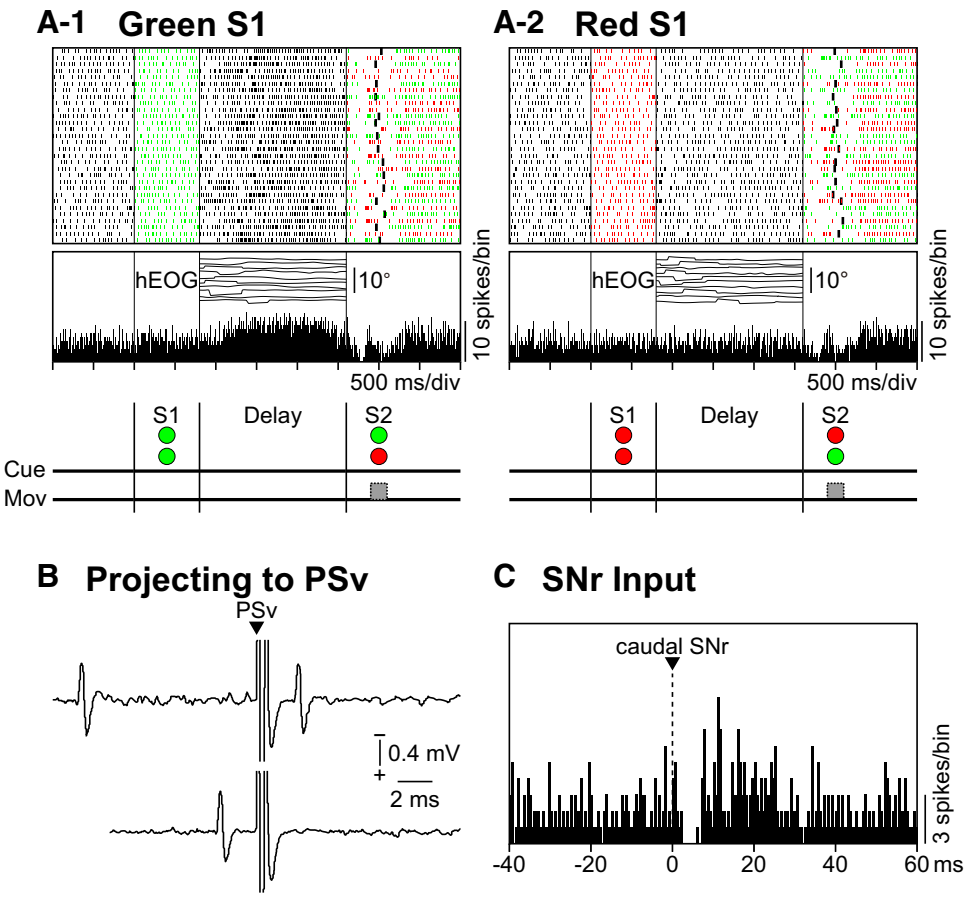

FIG. 2. A thalamic relay neuron with delay-related activity dependent on S1 color. *A*: rasters and summed histograms of the spike discharge of this neuron, recorded in the mediodorsal nucleus pars parvocellularis (MDpc; **x** at AP +13 in Fig. 4*B*), in green S1 (*A-1*) and red S1 (*A-2*) trials. The unit discharge during the presentation of green and red stimuli (S1, S2) is indicated by green and red rasters, respectively. Thick marks in the rasters signify the onset of left-hand movement. This neuron had a sustained discharge during delay period only after green S1 presentation. It also showed decreased S2-related activity that was nondifferential between go and no-go trials. Horizontal electrooculograms (hEOGs, 10 sweeps) during the delay period in the green S1 (*A-1*) and red S1 (*A-2*) trials showed no difference between the 2 kinds of trials. Upward deviation signifies rightward eye movement. *B*: antidromic activation (*top*) induced by stimulation of the prefrontal area ventral to the principal sulcus (PSv), and its collision interaction (*bottom*). Ten sweeps of the triggering and stimulation-evoked action potentials were averaged. The antidromic responses occurred 2.2 ms after PSv stimulation. *C*: orthodromic inhibition induced by stimulation of the substantia nigra pars reticulata (SNr). Its neuronal activity was suppressed 2.4 ms after stimulation of the caudal SNr (bin width of 0.5 ms, 120 sweeps summed).

