

Neural Coding of “Attention for Action” and “Response Selection” in Primate Anterior Cingulate Cortex

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Noninvasive imaging techniques showed that the anterior cingulate cortex is related to higher-order cognitive and motor-related functions in humans. To elucidate the cellular mechanism of such cingulate functions, single-unit activity was recorded from three cingulate motor areas of macaque monkeys performing delayed conditional Go/No-go discrimination tasks using spatial (location) and nonspatial (color) visual cues. Unlike prefrontal neurons, only a few neurons coded the visual information on individual features (e.g., “left” or “red”) in all of the rostral (CMAr), dorsal (CMAd), and ventral (CMAv) cingulate motor areas. Instead, many neurons in the CMAr exhibited the attention-like activity anticipating the second (conditioned) visual cues, with the specificity to visual category (“location” or “color”). In addition, there were a number of CMAr neurons specific to motor response (*Go* or *No-go*) in relation to the second visual cues. Some of the visual category-specific neurons in the CMAr further displayed the motor response-specific activity. On the other hand, many of the task-related CMAd and CMAv neurons seemed to be implicated directly in motor functions, such as preparation and execution of movements in *Go* trials. The present results suggest that the CMAr neurons may participate in cognitive and motor functions of “attention for action” and “response selection” for an appropriate action according to an intention, whereas the CMAd and CMAv neurons may be involved in “motor preparation and execution”.

Key words: Go/No-go discrimination; anterior attention system; motor decision; cingulate motor areas; single-unit recording; macaque monkey

Introduction

Recent functional-imaging studies have revealed that the anterior cingulate cortex (ACC) in humans plays key roles in cognitive and motor functions (Paus, 2001). One of the major cognitive functions of the ACC is thought to be “attention for action”, an attentional process guiding to focus on specific feature or category (location, speed, color, shape, etc.) of external targets for selecting an appropriate action (Posner et al., 1988; Corbetta et al., 1991). In particular, the attentional activity of the ACC is greatly enhanced in certain paradigms using incongruent stimuli (Stroop task: Pardo et al., 1990; Carter et al., 2000; MacDonald et al., 2000) (but see Banich et al., 2000) (flanker task: Botvinick et al., 1999; Casey et al., 2000). In the Stroop task, subjects have to name the color of congruent stimuli (e.g., the word “red” displayed in red color) or of incongruent stimuli (“red” in green color), so higher attention to a specific feature or category is needed in the incongruent condition where one feature (word)

conflicts with another (color). These suggest that the human ACC might particularly have a function of monitoring the conflicts among feature or category to select proper actions as part of the anterior attention system (conflict monitoring). On the other hand, it has previously been shown that the ACC and its adjacent cingulate areas are involved in motor-related functions such as “response selection” and “motor preparation and execution” (Frith et al., 1991; Paus et al., 1993; Grafton et al., 1996, 1998; Larsson et al., 1996; Petit et al., 1998; Deiber et al., 1999), and that lesions of these cingulate areas result in impairments of motor performance in human patients (Stephan et al., 1999; Turken and Swick, 1999).

On the basis of these observations in humans, Picard and Strick (1996, 2001) have proposed that three distinct cingulate zones, consisting of the anterior rostral cingulate zone (RCZa), the posterior rostral cingulate zone (RCZp), and the caudal cingulate zone (CCZ), are functionally associated with conflict monitoring, response selection, and motor execution, respectively. They have also considered that the RCZa, RCZp, and CCZ in humans may be comparable to the rostral, ventral, and dorsal divisions of the cingulate motor area (CMAr, CMAv, and CMAd) in the macaque monkey, respectively (Picard and Strick, 1996, 2001). So far, many electrophysiological investigations using awake monkeys have shown that these cingulate motor areas (CMAs) contribute to motor or motor-related functions (Shima et al., 1991; Cadoret and Smith, 1995, 1997; Procyk et al., 2000;

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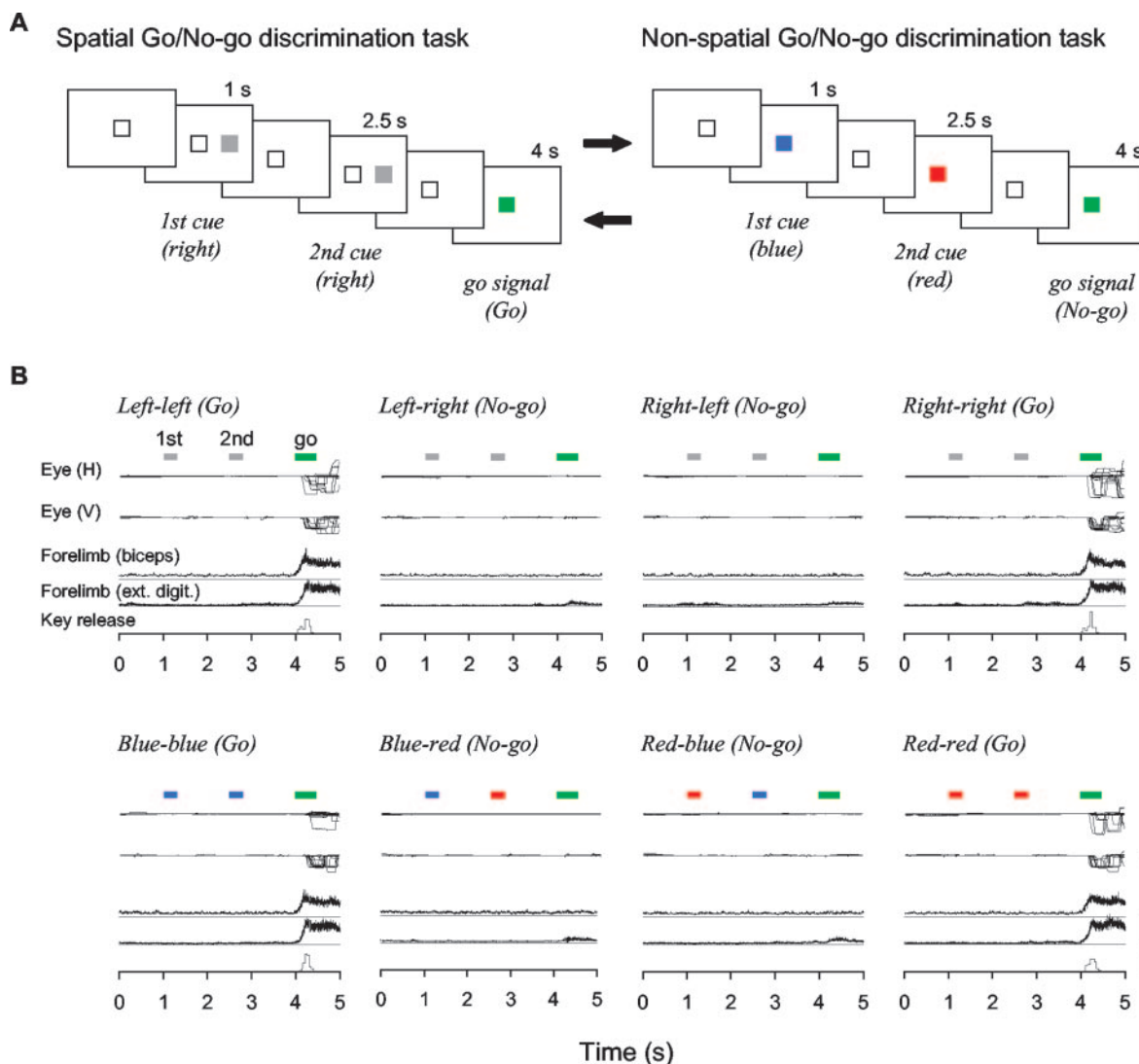


Figure 1. Task procedures and monkey's task performance. *A*, Delayed conditional Go/No-go discrimination tasks using spatial (location, left or right) and nonspatial (color, blue or red) visual cues. Left and right panels illustrate two examples of spatial (right-right, Go) and nonspatial (blue-red, No-go) trials, respectively (for details, see Materials and Methods). *B*, No ocular or manual movements during the Go/No-go discrimination trials. Horizontal (H) and vertical (V) eye positions (first and second traces, superimposed from 12 trials), rectified EMGs of the forelimb used for key press (third and fourth traces, averaged from 50 trials), and the timing of key release (bottom histogram) in each cue combination of the discrimination tasks. Scale bars: 20° for eye positions (top); 20 μ V for EMG (middle); 0.25 probability with 50 msec bin for key release timing (bottom).