The frequency and amplitude of the horizontal component of saccadic eye movement during the delay period were not different between the green S1 and the red S1, as shown in hEOG (Fig. 2, *A-1* and *A-2*). The responding hand did not exhibit any EMG activity during the delay period (data not shown).

S2-RELATED ACTIVITY. Of the 28 task-relevant neurons, roughly 70% ($n = 20$) changed their firing rate (16 increased, 4 decreased) in response to S2 (Tables 1 and 2). The onset latencies of the 20 S2-related responses averaged 96.5 ± 36.5 ms (range: 55–185 ms), not significantly different from those of the 7 S1-related responses (*t*-test, $P > 0.93$). Of the 20 S2-related neurons, 10 neurons (50%; 7 MDmf/pc, 3 VAmc) exhibited different S2-related discharge rate between go and no-go trials with no color preference for S2 [two-way ANOVA, P(go/ng) <0.05; P(color) ≥ 0.05; and P(go/ng × color) ≥ 0.05; Table 3]: 8 increased, 2 decreased; onset latency 91.5 ± 24.8 ms; range: 55–125 ms. None of them showed reciprocal (i.e., increased vs. decreased) S2-related responses between go and no-go trials. Three other neurons (15%; MDmf/pc) exhibited not only go/no-go differential but also color preferential increases to S2 [two-way ANOVA, P(go/ng) <0.05 and P(color) <0.05; latency 63.3 ± 10.4 ms; range: 55–75 ms], whereas the remainder ($n = 7$, 35%; 4 MDmf/pc, 3 VAmc) displayed neither go/no-go differential nor color selective activity to S2 [two-way ANOVA, P(go/ng) ≥ 0.05 and P(color) ≥ 0.05; 5 increased, 2 decreased; latency 117.9 ± 46.1 ms; range: 80–185 ms; Table 3]. The onset latencies were not significantly different among the three populations (Tukey–Kramer's post hoc test, $P > 0.05$). We refer to the 10 go/no-go differential S2-related neurons with no color preference for the cue as *go/no-go S2-related* neurons. An example of go/no-go S2-related neurons is shown in Fig. 3. This neuron responded robustly to go S2 but faintly to no-go S2, with no other event-related responses (Fig. 3, *A-1*, *A-2*, and *A-3*). The neuron, receiving inhibitory afferents from the caudal SNr, projected to the PSv (Fig. 3, *B* and *C*). The go and no-go S2-related unit discharge was not implicated in the horizontal component of the monkey's eye movement (Fig. 3, *A-1* and *A-2*) and the neuronal activity was also not relevant to the lever lifting because the neuron exhibited a less vigorous burst in summed histograms aligned at the initiation of the movement than at that of go S2 (Fig. 3, *A-1* and *A-3*).