Akkal et al., 2002; Russo et al., 2002), as well as to emotional or motivational functions (Nishijo et al., 1997; Shima and Tanji, 1998; Shidara and Richmond, 2002). However, it remains poorly understood whether the monkey CMAs can participate in cognitive (attentional) functions leading to appropriate actions. In the present study, we recorded single-unit activity from the CMAR, CMAd, CMAv, and the dorsolateral prefrontal cortex (PFC) of macaque monkeys trained to perform delayed conditional Go/No-go discrimination tasks, to elucidate the cellular mechanisms of attention for action, response selection, and motor preparation and execution.

Materials and Methods

Subjects. Two female Japanese monkeys (*Macaca fuscata*) weighting 6.2 (monkey H) and 6.8 kg (monkey R) were used in this study. Each monkey, whose body weight was monitored periodically, was deprived of water in her home cage, but could get sufficient amount of water every weekend, in addition to daily supply of juice as reward for task performance in the laboratory. Feed with vegetables and fruits was given in the home cage everyday. All experiments were approved by the Animal Care

and Use Committee of the Tokyo Metropolitan Institute for Neuroscience and were performed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, 1996) and the Guideline for Care and Use of Animals (Tokyo Metropolitan Institute for Neuroscience, 2000).

Apparatus. The monkeys were seated in a monkey chair and faced a 17 inch cathode-ray tube (CRT) monitor (FlexScan F520; Eizo Nanao, Ishikawa, Japan) that was placed 60 cm apart from their faces in a curtained dim compartment. The heads of the monkeys were restrained to a stereotaxic frame attached onto the chair. A key (6.0 \times 3.5 cm acrylic plate), which was reachable with either hand, was located in front of the trunk. The eye position of the monkeys was monitored by the field coil and the associated electronic equipment (MEL-22U; Enzanshi Kogyo, Tokyo, Japan). The TEMPO system with three Windows/MS-DOS computers (Reflective Computing, St. Louis, MO) was used for controlling the task and sampling all data on line.

Behavioral task. The monkeys were trained to perform self-paced, delayed conditional Go/No-go discrimination (Konorski-type) tasks (Watanabe, 1986a,b) using spatial (location) and nonspatial (color) visual cues (Fig. 1A). These types of discrimination tasks make it possible to isolate cognition-related neuronal responses from motor-related ones

Table 1. Temporal changes of task-related activities in cingulate and prefrontal cortices

Area	Total units	Task periods ^a					
		1st cue	1st delay	2nd cue	2nd delay	Go signal	Reward
CMAr (area 24c)	117	13 (11.1)	33 (28.2)	30 (25.6)	41 (35.0)	31 (26.5)	31 (26.5)
CMAv (areas 6c/23c)	122	11 (9.0)	30 (24.6)	31 (25.4)	53 (43.4)	45 (36.9)	46 (37.7)
PFC (area 46)	33	10 (30.3)	11 (33.3)	11 (33.3)	14 (42.4)	13 (39.4)	9 (27.3)

^a The number and percentage (in parentheses) of task-related neurons with differential or nondifferential activity in individual task periods: 1st cue period, 1–1.3 sec; 1st delay, 1.3–2.5 sec; 2nd cue, 2.5–2.8 sec; 2nd delay, 2.8–4 sec; go signal, 4–4.5 sec; reward, 4.5–5 sec.

temporally. The Go/No-go discrimination task started once the monkeys pressed the key for >0.5 sec and fixated on a small fixation square (0.5 × 0.5° in visual angle) on the CRT monitor. In the spatial discrimination task, location-related visual cues using a 0.5°-sized gray square were randomly displayed 5° on either the left or right side of the fixation square for 0.3 sec twice at 1 and 2.5 sec after the start of trials. Subsequently, a go signal (0.5°-sized green square) was displayed at the fixation position for 0.5 sec at 4 sec after the start. If the two visual cues were presented in the same position, the monkeys had to release the key when the go signal appeared (“Go” trials), and if they were presented in the different positions, the monkeys had to keep pressing the key until the fixation square disappeared at 5 sec after the start (“No-go” trials), to obtain a drop of juice as reward. The reward was delivered symmetrically at the end of both Go and No-go trials and was followed by an intertrial interval of 1–2 sec. In the nonspatial discrimination task, blue and red squares as color-related visual cues, which were displayed in the position of the fixation square, were used instead of the location-related visual cues. The luminance of all the visual cues was adjusted to be the same by the VideoSYNC module of the TEMPO system. The monkeys had to execute or withhold the key release when the two cues were in the same or different colors, respectively. If the eye position was out of an acceptable area (within 2–4° from the center of the fixation point) or if the key was released by mistake in the course of trial, the trial was aborted immediately with an error buzzer. The spatial and nonspatial discrimination tasks were alternately changed after every correct trial, and the monkeys, therefore, were able to presume a task type in the next trial (location or color) in advance. The monkeys were not required for the fixation in the initial training term (3–6 months) before search coil implantation. Extracellular unit recordings were performed once the final-form tasks with the fixation were accomplished constantly (>90% correct) in the second training term (1–3 months).

Surgical procedures. Under general anesthesia with sodium pentobarbital (25–30 mg/kg, i.v.) after induction with ketamine (4–6 mg/kg, i.m.) and xylazine (1 mg/kg, i.m.), the monkeys were positioned in a stereotaxic apparatus (SN-2N; Narishige, Tokyo, Japan). After exposure of the skull, small stainless steel bolts with their tips flattened were screwed in the skull as anchors. Two receptacles for head fixation were bound to the anchor bolts with dental acrylic resin, and a small pin was also attached as a stereotaxic reference marker. To monitor eye movement, a search coil was placed under the conjunctiva of one eye, and the connector was fixed to the head (Mano et al., 1991). The monkeys were given enough food and water, and antibiotics were administered systemically for 4–7 d after the surgical operation. After recovery from the operation and then the second training term, the head was fixed in the stereotaxic frame under the anesthesia with ketamine (4–6 mg/kg, i.m.) and xylazine (1 mg/kg, i.m.), and a small portion of the skull over the cingulate sulcus or the principal sulcus was surgically removed to gain access to target cortical areas. A recording chamber (inner space, 15 × 30 mm) with a transparent acrylic lid was set over the removed skull portion. The monkeys were allowed to recover fully from the second operation for several days with sufficient food and water.

Electrophysiological recordings. A glass-coated Elgiloy microelectrode (1.0–1.5 MΩ at 1 kHz) was inserted into the CMAr (area 24c), CMAv (area 6c), and CMAv (area 23c) [monkeys H and R; anterior (A) 32–0 mm, lateral (L) 3–6 mm in stereotaxic coordinate] or into the dorsolateral PFC (area 46) (monkey R; A 37–32 mm, L 8–12 mm) vertically by a microdrive (MO-95S; Narishige) that was installed in a three-dimensional micromanipulator (1460–61; David Kopf Instruments, Tujunga, CA) in the stereotaxic frame. Single-unit activity in these cortical

areas, which were situated on the side contralateral to the hand used for key pressing, was amplified at 5000-fold gain, filtered at 0.2–2 kHz, and isolated with a laboratory-made amplifier and window discriminator. The isolated unit signals were acquired digitally by the TEMPO system at 1 kHz only during successful trials. This system was also set up to record the horizontal and vertical eye positions, electromyograph (EMG), and other task-related events simultaneously. The EMG (amplified at 50,000-fold gain, filtered at 0.005–3 kHz, and sampled at 1 kHz) of *M. biceps brachii* and *M. extensor digitorum* was obtained with Ag–AgCl surface electrodes in some experiments, to confirm the absence of unnecessary movements of the forelimb during trials. To ensure the somatotopic organization of the recorded CMAs, neuronal responses to somatosensory stimuli (proprioceptive or cutaneous) were examined by passive joint movements or by stroking the skin with a brush, and intracortical microstimulation (ICMS; 22 or 40 pulses, 200 μs duration, 20–50 μA) was applied to observe evoked muscular movements (Akazawa et al., 2000; Takada et al., 2001). At the end of all recording experiments, several sites were marked with iron deposit as reference by passing positive DC current (300 μC) through the electrode.

Histology. The monkeys were deeply anesthetized with an overdose of sodium pentobarbital (50 mg/kg, i.v.), and perfused transcardially with PBS, pH 7.3 (3 l), followed by a fixative (5 l) containing 8% formalin and 2% K₄Fe(CN)₆ in 0.1 M phosphate buffer (PB), pH 7.3, a 10% sucrose solution (2 l), and finally a 30% sucrose solution (1.5 l) in 0.1 M PB (Mano et al., 1991). The brain was removed from the skull, stored in a 30% sucrose solution in 0.1 M PB at 4°C, and then cut into 50-μm-thick coronal sections. The sections were mounted onto gelatin-coated glass slides, Nissl-stained with Neutral red, and then observed under a light microscope to reconstruct the recording sites. The border between the CMAr and the CMAv or between the CMAr and the CMAv was determined by the neuronal responses to sensory stimuli and the muscular movements evoked by ICMS (Luppino et al., 1991; Akazawa et al., 2000; Takada et al., 2001), and confirmed in relation to the position of the genu of the arcuate sulcus (Dum and Strick, 1991; Luppino et al., 1991; Matelli et al., 1991).

Data analysis. To screen the task-related unit activity from all the recorded units, rasters and peristimulus time histograms (PSTHs) (bin width, 50 msec) aligned with the cue presentation were made individually for eight cue combinations of the tasks. The firing rates in sliding time windows, which ranged for 250 msec and shifted every 50 msec (one bin), were compared statistically with the baseline firing rate during the pre-cue period at 0–1 sec in each cue combination, and the activity above the significance level of $p < 0.01$ (Student's *t* test) was defined as “task-related” activity in the time window of the cue combination. Then, the specificity of task-related activity to individual visual features (left, right, blue, or red), visual categories (location or color), or motor responses (Go or No-go) was estimated at the higher significance level of $p < 0.001$ in the same time windows, and the specificity was summed up in individual neuronal groups. In this way, we analyzed the temporal changes in neuronal population activity specific to visual features, visual categories, and motor responses in each of the recorded regions. All data in the text are expressed as the mean ± SD, and Student's *t* test, ANOVA, or χ^2 test was applied for statistical comparisons.

Results

Task performance

The two monkeys proficiently performed the delayed conditional Go/No-go discrimination tasks using spatial and nonspatial vi-

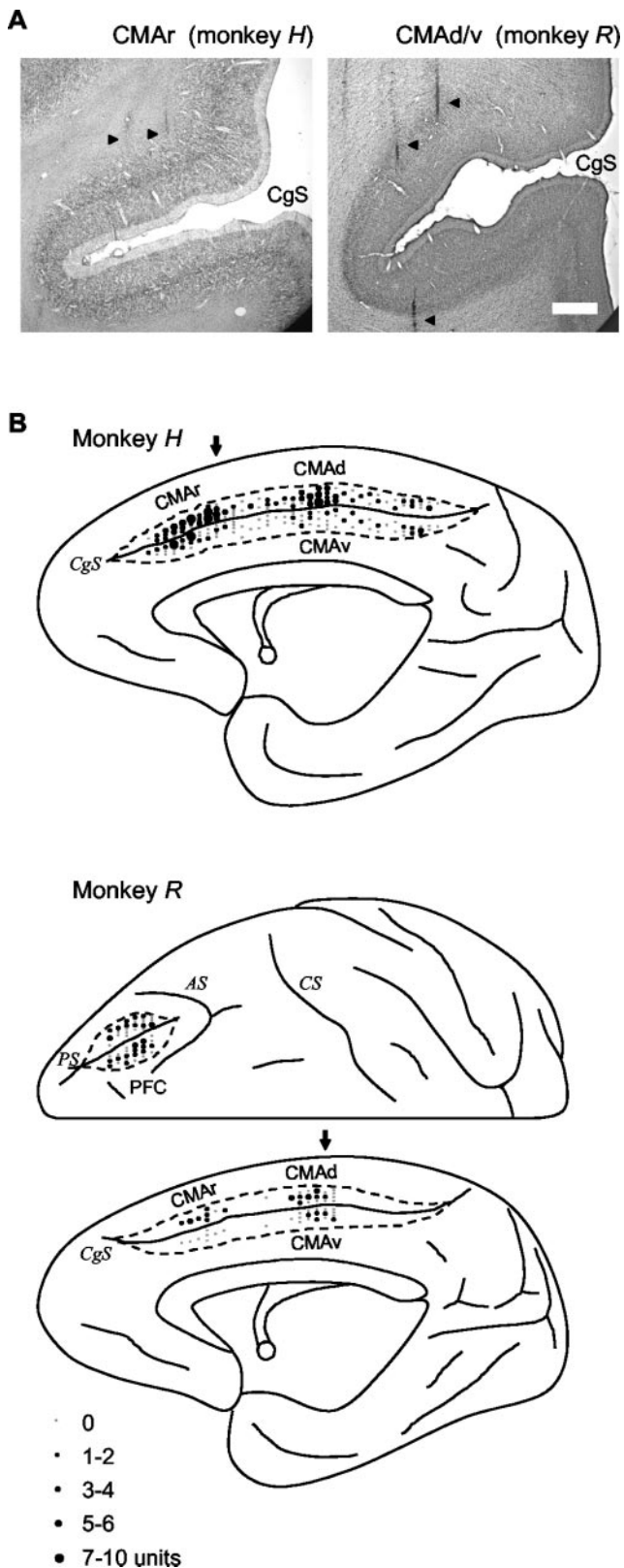


Figure 2. Distribution of task-related neurons recorded from the cingulate and prefrontal cortices. *A*, Photomicrographs of coronal sections of the rostral cingulate motor area (CMAR) recorded in monkey H (left) and the dorsal and ventral cingulate motor areas (CMAAd/v) recorded in monkey R (right). Arrowheads indicate penetration tracks of the electrode. CgS, Cingulate sulcus. Scale bar, 1 mm. *B*, Medial and dorsal views summarizing the number of task-related units (black dots) recorded on the dorsal and ventral banks of cingulate sulcus (i.e., CMAr, CMAAd, and CMAv) in monkeys H (top) and R (bottom). The task-related neurons in the dorsolateral PFC were recorded from monkey R. The cingulate and principal sulci are unfolded. The size of dots

visual cues (Fig. 1A) during daily unit recordings. They successfully maintained the fixation on the center of the CRT monitor, and little change in EMG activity was observed in the forelimb on the side ipsilateral to key pressing until the key was released in each task trial (Fig. 1B). The reaction times of Go responses, from the onset of go signal to the key release, were 207.3 ± 24.6 msec (left–left cue combination), 219.0 ± 25.3 msec (right–right), 189.8 ± 34.3 msec (blue–blue), and 197.6 ± 44.7 msec (red–red) in the monkey H, and 192.5 ± 22.8 msec (left–left), 181.6 ± 23.2 msec (right–right), 196.3 ± 20.4 msec (blue–blue), and 190.2 ± 33.0 msec (red–red) in the monkey R (averaged values from separate experiments in seven days, respectively). The reaction times were not significantly different among the eight cue combinations in the two monkeys (two-way ANOVA; cue $p > 0.8$, monkey $p > 0.1$, interaction $p > 0.2$).