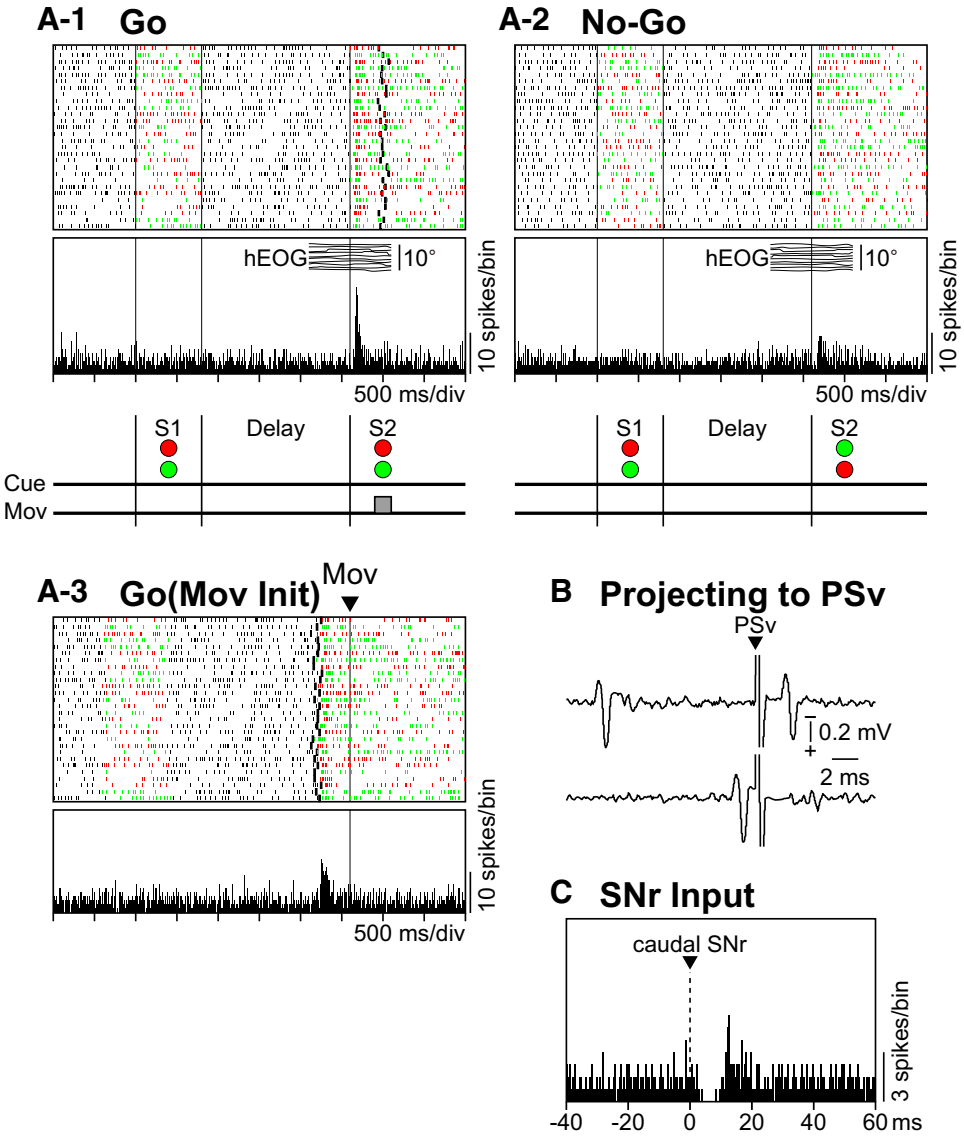

FIG. 3. A thalamic relay neuron with S2-related differential activity between go and no-go trials. *A*: rasters and summed histograms of the spike discharge of this neuron aligned at cue (S1, S2) initiation in go (*A-1*) and no-go (*A-2*) trials and at movement initiation in go trials (*A-3*). This neuron was located in the mediodorsal nucleus pars multiformis (MDmf at the border with the MDpc; **y** at AP +14 in Fig. 4*B*). Thick marks in the rasters of *A-1* and *A-3* signify the onset of left-hand movement and S2 presentation, respectively. It was vigorously activated by go S2 but weakly by no-go S2. hEOGs (10 sweeps) between 500 ms preceding the initiation of S2 and 500 ms after its initiation are shown in the go and no-go trials; they were not different between both trials. Upward deviation signifies rightward eye movement. *B*: antidromic activation (*top*) induced by PSv stimulation and its collision interaction (*bottom*). The antidromic responses occurred 2.0 ms after PSv stimulation. *C*: peristimulus time histograms (PSTHs) showing SNr-induced orthodromic inhibition. Its spike discharge was suppressed 3.9 ms after stimulation of the caudal SNr (bin width of 0.5 ms, 100 sweeps summed). Conventions in *B* and *C* are identical to those in Fig. 2, *B* and *C*, respectively.