Prefrontal and cingulate neurons with task-related activity

A total of 272 task-related neurons were obtained from cingulate and prefrontal cortices of the two monkeys performing the Go/No-go discrimination tasks (Table 1, Fig. 2A,B) (206 neurons from monkey H and 66 from monkey R). The task-related cingulate neurons were concentrated in rostral (CMAR) and caudal (CMAAd and CMAv) portions on the dorsal and ventral banks of the cingulate sulcus (Fig. 2B), each of which corresponded to the forelimb representation identified according to neuronal responses to somatosensory stimuli or body part movements evoked by intracortical microstimulation (data not shown). Because there were no considerable differences between neuronal activities in the CMAAd and the CMAv (see Fig. 7) (see also Shima et al., 1991; Russo et al., 2002), CMAAd and CMAv neurons were grouped as “CMAAd/v” neurons (Table 1: CMAAd, $n = 98$; CMAv, $n = 24$). In additional experiments, prefrontal neurons were recorded from area 46 (monkey R, right hemisphere) just to confirm well characterized neuronal activity coding visual information in the dorsolateral PFC (Watanabe, 1986a). The task-related neuronal population responding to the first visual cues was much smaller in the CMAR and CMAAd/v than in the PFC (Table 1) (χ^2 test; $p < 0.005$), whereas the population responding to the second visual cues was not significantly different among these three areas ($p > 0.6$). Thus, the CMA neurons had a tendency to respond to the second (conditioned) visual cues that were related to the selection of motor responses, but not to respond to the first visual cues.

Of the 272 task-related neurons, cognitive or motor-related neurons with differential activity were classified into (1) visual feature-specific neurons, (2) visual category-specific neurons, (3) Go-dominant cue-associated neurons, (4) No-go-dominant cue-associated neurons, (5) motor preparation-related neurons, and (6) motor execution-related neurons. Briefly, the visual feature-specific neurons were defined to exhibit the specificity to one cue feature (i.e., left, right, blue, or red) (Fig. 3A), whereas the visual category-specific neurons were defined to display the specificity to one cue category (i.e., location or color) (Fig. 3B). The Go-dominant and No-go-dominant cue-associated neurons were motor-related neurons responding to cue presentation specifically in Go and

← represents the number of task-related neurons; the smallest dots indicate the penetration tracks with no task-related activity recorded. The coronal sections shown in A are obtained from the rostrocaudal levels indicated by arrows. AS, Arcuate sulcus; CS, central sulcus; PS, principal sulcus.

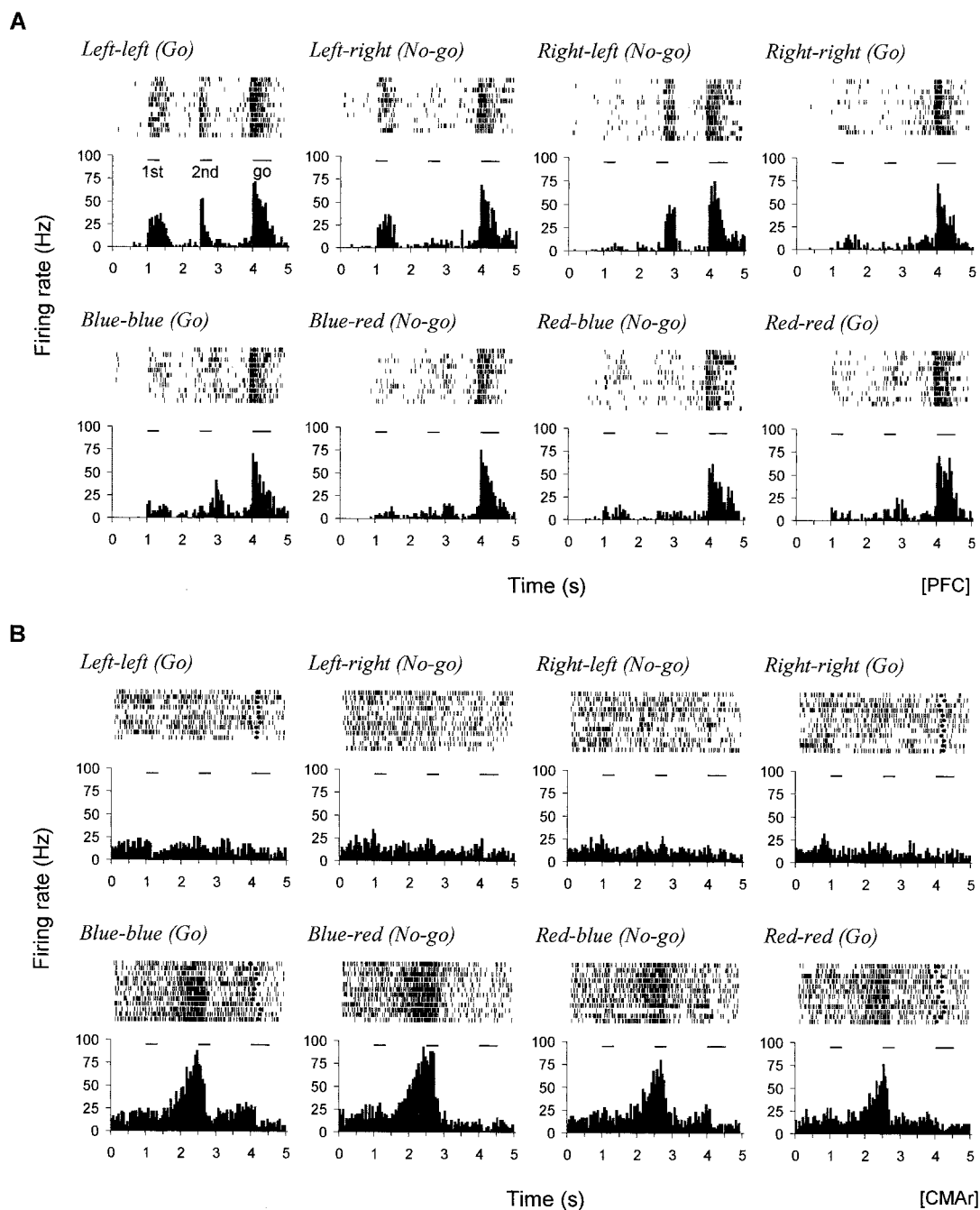


Figure 3. Visual feature-specific or visual category-specific neuronal activity. *A*, Neuronal activity specific to the visual feature “left” (visual feature-specific neuron). This neuron, which was recorded in the PFC, also responded to the green go signal in all cue combinations. Rasters (top) and PSTH (at 50 msec bin; bottom) of the activity are aligned in each cue combination. The two visual cues and the go signal were displayed at 1, 2.5, and 4 sec (indicated by “1st,” “2nd,” and “go” bars). The filled circle in each raster of Go trial indicates the timing of key release. *B*, Neuronal activity exhibiting anticipatory responses toward the second cue presentations related to the visual “color” category (visual category-specific neuron). This neuron was recorded in the CMAR. Note that there are no significant differences in the response magnitude between the Go and the No-go trials.

No-go trials, respectively (Fig. 4*A,B*). A prolonged activity before the Go response (key release) was evoked in the motor preparation-related neurons (Fig. 5*A*), whereas a strong activity coinciding with the Go response was elicited in the motor execution-related neurons (Fig. 5*B*).

Visual feature-specific or visual category-specific neurons

A PFC neuron responding to a specific visual feature of the presented cues is exemplified in Figure 3*A* (visual feature-specific neuron). Because this neuron displayed a strong activity in

response to the left location cue, such visual feature-specific neurons responded to one visual feature of the cues presented during the first and second cue periods, irrespective of the Go or No-go motor response. Consistent with previous studies (colors: Watanabe, 1986a; locations: Funahashi et al., 1993), the neurons exhibiting visual feature-specific activity were frequently found in the PFC (Fig. 6*A*, inset) (left 12%, right 3%, blue 3%, and red 3% of 33 neurons). In contrast, only a small number of visual feature-specific neurons were observed in the CMAR (Fig. 6*A*) (left 1.7%, right 0%, blue 0%, and red 0%

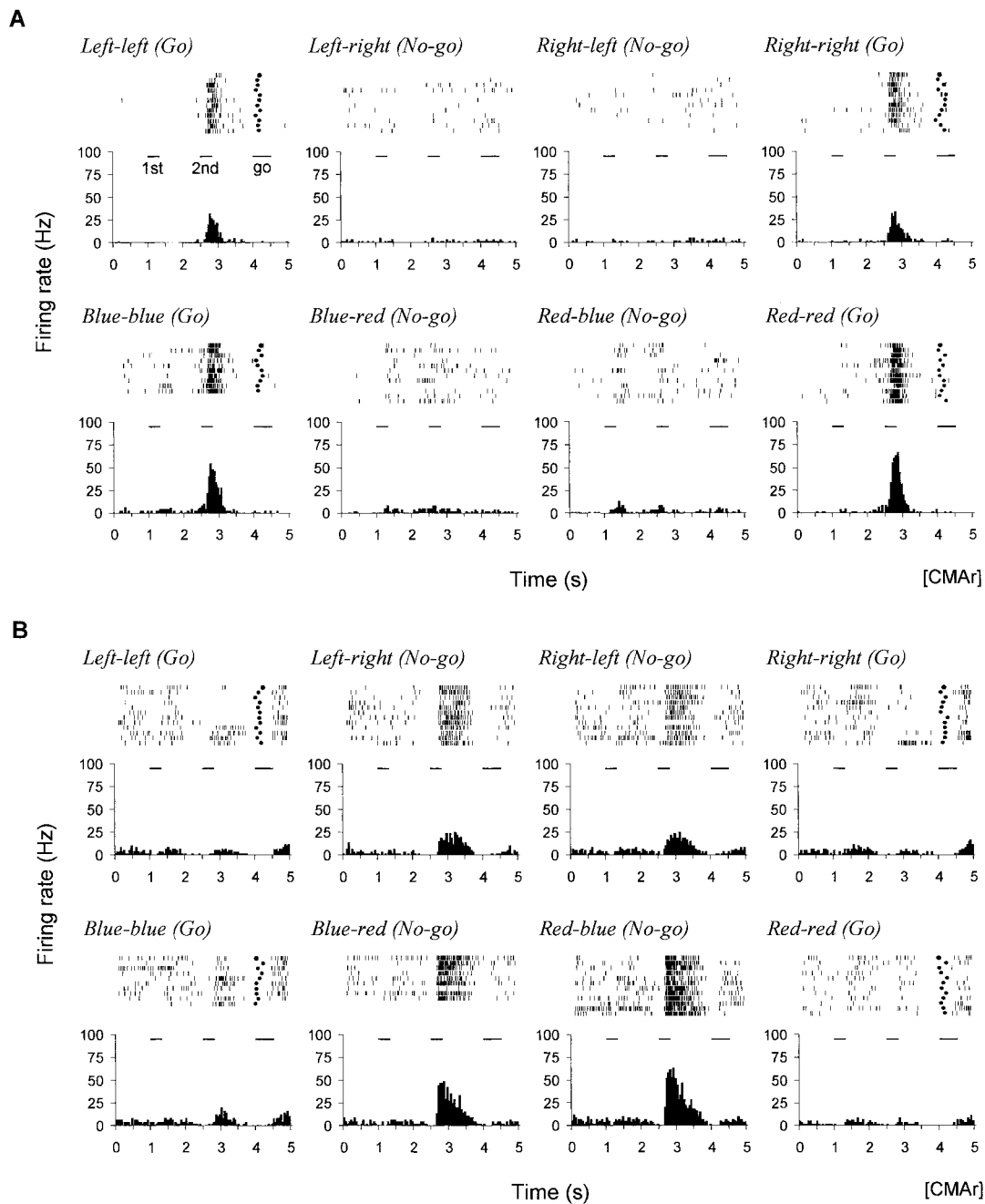


Figure 4. Go or No-go response-specific neuronal activity in response to visual cue presentation. *A*, Neuronal activity responding specifically to the second visual cues in Go trials only (Go-dominant cue-associated neuron). *B*, Neuronal activity responding specifically to the second visual cues in No-go trials only (No-go-dominant cue-associated neuron). Both of the neurons in *A* and *B* were recorded in the CMAR. Note that the activity evoked by the color-related cues is significantly larger than the activity by the location-related cues in these two cases.

of 117 neurons) and CMAd/v (Fig. 6*A*) (left 0.8%, right 0.8%, blue 0%, and red 0% of 122 neurons), which is consistent with a previous report (Akkal et al., 2002). Thus, the visual feature-specific neuronal population obtained in the PFC was significantly larger than those in the CMAR and CMAd/v (χ^2 test; $p < 0.001$).

Many neurons having the specificity to visual category (location or color) were recorded in both the CMAR (Fig. 6*B*) (location 12.8%, color 12.0%) and the PFC (Fig. 6*B*, inset) (location 33%, color 15%) (visual category-specific neurons), whereas significantly fewer neurons in the CMAd/v exhibited the specificity to visual category (Fig. 6*B*) (location 6.6%, color 4.1%; χ^2 test; $p <$

0.001). However, large differences in the temporal changes of visual category-specific activity were detected between the CMAR and the PFC (Fig. 6*B*). The activity of PFC neurons was kept high even during the first cue and first delay periods of the discrimination tasks, whereas very few neurons in the CMAR responded to the appearance of the first visual cue. Instead, most of the visual category-specific CMAR activities were associated with the second display of visual cues. Because the CMAR neuron shown in Figure 3*B* had a gradually increasing (anticipatory) activity toward the second color cues, the category-specific activity in the CMAR was elevated transiently just before or after the appearance of the second visual cues (Fig. 6*B*, left, a, b).