MVT-PHASE ACTIVITY. Only three neurons exhibited enhanced discharge rate during the Mvt epoch (Table 3); two started their faint activity 115 and 170 ms preceding the initiation of the movement, whereas one started moderate response 20 ms after its initiation.

Task-related neurons projecting to other FRC

We found 12 task-related neurons projecting to cortical regions other than the PSv; 5 projected to other PFC (the PFC dorsal to the PS: PSd; dorsal part of the dorsolateral PFC: PFd; medial PFC: PFm; and orbitofrontal area: OF), 6 projected to motor areas (the primary motor area: M; premotor area: PM; and supplementary motor area: SMA), and one to both other PFC and motor areas (Table 1; see Fig. 1 in Tanibuchi et al. 2009). The 12 neurons were also further examined in the same manner as the 28 neurons projecting to the PSv, as shown in Table 3.

Six neurons (5 VAmc; 1 VA pars parvocellularis: VApc) projecting to other PFC, one of which terminated in both the other PFC and motor areas, showed S1-related ($n = 2$), delay-related ($n = 4$), S2-related ($n = 2$), and/or Mvt-phase ($n = 4$) responses; with regard to the color selectivity and go/no-go differential activity, one delay-related response showed color selectivity (Tables 1 and 3). Of the four Mvt-phase responses, one started sustained activity 135 ms before the movement initiation and lasted beyond its termination and three others, exhibiting significant but weak activity, started between 30 ms before and 40 ms after the movement initiation.

Seven neurons (2 VAmc, 5 VApc) projecting to motor areas, one of which projected to multiple areas, showed S1-related ($n = 2$), delay-related ($n = 6$), and/or Mvt-phase ($n = 3$) activity (Table 1). Of the six delay-related neurons, one exhibited elevated discharge rate with color selectivity during the delay period (Table 3). Of the three Mvt-phase neurons, one projecting to the PMv showed attenuated activity starting 150 ms before the movement initiation, whereas two others projecting to the PMd began enhanced firing 30 and 60 ms, respectively, after its initiation.

Thalamic location of task-related neurons

Forty neurons with task-relevant activity were recorded primarily in the MDmf/pc ($n = 19$) and VAmc ($n = 15$), but also in the VApc ($n = 6$) (Fig. 4*A*). There were different connectional findings between the task-related neurons in the MDmf/pc and those in the VAmc, which reflect those of the 70 thalamocortical neurons with nigral input identified (see Tanibuchi et al. 2009). Nearly all ($n = 18$) of the 19 MD neurons received nigrothalamic afferents from the caudal SNr and sent thalamocortical fibers to the PSv. Meanwhile, three fourths ($n = 11$) of the 15 VAmc neurons, receiving afferents from the rostral SNr, projected to the PSv ($n = 5$), other PFC ($n = 4$), motor areas ($n = 1$), or both other PFC and motor areas ($n = 1$), whereas one fourth ($n = 4$) of them, receiving afferents from the caudal SNr, projected exclusively to the PSv. The recording sites of S1-, delay-, and/or S2-related neurons ($n = 38$) are plotted in Fig. 4*B*. No Mvt-phase responses are plotted