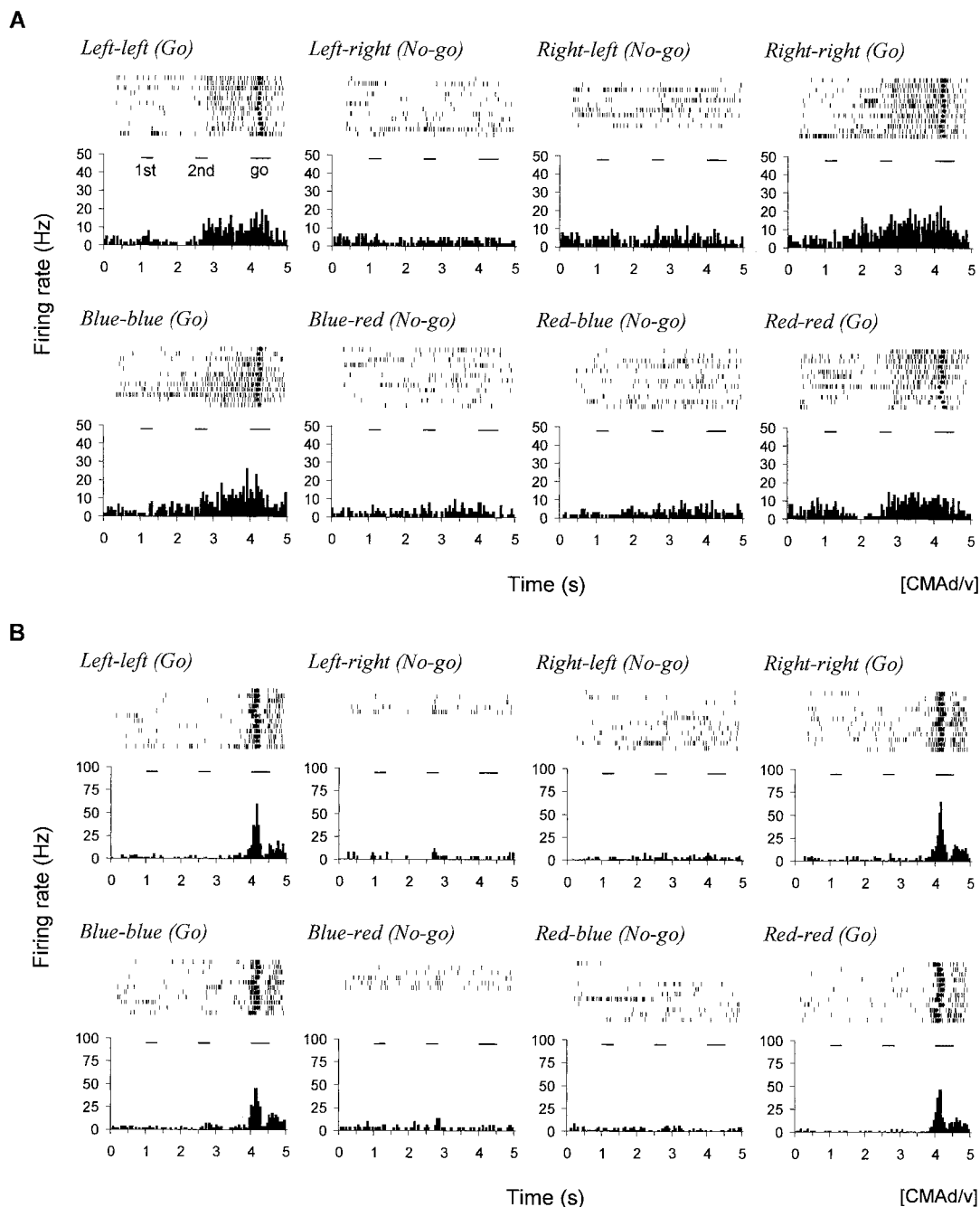


Figure 5. Go response-specific neuronal activity related to forelimb movement. *A*, Neuronal activity sustained during the second visual cue, delay, and go periods in Go trials (motor preparation-related neuron). *B*, Neuronal activity exhibiting a sharp peak preceding the key release movement (dot in each raster) in Go trials (motor execution-related neuron). This neuron responded similarly when the key was released at the end of No-go trials (data not shown). Both of the neurons in *A* and *B* were recorded in the CMAd/v.

Go or No-go response-specific neurons

As exemplified in Figure 4, the CMAR contained many neurons responding specifically to the second visual cues that indicated the Go or No-go trial. The Go response-specific neuronal activity evoked during and immediately after the second cue display was frequently recorded not only in the CMAR (21.4% of 117 neurons), but also in the CMAd/v (27.9% of 122 neurons) (Go-dominant cue-associated neurons) (Fig. 7*A*) (χ^2 test; $p > 0.2$). In contrast, the No-go response-specific activity in the same period was much more prominent in the CMAR (14.5%) than in the CMAd/v (4.9%) (No-go-dominant cue-associated neurons) (Fig. 7*B*) (χ^2 test; $p < 0.02$). As previously reported (Watanabe,

1986b), subpopulations of the PFC neurons responded to the second cue presentations specifically in either Go (12.1% of 33 neurons) or No-go (18.2%) trials (data not shown).

In addition, we found a number of CMAR and CMAd/v neurons displaying the activity that would be related to preparation or execution of manual movements (Shima et al., 1991; Russo et al., 2002). Figure 5, *A* and *B*, shows the CMAd/v neurons that exhibited a motor preparatory (or set-related) activity in the second delay period (motor preparation-related neuron), and an activity time-locked precisely to the key release movement in the go signal period (motor execution-related neuron), respectively. There were no particular differences between the CMAR and the

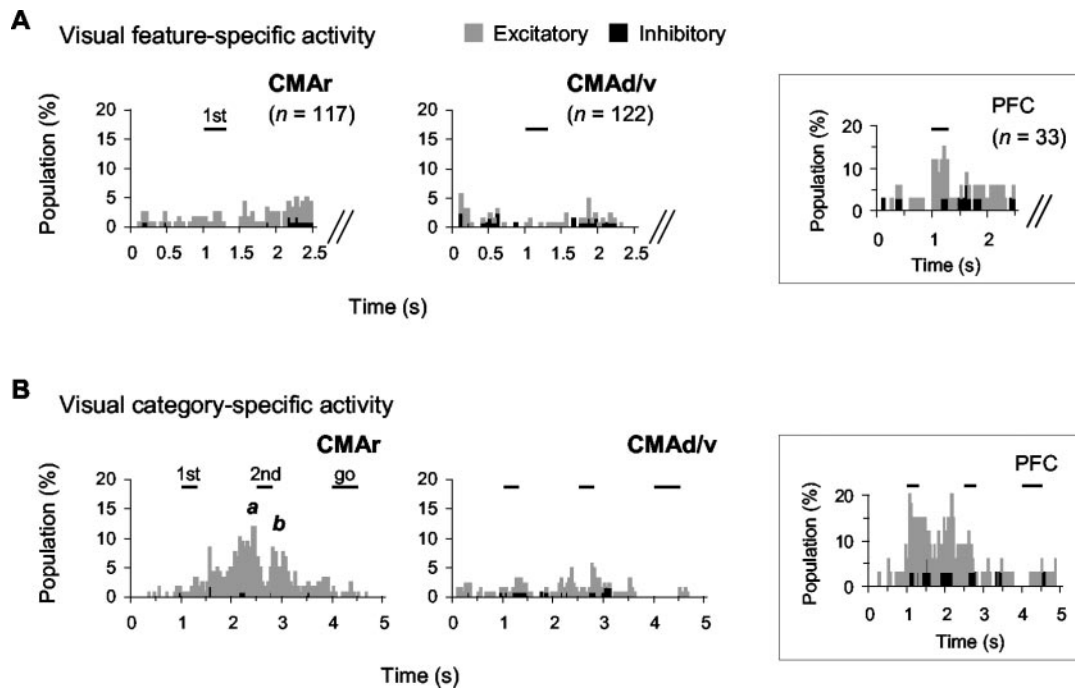


Figure 6. Neuronal populations showing visual feature-specific or visual category-specific activity in the CMAs. *A*, Temporal patterns of neuronal populations in response to individual visual features (either left, right, blue, or red) in the CMAR (left; $n = 117$ task-related neurons) and CMAd/v (right; $n = 122$). The percentage of neurons with significantly differential activity was estimated at $p < 0.001$ level in a certain time defined by 250 msec sliding time windows (gray, excitatory responses; black, inhibitory responses; for details, see Materials and Methods). Inset, Temporal pattern of a visual feature-specific population in the PFC ($n = 33$). Note that unlike PFC neurons, only a few neurons respond specifically to visual features of the first cue presentation in the CMAR and CMAd/v. *B*, Temporal patterns of neuronal populations in response to visual categories (either location or color) in the CMAR (left) and CMAd/v (right). Inset, Temporal pattern of a visual category-specific population in the PFC. Note that the CMAR population activity has two distinct peaks specific to the visual categories immediately before (a) and after (b) the second cue period (Fig. 7C).

CMAd/v in such movement-related neuronal activities (Fig. 7A) [late phase of second delay period (preparation), CMAR 26.5% vs CMAd/v 28.7%, χ^2 test, $p > 0.7$; go signal period (execution), CMAR 12.8% vs CMAd/v 12.3%, $p > 0.9$]. Likewise, no differences between the CMAd and the CMAv were clearly detected in the motor-related activity in our experimental conditions (Fig. 7A,B, insets) (χ^2 test, second delay period, $p > 0.3$; go signal period, $p > 0.9$).

Cognitive and motor-related functions in the CMAR neurons

As illustrated in Figure 8, the spatial distribution of location-dominant neurons almost overlapped that of color-dominant neurons within the CMAR where the motor-related (i.e., Go-dominant cue-associated, motor preparation-related, and motor execution-related) neurons were concentrated considerably. The No-go-dominant cue-associated neurons were also distributed in the same area of the CMAR restrictedly. Therefore, we examined whether the information on both the visual category and the motor response can be conveyed in single task-related CMAR neurons, by focusing on the visual category-specific neurons analyzed in Figure 6B, left (17 neurons at the peak *a*, location $n = 9$, color $n = 8$; 11 neurons at the peak *b*, location $n = 6$, color $n = 5$). More than half of CMAR neurons displaying the category specificity at the peak *a* (at 2.25–2.5 sec, immediately before the second cue presentation) had the specificity to the motor response (Go or No-go) in the second cue and delay periods (Fig. 7C, left) ($n = 10$ of 17). Similarly, the category-specific CMAR neurons consisting of the peak *b* (at 2.75–3.0 sec, just after the second cue presentation) also exhibited the response specificity in the second cue and delay periods (Fig. 7C, right) ($n = 8$ of 11). In fact, the two representative neurons in Figure 4 showed the differential

cognitive activity about the visual category (color > location), in addition to the differential motor-related activity reflecting the Go or No-go response. On the basis of these results, a population of CMAR neurons, but not of CMAd or CMAv neurons, may participate in the attention to a visual category as well as in the selection of a proper action during the performance of the Go/No-go discrimination tasks.

Discussion

The delayed conditional Go/No-go discrimination tasks that we adopted here are very advantageous to deal with cognitive and motor functions separately, because the activity responding to the first visual cues will relate purely to the processing of sensory information, whereas the activity to the second cues will relate not only to sensory information processing but also to the selection of an appropriate movement. Most of the visual category-specific neurons in the CMAR were activated exclusively in relation to the second (conditioned) cues with the specificity to either location or color, as represented by a visual category-specific neuron displaying a build-up activity toward the second color cues (Fig. 3B). These neurons might play a critical role in attention for action, rather than in earlier attentional processes for visual recognition such as attention to color (for review, see Posner et al., 1988), because (1) the CMAR neurons responded specifically to the second cues as a determinant for action, but neither to the first cues nor to the green go signal (Fig. 6B); (2) there exist a certain population of motor-related CMAR neurons with the attention-like activity (Fig. 7C); and (3) the human ACC is not activated directly in association with selective attention to shape, color, or speed (Corbetta et al., 1991). The abundance of such

neurons with attention for action-like activity may be characteristic of the CMAR in the primate cerebral cortex.

It has been proposed that the RCZa of the human ACC may be associated with monitoring the conflicts among visual features in the Stroop task (Picard and Strick, 2001). Generally, the ACC activation for color naming is much larger than the activation for word reading in the Stroop task in human subjects (Ruff et al., 2001). In our experiments, however, the extent of color-specific activity was almost comparable to that of location-specific activity in the monkey CMAR (see Results). This is probably because the present Go/No-go discrimination task requires neutral motor responses independent of color and location, unlike verbal responses in the Stroop task. In both humans and monkeys, these cognitive functions will depend on the attentional process to discriminate individual features and to focus on one specific feature for a correct response. Accordingly, it is quite possible that attention for action might underlie the conflict-monitoring function in the CMAR of humans and nonhuman primates, which corresponds putatively to the RCZa defined in previous human imaging studies.

On the other hand, a number of CMAR neurons exhibited the No-go-specific activity responding to the second cues. It is well known that No-go-specific neurons are located in the dorsolateral PFC (Watanabe, 1986b; Sakagami and Niki, 1994) and the supplementary motor area (Kurata and Tanji, 1985), but not in the pre-motor cortex (Wise et al., 1983; Weinrich et al., 1984), in monkeys. Moreover, the ACC, including the CMAR, has been shown to connect directly with the dorsolateral PFC (Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Lu et al., 1994; Petrides and Pandya, 2001) and the presupplementary motor area (pre-SMA) (Morecraft and Van Hoesen, 1992, 1993; Wang et al., 2001). Therefore, it is likely that neurons in the CMAR (and also in the pre-SMA) share higher-order cognitive as well as motor information with those in the dorsolateral PFC (Watanabe, 1986a; Funahashi et al., 1993). In addition, Shima and Tanji (1998) have demonstrated that some groups of CMAR neurons mediate a process of voluntary selection of suitable movements in a reward-based manner. These data suggest that the CMAR, along with the dorsolateral PFC and pre-SMA, may be implicated in decision-making of motor actions in monkeys. In humans, however, the specific activation for response selection has been mapped not in the RCZa (putative human CMAR counterpart) but in the RCZp (CMAv counterpart) (see Picard and Strick, 1996, 2001). This discrepancy may result from the difference in the functional development and differentiation of the cingulate cortex between humans and nonhuman primates. It should be emphasized here