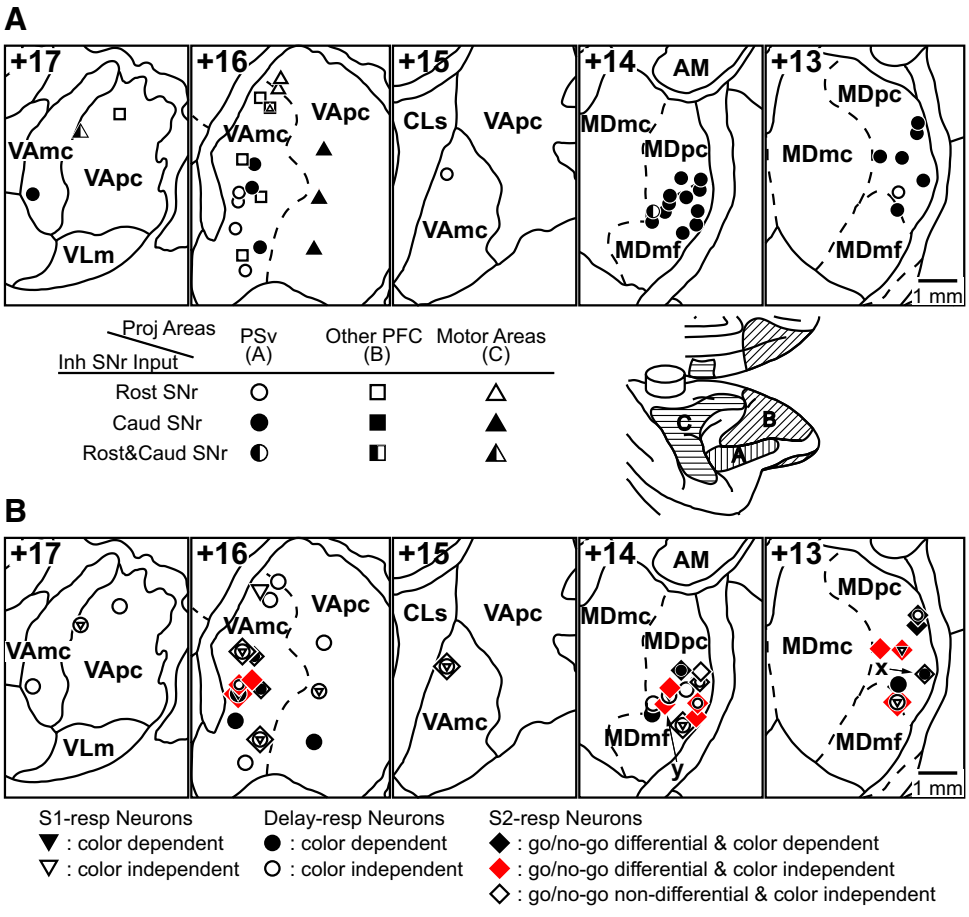

FIG. 4. Thalamic location of neurons with task-relevant activity. They are plotted on coronal sections of the macaque mediodorsal (MD) and ventral anterior (VA), thalamus spanning from AP +13 to +17 mm in front of the interaural line. *A*: recording sites ($n = 40$) representing nigral sourcing portions and cortical projection areas. *B*: recording sites ($n = 38$) representing S1-, delay-, and/or S2-related activity. Neuronal responses in relation to single and multiple task events are signified by symbols (shown at *bottom*) and their combinations, respectively. **x** and **y** refer to the neurons shown in Figs. 2 and 3, respectively.

in Fig. 4*B* because they mostly did not appear to be linked to the lever lifting, as mentioned in the DISCUSSION.

DISCUSSION

To our knowledge, only very few studies have explored task-relevant activity of neurons with afferents and efferents electrophysiologically identified (Nambu et al. 1990, 1991; Sommer and Wurtz 2002, 2004a,b). The present study investigated what signals are carried by thalamocortical neurons with SNr input during performance of a delayed conditional go/no-go discrimination task. Prominent critical task event-related responses were go/no-go S2-related activity and delay-related activity with color preference for S1, a majority of which were observed in thalamic relay neurons projecting to the PSv. Accordingly, neurons projecting to the PSv seem to play more important roles in the task performance than those projecting to other areas of the FRC. Although our sample size was limited on account of orthodromic and antidromic identification procedures, the present results provide intriguing clues for understanding the normal functions of the nigro-thalamocortical projections.

Go/no-go differential activity

Ten neurons, which projected to the PSv, showed go/no-go S2-related responses (Table 3). Because the 10 go/no-go S2-related responses showed neither color-preferential nor motor-related activity, they seemed to be related to some information processing at a cognitive stage after color-related signal processing. Cue-related neuronal activity, similar to the go/no-go S2-related activity in the present study, was found in and near the PSv where the 10 go/no-go S2-related neurons projected in the present study (Sakagami and Niki 1994; Sakagami et al. 2001; Watanabe 1986a). They mostly responded to the cue 50 to 200 ms after its presentation, which was similar to the onset latencies (55 to 125 ms) of the 10 go/no-go S2-related responses. Watanabe (1986a) tested unit activity in and around the macaque PSv on a delayed conditional go/no-go discrimination task with color discriminanda, which was similar to the task used in the present study. Some neurons exhibited a second cue-related activity differential between go and no-go trials with no color preference for the cue. Such cue-related responses are considered to code the behavioral meaning of the visual stimuli but not their specific color features. Accordingly, the go/no-go S2-related responses in the present study may make contributions to generating the go/no-go differential cue-related responses in the PSv.

Color-dependent activity

Nine delay-related and three S2-related responses showed color dependent activity to S1 and S2, respectively (Table 3).

DELAY-RELATED ACTIVITY. The delay-related responses with color preference for S1 could not be simply due to anticipating S2 presentation or expecting reward because the sustained activity showed color preference. They may preserve the color information of S1 during the delay period ("working memory"). Neurons with the same functional properties were found in the inferior dorsolateral PFC, inclusive of the PSv where the majority (7/9 = 78%) of the thalamic neurons exhibiting the color-dependent responses terminated in the present study (Freedman et al. 2001, 2003; Sakagami et al. 2001; Watanabe 1986a; Wilson et al. 1993). Taken together, the color preferential delay-related activity seems to have a major influence on the mnemonic processing of the color attribute in the PSv.

S2-RELATED ACTIVITY. The S2-related neurons that showed color preferential activity to S2 also displayed go/no-go differential S2-related activity (Table 3). They might be engaged in some color signal processing that is prerequisite for the issuance of go/no-go signals.

Other task-relevant activity

In addition to the go/no-go differential and the color dependent activity, S1- ($n = 11$), delay- ($n = 20$), and go/no-go nondifferential S2- ($n = 8$) related responses without color preference and Mvt-phase responses ($n = 10$) were observed (Table 3).

COLOR NONPREFERENTIAL AND GO/NO-GO NONDIFFERENTIAL ACTIVITY. Their functional properties are ambiguous in this task paradigm. One possible interpretation is that they could encode other attributes (e.g., shape, pattern) of the cue(s) or be simply due to expecting reward.

MVT-PHASE ACTIVITY. Only one neuron projecting to the PMv could be engaged in the preparation or execution of the lever lifting because it showed Mvt-phase response starting 150 ms before the initiation of the movement in go trials. Nine other Mvt-phase neurons, however, could not be directly concerned with motor functions because some of them showed faint Mvt-phase activity, others started Mvt-phase activity after the movement initiation, and/or still others lasted beyond its termination (see RESULTS).

Neural network carrying signals crucial for task performance

As discussed earlier, we consider that delay- and go/no-go differential S2-related responses with color preference and go/no-go S2-related responses are crucial for successful task performance (bold numerals in Table 3). In each of the three crucial response types, the ratio of its related neurons to task-tested neurons was statistically compared among neurons projecting to the PSv ($n = 33$), to other PFC ($n = 13$), and to motor areas ($n = 10$). Only go/no-go S2-related responses ($n = 10$) in neurons projecting to the PSv were significantly prominent among neurons projecting to the three cortical areas (χ^2 test, $P < 0.05$).

PSV–BG–THALAMIC LOOPS. MDmf/pc neurons with input from the caudolateral SNr carried most (7/10 = 70%) of the go/no-go S2-related signals to the PSv. In one of the same monkeys we found SNr neurons with go/no-go S2-related responses receiving cortical input from the PSv via the caudate nucleus, the majority of which were located in the caudolateral SNr where nigrothalamic neurons projected to the MDmf/pc (Jinnai et al. 1995; Kitano et al. 1998). On these results we framed a hypothesis that the go/no-go S2-related signals flow through the cortico–BG–thalamic loops comprising the caudolateral SNr–MDmf/pc–PSv projections. However, it should be noted that the go/no-go S2-related signals might travel