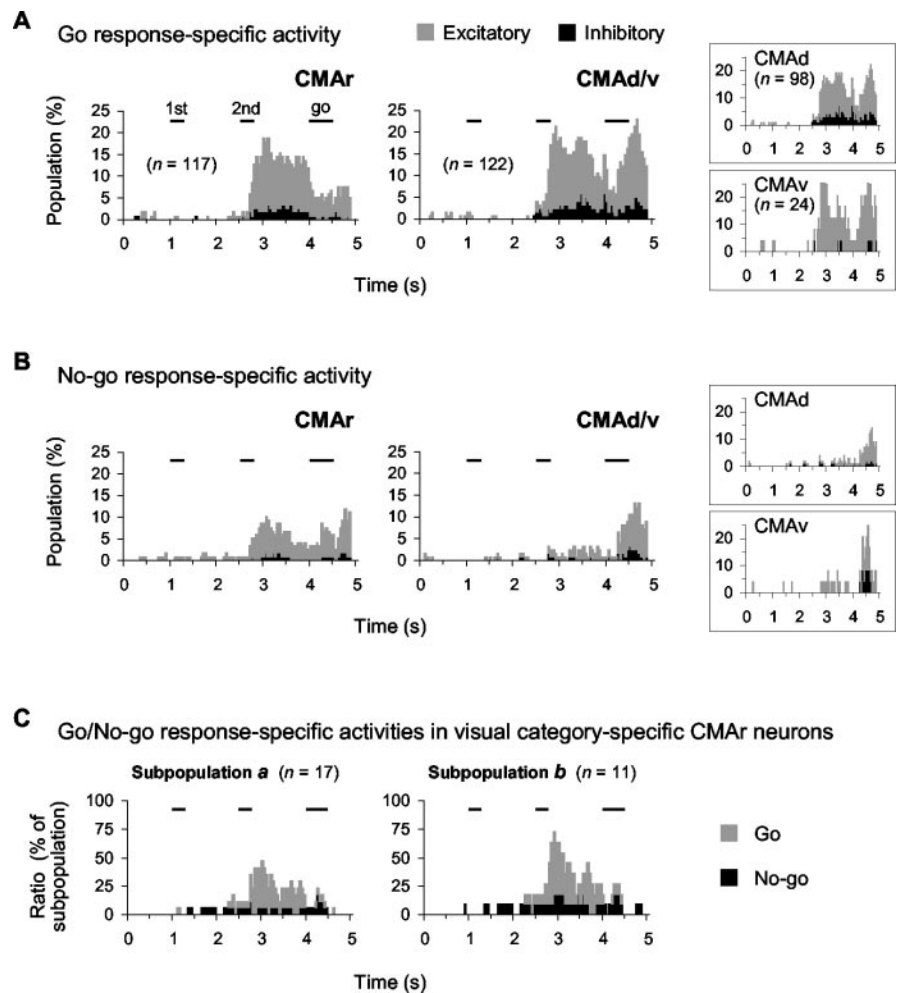


Figure 7. Neuronal populations showing Go or No-go response-specific activity in the CMAs. *A*, Temporal patterns of neuronal populations in response to Go trials ($p < 0.001$) in the CMAR (left; $n = 117$ task-related neurons) and CMAv (right; $n = 122$). The Go-specific activities are highly maintained after the display of the second visual cues in both the CMAR and the CMAv. Insets, Go-specific neuronal populations in the CMAAd (top; $n = 98$) and CMAv (bottom; $n = 24$). *B*, Temporal patterns of neuronal populations in response to No-go trials in the CMAR (left) and CMAv (right). The No-go-specific population is much larger in the CMAR than in the CMAv during the second visual cue and second delay periods. Insets, No-go-specific neuronal populations in the CMAAd (top) and CMAv (bottom). Note that the activity patterns of CMAAd and CMAv neurons are very similar to each other in *A* and *B*. *C*, Temporal patterns of neuronal populations displaying Go or No-go response-specific activity in visual category-specific subpopulations of CMAR neurons. The subpopulation a (left; $n = 17$) corresponds to the CMAR neurons active at the peak a, whereas the subpopulation b (right; $n = 11$) corresponds to the CMAR neurons active at the peak b (Fig. 6*B*, left). Note that many of the visual category-specific neurons in each subpopulation exhibit the specificity to Go (gray) or No-go (black) response ($p < 0.001$) immediately before or during the second visual cue and second delay periods.

that at least part of the CMAR neurons examined in our study displayed the response-specific activity coupled with the attention-like activity. Thus, the attentional activation of such CMAR neurons could provide a supportive process of motor decision-making achieved by a cooperative action of the PFC, pre-SMA, and CMAR.

Several investigations have demonstrated that the ACC is activated during working memory tasks in human (Petrides et al., 1993a,b; D'Esposito et al., 1995; Petit et al., 1998) and monkey subjects (Niki and Watanabe, 1976). Unlike the PFC neurons, however, neither the CMAR nor the CMAv neurons appeared to code the individual cue information during the first delay period of our discrimination tasks. This indicates that the CMAR does not seem to act as a memory buffer *per se* for working memory, but rather the attentional activity of CMAR neurons is likely to support a prefrontal function for working memory as a central

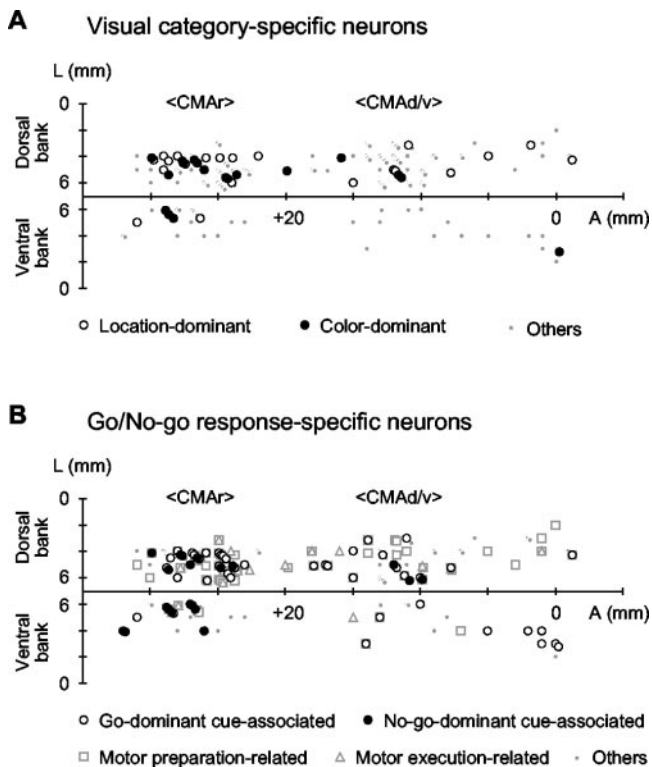


Figure 8. Spatial distributions of distinct types of cognitive and motor-related neuronal activities in the CMAs. *A*, Overlapped distribution of visual category-specific neurons in the CMAs (monkey H). Open circles, Neurons with location-dominant activity; closed circles, neurons with color-dominant activity; gray dots, other task-related neurons. Note that both types of the visual category-specific neurons are located predominantly in the CMAR. *B*, Overlapped distribution of Go/No-go response-specific cue-associated neurons in the CMAs of the same monkey. Open circles, Neurons with Go-dominant cue-associated activity; closed circles, neurons with No-go-dominant cue-associated activity; gray squares, motor preparation-related neurons (with Go-dominant activity during the second delay period); gray triangles, motor execution-related neurons (with Go-dominant activity in the go period); gray dots, other task-related neurons. Note that most of the No-go-dominant cue-associated neurons are located in the CMAR, whereas Go-dominant cue-associated, motor preparation- and execution-related neurons are distributed not only in the CMAR, but also in the CMAd and CMAv. *A*, Anterior (in millimeters) from the interaural line; *L*, lateral (in millimeters) from the midline. The dorsal and ventral banks of the CMAs are represented upward and downward, respectively.

executive system. Moreover, the ACC might be involved in other cognitive functions, such as pain representation (Talbot et al., 1991; Rainville et al., 1997), novelty detection (Berns et al., 1997), error detection (Holroyd et al., 1998; Gehring and Knight, 2000) (see also Niki and Watanabe, 1979), and monitoring of mistakable conditions (Carter et al., 1998). It is, therefore, possible that the ACC may work as a higher-order integrative system for cognitive and motor functions in humans and nonhuman primates, although we did not attempt to analyze neuronal activities of CMAs in terms of such a functional aspect.

Because the CMAR and CMAd/v are strongly interconnected with each other (Morecraft and Van Hoesen, 1993, 1998), the CMAd/v neurons, in turn, appear to participate in preparation and execution of the movements selected by CMAR neurons. The CMAd and CMAv are apparently two distinct motor areas with individual cytoarchitectonic criteria and somatotopic representations (Luppino et al., 1991; Matelli et al., 1991; Morecraft and Van Hoesen, 1992; He et al., 1995; Akazawa et al., 2000; Takada et al., 2001), and their functional roles are reportedly differentiated in a complicated motor task requiring sequential movements (Picard and Strick, 1997). In our experimental conditions, how-

ever, there were no significant differences between the response patterns of CMAd and CMAv neurons, as previously described (Shima et al., 1991; Russo et al., 2002). Because the CMAd and CMAv are linked not only to many of the frontal motor-related areas including the primary motor cortex (Morecraft and Van Hoesen, 1992, 1993; Lu et al., 1994; Wang et al., 2001), but also to the spinal cord directly (Dum and Strick, 1991, 1996; He et al., 1995), it seems likely that the CMAd and CMAv, together with other motor-related areas, would plan the actual movement patterns and send motor commands to the spinal cord.

In conclusion, our electrophysiological study using task-performing monkeys has revealed that the primate CMAs may actively participate in cognitive and motor functions, including attention for action, response selection, and motor preparation and execution, to translate an intention to an appropriate action.

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