through other brain regions because the MDmf/pc receives profuse afferents not only from the SNr but also from the PFC, superior colliculus (SC), and reticular thalamic nucleus (R) (Giguere and Goldman-Rakic 1988; Guillery and Harting 2003; Harting et al. 1980; McFarland and Haber 2002; Preuss and Goldman-Rakic 1987; Russchen et al. 1987; Siwek and Pandya 1991). Also, the go/no-go S2-related activity in the MDmf/pc might be generated by the integration of signals coming from the four divisions. At all events the rostrolateral MD–PSv pathways might be critically responsible for the selection of appropriate behavior (i.e., suppress some behavioral responses and carry out others) to environmental stimuli. Their dysfunction might result in inappropriate behavior, as demonstrated by lesion studies in human and nonhuman primates. Monkeys with lesions of the inferior dorsolateral PFC were unable to withhold go response to auditory or visual cues requiring no-go response (Iversen and Mishkin 1970). Patients with lesions of the thalamic nuclei including the MDmf/pc and the inferior dorsolateral PFC could not perform appropriate behavior to the events and stimuli that they experienced in their daily lives (e.g., utilization behavior, i.e., exaggerated behavior to external cues, imitation behavior, perseveration) (Hashimoto et al. 1995; Lhermitte 1983; Lhermitte et al. 1986; Milner 1964). Specifying the physiological functions of single neurons with afferent and efferent connections offers insight into the pathophysiology of such symptoms, as mentioned earlier.

ACKNOWLEDGMENTS

We thank Dr. A. Nambu (National Institute for Physiological Science, Japan) for the review and helpful advice on earlier manuscripts.

REFERENCES

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9: 357–381, 1986.

Freedman DJ, Riesenhuber M, Poggio T, Miller EK. Categorical representation of visual stimuli in the primate prefrontal cortex. *Science* 291: 312–316, 2001.

Freedman DJ, Riesenhuber M, Poggio T, Miller EK. A comparison of primate prefrontal and inferior temporal cortices during visual categorization. *J Neurosci* 23: 5235–5246, 2003.

Fuster JM, Alexander GE. Firing changes in cells of the nucleus medialis dorsalis associated with delayed response behavior. *Brain Res* 61: 79–91, 1973.

Giguere M, Goldman-Rakic PS. Mediodorsal nucleus: areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. *J Comp Neurol* 277: 195–213, 1988.

Guillery RW, Harting JK. Structure and connections of the thalamic reticular nucleus: advancing views over half a century. *J Comp Neurol* 463: 360–371, 2003.

Harting JK, Huerta MF, Frankfurter AJ, Strominger NL, Royce GJ. Ascending pathways from the monkey superior colliculus: an autoradiographic analysis. *J Comp Neurol* 192: 853–882, 1980.

Hashimoto R, Yoshida M, Tanaka Y. Utilization behavior after right thalamic infarction. *Eur Neurol* 35: 58–62, 1995.

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

Hikosaka O, Wurtz RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses related to fixation of gaze. *J Neurophysiol* 49: 1254–1267, 1983b.

Hikosaka O, Wurtz RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J Neurophysiol* 49: 1268–1284, 1983c.

Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Exp Brain Res* 11: 376–386, 1970.

Jinnai K, Kitano H, Tanibuchi I. Cortical and amygdala input to substatia nigra. *4th IBRO World Congress Neurosci Abstr* 323, 1995.

Kitano H, Tanibuchi I, Jinnai K. 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, 1998.

Lhermitte F. "Utilization behavior" and its relation to lesions of the frontal lobes. *Brain* 106: 237–255, 1983.

Lhermitte F, Pillon B, Serdaru M. Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: a neuropsychological study of 75 patients. *Ann Neurol* 19: 326–334, 1986.

McFarland NR, Haber SN. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J Neurosci* 22: 8117–8132, 2002.

Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J Neurosci* 16: 5154–5167, 1996.

Milner B. Some effects of frontal lobectomy in man. In: *The Frontal Granular Cortex and Behavior*, edited by Warren JM, Akert K. New York: McGraw-Hill, 1964, p. 313–334.

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

Nambu A, Yoshida S, Jinnai K. 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, 1991.

Niki H. Prefrontal unit activity during delayed alternation in the monkey. I. Relation to direction of response. *Brain Res* 68: 185–196, 1974a.

Niki H. Prefrontal unit activity during delayed alternation in the monkey. II. Relation to absolute versus relative direction of response. *Brain Res* 68: 197–204, 1974b.

Niki H. Differential activity of prefrontal units during right and left delayed response trials. *Brain Res* 70: 346–349, 1974c.

O'Scalaidhe SP, Wilson FA, Goldman-Rakic PS. Areal segregation of face-processing neurons in prefrontal cortex. *Science* 278: 1135–1138, 1997.

Preuss TM, Goldman-Rakic PS. Crossed corticothalamic and thalamocortical connections of macaque prefrontal cortex. *J Comp Neurol* 257: 269–281, 1987.

Rao SC, Rainer G, Miller EK. Integration of what and where in the primate prefrontal cortex. *Science* 276: 821–824, 1997.

Russchen FT, Amaral DG, Price JL. The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, *Macaca fascicularis*. *J Comp Neurol* 256: 175–210, 1987.

Sakagami M, Niki H. Encoding of behavioral significance of visual stimuli by primate prefrontal neurons: relation to relevant task conditions. *Exp Brain Res* 97: 423–436, 1994.

Sakagami M, Tsutsui K, Lauwereyns J, Koizumi M, Kobayashi S, Hikosaka O. A code for behavioral inhibition on the basis of color, but not motion, in ventrolateral prefrontal cortex of macaque monkey. *J Neurosci* 21: 4801–4808, 2001.

Siwek DF, Pandya DN. Prefrontal projections to the mediodorsal nucleus of the thalamus in the rhesus monkey. *J Comp Neurol* 312: 509–524, 1991.

Sommer MA, Wurtz RH. A pathway in the primate brain for internal monitoring of movements. *Science* 296: 1480–1482, 2002.

Sommer MA, Wurtz RH. What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. *J Neurophysiol* 91: 1381–1402, 2004a.

Sommer MA, Wurtz RH. What the brain stem tells the frontal cortex. II. Role of the SC-MD-FEF pathway in corollary discharge. *J Neurophysiol* 91: 1403–1423, 2004b.

Tanibuchi I, Goldman-Rakic PS. Dissociation of spatial-, object-, and sound-coding neurons in the mediodorsal nucleus of the primate thalamus. *J Neurophysiol* 89: 1067–1077, 2003.

Tanibuchi I, Goldman-Rakic PS. Comparison of oculomotor neuronal activity in paralaminar and mediodorsal thalamus in the rhesus monkey. *J Neurophysiol* 93: 614–619, 2005.

Tanibuchi I, Kitano H, Jinnai K. Substantia nigra output to prefrontal cortex via thalamus in monkeys. I. Electrophysiological identification of thalamic relay neurons. *J Neurophysiol* 102: 2933–2945, 2009.

Tanji J, Kurata K. Comparison of movement-related activity in two cortical motor areas of primates. *J Neurophysiol* 48: 633–653, 1982.

Watanabe M. Prefrontal unit activity during delayed conditional go/no-go discrimination in the monkey. I. Relation to the stimulus. *Brain Res* 382: 1–14, 1986a.

Watanabe M. Prefrontal unit activity during delayed conditional go/no-go discrimination in the monkey. II. Relation to go and no-go responses. *Brain Res* 382: 15–27, 1986b.

Watanabe Y, Funahashi S. Neuronal activity throughout the primate mediodorsal nucleus of the thalamus during oculomotor delayed responses. I. Cue-, delay-, and response-period activity. *J Neurophysiol* 92: 1738–1755, 2004a.

Watanabe Y, Funahashi S. Neuronal activity throughout the primate mediodorsal nucleus of the thalamus during oculomotor delayed responses. II. Activity encoding visual versus motor signal. *J Neurophysiol* 92: 1756–1769, 2004b.

Wilson FA, O'Scalaidhe SP, Goldman-Rakic PS. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* 260: 1955–1958, 1993.